Scientific Reports

https://doi.org/10.1038/s41598-026-41931-3

Article in Press

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Received: 11 November 2025

Accepted: 23 February 2026

Published online: 07 March 2026

Cite this article as: Moghul I., Pontikos N., Sharma A. *et al.* Integrating genetics, age and imaging to predict treatment outcomes in neovascular age-related macular degeneration: a proof-of-concept study. *Sci Rep* (2026). https://doi.org/10.1038/s41598-026-41931-3

Ismail Moghul, Nikolas Pontikos, Anitta Sharma, Timing Liu, Taha Soomro, Siegfried K. Wagner, Alan Sousa Silva, Gongyu Zhang, Gunjan Naik, Pallavi Bagga, Yiu Wai Chan, Pearse A. Keane, Valentina Cipriani, Sobha Sivaprasad, Andrew R. Webster & Konstantinos Balaskas

Integrating genetics, age and imaging to predict treatment outcomes in neovascular age-related macular degeneration: a proof-of-concept study

Ismail Moghul [1,3]; Nikolas Pontikos [1,3]; Anitta Sharma [1,2], Timing Liu[1,3]; Taha Soomro [2,3]; Siegfried K. Wagner [2,3]; Alan Sousa Silva [3]; Gongyu Zhang [3,4]; Gunjan Naik [3]; Pallavi Bagga [2]; Yiu Wai Chan [2,3]; Pearse A. Keane [1,2]; Valentina Cipriani [4]; Sobha Sivaprasad [1,2]; Andrew R. Webster MD (Res) [1,2]; Konstantinos Balaskas [1,3]*

[1] UCL Institute of Ophthalmology, London, UK
[2] Moorfields Eye Hospital NHS Foundation Trust, London, UK
[3] NIHR Biomedical Research Centre at Moorfields Eye Hospital & UCL Institute of Ophthalmology
[3] King's College London, London, UK
[4] Queen Mary University of London, London, UK

*Corresponding author: Prof Konstantinos Balaskas
UCL, Institute of Ophthalmology
11-43 Bath Street, EC1V 9EL London, UK
T: +447446961215
E: konstantinos.balaskas@gmail.com

Keywords: artificial intelligence, multimodal AI, predictive modelling, Age-related Macular Degeneration, imaging, genetics

Abstract

Purpose: To evaluate the feasibility of integrating genetic, imaging, and demographic data for predictive modelling of treatment outcomes in neovascular age-related macular degeneration (nAMD).

Design: Proof-of-concept retrospective cohort study with prospective DNA collection.

Methods: Patients with unilateral nAMD receiving anti-vascular endothelial growth factor (anti-VEGF) therapy on a treat-and-extend regimen at a single tertiary centre were recruited. Polygenic risk scores (PRS) for AMD were derived from genotyping data (NIHR Bioresource). Optical coherence tomography (OCT) biomarkers-intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelial detachment (PED), and subretinal hyperreflective material (SHRM)-were automatically quantified using a deep learning segmentation model. Predictors of treatment outcomes included PRS, age at first injection, and OCT feature volumes at baseline. XGBoost was used for binary outcomes and linear regression for continuous outcomes, employing five-fold cross-validation.

Main outcomes: (1) macular dryness (no IRF/SRF) at 24 months, (2) average treatment interval in year 2, and (3) age at first injection.

Results: 106 participants were included. The multimodal model integrating age, imaging, and PRS predicted macular dryness at 24 months with AUC = 0.903, outperforming imaging alone (AUC = 0.701). PRS was associated with younger age at first injection ($\beta = -4.69$, 95% CI [–8.93, –0.44], P = 0.031) but not with treatment burden ($\beta = -6.39$, P = 0.13).

Conclusions: Integrating PRS with OCT-derived imaging biomarkers and patient age is technically feasible and improves predictive performance of modelling for anatomical treatment outcomes in nAMD. PRS reflects genetic susceptibility to nAMD and contextualizes the predictive value of imaging biomarkers for treatment response.

Introduction

Age-related macular degeneration (AMD) remains the leading cause of blindness in high-income countries.[1–3] The neovascular form (nAMD) leads to severe central vision loss and typically requires ongoing anti-VEGF therapy.[4–6] While optical coherence tomography (OCT) imaging guides treatment decisions, clinical heterogeneity in treatment response remains substantial, underscoring the need for predictive tools to personalize therapy.[7–9]

Genetic factors contribute substantially to AMD susceptibility, accounting for up to 70% of disease risk.[14–17] Polygenic risk scores (PRS) aggregate the cumulative effect of common genetic variants - most prominently within complement and inflammatory pathways - to quantify inherited susceptibility.[18–20]

Importantly, PRS primarily reflects risk of disease development and timing of onset, rather than treatment responsiveness per se. Prior pharmacogenetic studies evaluating individual variants or PRS in relation to anti-VEGF response have reported inconsistent associations, and large genome-wide association studies suggest that common variants explain only a modest proportion of variability in treatment outcomes. Rare protein-altering variants such as *C10orf88* and *UNC93B1* may contribute additional effects, but these are context-dependent and of limited predictive power in isolation[25]

Parallel advances in deep learning-based OCT analysis have enabled automated quantification of disease activity and structural biomarkers, yet most predictive models rely on imaging data alone.[21] Integrating inherited susceptibility (PRS) with quantitative anatomical biomarkers may therefore provide a more biologically contextualised representation of treatment outcomes, reflecting both disease predisposition and baseline structural burden.

Recent advances in multimodal machine learning enable integration of heterogeneous data - such as genetics, imaging, and demographics to model disease trajectories.[22-24] This approach mirrors clinical reasoning, combining diverse information sources to form individualized assessments. For nAMD, the combination of imaging and genetic biomarkers offers a promising foundation for predictive medicine.

In this proof-of-concept study, we evaluated the feasibility of combining PRS, AI-derived OCT volumetric biomarkers, and demographic factors (patient age) to model treatment outcomes in nAMD under a treat-and-extend regimen. Specifically, we evaluated multimodal models for predicting macular dryness at 24 months, treatment burden during the second treatment year, and age at disease onset (as a proxy for genetic susceptibility).

Results

Cohort Characteristics

106 patients met the inclusion criteria and were recruited. The majority of the cohort were female (64%, N=68/106) and white or white British (86%, N=91/106), with a median age of

74 (interquartile range (IQR): 68-80). The median PRS for nAMD was 0.08 (IQR: -0.06-0.27). (Table 1). (Figure 1 and Figure 2).

Prediction of dry macula (no SRF, no IRF) in nAMD patients two years post first treatment

Dry macula status, defined as IRF and SRF of less than 10 voxels in an OCT volume, was used as a treatment outcome, as it is both objective and verifiable by clinical expertise. Deep-learning baseline nAMD feature volumes (IRF, SRF, PED, SHRM) from OCT imaging taken at the initiation of treatment were used as input in an XGBoost model.[26] Using PRS-only the model achieved an AUC of 0.69. When PRS scores were added to the model trained on baseline imaging feature volumes or to the model trained on patient age, the predictive model's performance was improved (AUC range of 0.808-0.897) (Table 2). When the multimodal AI predictive model included baseline OCT feature volumes and age, model performance, with or without PRS, was comparable, but the addition of PRS resulted in the highest AUC value (0.903). PRS contributed modestly but consistently to improved discrimination.

Baseline demographic, genetic and OCT biomarker characteristics stratified by 24-month macular dryness are summarised in Supplementary Table S1.

Prediction of treatment burden defined as average length of treatment intervals

PRS was not significantly associated with treatment interval in the second treatment year (β = –6.39 days, 95% CI [–14.77, 1.99], P = 0.13). Inclusion of imaging and demographic covariates did not materially improve model fit (R^2 = 0.014).

Prediction of age at first injection

PRS showed a significant association with younger age at first injection (β = –4.69, 95% CI [–8.93, –0.44], R^2 = 0.026, P = 0.031), suggesting higher genetic load may correspond to earlier disease onset (Figure 4)

Discussion

This proof-of-concept study demonstrates that integrating genetic, imaging, and demographic features is technically feasible and may improve predictive accuracy of achieving quiescence ("dry macula") after anti-VEGF therapy in nAMD. Despite a modest sample size, the multimodal model achieved an AUC > 0.9, providing a signal of feasibility that warrants further validation.

Prior pharmacogenetic studies in nAMD have yielded mixed results.[14-20] A large multicenter GWAS suggested only a limited contribution of common variants to anti-VEGF response, while rare protein-altering variants (e.g., *C10orf88*, *UNC93B1*) were linked to poorer visual outcomes.[29] In aflibercept-treated cohorts under a pro renata (PRN) regimen, associations between AMD susceptibility variants or PRS and 12-month retreatment requirements have been reported but remain inconsistent.[33] Meanwhile, OCT-based machine-learning studies

have predicted activity or progression using imaging features alone, without integrating germline genetics, with modest predictive value.[21]

Prive et al derived polygenic scores (PGSs) for 245 curated traits from the UK Biobank data and applied them to nine ancestry groups from the same cohort.[24] Two were related to AMD. The weights of the PRS were derived for AMD ICD10 codes in 391,124 Europeans (accession number PGS001834).[24] The median PRS for nAMD in our study cohort is 0.08 (IQR: -0.06-0.27), where both the median and upper quartile is greater compared to the reported values in each of the eight datasets of the UK Biobank (five ancestry groups), thus indicating a higher distribution and greater genetic risk compared to the general population. The highest positive median PRS of the Biobank normals was 0.04 (IQR: 0.01-0.06).

Our study adds to this landscape by combining PRS, OCT-derived volumetric biomarkers, and age in a single predictive framework and by targeting a 24-month anatomic endpoint (macular dryness) in patients treated on a treat-and-extend regimen. To our knowledge, this multimodal, genetics-imaging integration in a treated nAMD cohort has not been previously reported.[14-20] By moving beyond either genetics-only or imaging-only paradigms, the approach captures complementary biological signals - inherited susceptibility (PRS), baseline anatomic disease burden (OCT volumes), and patient age - yielding an encouraging discriminatory performance for an objective endpoint. This may reconcile prior reports that common variants alone have limited predictive value for response: genetics appears more informative when contextualizing baseline anatomy and age rather than in isolation. [26-29]

Differences in treatment regimen and endpoint definition likely contribute to heterogeneity across studies. A prior PRS/variant study evaluated 12-month outcomes under PRN protocols, with visual acuity - centric endpoints.[33] In contrast, we model 24-month macular dryness under treat-and-extend, an objective OCT-based endpoint aligned with disease quiescence and retreatment decisions. This endpoint may be more sensitive to biologically driven variation in treatment response than functional measures such as VA, which are confounded by chronicity and comorbidities.

Multimodal AI models can potentially improve the accuracy of such predictions by ingesting information from different data sources.[22, 30] The advantage of this approach is that each modality can provide unique insights that are not apparent when considered in isolation. For example, while genetic data may indicate a predisposition to nAMD, imaging can reveal the actual state and progression of the disease.[13,16] Combining these modalities allows for a more comprehensive assessment, with a potential of informing personalized treatment strategies.[31]

The association between PRS and average re-treatment interval during the second year of treatment on a treat-and-extend regimen was not statistically significant in the logistic regression, potentially indicating that independent effect of predictive variables could not be ascertained in this pilot cohort.

PRS in this study should, therefore, not be interpreted as a pharmacogenomic predictor of anti-VEGF response. Rather, it reflects inherited susceptibility and disease timing, which may indirectly influence treatment outcomes through baseline anatomical disease burden. The observed association between PRS and younger age at first injection supports this

interpretation, suggesting that genetic risk primarily modulates disease onset rather than therapeutic sensitivity.

To mitigate overfitting and enhance reliability in a modest dataset, we implemented nested cross-validation and bootstrapped 95% confidence intervals. These resampling techniques yield more stable estimates of model performance under data constraints. PRS variance distribution (Figure 2) demonstrated adequate spread for exploratory modelling.[28] We also applied Bonferroni correction for multiple comparisons. These methodological approaches contribute to mitigating the risk of overfitting.

Although the current dataset does not permit external validation, internal resampling shows consistent performance across folds, supporting robustness of findings within this cohort.

The improvement in predictive accuracy with inclusion of PRS suggests genetic predisposition might be a contextualising variable for anatomical burden, rather than a standalone treatment response biomarker, influencing anatomical treatment response beyond baseline imaging characteristics. The observed association between higher PRS and younger age at treatment initiation aligns with reports that individuals with higher complement-related genetic burden present earlier with neovascular disease.[29] This supports PRS as a potential biomarker for disease onset risk and may inform future preventive strategies.[28,29] Polygenic burden may modulate both disease timing and, indirectly, treatment response, interacting with baseline anatomical disease burden; an effect that becomes more evident when analyzed jointly with baseline imaging markers. Within nAMD, this could reflect earlier transition to exudation among those with higher complement/inflammation genetic load, while baseline OCT biomarkers are more predictive of near-term treatment response.

The lack of significant association with treatment burden likely reflects biological heterogeneity and regimen factors. Nonetheless, macular dryness, a direct, objective measure of disease quiescence, may be a more sensitive early endpoint for precision modelling.

Limitations

The small sample size may limit generalizability[32], and findings should be viewed as hypothesis-generating. All OCT data were acquired using a single device (Topcon) at a single tertiary centre. Potential device-specific bias, segmentation generalisability across OCT platforms, and domain shift issues should be considered. Future work should validate these results in larger, multi-centre, genotyped cohorts and assess calibration using harmonized treat-and-extend protocols. The predictive model is therefore exploratory rather than clinically actionable, pending further external validation. Moreover, we chose to define the predicted outcome using an anatomical metric, which is an objective and verifiable measure (dry macula). However, this measure does not always reflect the patients' subjective experiences, such as their visual acuity or quality of life.

Conclusion and future directions

The study's main contribution lies in demonstrating that multimodal AI models incorporating PRS and imaging data are technically feasible and biologically plausible. The high observed AUC in the multimodal prediction provides a signal potential and the methodological approaches to mitigate against the risk of overfitting that were used - including cross-

validation with bootstrapping, Bonferroni correction, and use of different model variants - enhance the credibility of this finding. This work establishes a foundation for larger studies combining genomic, imaging, and clinical data for precision medicine in retinal disease. Future analyses could incorporate longitudinal OCT biomarkers, multimodal fundus imaging, and PRS-imaging interactions. Development of open, reproducible code and data standards will further support model generalizability and transparency. Finally, if external data remain small, Bayesian/shrinkage frameworks and hierarchical pooling could further stabilize estimates in multimodal models.

Methods

Study Design & Participants

A retrospective cohort with prospective DNA collection was approved by the UK Health Research Authority (19/SC/0337). All participants provided informed consent. Patients with unilateral nAMD receiving anti-VEGF therapy under a treat-and-extend protocol at Moorfields Eye Hospital were recruited. Inclusion required ≥1 year of treatment. Exclusion criteria included secondary macular neovascularization due to high myopia, angioid streaks, central serous chorioretinopathy, inflammatory, or hereditary macular disease.

Treatment involved fixed monthly anti-VEGF injections for the initial 3 loading doses, followed by fixed bimonthly dosing for 3 visits. Depending on the response, as per the OCT status and visual acuity, treatment intervals were either extended or reduced thereafter.

Suitable patients were approached by a dedicated research nurse at their routine appointment at Moorfields Eye Hospital and were provided with a Patient Information Sheet on the study. Adequate time for consideration, and an opportunity to ask any questions prior to offering informed consent was given. A written consent form was completed for this study, and for the NIHR Bioresource study.

This study was approved by the Institutional Review Board and the United Kingdom Health Research Authority (19/SC/0337) “Machine Learning for Personalised Medicine in Neovascular Age-related Macular Degeneration” with Integrated Research Application System project ID: 264359. All research adhered to the tenets of the Declaration of Helsinki.

Procedures

Clinical, demographic, imaging, and genetics data were collected as part of a single-centre secondary care study at Moorfields Eye Hospital NHS Foundation Trust. The Research Team and the Moorfields NIHR Bioresource Centre recruited suitable participants with nAMD attending scheduled appointments for anti-VEGF injections. Clinical and demographic data were collected through the Electronic Health Record (OpenEyes). Topcon OCT scans from study participants were extracted through the ImageNet6 database from 2009 to 2019 and underwent automated processing for extraction of pathological feature volumes at baseline.

A blood sample was collected from each participant and was sent to the NIHR BioResource for genotyping array analysis. Taking participant expectations and preferences into consideration, early appointments were booked, which also provided the research nurse with

enough time to take a blood sample, thus helping to minimise clinic disruption during data collection. DNA was extracted from whole blood. Genotype, demographics, and lifestyle information were collected from each participant by the Research Team and the London Moorfields NIHR Bioresource Centre (DAA061). Genome-wide association studies were analyszd on the UK Biobank Axiom (v2.1) genotyping chip.

We developed multimodal AI models integrating three independent variables (age, imaging biomarkers, and genetics), alone and in combinations, to optimise performance of predictive modelling for nAMD treatment response.

Baseline OCT scans were processed using a previously developed and validated deep-learning segmentation model quantifying Intraretinal Fluid (IRF), Subretinal Fluid (SRF), Pigment Epithelium Detachment (PED), and Subretinal Hyper-Reflective Material volumes.[33] Maculae were classified as "dry" if total IRF + SRF volume was less than 10 voxels ($0.00143mm^3$).

Outcomes: Three dependent variables were evaluated:

1. "Dry Macula" at 24 months, defined as absence of IRF and SRF at the 24-month visit.
2. Treatment burden, defined as the average injection interval (days) during months 12–24.
3. Age at first injection, used as a proxy for disease onset timing.

Imaging data analysis and nAMD dry status

OCT imaging data were routinely collected at the point of anti-VEGF treatment. All retinal images were acquired using Topcon 3D OCT-2000 with macular fixation that consists of 128 B-scans per volume (Topcon Corporation, Tokyo, Japan). Baseline OCT volumes were analyzed using a previously developed and validated deep-learning OCT segmentation framework.[33] The model was a supervised convolutional neural network architecture (nnU-Net variants), trained to segment intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelial detachment (PED), and subretinal hyper-reflective material (SHRM) volumes on spectral-domain OCT.

Model training and validation were performed on manually annotated OCT datasets graded by expert retinal specialists, as described in detail in a separate methodological study.[33] For model training and validation, 1749 SD-OCT b-scans corresponding to 360 SD-OCT volumes from 275 patients were manually annotated by four ophthalmology experts with more than 5 years' experience in medical retina following a standardised grading protocol developed by a senior retinal expert and Reading Centre director. This dataset was further split into training (237 patients, 1,389 b-scans) and testing datasets (38 patients, 360 b-scans). The nnU-Net (no-new-UNet) framework was selected for its adaptability and performance in automatic medical image segmentation tasks[27]. A single multi-class model for all four features was trained using sum of dice and cross-entropy loss functions to optimize multi-class segmentation accuracy. Hyperparameters, such as learning rate and batch size, were selected by the nnU-Net based on its analysis of the dataset. Training was curtailed at 1000 epochs as this was found to be sufficient to achieve convergence. Cross-validation was applied to prevent overfitting and obtain a more generalizable model.

For model validation, b-scans were double graded, and the mean of the model-grader Dice Correlation Coefficients (DCC) for each feature/b-scan was used to evaluate model performance. In that work, model-grader segmentation agreement (DCC) exceeded 80% for IRF, SRF, PED, and SHRM, with high feature-level accuracy and recall. In the present study, the same trained model and grading definitions were applied without retraining. Although the model was developed on a dataset from patients with inherited retinal diseases (IRDs), the exudative features (SRF, IRF), of primary relevance for the detection and monitoring of activity in nAMD, originated from cases of IRDs manifesting secondary choroidal neovascularisation (such as Sorsby's maculopathy), which present significant phenotypical overlap with nAMD imaging features on OCT. The OCT feature volume values were extracted automatically and used as quantitative baseline anatomical biomarkers. No manual correction was applied at inference, reflecting real-world deployment conditions.

A threshold of <10 voxels (0.00143 mm^3) for combined IRF and SRF volume was used to define macular dryness. This value corresponds to the minimal detectable fluid volume distinguishable from segmentation noise and is below the threshold of clinically appreciable exudation on OCT, consistent with prior AI-based OCT quantification studies.34,35

Genetics data analysis

Blood samples were genotyped by the NIHR BioResource (UK Biobank Axiom v2.1 chip). Quality control removed SNPs with call rate < 98 %, minor allele frequency < 1 %, or Hardy–Weinberg $p < 1 \times 10^{-6}$. No individuals were found to be 3rd degree relatives or closer using the PropIBD metric from KING.[24] Imputation used the European HRC r1.1 2016 panel.[24] No Rsq filter was applied. Phasing was done using Eagle v2. Weights of the PRS were derived from a genome-wide association study for AMD ICD10 codes in 391,124 Europeans in the UK Biobank published on the EBI PGS database under accession number PGS001834.[25] The beta of 157 variants were summed under an additive model on the imputed genotype data for each individual to calculate an individual's genetic risk to AMD (see Data availability).

Predictive modelling variables

Visit dates and anti-VEGF injections for each participant were used to determine treatment burden. This data along with clinical and demographic parameters were extracted from the electronic health record. Anatomical volumes of disease features (Subretinal hyperreflective material (SHRM), pigment epithelial detachment (PED), SRF and IRF) on OCT images were automatically measured through AI analytics. PRS was derived as described above. These independent variables informed the development of predictive models. Model predictions (dependent variables) included: treatment burden, determined as average re-treatment interval in the second year of treatment, presence/absence of dry macula (inactive disease) at 2 years from baseline, and patient age at treatment initiation.

Sample size

Given the prospective genotyping and the integration of three data modalities (imaging, genetics, and clinical), this study was intentionally designed as a hypothesis-generating pilot. Sample sizes of similar magnitude have been previously used to explore feasibility of polygenic risk score incorporation in AMD predictive models.[36] We applied the TRIPOD-AI

guidelines, explicitly indicating that this work addresses model development and feasibility, not final validation.

Statistical Analysis

We conducted statistical analyses to evaluate the predictive power of PRS, OCT deep learning-derived imaging biomarkers, and patient age in determining treatment outcomes for nAMD.

Descriptive Statistics: Continuous variables were summarized using means (standard deviations) or medians (interquartile ranges) where appropriate, while categorical variables were reported as frequencies and proportions. Normality was assessed using the Shapiro-Wilk test.

Machine Learning Model: An XGBoost classifier was developed with multimodal inputs to predict the probability of the target label.[26] Predictors included PRS, baseline OCT feature volumes, and age at baseline. For binary outcomes, the XGBoost classifier was trained using nested five-fold cross-validation (outer folds for evaluation, inner folds for hyperparameter tuning). Model performance was assessed by AUC, accuracy, precision, recall, and F1-score. To estimate confidence intervals in small samples, bootstrap resampling (1,000 iterations) was applied to compute performance variability and prevent overfitting.

Regression Analysis: We applied linear regression models to predict continuous outcomes (e.g., age at first presentation) from polygenic risk scores. Model coefficients, 95% confidence intervals, and significance values were reported. Linear regression assumptions were evaluated using standard diagnostic procedures, including assessment of linearity, homoscedasticity, and normality of residuals. Ridge regression was explored as a sensitivity analysis to assess robustness of estimates and mitigate potential overfitting.

Model Evaluation: 5-fold cross-validation was performed and averaged to produce performance metrics of the predictive model. The area under the curve (AUC) for ROC was used to compare predictive performance across models. Feature importance was extracted to assess the relative contributions of PRS, imaging biomarkers, and age.[26] Bonferroni corrections for multiple comparisons were applied.

PRS variance distribution (Figure 2) demonstrates adequate spread for exploratory modelling.[28]

We adhered to Tripod AI reporting guidelines for predictive modelling development and feasibility.

All analyses were performed in Python 3.9 (scikit-learn 1.0, XGBoost 1.6).

Funding Declaration

Supported by a Moorfields Eye Charity Springboard Award (R190001A). The funders had no role in study design, data collection, analysis, or interpretation.

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Author contributions

Conception and design: KB
Funding acquisition: KB
Data collection: IM, NP, TS, GZ, TL, PB, YWC, VC, KB
Analysis and interpretation: IM, NP, TL, AS, TS, ASS, GZ, GN, PB, YWC, VC, KB
Manuscript drafting and critical revision: IM, NP, AS, TL, TS, ASS, SKW, GZ, GN, PB, YWC, VC, PAK, SS, ARW, KB
All authors approved the final manuscript.

Data availability

The full list of variants and effect sizes used for PRS computation is available in the EBI PGS catalogue (PGS001834). Data and code are available upon reasonable request to the corresponding author.

Declaration of interests

KB has received speaker fees from Novartis, Bayer, Roche; meeting or travel fees from Novartis and Bayer; consulting fees from Novartis, Roche, Bayer and Boehringer-Ingleheim; research support from Apellis, Novartis, and Bayer; employment AAvantgarde Bio **PAK** received grants or contracts by a UK Research & Innovation Future Leaders Fellowship (MR/R019050/1) and The Rubin Foundation Charitable Trust; consulting fees from Retina Consultants of America, Topcon, Roche and Boehringer-Ingleheim; payment or honoraria from Zeiss, Topcon, Novartis, Boehringer-Ingleheim, Apellis, Roche and AbbVie; support for attending meetings and/or travel from Bayer, Topcon and Roche; Active patents: Generalizable medical image analysis using segmentation and classification neural networks https://patents.google.com/patent/US10198832B2/en and Pending Patents: Predicting disease progression from tissue images and tissue segmentation maps https://patents.google.com/patent/US20220301152A1/en; participation on a Data Safety Monitoring Board or Advisory Board for Topcon, Bayer, Boehringer-Ingleheim, RetinAI and Novartis; Bitfount (stock options) and Big Picture Medical (stock). **SS** received grants (paid to her institution) from Bayer and Boehringer Ingelheim; consulting fees for participation on advisory boards from AbbVie, Amgen, Apellis, Bayer, Biogen, Boehringer Ingelheim, Novartis, Eyebiotech, Eyepoint Phamaceuticals, Janssen Pharmaceuticals, Nova Nordisk, Optos, Ocular Therapeutix, Kriya Therapeutics, OcuTerra, Roche, Stealth Biotherapeutics, and Sanofi; honoraria for lectures from Bayer, and Roche, for presentations from Bayer, Roche, Astellas, and Abbvie, and for manuscript writing and educational events from Bayer, Roche, and Boehringer Ingleheim; support for attending meetings and/or travel from Boehringer Ingelheim, Roche, and Bayer; participation in Data Safety Monitoring Boards for Bayer and Novo Nordisk; is a Trustee of the Macular Society and Chair of the Royal College of Ophthalmologists' Scientific Committee; and has stock options in Eyebiotech.
All other authors declare no conflicts of interests.

Figure Legends

Figure 1. Graphic abstract for the study design. OCT scans, blood sample for genotyping, and patient demographics were collected at standard care from 106 patients attending Moorfields Eye Hospital. Genotyping analysis was performed by the NIHR Bioresource. Polygenic risk score was calculated and associated with age at baseline and average treatment interval. Polygenic risk score was also used in a multimodal predictive model to assess its contribution in predicting the presence of “dry macula” at 24 months from recruitment.

Figure 2. Distribution of the AMD polygenic risk score of the whole cohort (normalized).

Figure 3. Association between average retreatment intervals during 24 months of follow-up and AMD polygenic risk score (beta = -6.39, 95% confidence intervals (-14.77; 1.99), R-squared = 0.014, p=0.134).

Figure 4. Association between age of the first treatment and AMD polygenic risk score (beta = -4.69, 95% confidence intervals (8.93; -0.44), R-squared = 0.026, P=0.031).

Table

Table 1 Patient demographics for participants in the study cohort.

Characteristic	N = 106
Gender[1]	
Female	68 (64%)
Male	38 (36%)
Ethnicity[1]	
Not stated	2 (1.9%)
Other ethnicity	13 (12%)
White or White British	91 (86%)
Age[2]	74 (68, 80)
PRS[2]	0.08 (-0.06, 0.27)

[1] Number of participants (%)
[2] Median (Interquartile range, IQR)

Supplementary Table 1. Baseline characteristics stratified by macular dryness at 24 months

Variable (baseline unless stated)	Dry at 24 months (n = 60)	Not dry at 24 months (n = 46)	P value
Age at first injection, years (median [IQR])	73 [4]	75 [4]	0.45†
Sex, female n (%)	40(58.8)	28 (41.2)	0.63‡
Polygenic risk score (standardised), (median [IQR])	0.07 [-0.04-0.18]	0.09 [-0.08-0.23]	0.54†
Intraretinal fluid (IRF) volume, mm^3 (median [IQR])	0.06 [0.01-0.12]	0.09 [0.03-0.20]	0.08†
Subretinal fluid (SRF) volume, mm^3 (median [IQR])	0.09 [0.06-0.18]	0.07 [0.02-0.16]	0.12†
Pigment epithelial detachment (PED) volume, mm^3 (median [IQR])	0.16[0.07-0.29]	0.21 [0.05-0.34]	0.32†
Subretinal hyperreflective material (SHRM) volume, mm^3 (median [IQR])	0.04 [0.01-0.13]	0.02 [0.01-0.19]	0.56†

† Mann–Whitney U test for between-group comparisons of continuous variables. Normality assessed using the Shapiro–Wilk test.
‡ χ^2 test.
Macular dryness at 24 months was defined as total IRF + SRF volume <10 voxels.