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Prediction of Age-related Macular Degeneration in the General Population:

The Three Continent AMD Consortium

Gabriëlle H.S. Buitendijk, MD, MSc^{1,2}, Rohtchina Elena, MAppStat³, Chelsea Myers, MStat⁴, Cornelia M. van Duijn, PhD², Kristine E. Lee, MS⁴, Barbara E.K. Klein, MD, MPH⁴, Stacy M. Meuer, BS⁴, Paulus T.V. M. de Jong, MD, PhD^{5,6,7}, Elizabeth G. Holliday, PhD⁸, Ava G. Tan, MAIT, MPH³, André G. Uitterlinden, PhD^{2,9,10}, Theru A. Sivakumaran, PhD^{11,12}, John Attia, MD, PhD^{8,13}, Albert Hofman, MD, PhD^{2,10}, Paul Mitchell, MD, PhD³, Johannes R. Vingerling, PhD^{1,2}, Sudha K. Iyengar, PhD¹², A.Cecile J.W. Janssens, PhD^{2,14}, Jie Jin Wang, MMed, PhD^{3,15,§}, Ronald Klein, MD, MPH^{4,§}, and Caroline C.W. Klaver, MD, PhD^{1,2,§,*}

¹Department of Ophthalmology, Erasmus Medical Center, Rotterdam, The Netherlands

²Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands ³Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, Australia ⁴Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin ⁵Department of Ophthalmogenetics, Netherlands Institute of Neurosciences, An Institute of the Royal Netherlands Academy of Arts and Sciences (KNAW), Amsterdam, The Netherlands ⁶Department of Ophthalmology, Academic Medical Center, Amsterdam, The Netherlands ⁷Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands ⁸Centre for Clinical Epidemiology and Biostatistics, and School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia ⁹Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands ¹⁰Netherlands Consortium for Healthy Aging, Netherlands Genomics Initiative, the Hague, The Netherlands ¹¹Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio ¹²Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, Ohio ¹³Department of Medicine, John Hunter Hospital and Hunter Medical Research Institute, Newcastle, New South Wales, Australia ¹⁴Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia ¹⁵Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia

Abstract

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Correspondence: Caroline C. W. Klaver, MD, PhD, Department of Ophthalmology, Erasmus Medical Center, P.O. Box 2040, NL-3000 CA Rotterdam, The Netherlands. c.c.w.klaver@erasmusmc.nl.

* Author information concerning the BMES Genome-Wide Association Study team and the Wellcome Trust Case Control Consortium 2 can be found in Appendix 1 (available at <http://aaojournal.org>).

§J.J.W., R.K., and C.C.W.K. contributed equally.

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Purpose—Prediction models for age-related macular degeneration (AMD) based on case-control studies have a tendency to overestimate risks. The aim of this study is to develop a prediction model for late AMD based on data from population-based studies.

Design—Three population-based studies: the Rotterdam Study (RS), the Beaver Dam Eye Study (BDES), and the Blue Mountains Eye Study (BMES) from the Three Continent AMD Consortium (3CC).

Participants—People (n = 10106) with gradable fundus photographs, genotype data, and follow-up data without late AMD at baseline.

Methods—Features of AMD were graded on fundus photographs using the 3CC AMD severity scale. Associations with known genetic and environmental AMD risk factors were tested using Cox proportional hazard analysis. In the RS, the prediction of AMD was estimated for multivariate models by area under receiver operating characteristic curves (AUCs). The best model was validated in the BDES and BMES, and associations of variables were re-estimated in the pooled data set. Beta coefficients were used to construct a risk score, and risk of incident late AMD was calculated using Cox proportional hazard analysis. Cumulative incident risks were estimated using Kaplan–Meier product-limit analysis.

Main Outcome Measures—Incident late AMD determined per visit during a median follow-up period of 11.1 years with a total of 4 to 5 visits.

Results—Overall, 363 participants developed incident late AMD, 3378 participants developed early AMD, and 6365 participants remained free of any AMD. The highest AUC was achieved with a model including age, sex, 26 single nucleotide polymorphisms in AMD risk genes, smoking, body mass index, and baseline AMD phenotype. The AUC of this model was 0.88 in the RS, 0.85 in the BDES and BMES at validation, and 0.87 in the pooled analysis. Individuals with low-risk scores had a hazard ratio (HR) of 0.02 (95% confidence interval [CI], 0.01–0.04) to develop late AMD, and individuals with high-risk scores had an HR of 22.0 (95% CI, 15.2–31.8). Cumulative risk of incident late AMD ranged from virtually 0 to more than 65% for those with the highest risk scores.

Conclusions—Our prediction model is robust and distinguishes well between those who will develop late AMD and those who will not. Estimated risks were lower in these population-based studies than in previous case-control studies.

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly of industrialized countries.^{1,2} Approximately 21 million elderly individuals are affected worldwide, and this number is expected to increase dramatically with the aging population.^{3,4} Age-related macular degeneration can be divided into several stages: early AMD, characterized by subcellular deposits (drusen) and pigmentary changes, and late AMD, subdivided into atrophy of the retinal pigment epithelium (dry AMD) and choroidal neovascularization (wet AMD). Despite improved treatment options, late AMD can cause irreversible blindness, whereas severe stages of early AMD are mostly asymptomatic but signal a high risk of progression to late AMD.⁵

Age, early AMD phenotype, and genetic and environmental factors play important roles in the pathogenesis of late AMD.^{6–11} These factors may be used to predict this end stage and to

identify high-risk individuals. Reasons for assessing predictive values may be risk-dependent (personalized) patient care and surveillance strategies for therapy. Future intervention research, such as randomized, controlled clinical trials, can use prediction models to select individuals with a high risk of outcome events.

Previously reported prediction models were based on selections of cases and nonaffected controls.^{12–28} Most studies compared only the extreme ends of disease, excluding the majority of the population with an intermediate disease risk. This has inherent methodological concerns because the disease risk is overestimated by design. Population-based studies include a whole spectrum of risk levels, and therefore findings from these studies would be more generalizable²⁹ and better suited for clinical implementation.

In this study, we present a prediction model for late AMD based on population-based cohort studies from 3 continents. We optimized a prediction model in one of the cohorts and subsequently validated it in the other 2 cohorts. We included established genetic, environmental, and clinical risk factors in the model, assessed relative and cumulative risks, and provided a risk score that can be used to estimate the risk of AMD in individuals.

Methods

For this article, we followed the guidelines for genetic risk prediction studies.³⁰

Study Populations

The Three Continent AMD Consortium (3CC) consists of 4 population-based studies: the European Rotterdam Study (RS), the American Beaver Dam Eye Study (BDES), the Los Angeles Latino Eye Study, and the Australian Blue Mountains Eye Study (BMES). For the purposes of this study, the Los Angeles Latino Eye Study was excluded because of the absence of genotype and follow-up data.

The RS is a prospective, population-based cohort study investigating chronic diseases in the elderly. All inhabitants aged 55 years and older living in a suburb of Rotterdam, The Netherlands, were invited to participate in the study.^{31,32} Of the initial cohort of 10 275 eligible individuals, 7983 (78% of those eligible) participated in the overall study (98% were white). The ophthalmologic part began later and included 6780 participants (78% of those eligible). Baseline examinations took place from 1990 to 1993, and 4 follow-up examinations were performed in 1993–1995, 1997–1999, 2002–2004, and 2009–2011. The Erasmus Medical Center Ethics Committee approved the study, which complies with the Declaration of Helsinki. All participants gave written informed consent for participation in the study.

The BDES is a prospective cohort study investigating eye diseases among the population of Beaver Dam, Wisconsin.³³ To identify all residents in the city or township of Beaver Dam who were aged 43 to 84 years, a private census was performed from 1987 to 1988. Of the 5924 eligible individuals, 4926 (83% of those eligible) participated in the baseline examination between 1988 and 1990 (99% were white). There were follow-up examinations every 5 years: 1993–1995, 1998–2000, 2003–2005, and 2008–2010. The BDES was

approved by the institutional review board from the University of Wisconsin-Madison and adhered to the tenants of the Declaration of Helsinki. All participants provided signed, informed consent for participation in the study.

The BMES is a prospective cohort study of eye diseases and other health outcomes in an urban population.³⁴ All residents aged 49 years or older, living in 2 postcode areas of the Blue Mountains region in West Sydney, Australia, were invited to participate in the study. In 1992–1994, baseline examinations were performed in 3654 participants (82.4% of those eligible). Reexaminations were performed after 5, 10, and 15 years (in 1997–1999, 2002–2004, and 2007–2009, respectively). All BMES examinations were approved by the human research ethics committees of the Western Sydney Area Health Service and the University of Sydney and complied with the Declaration of Helsinki. All participants provided written, informed consent for participation in the study.

Participants were eligible for the current analysis when genotype data, as well as gradable fundus photographs at baseline and at least 1 follow-up eye examination were available (Fig 1, available at <http://aaojournal.org>). People with late AMD at baseline were excluded. This resulted in 4753 (RS), 3542 (BDES), and 1811 (BMES) participants available for analysis, with a median follow-up of 10.7 years in RS (interquartile range [IQR], 12.8), 15.6 years in BDES (IQR, 10.4), and 11.8 years in BMES (IQR, 5.6). In total, 10 106 participants with a median follow-up of 11.1 years (IQR, 11.0) were included in the analysis. To investigate possible selection bias, we analyzed whether people excluded from this study differed in the baseline level of AMD from those who were included. The 2 groups did not differ in early AMD levels (10–40) after adjustment for age and sex ($P = 0.95$).

Diagnosis of Age-Related Macular Degeneration

All participants underwent fundus photography after pharmacologic mydriasis. Fundus transparencies of all studies were graded according to the Wisconsin Age-Related Maculopathy Grading^{35,36} by trained graders under the supervision of senior retinal specialists or senior researchers (RS: P.T.V.M.dJ., J.R.V., C.C.W.K.; BDES: B.E.K.K., R.K.; BMES: P.M., J.J.W.). The graded fundus photographs were classified using a classification common to all studies: the 3CC AMD severity scale³⁷ (Table 1, available at <http://aaojournal.org>). All prevalent and incident late AMD cases from each of these 3 studies were cross-checked by investigators of the other 2 studies, with consensus obtained via discussion during multiple teleconferences. The eyes of each participant were graded and classified separately, and the eye with the more severe grade was used to classify the person.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes. All eligible study participants in the RS were genotyped with the Illumina Infinium II HumanHap550 array or Taqman assays (Applied Biosystems, Foster City, CA). HapMap CEU data (release #22) was used for imputation.

DNA from BDES participants was extracted from the buffy coats of blood obtained at baseline examinations or subsequent examinations that were stored frozen at -80°C . DNA

samples arrayed in 96-well plates were submitted for genotyping via an Illumina iSelect Custom Genotyping Panel (Illumina Inc., Hayward, CA) at the Genomics Core Facility at Case Western Reserve University or via the KASP Assay at LCG Genomics (Teddington, Middlesex, UK). The data collected were analyzed using Illumina's Genome Studio or the KASP SNP Genotyping System. The assays were controlled for quality by examining cluster separation values and call frequency. Untyped single nucleotide polymorphisms (SNPs) were imputed using HapMap CEU (release #22) as reference.

In the BMES, all participants with DNA available were genotyped using Illumina Human670-Quad v1 custom array at the Wellcome Trust Centre for Human Genetics, Sanger Institute, Cambridge, UK, as part of the Wellcome Trust Case Control Consortium 2. A smaller subset of participants (N = 1356) was also independently genotyped using the Illumina 610-Quad genotyping array at the Hunter Medical Research Institute, Newcastle, Australia. After quality control, the genotyped data were imputed from the 1000 Genomes (version 1) reference using IMPUTE software.

Selection of Single Nucleotide Polymorphisms

For selection of AMD genes, we reviewed publications on AMD genetics^{38,39} and prediction of AMD.^{12–28} From these, we selected 41 tag SNPs that were available in all 3 cohorts and that were not in linkage disequilibrium ($r^2 < 0.60$). Genotypes of SNPs were coded as 0 for carriers of 2 major alleles, 1 for the heterozygous genotype, and 2 for carriers of 2 minor alleles. When none of the cases were carriers of 2 minor alleles, genotypes of the SNPs were coded as 0 for carriers of 2 major alleles and 1 for all carriers of at least 1 minor allele. As a first step, each SNP was tested for association with late AMD in all 3 cohorts.

For each locus with multiple SNPs, we performed a backward Cox proportional hazard analysis to determine the best predictive SNPs for incident late AMD within each locus with data from the RS.

Assessment of Nongenetic Variables

All nongenetic variables used in the analyses were assessed using baseline data. Information on cigarette smoking was obtained in an interview at baseline and categorized as never, former, and current. Height, weight, and blood pressure were measured at the beginning of baseline examination. Body mass index (BMI) was calculated by dividing weight (kilograms) by the height (meters squared). The BMI variable was categorized as not overweight or obese (BMI < 25) and overweight or obese (BMI ≥ 25). Age (years) at baseline was categorized in 3 categories; <65, 65–75, and >75 years. Baseline AMD grading was entered into the analysis as categorized variables with levels 10 to 40.

Statistical Analyses

Throughout the entire study, incident late AMD was used as the outcome variable; nonincident late AMD, including those participants remaining at an early AMD stage, was used as the reference group. All analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL).

Variables were analyzed for association with incident late AMD in the 3 cohorts using Cox proportional hazard analysis, adjusting for age and sex. We constructed 5 different models based on a minimal and a maximal selection of clinical, genetic, and environmental factors. Model 1 was a minimal model including only age and sex; model 2 was a nongenetic model including age, sex, and environmental and ocular factors; model 3 was a minimal genetic model including age, sex, and major genetic AMD risk variants (*CFH* Y402H, *ARMS2* A69S, *C3* R102G, *C2* L9H, *CB* R32Q); model 4 was a maximal genetic model including age, sex, and 26 genetic AMD risk variants (see “Selection of Single Nucleotide Polymorphisms”); and model 5 was a maximal gene–environmental model including age, sex, environmental and ocular factors, and the 26 genetic AMD risk variants. For each model, we calculated the area under the curve (AUC) of incident late AMD in the RS and validated the best model in the BDES/BMES.

Subsequently, we estimated the association of all variables in the best model using multivariate Cox proportional hazard analysis in the pooled dataset of all 3 cohorts and calculated the AUC. Calibration of the model was tested using the Hosmer–Lemeshow test. This goodness-of-fit test shows how well the predicted risks match the observed risks. To test whether nonmajor genetic AMD risk variants could be discarded from this model without jeopardizing the AUC, backward regression (eliminating SNPs with $P > 0.05$) using Cox proportional hazard analysis was carried out and the AUC of the new model was calculated within the pooled dataset. In this dataset, we estimated the beta coefficient of each variable from the best model using multivariate Cox proportional hazard analysis. The estimated beta coefficient of a variable was the individual risk score of that variable. Next, we created a summary risk score based on the sum of the beta coefficients from the multivariate Cox proportional hazard analysis. Risk scores were rounded off, and frequencies of the risk scores were plotted stratified for incident late AMD and no AMD. We calculated the risk of incident late AMD with the middle risk score (3) as the reference using Cox proportional hazard analysis. Risk scores at the extreme ends were pooled to increase sample size because of limited numbers.

We calculated the cumulative risk of incident late AMD per risk score. We assigned the age of onset for incident late AMD as the median between the examination at which late AMD was first observed and the previous examination. For participants who did not develop late AMD, we used age at last examination for censoring. All participants aged 90+ years were censored at age 90 years to maintain unbiased estimates. Risks were calculated using Kaplan–Meier product-limit analysis. Participants who died or were lost to follow-up were censored at the time of the last examination. Cumulative risks stratified for the risk score were compared with the overall cumulative risk based on incidence of late AMD (prior risk) using log-rank tests of equality (Mantel–Cox).

Missing data were encountered in the analysis of each model. Only participants with data on all variables in the model entered the analysis.

Results

In total, 363 participants developed incident late AMD during a median follow-up time of 11.1 years (IQR, 11.0), of whom 132 were in the RS (follow-up 10.7 years; IQR, 12.8), 153 were in the BDES (follow-up 15.6 years; IQR, 10.4), and 78 were in the BMES (follow-up 11.8 years; IQR, 5.6). Incidence rates for the 3 studies were 2.89, 2.96, and 3.66 per 1000 person-years for the RS, BDES, and BMES, respectively. The distribution of demographic characteristics and environmental risk factors differed slightly among the 3 cohorts (Table 2). Because the inclusion criteria for age were higher than for the other studies, participants in the RS were older. Early AMD (level 20–40) at baseline was more frequent in RS participants, BMI was higher in BDES participants, and current smoking was less frequent in BMES participants. The frequency of genetic risk alleles was not significantly different among the 3 studies, although there were slight differences in genotype distributions. Visual inspection of a principle component analysis of all genetic data against HapMap CEU data (National Center for Bio-technology Information build 36, release 22) as reference showed similar plots for the 3 cohorts (data not shown).

Risk factors were tested separately for association with incident late AMD in all cohorts, adjusting for age and sex (Table 3, available at <http://aaojournal.org>). Most SNPs in the genes *CFH*, *ARMS2*, and *CFHR5* were significant in all 3 cohorts ($P < 0.05$). The SNPs in the genes *LIPC*, *TIMP3*, *ADAMTS9*, *IER3/DDRI*, *TNFRSF10A*, *TGFBRI*, and *B3GALT1* were not significant in any single cohort. In all other genes, SNPs were significant in at least 1 of the cohorts. In all 3 studies, increasing severity levels of early AMD stages at baseline, based on the 3CC AMD severity scale (Table 1, available at <http://aaojournal.org>), were associated with a highly significant risk of incident late AMD. Of the environmental risk factors, current smoking showed a significant association in the RS and BMES, but BMI showed no significant association with incident late AMD in all 3 cohorts. To determine the best set of markers for each locus, all SNPs were analyzed per locus in a multivariate Cox proportional hazard analysis. A total of 26 SNPs were found to be suitable for further analyses.

Prediction models were built using various sets of risk factors and tested in the RS (Table 4). Model 1, a minimal model that included only age and sex, provided an AUC of 0.60 (95% confidence interval [CI], 0.55–0.65). Adding environmental and ocular factors improved the AUC to 0.78 (95% CI, 0.74–0.82, model 2). Adding only major AMD genes to model 1 increased the AUC to 0.73 (95% CI, 0.69–0.78, model 3). Next, a maximal genetic model was created that included all 26 SNPs. This increased the AUC to 0.82 (95% CI, 0.79–0.86, model 4). Finally, we combined all variables from models 1 to 4 to assess the best possible prediction. This resulted in an AUC of 0.88 (95% CI, 0.85–0.90, model 5). Validation of this model in the pooled dataset of the BDES and BMES (Table 5) showed an AUC of 0.85 (95% CI, 0.82–0.88). To further improve the prediction model, we pooled all 3 cohorts and re-estimated the risks of the variables included in model 5 (Table 6). The AUC in the 3 cohorts combined was 0.87 (95% CI, 0.85–0.89), and the model had a good calibration ($P = 0.55$). We also investigated the possibility of minimizing this model. By using backward regression, 13 SNPs could be excluded from the model and provided a somewhat lower

AUC of 0.86 (95% CI, 0.84–0.88) (Table 7, available at <http://aaojournal.org>). The model with the best AUC in the 3 cohorts combined dataset was used for further analyses.

We calculated a risk score (Table 6) based on the beta coefficients from the pooled analysis, which ranged from –3.99 to 7.56. We rounded off the estimates and plotted their distribution stratified for incident or no incident late AMD (Fig 2). The plot showed a bimodal distribution with a large frequency difference between the groups for scores <2 and scores >3. The frequencies of risk scores 2 and 3 showed relatively small differences between cases and noncases. Of note, all participants ($n = 8$) with risk score 8 had risk alleles in the *CFH*, *ARMS2*, and *C3* genes and no protective alleles in *C2/CFB*. In contrast, all those with risk score –3 ($n = 29$) carried a protective variant in *C2/CFB* and were free of variants in *CFH* and *ARMS2*, except 1 person who carried a heterozygous variant in *ARMS2*. Risk of incident late AMD for individuals with a risk score of 6 to 8 showed a hazard ratio (HR) of 23.2 (95% CI, 15.9–34.0). Risk of incident late AMD for individuals with a risk score of –3 to 0 showed an HR of 0.02 (95% CI, 0.01–0.04).

Cumulative risk of incident late AMD was calculated for each risk score and compared with the overall cumulative risk of incident late AMD. Individuals ($n = 181$) with a risk score 6 to 8 had a cumulative risk of 65.6% (standard error [SE], 0.057) to develop late AMD at age 90 years, and those ($n = 2751$) with a risk score of –3 to 0 had virtually no risk of developing incident late AMD (0.5%; SE, 0.002). The overall risk of AMD for our study population before testing was 17.4% (SE, 0.013) at age 90 years (Fig 3), which was significantly different from all strata apart from risk score 3 ($P = 0.71$).

Discussion

In 3 independent population-based studies from 3 continents, we investigated all well-known genetic and nongenetic risk factors for AMD. We found that the best prediction for late AMD was based on age, sex, 26 genetic variants, 2 environmental variables, and early AMD phenotype. The accuracy of a prediction model including all these variables was 0.88 in the RS. Because similar risk estimates were found in the BDES and BMES, the model proved to be well generalizable to people of Caucasian descent living on other continents. Translation of the model to the individual level provided good discrimination between those with a high lifetime risk of late AMD and those with virtually no risk, a risk difference of 65%.

A major strength of our study is the inclusion of a general population unbiased by AMD risk factors. The study samples had included a wide spectrum of AMD lesion phenotypes but not only the extreme ends of disease, which is representative of real scenarios in the population. Inclusion of a wide spectrum of risk factor distributions and various levels of risk profiles of our population-based samples ensures a realistic, less biased prediction for all risk categories. Additional strengths are the use of longitudinal observational samples to predict incident cases and validation in 2 independent population-based cohorts with similar study designs. All the strengths facilitate our comprehensive analyses and calculation of cumulative risk of incident late AMD.

Limitations included the relatively low number of incident late AMD cases ($n = 363$), hampering further risk estimation to AMD subtypes. In addition, we did not include several risk factors, such as dietary factors, biomarkers, or rare genetic variants.^{10,40–43} Dietary factors and biomarkers are difficult variables to obtain, but their inclusion would have improved the sensitivity of the predictive value. Inclusion of genetic mutations is unlikely to contribute to population risk because of their low frequencies. Finally, the 3 cohorts had subtle differences in methodology, which have been discussed by Klein et al.³⁷

Most previously published AMD prediction models have been based on case-control studies (Table 8).^{12–28} Most of these models included demographic, genetic, and environmental factors and reached a good prediction for AMD (AUC, 0.68–0.94). The study that reported the highest AUC (0.94) included complement activation.²² However, measurement of activation fragments requires rather intense workup and specific expertise and is therefore unlikely to occur in a standard clinical setting. The other studies have some drawbacks as well. Gold et al¹⁴ reported a sensitivity of 70% and a specificity of 50% for their model, making the prediction of low-risk outcomes inaccurate. Hageman et al¹⁶ showed a better specificity and sensitivity, but their model did not incorporate any nongenetic factors, including age.¹⁶ Furthermore, their model was based on prevalence data, which is less appropriate for estimation of prognosis.⁴⁴ Most other case-control studies also lacked follow-up data. The reports with follow-up data were almost inclusively based on data from the Age-Related Eye Disease Study.^{20,23,24,27} Although the investigated people are from the same source population, the prediction studies using this population differed substantially from each other in design and inclusion of risk factors, leading to great variation in prediction outcomes. Our study shows that the sensitivity of risk prediction depends on the number of variables included in the model, and highest sensitivity is achieved with a full model including the major genes, many of the recently discovered minor genetic variants, smoking, BMI, and existing AMD phenotypes.

What may be the benefits of prediction tests? Most current counseling provided to family members of late AMD cases is based on clinical parameters. A prediction test may improve the identification of true high-risk individuals. Because the estimation of cumulative risk of incident AMD makes the risk apparent, it may encourage individuals to alter their lifestyle with the aim of decreasing the risk of AMD. For instance, one can stop smoking, eat foods rich in antioxidants, and increase physical exercise to lower risk of progression to late AMD.^{9,45} There may be benefits for patients with late AMD. Various studies have shown that patients with neovascular AMD who do not respond to anti-VEGF therapy are at higher genetic risk.^{46–29} These patients may need more intensive treatment regimens. Last, current intervention trials select study participants mainly on the basis of phenotypes. Inclusion of high-risk individuals, identified by a prediction test, may improve homogeneity of the study population and prediction of AMD outcome events.

In conclusion, a risk score based on a large number of genetic risk variants for AMD, the environmental factors smoking and BMI, and early AMD phenotype provided a good prediction of incident late AMD cases in this study. A model incorporating nongenetic factors performed better than a model based on a minimal number of genetic factors, but after inclusion of many genes the model performed better than a model including only

nongenetic factors. Inclusion of all risk factors provided the best prediction. Because personalized medicine is the future, prediction tests will become more thoroughly implemented as clinical tools. In such case, only comprehensive tests will be useful for AMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol*. 2004; 122:477–85. [PubMed: 15078664]
2. Klaver CC, Wolfs RC, Vingerling JR, et al. Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam Study. *Arch Ophthalmol*. 1998; 116:653–8. [PubMed: 9596502]
3. Augood CA, Vingerling JR, de Jong PT, et al. Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). *Arch Ophthalmol*. 2006; 124:529–35. [PubMed: 16606879]
4. Fact Sheet no 282. World Health Organization; Nov. 2004 VISION 2020: The Right to Sight, the global initiative for the elimination of avoidable blindness: magnitude and causes of visual impairment. Available at: http://whqlibdoc.who.int/fact_sheet/2004/FS_282.pdf [Accessed July 28, 2013]
5. van Leeuwen R, Klaver CC, Vingerling JR, et al. Epidemiology of age-related maculopathy: a review. *Eur J Epidemiol*. 2003; 18:845–54. [PubMed: 14561043]
6. Klaver CC, Assink JJ, Vingerling JR, et al. Smoking is also associated with age-related macular degeneration in persons aged 85 years and older: the Rotterdam Study [letter]. *Arch Ophthalmol*. 1997; 115:945. [PubMed: 9230849]

7. Seddon JM, Ajani UA, Mitchell BD. Familial aggregation of age-related maculopathy. *Am J Ophthalmol.* 1997; 123:199–206. [PubMed: 9186125]
8. Despret DD, Klaver CC, Witteman JC, et al. Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. *JAMA.* 2006; 296:301–9. [PubMed: 16849663]
9. Ho L, van Leeuwen R, Witteman JC, et al. Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and omega-3 fatty acids: the Rotterdam study. *Arch Ophthalmol.* 2011; 129:758–66. [PubMed: 21670343]
10. van Leeuwen R, Boekhoorn S, Vingerling JR, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA.* 2005; 294:3101–7. [PubMed: 16380590]
11. Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration and smoking The Rotterdam Study. *Arch Ophthalmol.* 1996; 114:1193–6. [PubMed: 8859077]
12. Chen Y, Zeng J, Zhao C, et al. Assessing susceptibility to age-related macular degeneration with genetic markers and environmental factors. *Arch Ophthalmol.* 2011; 129:344–51. [PubMed: 21402993]
13. Gibson J, Cree A, Collins A, et al. Determination of a gene and environment risk model for age-related macular degeneration. *Br J Ophthalmol.* 2010; 94:1382–7. [PubMed: 20576771]
14. Gold B, Merriam JE, Zernant J, et al. AMD Genetics Clinical Study Group. Variation in factor B (*BF*) and complement component 2 (*C2*) genes is associated with age-related macular degeneration. *Nat Genet.* 2006; 38:458–62. [PubMed: 16518403]
15. Grassmann F, Fritsche LG, Keilhauer CN, et al. Modelling the genetic risk in age-related macular degeneration. *PLoS One.* 2012; 7:e37979. serial online. Available at: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0037979>. [PubMed: 22666427]
16. Hageman GS, Gehrs K, Lejnine S, et al. Clinical validation of a genetic model to estimate the risk of developing choroidal neovascular age-related macular degeneration. *Hum Genomics.* 2011; 5:420–40. [PubMed: 21807600]
17. Hughes AE, Orr N, Patterson C, et al. Neovascular age-related macular degeneration risk based on *CFH*, *LOC387715/HTRA1*, and smoking. *PLoS Med.* 2007; 4:e355. serial online. Available at: <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0040355>. [PubMed: 18162041]
18. Jakobsdottir J, Conley YP, Weeks DE, et al. *C2* and *CFB* genes in age-related maculopathy and joint action with *CFH* and *LOC387715* genes. *PLoS One.* 2008; 3:e2199. serial online. Available at: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0002199>. [PubMed: 18493315]
19. Jakobsdottir J, Gorin MB, Conley YP, et al. Interpretation of genetic association studies: markers with replicated highly significant odds ratios may be poor classifiers. *PLoS Genet.* 2009; 5:e1000337. serial online. Available at: <http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000337>. [PubMed: 19197355]
20. Klein ML, Francis PJ, Ferris FL III, et al. Risk assessment model for development of advanced age-related macular degeneration. *Arch Ophthalmol.* 2011; 129:1543–50. [PubMed: 21825180]
21. McKay GJ, Dasari S, Patterson CC, et al. Complement component 3: an assessment of association with AMD and analysis of gene-gene and gene-environment interactions in a Northern Irish cohort. *Mol Vis.* 2010; 16:194–9. serial online. Available at: <http://www.molvis.org/molvis/v16/a24/>. [PubMed: 20157618]
22. Reynolds R, Hartnett ME, Atkinson JP, et al. Plasma complement components and activation fragments: associations with age-related macular degeneration genotypes and phenotypes. *Invest Ophthalmol Vis Sci.* 2009; 50:5818–27. [PubMed: 19661236]
23. Seddon JM, Reynolds R, Maller J, et al. Prediction model for prevalence and incidence of advanced age-related macular degeneration based on genetic, demographic, and environmental variables. *Invest Ophthalmol Vis Sci.* 2009; 50:2044–53. [PubMed: 19117936]
24. Seddon JM, Reynolds R, Yu Y, et al. Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors. *Ophthalmology.* 2011; 118:2203–11. [PubMed: 21959373]

25. Spencer KL, Olson LM, Schnetz-Boutaud N, et al. Using genetic variation and environmental risk factor data to identify individuals at high risk for age-related macular degeneration. *PLoS One*. 2011; 6:e17784. serial online. Available at: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0017784>. [PubMed: 21455292]
26. Ying GS, Maguire MG, Complications of Age-related Macular Degeneration Prevention Trial Research Group. Development of a risk score for geographic atrophy in Complications of the Age-Related Macular Degeneration Prevention Trial. *Ophthalmology*. 2011; 118:332–8. [PubMed: 20801521]
27. Yu Y, Reynolds R, Rosner B, et al. Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multistate Markov models. *Invest Ophthalmol Vis Sci*. 2012; 53:1548–56. [PubMed: 22247473]
28. Zanke B, Hawken S, Carter R, Chow D. A genetic approach to stratification of risk for age-related macular degeneration. *Can J Ophthalmol*. 2010; 45:22–7. [PubMed: 20130705]
29. Szklo M. Population-based cohort studies. *Epidemiol Rev*. 1998; 20:81–90. [PubMed: 9762511]
30. Janssens AC, Ioannidis JP, Bedrosian S, et al. Strengthening the reporting of genetic risk prediction studies (GRIPS): explanation and elaboration. *Eur J Epidemiol*. 2011; 26:313–37. [PubMed: 21424820]
31. Hofman A, van Duijn CM, Franco OH, et al. The Rotterdam Study: 2012 objectives and design update. *Eur J Epidemiol*. 2011; 26:657–86. [PubMed: 21877163]
32. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991; 7:403–22. [PubMed: 1833235]
33. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. *Ophthalmology*. 1991; 98:1310–5. [PubMed: 1923372]
34. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study *Ophthalmology*. 1995; 102:1450–60.
35. Bird AC, Bressler NM, Bressler SB. International ARM Epidemiological Study Group. An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Surv Ophthalmol*. 1995; 39:367–74. [PubMed: 7604360]
36. Klein R, Davis MD, Magli YL, et al. The Wisconsin Age-Related Maculopathy Grading System. *Ophthalmology*. 1991; 98:1128–34. [PubMed: 1843453]
37. Klein R, Meuer SM, Myers CE, et al. Harmonizing the classification of age-related macular degeneration in the Three Continent AMD Consortium. *Ophthalmic Epidemiol*.
38. AMD Gene Consortium. Seven new loci associated with age-related macular degeneration. *Nat Genet*. 2013; 45:433–9. [PubMed: 23455636]
39. Kopplin LJ, Igo RP Jr, Wang Y, et al. Genome-wide association identifies *SKIV2L* and *MYRIP* as protective factors for age-related macular degeneration. *Genes Immun*. 2010; 11:609–21. [PubMed: 20861866]
40. Chiu CJ, Milton RC, Klein R, et al. Dietary compound score and risk of age-related macular degeneration in the Age-Related Eye Disease Study. *Ophthalmology*. 2009; 116:939–46. [PubMed: 19410952]
41. Smailhodzic D, Klaver CC, Klevering BJ, et al. Risk alleles in *CFH* and *ARMS2* are independently associated with systemic complement activation in age-related macular degeneration. *Ophthalmology*. 2012; 119:339–46. [PubMed: 22133792]
42. Stone EM, Braun TA, Russell SR, et al. Missense variations in the fibulin 5 gene and age-related macular degeneration. *N Engl J Med*. 2004; 351:346–53. [PubMed: 15269314]
43. Tan JS, Wang JJ, Flood V, et al. Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Ophthalmology*. 2008; 115:334–41. [PubMed: 17664009]
44. Rothman, KJ.; Greenland, S.; Lash, TL. *Modern Epidemiology*. 3rd. Rothman, KJ.; Greenland, S.; Lash, TL., editors. Vol. 33. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2008.
45. Mares JA, Volland RP, Sondel SA, et al. Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. *Arch Ophthalmol*. 2011; 129:470–80. [PubMed: 21149749]

46. Abedi F, Wickremasinghe S, Richardson AJ, et al. Variants in the *VEGFA* gene and treatment outcome after anti-VEGF treatment for neovascular age-related macular degeneration. *Ophthalmology*. 2013; 120:115–21. [PubMed: 23149126]
47. Boltz A, Rieß M, Jonas JB, et al. Role of vascular endothelial growth factor polymorphisms in the treatment success in patients with wet age-related macular degeneration. *Ophthalmology*. 2012; 119:1615–20. [PubMed: 22521084]
48. Brantley MA Jr, Fang AM, King JM, et al. Association of complement factor H and LOC387715 genotypes with response of exudative age-related macular degeneration to intravitreal bevacizumab. *Ophthalmology*. 2007; 114:2168–73. [PubMed: 18054635]
49. Smailhodzic D, Muether PS, Chen J, et al. Cumulative effect of risk alleles in *CFH*, *ARMS2*, and *VEGFA* on the response to ranibizumab treatment in age-related macular degeneration. *Ophthalmology*. 2012; 119:2304–11. [PubMed: 22840423]

Figure 2.

Distribution of risk score in incident late age-related macular degeneration (AMD) and no late AMD in the Three Continent AMD Consortium, and hazard ratio (HRs) of incident late AMD. The x-axis represents the risk score category, the left y-axis represents frequency as percentages, and the right y-axis represents the HR of incident late AMD. The *dark grey bars* represent no late AMD, and the *light grey bar* represents incident late AMD. The *black line* represents the HR of incident late AMD. Category 3 is the reference category (R) and has an HR of 1.00. Risk scores -3 to 0 and 6 to 8 were combined for HR. Error bars indicate the 95% confidence interval of the HRs.

Figure 3.

Cumulative risk of incident late age-related macular degeneration (AMD) prior to and after testing of prediction model in the Three Continent AMD Consortium (3CC). **A**, Overall cumulative risk of incident late AMD in 3CC; the x-axis represents the age of onset for incident late AMD cases and age at last examination for noncases; y-axis represents the cumulative risk of incident late AMD. The number at risk for each decade is presented underneath the figure. **B**, Cumulative risk of incident late AMD stratified for risk strata 0–6 in 3CC; x-axis represents the age of onset for incident late AMD cases and age at last examination for noncases; y-axis represents the cumulative risk of incident late AMD. The risk scores are depicted by various colors. The number at risk for each decade and each risk score is presented underneath the figure.

Table 2
General Characteristics of Participants Included in the Analysis

Age Inclusion Variables	RS age 55+ (N = 4753),	BDES age 45+ (N = 3542),	BMES age 49+ (N = 1811),
Mean age, yrs (SD)	67.6 (7.8)	60.2 (10.4)	64.0 (8.3)
Age categorized (yrs)			
65	42.5	67.3	56.8
65–75	39.1	24.0	33.1
75+	18.4	8.7	10.1
Male sex	42.4	42.5	42.8
AMD baseline grade			
Level 10	83.8	80.2	87.4
Level 20	9.1	14.0	8.8
Level 30	6.0	5.2	3.4
Level 40	1.1	0.6	0.3
Smoking			
Never	33.9	45.1	51.4
Past	43.5	34.9	37.1
Current	22.6	20.0	11.5
Mean BMI, kg/m ² (SD)	26.3 (3.6)	28.8 (5.4)	26.2 (4.2)
BMI categorized			
25	38.3	24.9	41.7
25+	61.7	75.1	58.3
CFH (Y402H) rs1061170			
TT	41.8	39.7	42.5
TC	45.0	47.0	46.5
CC	13.1	13.4	11.0
CFH rs12144939			
GG	64.3	64.2	65.1
GT	31.8	31.3	30.8
TT	3.9	4.5	4.1
CFH rs800292			
GG	52.6	59.8	56.9
GA	40.0	35.0	37.2
AA	5.3	5.3	6.0
ARMS2 (A69S) rs10490924			
GG	62.6	60.7	62.0
GT	33.6	34.8	34.0
TT	3.8	4.5	4.0
C2/CFB (L9H) rs4151667			
TT	90.8	90.7	91.1
TA/AA	9.2	9.3	8.9

Age Inclusion Variables	RS age 55+ (N = 4753),	BDES age 45+ (N = 3542),	BMES age 49+ (N = 1811),
<i>C2/CFB</i> (R32Q) rs641153			
GG	84.4	83.7	81.9
GA/AA	15.6	16.3	18.1
<i>C3</i> (R102G) rs2230199			
CC	61.3	64.8	67.9
CG	33.9	31.2	28.8
GG	4.8	4.0	3.3
<i>C3</i> rs433594			
GG	39.4	39.4	35.1
GA	45.7	46.0	49.3
AA	14.9	14.6	15.6
<i>CFI</i> rs10033900			
CC	27.4	25.6	27.6
CT	48.6	50.7	50.1
TT	24.0	23.7	22.4
<i>LPL</i> rs256			
CC	73.1	72.6	72.3
CT/TT	26.9	27.4	27.7
<i>LIPC</i> rs12912415			
AA	71.5	70.8	72.6
AG/GG	28.5	29.2	27.4
<i>MYRIP</i> rs2679798			
AA	30.3	34.5	29.9
AG	49.7	47.5	48.9
GG	20.0	18.1	21.1
<i>SKIV2L</i> rs429608			
GG	74.4	74.7	71.4
GA	23.6	23.1	26.7
AA	2.0	2.2	1.9
<i>ABAC1</i> rs1883025			
CC	54.4	56.3	55.5
CT	39.3	38.3	37.8
TT	6.3	5.4	6.7
<i>CETP</i> rs3764261			
CC	46.4	44.5	45.3
CA	43.1	44.8	45.6
AA	10.5	10.7	9.1
<i>TIMP3</i> rs5749482			
GG	78.7	78.0	75.8
CG/CC	21.3	22.0	24.2
<i>VEGFA</i> rs943080			

Age Inclusion Variables	RS age 55+ (N = 4753),	BDES age 45+ (N = 3542),	BMES age 49+ (N = 1811),
CC	24.9	26.6	26.6
TC	49.8	48.9	49.7
TT	25.3	24.4	23.8
<i>COL8A1</i> rs13081855			
GG	82.4	82.8	82.3
GT	16.9	16.3	16.9
TT	0.7	0.9	0.8
<i>TNFRSF10A</i> rs13278062			
TT	28.0	26.3	27.0
GT	49.8	51.7	49.9
GG	22.2	21.9	23.1
<i>FRK/COL10A1</i> rs3812111			
TT	42.9	38.6	39.1
AT	44.8	47.3	46.9
AA	12.3	14.1	14.0
<i>SLC16A8</i> rs8135665			
CC	63.1	65.0	61.8
CT	32.7	31.3	33.7
TT	4.2	3.7	4.4
<i>ADAMTS9</i> rs6795735			
CC	33.9	33.5	36.6
TC	50.1	49.2	46.2
TT	15.9	17.3	17.2
<i>TGFBR1</i> rs334353			
TT	58.1	54.7	54.8
GT	36.1	39.0	38.8
GG	5.9	6.3	6.5
<i>RAD51B</i> rs8017304			
AA	38.2	38.8	41.9
AG	46.6	47.9	44.1
GG	15.2	13.3	14.0
<i>IER3/DDR1</i> rs3130783			
AA	64.5	64.9	62.3
AG	32.0	26.0	33.4
GG	3.5	9.2	4.3
<i>B3GALT1</i> rs9542236			
TT	31.0	31.9	33.1
CT	48.7	49.3	48.1
CC	20.3	18.7	18.8

Data are percentages unless otherwise indicated.

AMD = age-related macular degeneration; BDES = Beaver Dam Eye Study; BMES = Blue Mountain Eye Study; BMI = body mass index; RS = Rotterdam Study; SD = standard deviation.

Table 4
Predictive Values for the Tested Models in the Rotterdam Study

Model	Variables	AUC (95% CI)	SE	No Late AMD/Late AMD
1	Minimal model Age Sex	0.60 (0.55–0.65)	0.023	4621/132
2	Nongenetic model Age Sex AMD baseline grade Smoking BMI	0.78 (0.74–0.82)	0.022	4561/132
3	Minimal genetic model Age Sex <i>ARMS2</i> rs10490924 <i>CFH</i> rs1061170 <i>C2/CFB</i> rs641153 <i>C3</i> rs2230199 <i>C2/CFB</i> rs4151667	0.73 (0.69–0.78)	0.022	4226/121
4	Maximal genetic model Age Sex <i>ARMS2</i> rs10490924 <i>CFH</i> rs800292 <i>CFH</i> rs12144939 <i>CETP</i> rs3764261 <i>C2/CFB</i> rs641153 <i>COL8A1</i> rs13081855 <i>C2/CFB</i> rs4151667 <i>C3</i> rs433594 <i>TGBR1</i> rs334353 <i>SKIV2L</i> rs429608 <i>C3</i> rs2230199 <i>VEGFA</i> rs943080 <i>ADAMTS9</i> rs6795735 <i>CFH</i> rs1061170 <i>TIMP3</i> rs5749482 <i>IER3/DDR1</i> rs3130783 <i>LPL</i> rs256 <i>MYRIP</i> rs2679798 <i>SLC16A8</i> rs8135665	0.82 (0.79–0.86)	0.016	4226/121

Model	Variables	AUC (95% CI)	SE	No Late AMD/Late AMD
	<i>RAD51B</i> rs8017304	0.88 (0.85–0.90)	0.015	4171/121
	<i>CFI</i> rs10033900			
	<i>FRK/COL10A1</i> rs3812111			
	<i>ABCA1</i> rs1883025			
	<i>B3GALT</i> rs9542236			
5	<i>LIPC</i> rs12912415	0.88 (0.85–0.90)	0.015	4171/121
	<i>TNFRSF10A</i> rs13278062			
	Maximal gene-environment model			
	Age			
	Sex			
	<i>ARMS2</i> rs10490924			
	<i>CFH</i> rs12144939			
	<i>CFH</i> rs800292			
	<i>C3</i> rs433594			
	<i>C2/CFB</i> rs641153			
	<i>TGBR1</i> rs334353			
	<i>SKIV2L</i> rs429608			
	<i>CETP</i> rs3764261			
	<i>C2/CFB</i> rs4151667			
	<i>IER3/DDR1</i> rs3130783			
	<i>C3</i> rs2230199			
	<i>ADAMTS9</i> rs6795735			
	<i>LPL</i> rs256			
	<i>COL8A1</i> rs13081855			
	<i>SLC16A8</i> rs8135665			
	<i>FRK/COL10A1</i> rs3812111			
	<i>CFH</i> rs1061170			
	<i>TIMP3</i> rs5749482			
	<i>VEGFA</i> rs943080			
	<i>MYRIP</i> rs2679798			
	<i>CFI</i> rs10033900			
	<i>TNFRSF10A</i> rs13278062			
	<i>RAD51B</i> rs8017304			
	<i>B3GALT</i> rs9542236			
	<i>ABCA1</i> rs1883025			
	<i>LIPC</i> rs12912415			
	AMD baseline grade			
	Smoking			
	BMI			

AMD = age-related macular degeneration; AUC = area under the curve; BMI = body mass index; CI = confidence interval; SE = standard error.

Table 5
Model 5, the Maximal Gene-Environment Model, in the Three Cohorts

Study	AUC (95% CI)	SE	No Late AMD/Late AMD
RS	0.88 (0.85–0.90)	0.015	4171/121
BDES + BMES pooled	0.85 (0.82–0.88)	0.015	3634/156
3CC*	0.87 (0.85–0.89)	0.010	7805/277

3CC = Three Continent AMD Consortium; AMD = age-related macular degeneration; AUC = area under the curve; BDES = Beaver Dam Eye Study; BMES = Blue Mountain Eye Study; CI = confidence interval, RS = Rotterdam Study; SE = standard error.

* Based on risk estimates reanalyzed in the complete data set.

Table 6
Risk Estimates from Cox Proportional Hazard Analysis Based on the Three Continent AMD Consortium

Variable	Code	Beta Coefficient per Code
Age	<65 = 0/65–75 = 1/75+ = 2	0/1.558/2.433
Sex	M = 0/F = 1	0/0.320
<i>ARMS2</i> rs10490924	GG = 0/GT = 1/TT = 2	0/0.779/1.720
<i>CFH</i> rs800292	GG = 0/GA = 1/AA = 2	0/–0.899/–1.614
<i>C2/CFB</i> rs4151667	TT = 0/TA or AA = 1	0/–1.245
<i>CFH</i> rs12144939	GG = 0/GT = 1/TT = 2	0/–0.947/–1.195
<i>COL8A1</i> rs13081855	GG = 0/GT = 1/TT = 2	0/0.223/0.890
<i>C3</i> rs2230199	CC = 0/GC = 1/GG = 2	0/–0.033/0.755
<i>SLC16A8</i> rs8135665	CC = 0/TC = 1/TT = 2	0/0.313/0.648
<i>C3</i> rs433594	GG = 0/GA = 1/AA = 2	0/–0.110/–0.591
<i>C2/CFB</i> rs641153	GG = 0/GA or AA = 1	0/–0.592
<i>SKIV2L</i> rs429608	GG = 0/GA = 1/AA = 2	0/0.027/0.590
<i>CETP</i> rs3764261	CC = 0/CA = 1/AA = 2	0/0.215/0.478
<i>ADAMTS9</i> rs6795735	CC = 0/TC = 1/TT = 2	0/0.130/0.424
<i>RAD51B</i> rs8017304	AA = 0/AG = 1/GG = 2	0/–0.414/–0.138
<i>TIMP3</i> rs5749482	GG = 0/GC or CC = 1	0/–0.357
<i>TGBR1</i> rs334353	TT = 0/TG = 1/GG = 2	0/0.039/–0.336
<i>CFH</i> rs1061170	TT = 0/TC = 1/CC = 2	0/0.175/0.278
<i>FRK/COL10A1</i> rs3812111	TT = 0/TA = 1/AA = 2	0/–0.278/–0.118
<i>CFI</i> rs10033900	CC = 0/TC = 1/TT = 2	0/–0.070/–0.223
<i>TNFRSF10A</i> rs13278062	TT = 0/TG = 1/GG = 2	0/0.093/0.196
<i>B3GALTL</i> rs9542236	TT = 0/TC = 1/CC = 2	0/–0.231/–0.169
<i>IER3/DDR1</i> rs3130783	AA = 0/AG = 1/GG = 2	0/0.029/0.166
<i>MYRIP</i> rs2679798	AA = 0/AG = 1/GG = 2	0/0.059/0.156
<i>VEGFA</i> rs943080	CC = 0/TC = 1/TT = 2	0/0/0.098
<i>ABCA1</i> rs1883025	CC = 0/TC = 1/TT = 2	0/–0.046/0.076
<i>LIPC</i> rs12912415	AA = 0/AG or GG = 1	0/–0.098
<i>LPL</i> rs256	CC = 0/TC or TT = 1	0/–0.048
AMD baseline grade	Level 10 = 0/Level 20 = 1/Level 30 = 2/Level 40 = 3	0/1.458/2.560/3.398
Smoking	Never = 0/Past = 1/Current = 2	0/0.164/0.651
BMI (kg/m ²)	<25 = 0/25+ = 1	0/0.007

AMD = age-related macular degeneration; BMI = body mass index; F = female; M = male.

Prediction Models in the Literature

Table 8

Author	Year	Study Population/ Design	Noncases/ Cases	Follow-up	Prediction Model Variables			AUC	Sensitivity	Specificity	Validation in Independent Dataset?	Remarks
					Demographic	Environmental	Ocular					
Grold et al ¹⁴	2006	Case-control	114/350				<i>CFH, C2/CB</i>		0.74	0.56	Yes	
Hughes et al ¹⁷	2007	Case-control	266/401		Smoking		<i>CFH, ARMS2</i>				No	Risk score only CNV case
Jakobsdottir et al ¹⁸	2008	Case-control and family cohort	168/187; 1095/429		Age, sex	Smoking	<i>CFH, ARMS2, C2/FB</i>		0.70	0.74	No	
Jakobsdottir et al ¹⁹	2009	Case-control and family cohort	168/187; 1095/429				<i>CFH, ARMS2, C2/FB</i>	0.79			No	
Seddon et al ²³	2009	AREDS, RCT	1167/279	6.3 yrs	Age, sex	Education, smoking, BMI, antioxidant/zinc or both	<i>CFH, ARMS2, C2/FB, C3</i>	0.822	0.83	0.68	No	Baseline grade
Reynolds et al ²²	2009	Case-control	60/110		Age, sex	Smoking, BMI, action fragments	<i>CFH, ARMS2, C2/FB, C3, CFI</i>	0.94			No	
Gibson et al ¹³	2010	Case-control	470/470		Age, sex	Smoking	<i>CFH, ARMS2, C3, SERPING1</i>	0.83	0.76	0.76	No	
McKay et al ²¹	2010	Case-control	436/437		Age	Smoking	<i>CFH, ARMS2, C2/FB, C3</i>	0.86			No	
Zanke et al ²⁸	2010	Risks from literature	NA			Smoking	<i>CFH, ARMS2, C3, miA49/7G</i>				No	
Chen et al ¹²	2011	AREDS (723), case-control (1121)	509/1335		Age, sex	Smoking, BMI	<i>CFH, ARMS2, C2/FB, C3</i>	0.82	0.755	0.747	No	
Hageman et al ¹⁶	2011	Case-control	467/482				<i>CFH, ARMS2, C2/FB, C3, CFHR4, CFHR5, F13B</i>	0.80	0.82	0.63	Yes	Only CNV cases
Klein et al ²⁰	2011	AREDS, RCT	2034/688	9.3 yrs	Age	Family history, smoking	<i>CFH, ARMS2</i>	0.872 [‡]			Yes	
Seddon et al ²⁴	2011	AREDS, RCT	2118/819	9.2 yrs	Age, sex	Education, smoking, BMI, antioxidant	<i>CFH, ARMS2, C2/FB, C3</i>	0.908 [*] 0.876 [‡]			No	
Spencer et al ²⁵	2011	Case-control	216/349		Age	Smoking	<i>CFH, ARMS2, C2/FB, C3</i>	0.84	0.770	0.741	Yes	Outcome is early and late AMD
Spencer et al ²⁵	2011	Nested case-control	148/85		Age	Smoking	<i>CFH, ARMS2, C2/FB, C3</i>		0.633	0.707	Yes	Outcome is early and late AMD
Ying et al ²⁶	2011	CAPT, trial	618/324	5 yrs	Age	Smoking, hypertension	...	0.68			No	Only GA cases
Grassmann et al ¹⁵	2012	Case-control	786/986				<i>CFH, ARMS2, C2/FB, LIPC, APOE, PLA2G12A, TIMP3</i>	0.813			No	
Yu et al ²⁷	2012	AREDS, RCT	1112/1448	10.3 yrs	Age, sex	Education, smoking, BMI, antioxidant	<i>CFH, ARMS2, C2/FB, C3, CFI, LIPC, CFI, LIPC, TIMP3, CHTF ABCA1, COLEMA1, APOE</i>	0.895 [*] 0.883 [‡]			No	Outcome is early and late AMD

AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; AUC = area under the curve; BMI = body mass index; randomized controlled trial.

* Based on 10-year follow-up.

[‡] Based on 5-year follow-up.