47 Ladas Super Formula: Origin and Evolution with AI

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Introduction

The first formulas to determine the power of an IOL to achieve a specific refractive outcome were introduced in the 1970s by Colenbrander, Fyodorov, and Binkhorst. [1–3] Over the ensuing 50 years, many significant advances have been made to improve outcomes. Reasons for this have been more precise measurements of the structural variables of the eye in addition to improved theoretical analysis of these variables. Further, "adjustments" to these formulas were made when the formulas appeared to underperform. Our interest and contribution are the way we visualize formulas, compare them, combine them, and ultimately adjust them using artificial intelligence. Our ability to achieve this has occurred because computing power and modeling advancements have made this much more viable.

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Formulas throughout the years have been described in multiple ways, one of which is by "generations." [4] However, some formulas do not uniquely fit into a specific category. The SRK I was a regression-based formula characterized as the first generation and used actual outcome data for its development. [5, 6] This first empiric formula was further modified by axial length. [7] Perhaps, this was the first attempt at "adjusting" a formula.

The next generation of formulas was theoretical in that they used the measurement of axial length and corneal power to predict the effective lens position of the implanted IOL. These formulas included the Hoffer Q, Holladay 1, and SRK/T. [8–10] Further, important to our work is that particular formulas have been proven to work best with specific eyes. For instance, it was generally accepted that the Hoffer Q worked particularly well with short eyes, Holladay 1 with average eyes, and SRK/T with longer eyes. This was likely related to the way that the effective lens position was calculated by each formula.

There has also been much interest and work over the last 25 years to determine the variables beyond axial length and corneal power that may lead to improved outcomes. Additional variables have been shown to improve outcomes when accounted for individually. For instance, the Wang-Koch adjustment for axial length has been applied to eyes greater than 25 mm. [11, 12] It is doubtful that any axial length adjustment should

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start and stop at exactly 25 mm. Others have proposed incorporating additional variables to account for a multitude of factors. The Holladay 2 formula released in 1996 includes additional variables of lens thickness, corneal diameter distance, preoperative refraction, and age [13]. Other potential variables that have been suggested to have an effect on IOL prediction include equatorial lens position, age, race, gender, aphakic refraction, relative ratio of various eye segments, C-factor, posterior corneal power, corneal thickness, specific lens design, and exact power of the IOL [4, 14–19]. These variables do not occur in a vacuum and are likely intimately related to other variables such as ACD.

So, with the following assumptions we started to work on and continue to modify our formula. These assumptions include that specific formulas perform better in certain eyes, targeted "adjustments" can improve outcomes, and there are multiple variables that can be used with these adjustments. If now one takes into consideration the computing power that is available, there seems to be a path forward that uses all of these ideas to optimize outcomes.

LSF 1.0

The first step for our group in developing and working with formulas was to start thinking about them differently. Although various theoretical formulas seemed to use different constants and variables, their mathematical structure was very similar. This "visual" interpretation of formulas has been used in other mathematical disciplines. Using the best "peer-reviewed" literature, we created a formula that used multiple parts of various formulas and added adjustments. Figure 47.1 shows what the formula looked like graphically when it was first published. [20] This initial iteration that we described in the article included parts of the Hoffer Q, the Holladay 1, and the SRK/T. Further, the Wang-Koch adjustment was

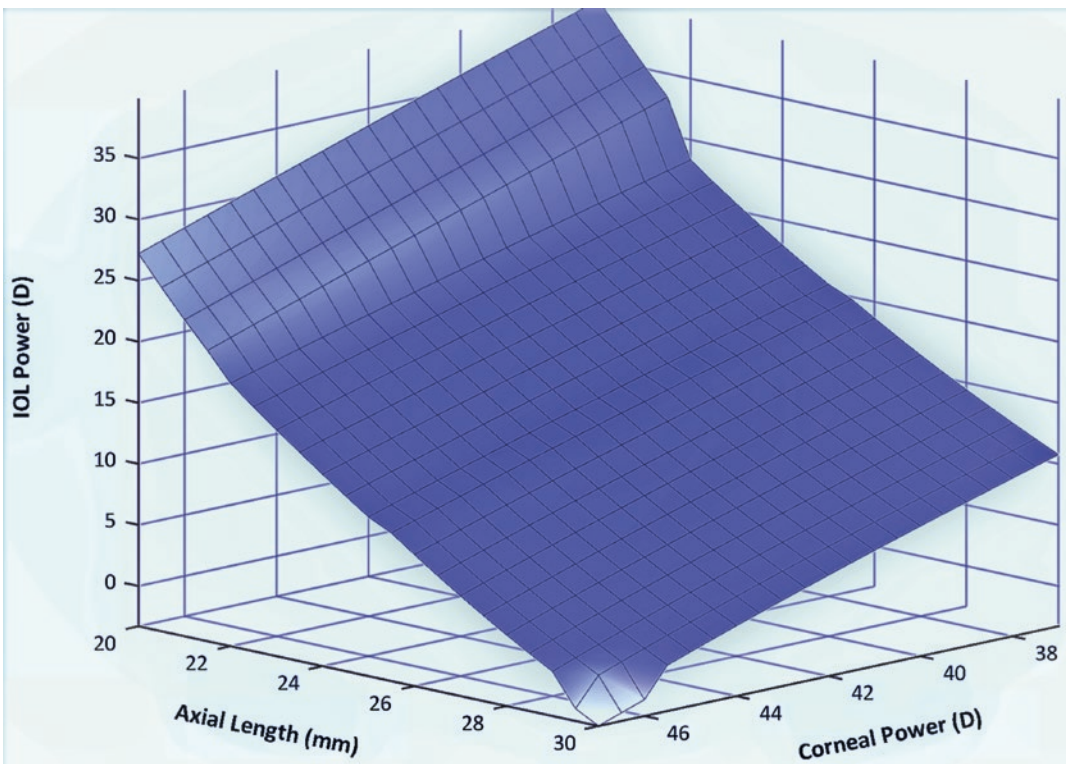

Fig. 47.1 Original Super Formula LSF 1.0 with adjustments

used where appropriate. We certainly could have chosen more formulas and adjustments to include but decided upon this for our initial iteration. Further, as mentioned in our original article, we felt that this approach leads to a better conceptual understanding of formulas and becomes a framework for further improvements.

One additional but important facet of thinking about these formulas differently is that specific formulas and specific variables within them can be compared. For instance, Fig. 47.2 demonstrates a graphical analysis of where formulas diverge in their prediction by more than one diopter. The green areas demonstrate when formulas, given a set of variables, are similar. The red areas show when the predictions diverge. Resolving these areas of greatest discrepancy is of clinical relevance as we try to understand and improve formulas in these particular regions.

Analyzing the differences between formulas can allow for better allocation of resources to determine where advances will likely come from and what variables will lead to them. Also, we are able to observe subtle differences in how a particular variable such as ELP calculation can affect a particular formula [21].

The use of multiple formulas leads to better outcomes by selecting the most accurate formula for a particular eye and has been demonstrated in the literature throughout the years. Data presented from our group at ASCRS also demonstrated superior results when compared against modern formulas with this approach reaching 85% of eyes within 0.5 diopters of predicted refraction, which was the best of all formulas tested [22].

To our knowledge, only one other study has attempted to analyze the original iteration. Cooke

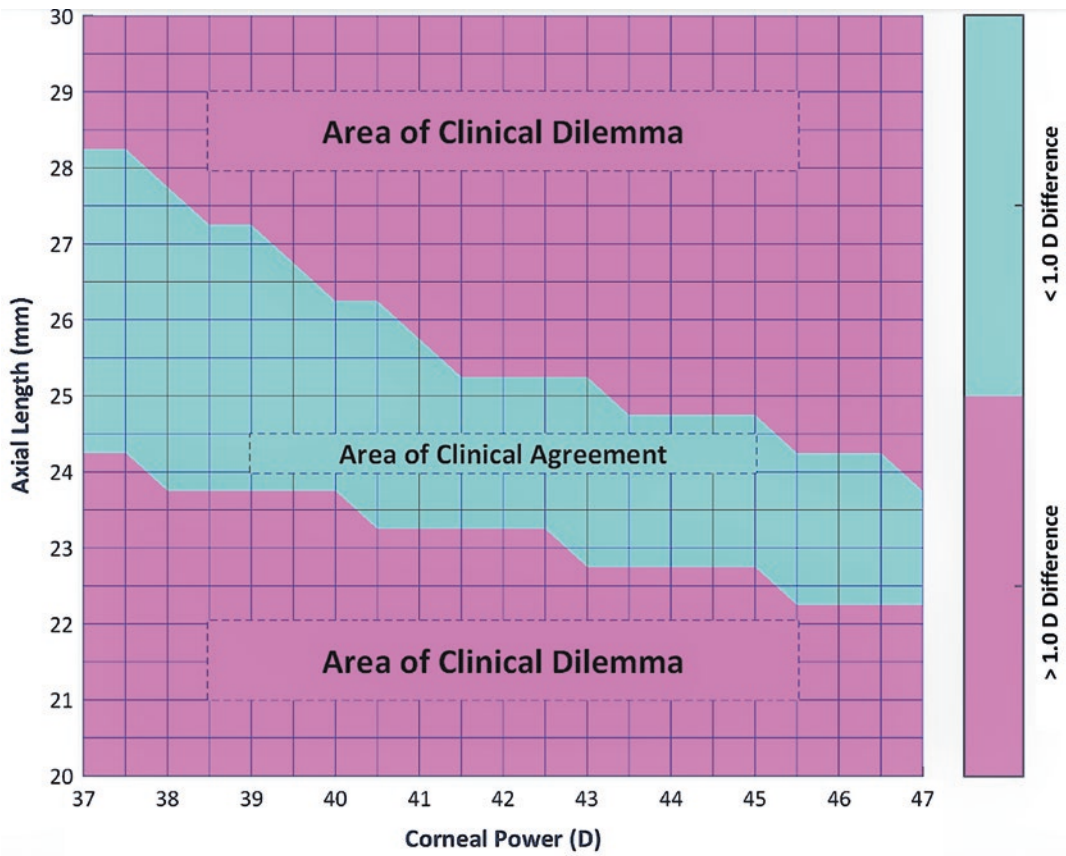

Fig. 47.2 Ladas-Siddiqui plot showing areas of agreement and divergence among formulae

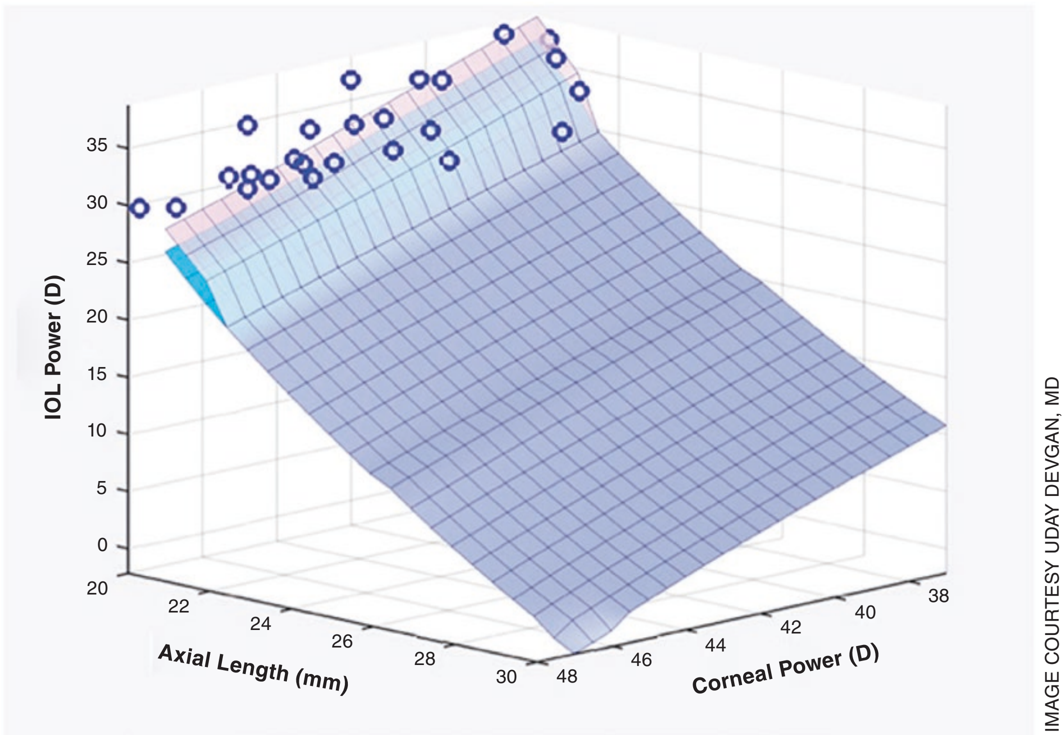

Fig. 47.3 Schematic of "targeted" adjustments

et al. published a paper where they demonstrated that in eyes of all axial lengths, it performed well with approximately 80% within 0.5 diopters of predicted refraction [23]. This was one of the best-performing formulas; however, the author attempted to program it himself without contacting our group so we are not sure that it was done correctly and included all adjustments. The authors also made an interesting comment in the manuscript that is pertinent to our discussion here. He noted, "one peculiarity of the Super Formula is that it could not be optimized. The mean prediction error could not be brought to zero." Optimizing it correctly by accounting for the different regions of the formula would have perhaps resulted in even better performance.

The ultimate benefit of the super formula is that it is a framework to adjust and improve going forward. With this approach, one can adjust or target short eyes rather than move an A-constant up or down across a range of eyes. For instance, Fig. 47.3 is a schematic of how a particular region (short axial length) can be targeted and adjusted without influencing other regions of the formula. This is similar to what is done with the well-accepted Wang-Koch adjustment for long eyes.

LSF 2.0. The Introduction of AI

After deciding on a starting point or "framework," we began to refine and improve the original LSF 1.0 formula. Historically, as mentioned previously, a formula was adjusted by moving the A-constant up or down across the entire spectrum of eyes. Indeed, surgeons were told to "personalize" a formula based on twenty or so cases. The thought of adjusting formulas based on relatively few outcomes is not uncommon. For example, instances of a specific formula recommendation or "adjustment" to a particular set of eyes have been based on studies with less than 100 outcomes [8, 11, 24, 25]. These thought leaders had less resources and outcome data to work with. Further, as new IOLs came on the market, the Users Group for Interferometry (ULIB) was

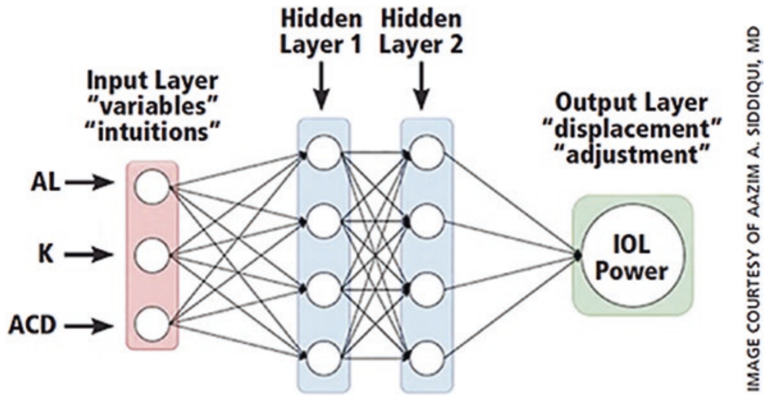

Fig. 47.4 Schematic of our AI algorithm used to adjust a formula

developed to hone A-constants for large groups of surgeons. While all of this was certainly helpful and improved outcomes, it seemed to us that outcome analysis could be improved upon by treating "adjustments" differently.

Thus, further advancements and adjustments are unlikely to be conceived as single variables or discrete formulas, and progress using such approaches likely would be inefficient compared to machine learning methods. Artificial intelligence and deep learning seem particularly suited for this task and have the ability to "weigh" the effect of multiple variables on reaching a desired outcome.

There are two categories of machine learning, and both could be applicable to cataract surgery and IOL calculations. These include unsupervised and supervised learning. Unsupervised learning uses input data to discover similarities among datasets. Unsupervised learning has been used by our group to predict which eyes are particularly susceptible to poor refractive outcomes, for instance, predicting eyes that are likely to have an outcome of greater than one diopter of targeted refraction.

Supervised learning, which is more pertinent to our discussion here, is the other branch of machine learning that utilizes outcome data, in addition to the input variables, to develop a predictive model. This is the type of learning that we primarily use to improve formulas. Regression-based supervised learning uses specific algorithms to establish the relationship between the input variables it is given and the outcome. Cataract surgery and IOL calculations are particularly suited to this task in medicine. This is because cataract surgery is precise, its inputs and outcomes are mathematical, and the outcome is known within a matter of weeks. Methods of supervised nonlinear regression machine learning models that we use include support vector regression, extreme gradient boost, and neural networks.

As mentioned earlier, our approach to AI differs from others in that it starts with a "blueprint" or framework formula (the original LSF) and uses outcome data to "adjust" each eye individually. The approach described in this paper is contrasted with forms of deep learning such as the Hill-RBF (radial basis function) that "back calculate" an algorithm from a fixed dataset. With our approach, there are no instances where a calculation is "out of bounds" because of paucity of data [26]. A schematic of our methodology is demonstrated in Fig. 47.4. As seen in the figure, we use the input variables of axial length, corneal power, and ACD and then develop an algorithm that "predicts" the error. This error would be seamlessly used to adjust an eye with similar input variables. By doing this, we mitigate the potential downsides of AI while maximizing its ability to refine a formula. Also, this particular approach can be used to add additional input variables such as posterior corneal power or total corneal power.

Our initial algorithm to introduce AI used vetted and refined outcome data supplied by in-house data and trusted colleagues. The use of outcome data for AI and its reliability cannot be emphasized enough. We feel that our concept of adjusting a baseline formula is novel and unique. The LSF 2.0 included further adjustments based on outside studies that included 8000 eyes and an in-house library of outcome data that included 3000 eyes. This was used to adjust the formula and was tested on our internal data. We currently have more than 6000 eyes available in our library data and continue to test, refine, and introduce new algorithms.

Our formula has recently been tested and performed well compared to all modern formulas with one of the lowest mean absolute errors [27]. Indeed, the results of this study are shown in the table below. The predicted error demonstrated the lowest standard deviation of all formulas tested as well as superior results for eyes within predicted refraction.

PE ± SD	MedAE	PE ≤ ±0.50 D	PE ≤ ±1.00 D
−0.003 ± 0.366	0.220	85.71%	98.90%

In addition to creating AI-enhanced formulas from our original baseline formula, we are also able to improve existing formulas. Recent work from our group has demonstrated that we can improve multiple generations of formulas with our methodology [28]. Indeed, multiple supervised learning algorithms were used to improve the MAE, MedAE, and eyes within 0.5 diopters of the target with various formulas. Other work presented elsewhere has shown that this can be done with other formulas such as the Barrett Universal II and Haigis. Interestingly, when we enhance a formula with a specific set of variables, we see each formula improve to a similar threshold. From a theoretical standpoint, it is perhaps predictable that each algorithm was able to predict and adjust each of the formula's "errors" individually and for each eye in a way that could never be written in a mathematical formula by a human.

The most recent version of our formula can be found at www.iolcalc.com. The formula is updated as needed and will continue to evolve. The input of the formula is straightforward, and biometer inputs can be uploaded and autopopulated to the interface seen below in Fig. 47.5.

The Ladas Super Formula can also be accessed securely via a smartphone application (Fig. 47.6).

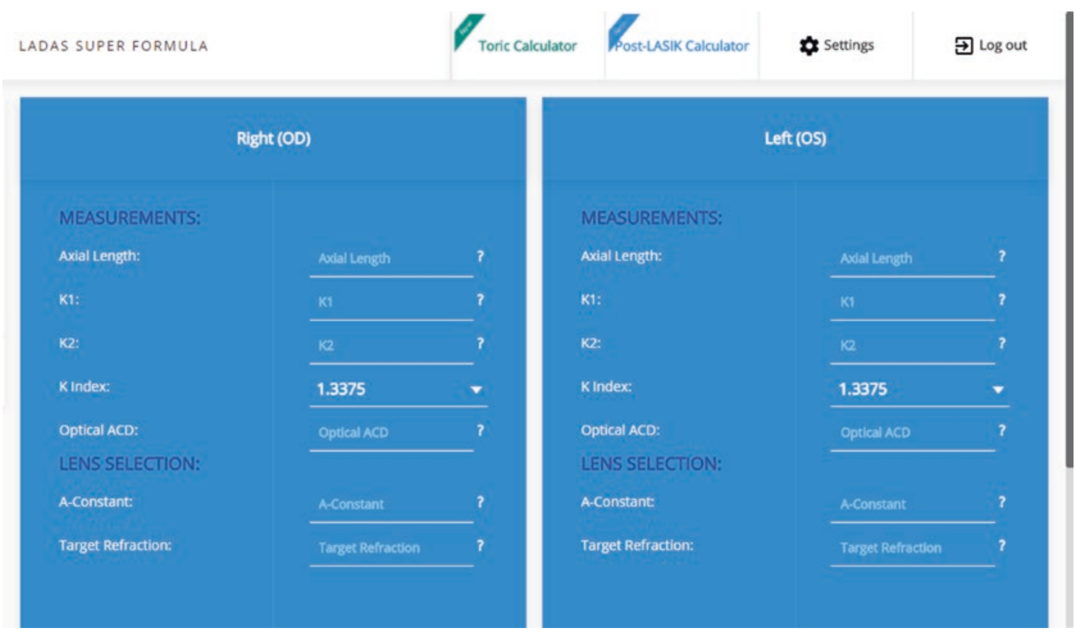

Fig. 47.5 Data input screen on iolcalc.com

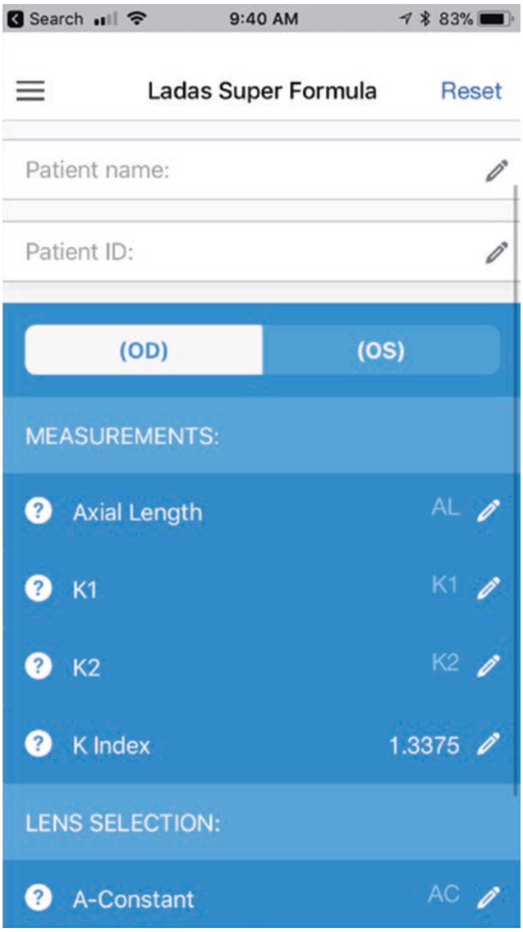

Fig. 47.6 Smart phone app for calculations and input of outcome data

Automation of the Process and Next Steps

Generally, refining IOL formulas has required the availability of accurate postoperative data. Usually, these data are composed of preoperative biometry and postoperative manifest refraction (MRx) data taken from multiple high-volume surgeons. However, MRx measurements are often suboptimal due to technique variability, room length, patient's subjective participation, and time taken to perform measurements. The use of autorefraction (ARx) or wavefront data can potentially help eliminate most issues that occur with MRx acquisition. However, the correlation between ARx and MRx for the purposes of IOL formula optimization is still unclear and is being currently investigated in ongoing studies. Given a correlation exists between the two modalities for this purpose, then integration of AI in this schema may be useful by allowing the collection of big data and leading to the development of AI-based IOL formulas.

We have presented a pilot study that demonstrated no significant difference between the spherical equivalent of manifest refraction and autorefraction in pseudophakic eyes [29]. Further, we can demonstrate that MRx can be substituted with ARx for basic refinement of formulas.

There are many potential benefits of AI integration in automated refraction. Customized AI-IOL calculation formulas may be developed for a given surgeon using the surgeon's own postoperative data. This could help account for surgeon-to-surgeon variation, which is responsible for a significant portion of error in current IOL calculation methodologies. This could also allow for a system of optimization, which improves upon itself in a recurrent manner. Furthermore, with the "big data" stored within an automated refractor, it will be able to characterize an eye as one with "standard" parameters or one with "unusual" parameters. Thus, AI could preoperatively highlight eyes that are "at risk" for a postoperative refractive surprise.

Conclusion

It takes time for ideas to catch on, but the use of artificial intelligence will definitely be a part of the future of IOL calculations. While better mathematical algorithms will certainly be developed by our group and others in and outside ophthalmology, I believe our approach that uses both deep learning algorithms coupled with the accumulation of massive amounts of objective postoperative data to further refine formulas will eventually become the norm. Only time will tell.

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