An Ensemble-Based Approach for Estimating Personalized Intraocular Lens Power

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An ensemble-based approach for estimating personalized intraocular lens power

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ABSTRACT

This study introduced a new approach for the calculation of personalized intraocular lens power, which used an ensemble of regression models to devise a more accurate and robust prediction of the effective lens position. The concept of cross-validation is used to rigorously assess the performance of the devised formula against the most commonly used published formulae. The results from this study show that overall, the proposed approach outperforms the most commonly used modern formulae (namely, SRK/T, Hoffer Q, Holladay I, and Haigis) in terms of mean absolute prediction errors and prediction accuracy i.e., the percentage of eyes within $\pm 0.5D$ and $\pm 1 D$ ranges of prediction, for various ranges of axial lengths of the eyes. The results are obtained using three models of lens (two monofocal and one multifocal). Furthermore, the proposed formula exhibited some promising features in terms of robustness. This particular characteristic enables the new formula to cope with the variations in the axial length, the pre-operative anterior chamber depth as well as the keratometric readings of the corneal power; hence mitigating the impact of measurement accuracy for these parameters.

INTRODUCTION

Cataract surgery has consistently advanced technologically over the past 20 years in relation to surgical instruments, intraocular lens (IOL) designs as well as biometry techniques. Despite these advances, refractive surgical surprises still remain one of the most paramount concerns for surgeons, post IOL implantation.

In addition to various pre-operative measurements and surgical precautions, accurate calculation of the IOL power is the key factor to mitigate refractive surprises in cataract surgery. Modern formulae used to estimate the power of the IOL to be implanted are derived from thin lens geometrical optics, combined with various patient specific pre-operative measurements. However, the concept of thin lens geometrical optics requires the knowledge of the eventual post-operative position of the IOL behind the cornea. This position, also referred to as the effective lens position (ELP), is defined as the axial depth from the cornea to the optical center of the IOL. Since, the ELP is not measurable pre-operatively, modern formulae for IOL power calculation resort to various prediction techniques to estimate it. An accurate prediction of the ELP is considered to be crucial for the calculation of the required power for a given IOL. However, the ELP is prone to significant variations between different eyes. These variations may be attributed to various factors, including patient anatomical and physiological factors, IOL design as well as surgical techniques.

The most widely used formulae to estimate the IOL power, and which are currently the industry norms and are published in an implementable form, include the SRK/T formula¹, the Hoffer Q formula², the Holladay I formula³ and the Haigis formula⁴. The first three formulae used two pre-operative measurements, namely the axial length of the eye (L) and the average corneal power, denoted K – derived from of the average keratometric readings in diopters, which are combined with an additional single constant (A-constant for SRK/T, pACD - “Personalized” Anterior Chamber Depth - for Hoffer Q and SF - Surgeon Factor - for Holladay I) associated with each IOL type, and also referred to as the IOL constant, to estimate the required power for a given IOL. On the other hand, the Haigis formula⁴ used three pre-operative measurements (L, K and the pre-operative

measured anterior chamber depth - ACD), which are used to estimate the three constants of the formula (a_0 , a_1 , a_3) associated with each IOL type. Other well-known formulae for IOL power calculation include: (i) the Barrett formula⁵, which used L and K, combined with a single IOL constant (LF – Lens Factor), to estimate the IOL power; (ii) the Olsen formula⁶, which used five pre-operative measurements (namely, L, K, ACD, pre-operative refraction, and lens thickness) combined with a single IOL constant, to estimate the IOL power; (iii) the Barrett Universal II formula⁷ used five pre-operative measurements (namely, L, K, ACD, lens thickness, horizontal white-to-white) whereas the Holladay II formula used seven pre-operative measurements i.e. two more measurements in addition to those used in the Barrett Universal II, namely the pre-operative refraction and the patient age; however, since these formula have not been published, the details regarding their IOL power calculation and the IOL constant(s) estimation are not available. Note that other formulae for IOL power calculation have been introduced using various predictive models namely, neural networks^{8,9}. These formulae are not considered in this study due to their unavailability in an implementable form. The most well-known of these formulae is probably the Hill-RBF method⁹, which is purely data driven, and used artificial neural network to estimate directly the IOL power. In contrast with this method, the approach presented in this paper used an ensemble of regression models to provide a more accurate prediction of the ELP, thus it combines both geometric optics and machine learning.

The fundamental difference between modern formulae for IOL power calculation lies in the prediction model used to estimate the ELP. Basically, each formula used a single ad hoc regression model, generally devised from clinical experience and manipulation of retrospective empirical data, to predict the ELP. Hence, some formulae tend to outperform others depending on the type of pre-operative measurements and/or the cohort of patients, leading to the high disparity in the conclusions drawn in many analyses comparing formulae for IOL power calculations, e.g.,¹⁰⁻¹⁵. In view of the high sensitivity of the ELP, stemming from the complex relationship with its potential influencing factors, advanced prediction techniques would be the most natural approach for improving the prediction accuracy of the ELP.

Machine Learning Techniques (MLTs) are known to be the most advanced tools for detecting patterns in complex data and making predictions based on these discovered patterns¹⁶. MLTs have been widely used as prediction models in many research areas ranging from medical science to engineering. An ensemble method is a class of MLTs, which utilizes numerous prediction models to construct a predictor ensemble that outperforms any of the single models in the ensemble, in particular when there is a diversity in the outcomes yielded by the individual models.

This study proposed a new approach for IOL power estimation (called the MM formula), which used an ensemble of regression models to obtain a more accurate prediction of the ELP. Hence, as opposed to most of the modern IOL power calculation formulae, the MM formula has a very high number of IOL constants, which are optimally devised, stored and managed through the machine learning ensemble model used.

To assess the performance of the MM formula, three lens models, namely Monofocal Alcon AcrySof IQ SN60WF, Monofocal Lenstec Softec HDO and the Multifocal Zeiss AT LISA tri839 MP, have been considered and the results have been presented for various ranges of axial length. Furthermore, in contrast with most of the studies in the literature, which used a single test set to assess the performance of formulae for IOL power calculation, this study used the concept of cross-validation to carry out a rigorous assessment of the performance of the formulae. The cross-validation technique is the most effective framework to assess how a predictive model generalizes to independent datasets. It enables one to generate both training and test samples, which are sufficiently large and diverse in order to be representative. As such it addresses not only the problem of the small sample size of eyes with short and long axial length in most of the study cohorts but also enable to assess the formulae on a variety of training and test sets. Hence, it is the most appropriate approach to assess the performance of IOL calculation formulae, which are essentially predictive models.

METHODS

Background

The most commonly known IOL power calculations formulae can be categorized into two main approaches: the first one is purely based on a linear regression analysis of retrospective cases, whereas the second one is based on a geometrical optics solution. The first IOL power calculation formula, based on linear regression, is the SRK formula^{17, 18}, which regressed the required IOL power for emmetropia (P in diopters) on two pre-operative measurements, namely the axial length (L) in millimeters and the average keratometric readings ($K = (K_1 + K_2)/2$) in diopters, as follows:

$$P = A - 2.5L - 0.9K. \quad (1)$$

The above formula, which is a purely statistical solution for the IOL power calculation problem, suffers from classical linear regression shortcomings, including the regression to mean problem. In other words, the more common the values of the parameters L and K , the more accurate the predicted power P , while unusual values of K and L result in very poor estimates of the power P . To address this issue, various adjustments have been suggested to the model, including the personalization of the constant A , or the introduction of different values of the regression coefficient depending on the size of the axial length, L ¹⁹. Despite these improvements, nowadays geometrical optics-based formulae are preferred to the SRK formulae¹⁷⁻¹⁹.

The first IOL power calculation formulae, based on geometrical optics²⁰⁻²⁴, consist of different variants of the following vergence formula (2), derived from a two-lens system (eye-IOL) model of an operated eye after cataract removal and insertion of an IOL.

$$P = n_{vit} / (L - d) - n_{aq} / [(n_{aq}/P_c) - d], \quad (2)$$

where

- P is the required IOL power for emmetropia (in diopters);
- n_{aq} is the refractive index of the aqueous humor and n_{vit} is the refractive index of the vitreous humor;
- P_c is the average corneal power (in diopters) and is a function of the average

keratometric readings $K = (K_1 + K_2)/2$;

- L is the axial depth from the corneal apex to the retina, also known as the axial length of the eye;
- d is the axial depth from the corneal apex to the optical center of the IOL, also known as effective/estimated lens position (ELP) or the post-operative Anterior Chamber Depth (ACD).

Initially, all the variants of the formula (2) used a constant value for the ELP, d, for each IOL type, which is derived using the parameters (K and L) of an average eye. This constant value of the ELP is also known as the ACD constant. In the early eighties new studies observed some inter-subject variation in the value of the ELP, and in particular the available formulae proved to be deficient for eyes with unusually short or long axial lengths. The variation in the ELP can be attributed to various factors, including:

- Patient-specific anatomical and physiological factors such as ocular dimensions, age, gender, and ethnicity;
- IOL design-specific configuration details such as the optic shape factor, the compressibility of materials, the haptic angulation;
- Surgeon as well as surgical instrument and technique specific idiosyncrasies such as
 - the IOL implantation location e.g., angle-supported, iris-supported, sulcus-supported, or in-the-bag;
 - the manipulation of the IOL during implantation;
 - the type, the size, and the structure of the incision;
 - as well as the size, the construction (manual or automated), and the configuration of the capsulorhexis.

In the late eighties, new formulae using a patient-specific modified ELP value, which considered biometry values specific to an individual patient for a particular IOL, emerged. These new formulae are referred to as modern IOL formulae¹⁻⁶.

Overview of modern formulae for IOL power estimation

Modern formulae for IOL power estimation, such as SRK/T¹, Hoffer Q², Holladay I³ and Haigis⁴ are based on the vergence formula (3) derived from a three-lens system (spectacle-eye-IOL), and they differ from each other merely in the approach used to estimate the effective lens position, d.

$$P = n_{vit} / (L - d) - n_{aq} / [(n_{aq} / (P_c + R_x / (1 - b R_x))) - d], \quad (3)$$

where

- R_x is the desired postoperative refraction (in diopters) or the refraction of the spectacle;
- P is the required IOL power for the desired postoperative refraction (in diopters);
- b is the vertex distance ($\sim 12\text{mm}$);
- n_{aq} , n_{vit} , P_c , L and d are as defined in equation (2).

The ELP is very difficult to predict and its estimation is considered critical for an accurate prediction of the required IOL power for a given lens. The main idea behind modern formulae, such as¹⁻⁶, is to improve the IOL power accuracy by estimating the ELP, d, through a regression analysis on retrospective cases. For this methodology to be effective, consistency is required throughout the entire process, including the surgical technique used, the biometry instruments as well as the design and manufacturing of the IOL.

The main adjustment to the geometrical optics formula (3), by the modern formulae, was the estimation of the ELP as a function of pre-operative measurements, such as the axial length in millimeters (L), corneal power in diopters, derived from the keratometric readings (K_1 and K_2), and the anterior chamber depth (ACD).

The most commonly used and well-known modern formulae for IOL power calculation include SRK/T¹, Hoffer Q², Holladay I³ and Haigis⁴. These formulae were published during the 1990s, and are currently the industry norm.

- The SRK/T formula¹ estimates the ELP as the sum of a scaled constant, denoted

A_{constant} , and a function of the average keratometric reading, K , and the axial length, L , i.e.,

$$\text{ELP}_{\text{SRKT}} = 0.62467 \times A_{\text{constant}} + f(K, L).$$

- The Hoffer Q formula² estimates the ELP as a sum of an ad hoc constant, called the "personalized" ACD and denoted $p\text{ACD}$, and a function of K and L . In other words,

$$\text{ELP}_{\text{HofferQ}} = p\text{ACD} + f(K, L).$$

- The Holladay I formula³ estimates the ELP as a sum of an ad hoc constant, called the surgeon factor and denoted SF , and a function of K and L , i.e.,

$$\text{ELP}_{\text{HolladayI}} = \text{SF} + f(K, L).$$

- The Haigis formula⁴ went one step further, by including the pre-operative ACD in the estimation of the ELP, as follows:

$$\text{ELP}_{\text{Haigis}} = a_0 + a_1 \text{ACD}_{\text{Pre-operative}} + a_2 L.$$

Note that the pre-operative keratometric readings K_1 and K_2 are implicitly used, in the ELP for the Haigis formula, through the process for estimating the constants (a_0 , a_1 , a_2).

The constants A_{constant} , $p\text{ACD}$, SF and (a_0 , a_1 , a_2) are derived from historical data of retrospective cases and are expected to capture the complex relationship for each IOL/surgeon pair.

A new formula using an ensemble-based model to estimate the ELP

Although the main aim of modern formulae is to “personalize” the IOL power calculation through linear regression models for predicting the ELP (where the parameters of the models are the A -constant for SRKT, the $p\text{ACD}$ for Hoffer Q, the SF for Holladay, and the constants a_0 , a_1 , a_2 for Haigis, respectively), in practice the parameters of the models (i.e. the lens constants) are initially made available by the lens manufacturer and subsequently optimized and published on some databases such as ULIB²⁵, using data from various surgeons or a selected number of surgeons. Hence, surgeons who did not contribute to the data used to estimate these constants or who used

different surgical techniques could be exposed to refractive surprises if they used the published IOL constants. Furthermore, it is well recognized that current modern formulae still demonstrate significant errors in the predicted IOL power in more unusual cases where there are extreme values of either axial length or corneal power²⁶. For example, in short eyes with flat cornea, and long eyes with a steep cornea, the discrepancy can be up to $\pm 2D$ and $\pm 1.3D$, respectively.

This newly developed MM formula, which leverage both thin lens geometric optics and machine learning, goes a step further in an attempt to reduce the effects of these discrepancies, by introducing an ensemble-based approach to estimate the effective lens position, d , for each lens model using four pre-operative variables as follows:

$$ELP_{MM} = f(ACD_{Pre-operative}, K_1, K_2, L), \quad (4)$$

where

- $ACD_{Pre-operative}$ is the pre-operative anterior chamber depth;
- K_1 and K_2 are the keratometric readings of the corneal power;
- f is a high-dimensional function, relating the effective lens positions to the four predictor variables, derived through a training of a machine learning ensemble-based model.

Using the above four pre-operative variables to estimate the ELP, d , for each lens model, the new formula attempts to capture both surgeon as well as surgical instrument and technique specific idiosyncrasies. Furthermore, the four variables, used in (4), have been identified through a feature selection approach, and are deemed to be the most influential parameters in the prediction of the ELP. In contrast with the single linear regression model, which is commonly used to estimate the ELP^{1-6} , machine learning is the most natural tool able to capture the complex relationship between the ELP, the post-operative patient data, the surgeon as well as features specific to surgical instruments and techniques for each lens model. Using a machine learning framework, the model, proposed to predict the ELP and calculate the IOL power, is not only surgeon-specific but is also self-sustained since the more the historical data available the more “personalized”

and accurate the IOL power estimation.

The fundamental difference between the MM formula and the four most commonly used formulae can be summarized as follows. For a given lens model and some given keratometric readings (K_1 and K_2), the SRK/T and Hoffer Q formulae consider a quasi-linear relationship between the post-operative ACD (i.e., ELP) and the axial length, whereas the Holladay I formula assumes a piecewise linear relationship between the post-operative ACD (ELP) and the axial length, regardless of any other measurements including the pre-operative ACD, as illustrated in Figure 1 (top). On the other hand, the Haigis formula assumes that the post-operative ACD (ELP) depends linearly on the pre-operative measured ACD and the axial length while the MM formula assumes a non-linear relationship between the post-operative ACD (ELP) and the following variables: the pre-operative ACD and the axial length, as illustrated in Figure 1 (bottom). In contrast with most of the modern formulae for IOL power calculation, which used one or three IOL constants, the MM formula has a very high number of IOL constants, which are optimized, stored and managed via the ensemble model used.

RESULTS

Participants

The participants consist of a cohort of 681 patients who had implantation of monofocal or multifocal intraocular lenses (IOLs) from Cathedral Eye Clinic, Belfast. More specifically, 265 eyes, 256 eyes and 160 eyes were implanted with Monofocal Alcon AcrySofIQ SN60WF, Monofocal Lenstec Softec HDO and Multifocal Zeiss AT LISA tri839 MP, respectively. Patients were thoroughly assessed and informed of the risks of the procedure and all patients gave their informed consent for their anonymized data to be used for audit and research purposes. The Cathedral Eye Clinic Ethics Committee approved this study as an audit study and gave the study the following reference number: CECREC18–02. This research study adhered to the tenets of the Declaration of

Helsinki. The patients received multifocal IOLs following either refractive lens exchange (RLE) or cataract extraction surgery. The summary statistics of the patients are presented in Table 1a and Table 1b. The post-operative data used for this study included manifest refraction obtained 3 months and 6 months post-operatively, and included only one eye per patient.

To carry out a rigorous comparison between the MM formula and the four most commonly used formulae, namely SRK/T, Hoffer Q, Holladay I and Haigis, we used the same data set to train the ensemble model for the MM formula and optimize the IOL constants for the four formulae, namely the A-constant for SRK/T formula, the personalized anterior chamber depth – pACD - for Hoffer Q formula, the surgeon factor – SF – for Holladay I formula and the three regression parameters (a_0 , a_1 , a_2) for Haigis formula.

Most of the studies, comparing formulae for IOL power calculation, used a holdout method, which consists of splitting the data into two sets, namely the training set and the test set, respectively. The training data set referred to patients' data used to optimize the parameters of the formulae (e.g., A-constant for SRK/T, pACD for Hoffer Q, SF for Holladay I, the three constants (a_0 , a_1 , a_2) for Haigis) whereas the test set, referred to patients' data not included in the optimization process. The prediction errors made using the test set are used to evaluate the performance of the formula. However, such an evaluation process may have a high variance, since it depends heavily on the nature of the data in both the training and the test sets. Therefore, this approach of comparing formulae for IOL power calculation, is prone to bias since it may differ significantly depending on the data, which happened to be in the test set.

One way to address the aforementioned limitations of the handout method is to use the cross-validation technique, also known as the k-fold cross-validation. In this approach, the data set is split into k subsets, and the holdout method is applied k times as follows: at each step, (k - 1) subsets are combined to form the training set whereas the remaining dataset is used as the test set. Then, the prediction errors made during the test are given by the accumulated errors from the k trials. Another variant of the k-fold cross-validation method consists of randomly splitting the data into training and test sets (k-fold) and the

handout method is applied at each iteration. Such an approach, also known as the Monte-Carlo cross-validation, and illustrated in Figure 2, has been used in this study as it enables to assess how well an IOL power calculation formula will generalize to new data.

Summary statistics of the optimized IOL constants, for the four formulae and the three type of lenses, obtained from the Monte-Carlo k-fold cross-validation process (with $k=100$), are presented in Table 2.

To assess the performance of the MM formula, three lens models were considered, namely Monofocal Alcon AcrySof IQ SN60WF, Monofocal Lenstec Softec HDO and Multifocal Zeiss AT LISA tri839 MP. The performance of the MM against the other four formulae, with respect to the axial length, was also presented, using the following categorization: short eyes (i.e., Axial Length < 22mm), medium eyes (i.e., $22\text{mm} \leq \text{Axial Length} \leq 24.5\text{mm}$), long medium eyes (i.e., $24.5\text{mm} < \text{Axial Length} \leq 26\text{mm}$) and long eyes (i.e., Axial Length > 26mm). Tables 3a, 3b, 4a, 4b, 5a and 5b present the summary statistics of the cross-validation prediction results for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for long eyes, long medium eyes, short eyes, medium eyes and all eyes, respectively. These results were obtained using the optimized IOL constant for the formulae SRK/T, Hoffer Q, Holladay I and Haigis, presented in Table 2, and the same data used to optimize these IOL constants were used to train the MM formula and store the corresponding ensemble model.

Statistical Analysis

The prediction error, for a given patient, is the difference between the achieved post-operative refraction and the refraction predicted by the formulae given the power of the inserted IOL.

The normality of the prediction errors as well as the absolute prediction errors for each of the formula and for each eye type are assessed using the Shapiro-Wilk normality test, which suggested that none is normally distributed ($p\text{-value} < 0.001$ in all the cases). Therefore, non-parametric tests, with the significance level set to 0.05, are used for the statistical analysis. Wilcoxon signed-rank (1 sample) test was used to assess whereas the median

values for both the prediction errors and the absolute prediction errors are equal to zero for each of the formula and for each eye type. The results for the median of the prediction errors are presented in Tables 3c, 4c, 5c. The results for the median of the absolute prediction errors suggested that in all cases the median value is statistically different from zero (p -value <0.001 in all case).

The Friedman test was used to compare the median absolute prediction error across the five formulae for each eye type. The results suggested that in all cases there was a statistically difference across the formulae. Then, the pairwise comparison of the median absolute prediction error (MM against each of the four other formulae, and for each eye type) was performed using the Wilcoxon signed-rank (paired samples). The corresponding results as well as those of the Friedman test are presented in Tables 3d, 4d, 5d.

The Cochran's Q test was used to compare the prediction accuracy across the five formulae for each eye type. The prediction accuracy is defined by the percentage of eyes with the prediction error within $\pm 0.5D$, $\pm 1.0D$, and $\pm 1.5D$, respectively. The corresponding results are presented in Tables 3e, 4e, 5e. The pairwise comparison of the prediction accuracy (MM against each of the four other formulae, and for each eye type) was performed using the McNemar test. The corresponding results are presented in Tables 3f, 4f, 5f.

The implementation of the formulae as well the statistical analyses were carried out using Python 3.7.6 (python.org)

DISCUSSION

For the IOL model Monofocal Alcon AcrySof IQ SN60WF, the results in Tables 3a-3f, show that, overall, the MM formula outperforms the other four formulae (namely, SRK/T, Hoffer Q, Holladay I, Haigis). For long eyes, the MM formula and the Haigis formula outperformed the other formulae in terms of prediction accuracy, i.e., the percentage of eyes with the prediction error within $\pm 0.5D$, $\pm 1.0D$, and $\pm 1.5D$, respectively. On the other hand, the MM formula had the lowest median absolute

prediction error. For long medium eyes, the MM formula was the second best behind the Holladay I formula in terms of prediction accuracy. However, the MM formula has the lowest median absolute prediction error. For short eyes, overall, the MM formula was the second best in terms of prediction accuracy, but with the lowest median absolute prediction error. For medium and all eyes, overall, the MM formula outperformed the other formulae with the higher prediction accuracy and the lowest median absolute prediction error.

For the IOL model Monofocal Lenstec Softec HDO, the results in Tables 4a-4f, show that, overall, the MM formula performed better compared to the other formulae. For long and long medium eyes, MM formula achieved the highest performance in terms of prediction accuracy and low median absolute prediction error. For short eyes, the MM formula was outperformed by the Haigis formula in terms of prediction accuracy whereas the Hoffer Q formula has the lowest median absolute prediction error. For medium and all eyes, overall, the MM formula outperformed the other formulae with the higher prediction accuracy and the lowest median absolute prediction error.

For the IOL model Multifocal ZEISS AT LISA tri839 MP, the results in Tables 5a-5f, show that, overall, the MM formula outperformed the formulae. For long, long medium and short eyes, MM formula achieved the highest performance in terms of prediction accuracy and it has the lowest median absolute prediction error for long and short eyes. For medium and all eyes, overall, the MM performed similarly to the best performing formula.

Overall, the results reported in this study, which are comparable to those presented in the literature^{9-11, 13, 14, 26}, show that the MM formula outperforms the four commonly used modern formulae in terms of median absolute error as well as prediction accuracy, in particular, in the range ± 0.5 D and ± 1 D for various ranges of axial length. This robustness of the MM formulae enables the method to cope with the variation of the axial length (L), the pre-operative ACD and keratometric readings (K_1 and K_2), hence mitigating the impact of measurement errors for these parameters. Using all lens models,

for both average eyes as well as more challenging eyes (namely, short eyes, long medium eyes and long eyes), the results for post-refractive outcomes for the MM formula are overall superior compared to the other four formulae, although all the formulae exceeded the benchmark of 85% of refraction within $\pm 1D$ of prediction recommended by Gale et al.²⁷, except some cases for the SRK/T formulae.

However, the MM formula has some limitations, which are inherent to machine learning techniques. Although ML techniques have demonstrated many successful applications in various fields, they have some fundamental limitations, which could hinder their effectiveness in some real-world scenarios. In particular, ML techniques required a large amount of structured training dataset in order to learn patterns effectively. Furthermore, ML techniques encode correlation and not causation and the accuracy of their prediction revolve around the quality of the data.

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Author contributions

SM and JEM designed the concept of this study, collected the data, interpret the results and write up the manuscript. SM implemented the formulae and conducted the statistical analysis.

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Competing interests

Neither author has a financial or proprietary interest in any material mentioned.

Table 1a: Summary of demographics and biometry. AL = Axial Length; K1 = Flat Keratometry readings; K2 = Steep Keratometry readings; SD= Standard Deviation.

Demographics and biometry							
Lens model	Sample Size (Eyes) One eye per patient	Gender % Female %Male	Age (in years) Mean±SD Median Range	AL (in mm) Mean±SD Median Range	K1 (in D) Mean±SD Median Range	K2 (in D) Mean±SD Median Range	ACD (in mm) Mean±SD Median Range

Monofocal Alcon AcrySofIQ SN60WF	265	52% 48%	66±10 67 36 - 90	23.80±1.53 23.49 20.50 -29.63	43.06±1.83 43.19 35.56 - 47.20	43.84±1.94 43.83 36.06 - 48.70	3.24±0.41 3.00 2.17 - 4.80
Monofocal Lenstec Softec HDO	256	50% 50%	71±10 73 45 – 94	23.59±1.42 23.46 20.06 -29.37	43.25±1.65 43.38 35.70 - 46.88	44.03±1.69 44.12 36.20 - 48.49	3.21±0.39 3.00 2.33 - 4.22
Multifocal ZEISS AT LISA tri839 MP	160	60% 40%	58±7 58 44 – 92	23.55±1.32 23.42 20.48 -27.85	42.86±1.50 42.72 38.38 - 47.34	43.50±1.54 43.47 38.96 - 47.77	3.22±0.35 3.00 2.37 - 4.22

Table 1b: Distribution of eyes implanted with the three lens models by axial length (AL).

Distribution of eyes by axial length (AL)						
Lens model	Sample Size (Eyes) One eye per Patient	Long eyes AL>26mm	Long medium eyes 24.5mm < AL and AL<=26mm	Medium eyes 22mm<= AL and AL<=24.5mm	Short eyes AL<22mm	All eyes
Monofocal		11%	18%	62%	9%	100%

Alcon AcrySofIQ SN60WF	265					
Monofocal LensteC Softec HDO	256	5%	13%	72%	10%	100%
Multifocal ZEISS AT LISA tri839 MP	160	6%	10%	77%	7%	100%

Table 2: Summary statistics of the optimized IOL constants estimated from the training sets and used for the test sets during the cross-validation process. Note that at each iteration of the cross-validation, new optimized IOL constants are generated. SD=Standard Deviation.

	Summary statistics - Optimized IOL constants			
IOL model	IOL constants	Mean$\pm$SD	Median	Range
Monofocal Alcon AcrySofIQ SN60WF (Bootstrap sample size: 2486)	SRK/T (A-Constant)	118.861 $\pm$ 0.021	118.87	118.808 to 118.919
	Hoffer Q (pACD)	5.738 $\pm$ 0.007	5.736	5.722 to 5.764
	Holladay I (SF)	2.065 $\pm$ 0.01	2.066	2.037 to 2.098
	Haigis (a ₀)	-0.966 $\pm$ 0.147	-0.952	-1.322 to -0.559

	Haigis (a_1)	0.293±0.023	0.293	0.24 to 0.379
	Haigis (a_2)	0.222±0.008	0.222	0.2 to 0.238
Monofocal Lenstec Softec HDO (Bootstrap sample size: 2372)	SRK/T (A-Constant)	117.976±0.018	117.979	117.902 to 118.018
	Hoffer Q (pACD)	5.35±0.008	5.35	5.328 to 5.377
	Holladay I (SF)	1.614±0.008	1.615	1.595 to 1.633
	Haigis (a_0)	-1.207±0.168	-1.186	-1.811 to -0.758
	Haigis (a_1)	0.252±0.028	0.254	0.192 to 0.315
	Haigis (a_2)	0.22±0.009	0.22	0.194 to 0.249
Multifocal ZEISS AT LISA tri839 MP (Bootstrap sample size: 1100)	SRK/T (A-Constant)	118.73±0.02	118.727	118.665 to 118.785
	Hoffer Q (pACD)	5.639±0.008	5.64	5.618 to 5.659
	Holladay I (SF)	1.97±0.013	1.971	1.934 to 1.992
	Haigis (a_0)	-0.146±0.299	-0.171	-0.968 to 0.687
	Haigis (a_1)	0.272±0.05	0.28	0.13 to 0.442
	Haigis (a_2)	0.184±0.016	0.185	0.129 to 0.224

Table 3a: Summary statistics of the cross-validation results for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for long, long medium and short eyes. % Rx: Percentage of eyes within a given range of prediction error; MPE: Mean prediction error; MedPE: Median prediction error; Range PE: Range of the prediction error; MAPE: Mean absolute prediction error; MedAPE: Median absolute prediction error; SD: Standard Deviation.

Monofocal Alcon AcrySof IQ SN60WF					
Summary statistics of cross-validation results for long, long medium and short eyes					
Long eyes (Bootstrap sample size: 282)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within ±0.5D	23.40%	40.80%	39.00%	62.40% ^a	64.20% ^a
% Rx within ±1.0D	51.80%	80.90%	72.70%	92.20% ^a	92.20% ^a

% Rx within $\pm 1.5D$	79.10%	92.20%	88.30%	100.00% ^a	100.00% ^a
MPE $\pm$ SD	-0.89 $\pm$ 0.86	0.59 $\pm$ 0.55	0.74 $\pm$ 0.63	0.26 $\pm$ 0.52	0.16 $\pm$ 0.51
MedPE	-0.92	0.6	0.7	0.19	0.03
Range PE	-2.51 to 1.13	-0.28 to 1.96	-0.27 to 2.35	-0.63 to 1.49	-0.65 to 1.33
MAPE $\pm$ SD	1.05 $\pm$ 0.67	0.66 $\pm$ 0.47	0.78 $\pm$ 0.58	0.47 $\pm$ 0.36	0.41 $\pm$ 0.34
MedAPE	0.97	0.6	0.7	0.4	0.35
Long medium eyes (Bootstrap sample size: 452)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	19.90%	80.10% ^a	87.60%	77.70%	82.10% ^a
% Rx within $\pm 1.0D$	32.30%	95.40%	100.00% ^a	100.00% ^a	100.00% ^a
% Rx within $\pm 1.5D$	50.20%	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
MPE $\pm$ SD	-1.31 $\pm$ 0.99	0.22 $\pm$ 0.38	-0.04 $\pm$ 0.35	-0.01 $\pm$ 0.39	-0.09 $\pm$ 0.35
MedPE	-1.49	0.26	-0.14	0 ^b	-0.07
Range PE	-2.99 to 0.83	-0.61 to 1.04	-0.7 to 0.79	-0.8 to 0.94	-0.87 to 0.79
MAPE $\pm$ SD	1.41 $\pm$ 0.85	0.36 $\pm$ 0.25	0.3 $\pm$ 0.19	0.3 $\pm$ 0.25	0.28 $\pm$ 0.23
MedAPE	1.49	0.38	0.27	0.25	0.21
Short eyes (Bootstrap sample size:218)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	65.60%	59.60% ^a	66.10%	60.60%	56.90% ^a
% Rx within $\pm 1.0D$	89.00%	100.00%	95.40% ^a	89.00%	93.60% ^a
% Rx within $\pm 1.5D$	97.70% ^a	100.00% ^a	100.00% ^a	100.00% ^a	97.70% ^a
MPE $\pm$ SD	0.08 $\pm$ 0.6	-0.22 $\pm$ 0.46	-0.22 $\pm$ 0.49	0.08 $\pm$ 0.55	0.17 $\pm$ 0.58
MedPE	0.15	-0.3	-0.27	-0.03 ^b	0.12
Range PE	-1.18 to 1.59	-0.78 to 0.94	-0.99 to 1.04	-0.86 to 1.42	-0.91 to 1.54
MAPE $\pm$ SD	0.44 $\pm$ 0.41	0.45 $\pm$ 0.24	0.46 $\pm$ 0.28	0.42 $\pm$ 0.36	0.45 $\pm$ 0.4
MedAPE	0.28 ^a	0.4	0.39	0.42	0.28 ^a
^a No statistically significant difference at level 0.05					
^b No statistically significant difference from zero at level 0.05					

Table 3b: Summary statistics of the cross-validation results for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for medium and all eyes. % Rx: Percentage of eyes within a given range of prediction error; MPE: Mean prediction error; MedPE: Median prediction error; Range PE: Range of the prediction error; MAPE: Mean absolute prediction error; MedAPE: Median absolute prediction error; SD: Standard Deviation.

Monofocal Alcon AcrySof IQ SN60WF					
Summary statistics of cross-validation results for medium and all eyes					
Medium eyes (Bootstrap sample size: 1534)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	68.80%	74.30% ^a	72.40%	72.60%	75.70% ^a
% Rx within $\pm 1.0D$	94.10%	93.70%	92.90%	96.10% ^a	96.40% ^a
% Rx within $\pm 1.5D$	97.20% ^a	97.80% ^a	98.00% ^a	98.00% ^a	97.80% ^a

MPE $\pm$ SD	0.05 $\pm$ 0.55	-0.06 $\pm$ 0.54	-0.17 $\pm$ 0.52	-0.05 $\pm$ 0.52	-0.03 $\pm$ 0.52
MedPE	0.04	-0.03	-0.15	-0.03	-0.01 ^b
Range PE	-2.1 to 1.89	-2.35 to 1.84	-2.23 to 1.73	-2.51 to 1.65	-2.3 to 1.67
MAPE $\pm$ SD	0.42 $\pm$ 0.37	0.39 $\pm$ 0.38	0.4 $\pm$ 0.37	0.38 $\pm$ 0.36	0.37 $\pm$ 0.36
MedAPE	0.35	0.28	0.29	0.28	0.27
All eyes (Bootstrap sample size: 2486)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm$ 0.5D	54.50%	70.20%	70.80%	71.30%	73.90%
% Rx within $\pm$ 1.0D	77.60%	93.10%	92.10%	95.70%	96.30%
% Rx within $\pm$ 1.5D	86.60%	97.80%	97.50%	98.80%	98.40%
MPE $\pm$ SD	-0.3 $\pm$ 0.89	0.05 $\pm$ 0.56	-0.05 $\pm$ 0.58	0.01 $\pm$ 0.52	-0.0 $\pm$ 0.5
MedPE	-0.06	0.05	-0.12	0 ^b	0 ^b
Range PE	-2.99 to 1.89	-2.35 to 1.96	-2.23 to 2.35	-2.51 to 1.65	-2.3 to 1.67
MAPE $\pm$ SD	0.67 $\pm$ 0.66	0.42 $\pm$ 0.37	0.43 $\pm$ 0.39	0.38 $\pm$ 0.35	0.36 $\pm$ 0.35
MedAPE	0.45	0.33	0.31	0.29	0.27
^a No statistically significant difference at level 0.05					
^b No statistically significant difference from zero at level 0.05					

Table 3c: Comparison of the median prediction error to zero for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) and for the different types of eyes (long, long medium, medium, short and all eyes), using Wilcoxon (1 sample) signed rank test at a statistical significance level of 5%.

Monofocal Alcon AcrySofIQ SN60WF					
Comparison of the median prediction error to zero					
p-values for Wilcoxon (1 sample) signed rank test					
	SRK/T	Hoffer Q	Holladay I	Haigis	MM
Long eyes	< 0.001	< 0.001	< 0.001	< 0.001	0.4302 ^a
Long medium eyes	< 0.001	< 0.001	0.001	0.7507 ^a	< 0.001
Medium eyes	< 0.001	0.0007	< 0.001	0.0011	0.0915 ^a
Short eyes	0.0043	< 0.001	< 0.001	0.4602 ^a	< 0.001
All eyes	< 0.001	< 0.001	< 0.001	0.8405 ^a	0.5777 ^a

^a No statistically significant difference from zero at level 0.05

Table 3d: Top - Comparison of the median absolute prediction errors of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for the different types of eyes (long, long medium, medium, short and all eyes), using the Friedman test at a statistical significance level of 5%.

Bottom – Pairwise comparison of the median absolute prediction errors between the MM formula and each of the other four formulae (SRK/T, Hoffer Q, Holladay I and Haigis) for the different types of eyes (long, long medium, medium, short and all eyes), using the Wilcoxon test at a statistical significance level of 5%.

Monofocal Alcon AcrySofIQ SN60WF					
Comparison of the median absolute prediction error for the five formulae					
p-values for Friedman test					
	Long eyes	Long medium eye	Medium eyes	Short eyes	All eyes
p-Values	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Pairwise comparison of the median absolute prediction error					
p-values for Wilcoxon (2 paired samples) signed rank test					
Formulae pair	Long eyes	Long medium Eye	Medium eyes	Short eyes	All eyes
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b	0.901 ^a	< 0.001 ^b
MM vs Hoffer Q	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Holladay I	< 0.001 ^b	0.007 ^b	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Haigis	< 0.001 ^b	0.001 ^b	< 0.001 ^b	0.001 ^b	< 0.001 ^b
^a No statistically significant difference at level 0.05					
^b MM formula underperformed at significance level 0.05					

Table 3e: Comparison of the prediction accuracy (i.e., the percentage of eyes within a given range of prediction error) of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for the different types of eyes (long, long medium, medium, short and all eyes), using the Cochran Q test, at a statistical significance level of 5%.

Monofocal Alcon AcrySofIQ SN60WF			
Comparison of the prediction accuracy for the five formulae			
p-values for Cochran's Q test			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
Long eyes	< 0.001	< 0.001	< 0.001
Long medium eyes	< 0.001	< 0.001	< 0.001
Medium eyes	< 0.001	< 0.001	0.063 ^a
Short eyes	< 0.001	< 0.001	0.732 ^a
All eyes	< 0.001	< 0.001	< 0.001
^a No statistically significant difference at level 0.05			

Table 3f: Pairwise comparison of the prediction accuracy (i.e., the percentage of eyes within a given range of prediction error) between the MM formula and each of the other four formulae (SRK/T, Hoffer Q, Holladay I and Haigis) for the different types of eyes (long, long medium, medium, short and all eyes), using the McNemar test at a statistical significance level of 5%.

Monofocal Alcon AcrySof IQ SN60WF			
Pairwise comparison of the prediction accuracy			
p-values for McNemar test			
Long eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Holladay I	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Haigis	0.603 ^a	0.999 ^a	0.999 ^a
Long medium eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b

MM vs Hoffer Q	0.435 ^a	< 0.001 ^b	0.999 ^a
MM vs Holladay I	0.001 ^c	0.999 ^a	0.999 ^a
MM vs Haigis	< 0.001 ^b	0.999 ^a	0.999 ^a
Medium eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	0.523 ^a
MM vs Hoffer Q	0.077 ^a	< 0.001 ^b	0.999 ^a
MM vs Holladay I	< 0.001 ^b	< 0.001 ^b	0.134 ^a
MM vs Haigis	< 0.001 ^b	0.441 ^a	0.134 ^a
Short eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^c	0.004 ^b	0.752 ^a
MM vs Hoffer Q	0.581 ^a	0.001 ^c	0.074 ^a
MM vs Holladay I	0.019 ^c	0.134 ^a	0.074 ^a
MM vs Haigis	0.013 ^c	0.004 ^b	0.074 ^a
All eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	< 0.001 ^b	< 0.001 ^b	0.01 ^b
MM vs Holladay I	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Haigis	< 0.001 ^b	0.021 ^b	0.008 ^c
^a No statistically significant difference at level 0.05			
^b MM formula outperformed at significance level 0.05			
^c MM formula underperformed at significance level 0.05			

Table 4a Summary statistics of the cross-validation results for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for long, long medium and short eyes. % Rx: Percentage of eyes within a given range of prediction error; MPE: Mean prediction error; MedPE: Median prediction error; Range PE: Range of the prediction error; MAPE: Mean absolute prediction error; MedAPE: Median absolute prediction error; SD: Standard Deviation.

Monofocal Lenstec Softec HDO					
Summary statistics of cross-validation results for long, long medium and short eyes					
Long eyes (Bootstrap sample size: 107)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	38.30%	37.40%	41.10%	67.30%	72.90%
% Rx within $\pm 1.0D$	74.80%	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
% Rx within $\pm 1.5D$	81.30%	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
MPE $\pm$ SD	-0.79 $\pm$ 0.69	0.36 $\pm$ 0.53	0.46 $\pm$ 0.44	0.05 $\pm$ 0.49	0.01 $\pm$ 0.44
MedPE	-0.52	0.41	0.64	0.21	0.17 ^b
Range PE	-2.34 to 0.01	-0.74 to 0.99	-0.51 to 0.94	-0.97 to 0.66	-0.96 to 0.56
MAPE $\pm$ SD	0.79 $\pm$ 0.69	0.6 $\pm$ 0.23	0.61 $\pm$ 0.2	0.41 $\pm$ 0.28	0.36 $\pm$ 0.25

MedAPE	0.52	0.69	0.64	0.36	0.27
Long medium eyes (Bootstrap sample size:306)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	24.50%	69.60%	83.70% ^a	82.00% ^a	81.40% ^a
% Rx within $\pm 1.0D$	43.50%	97.40% ^a	98.00% ^a	98.70% ^a	98.00% ^a
% Rx within $\pm 1.5D$	63.10%	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
MPE $\pm$ SD	-1.08 $\pm$ 0.84	0.23 $\pm$ 0.41	0.07 $\pm$ 0.43	0.05 $\pm$ 0.39	0.07 $\pm$ 0.41
MedPE	-1.33	0.23	-0.04 ^b	0.01	0 ^b
Range PE	-2.43 to 0.73	-0.78 to 1.11	-0.63 to 1.41	-1.03 to 1.01	-0.91 to 1.3
MAPE $\pm$ SD	1.18 $\pm$ 0.7	0.38 $\pm$ 0.29	0.34 $\pm$ 0.27	0.33 $\pm$ 0.23	0.32 $\pm$ 0.27
MedAPE	1.33	0.28	0.31	0.3	0.25
Short eyes (Bootstrap sample size: 228)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	41.20%	55.70% ^a	43.40%	53.10% ^a	53.10% ^a
% Rx within $\pm 1.0D$	64.00%	85.50% ^a	86.00% ^a	93.90%	84.20% ^a
% Rx within $\pm 1.5D$	88.60%	100.00%	100.00%	100.00%	97.40%
MPE $\pm$ SD	0.54 $\pm$ 0.8	-0.28 $\pm$ 0.55	-0.09 $\pm$ 0.62	0.09 $\pm$ 0.62	0.08 $\pm$ 0.69
MedPE	0.52	-0.29	-0.02 ^b	0.07 ^b	-0.06 ^b
Range PE	-0.74 to 2.14	-1.23 to 0.79	-1.13 to 1.13	-1.0 to 1.42	-1.11 to 1.7
MAPE $\pm$ SD	0.77 $\pm$ 0.58	0.52 $\pm$ 0.34	0.52 $\pm$ 0.36	0.52 $\pm$ 0.35	0.59 $\pm$ 0.36
MedAPE	0.63	0.42	0.54	0.43 ^a	0.44 ^a
^a No statistically significant difference at level 0.05					
^b No statistically significant difference from zero at level 0.05					

Table 4b: Summary statistics of the cross-validation results for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for medium and all eyes. % Rx: Percentage of eyes within a given range of prediction error; MPE: Mean prediction error; MedPE: Median prediction error; Range PE: Range of the prediction error; MAPE: Mean absolute prediction error; MedAPE: Median absolute prediction error; SD: Standard Deviation.

Monofocal Lenstec Softec HDO					
Summary statistics of cross-validation results for medium and all eyes					
Medium eyes (Bootstrap sample size: 1731)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	69.80%	71.20%	74.60%	70.40%	78.70%
% Rx within $\pm 1.0D$	93.60%	95.50%	95.60%	96.00%	96.90%
% Rx within $\pm 1.5D$	99.70% ^a	99.70% ^a	99.50% ^a	99.70% ^a	99.70% ^a
MPE $\pm$ SD	0.24 $\pm$ 0.46	-0.02 $\pm$ 0.49	-0.07 $\pm$ 0.45	-0.02 $\pm$ 0.48	-0.02 $\pm$ 0.45
MedPE	0.23	-0.02 ^b	-0.06	-0.02 ^b	-0.03 ^b
Range PE	-1.64 to 1.39	-2.32 to 1.37	-2.19 to 1.21	-2.54 to 1.28	-2.29 to 1.21
MAPE $\pm$ SD	0.41 $\pm$ 0.31	0.37 $\pm$ 0.32	0.34 $\pm$ 0.3	0.36 $\pm$ 0.31	0.34 $\pm$ 0.3

MedAPE	0.35	0.27 ^a	0.27 ^a	0.26 ^a	0.26 ^a
All eyes (Bootstrap sample size: 2372)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	59.80%	68.00%	71.20%	70.10%	76.30%
% Rx within $\pm 1.0D$	83.50%	95.00%	95.20%	96.30% ^a	96.00% ^a
% Rx within $\pm 1.5D$	93.10%	99.80%	99.70% ^a	99.80%	99.50% ^a
MPE $\pm$ SD	0.05 $\pm$ 0.76	0.0 $\pm$ 0.51	-0.03 $\pm$ 0.48	0.0 $\pm$ 0.49	0.0 $\pm$ 0.47
MedPE	0.17	0.03 ^b	-0.04	0 ^b	-0.02 ^b
Range PE	-2.43 to 2.14	-2.32 to 1.37	-2.19 to 1.41	-2.54 to 1.42	-2.29 to 1.7
MAPE $\pm$ SD	0.56 $\pm$ 0.51	0.39 $\pm$ 0.32	0.37 $\pm$ 0.31	0.38 $\pm$ 0.31	0.36 $\pm$ 0.31
MedAPE	0.41	0.31	0.3	0.31	0.28
^a No statistically significant difference at level 0.05					
^b No statistically significant difference from zero at level 0.05					

Table 4c: Comparison of the median prediction error to zero for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) and for the different types of eyes (long, long medium, medium, short and all eyes), using Wilcoxon (1 sample) signed rank test at a statistical significance level of 5%.

Monofocal Lenstec Softec HDO					
Comparison of the median prediction error to zero					
p-values for Wilcoxon (1 sample) signed rank test					
	SRK/T	Hoffer Q	Holladay I	Haigis	MM
Long eyes	< 0.001	< 0.001	< 0.001	0.039	0.092 ^a
Long medium eyes	< 0.001	< 0.001	0.169 ^a	0.037	0.064 ^a
Medium eyes	< 0.001	0.367 ^a	< 0.001	0.253 ^a	0.164 ^a
Short eyes	0.0043	< 0.001	0.410 ^a	0.091 ^a	0.066 ^a
All eyes	< 0.001	0.127 ^a	< 0.001	0.275 ^a	0.701 ^a
^a No statistically significant difference from zero at level 0.05					

Table 4d: Top - Comparison of the median absolute prediction errors of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for the different types of eyes (long, long

medium, medium, short and all eyes), using the Friedman test at a statistical significance level of 5%.

Bottom – Pairwise comparison of the median absolute prediction errors between the MM formula and each of the other four formulae (SRK/T, Hoffer Q, Holladay I and Haigis) for the different types of eyes (long, long medium, medium, short and all eyes), using the Wilcoxon test at a statistical significance level of 5%.

Monofocal Lenstec Softec HDO					
Comparison of the median absolute prediction error for the five formulae					
p-values for Friedman test					
	Long eyes	Long medium eye	Medium eyes	Short eyes	All eyes
p-Values	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Pairwise comparison of the median absolute prediction error					
p-values for Wilcoxon (2 paired samples) signed rank test					
Formulae pair	Long eyes	Long medium Eye	Medium eyes	Short eyes	All eyes
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	< 0.001 ^b	< 0.001 ^b	0.785 ^a	0.032 ^c	< 0.001 ^b
MM vs Holladay I	< 0.001 ^b	< 0.001 ^b	0.785 ^a	< 0.001 ^b	< 0.001 ^b
MM vs Haigis	< 0.001 ^b	0.002 ^b	0.999 ^a	0.047 ^c	< 0.001 ^b
^a No statistically significant difference at level 0.05					
^b MM formula underperformed at significance level 0.05					
^c MM formula underperformed at significance level 0.05					

Table 4e: Comparison of the prediction accuracy (i.e., the percentage of eyes within a given range of prediction error) of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for the different types of eyes (long, long medium, medium, short and all eyes), using the Cochran Q test, at a statistical significance level of 5%.

Monofocal Lenstec Softec HDO			
Comparison of the prediction accuracy for the five formulae			
p-values for Cochran's Q test			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
Long eyes	< 0.001	< 0.001	< 0.001
Long medium eyes	< 0.001	< 0.001	< 0.001
Medium eyes	< 0.001	< 0.001	0.111 ^a
Short eyes	< 0.001	< 0.001	< 0.001
All eyes	< 0.001	< 0.001	< 0.001
^a No statistically significant difference at level 0.05			

Table 4f: Pairwise comparison of the prediction accuracy (i.e., the percentage of eyes within a given range of prediction error) between the MM formula and each of the other four formulae (SRK/T, Hoffer Q, Holladay I and Haigis) for the different types of eyes (long, long medium, medium, short and all eyes), using the McNemar test at a statistical significance level of 5%.

Monofocal Lenstec Softec HDO			
Pairwise comparison of the prediction accuracy p-values for McNemar test			
Long eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	< 0.001 ^b	0.999 ^a	0.999 ^a
MM vs Holladay I	< 0.001 ^b	0.999 ^a	0.999 ^a
MM vs Haigis	0.041 ^b	0.999 ^a	0.999 ^a
Long medium eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	< 0.001 ^b	0.789 ^a	0.999 ^a
MM vs Holladay I	0.211 ^a	0.999 ^a	0.999 ^a
MM vs Haigis	0.864 ^a	0.752 ^a	0.999 ^a
Medium eyes			

	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	0.999 ^a
MM vs Hoffer Q	< 0.001 ^b	< 0.001 ^b	0.999 ^a
MM vs Holladay I	< 0.001 ^b	< 0.001 ^b	0.617 ^a
MM vs Haigis	< 0.001 ^b	< 0.001 ^b	0.999 ^a
Short eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	0.003 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	0.585 ^a	0.770 ^a	0.041 ^c
MM vs Holladay I	0.001 ^b	0.607 ^a	0.041 ^c
MM vs Haigis	0.831 ^a	< 0.001 ^c	0.041 ^c
All eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	< 0.001 ^b	0.013 ^b	0.023 ^c
MM vs Holladay I	< 0.001 ^b	0.013 ^b	0.343 ^a
MM vs Haigis	< 0.001 ^b	0.391 ^a	0.023 ^c
^a No statistically significant difference at level 0.05			
^c MM formula outperformed at significance level 0.05			
^c MM formula underperformed at significance level 0.05			

Table 5a: Summary statistics of the cross-validation results for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for long, long medium and short eyes. % Rx: Percentage of eyes within a given range of prediction error; MPE: Mean prediction error; MedPE: Median prediction error; Range PE: Range of the prediction error; MAPE: Mean absolute prediction error; MedAPE: Median absolute prediction error; SD: Standard Deviation.

Multifocal ZEISS AT LISA tri839 MP					
Summary statistics of cross-validation results for long, long medium and short eyes					
Long eyes (Bootstrap sample size: 69)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	27.50%	26.10%	52.20%	50.70%	66.70%
% Rx within $\pm 1.0D$	58.00%	71.00%	88.40%	88.40%	100.00%
% Rx within $\pm 1.5D$	91.30%	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
MPE $\pm$ SD	-0.58 $\pm$ 0.73	0.67 $\pm$ 0.5	0.54 $\pm$ 0.42	0.36 $\pm$ 0.47	0.11 $\pm$ 0.46
MedPE	-0.58	0.77	0.43	0.5	0.13
Range PE	-2.03 to 0.57	-0.2 to 1.46	-0.03 to 1.28	-0.46 to 1.08	-0.75 to 0.91
MAPE $\pm$ SD	0.78 $\pm$ 0.5	0.7 $\pm$ 0.44	0.55 $\pm$ 0.41	0.56 $\pm$ 0.21	0.39 $\pm$ 0.26
MedAPE	0.58	0.77	0.43	0.5	0.4
Long medium eyes (Bootstrap sample size: 112)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	44.60%	92.00% ^a	87.50% ^a	80.40%	87.50% ^a

% Rx within $\pm 1.0D$	51.80%	100.00% ^a	100.00% ^a	99.10% ^a	99.10% ^a
% Rx within $\pm 1.5D$	59.80%	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
MPE $\pm$ SD	-0.99 $\pm$ 1.32	0.09 $\pm$ 0.37	-0.05 $\pm$ 0.36	0.01 $\pm$ 0.39	-0.03 $\pm$ 0.42
MedPE	-0.28	0.14 ^b	0.12 ^b	-0.01 ^b	0.2 ^b
Range PE	-2.86 to 0.56	-0.46 to 0.96	-0.78 to 0.51	-0.61 to 1.02	-1.01 to 0.56
MAPE $\pm$ SD	1.26 $\pm$ 1.06	0.31 $\pm$ 0.22	0.31 $\pm$ 0.19	0.3 $\pm$ 0.25	0.37 $\pm$ 0.21
MedAPE	0.51	0.24	0.25	0.22	0.3
Short eyes (Bootstrap sample size: 73)					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	69.90%	61.60%	83.60% ^a	57.50%	87.70% ^a
% Rx within $\pm 1.0D$	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
% Rx within $\pm 1.5D$	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
MPE $\pm$ SD	0.25 $\pm$ 0.36	-0.05 $\pm$ 0.5	-0.04 $\pm$ 0.44	0.22 $\pm$ 0.51	0.08 $\pm$ 0.4
MedPE	0.24	-0.2 ^b	-0.12 ^b	0.2	0 ^b
Range PE	-0.35 to 0.87	-0.82 to 0.65	-0.77 to 0.52	-0.62 to 0.95	-0.54 to 0.92
MAPE $\pm$ SD	0.37 $\pm$ 0.24	0.44 $\pm$ 0.24	0.39 $\pm$ 0.20	0.48 $\pm$ 0.28	0.37 $\pm$ 0.19
MedAPE	0.35 ^a	0.47 ^a	0.44 ^a	0.44	0.37 ^a
^a No statistically significant difference at level 0.05					
^b No statistically significant difference from zero at level 0.05					

Table 5b: Summary statistics of the cross-validation results for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for medium and all eyes. % Rx: Percentage of eyes within a given range of prediction error; MPE: Mean prediction error; MedPE: Median prediction error; Range PE: Range of the prediction error; MAPE: Mean absolute prediction error; MedAPE: Median absolute prediction error; SD: Standard Deviation.

Multifocal ZEISS AT LISA tri839 MP					
Summary statistics of cross-validation results for medium and all eyes					
Medium eyes					
Bootstrap sample size: 846					
Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	76.70%	76.50%	81.20% ^a	74.50%	80.60% ^a
% Rx within $\pm 1.0D$	96.60% ^a	97.60%	97.60%	98.60%	96.60% ^a
% Rx within $\pm 1.5D$	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
MPE $\pm$ SD	0.15 $\pm$ 0.4	-0.01 $\pm$ 0.42	-0.08 $\pm$ 0.39	-0.03 $\pm$ 0.41	0.01 $\pm$ 0.42
MedPE	0.11	-0.01 ^b	-0.1	-0.03	-0.03 ^b
Range PE	-0.78 to 1.39	-0.84 to 1.36	-0.94 to 1.22	-0.87 to 1.31	-0.95 to 1.33
MAPE $\pm$ SD	0.32 $\pm$ 0.27	0.33 $\pm$ 0.26	0.31 $\pm$ 0.24	0.32 $\pm$ 0.27	0.33 $\pm$ 0.26
MedAPE	0.24 ^a	0.27 ^a	0.24	0.23 ^a	0.29 ^a
All eyes					
Bootstrap sample size: 1100					

Statistics	SRK/T	Hoffer Q	Holladay I	Haigis	MM
% Rx within $\pm 0.5D$	69.90%	73.90%	80.20% ^a	72.50%	80.90% ^a
% Rx within $\pm 1.0D$	89.80%	96.40% ^a	97.50% ^a	98.10% ^a	97.30% ^a
% Rx within $\pm 1.5D$	95.40%	100.00% ^a	100.00% ^a	100.00% ^a	100.00% ^a
MPE $\pm$ SD	-0.01 $\pm$ 0.69	0.04 $\pm$ 0.45	-0.04 $\pm$ 0.42	0.01 $\pm$ 0.44	0.01 $\pm$ 0.42
MedPE	0.07	0.03 ^b	-0.03	0 ^b	0 ^b
Range PE	-2.86 to 1.39	-0.84 to 1.46	-0.94 to 1.28	-0.87 to 1.31	-1.01 to 1.33
MAPE $\pm$ SD	0.45 $\pm$ 0.53	0.36 $\pm$ 0.29	0.33 $\pm$ 0.26	0.34 $\pm$ 0.27	0.34 $\pm$ 0.25
MedAPE	0.28	0.28 ^a	0.26	0.25 ^a	0.31 ^a
^a No statistically significant difference at level 0.05					
^b No statistically significant difference from zero at level 0.05					

Table 5c: Comparison of the median prediction error to zero for each of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) and for the different types of eyes (long, long medium, medium, short and all eyes), using Wilcoxon (1 sample) signed rank test at a statistical significance level of 5%.

Multifocal ZEISS AT LISA tri839 MP					
Comparison of the median prediction error to zero					
p-values for Wilcoxon (1 sample) signed rank test					
	SRK/T	Hoffer Q	Holladay I	Haigis	MM
Long eyes	< 0.001	< 0.001	< 0.001	< 0.001	0.027
Long medium eyes	< 0.001	0.122 ^a	0.102 ^a	0.556 ^a	0.736 ^a
Medium eyes	< 0.001	0.316 ^a	< 0.001	0.017	0.557 ^a
Short eyes	< 0.001	0.543 ^a	0.662 ^a	0.002	0.149 ^a
All eyes	< 0.001	0.060 ^a	< 0.001	0.803 ^a	0.592 ^a
^a No statistically significant difference from zero at level 0.05					

Table 5d: Top - Comparison of the median absolute prediction errors of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for the different types of eyes (long, long medium, medium, short and all eyes), using the Friedman test at a statistical significance level of 5%.

Bottom – Pairwise comparison of the median absolute prediction errors between the MM formula and each of the other four formulae (SRK/T, Hoffer Q, Holladay I and Haigis) for the different

types of eyes (long, long medium, medium, short and all eyes), using the Wilcoxon test at a statistical significance level of 5%.

Multifocal ZEISS AT LISA tri839 MP					
Comparison of the median absolute prediction error for the five formulae					
p-values for Friedman test					
	Long eyes	Long medium eye	Medium eyes	Short eyes	All eyes
p-Values	0.005	< 0.001	< 0.001	< 0.001	< 0.001
Pairwise comparison of the median absolute prediction error					
p-values for Wilcoxon (2 paired samples) signed rank test					
Formulae pair	Long eyes	Long medium Eye	Medium eyes	Short eyes	All eyes
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	0.290 ^a	0.811 ^a	< 0.001 ^c
MM vs Hoffer Q	< 0.001 ^b	0.002 ^c	0.340 ^a	0.060 ^a	0.327 ^a
MM vs Holladay I	0.023 ^b	< 0.001 ^c	0.001 ^b	0.159 ^a	0.044 ^c
MM vs Haigis	< 0.001 ^b	< 0.001 ^c	0.132 ^a	0.012 ^b	0.766 ^a
^a No statistically significant difference at level 0.05					
^b MM formula outperformed at significance level 0.05					
^c MM formula underperformed at significance level 0.05					

Table 5e: Comparison of the prediction accuracy (i.e., the percentage of eyes within a given range of prediction error) of the five formulae (SRK/T, Hoffer Q, Holladay I, Haigis and MM) for the different types of eyes (long, long medium, medium, short and all eyes), using the Cochran Q test, at a statistical significance level of 5%.

Multifocal ZEISS AT LISA tri839 MP			
Comparison of the prediction accuracy for the five formulae			
p-values for Cochran's Q test			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
Long eyes	< 0.001	< 0.001	0.002
Long medium eyes	0.002	< 0.001	0.002
Medium eyes	< 0.001	< 0.001	0.999 ^a
Short eyes	< 0.001	0.999 ^a	0.999 ^a
All eyes	< 0.001	< 0.001	0.002
^a No statistically significant difference at level 0.05			

Table 5f: Pairwise comparison of the prediction accuracy (i.e., the percentage of eyes within a given range of prediction error) between the MM formula and each of the other four formulae (SRK/T, Hoffer Q, Holladay I and Haigis) for the different types of eyes (long, long medium, medium, short and all eyes), using the McNemar test at a statistical significance level of 5%.

Multifocal ZEISS AT LISA tri839 MP			
Pairwise comparison of the prediction accuracy p-values for McNemar test			
Long eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	0.041 ^b
MM vs Hoffer Q	< 0.001 ^b	< 0.001 ^b	0.999 ^a
MM vs Holladay I	< 0.001 ^b	0.013 ^b	0.999 ^a
MM vs Haigis	< 0.001 ^b	0.013 ^b	0.999 ^a
Long medium eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	0.383 ^a	0.999 ^a	0.999 ^a
MM vs Holladay I	0.999 ^a	0.999 ^a	0.999 ^a
MM vs Haigis	0.013 ^b	0.999 ^a	0.999 ^a
Medium eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	0.001 ^b	0.999 ^a	0.999 ^a

MM vs Hoffer Q	0.006 ^b	0.008 ^c	0.999 ^a
MM vs Holladay I	0.699 ^a	0.008 ^c	0.999 ^a
MM vs Haigis	<0.001 ^b	< 0.001 ^c	0.999 ^a
Short eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	0.002 ^b	0.999 ^a	0.999 ^a
MM vs Hoffer Q	0.002 ^b	0.999 ^a	0.999 ^a
MM vs Holladay I	0.646 ^a	0.999 ^a	0.999 ^a
MM vs Haigis	<0.001 ^b	0.999 ^a	0.999 ^a
All eyes			
	% Rx within $\pm 0.5D$	% Rx within $\pm 1.0D$	% Rx within $\pm 1.5D$
MM vs SRK/T	< 0.001 ^b	< 0.001 ^b	< 0.001 ^b
MM vs Hoffer Q	< 0.001 ^b	0.100 ^a	0.999 ^a
MM vs Holladay I	0.580 ^a	0.814 ^a	0.999 ^a
MM vs Haigis	< 0.001 ^b	0.124 ^a	0.999 ^a
^a No statistically significant difference at level 0.05			
^c MM formula outperformed at significance level 0.05			
^c MM formula underperformed at significance level 0.05			

Figures

Figure 1

A comparative illustration of the relationship between the post-operative ACD (i.e., ELP) and the measured pre-operative ACD and the axial length for the following formulae: SRK/T, Hoffer Q, Holladay I, Haigis and MM, for a given lens and some given keratometric readings K_1 and K_2 .

Figure 2

Illustration of the concept of k-fold cross-validation. Summary statistics of the optimized IOL constants, for the four formulae and the three type of lenses, obtained from the Monte-Carlo k-fold cross-validation process (with $k=100$), are presented in Table 2.