Intraocular Lens Power Calculation—Comparing Big Data Approaches to Established Formulas



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• PURPOSE: To evaluate the predictive performance of traditional intraocular lens (IOL) power calculation formulas (e.g., SRK/T, Haigis, Hoffer Q, and Holladay I) compared to advanced regression models, including classical linear models, regression splines, and random forest regression, in predicting postoperative refraction following cataract surgery.

• DESIGN: Retrospective, comparative analysis of IOL power calculations.

• SUBJECTS: The study included 886 eyes from 631 patients who underwent cataract surgery with monofocal aspherical IOL implantation.

• METHODS: Biometric measurements were obtained using optical biometry (IOLMaster 700), and postoperative refraction was assessed at least 4 weeks after surgery. Formula constants for 5 IOL formulas (SRK/T, Haigis, Hoffer Q, Holladay I and Castrop V1) were optimized using root mean squared error (RMSE). Regression models (classical linear model, regression splines, and random forest regression) were trained on 4 datasets categorized by axial length (AL); normal, short, long, and random. Model performance was assessed using mean absolute error (MAE), RMSE, and prediction error variance, for both in-sample and out-of-sample predictions.

• MAIN OUTCOME MEASURES: The primary parameters measured were MAE, RMSE, and prediction error variance.

• RESULTS: Regression models outperformed traditional IOL formulas in in-sample prediction error. Overall, linear regression models performed similarly to traditional formulas with respect to out-of-sample prediction error. The lowest out-of-sample prediction error

Accepted for publication February 6, 2025.

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Inquiries to Jascha A. Wendelstein, University Eye Hospital, Ludwig-Maximilians-University, Munich, Germany; e-mail: Jascha.Wendelstein@med.uni-muenchen.de (MAE = 0.279, RMSE = 0.359) was achieved with a model where effects of some covariates (R2, AL, CCT) were modelled as nonlinear via regression splines. This model outperformed all traditional formulas, and the Castrop formula, which had the lowest errors among the formulas (MAE = 0.284, RMSE = 0.359). Random forest regression showed strong in-sample performance but poor out-of-sample generalizability due to overfitting.

• CONCLUSIONS: Regression models which allow for nonlinear effects, e.g. based on regression splines, provide a promising alternative to traditional IOL formulas for predicting postoperative refraction. Linear regression and random forest regression models can reduce in-sample error, however, their clinical utility is currently limited by out-of-sample performance. Future work should focus on improving generalizability and integrating machine learning models into clinical practice to enhance refractive outcomes, especially for eyes with atypical anatomy. (Am J Ophthalmol 2025;273: 141-150. © 2025 The Authors. This Published by Elsevier Inc. is an open license article under the CC BY access (http://creativecommons.org/licenses/by/4.0/))

INTRODUCTION

ATARACT SURGERY IS 1 OF THE MOST COMMON and successful procedures performed worldwide, with intraocular lens (IOL) implantation significantly improving visual outcomes for millions of patients annually.^{1,2} However, achieving the desired postoperative refractive outcomes remains a challenge, particularly as patient expectations for precision continue to rise.³⁻⁶ Accurate prediction of postoperative refraction is critical, as refractive errors can result in the need for additional corrective measures, impacting patient satisfaction and quality of life.

Historically, the prediction of postoperative refraction has been guided by IOL power calculation formulas, which rely on biometric measurements of the eye such as ax-

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ial length (AL), anterior chamber depth (ACD), and keratometry (K) readings.^{7,8} These formulas, including SRK/T, Haigis, Hoffer Q, and Holladay I, are based on combinations of vergence calculation and empirical components such as ELP prediction, and while they generally perform well, their accuracy can vary depending on the characteristics of the patient's eye.⁹ Recent advancements in biometry, such as the introduction of optical biometry, nowadays usually in the form of swept-source optical coherence tomography (SS-OCT), have improved the precision of ocular measurements. However, challenges in prediction accuracy persist, especially in cases with atypical eye anatomies, such as short or long axial lengths.¹⁰⁻¹²

In light of these challenges, alternative approaches to postoperative refraction prediction have been explored, including the use of advanced statistical models and machine learning algorithms.^{7,13-20} These methods have the potential to offer more individualized predictions by capturing complex relationships between biometric variables and refractive outcomes.

In this study, we compare the performance of all openly disclosed IOL power calculation formulas including classical formulas and a new generation IOL power calculation formula with 3 regression-based models, including classical linear models, regression splines, and random forest regression, to evaluate their ability to predict postoperative refraction following cataract surgery. In particular, we focus on comparing in-sample and out-of-sample prediction errors. Furthermore, we explore the performance of regression models trained on different subsets of data, including those with normal axial lengths and random distributions of ocular measurements, to determine the most effective approach for optimizing postoperative refractive outcomes.

METHODS

• ETHICS: This retrospective study adhered to the tenets of the Declaration of Helsinki. Ethics approval was obtained from the study institution's Institutional Review Board, and HIPAA regulations were followed (Ärztekammer des Saarlandes, 157/21).

• PATIENT ELIGIBILITY: The study population consisted of 886 consecutive eyes of 631 patients who underwent cataract surgery with a monofocal 1-piece hydrophobic aspherical IOL implantation (IOL model: Vivinex, Hoya Surgical Optics, Singapore) by experienced surgeons at the study institution (Augen- und Laserklinik Castrop Rauxel, Germany).

Further inclusion criteria were complete biometric measurements with the mark "Successful," postoperative subjective refraction, and a corrected distance visual acuity of 0.2 logMAR or better. Exclusion criteria were any history of ophthalmic surgery (except cataract surgery), perioperative or postoperative complications, and any other ocular pathologies influencing the biometric measurements such as corneal pathologies, and retinal pathologies.

Optical biometry was performed with an SS-OCT biometer (IOLMaster 700; Carl Zeiss Meditec AG [soft-ware v. 1.70.14.53814-1.80.10.61129]) measuring the AL, ACD, lens thickness (LT), white-to-white (WTW), central corneal thickness (CCT), corneal front surface radii in the flat (R1) and steep meridians (R2), corneal back surface radii in the flat (PR1), and steep meridians (PR2). Subjective manifest refraction (sphere, cylinder, and axis) and visual acuity were measured by experienced clinicians/optometrists at least 4 weeks after surgery. Postoperative refractions were performed with adjustments for a lane length of 6 m.*IOL Power Calculation*

Four different training sets of 200 observations were generated: (1) the *normal training* set, which only included observations with normal AL (23-25mm); (2) the *random* set, consisting of randomly drawn observations from the entire set; and (3) the *short* AL and 4) *long* AL sets, which included a higher proportion of short (<23mm) or long (>25mm) eyes, respectively.

Each of the 4 different training sets was used to calibrate 5 disclosed and openly available formulas; SRK/T, Haigis, Hoffer Q, Holladay I and Castrop (V1),¹⁰ to a specific environment using a comparison of diverse optimization metrics, including root mean squared error (RMSE), mean error (ME), median error (medE) and mean absolute error (MAE). RMSE was selected as the metric for constant optimization after the predictive performance of the 5 formulas, and different optimization metrics were compared using mean, median, mean absolute error (MAE), and RMSE, and all yielded similar results. The resulting postoperative refraction is referred to as the achieved refraction, while the prediction of the refraction, based on ocular measurements and the power of the implanted lens, is denoted as target refraction. The prediction error is defined as the difference between the achieved refraction and the target refraction.

The 3 regression models used in this study were the classical linear model, regression splines, and random forest regression. The significance level for the testing of regression coefficients was set to $\alpha = 0.05$.

Linear Regression: This is a traditional statistical approach where the relationship between biometric variables and postoperative refraction is modeled using a straight-line equation. It assumes that changes in input variables lead to proportional changes in the predicted outcome.

Regression Splines: Unlike simple linear models, splines divide the data into segments and fit smooth, flexible curves rather than straight lines. This allows for more accurate modeling of complex, nonlinear relationships, such as the way axial length and corneal curvature interact with refractive outcomes. By smoothing the curve, regression splines can provide better predictions without the need for rigid assumptions about data behavior.

Random Forest Regression: This machine learning technique builds multiple decision trees based on different subsets of the data. Each tree makes a prediction, and the final output is the average of all these predictions. While random forests excel at capturing complex interactions between variables, they are prone to overfitting, meaning they might perform well in training but not generalize as effectively to new data. A thorough descriptive analysis was first conducted to identify relationships in the data, providing a foundational understanding of the variables and their interaction effects. A linear model with main effects of all covariates was fitted for the response variable achieved refraction with the R-function lm using the normal training set for predicting postoperative refraction. For predicting postoperative refraction, a linear model with main effects of all covariates was fitted for the response variable achieved refraction with the R-function lm using the normal training set. This model was named M1LMnormal. A stepwise backward selection on the main effects model M1LMnormal with respect to the Akaike information criterion (AIC) was performed with the R-function step AIC from the package MASS. The selection begins with the full model and gradually removes covariates (Laterality, R1, R2, AL, ACD, IOL Power, CCT, LT, WTW) or interaction terms from the regression model at each step to find the reduced model with the lowest AIC. The resulting model was denoted by M2LMnormal. Finally, the next step was a backward selection performed on a model considering all possible 2-way interactions. The resulting model was denoted by M3LMnormal.

Next, the *random* training set was used to fit the regression models. For the linear model, a stepwise backward selection on the main effects model with respect to the Akaike information criterion (AIC) was denoted by *M1LMrandom* and the model with all possible 2-way interactions after stepwise model selection was denoted by *M2LMrandom*.

For regression splines (cubic spline), the effects of metric covariates on the achieved refraction were modelled nonlinearly by penalized splines with a second-order difference penalty on their coefficients using the R-function *gam* from the *mgcv* package. The smoothing parameter for the penalty was automatically chosen via generalized cross-validation. First, effects of all covariates were modelled by P-splines and the model was denoted by *M1splines*. Next, a less complex model *M2splines* was fitted, where linear effects were modeled with parametric effects and covariates with nonsignificant effects were omitted from the model.

Random forest models were fitted to the response using R-function *caret*. 10-fold cross-validation was used to train and evaluate the model. The best fit in terms of RMSE was determined from a grid of hyperparameters. These hyperparameters include the number of variables randomly sampled as candidates at each split (*mtry* = (3, 5, 7, 9)) and the minimum size of terminal nodes (*min, node, size* = (1, 3, 5)). Another important hyperparameter, known as the

TABLE 1. Out-of-Sample Prediction Error for Different
Formulas and Splits for Optimization Metric RMSE

Formula	Split	MAE	RMSE	Variance
Haigis	Normal	0.327	0.414	0.170
	Random	0.317	0.407	0.166
	Short	0.325	0.407	0.152
	Long	0.306	0.389	0.152
Hoffer Q	Normal	0.351	0.499	0.247
	Random	0.348	0.498	0.248
	Short	0.335	0.485	0.225
	Long	0.330	0.425	0.178
Castrop	Normal	0.280	0.355	0.126
	Random	0.284	0.360	0.129
	Short	0.278	0.354	0.124
	Long	0.277	0.348	0.121
SRKT	Normal	0.342	0.442	0.196
	Random	0.343	0.447	0.197
	Short	0.328	0.419	0.176
	Long	0.330	0.431	0.183
Holladay 1	Normal	0.334	0.434	0.188
	Random	0.329	0.429	0.184
	Short	0.318	0.413	0.170
	Long	0.317	0.412	0.169

splitting rule, was the criterion used to determine how to split the data at each node. The splitting rules considered in this context included *variance*, which selects splits based on variance reduction, and *Extra Trees*, which randomly selects splitting points.

The MAE, RMSE, and the variance of the out-of-sample prediction error were used to compare the prediction performance of the various described models and the 5 IOL calculation formulas.

RESULTS

Table 1 shows the MAE, RMSE and variance of the outof-sample prediction error for different training splits separately for each formula. Except for the SRK/T formula, we observed that using the long training set to build the model results in the smallest MAE, RMSE and variance. The results for the different splits were almost identical for the Castrop formula.

• NORMAL TRAINING SET:

Linear model

The MAE, RMSE and variance of the in-sample prediction error for formulas with the optimization metric RMSE and regression models trained on the *normal* training set were compared (Table 2). The regression models had a notably smaller in-sample prediction error than the formu-

TABLE 2. In-Sample Prediction Error for Formulas With Optimization Metric RMSE and Regression Models Trained on Normal Training set

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	Formula/Model	MAE	RMSE	Variance
	Haigis	0.273	0.359	0.130
	SRKT	0.320	0.418	0.175
	Holladay1	0.291	0.384	0.148
	HofferQ	0.298	0.390	0.153
	Castrop	0.281	0.359	0.130
	M2LMnormal	0.240	0.321	0.104
	M3LMnormal	0.218	0.290	0.084

TABLE 3. Out-of-Sample Prediction Error for Formulas With
Optimization Metric RMSE and Regression Models Trained
on Normal Training Set

Formula/Model	MAE	RMSE	Variance
Haigis	0.327	0.414	0.170
SRKT	0.342	0.442	0.195
Holladay1	0.334	0.434	0.188
HofferQ	0.351	0.499	0.247
Castrop	0.280	0.355	0.126
M2LMnormal	0.368	0.514	0.237
M3LMnormal	0.375	0.534	0.274

las. The M3LMnormal regression model yielded the smallest in sample prediction errors with MAE of 0.218, RMSE of 0.290, and variance of 0.084. For the out-of-sample prediction error, the Castrop formula had the lowest MAE, RMSE, and variance at 0.280, 0.355, and 0.126 respectively, compared to the other formulas and regression models (Table 3). M2LMnormal performed slightly better than M3LMnormal, but both models had less accurate results compared to the formulas. The in-sample prediction error was smaller than the out-of-sample error for the regression models. For M3LMnormal, the correlation between predicted target refraction and the observed achieved refraction was high but prediction errors were large particularly for eyes with short and long axial lengths (Figure 1). This suggests that the normal training set which comprises only eyes with normal axial length, might not be appropriate to build a good prediction model for all eyes. Hence, in the next steps, the random training set, which contains a random sample of all eyes, was used as the training set.

• RANDOM TRAINING SET:

Linear model

Model M2LMrandom performed better than model M1LMrandom with respect to in-sample prediction error (Table 4). For out-of-sample prediction error, the regression models performed on the same level as most of

TABLE 4. In-Sample Prediction Error for Formulas With Optimization Metric RMSE and Regression Models Trained on Random Training Set

Formula/Model	MAE	RMSE	Variance
Haigis	0.311	0.388	0.150
SRKT	0.324	0.410	0.169
Holladay1	0.318	0.408	0.168
HofferQ	0.332	0.419	0.174
Castrop	0.271	0.347	0.121
M1LMrandom	0.291	0.378	0.144
M2LMrandom	0.215	0.274	0.075
M2splines	0.236	0.306	0.094
Random forest regression	0.202	0.263	0.070

TABLE 5. Out-of-Sample Prediction Error for Formulas With Optimization Metric RMSE and Regression Models Trained on Random Training Set

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Formula/Model	MAE	RMSE	Variance	
Haigis	0.317	0.407	0.166	
SRKT	0.343	0.447	0.197	
Holladay1	0.329	0.429	0.184	
HofferQ	0.348	0.498	0.248	
Castrop	0.284	0.359	0.129	
M1LMrandom	0.333	0.436	0.190	
M2LMrandom	0.304	0.397	0.158	
M2splines	0.279	0.359	0.129	
Random forest regression	0.569	0.754	0.570	

the formulas, with the exception of the Castrop formula, which gave by far the best out-of-sample predictions with MAE of 0.284, RMSE of 0.359, and variance of 0.129 (Table 5). The MAE, RMSE and variance are slightly smaller for the in-sample error compared to the out-of-sample error for the formulas and *M1LMrandom* (Table 4 and 5). For *M2LMrandom* the in-sample error. Fitted values were around zero for most observations and, for some, around –2.5 (Figure 2). The distribution of the residuals did not substantially deviate from the normal distributions, however indicated heteroscedasticity (Figure 2). There were no highly influential observations (Figure 2).

Regression splines

For the M2splines model the in-sample prediction error was lower than the out-of-sample error with respect to MAE, RMSE, and variance (Table 4 and 5), but it performed similarly to the Castrop formula for the out-of-sample prediction error with a slightly better MAE at 0.279 for M2splines versus 0.284 for Castrop (Table 5). Overall, the M2splines model had lower MAE, RMSE, and variance of both insample as well as out-of-sample prediction error than all formulas. Further splines models (cubic spline (polynomial or-



FIGURE 1. Scatterplots of TR and AR and PE and AL for the linear model after stepwise selection with 2-way interactions (M3LMnormal). TR = target refraction; AR = achieved refraction; PE = prediction error; AL= axial length.

der 3) with a penalization term to control overfitting) with interaction terms reduced the in-sample error, but did not lead to an improvement in the out-of-sample error, indicating overfitting to the training data. Hence only prediction performance of the *M2splines* model without interaction was investigated. For this model, target and achieved refraction were highly correlated and there was no association between the prediction error and the axial length (Figure 3).

Random forest regression

The scatter plot of target versus achieved refraction shows deviations from the main diagonal for the training data and large deviations in the test data with similar ranges for myopic and hyperopic (Figure 4). In the training set prediction errors were small and slightly positive for myopic and negative for hyperopic eyes. However, in the test data prediction errors had large prediction errors, particularly for long eyes (Figure 5). Overall, random forest regression resulted in the lowest MAE, RMSE and variance in the in-sample prediction of all models and formulas but performed worst in out-of-sample prediction (Table 4 and 5).

DISCUSSION

This study aimed to evaluate the performance of traditional physical optics-based IOL power calculation formulas against 3 regression-based models for predicting postoperative refraction following cataract surgery. Our findings demonstrate that while some regression models like regression splines offer promising results, physical optics-based formulas, such as the 4 classical formulas and the Castrop formula, remain highly effective in real-world clinical settings.

Linear models are among the most commonly used in clinical research, as they assume a straight forward, proportional relationship between input variables (such as AL or corneal curvature) and the predicted outcome. While simple and interpretable, linear models may not fully capture more complex, nonlinear relationships inherent in biological systems. Regression splines offer a more flexible alternative by dividing the data into segments and fitting smooth, piecewise polynomial functions, allowing for gradual changes in the relationship between variables. This makes them particularly useful when the association between biometric parameters and refractive outcomes is not strictly linear. Random forest regression, on the other hand, is a machine learning technique that builds multiple decision trees and aggregates their predictions to identify patterns in the data. Unlike traditional regression models, random forest does not rely on predefined assumptions about variable relationships, making it well-suited for capturing complex interactions.

Linear models and regression splines demonstrated balanced performance. The out-of-sample performance was comparable to that of traditional formulas for the linear models. However, the *M2splines* model achieved the most accurate out-of-sample predictions among all of the regres-



FIGURE 2. Residual analysis for the linear model with 2-way interactions resulting after backward step-wise selection (M2LMrandom).

sion models and formulas, suggesting that nonlinear relationships between biometric parameters and refractive outcomes can be captured effectively without overfitting. In this model, penalized splines allowed nonlinear effects between biometric covariates, such as AL, CCT, and the corneal radius of curvature of the flat meridian to be modeled. Their relatively low prediction errors suggest that they could be an effective alternative for improving refractive outcomes. The use of regression splines in IOL prediction has been limited thus far with only 1 model using a combination of support vector machines with a Gaussian kernel radial basis function and multivariate adaptive regression spline, designated Karmona.²¹ Karmona emerged as the most accurate to predict IOL power among Haigis, Holladay 2, Barrett Universal II, and Hill-RBF v2.0,²¹ suggesting that regression splines hold promise in designing future formulas. In our study the M2splines model just barely surpassed the Castrop formula in out-of-sample prediction error, which consistently had the lowest MAE, RMSE, and

variance in both in-sample and out-of-sample predictions among the formulas.

Interestingly, while outperforming other methods for insample predictions, the random forest regression performed the worst in terms of out-of-sample accuracy. This discrepancy suggests that random forest models may be prone to overfitting, particularly in the context of small or highly variable datasets. There is very little literature to compare to the use of random forests in IOL calculation, with different studies reporting superior algorithms and methods.²²⁻²⁴ Despite its potential to handle complex, nonlinear interactions between variables, the inability of random forest regression to generalize well across different patient populations may limit its clinical utility for IOL power calculation without further refinement. Reliable, consistent outof-sample performance is key in the real-world application of newer formulas as many eyes will lie outside of the training dataset.



FIGURE 3. Scatterplots of TR and AR and PE and AL for model M2splines. TR = target refraction; AR = achieved refraction; PE = prediction error; AL = axial length.



FIGURE 4. Scatterplots of TR and AR and PE and AL for the random forest regression. TR = target refraction; AR = achieved refraction; PE = prediction error; AL = axial length.



FIGURE 5. Boxplots of the out-of-sample prediction error separately for each AL category for the random forest regression. AL = axial length.

In line with previous literature, the traditional IOL formulas performed well overall.²⁵ However, while the traditional formulas are robust, depending on their lens position algorithms and other empirical parts, their accuracy can be limited in patients with atypical ocular anatomy, such as those with short or long AL, where the error margins are generally higher.^{10,11} While these time-tested formulas still play a role in clinical practice, newer data-driven approaches may offer potential, if sufficient case numbers of these atypical eyes are available for training algorithms. In particular, an area of study showing promise is hybrid or ensemble models combining the strength of both traditional formulas with machine learning.²⁶ Furthermore, instead of using purely empirical prediction models, a combination of physical optics and empirical regression-based models may also show potential to increase the performance in atypical eyes.14,27

Interestingly, an optimization based on the "long" subset of eyes, which included a higher proportion of long AL eyes, yielded the best out-of-sample prediction performance in most formulas, except for the SRK/T formula. Conversely, the short training set lacked prediction accuracy, particularly for long AL eyes. Therefore, it may be recommended to consider long AL eyes in formula optimization. The effects of this observation may be dependent on the IOL model.²⁸

A strength of this study design was a large dataset of eyes meeting the optimal numbers for constant optimization as discussed by Langenbucher et al.²⁹ Further research should focus on increasing the sample size for these outlier populations or exploring additional techniques, such as regularization or ensemble learning, to improve generalizability across diverse eye anatomies.

The limitations of this study include the retrospective monocentric design, and the limitation to 1 single IOL platform. Furthermore, due to the calibration processes, we included only disclosed and published formulas or formula versions (such as Castrop V1) into our study. Therefore, we were not able to compare results to some other popularly used new-generation IOL calculation formulas, such as Barrett Universal 2, Castrop V2, EVO 2.0, Hoffer QST, Kane, PEARL-DGS, and others. The multitude of optimization processes performed in this study led to the decision to omit all undisclosed formulas. Only purely empirical models were tested, whereas combinations of physical optics and empirical regression based prediction models were not tested. Finally, this study did not include external validation. In the future, testing the models on independent datasets would help demonstrate their robustness and generalizability.

In conclusion, this study highlights the potential of regression-based models as an alternative or complement to traditional IOL formulas for predicting postoperative refraction after cataract surgery. Nonlinear models such as regression splines can perform at a level comparable and sometimes superior to complex theoretical-optical formulas. However, while linear and random forest models can reduce in-sample error, their practical application was limited by their out-of-sample performance, which remained inferior to that of the most traditional formulae. Future research should focus on improving the generalizability of these advanced models and investigating ways to integrate them with existing clinical tools to enhance the accuracy of refractive outcomes, particularly in eyes with unusual biometric profiles.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

LIAM D. REDDEN: Writing - review & editing, Writing – original draft. BIRGIT GRUBAUER: Writing – review & editing, Writing - original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. PETER HOFF-MANN: Writing - review & editing, Supervision, Data curation. ACHIM LANGENBUCHER: Writing - review & editing, Supervision, Methodology, Formal analysis. KAMRAN M. RIAZ: Writing - review & editing, Supervision. DAMIEN GATINEL: Writing - review & editing, Supervision. HELGA WAGNER: Writing - review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization. JASCHA A. WENDEL-STEIN: Writing - review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Jascha A. Wendelstein reports a relationship with Carl Zeiss Meditec AG, Rayner, Alcon, Bausch and Lomb, and Johnson & Johnson Vision that includes: speaking and lecture fees. Achim Langenbucher reports a relationship with Hoya Surgical and Johnson & Johnson Vision that includes: speaking and lecture fees. Kamran M. Riaz reports a relationship with Ambrx, Inc., Bausch and Lomb, Exelexis, Inc., ImmunoGen, and Neumora Therapeutics that includes: consulting or advisory. Kamran M. Riaz reports a relationship with Bausch and Lomb, CorneaGen, and MedScape that includes: speaking and lecture fees. Kamran M. Riaz reports a relationship with Aurion Therapeutics, Inc. that includes: travel reimbursement. Peter Hoffman reports a relationship with Hurion Therapeutics, Inc. that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Funding/Support: The authors confirm that the study was not granted or supported by any governmental or nongovernmental organization. Financial Disclosures: Dr. Wendelstein reports speaker fees from Carl Zeiss Meditec AG, Alcon, Rayner, Bausch and Lomb, and Johnson & Johnson Vision outside of the submitted work. Dr. Langenbucher reports speaker fees from Hoya Surgical and Johnson & Johnson Vision outside the submitted work. Dr. Hoffmann reports speaker fees from Heidelberg Engineering, Hoya Surgical and Johnson & Johnson Vision outside the submitted work. Dr. Riaz reports consulting roles with Ambrx, Inc., Bausch and Lomb, Exelexis, Inc., ImmunoGen, and Neumora Therapeutics; speaking fees from Bausch and Lomb, CorneaGen, and MedScape; and travel fees from Aurion Therapeutics, Inc., outside of the submitted work. None of the other authors reports financial or proprietary interests.

Declaration of competing interest: The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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