The PEARL-DGS Formula: The Development of an Open-source Machine Learning–based Thick IOL Calculation Formula

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• PURPOSE: To describe an open-source, reproducible, step-by-step method to design sum-of-segments thick intraocular lens (IOL) calculation formulas, and to evaluate a formula built using this methodology.
• DESIGN: Retrospective, multicenter case series
• METHODS: A set of 4242 eyes implanted with Finevision IOLs (PhysIOL, Liège, Belgium) was used to devise the formula design process and build the formula. A different set of 677 eyes from the same center was kept separate to serve as a test set. The resulting formula was evaluated on the test set as well as another independent data set of 262 eyes.
• RESULTS: The lowest standard deviation (SD) of prediction errors on Set 1 were obtained with the PEARL-DGS formula (±0.382 D), followed by K6 and Olsen (±0.394 D), EVO 2.0 (±0.398 D), RBF 3.0, and BUII (±0.402 D). The formula yielding the lowest SD on Set 2 was the PEARL-DGS (±0.269 D), followed by Olsen (±0.272 D), K6 (±0.276 D), EVO 2.0 (±0.277 D), and BUII (±0.301 D).
• CONCLUSION: Our methodology achieved an accuracy comparable to other state-of-the-art IOL formulas. The open-source tools provided in this article could allow other researchers to reproduce our results using their own data sets, with other IOL models, population settings, biometric devices, and measured, rather than calculated, posterior corneal radius of curvature or sum-of-segments axial lengths. (Am J Ophthalmol 2021;232: 58–69. © 2021 Published by Elsevier Inc.)

THIRD-GENERATION INTRAOCULAR LENS (IOL) calculation formulas such as Haigis,[1] Hoffer-Q,[2-5] Holladay 1,[6] and SRK/T[7,8] were published 3 decades ago and are still commonly used by ophthalmologists because of their excellent performance. Those formulas are based on thin-lens equations and on linear or multiple regression techniques to predict the effective lens position (ELP). The methodology followed for their development has been previously published, allowing eye surgeons to understand their inner workings (Figure 1).

A number of more recent formulas have been proven to offer equal or even greater prediction accuracy than classical third-generation formulas.[9-13] Those formulas were not published, neither were the rules used to perform the prediction. The underlying reasoning leading to the definition of those rules are also not currently available to the eye surgeon community.

Thick-lens equations are relevant to building IOL formulas because they allow to take both the optical effects of the corneal and intraocular lens thicknesses and their shapes into account.[14-18] Sum-of-segments axial length (AL) calculation has been recently suggested to allow for a better evaluation of the anatomical axial length.[17,19] The PEARL-DGS formula (Postoperative spherical Equivalent prediction using ARtificial intelligence and Linear algorithms, developed by Debellemanière, Gatinel and Saad) is an iterative work aimed at determining the potential of artificial intelligence techniques, with respect to the contribution of optics in IOL calculation formulas.[20–25] In this article, we present a specific version of the formula, built with IOL characteristics obtained from the IOL manufacturer, based on the prediction of the theoretical internal lens position (TILP), defined as the distance between the posterior corneal surface and the anterior IOL surface, back-calculated from postoperative data.

A basic multiple regression was used to predict the TILP from biometric parameters, to highlight the nonlinear phenomena in the lens position prediction process that more complex algorithms aim to correct.

Jupyter is an open-source application allowing sharing of Python code in the form of a succession of cells, called Notebooks, facilitating research sharing and reproducibility.

Our goal was to describe a standardized, open-source process to design a thick-lens IOL calculation formula based on the prediction of the TILP using of sum-of-segments AL and independent control of all the refractive indices of the

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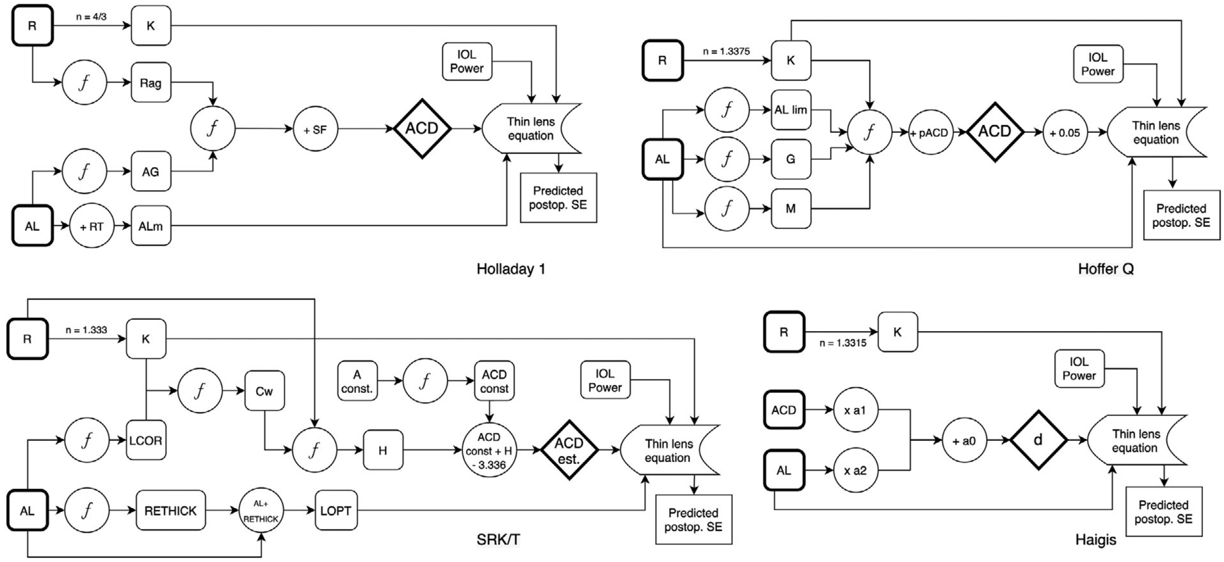

FIGURE 1. Inner working of the 4 classical thin lens formulas. The acronyms of the original publications are used in the diagrams. Any transformation different from a multiplication or an addition is represented by a "f" ("function") round cell on the diagram. ACD = anatomic anterior chamber measured from corneal epithelium to lens, AG = anterior chamber diameter from angle to angle, ALm = modified AL, Cw = computed corneal width, H = corneal height, K = corneal power, LCOR = corrected AL, RETHICK = retinal thickness, RT = retinal thickness.

TABLE 1. Fundamental Paraxial Optics Equations

	Formula	Explanation
Eq. 1	$P = (\frac{n_{right} - n_{left}}{r})$	Surface power for a given radius r and surrounding refractive index n_{right} and n_{left}
Eq. 2	$P_{both} = P_{left} + P_{right} - (P_{left} \times P_{right} \times d \ / \ n)$	Gullstrand formula: equivalent power of a thick lens. P_{left} and P_{right} are the power of each lens surface. d is the distance between the lenses and n is the lens refractive index
Eq. 3	$f = -n_{left} \ / \ P$	Front focal length of a lens.[a]
Eq. 4	$f' = n_{right} \ / \ P$	Back focal length of a lens [b]
Eq. 5	$H = d \times f_{both} \ / \ f_{right}$	Distance from the left vertex to the first principal plane of a 2-lens system. d is the distance between the lenses.[c]
Eq. 6	$H' = -d \times f'_{both} \ / \ f'_{left}$	Distance from the right vertex to the second principal plane of a 2-lens system. d is the distance between the lenses.[c]
Eq. 7	$d_o = d - H'_{left} + H_{right}$	Optical distance between 2 [a] lens systems

Signs in the equation respect the cartesian sign convention: distances to the left are negative, and distances to the right are positive.
[a] The front focal length of a thick lens is expressed from its first principal plane.
[b] The back focal length of a thick lens is expressed from its second principal plane.
[c] If the system is itself composed of a lens system, d must be calculated according to the appropriate principal plane positions using Eq. 7.

eye segments, and to evaluate the performances of a formula built with this methodology.

METHODS

The equations involved in this work are presented in Tables 1 and 2. A Jupyter Notebook detailing the entire formula building, training, and prediction process along with the related Python functions is provided. The source code is also available under the open-source standard MIT license at the project page at https://github.com/gdebel/pearldgs_toolbox. All the distance values in this work are in meters.

The data sets were composed of anonymized data from patients who underwent uncomplicated cataract surgery with an implantation of a Finevision IOL (PhysIOL, Liège,

TABLE 2. Main Equations Used in the Formula

Eq. 8	$AL_{opt} = T_{cornea} + TILP + T_{iol} + H'_{iol} + H'_{eye} + f'_{eye}$	Calculation of the distance between the anterior corneal surface and the back focal point of the eye. T represents the thickness of the considered segment. The eye is emmetropic when $AL_{opt} - AL = 0$.
Eq. 9	$TILP = \frac{-B \pm \sqrt{C}}{2 \times P_{cornea} \times P_{iol}} + H'_{cornea} - H_{iol}$ with $C = B^2 - 4 \times P_{cornea} \times P_{iol} \times (A \times (n_{aq} \times P_{cornea} + n_{aq} \times P_{iol}) - n_{vit} \times n_{aq})$ and $B = \frac{n_{vit} \times n_{aq}}{f_{cornea}} - n_{aq} \times P_{cornea} - n_{aq} \times P_{iol} - P_{cornea} \times P_{iol} \times A$ and $A = AL - T_{cornea} + H_{iol} - H'_{cornea} - T_{iol} - H'_{iol}$	Back-calculation of the theoretical physical distance between the posterior corneal surface and the anterior IOL surface. The sign of the second term of the numerator in the main equation must be negative for positive IOLs and positive for negative IOLs.
Eq. 10	$SE_{cornea} = SE_{spectacles} / (1 - d_v \times SE_{spectacles})$	Spectacle plane refraction to corneal plane refraction conversion. d_v is the vertex distance of spectacle lenses.
Eq. 11	$P_{ant.\ cornea\ corrected} = \frac{P_{cornea\ corrected} \times n_{co} - P_{post.\ cornea} \times n_{co}}{n_{co} - P_{post.\ cornea} \times T_{cornea}}$ with $P_{cornea\ corrected} = P_{cornea} + SE_{cornea}$	Calculation of the emmetropizing anterior corneal surface. This equation allows to use eq. 9 to back-calculate the TILP for the eyes that have a postoperative spherical equivalent different from plano.
Eq. 12	$P_{ant.\ cornea} = \frac{n_{aq} \times n_{cornea} - P_{post.\ cornea} \times n_{cornea} \times E}{E \times (n_{cornea} - T_{cornea} \times P_{post.\ cornea}) + n_{aq} \times T_{cornea}}$ with $E = TILP + H_{iol} - \frac{D \times n_{aq}}{D \times P_{iol} - 1}$ and $D = \frac{AL - T_{cornea} - TILP - T_{iol} - H'_{iol}}{n_{vit}}$	Calculation of the emmetropizing anterior corneal surface power using the predicted TILP value and the optical parameters of the eye
Eq. 13	$SE_{cornea\ predicted} = P_{cornea\ (emmetropia)} - P_{cornea\ (real)}$	Calculation of the predicted postoperative refraction (corneal plane).
Eq. 14	$SE_{spectacles} = SE_{cornea} / (1 + d_v \times SE_{cornea})$	Corneal plane refraction to spectacle plane refraction conversion. d_v is the vertex distance of spectacle lenses.
Eq. 15	$CMAL_{modified} = CMAL + AL\ correction\ factor$ with $AL\ correction\ factor = \lvert threshold - AL \rvert * weight$	Corrected CMAL calculation, used as an input in the TILP prediction algorithm. NB = the optical equations use the nonmodified CMAL value.

CMAL = Cooke-modified axial length, TILP = theoretical internal lens position.
Lengths are in meters.

Belgium). Manifest refraction was performed between 1 and 3 months after surgery, with an optometrist.

Training set and Test Set 1 consisted of eyes operated from April 2017 to December 2019, measured preoperatively with the Lenstar 900 (Haag-Streit AG, Koeniz, Switzerland, EyeSuite software i8.2.2.0). To avoid any group similarities, patients from Test Set 1 having their contralateral eye in the training set were removed from the test set, leaving 677 eyes from 677 patients. Test Set 2 was composed of 262 eyes from 132 patients, measured preoperatively with the IOLMaster700 (Carl Zeiss Meditec AG, Jena, Germany, software version 1.80.10.61129). The retrospective data query was approved by the Ethics Review Board of the Canadian Ophthalmic Research Centre and by the Regional Committee for Medical and Health Research Ethics, Norway. The study conformed to the tenets of the Declaration of Helsinki.

• **INTRAOCULAR LENS:** The PhysIOL FineVision Micro F is a 25% hydrophilic acrylic trifocal IOL. It has a 4-loop, single-piece design with 5 degrees of haptic angulation. Its optic is biconvex aspheric and 6.15 mm in diameter. Its overall diameter is 10.75 mm. Its refractive index is 1.46. Its radius of curvatures and hydrated thicknesses for each power were provided by PhysIOL.

• **POSTERIOR CORNEAL RADIUS PREDICTION:** In thin-lens formulas, the total corneal power is inferred from the anterior radius of curvature, using the keratometric index. This method is based on the assumption that the relationship between the anterior radius and the posterior radius is the same along the entire anterior corneal radius. In this work, we used a previously determined anterior radius–posterior radius relationship using data from the Pentacam Scheimpflug camera (Oculus Optikgeräte GmbH, Wetzlar, Germany). The posterior radius of curvature (PRC) was set to the anterior radius of curvature (ARC) × 1.45659603 – 0.00443874 if ARC < 0.00697, and ARC × 0.90649864 – 0.0006091 if ARC ≥ 0.00697.

• **SUM-OF-SEGMENTS AL CALCULATION:** We used the regression published by Cooke and associates[17] to calculate the Cooke-modified axial length (CMAL). This regression allows close approximation of the sum-of-segments AL value using the AL and lens thickness measurements delivered by the biometer, when the optical path length (OPL) in the air for each eye segment is not available, which is the case for most data sets. The CMAL was used in both the formula training process and the spherical equivalent prediction process. CMAL was calculated as follows:

$\text{CMAL} = \frac{1.23853 + 958.55 \times AL - 54.67 \times LT}{1{,}000}$ (where AL is the axial length in meters and LT, lens thickness in meters). Two hundred micrometers were added to this value to account for the retinal thickness, as suggested by David Cooke (personal communication, February 4, 2021).

• **LENS POSITION BACK-CALCULATION:** ELP is usually defined as the distance from the anterior corneal surface to the principal plane of an infinitely thin IOL. This value depends on the physical position of the IOL in the eye, but also on corneal thickness and on IOL geometry. The latter varies between IOL models and power. Actual lens position (ALP) has been defined as the physical distance measured from the anterior corneal surface to the anterior IOL surface.[26,27] To use a value independent from both corneal thickness and IOL geometry, we defined the internal lens position (ILP) as the physical distance between the posterior corneal surface and the anterior IOL surface, and the theoretical internal lens position (TILP) as the back-calculated version of the ILP.

The formula we propose is derived from thick-lens equations based on paraxial approximation (Eqs. 1-7, Table 1). Here the schematic eye is represented as an optical system combining the cornea and the IOL, with each "lens" being defined by its anterior and posterior radius of curvature, its refractive index, and its thickness. In our model, the refractive index of the vitreous is not equated to the refractive index of the aqueous. The eye is emmetropic when the back focal point of the entire optical system is located on the retinal pigment epithelium, that is, when the distance between the anterior corneal surface and the back focal point of the whole eye (AL_{opt}) is equal to the sum-of-segments axial length CMAL. AL_{opt} is calculated using Eq. 8. The equation $AL_{opt} - \text{CMAL} = 0$ can be solved for the TILP, if all the other optical parameters of the eye are known (Eq. 9). When the postoperative eye is emmetropic, the calculation is straightforward. If the postoperative eye is myopic or hyperopic, the postoperative refraction must be converted to the corneal plane (Eq. 10) and added to the corneal power as first published by Hoffer in 1981.[28] The anterior corneal power is then recalculated to fit the corrected corneal power (Eq. 11) and the TILP calculation can be performed.

• **TILP PREDICTION:** Once the TILP was calculated for the eyes comprising the training set, it was used as the designated target to predict using an algorithm, with the biometric parameters as features. Any algorithm could theoretically be chosen to perform the prediction. In this work, a multiple linear regression was used, with CMAL, anterior radius of curvature (ARC), aqueous chamber depth (AQD), lens thickness, central corneal thickness, and white-to-white diameter as independent variables. The algorithm output, called $TILP_{predicted}$, was used in the equations to calculate the predicted spherical equivalent.

• **PREDICTED POSTOPERATIVE SPHERICAL EQUIVALENT CALCULATION:** The equation $AL_{opt} - \text{CMAL} = 0$ was solved for the anterior corneal power (Eq. 12), allowing to calculate the anterior corneal power to achieve emmetropia for a given $TILP_{predicted}$ value. The total corneal power to achieve emmetropia was then calculated using Eq. 2. The difference between the latter and the real total corneal power, corresponding to the predicted refraction in the corneal plane (Eq. 13), was converted to the predicted refraction in the spectacle plane (Eq. 14).

• **DETERMINATION OF THE OPTIMAL CORNEAL REFRACTIVE INDEX:** Refractive index values of the Atchison model eye[29] were used for the aqueous (1.3374) and the vitreous (1.336). The refractive index of the Finevision IOL was provided by PhysIOL. The refractive index of the cornea varies strongly in the literature, from 1.337 to 1.432.[30] To determine the optimal corneal refractive index to use in the equations, the whole process of formula building and evaluation was realized for a wide range of corneal refractive index values, in a loop. For each corneal index value, all other parameters remaining equal, the TILP value was back-calculated for each eye of the training set. A multiple regression was fitted to predict this value from the preoperative biometric measurements. The $TILP_{predicted}$ was then predicted using this regression, the predicted spherical equivalent of the resulting formula was computed, and the standard deviation of the prediction error (PE) was calculated. The corneal refractive index yielding the lowest standard deviation was retained.

• **ALGORITHM ADAPTATION TO EXTREME AXIAL LENGTHS:** Although the evolution of the lens position is proportional to the axial length for standard eyes, this is no longer the case for extreme eyes. However, eyes with extremely short or extremely long axial lengths constitute only a fraction of any cataract surgery data set. Hence, lens position prediction algorithms can fail to capture the specificities of the evolution of the lens position along the range of axial length, thus being less accurate for those eyes. To overcome this problem, the mean reference TILP values and the mean predicted TILP values were plotted as a function of the axial length, rounded to 0.25 mm. Lower and upper axial length thresholds were determined visually by inspecting the resulting plot. An AL correction factor was calculated by multiplying the difference between the chosen threshold and the actual axial length by a weight. The value of the axial length used as an input in the TILP prediction algorithm ($CMAL_{corrected}$) was calculated by adding a correction factor to CMAL (Eq. 15). The value of the weight was determined independently, for both short and long eyes. The value of the axial length used in the optical equations was left untouched and always equal to the CMAL, whatever its value.

TABLE 3. Demographics of the Patient Population.

Cases	Training set (n = 4242)	Test Set 1 (n = 677)	Test Set 2 (n = 262)	Total Test Sets (n = 939)
Left eye, n (%)	2123 (50.0)	247 (36.5)	130 (49.6)	377 (40.1)
Female sex, n (%)	2264 (53.4)	389 (57.5)	84 (63.6)	473 (58.5)
Short eyes (AL ≤ 22mm), n (%)	344 (8.11)	65 (9.6)	7 (2.7)	72 (7.7)
Long eyes (AL ≥ 26 mm), n (%)	101 (2.4)	22 (3.2)	6 (2.3)	28 (3.0)
Age (y)	57.2 ± 6.2	57.0 ± 6.1	57.0 ± 4.8	57.0 ± 5.9
IOL power (D)	22.30 ± 3.01	22.19 ± 3.28	21.39 ± 2.96	21.97 ± 3.22
Axial length (mm)	23.37 ± 1.09	23.38 ± 1.13	23.74 ± 0.99	23.48 ± 1.10
Mean keratometry (D)	43.34 ± 1.45	43.44 ± 1.43	42.96 ± 1.38	43.31 ± 1.43
Anterior chamber depth (mm)	3.17 ± 0.33	3.19 ± 0.33	3.24 ± 0.27	3.20 ± 0.32
Lens thickness (mm)	4.41 ± 0.32	4.40 ± 0.32	4.35 ± 0.30	4.39 ± 0.32
Central corneal thickness (mm)	0.549 ± 0.03	0.551 ± 0.03	0.554 ± 0.03	0.552 ± 0.03
Corneal diameter (mm)	12.2 ± 0.4	12.2 ± 0.5	12.1 ± 0.4	12.2 ± 0.4
Postoperative SE (D)	–0.153 ± 0.393	–0.140 ± 0.419	0.138 ± 0.332	–0.062 ± 0.416

AL = axial length, D = diopter, IOL = intraocular lens, SE = spherical equivalent.

Unless otherwise noted, values are mean (SD). Keratometry is estimated from the anterior corneal radius using a keratometric index of 1.3375.

• **IOL CONSTANT ADJUSTMENT:** A variable was added to the predicted TILP value, to allow the adjustment of the formula and set the mean PE to zero. This variable was set as positive (to increase the predicted TILP value) if the mean PE for the test data set was toward a mean hyperopic PE, or negative (to decrease the predicted TILP value) if the mean prediction for the test data set was toward a mean myopic PE.

• **EVALUATION OF THE FORMULA:** At the end of the formula development process, the predictions of the resulting formula were computed for the eyes comprising test Sets 1 and 2. The open-source Haigis,[1] Hoffer Q,[2–5] Holladay 1,[6] and SRK/T[7,8] formulas were translated to Python code and verified for a large range of AL, K, and ACD values using the output delivered by the IOLMaster 700.

For each set, the predictions of the Haigis formula with simple and triple optimization, and the predictions of Hoffer-Q, Holladay 1, and SRK/T formulas with and without Wang-Koch modification[31,32] were computed. Predictions of the Barrett Universal II (BUII)[15,31] were computed using the Lenstar software (EyeSuite i8.0.0.0, Haag-Streit AG). Predictions of the Olsen[9,33] formula were generated using the PhacoOptics software (version 1.10.100.2020, IOL Innovations Aps) with the following parameters: basic form of convexity 1:1, central thickness 0.95 mm, spherical aberration –0.11 μm, refractive index 1.46. Original (linear regression) Holladay 2[34] formula was computed using the Holladay IOL Consultant software (2014.0607). Predictions of the EVO,[35] T2,[36] and Radial Basis Function 3.0[37] (RBF 3.0) formulas were obtained from the authors. The latter was only available for the test set because of the smaller size of the second set and the different constant, which was an obstacle for the optimization of this formula. K6 is a thin-lens formula developed by Dr David Cooke (Michigan, USA)[38] where the ELP is computed with thick-lens calculations, the axial length is internally modified to simulate sum-of-segment axial length, and 6 variables (Ks, ACD, lens thickness, AL, white-to-white diameter, and central corneal thickness) are used to optimize total corneal power. Predictions were obtained from the author.

All the formula constants were adjusted to obtain a mean refraction error equal to zero for each set. The standard deviation (SD), mean (MAE) and median (MedAE) absolute PE, and minimum (MinE) and maximum (MaxE) PEs were calculated. Prediction error distribution was tested for normality using D'Agostino K-squared test. Statistical analysis of PEs between formulas was conducted according to the heteroscedastic method described by Holladay and associates[39,40] using the R programming language.[41] Percentage of eyes with a PE within 0.25, 0.50, 0.75, and 1.00 D were compared using Cochran Q test, and McNemar test was applied for subsequent paired formula comparison. A P value ≤.05 was considered significant. Holm-Bonferroni P value sequential correction was applied for multiple comparisons.

RESULTS

• **DEMOGRAPHICS AND IOL CONSTANT ADJUSTMENT:** Demographics of the patient's population are shown in Table 3 for both test sets and for the training set. Optimized lens constants are shown in Table 4. Patient's mean

TABLE 4. Optimized Constants of the Evaluated Data Sets

Formula	Formula-specific Optimized Lens Constant	
	Test Set 1	Test Set 2
Barrett U. II	1.926	2.053
EVO 2.0	119.04	119.26
Haigis (single opt.)	1.345 (0.4, 0.1)	1.473 (0.4, 0.1)
Haigis (triple opt.)	–0.32 (0.371, 0.176)	0.0348 (0.463, 0.152)
Hill-RBF 3.0	119.03	—
Hoffer Q	5.584	5.715
Hoffer Q + WK	5.560	5.688
Holladay 1	1.849	1.976
Holladay + WK	1.845	1.974
Holladay 2	5.522	5.649
Olsen	4.69	4.82
Pearl	119.056	119.277
SRK/T	119.129	119.354
SRK/T + WK	119.127	119.353
T2	119.066	119.270
K6	119.041	119.269

age was relatively young (57 years) in both sets, because of the high prevalence of presbyopic refractive lens exchange procedures. Short eyes percentage was 3 times greater in Set 1 than in Set 2: this fact was likely explained by differing thresholds for multifocal implantation.

• **OPTIMIZED CORNEAL REFRACTIVE INDEX CALCULATION:** Overall operation of the formula calculation process is presented in Figure 2. Corneal indices ranging from 1.3 to 1.4 in steps of 0.001 were empirically evaluated. The SD of the resulting predictions described a concave upward curve and ranged from ±0.363 D for a corneal index of 1.363 to ±0.374 D for a corneal index of 1.3 (Figure 3). A corneal index of 1.376 yielded an SD of ±0.364 D. Consequently, the selected corneal index value was 1.363.

• **PREDICTION ERROR AND COMPARISON WITH OTHER FORMULAS:** Results are presented in Table 5. D'Agostino K-squared test performed on formulas' mean PE consistently yielded *P* values below the .05 threshold, thus indicating a non-normal distribution of mean PE. The heteroscedastic analysis described by Holladay[39] was then chosen to perform the statistical analysis between PE: the resulting *P* values are presented in Supplementary Materials S1 and S2. The lowest SD of PEs on Set 1 were obtained with the PEARL formula (±0.382 D), followed by K6 and Olsen (± 0.394 D), then EVO 2.0 (±0.398 D), then RBF 3.0 and BUII (± 0.402 D). Ranking by MAE followed the same order, ranging from 0.286 to 0.305 D. The best results on short eyes were achieved by BUII which allowed an MAE of 0.404 D, followed by RBF (0.428 D), Holladay 1 (0.441 D), PEARL (0.443) and Hoffer Q (0.443 D). In long eyes, the best results were achieved by the custom PEARL formula with an MAE of 0.240 D, followed by the Olsen formula (0.257 D), Holladay 1 + WK (0.267 D), RBF 3.0 (0.272 D), and EVO 2.0 (0.272 D) Table 6.

Results obtained on Set 2 largely mirrored the outcomes on Set 1. The formula yielding the lowest SD was the PEARL (±0.269 D), followed by Olsen (±0.272 D), K6 (±0.276 D), EVO 2.0 (±0.277 D), and BUII (±0.301 D). MAE ranged from 0.203 to 0.226 D. The best MAE on short eyes were obtained using the Olsen (0.088 D) and PEARL formulas (0.116 D) followed by EVO 2.0 (0.117 D), K6 (0.210 D), and BUII (0.228 D). Best MAE on long eyes were obtained with the SRK/T formula (0.162 D), followed by SRK/T + WK (0.184 D), Holladay 1 + WK (0.204 D), T2 (0.211 D), and BUII (0.218 D).

Percentage of cases within 0.25-, 0.50-, 0.75-, and 1.00-D range of absolute PE were computed for all eyes of the test sets. Cochran *Q* test was statistically significant for every absolute PE category, thus indicating statistical difference between formulas. PEARL formula had the higher percentage of eyes below 0.25 D of absolute PE. McNemar test with Holm *P* value adjustment showed no statistical difference with K6, Olsen, BUII, and EVO 2.0 in this category. The PEARL formula also had a higher percentage of eyes below 0.50 D of absolute PE (no statistical difference with K6, Olsen, and EVO 2.0). The Olsen formula had the higher percentage of eyes below 0.75 D of absolute PE (no statistical difference with PEARL, K6, EVO 2.0, and BUII), and EVO 2.0 had the highest percentage of eyes below 1.00 D of error (no statistical difference with every other formula except SRK/T and SRK/T + WK).

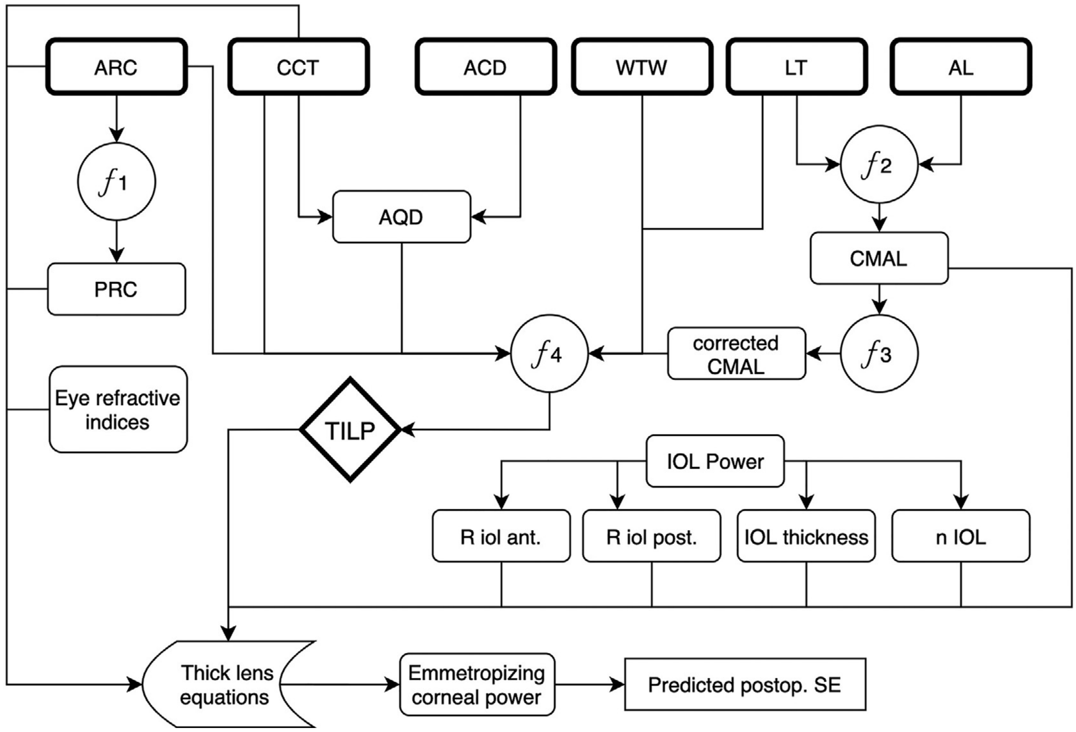

FIGURE 2. Inner workings of the PEARL formula. The posterior corneal radius is calculated from the anterior corneal radius using a linear function (f1). CMAL is calculated from the original AL and LT, and used in the optical part of the formula (f2). CMAL is also corrected if its value is below or above a determined AL threshold (f3) (see Figure 4), and the resulting value is used as an input in the TILP prediction part of the formula along with the ARC, CCT, AQD, WTW, and LT (f4). AQD = aqueous chamber depth, ARC = anterior radius of curvature, CCT = central corneal thickness, CMAL = Cooke-modified axial length, LT = lens thickness, TILP = theoretical internal lens position, WTW = white-to-white diameter.

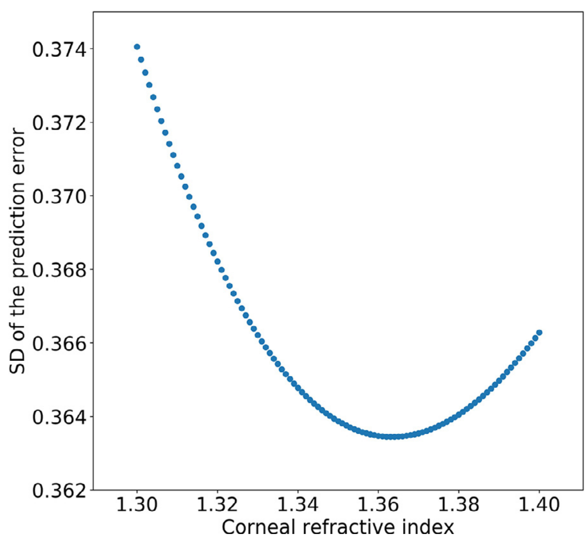

FIGURE 3. Empirical determination of the optimal corneal refractive index. For each index value, the whole formula-building process was repeated in a loop and the corresponding standard deviation of the prediction error was calculated. The corneal index yielding the lowest standard deviation was retained.

DISCUSSION

Most published formulas are based on predefined rules to calculate the lens position (Figure 1). Those rules are IOL model aspecific: they can be used for any IOL model by adjusting a constant, which acts as an offset. A notable exception is the Haigis formula in triple optimized mode.[1] The ELP calculation in the Haigis formula relies on the application of coefficients (a1 and a2) to the ACD and AL values respectively, added to an offset (a0) without any additional rule. The triple optimization is performed by calculating the optical ELP yielding the postoperative spherical equivalent for each eye of the surgeon's data set, and by fitting a multiple regression to this value, using ACD and AL as independent variables.[1,42] This operation results in the determination of 2 coefficients (a1 and a2) and 1 intercept value (a0). It can be considered as a complete retraining of the formula rather than a regular IOL constant adjustment, allowing the surgeon to determine the ELP calculation coefficients fitting best to his own favorite lens and surgical habits, but also to their own patient population characteristics. The performances of

TABLE 5. Prediction Performances of the Evaluated Formulas

Formula	Whole Data Set					Short Eyes (≤22 mm)			Long Eyes (≥26 mm)		
	SD	MAE	MedAE	Max. myopic PE	Max. hyperopic PE	SD	ME	MAE	SD	ME	MAE
Set 1											
BU II	0.402	0.305	0.24	–1.76	1.6	0.511	0.081	0.404	0.372	–0.088	0.308
EVO 2.0	0.398	0.299	0.239	–1.694	1.535	0.584	0.138	0.472	0.326	–0.119	0.272
Haigis (single opt.)	0.435	0.334	0.277	–1.724	1.863	0.564	–0.099	0.463	0.336	0.232	0.335
Haigis (triple opt.)	0.429	0.329	0.265	–1.694	1.702	0.576	0.128	0.479	0.333	0.048	0.272
Hoffer Q	0.445	0.344	0.293	–1.808	1.636	0.545	–0.094	0.443	0.396	0.241	0.393
Hoffer Q + WK	0.447	0.345	0.285	–1.773	1.667	–	–	–	0.364	–0.361	0.387
Holladay 1	0.433	0.331	0.272	–1.807	1.887	0.557	0.051	0.441	0.423	0.225	0.37
Holladay 1 + WK	0.43	0.327	0.267	–1.801	1.892	–	–	–	0.37	0.057	0.267
Holladay 2	0.432	0.331	0.27	–1.72	1.855	0.57	–0.049	0.458	0.345	0.18	0.309
K6	0.394	0.293	0.224	–1.672	1.554	0.539	0.223	0.457	0.354	–0.164	0.298
Olsen	0.394	0.296	0.225	–1.67	1.79	0.575	0.106	0.467	0.317	–0.105	0.257
Pearl	0.382	0.286	0.229	–1.703	1.589	0.546	0.067	0.443	0.32	–0.019	0.24
RBF 3.0	0.402	0.303	0.236	–1.727	1.738	0.529	0.101	0.428	0.35	–0.083	0.272
SRK/T	0.457	0.349	0.276	–1.806	2.157	0.613	0.133	0.479	0.43	–0.015	0.338
SRK/T + WK	0.457	0.347	0.274	–1.805	2.159	—	—	—	0.393	–0.068	0.286
T2	0.437	0.331	0.262	–1.805	1.746	0.603	0.106	0.474	0.368	–0.109	0.301
Set 2											
BU II	0.301	0.226	0.185	–0.985	1.13	0.307	0.002	0.228	0.255	–0.029	0.218
EVO 2.0	0.277	0.208	0.169	–0.871	0.902	0.16	0.047	0.117	0.278	–0.034	0.235
Haigis (single opt.)	0.325	0.257	0.205	–1.056	0.82	0.345	–0.158	0.289	0.276	0.25	0.261
Haigis (triple opt.)	0.319	0.245	0.192	–0.979	0.894	0.314	0.074	0.244	0.285	0.118	0.232
Hoffer Q	0.352	0.279	0.229	–1.172	0.916	0.394	–0.207	0.349	0.282	0.291	0.291
Hoffer Q + WK	0.351	0.281	0.233	–1.131	0.956	—	—	—	0.286	–0.266	0.344
Holladay 1	0.336	0.26	0.215	–1.146	1.021	0.351	–0.088	0.275	0.272	0.299	0.302
Holladay 1 + WK	0.334	0.257	0.214	–1.143	1.025	—	—	—	0.274	0.138	0.204
Holladay 2	0.327	0.253	0.198	–1.035	0.915	0.304	–0.174	0.302	0.262	0.204	0.221
K6	0.276	0.212	0.165	–0.812	0.844	0.141	0.21	0.21	0.255	–0.09	0.237
Olsen	0.272	0.209	0.178	–0.765	0.85	0.122	0.055	0.088	0.305	–0.046	0.248
Pearl	0.269	0.203	0.159	–0.856	0.816	0.149	0.056	0.116	0.299	0.064	0.23
SRK/T	0.36	0.274	0.216	–1.294	1.109	0.305	–0.056	0.235	0.215	0.109	0.162
SRK/T + WK	0.36	0.274	0.216	–1.293	1.11	—	—	—	0.248	0.068	0.184
T2	0.335	0.258	0.205	–1.139	1.063	0.319	–0.061	0.251	0.25	–0.023	0.211

MAE = mean absolute prediction error, ME = mean prediction error, MedAE = median absolute prediction error, PE = prediction error; SD = standard deviation.

The intraocular lens constants were adjusted to obtain whole data set mean prediction errors equal to 0.00 for every formula.

the Haigis formula, which is paradoxically the simplest of the published thin-lens formulas, are remarkable.[13]

However, IOL formulas based on thin-lens equations ignore the optical effects of lens thicknesses and shape factors. Consequently, the positions of the principal planes of the cornea, which are anterior to the anterior corneal surface, are neglected in thin-lens formulas, or accounted for by using a constant. The displacement of the object principal plane relative to the physical position of the lens, induced by asymmetrical IOL shapes, are also not taken into account.[43] The extreme constants of the Alcon MA60MA IOL, which differ between the positive and negative versions of this model because of its meniscus design and asymmetrical shape, are an illustration of this limitation.[44]

Our work suggests that IOL-specific thick-lens formulas, predicting a data-inferred approximation of the physical position of the IOL in the eye, could increase IOL calculation accuracy. The methodology we describe is not fundamentally different from the one first proposed by Haigis: it is based on the direct prediction of the lens position using an algorithm trained to predict a target inferred from biometric values, IOL characteristics, and postoperative refractive outcomes. We made the choice to predict a value inferred from data rather than physical measurements (postoperative measurement of the physical position of the IOL) because this method accounts for the assumptions made for the unknown parameters of the eyes. For example, the lens position value to achieve emmetropia for a given eye will

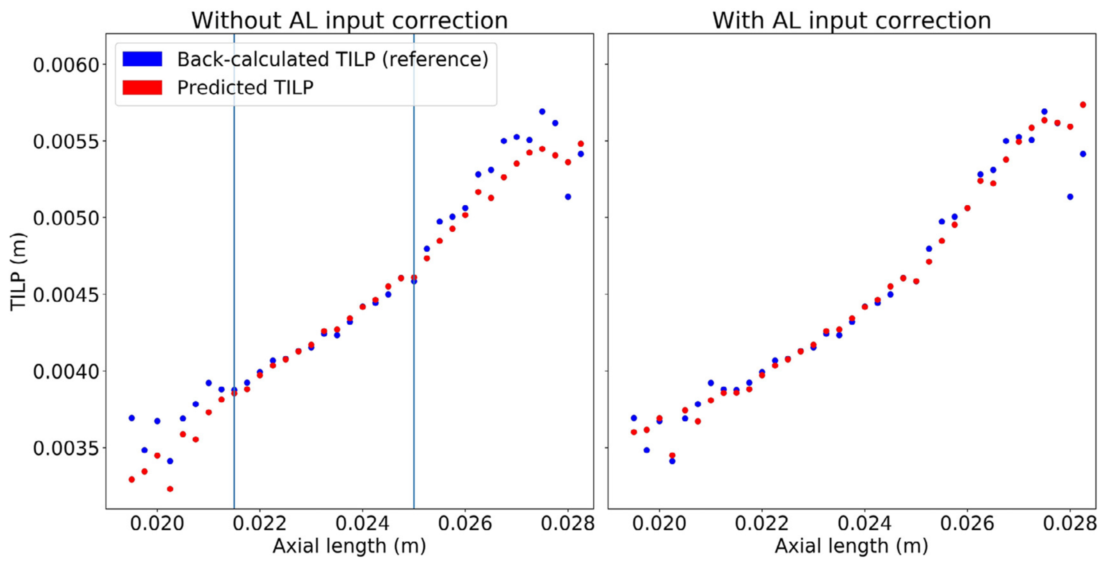

FIGURE 4. Effect of the AL input correction on the TILP prediction for short and long eyes. Mean reference TILP values (blue) and predicted TILP values (red) are plotted against original AL values rounded to 0.25 mm. The vertical lines in panel A at 21.5 and 25 mm were determined visually. Above and below those limits, a correction factor proportional to the difference between the AL value and the limit is applied to the CMAL, before the latter is used as an input in the multiple regression used to predict the TILP. The effect of the correction is shown on panel B. AL = axial length, CMAL = Cooke-modified axial length, TILP = theoretical internal lens position.

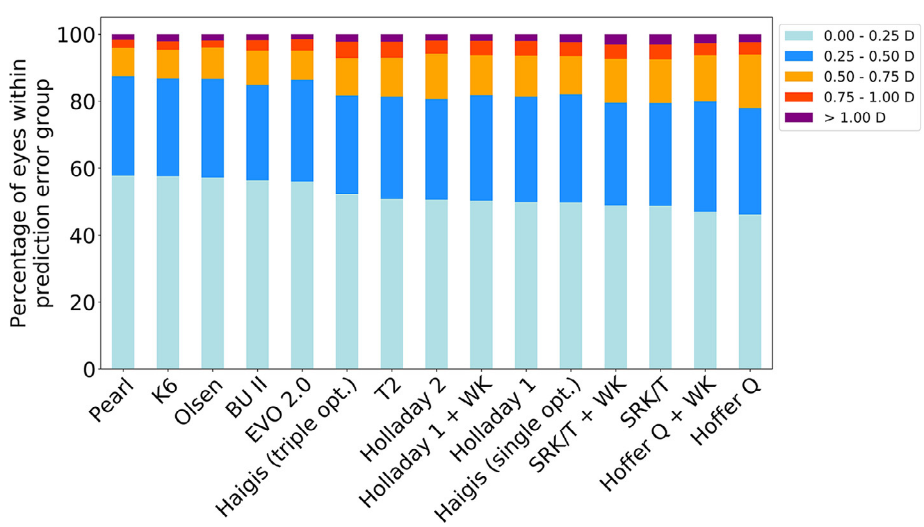

FIGURE 5. Percentages of prediction error category for each formula, for the 2 data sets.

not be the same for different vitreous or corneal indices, or for different posterior corneal curvature values.

Although the formula created with the described process was as accurate as the best-performing formulas among the ones evaluated, the goal of the article is not to claim any particular superiority of our approach, but rather an attempt to provide tools and encourage open research methodology regarding IOL formula design. K6, EVO 2.0, Olsen, BUII, and RBF 3.0 formulas allowed excellent prediction accuracy without benefiting from precise IOL geometric information. In particular, the performances obtained with this particular IOL model may not be as good for other lenses.

The best empirical corneal refractive index was determined using a data-based reasoning. The optimal corneal index (1.363) was different from the frequently accepted physiological corneal index (1.376). A possibility is that this nonphysiological index accounts for bias originating from the arbitrarily chosen refractive indices of the other structures of the eye. It also can be hypothesized that this value accounts for a bias coming from the determination of

TABLE 6. Percentages of Eyes in Every Prediction Error Category, Ranked by Percentage in the 0.00- to 0.25-D Category (see Figure 5)

Formula	0.00-0.25 D	0.25-0.50 D	0.50-0.75 D	0.75-1.00 D	>1.00 D
Pearl	57.72	87.43	95.84	98.29	1.7
K6	57.61	86.68	95.31	97.87	2.13
Olsen	57.19	86.58	95.95	98.08	1.92
BU II	56.34	84.88	95.1	98.19	1.81
EVO 2.0	56.02	86.37	95.1	98.51	1.49
Haigis (triple opt.)	52.29	81.68	92.86	97.76	2.24
T2	50.8	81.36	92.97	97.76	2.24
Holladay 2	50.59	80.62	94.15	98.09	1.92
Holladay 1 + WK	50.27	81.79	93.61	97.98	2.02
Holladay 1	49.84	81.36	93.5	97.97	2.02
Haigis (single opt.)	49.73	82	93.4	97.66	2.34
SRK/T + WK	48.88	79.55	92.54	96.91	3.09
SRK/T	48.67	79.45	92.44	96.91	3.09
Hoffer Q + WK	46.96	79.87	93.61	97.23	2.77
Hoffer Q	46.11	77.95	93.92	97.65	2.34

the anterior/posterior corneal radius relationship using the Pentacam camera, while it was the Lenstar biometric device that was used to measure the anterior corneal radius for the eyes used to build the formula and perform the calculations. The formulas and functions provided in this article could allow other teams to determine the best empirical corneal index using their own data and devices; they could also be used without changes to back-calculate more accurately the TILP if biometers were eventually able to measure the refractive indices of the eye structures preoperatively.[45]

To adjust the formula and set the mean PE to zero for each Test Set, the predicted TILP value was shifted upward or downward by a constant. This constant was identical for every eye in a given set. A similar shift is used on the PEARL online calculator[46] to adjust the prediction for a given SRK/T A constant. It is calculated using a linear relationship between the desired ILP shift and the SRK/T A constant of a given IOL model. This relationship was determined by the authors of the formula as follows: the adjusted SRK/T A constant for various data sets comprising different IOL models was calculated for each IOL model. Then, the ILP shift allowing to obtain a PEARL mean PE equal to zero was also calculated. A linear regression was then fitted to predict the desired ILP shift depending on the IOL A constant.

A common multiple linear regression was used in this work to help illustrate the importance of parameters not directly related to the TILP prediction, such as better accounting for axial length through the use of sum-of-segments AL. The use of a linear algorithm also allows to better visualize the threshold effects of the axial length on the lens position, which is no longer proportional to the AL above and below those thresholds. However, it is straightforward to use more complex algorithms using our methodology. We also obtained good results with support vector regression and/or gradient boosted trees: hence, these algorithms are used, along with linear regression, in the online PEARL formula. The good performances obtained in this work using only a multiple linear regression suggest that the closest possible physical approximation of the eye's optical processes in IOL formulas can only be beneficial, whatever the underlying complexity of the lens position prediction algorithm. The use of optics in machine learning–based IOL formulas could be assimilated to a "meta" inductive bias,[47] allowing the formula to better generalize. Hence, we support the use of optical models as complete as possible in IOL calculation, and we suggest using predictive methods to perform the lens position prediction only. In this case, the lens position values used to train the algorithm should be back-calculated from available data to fit the chosen optical model.

The methodology described in the article relies on predicted posterior corneal curvature values and approximated sum-of-segments axial length. However, the formulas and Python functions that we provide can be used with measured posterior corneal radius values following the same logic of formula design, thus allowing surgeons to take advantage of the availability of this measurement on certain biometers. Similarly, the use of CMAL could be straightforwardly replaced by a biometer-specific measured sum-of-segments axial length value. Using measured posterior corneal radius and more accurate AL measurements should be beneficial to back-calculate the lens position more precisely when developing the formula. This allows a closer approximation of this value by the chosen predictive algorithm, as well as calculation of the predicted spherical equivalent, once the formula is developed.

We suggest that disclosure of IOL radius of curvatures, thicknesses, and refractive indices by IOL manufacturers could be beneficial for the teams working on the topic of

IOL calculation, especially when dealing with asymmetrical IOLs, both for the development and prediction phases. When the IOL specificities are unknown, we suggest that IOL formula inventors study the IOL power–specific PE as described in the provided Jupyter Notebook.

We are now entering an era where surgical procedures are standardized, large data sets are increasingly available, and biometer platform accuracy is improving at a fast pace. Widely available optical parameters need to be reciprocated by manufacturers, to better optimize IOL formulas to keep pace with the new landscape of modern day refractive cataract surgery. We also advocate for open-source release of research involving IOL calculation, which can only benefit the eye surgeon community and their patients.

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