Development of a Risk Score for Geographic Atrophy in Complications of the Age-related Macular Degeneration Prevention Trial

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Objective: To develop a risk score for developing geographic atrophy (GA) involving easily obtainable information among patients with bilateral large drusen.

Design: Cohort study within a multicenter randomized clinical trial.

Participants: We included 1052 participants with ≥10 large (>125 μm) drusen and visual acuity ≥20/40 in each eye.

Methods: In the Complications of Age-related Macular Degeneration (AMD) Prevention Trial (CAPT), 1 eye of each participant was randomly assigned to laser treatment and the contralateral eye was assigned to observation to evaluate whether laser treatment of drusen could prevent vision loss. Gradings by a reading center were used to identify: CAPT end point GA (total area of GA [>250 μm] > 1 disc area), GA (>175 μm) involving the foveal center (CGA), and GA of any size and location (any GA). Established risk factors (age, smoking status, hypertension, Age-related Eye Disease Study simple severity scale score), both with and without a novel risk factor (night vision score), were used in assigning risk points. The risk scores were evaluated for the ability to discriminate and calibrate GA risk.

Main Outcome Measures: Development of end point GA, CGA, and any GA.

Results: Among 942 CAPT participants who completed 5 years of follow-up and did not have any GA at baseline, 6.8% participants developed CAPT end point GA, 9.6% developed CGA, and 34.4% developed any GA. The 5-year incidence of end point GA in 1 or both eyes of a participant increased with the 15-point GA risk score, from 0.6% for <7 points to 15% for ≥12 points. The 5-factor risk score predicted development of GA moderately well with the area under the receiver operating characteristic curve (AUC) 0.76 (95% confidence interval [CI], 0.71–0.81) for end point GA; 0.76 (95% CI, 0.71–0.80) for CGA, and 0.68 (95% CI, 0.65–0.72) for any GA. Prediction from the risk score without the night vision score had lower AUCs (range, 0.67–0.72).

Conclusions: If validated in other patients, the GA risk score will be useful for identifying high-risk patients for clinical trials of prevention of GA and for clinical assessment of GA risk in early AMD patients.

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. Choroidal neovascularization (CNV) and geographic atrophy (GA) are 2 forms of end-stage AMD. Geographic atrophy is responsible for about 10% of the severe vision loss attributed to the AMD,[1] and affects approximately 900 000 persons in the United States.[2] Anti-vascular endothelial growth factor therapy has been proven to be highly effective in reducing the vision loss in patients with CNV.[3,4] Although several agents to prevent the development or arrest the progression of GA are currently under investigation in clinical trials, none have yet been shown to be effective.

Geographic atrophy progresses gradually over time, and the causes are largely unknown. However, data from large, observational studies and clinical trial cohorts have consistently identified age, current smoking status, hypertension, drusen size or area, and pigmentary changes as risk factors.[5–15] Recent investigations have identified genes associated with GA, including complement factor H, complement factor B, LOC387715, and complement C3 variant.[16–18] More recently, night vision as assessed by a 10-item questionnaire was found to be highly predictive of the development of GA, independent of other established risk factors.[19]

In this article, we describe the development and evaluation of risk scores for the development of GA within 5 years based only on readily available risk factors. Risk scores are useful for both clinical research studies and individual patient care. Predictive summary scores were first introduced by the Framingham Heart Study Group for the 10-year risk of coronary heart disease[20] and have been applied to many disease areas, including the development of glaucoma for

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patients with ocular hypertension.[21–23] Although a prediction model including ocular, environmental, and genetic risk factors for advanced AMD (GA and CNV combined) has been developed recently,[18] a risk score for GA alone has not been developed.

Methods

Details of the design and methods of the clinical trial have been reported elsewhere[24,25]; only major features related to this paper are described here. The Complications of Age-related Macular Degeneration Prevention Trial (CAPT) was a multicenter, randomized clinical trial to evaluate low-intensity laser treatment of eyes with drusen for the prevention of vision loss from AMD in participants with bilateral large drusen. For each participant, 1 eye was randomized to laser treatment with the contralateral eye assigned to observation. The CAPT results showed that there was no statistical difference between treated and observed eyes on visual acuity loss, incidence of CNV, or incidence of end point GA.[25]

A total of 1052 participants were enrolled into CAPT between May 1999 and March 2001 from 22 participating clinical centers. The institutional review board associated with each center approved the study protocol and written informed consent was obtained from each participant. Data management was compliant with Health Insurance Portability and Accountability Act guidelines. The conduct of the clinical trial adhered to the tenets of the Declaration of Helsinki. The CAPT eligibility criteria specified that each eye have ≥10 large drusen (≥125 μm in diameter). Neither eye was to have evidence of CNV, serous pigment epithelial detachment, GA within 500 microns of the foveal center or total area >1 Macular Photocoagulation Study disc area (DA).

At the initial visit and annual visits thereafter, certified photographers adhering to a standardized protocol for field definition and image sequencing took stereoscopic, color fundus photographs on film and a fluorescein angiogram on film, with frames from each eye. Color photographs were also taken at 6 months. All photographic images were graded independently by 2 trained readers in the CAPT Reading Center who later openly discussed their discrepancies to arrive at consensus. The fundus features described in the baseline grading included number of drusen, largest drusen size, drusen area, drusen confluence, GA, focal hyperpigmentation, and retinal pigment epithelium depigmentation.

Risk Factor Assessment

At initial visit, information regarding age, cigarette smoking status, and current use of medication for hypertension was collected through questioning participants by use of a standardized questionnaire. Blood pressure was measured once while the participant was sitting. Hypertension was defined as reported current use of antihypertensive medications, or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in participants not taking antihypertensive medications.

The score on the Age-related Eye Disease Study (AREDS) simple severity scale at study enrollment was determined using the following definition.[26] For each eye, 1 point was assigned for presence of large drusen and 1 point for presence of pigmentary changes. The points from the 2 eyes are added together to provide the score, which can range from 0 to 4.

At baseline, a 10-item night vision symptoms questionnaire (NVQ-10) was self-administered.[19] The first 4 items are on a 5-point scale from "None" to "Stopped doing because of my eyesight" and ask about the difficulty in seeing moving subjects, reading street signs when driving at night, difficulty in seeing street signs as a passenger in the car at night, and difficulty with the oncoming headlights or streetlights when driving at night. The next 6 items are on a 4-point scale from "Not at all" to "Very" and ask about how bothered the participant is by poor vision at night, problems in reading in dim light, a dark spot in the middle of vision in dim light, poor vision in dim lighting, problems adjusting to the dark when entering a theater, and trouble seeing the stars in the sky at night. For the night vision score, each item is scored between 100 (none or not at all) and 0 (stop doing because of eyesight, or very bothered). An overall NVQ-10 score for each participant was calculated based on the average score of 10 items. The score ranges from 0 to 100, with lower scores indicating worse night vision.

Geographic Atrophy Definitions

Readers in the CAPT Reading Center evaluated the annual follow-up fundus color photographs for the presence of GA, amount of GA (<0.028 DA [i.e., 250 μm in diameter], 0.028–1 DA, 1–2 DA, and >2 DA), presence of a new area of GA, considering only the central area within 500 μm of foveal center, only the annulus from 500 to 1500 μm, and only the annulus from 1500 to 3000 μm, and whether the total area of GA within 3000 μm of foveal center was >1 DA. Geographic atrophy was considered to be present when the color photographs showed an area of atrophy of the retinal pigment epithelium with 2 of the following 3 features: visible choroidal vessels, sharp edges, and a more or less circular shape. We defined "CAPT end point GA" as development of a total of >1 DA of new, additional atrophy when all areas of GA (>250 μm in diameter) within 3000 μm of the foveal center were combined. End point GA was used in CAPT to identify eyes that had progressed. We defined CGA as development of GA (>175 μm in diameter) involving the center of macula. In AREDS, CGA was used to identify eyes that had progressed. Any GA was defined as the presence of any size GA (i.e., including areas <0.028 DA) within 3000 μm of the foveal center. Evaluation of GA was not performed after an eye developed CNV because the neovascular complex and subsequent scarring often occupied or obscured the retinal area most likely to develop GA.

Statistical Analysis

Analyses were restricted to 942 CAPT participants who completed 5-year follow-up, did not have any GA at baseline, and had information available on all the baseline risk factors. The development of the risk score followed the approach used for the Framingham Study risk score.[27] Specifically, a multivariate logistic regression model was fit to the data and included 5 risk factors as predictors: Age (50–59, 60–69, 70–79, and ≥80 years), smoking status (never or former vs current), hypertension status (no vs yes), AREDS simple severity score (2, 3, or 4), and night vision score (<60, 60–75, 75–85, and >85). The outcome was the development of CAPT end point GA in 1 or both eyes (person-specific GA yes/no) during a 5-year follow-up period. Estimates of the regression coefficients corresponding to each level of a risk factor were obtained, and risk points were assigned for each level of a risk factor based on the value of the associated regression coefficient and the reference regression coefficient corresponding to 1 risk point. The risk score for a participant was determined as the total of risk points based on a participant's risk factor profile. Because the night vision questionnaire is not commonly administered in clinical practice, another risk points system was developed by using the same methodology described, but without the inclusion of the night vision score (i.e., only including age, smoking, hypertension, and AREDS simple scale score).

The performance of the derived risk score from the multivariate prediction model was evaluated based on the ability to distinguish high-risk participants from low-risk participants (discrimination) and on the agreement between the predicted risk associated with specific scores and the observed proportion developing the form of GA under consideration (calibration). Discrimination was summarized by the area under the receiver operating characteristic curve (AUC, or c-statistic), yielded by the logistic regression model that used only the risk score as a predictor. The AUC ranges from 0.5 to 1, with 0.5 indicating no discriminative ability and 1 indicating perfect discriminative ability. An AUC greater than 0.9 is considered excellent, >0.8 to 0.9 very good, 0.7 to 0.8 good, 0.6 to 0.7 average, and <0.6 poor.[28] The 95% confidence interval of the AUC was determined based on the bootstrap method involving 2000 samples.[29] The difference in AUC from the risk score with versus without consideration of the night vision score was assessed through comparison of correlated AUCs based on a bootstrap z-statistic approach.[30]

Calibration was assessed by the Brier score,[31] a standardized summary measure of the mean squared differences between the observed person-specific GA outcome (0 for without GA and 1 for with GA) and the predicted probability of person-specific GA from the logistic regression model using the risk score as the only predictor. The Brier score ranges from 0 (predictions and observed outcomes match perfectly) to 1 (predictions and observed outcomes totally mismatch). Additionally, to help in the choice of scores for identifying high-risk GA patients, we calculated the sensitivity and specificity associated with the various cut points of the risk score.

These assessments of the GA risk score were performed for CAPT end point GA, CGA, and any GA in 1 or both eyes (i.e., person specific) and in untreated eyes only. All data analyses were performed in SAS 9.1. (SAS Inc., Cary, NC).

Results

Of the 942 CAPT participants included in the analysis, mean age (standard deviation) at study entry was 71 (7.5) years old, with a range of 50 to 90 years; 5% were current smokers, and 64% had hypertension. Because of the CAPT eligibility criteria, all participants had large drusen in each eye; therefore, none of the participants had an AREDS severity score of 0 or 1. Twenty-one percent had an AREDS score of 2, and more than half (56%) had a score of 4 (Table 1). The mean (standard deviation) night vision score was 70 (20), with a range of 3 to 100. Over 5 years of follow-up, 64 (6.8%) participants developed CAPT end point GA, 90 (9.6%) developed CGA, and 324 (34.4%) developed any GA in 1 or both eyes.

Risk Score Development with Five Factors

In the multivariate analysis of all 5 risk factors (Table 1, middle columns), a higher AREDS severity score was significantly associated with increased risk of end point GA (odds ratio, 7.03 for severity score of 4 vs 2; $P<0.0001$), and a decreased night vision score was associated with an increased risk of GA (odds ratio, 4.37 for 4th quartile vs 1st quartile; $P = 0.0003$). Increased age was marginally associated with increased risk of GA ($P = 0.08$). Current smoking ($P = 0.49$) and hypertension ($P = 0.20$) were not associated with end point GA in this group of participants. However, because increased age, cigarette smoking, and hypertension have been identified as risk factors for GA in several other studies,[7,9,11–15] we retained them in the prediction model for developing the risk score. The final prediction model including all 5 factors predicted the risk of end point GA moderately well with an AUC of 0.77 (95% confidence interval, 0.71–0.83), and calibrated well as evaluated by the Hosmer-Lemeshow test, which showed no

Table 1. Risk Factors for the Development of End Point Geographic Atrophy (GA) in 1 or Both Eyes within 5 Years of Follow-up in Multivariate Logistic Regression Models with and without Night Vision Score

			Multivariate Model with Inclusion of Night Vision Score		Multivariate Model without Inclusion of Night Vision Score		
Risk Factors	**n**	**GA by 5 Years, n (%)**	*Regression Coefficient (SE)*	*Odds Ratio (95% CI)*	*Regression Coefficient (SE)*	*Odds Ratio (95% CI)*	**Risk Points***
Intercept			−6.29 (1.02)		−5.57 (0.93)		
AREDS simple scale				$P<0.0001$		$P<0.0001$	
2	199	3 (1.51)	Reference		Reference		0
3	214	11 (5.14)	1.38 (0.66)	3.98 (1.08–14.6)	1.28 (0.66)	3.59 (0.99–13.1)	4
4	529	50 (9.45)	1.95 (0.60)	7.03 (2.15–23.0)	1.93 (0.60)	6.88 (2.12–22.4)	5
Night vision score				$P = 0.0003$			
>85	231	7 (3.03)	Reference				0
75.1–85	211	8 (3.79)	0.20 (0.53)	1.23 (0.44–3.48)			1
60.1–75	237	19 (8.02)	1.05 (0.46)	2.87 (1.17–7.04)			3
≤60	263	30 (11.4)	1.48 (0.44)	4.37 (1.85–10.3)			4
Age (y)				$P = 0.08$		$P = 0.09$	
50–59	87	2 (2.30)	Reference		Reference		0
60–69	271	24 (8.86)	1.50 (0.76)	4.48 (1.02–19.8)	1.50 (0.81)	4.13 (0.95–18.0)	1
70–79	492	30 (6.10)	0.97 (0.75)	2.63 (0.60–11.5)	1.03 (0.75)	2.79 (0.65–12.0)	3
≥80	92	8 (8.70)	1.23 (0.82)	3.43 (0.69–17.2)	1.42 (0.75)	4.49 (0.91–22.1)	4
Smoking status				$P = 0.49$		$P = 0.39$	
Never/former	892	59 (6.61)	Reference		Reference		0
Current	50	5 (10.0)	0.36 (0.52)	1.43 (0.52–3.99)	0.46 (0.51)	1.58 (0.59–4.27)	1
Hypertension status				$P = 0.20$		$P = 0.29$	
No	338	18 (5.33)	Reference		Reference		0
Yes	604	46 (7.62)	0.37 (0.29)	1.45 (0.81–2.61)	0.30 (0.29)	1.36 (0.76–2.41)	1

AREDS = Age-related Eye Disease Study; CI = confidence interval; SE = Standard error.
*The regression coefficient 0.36 is considered as 1 risk point.

Table 2. Prediction of 5-Year Risk of Geographic Atrophy (GA) by Risk Score Involving 5 Risk Factors (n = 942 patients)

		End Point GA		CGA		Any Size GA	
GA Risk Score	n	*In Either Eye (n = 64)*	*In Untreated Eye (n = 45)*	*In Either Eye (n = 90)*	*In Untreated Eye (n = 68)*	*In Either Eye (n = 324)*	*In Untreated Eye (n = 214)*
0–6	165	1 (0.60)	0 (0.00)	2 (1.21)	1 (0.61)	21 (12.7)	13 (7.88)
7–8	205	7 (3.41)	4 (1.95)	5 (2.44)	4 (1.95)	57 (27.8)	34 (16.6)
9	150	6 (4.00)	3 (2.00)	12 (8.00)	9 (6.00)	48 (32.0)	35 (23.3)
10	99	6 (6.06)	4 (4.04)	11 (11.1)	7 (7.07)	34 (34.3)	19 (19.2)
11	98	11 (11.2)	8 (8.16)	17 (17.4)	12 (12.2)	45 (45.9)	29 (29.6)
12	128	20 (15.6)	15 (11.7)	21 (16.4)	15 (11.7)	61 (47.7)	45 (35.2)
>12	97	13 (13.4)	11 (11.3)	22 (22.7)	20 (20.6)	58 (59.8)	39 (40.2)
AUC (95% CI*)		0.76 (0.71–0.81)	0.79 (0.75–0.84)	0.76 (0.71–0.80)	0.77 (0.72–0.81)	0.68 (0.65–0.72)	0.68 (0.64–0.72)

AUC = area under the receiver operating characteristic curve; CGA = GA involving the foveal center; CI = confidence interval.
*Based on the bootstrap of 2000 samples.

difference ($P = 0.33$) between observed and expected number of patients with end point GA (Fig 1, available online at http://aaojournal.org).

Based on the regression coefficients from the multivariate logistic regression model, risk points were assigned to each level of a risk factor (last column of Table 1). We considered a participant aged 50 to 59 years, AREDS severity score of 2, night vision score >85, not currently smoking, and without hypertension as having the referent risk factor profile. Participants with this risk profile were assigned a risk point of 0. We arbitrarily assigned the regression coefficient of 0.36 associated with current smoking as equivalent to 1 risk point and divided each regression coefficient associated with different levels of the risk factors by 0.36 to determine the number of risk points (rounded to 1 digit). The risk score is the sum of the risk points from each of the 5 risk factors and can range from 0 to 15. The distribution of risk score for CAPT participants is shown in Figure 2 (available online at http://aaojournal.org). None of the participants had the maximum risk score of 15, 44 (4.67%) had a risk score of <4, and the majority (81%) of participants had a risk score of 7 to 13.

The 5-factor risk score is strongly predictive of CAPT end point GA (Table 2). The 5-year incidence of end point GA increased with GA risk score: 0.6% for ≤6 points, 3% for 7 to 8 points, 4% for 9 points, 6% for 10 points, 11% for 11 points, and 15% for ≥12 points. The AUC for end point GA is 0.76 (95% confidence interval, 0.71–0.81), indicating good prediction power. The risk score from all 5 risk factors has significantly greater prediction power than the risk score from other subsets of risk factors (AUC differences 0.03 to 0.13; all $P<0.03$; Table 3). When used alone, the AREDS simple scale score and the night vision score have similar predictive capability. Also, models that include age, smoking status, and hypertension have similar predictive capability whether the AREDS simple scale score or the night vision score is included in the model.

Despite the fact that the risk score was developed for prediction of CAPT end point GA, the risk score is also strongly predictive of the 2 other types of GA. The risk score for CGA has an AUC of 0.76 (0.71–0.80). The risk score is less predictive of any GA, with an AUC of 0.68 (0.65–0.72). When the risk score was applied to untreated eyes only, similar predictive capability was obtained (Table 2).

The sensitivity and specificity corresponding to the various cut points for the 5-factor risk score are shown in Table 4 (available online at http://aaojournal.org) for each type of GA. Using a cutpoint of ≥9 to define high risk provides sensitivity and specificity combinations of 88% and 41% for end point GA, 92% and 43% for CGA, and 76% and 47% for any GA, respectively. Higher specificity with lower sensitivity can be obtained by using a cutpoint of ≤8.

The risk score is shown to be well calibrated for end point GA and CGA. The Brier score is close to 0 (0.06 for end point GA, 0.08 for CGA, and 0.21 for any GA), indicating predictions by risk score and observed GA outcomes match moderately well.

Risk Score Development without Inclusion of Night Vision Score

A multivariate logistic regression model was fit that only included age, smoking, hypertension, and AREDS simple scale as predictors. Because the regression coefficients for each of risk factors were almost the same (with the exception of the intercept term) as those from the multivariate prediction model that included all 5

Table 3. Discrimination Capability of Alternative Logistic Regression Models for Development of Geographic Atrophy

Model	Risk Factors Included for Risk Score Calculation	AUC (95% CI)*	*P*-Value for Comparison with Model 1
1	Age, smoking status, hypertension, AREDS simple scale score, night vision score	0.76 (0.71–0.81)	
2	Age, smoking status, hypertension, AREDS simple scale score	0.67 (0.62–0.72)	<0.001
3	Age, smoking status, hypertension, night vision score	0.69 (0.63–0.75)	<0.001
4	AREDS simple scale score, night vision score	0.73 (0.68–0.79)	0.03
5	AREDS simple scale score only	0.63 (0.58–0.69)	<0.001
6	Night vision score only	0.65 (0.59–0.71)	<0.001

AREDS = Age-related Eye Disease Study; AUC = area under the receiver operating characteristic curve; CI = confidence interval.
*The AUC was determined based on the c-statistic from the logistic regression model. The 95% confidence interval was calculated based on bootstrap of 2000 samples.

risk factors (Table 1), the risk points corresponding to each level of a risk factor remained the same. The total risk score from the 4 risk factors ranges from 0 to 11, with the majority (80%) having a risk score of ≥5 (Table 5, available online at http://aaojournal.org).

The predictions of GA by risk score without consideration of night vision scores are summarized in Table 5. The 5-year incidence of GA increased with risk score for each of the types of GA considered. The AUC for end point GA decreased by 0.09 ($P<0.001$) relative to the risk score that included night vision score (Table 3). When CGA was considered, the AUC decreased by 0.05 ($P = 0.04$); however, there was no decrease in AUC for any GA. Using a cutpoint of ≥7 to define high risk provides sensitivity and specificity combinations of 91% and 33% for end point GA, 93% and 34% for CGA, and 86% and 40% for any GA.

Computation of Risk Scores and the Predicted Risk of Geographic Atrophy

To facilitate the use of the risk scores, we developed a worksheet (Fig 3). The total number of risk points and the associated predicted risk for each type of GA can be found in the lower panel. As an example, a 75-year-old patient with bilateral large drusen and depigmentation in only the right eye (AREDS simple scale score of 3), currently smoking, taking antihypertensive drugs, and with a night vision score of 65, has a total 5-factor risk score of 3 + 4 + 1 + 1 + 3 = 12. This corresponds to a predicted 5-year incidence of 16% each for end point GA and CGA, and 48% for any GA. If the night vision score is not available, the total points from the four factor scoring is 3 + 4 + 1 + 1 = 9, and the corresponding predicted 5-year incidence is 10% for end point GA, 17% for CGA, and 48% for any GA.

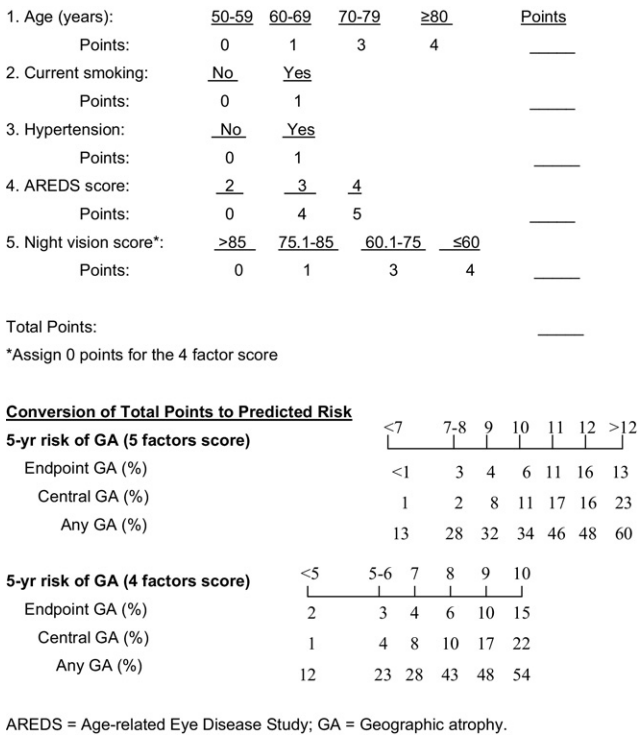

Figure 3. Worksheet to calculate the risk score and corresponding 5-year probability of developing various types of geographic atrophy.

Discussion

We developed a 15-point GA risk score from 5 easily accessible risk factors that predicts moderately well the 5-year risk of end point GA, CGA, and any GA (c-statistic, 0.68–0.79). This predictive power is similar to the predictive power of the Framingham risk score for coronary heart disease (c-statistic, 0.63–0.83),[20] similar to the recently developed risk score for glaucoma (c-statistic, 0.68–0.73),[21,22] and also similar to the prediction of advanced AMD using demographic and environmental variables (c-statistic, 0.73–0.76).[18] When the score is computed without consideration of night vision, there is a decrease in prediction power (c-statistic, 0.67–0.72).

To our knowledge, this is the first study to develop risk scores specifically for predicting GA rather than CNV and GA combined. Data from CAPT is especially well-suited for developing a model for GA because participants had substantial drusen burden (each eye have ≥10 large drusen [≥125 μm]), were followed prospectively for ≥5 years, and had yearly color photographs taken by certified photographers with interpretation at a central reading center. The long-term follow-up of these high-risk participants provided sufficient GA cases to develop a valid prediction model and derive risk scores from the resulting prediction model. Appropriate prediction models require ≥10 cases per predictor,[32] and our prediction model includes >12 GA cases per risk factor.

The absence of patients with AREDS simple scores of 0 and 1 in the CAPT population is a theoretical weakness in our development of GA risk scores. However, examination of the AREDS data on progression to central GA revealed that the 5-year risk for participants with AREDS score of 0 was 0.0% (0/1446) and was 0.5% (3/635) for participants with a score of 1.[26] Thus, the only patients with any substantial risk of developing GA are those with an AREDS simple score of ≥2.

The GA risk scores we developed may improve the design and analysis of clinical trials to prevent GA. Progression from drusen to GA takes years,[33] and only a small percentage of AMD patients develop GA, even among those starting with bilateral large drusen (6.8% for end point GA in CAPT participants, and 6% for CGA in AREDS participants).[7] Smaller sample sizes and/or shorter follow-up periods may be used if trials include only higher risk patients. Statistical analyses may be more precise if the baseline risk score is used as a covariate. In addition, enrolling the highest risk patients decreases the risk–benefit ratio in clinical trials. The night vision questionnaire may be used when screening patients to more finely stratify patients by risk of developing GA than is possible with knowledge of only age, cigarette smoking, hypertension, presence of large drusen, or pigmentation changes.

The GA risk scores also provide an easy way for ophthalmologists to estimate the 5-year risk of developing GA among their AMD patients. These estimates may help in explaining the implications of newly detected signs of early AMD to patients.

Our risk score was developed from readily available risk factors, and it does not consider other risk factors that are

more difficult to obtain, specifically the genetic risk factors. Complement factor H, complement factor B, LOC387715, and complement C3 variant were recently found to be associated with risk of GA.[16–18] Including these genetic risk factors and other risk factors (such as dietary or supplemental antioxidant intake) in the risk score development may improve its predictive power for GA. Seddon et al[18] recently developed a comprehensive predictive model for advanced AMD (CNV and GA combined) based on genetic, demographic, and environmental variables, and found that the AUC (c-statistic) improved from 0.73 to 0.83 when genetic data was included in the prediction model.

Despite the fact that our risk scores were developed to predict end point GA, they performed well for predicting CGA and any GA. In addition, very similar discrimination was obtained when it was applied to the untreated eye of CAPT participants. However, before it is taken for use in clinical practice and research, external validation[34] needs to be established by applying it to other independent AMD cohorts, such as by applying the risk score without consideration of night vision score to the AREDS datasets.

In summary, the GA risk scores developed from the CAPT data discriminated several levels of risk and provided accurate estimates of risk for the CAPT participants. If the discrimination and accuracy are validated in other independent groups of patients, they will provide useful tools for identifying high risk patients for clinical trials for prevention of GA and for GA risk assessment of AMD patients.

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