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History of the PEARL-DGS Formula

The Postoperative spherical Equivalent prediction using ARtificial Intelligence and Linear algorithms (PEARL) project aims to assess the potential of artificial intelligence (AI) techniques in the IOL calculation field, to determine the optimal architecture of those formulas, and to encourage open research in this field by publishing the experiments and the related code under an open-source license. It was initiated in 2017 in the Anterior Segment and Refractive Surgery Department at Rothschild Foundation by the authors of this chapter. It resulted in a succession of IOL calculation formulas known under the name “PEARL-DGS,” DGS representing the initials of the last names of the authors.

Description of the Current PEARL-DGS Formula

General Principles

The PEARL-DGS formula is a thick lens formula that uses AI techniques to predict the distance between the posterior corneal surface and

the anterior IOL surface (“theoretical internal lens position,” TILP) [1] (Fig. 52.1). The TILP is an anatomical distance, independent of both the lens principal plane positions and the corneal thickness. The reference TILP (the target to predict) corresponds to the value leading to the real postoperative SE when entered in thick lens equations along with the other optical parameters of the eye and IOL. The formula uses various machine learning algorithms and ensemble methods to predict this value. The refractive index values used in the formula are those of the Atchison eye model [2], except for the corneal index, which was determined empirically during the formula development process. The sum-of-segments AL, approximated by the Cooke-modified AL (CMAL), replaces the AL in the formula. As the thin lens approximation is not used, the real geometric parameters of the considered IOL are ideally used during the development process; otherwise, the formula can be developed using theoretical IOL parameters (for example, biconvex symmetric geometry) and a study of the mean TILP prediction error along the IOL power range is proposed.

Sum-of-Segments AL Calculation

Sum-of-segments AL is obtained by computing the geometric length of each ocular segment [3]

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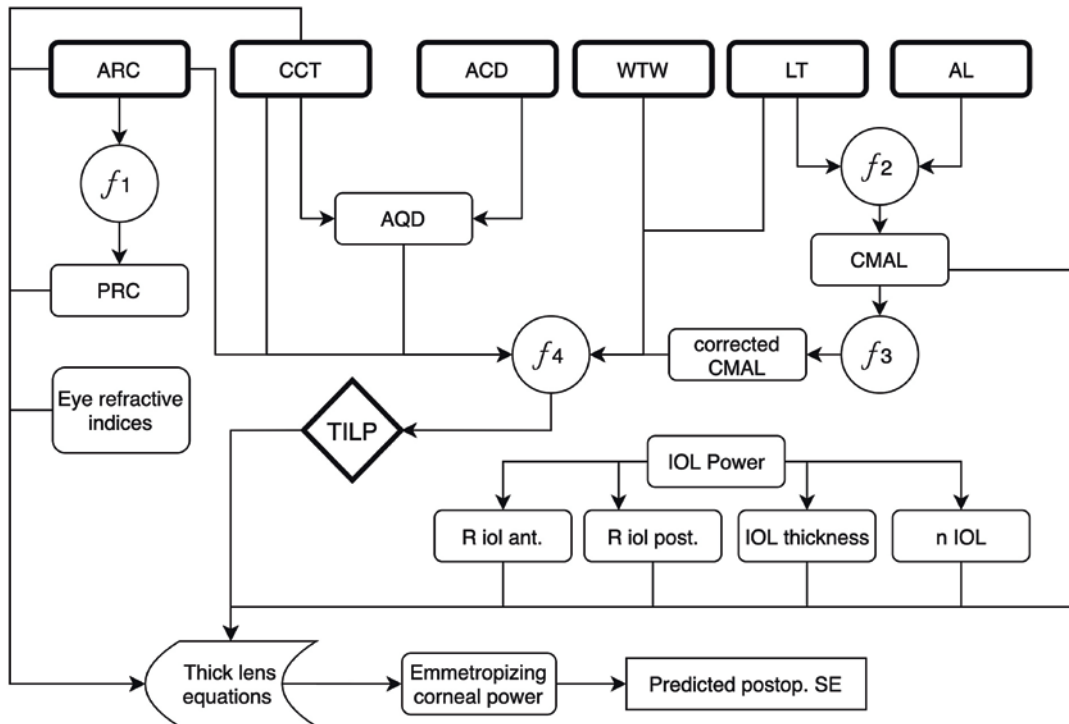


Fig. 52.1 General outline of the PEARL-DGS formula prediction process. The PRC is deduced from the ARC (f_1). AL and LT are used to calculate the CMAL (f_2). The CMAL is corrected before being used as an input to predict the TILP (f_3). The raw CMAL value is used in the optical part of the formula. The ARC and CCT are used in the optical part of the formula and also used as an input to

predict the TILP. CD, AQD, and LT are only used to predict the TILP. The TILP is then predicted using 6 biometric parameters (f_4). From Debellemanière et al.: The PEARL-DGS Formula: The Development of an Open-source Machine Learning-based Thick IOL Calculation Formula. *Am J Ophthalmol*. 2021 Dec;232:58–69

(calculated by dividing their optical path length by their own refractive index), rather than using the weighted-average refractive index of the whole eye as described by Haigis [4].

CMAL calculation allows to approximate the sum-of-segments AL in the absence of vitreous thickness value delivered by the biometer [5], which is the case in most clinical settings. CMAL is calculated using the equation $CMAL = (1.23853 + 958.55 \times AL - 54.67 \times LT)/1000$ (AL and LT in meters). Two hundred micrometers was added to this value to account for the retinal thickness, as suggested by Dr. David Cooke (personal communication, February 4, 2021).

In the formula, CMAL is calculated and replaces traditional AL; it is also calculated during the formula development process and the reference TILP is back-calculated using this value as the reference AL.

Optical Principles

The refractive index values of the Atchison eye model are used: n_{aqueous} is set to 1.3374, n_{vitreous} to 1.336, and n_{IOL} is equal to the real refractive of the IOL used in the formula development process. n_{cornea} was set to 1.363. The process that led to the choice of this value is described later in this chapter. The formula is entirely based on thick lens equations (Eqs. 52.1–52.7) (Table 52.1).

Posterior Corneal Radius Prediction

The PRC is inferred from the ARC using two linear regressions. Those regressions were determined using ARC and PRC values from 2052 rotating Scheimpflug camera system measurements (Pentacam, Oculus Optikgerate, Wetzlar, Germany) obtained on eyes with no his-

Table 52.1 Fundamental paraxial optics equations. Signs in the equation respect the Cartesian sign convention: Distances to the left are negative, and distances to the right are positive

	Formula	Explanation
(52.1)	$P = \left(\frac{n_{\text{right}} - n_{\text{left}}}{r} \right)$	Surface power for a given radius r and surrounding refractive index n_{right} and n_{left}
(52.2)	$P_{\text{both}} = P_{\text{left}} + P_{\text{right}} - (P_{\text{left}} \times P_{\text{right}} \times d/n)$	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
(52.3)	$f = -n_{\text{left}}/P$	Front focal length of a lens*
(52.4)	$f' = n_{\text{right}}/P$	Back focal length of a lens**
(52.5)	$H = d \times f_{\text{both}}/f_{\text{right}}$	Distance from the left vertex to the first principal plane of a two-lens system. d is the distance between the lenses***
(52.6)	$H' = -d \times f'_{\text{both}}/f'_{\text{left}}$	Distance from the right vertex to the second principal plane of a two-lens system. d is the distance between the lenses***
(52.7)	$d_o = d - H'_{\text{left}} + H_{\text{right}}$	Optical distance between two-lens systems

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Signs in the equation respect the cartesian sign convention: distances to the left are negative, and distances to the right are positive

* The front focal length of a thick lens is expressed from its first principal plane

** The back focal length of a thick lens is expressed from its second principal plane

*** If the system is itself composed of a lens system, d must be calculated according to the appropriate principal plane positions using Eq. 52.7

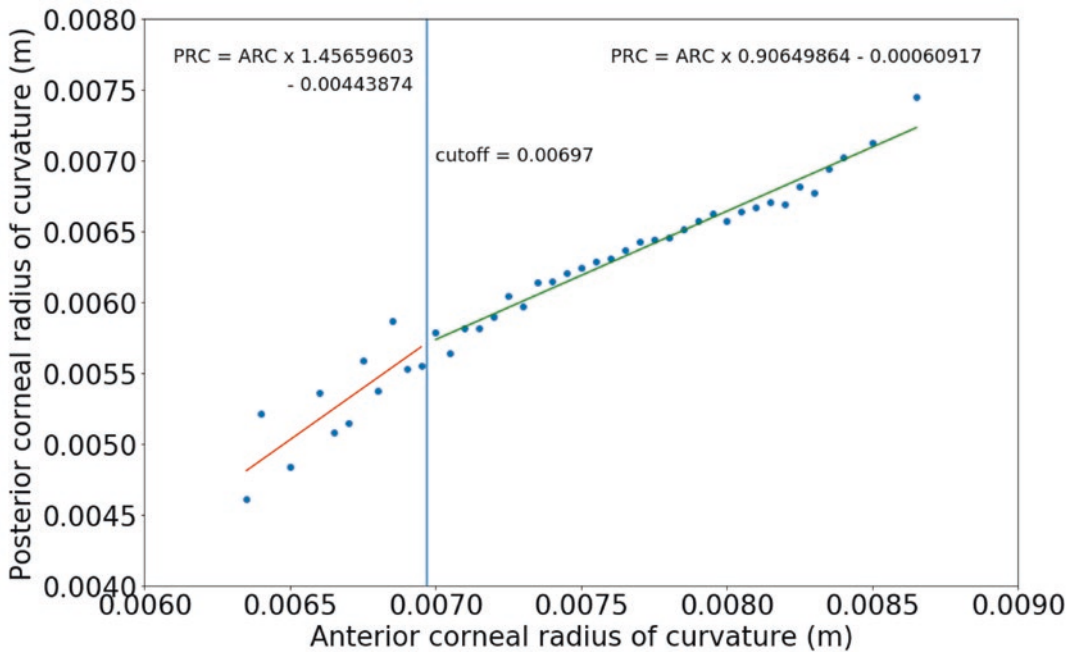


Fig. 52.2 Mean PRC for each ARC step (ARC values are rounded up to 0.05 mm). A cut-off at 7.00 mm was visually defined, and two linear regressions were fitted. The cut-off was then refined to 6.97 mm. From

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tory of corneal surgery. The mean PRC was calculated for each step of ARC values rounded to 0.05 mm. A threshold at 7.00 mm ARC was visually identified. Two linear regression algorithms were fitted on both sides of this threshold, which

was then slightly modified to 6.97 mm to allow a perfect transition between the PRC values obtained around the threshold.

The linear regressions are presented in Fig. 52.2.

TILP Back-Calculation

The formula is based on the prediction of the TILP value, defined as the theoretical distance between the posterior corneal surface and the anterior IOL surface that leads to the real postoperative SE when entered in thick lens equations along with the other optical parameters of the eye and IOL. The calculation of the TILP must be performed for each eye of the training set, to obtain the reference value that will be used as the target to predict in the algorithms.

The formula allowing this back-calculation is described in Eq. (52.10). If the eye is not emmetropic, the postoperative refraction is added to the total corneal power, and the anterior corneal radius is re-calculated to fit the new total corneal power value (Eqs. 52.8 and 52.9). Equation (52.10) can then be applied (Table 52.2).

TILP Prediction

The PEARL formula takes advantage of various algorithms such as gradient-boosted trees (XGBoost), support vector regression, neural networks (multi-layer perceptron regressor), and standard multiple regression to predict the TILP. The

hyperparameters of each model were determined using fivefold cross-validation on the training set.

Predicted SE Calculation

Once the TILP is predicted, it is necessary to calculate the associated refraction at the spectacle plane. This can be done by first calculating the emmetropizing anterior corneal radius, i.e., the theoretical anterior corneal radius leading to emmetropia if the predicted TILP is used in thick lens equations along with the other optical parameters of the eye and IOL, using Eq. (52.11). The emmetropizing total corneal power can then be calculated using this value, using Eq. (52.2). The predicted postoperative SE at the corneal plane is then obtained by subtracting the real total corneal power from the emmetropizing total corneal power (Eq. 52.12). The resulting refraction converted to the spectacle plane is the predicted postoperative SE (Eq. 52.13) (Table 52.3).

Corneal Index Optimization

The refractive index of the cornea varies from 1.337 to 1.432 in the literature [6]. In order to

Table 52.2 Equations used in the formula (lengths are in meters)

(52.8)	$SE_{\text{cornea}} = SE_{\text{spectacles}} / (1 - d_v \times SE_{\text{spectacles}})$	Spectacle plane refraction to corneal plane refraction conversion. d_v is the vertex distance of spectacle lenses
(52.9)	$P_{\text{ant.cornea corrected}} = \frac{P_{\text{cornea corrected}} \times n_{\text{co}} - P_{\text{post.cornea}} \times n_{\text{co}}}{n_{\text{co}} - P_{\text{post.cornea}} \times T_{\text{cornea}}}$ <p>With $P_{\text{cornea corrected}} = P_{\text{cornea}} + SE_{\text{cornea}}$</p>	Calculation of the emmetropizing anterior corneal surface. This equation allows the use of Eq. (52.10) to back-calculate the TILP for the eyes that have a postoperative spherical equivalent different from Plano
(52.10)	$TILP_t = \frac{-B \pm \sqrt{C}}{2 \times P_{\text{cornea}} \times P_{\text{iol}}} + H'_{\text{cornea}} - H_{\text{iol}}$ <p>with</p> $C = B^2 - 4 \times P_{\text{cornea}} \times P_{\text{iol}} \times (A \times (n_{\text{aq}} \times P_{\text{cornea}} + n_{\text{aq}} \times P_{\text{iol}}) - n_{\text{vit}} \times n_{\text{aq}})$ <p>and $B = \frac{n_{\text{vit}} \times n_{\text{aq}}}{f'_{\text{cornea}}} - n_{\text{aq}} \times P_{\text{cornea}} - n_{\text{aq}} \times P_{\text{iol}} - P_{\text{cornea}} \times P_{\text{iol}} \times A$</p> <p>and $A = AL - T_{\text{cornea}} + H_{\text{iol}} - H'_{\text{cornea}} - T_{\text{iol}} - H'_{\text{iol}}$</p>	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

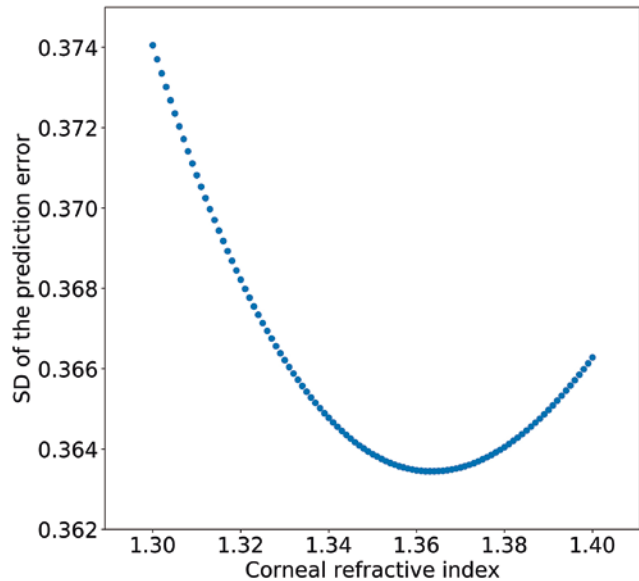
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Table 52.3 Equations used in the formula (lengths are in meters)

(52.11)	$P_{\text{ant.cornea}} = \frac{n_{\text{aq}} \times n_{\text{cornea}} - P_{\text{post.cornea}} \times n_{\text{cornea}} \times E}{E \times (n_{\text{cornea}} - T_{\text{cornea}} \times P_{\text{post.cornea}}) + n_{\text{aq}} \times T_{\text{cornea}}}$ <p>with $E = TILP + H_{\text{iol}} - \frac{D \times n_{\text{aq}}}{D \times P_{\text{iol}} - 1}$</p> <p>and $D = \frac{AL - T_{\text{cornea}} - TILP - T_{\text{iol}} - H'_{\text{iol}}}{n_{\text{vit}}}$</p>	Calculation of the emmetropizing anterior corneal surface power using the predicted TILP value and the optical parameters of the eye
(52.12)	$SE_{\text{cornea predicted}} = P_{\text{cornea (emmetropia)}} - P_{\text{cornea(real)}}$	Calculation of the predicted postoperative refraction (corneal plane)
(52.13)	$SE_{\text{spectacles}} = SE_{\text{cornea}} / (1 + d_v \times SE_{\text{cornea}})$	Corneal plane refraction to spectacle plane refraction conversion. d_v is the vertex distance of spectacle lenses

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Fig. 52.3 SD of the prediction error as a function of the corneal refractive index value used to develop the formula. From Debellemanière et al.: The PEARL-DGS Formula: The Development of an Open-source Machine Learning-based Thick IOL Calculation Formula. Am J Ophthalmol. 2021 Dec;232:58–69



determine the optimal corneal index to use in the formula, a systematic approach was applied, using the eyes of the training set, for a range of corneal refractive index values ranging between 1.30 and 1.40 by 0.001 steps. For each step, reference TILP was back-calculated, a multiple regression was fitted to predict the resulting value from biometric parameters, the predicted TILP was calculated using the regression, the predicted

postoperative SE was calculated, the prediction error was calculated, and the standard deviation (SD) of the mean prediction error (PE) was determined. The SD of the mean PE was plotted against the corneal refractive index value, and a concave upward curve was obtained. The refractive index value leading to the lowest SD was selected: in our case, this value was 1.363 (Fig. 52.3).

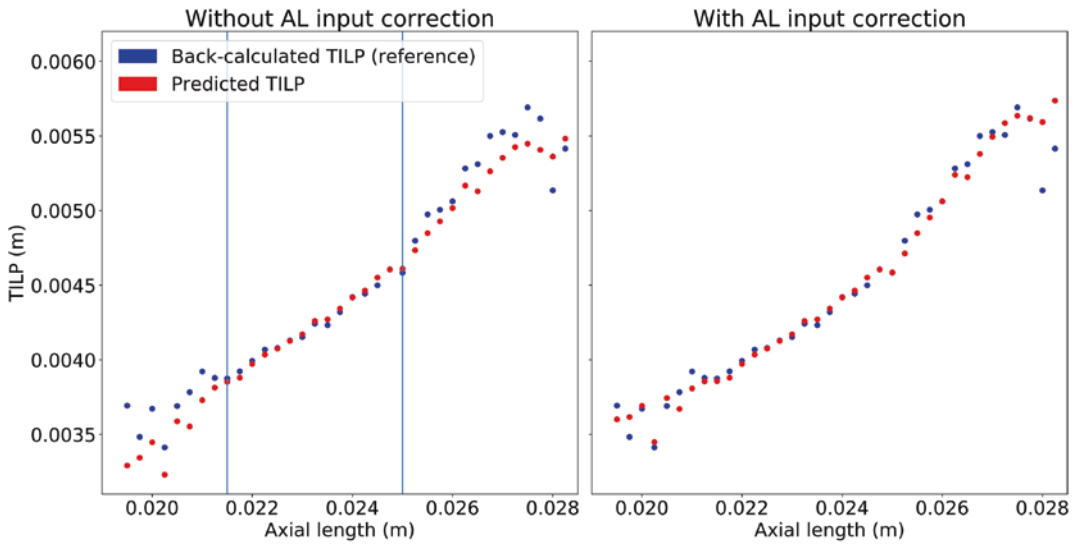


Fig. 52.4 Predicted TILP and back-calculated TILP are plotted against AL, without AL input correction (left) and with input correction (right). AL input correction in multiple regression allows to correct for the TILP prediction error that arises below 21.5 mm and beyond 25 mm. From

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Table 52.4 Modified CMAL calculation, to adapt the CMAL value used as an input in the multiple regression algorithm to the AL

(52.14) $CMAL_{modified} = CMAL + AL \text{ correction factor}$ With AL correction $factor = threshold - AL * weight$	Corrected CMAL calculation, used as an input in the TILP prediction algorithm. NB: The optical equations use the non-modified CMAL value
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Extreme AL Adjustment in the Multiple Regression Algorithm

The mean reference TILP values and mean predicted TILP values predicted by the final multiple regression algorithm were calculated for each AL value rounded to the nearest 0.25 mm. The resulting graph is shown in Fig. 52.4. Systematic and increasing errors were identified for very short and very long eyes, after a given threshold, proportional to the distance to this threshold. The error thresholds were visually defined as 21.5 mm and 26 mm, for short and long eyes, respectively.

A correction factor was applied to the CMAL value used as an input in the TILP predicting algorithm. This correction factor was defined as the absolute value of the difference between the

chosen upper/lower threshold and the AL of the considered eye, multiplied by a weight. This correction factor was added to the CMAL value used as an input in the algorithm if its AL was below the lower AL threshold or beyond the upper AL threshold. The optimal weight to apply to short and long eyes was systematically determined for both AL categories. The CMAL value used in the optical part of the equation was never modified (Table 52.4).

Formula Development for IOLs with Unknown Geometry

If a large dataset is available for an IOL of unknown geometry, we propose to apply the following four-step methodology:

- create a theoretical parameter table for the considered IOL, using the real refractive index of the IOL, a refractive index of 1.336 for the medium surrounding the lens (as required by the ISO 11979-2 norm) [7], and a symmetric biconvex shape
- follow the aforementioned formula development process
- calculate the mean TILP prediction error for each IOL power step and look for a pattern of TILP prediction error
- manually account for this error in the TILP prediction function, depending on the IOL power for which the prediction is made.

Prediction for IOLs with Unknown Geometry and No Available Data

To allow a SE prediction for IOLs with no data available, the adjusted SRK/T A constant for each IOL model of a large dataset comprising 28 IOL models was calculated. The predicted TILP was calculated. For each IOL model, this value was shifted by an equal amount for each eye until the mean prediction error was equal to zero for this model. A linear regression was fitted to predict the TILP shift associated with a given SRK/T A constant.

Performances of the PEARL Formula

In the main PEARL-DGS article [1], two test sets of 677 and 262 eyes were analyzed. The PEARL-DGS formula yielded the lowest SD on the first set (± 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), as well as the lowest SD on the second set (± 0.269 D), followed by Olsen (± 0.272 D), K6 (± 0.276 D), EVO 2.0 (± 0.277 D), and BUII (± 0.301 D).

Independent peer-reviewed studies evaluated and compared the PEARL-DGS formula along with other fourth-generation IOL calculation formulas. In three of seven studies, PEARL-DGS ranked first with a median absolute error (MedAE) varying between 0.190 and 0.310 and

a percentage of eyes with a postoperative refractive error of <0.5 diopter, varying between 74% and 87.1%. In a cohort of short axial eye length, Wendelstein et al. [8] showed that PEARL-DGS, Okulix, Kane, or Castrop formulas had the lowest MAE (0.260, 0.300, 0.300, and 0.270, respectively). Evaluating the refractive result of 171 eyes, Rocha de Lossada [8, 9] found that Barrett and PEARL-DGS performed best for medium eyes (MAE = 0.237 and 0.263, respectively; % eyes <0.5 D = 89.34 and 86.89%, respectively).

Table 52.5 presents and compares the performance of PEARL-DGS and new-generation IOL calculation formulas.

Perspectives

The accuracy of the postoperative refraction calculation depends on the accuracy of the parameters entered in the equation (biometric measurements, IOL geometrical parameters, refractive indices), on the accuracy of the physical lens position prediction, and on how closely the physical model used in the formula approximates the reality. It is therefore interesting to increase the accuracy of the biometric measurements, increase the number of biometric parameters that are measured or known with certainty rather than predicted or assumed, increase the accuracy of the physical models used to perform the calculation, and increase the accuracy of the IOL postoperative physical position.

The PEARL-DGS formula toolbox can be used without modification to back-calculate the TILP value using measured posterior corneal radius and refractive index values, which could increase its performance. Similarly, we advocate for the disclosure of IOL radius of curvatures, thicknesses, and refractive indices by IOL manufacturers.

Our method can also be used without modification to replace the CMAL sum-of-segments AL approximation by an exact, measured sum-of-segments AL value. This more precise way of measuring the AL should logically become the norm. One of the main obstacles for the wide

Table 52.5 Performance comparison of PEARL-DGS and IOL calculation formulas

Study	First Author	Corresponding Author	Country	Journal	Date	Subgroup
1	Giacomo Savini	Giacomo Savini	Italy	British Journal of ophthalmology	Jun-20	NA
2	Huanhuan Cheng	Mingxing Wu,	China	Journal of refractive surgery	Jul-20	Small groups
3	Leonardo Taroni	Leonardo Taroni	Italy	Journal of cataract and refractive surgery	Dec-20	NA
4	Diogo Hipólito-Fernandes	Diogo Hipólito-Fernandes	Portugal	British Journal of ophthalmology	Nov-20	ACD < 3.00 mm 3.00 < ACD < 3.5 mm ACD > 3.5 mm
6	Diogo Hipólito-Fernandes	Diogo Hipólito-Fernandes	Portugal	Clinical ophthalmology	Dec-20	
7	Jascha Wendelstein	Isaak Raphael Fischinger	Austria	British Journal of ophthalmology	Jan-21	All SA60AT (n = 111) ZCB00 (n = 39)

Study	MedAE (% eyes <0.50D)														
	Barrett Universal II without ACD	Barrett Universal II with ACD	EVO 2.0 without ACD	EVO 2.0 with ACD	Haigis	Hoffer Q	Holladay 1	Holladay 2AL	Kane	Naeser 2	Pearl DGS	RBF 2.0	SRK/T	T2	VRF
1	0.218 (88%)	0.218 (85.5%)	0.225 (87%)	0.233 (83.5%)	0.240 (82%)	0.229 (84%)	0.232 (88.5%)	0.228 (83%)	0.214 (86.5%)	0.256 (80%)	0.238 (84.5%)	0.215 (85%)	0.223 (86%)	0.228 (88.5%)	0.235 (84.5%)
2	NA	0.283	NA	0.293	0.322	0.379	0.376	0.325	0.286	NA	0.305	0.314	0.371	0.317	NA
3	NA	0.240 (86.81%)	NA	0.260 (86.81%)	0.244 (78.02%)	0.239 (82.42%)	0.257 (82.42%)	0.285 (82.42%)	0.232 (85.71%)	0.236 (79.12%)	0.190 (86.81%)	0.232 (85.71%)	0.238 (80.22%)	0.245 (85.71%)	0.234 (82.42%)

Table 52.5 (continued)

		MedAE (% eyes <0.50D)														
Study	Barrett Universal II without ACD	Barrett Universal II with ACD	EVO 2.0 without ACD	EVO 2.0 with ACD	Higgins	Hoffer Q	Holladay 1	Holladay 2AL	Kane	Naeser 2	Pearl DGS	RBF 2.0	SRK/T	T2	VRF	
4	Anterior chamber depth, lens thickness and intraocular lens calculation formula accuracy: Nineformulas comparison	NA	NA	0.297 (78%)	0.313 (72.7%)	0.295 (71.8%)	0.289 (74.4%)	NA	0.277 (80.2%)	NA	0.270 (81.1%)	0.280 (74.9%)	0.292 (76.7%)	NA	NA	
		0.29 (78%)	NA	0.297 (80.6%)	0.313 (76.6%)	0.295 (78.6%)	0.288 (79.3%)	NA	0.276 (81.6%)	NA	0.270 (79.9%)	0.280 (77.9%)	0.292 (77.9%)	NA	NA	
		0.310 (76.9%)	NA	0.285 (75.7%)	0.319 (75.7%)	0.347 (67.5%)	0.326 (75.7%)	NA	0.286 (76.3%)	NA	0.310 (74%)	0.320 (77.5%)	0.370 (71.6%)	NA	NA	
6	VRF-G, a new intraocular lens power calculation formula: A 13-formulas comparison study	0.291 (77.8%)	NA	0.282 (78.5%)	0.309 (74.5%)	0.317 (69.9%)	0.299 (74.3%)	NA	0.274 (79.3%)	0.309 (74.9%)	0.290 (76.9%)	0.291 (76.7%)	0.303 (75.1%)	0.291 (75.5%)	0.293 (76.7%)	
7	Project hyperopic power prediction: Accuracy of 13 different concepts for intraocular lens calculation in short eyes	NA	NA	0.300 (70%)	0.320 (68%)	0.380 (60.7%)	0.340 (66.7%)	0.380 (66%)	0.300 (78.7%)	NA	0.260 (80%)	0.320 (73.3%)	0.420 (76.9%)	NA	NA	
		0.320 (63.1%)	n	0.340 (71.2%)	0.310 (70.3%)	0.380 (62.2%)	0.360 (64%)	0.380 (64.9%)	0.300 (79.3%)	NA	0.270 (77.5%)	0.320 (73%)	0.450 (53.2%)	NA	NA	
		0.340 (61.5%)	n	0.260 (66.7%)	0.410 (61.5%)	0.340 (56.4%)	0.250 (74.4%)	0.410 (69.2%)	0.350 (76.9%)	NA	0.260 (87.2%)	0.350 (74.4%)	0.360 (59.3%)	NA	NA	
Study	VRF-G	Olsen	Lada SF	Castrop	Okulić	n	IOL	Mean AL +/-SD	Design							
1	Comparison of 13 formulas for IOL power calculation with measurements from partial coherence interferometry	NA	NA	NA	NA	200	Hoya SI255	23.66 +/- 1.23	Retrospective							
2	Refractive predictability using the IOLMaster 700 and artificial intelligence-based IOL power formulas compared to standard formulas	0.283	NA	NA	NA	410	Envista MX60	24.62 +/- 2.42	Retrospective							
3	Outcomes of IOL power calculation using measurements by a rotating camera combined with partial Scheimpflug coherence interferometry	NA	0.220	NA	NA	91	SN60WF	24.01 +/- 1.56	Prospective							
4	Anterior chamber depth, lens thickness and intraocular lens calculation formula accuracy: Nineformulas comparison	NA	NA	NA	NA	227	SN60WF	22.98 +/- 0.66	Retrospective							
		NA	NA	NA	NA	299		23.36 +/- 0.69								
		NA	NA	NA	NA	169		23.83 +/- 0.79								
6	VRF-G, a new intraocular lens power calculation formula: A 13-formulas comparison study	0.273 (79.5%)	NA	NA	NA	828	SN60WF	23.41 +/- 1.30	Retrospective							
7	Project hyperopic power prediction: Accuracy of 13 different concepts for intraocular lens calculation in short eyes	NA	0.330 (70%)	0.270 (74.7%)	0.300 (79.3%)	150	SA60AT or ZCB00	20.98 +/- 0.54	Retrospective							
		NA	0.330 (68.5%)	0.280 (73.9%)	0.300 (80.2%)	111	SA60 AT									
		NA	0.320 (74.4%)	0.270 (76.9%)	0.280 (76.9%)	39	ZCB00									

adoption of those kinds of innovations is that earlier formulas will perform differently when used with differently measured biometric parameters. Developing a proven, reproducible, and open-source formula-building process could allow researchers to permanently adapt a given formula to new innovations in biometric measurements and newly disclosed IOL parameters.

The advent of OCT in biometry opens new perspectives in the measurement of the anterior segment preoperatively. OCT imaging is unique in its potential ability to both find new biometric parameters (e.g., equatorial lens position [10]) and to directly use anterior segment images in deep learning algorithms, thus opening the door to the use of other powerful AI tools to predict the postoperative lens position.

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