· Clinical Research ·

A new software for automated counting of glistenings in intraocular lenses *in vivo*

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Abstract

● **AIM:** To assess the performance of a bespoke software for automated counting of intraocular lens (IOL) glistenings in slit-lamp images.

● **METHODS:** IOL glistenings from slit-lamp-derived digital images were counted manually and automatically by the bespoke software. The images of one randomly selected eye from each of 34 participants were used as a training set to determine the threshold setting that gave the best agreement between manual and automatic grading. A second set of 63 images, selected using randomised stratified sampling from 290 images, were used for software validation. The images were obtained using a previously described protocol. Software-derived automated glistenings counts were compared to manual counts produced by three ophthalmologists.

● **RESULTS:** A threshold value of 140 was determined that minimised the total deviation in the number of glistenings for the 34 images in the training set. Using this threshold value, only slight agreement was found between automated software counts and manual expert counts for the validating set of 63 images (κ=0.104, 95%CI, 0.040-0.168). Ten images (15.9%) had glistenings counts that agreed between the software and manual counting. There were 49 images (77.8%) where the software overestimated the number of glistenings.

● **CONCLUSION:** The low levels of agreement show between an initial release of software used to automatically count glistenings in *in vivo* slit-lamp images and manual counting indicates that this is a non-trivial application. Iterative improvement involving a dialogue between software developers and experienced ophthalmologists is required to optimise agreement. The results suggest that validation of software is necessary for studies involving semi-automatic evaluation of glistenings.

● **KEYWORDS:** new software; automated counting; glistenings; intraocular lenses; slit-lamp images

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INTRODUCTION

Glistenings are vacuoles that can develop within intraocular lenses (IOLs) implanted as part of routine cataract surgery. They occur in all materials used for IOLs but are mostly associated with hydrophobic acrylic polymers[1-11]. Glistenings form when water permeates through micro-channels within the material to create small fluid-filled inclusions that are typically up to 30 mm in size and may affect visual function[1,12-19]. Improved manufacturing processes have led to a reduction in the incidence of glistenings in IOL models[1,3]. Nevertheless, glistenings persist even in the latest so-called 'glistenings-free' materials[1,3,20].

Current methods for quantifying glistenings in clinical studies, (number and sometimes size and shape), have largely centred on subjective grading[1,3,12,17,20-21]. Image processing provides an objective method for quantifying glistenings from digital images either obtained *in vivo* or from laboratory studies. Most publications that have taken this approach have used a public domain image processing programme - Image J (National Institutes of Health, Bethesda. Available at: http://rsb.info.nih.gov/ij/. Accessed 1 March 2022.)[5,14,22-25]. These studies focus on the clinical or laboratory results, or clinical consequences of laboratory findings. As a result, very little detail is given about the methods used to quantify glistenings or results presented to confirm that the methods produce valid results.

Digital images obtained in laboratory studies can be imaged with uniform illumination, include the entire IOL and have far less variability than *in vivo* images. A few reports give details of the image processing steps and validation of the software methods against ground truth images[26]. In contrast, obtaining *in vivo* images poses a significant challenge due to multiple optical media and intraocular structures involved and the potential for artefacts in images such as IOL scratches and scuff marks, pigment granules, posterior capsule irregularities and the anterior capsulorrhexis. Furthermore, *in vivo* imaging is sensitive to movements of both the subject and the examiner as well as the ambient illumination. High-quality clinical imaging and automated image processing including utilization of artificial intelligence is becoming increasingly popular in ophthalmology[27-29].

The aim of the current work is to evaluate and validate the first release of bespoke software designed by Sparca Ltd. (Croydon, Surrey, United Kingdom) for the quantification of glistenings from *in vivo* slit-lamp images. To our best knowledge, it is the first study where software developers and clinicians with experience of IOL glistenings, image processing and evaluation, have collaborated to assess the performance of image processing software to quantify glistenings.

MATERIALS AND METHODS

Software Description The software was designed and developed by Sparca Ltd (Croydon, Surrey, United Kingdom), an ophthalmic software and technology firm. The technology is based on digital signal processing (DSP) and operates in both image processing and computer vision (CV) fields of study. The newly developed software and technology retains all original data points as part of the processing, ensuring accurate pixel and therefore data representation. This software is the first attempt by our team to deliver software that automatically detects and counts glistenings. The glistening analysis was designed to detect glistenings from *in vivo* digital slit-lamp images using a proprietary technique employing DSP and CV algorithms, which delineate the DSP signal based on channel and classify pixels as either glistening or not glistening. The data point classification can be manually controlled *via* a threshold setting that affects the specificity and sensitivity of the algorithm output. This is necessary given the variability of the *in vivo* images and the preferred subset classification, such as signal to noise ratio. The threshold is based on class-based pixel values, in which each pixel within the areas of interest is assigned to a class because of the quantification algorithm.

The major steps in obtaining glistenings counts are indicated in Figure 1. Semi-automatic glistenings detection begins with uploading an *in vivo* slit-lamp image into the online software system. A DSP iris detection algorithm is applied to the image and a circle fitted to the detected iris delineating the pupil. The software overlays five 1 mm^2 measurement squares in a vertical strip centred on the pupil. The user then chooses either

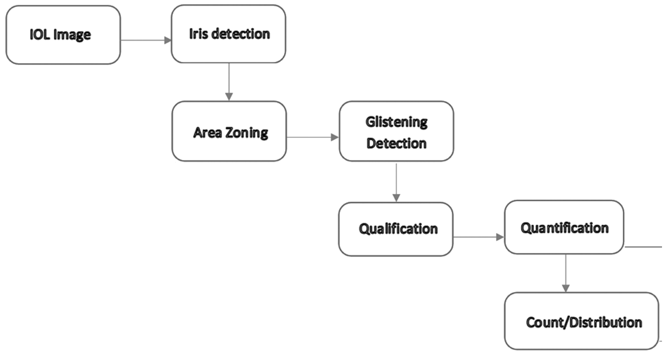

Figure 1 Steps taken by the software in obtaining glistenings counts
IOL: Intraocular lens.

the three central or all five 1 mm^2 measurement squares for analysis. The software deploys the glistenings quantification function, with the threshold selected by the user (range 0-254), and glistenings counts are presented based on distribution between the three or five areas, with results shown as a function of area. Figure 2 shows the software interface.

For the initial development of the software, a set of 12 anonymized images from previous studies[3,12] demonstrating a full range of IOL glistenings densities [grade 0-7 on the Guy's and St Thomas' Trust (GSTT) scale[12]] were used. In the images, glistenings were manually drawn and labelled pixel by pixel by one of the authors (Stanojcic N), who is experienced in glistenings imaging, grading, and counting. These were used as ground truth images when developing the alpha version of the software.

Training Set The training set comprised 34 images obtained from a previously published study from our group[12]. Images were obtained from patients implanted with the same-design monofocal, spherical, hydrophobic acrylic IOLs (Alcon AcrySof SA60AT) at different post-operative follow-up times (median 14mo, range 5-66mo). This study was approved by London Bloomsbury Research Ethics Committee (REC reference 17/LO/1074) and this research conformed to the tenets of the Declaration of Helsinki[12]. Images of glistenings were taken with a 5MP digital camera (Topcon DC-4, Topcon Corporation, Tokyo, Japan) mounted on a slit-lamp (Topcon SL-701, Topcon Corporation, Tokyo, Japan). All images were taken under the same mesopic conditions; the ambient illuminance on the slit-lamp table did not exceed 0.3 lx. A vertical slit beam, 10 mm high by 2 mm wide, was used at an angle of 40 degrees. Magnification was 16× with the slit-lamp set to maximum brightness to illuminate the centre of the IOL within the pupil. For the Topcon DC-4 camera, an ISO of 800 was used with a shutter speed of 1/30 second, a sharpness of '+32' (default), a denoising of '0' (default), a contrast of '50' (default) and the 'auto-brightness' setting at "off".

The initial software thresholds were chosen based on preliminary testing of the software by authors O'Brart D

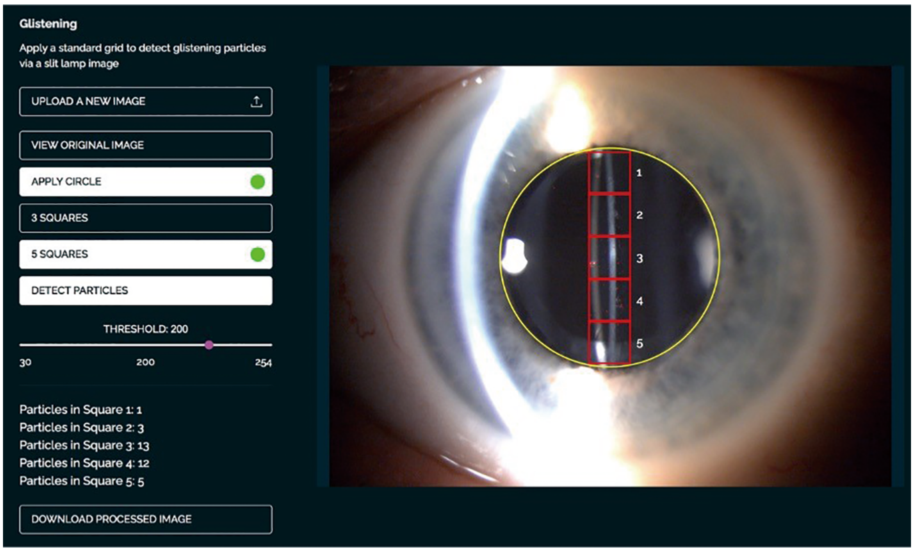

Figure 2 Software interface indicating steps in the detection process and a sample image with output.

and Stanojcic N on 8 images from a previous study[12]. Four images had less than five manually counted total glistenings and the remaining four images had more than 40 glistenings. At thresholds lower than 70, the software was incorrectly identifying image noise as glistenings. Based on preliminary findings, the graders agreed the following four threshold values for initial formal software testing: 70, 90, 170, and 254. Each image in the training set (n=34) was then analysed independently by the one author (Stanojcic N), using the software at these four pre-determined threshold values.

The glistenings counts generated by the software were then passed to an independent researcher for statistical analysis (Hull CC). The software counts were compared to the manual counts agreed between three experienced, ophthalmologist graders prior to the start of software development. For each threshold an error score was calculated by taking the automated software count and subtracting the expert agreed subjective count, considered the 'gold standard'. A negative score therefore meant the software was finding fewer glistenings than the manual graders. The total deviation was then computed by summing the error scores for the central 3 zones of all 34 images and threshold plotted against the total deviation to determine a threshold value that minimised the error. This threshold value was then applied to all images in the validating set to test the ability of the software to detect glistenings without user intervention.

Validating Set The validating set of images was a sub-sample (n=63) selected from a dataset of 278 images collected in a previous study where glistenings had been graded by three experts[3]. This study was approved by West Midlands Solihull Research Ethics Committee (REC reference 17/WM/0414) and this research conformed to the tenets of the Declaration of Helsinki[3]. Stratified sampling was used to create the sub-sample used in the current study so that the number of images with low, medium, and high numbers of glistenings was as balanced as possible. This is because there were a significant number of images with low levels of glistenings in the original data set. One expert grader (Stanojcic N) manually counted the number of glistenings in all 63 images prior to testing the software (In the original study only grades had been determined).

Manual counting of the total numbers of glistenings in each image (all five zones) was compared to the results from the software using the optimum threshold determined from the training set of images.

Statistical Analysis Agreement between the number of glistenings determined by software, and manual counting by an ophthalmologist experienced in glistenings evaluation (Stanojcic N), was assessed using both qualitative and quantitative methods. Scatter plots were used to indicate bias and agreement and Cohen's weighted kappa calculated to give a quantitative measure of agreement. Quadratic weighting was employed to give more credit to near disagreements in the number of glistenings found by each method. Data organisation and manipulation was carried out using Excel (Microsoft Corporation, WA, USA). Graphs and curve fitting were generated using SigmaPlot v14 (Systat Software Inc, Chicago, IL, USA) and agreement statistics calculated using the Real Statistics Resource Pack software Release 7.6 [copyright (2013-2021) Charles Zaiontz available from www.real-statistics.com].

RESULTS

Training Set The variation in the total deviation with threshold for the 34 images in the training set is shown in Figure 3. The relationship is non-linear and so a second-order polynomial curve fit was used, which had an R^2 of 96.8%. The polynomial only has one root within the valid range of threshold values (0 to 254), which was at 140. This threshold was used for subsequent testing using the validating set of images.

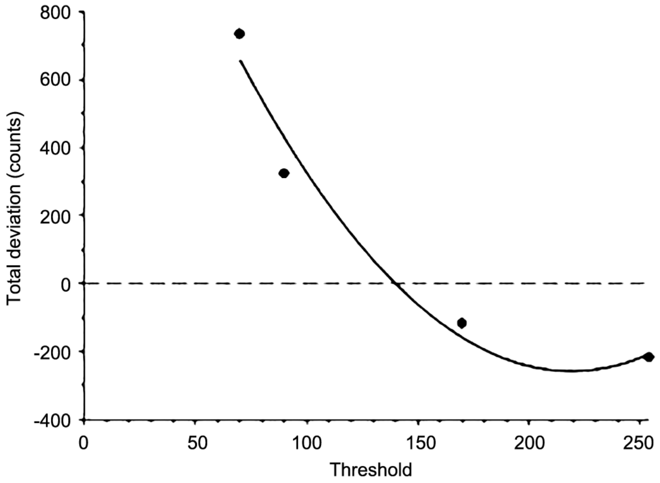

Figure 3 Variation in total deviation (automatic - manual count) for all images in the training set with threshold.

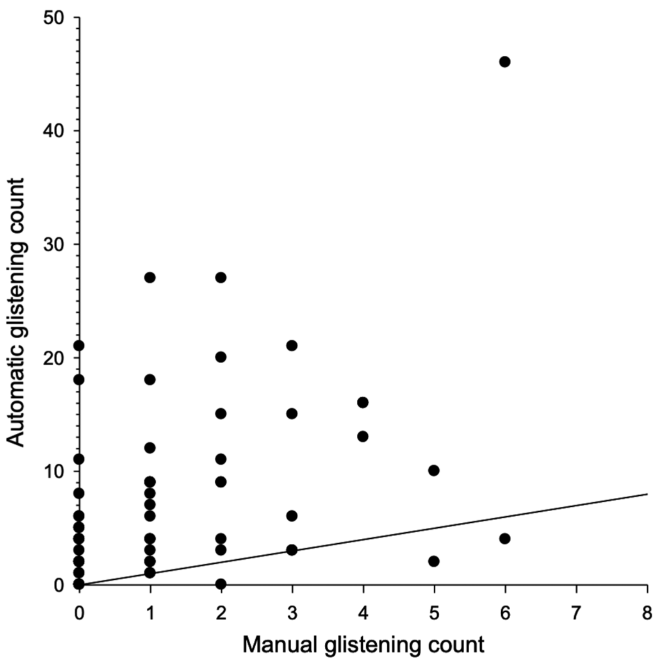

Figure 4 Scatter plot showing agreement between manual and automatic glistenings counts The line is the 1:1 agreement line. There are multiple overlying data points.

Validating Set Figure 4 shows the number of glistenings counted by a manual grader versus the number detected by the software. The line has a gradient of 1 and passes through the origin; points falling on this line represent perfect agreement between the two methods. Ten images (15.9%) had manual and automatic counts for glistenings that agreed but most data points (77.8%) lie above the agreement line indicating that the automated software is over-estimating the number of glistenings. Manual glistenings counts indicate very few glistenings, even when summed across all 5 zones, which is unsurprising since the images in the validating set were taken from a clinical trial comparing two glistenings resistant materials[3]. Cohen's weighted kappa (quadratic weighting) corroborated this observation and indicated only 'slight agreement' between the two methods (κ=0.104; 95%CI, 0.040-0.168) based on the interpretation suggested by Landis and Koch[30].

DISCUSSION

This study has described and validated the initial version of new software developed to count glistenings from *in vivo* slit-lamp images. Only slight agreement was found between automatic glistenings counts and manual counting by an experienced ophthalmologist. Our results indicate that detection of glistenings from *in vivo* slit-lamp images is non-trivial and therefore there is a need for careful testing and validation of the software. Very few studies that have used software for assessing glistenings have included details of the testing and validation of the software. This casts doubt on the results of clinical studies that use automated software counts without evidence of the validity of the methods. A careful and ongoing dialogue is needed between clinicians and software developers to avoid artefacts affecting the results and to optimise software parameters. It may also be necessary to have a pre-assessment phase, which is semi-automatic and requires the input of an experienced clinician.

Our results may have been affected if the training set is not representative of the validating set of images. This is because the training set resulted in a fixed (optimum) value for the threshold used by the glistenings detection algorithm. In our study, both sets of images were taken using the same slit-lamp system and protocol. However, although the same IOL had been implanted in all 34 patients in the training set, the follow-up times varied (median of 14mo; range 5 to 66mo)[12]. In comparison the validating set contained images from only two glistenings resistant IOLs at 12-month follow-up. As a result, very few glistenings were observed in this set of images potentially leading to a signal to noise ratio problem for the software where a similarly small number of artefacts detected (non-glistenings) will significantly impact the agreement. In contrast, the percentage error when a few artefacts are detected and added to a large glistenings count is much lower. Many modern IOLs develop only small numbers of glistenings so any software needs to perform well in this situation.

It is also appropriate to question the acceptance of manual counting as the "gold standard" for comparison. For the training set of 34 images, three graders had previously used the GSTT scale and had graded all five zones. The overall grade for each image was calculated as the sum of the grades for all five zones for each rater. Inter-rater reliability for grading was "good" with an intra-class correlation coefficient of 0.84 (CI: 0.72-0.91). The graders were ophthalmologists with different levels of experience lending support to the idea that manual grading is appropriate as a reference standard for clinical trials or testing the performance of semi-automatic or automatic methods.

Glistenings grades, rather than raw numbers, have been widely used in IOL research and may be more clinically relevant[1,3]. We have therefore investigated how well the software counts are associated with the grades determined by experienced graders. Arguably the grading scale with the best resolution for modern IOLs is the recently published GSTT scale. Its grade boundaries correspond to the much smaller numbers of glistenings that are commonly observed in modern IOL materials. To assess the association between software counts and manual grading, we took the median grade of the three ratters for the training set of 34 images mentioned above. The association between this grade and the number of glistenings counted by the software was 0.42 (Spearman's rho, P=0.015) indicating only a moderate association between software counts of glistenings and GSTT grades.

The most likely reason for poor agreement between automated and manual expert counts are artefacts such as anterior or posterior IOL surface particulates (*e.g.* pigment), IOL scratches and scuff marks [(*e.g.* from the IOL loading device or forceps), posterior capsule irregularities and vitreous floaters] that posed a challenge for the software. Unlike the software, expert graders can exclude artefacts based on subjective determination and experience. To assess how our results are affected by artefacts, we have conducted a sensitivity analysis on the agreement statistic. In this analysis we have progressively removed images with errors in total glistenings counts of more than 30 (one image), 20 (four images) and 10 (14 images) from the validation data set of 63 images. This resulted in weighted kappa statistics of 0.073 (CI: 0.017, 0.128), 0.114 (CI: 0.046, 0.182) and 0.165 (CI: 0.048, 0.282) respectively. Although the level of agreement improves, removing images that may have been affected by artefacts and where there are large differences in counts does not make a significant difference to the overall agreement which remains slight. This could be a signal to noise ratio problem where a difference in counts by only one or two when the number of glistenings is very small will still not produce a kappa value close to one. In contrast, even when there are differences in the number of glistenings counted by the two methods, it is possible to get a value for kappa close to unity provided the results from most images agree and also when there are relatively few images with large differences.

The issue of artefacts affecting the automated counting software has been explored further. Images were ranked according to the difference in the number of glistenings between the two methods and an experienced ophthalmologist reviewed the four images where the difference was 20 glistenings or more. The four images all exhibited one or a combination of the following: opacity or a scratch mark on the anterior surface of the IOL (presumed to be from a loading device or intra-operative manipulation with metallic instruments); posterior capsule irregularities combined with vitreous strands/floaters or pigment granules anywhere on IOL surface. In all instances glistenings in these areas were overestimated. IOL scratch marks do indeed appear like glistenings (granular metallic debris reflecting light) but their distribution pattern does not. Pigment granules on the IOL surface (anterior or posterior) also resemble glistenings in size and shape but their distribution pattern and proximity to the IOL surface do not.

In summary, we have presented findings to validate the initial release of new software designed to count glistenings in *in vivo* slit-lamp images. Our results demonstrate this is a challenging problem and an iterative development process is required between software developers and ophthalmologists to improve on software performance. Our results also indicate that studies using automated detection and counting software should provide appropriate detail and validation of their methods otherwise it is possible that additional and unwanted variability could affect results.

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Conflicts of Interest: Stanojcic N, None; **Hull CC,** None; **Mangieri E,** employee of Sparca Ltd; **Little N,** employee of Sparca Ltd; **O'Brart D** is a consultant for and holds equity in Sparca Ltd and also holds non-commercial research grants from Rayner Ltd. and Johnson and Johnson Inc. for intraocular lens research.

REFERENCES

1 Stanojcic N, Hull C, O'Brart DP. Clinical and material degradations of intraocular lenses: a review. *Eur J Ophthalmol* 2020;30(5):823-839.

2 Tandogan T, Auffarth GU, Son HS, Merz P, Choi CY, Khoramnia R. *In-vitro* glistening formation in six different foldable hydrophobic intraocular lenses. *BMC Ophthalmol* 2021;21(1):126.

3 Stanojcic N, O'Brart D, Hull C, Wagh V, Azan E, Bhogal M, Robbie S, Li JO. Visual and refractive outcomes and glistenings occurrence after implantation of 2 hydrophobic acrylic aspheric monofocal IOLs. *J Cataract Refract Surg* 2020;46(7):986-994.

4 Weindler JN, Łabuz G, Yildirim TM, Tandogan T, Khoramnia R, Auffarth GU. The impact of glistenings on the optical quality of a hydrophobic acrylic intraocular lens. *J Cataract Refract Surg* 2019;45(7):1020-1025.

5 Wang Q, Yildirim TM, Schickhardt SK, Łabuz G, Khoramnia R, Merz PR, Son HS, Munro DJ, Friedmann E, Auffarth GU. Quantification of the *in vitro* predisposition to glistening formation in one manufacturer's acrylic intraocular lenses made in different decades. *Ophthalmol Ther* 2021;10(1):165-174.

6 Colin J, Orignac I. Glistenings on intraocular lenses in healthy eyes: effects and associations. *J Refract Surg* 2011;27(12):869-875.

7 Johansson B. Glistenings, anterior/posterior capsular opacification and incidence of Nd: YAG laser treatments with two aspheric hydrophobic

acrylic intraocular lenses - a long-term intra-individual study. *Acta Ophthalmol* 2017;95(7):671-677.

8 Moreno-Montañés J, Alvarez A, Rodríguez-Conde R, Fernández-Hortelano A. Clinical factors related to the frequency and intensity of glistenings in AcrySof intraocular lenses. *J Cataract Refract Surg* 2003;29(10):1980-1984.

9 Chang A, Behndig A, Rønbeck M, Kugelberg M. Comparison of posterior capsule opacification and glistenings with 2 hydrophobic acrylic intraocular lenses: 5- to 7-year follow-up. *J Cataract Refract Surg* 2013;39(5):694-698.

10 Auffarth GU, Brézin A, Lignereux F, Khoramnia R, Yildirim TM, Kohnen T, Bianco J. Randomized multicenter trial to assess posterior capsule opacification and glistenings in two hydrophobic acrylic intraocular lenses. *Sci Rep* 2023;13(1):2822.

11 House P, Abdul Rahman A, Richards J, *et al*. Long-term clinical audit of glistenings in Alcon Acrysof intra-ocular lenses with and without yellow chromophore. *Clin Exp Ophthalmol* 2020;48(2):251-252.

12 Stanojcic N, O'Brart DPS, Maycock N, Hull CC. Effects of intraocular lens glistenings on visual function: a prospective study and presentation of a new glistenings grading methodology. *BMJ Open Ophthalmol* 2019;4(1):e000266.

13 Kawai KJ. An evaluation of glistening and stability of intraocular lens material manufactured by different methods. *Eur J Ophthalmol* 2021;31(2):427-435.

14 van der Mooren M, Safran S, Weeber HA, Piers P. Trend in Glistening density in Acrylic Intraocular Lenses and its relation to straylight performance. *Invest Ophthalmol Vis Sci* 2020;61:599.

15 Kanclerz P, Grzybowski A. Glistenings might be associated with disability glare. *Eur J Ophthalmol* 2022;32(1):NP296.

16 Stanojcic N, Hull C, O'Brart DPS. Reply to letter from Drs. Piotr Kanclerz and Andrzej Grzybowski entitled Glistenings might be associated with disability glare. *Eur J Ophthalmol* 2022;32(1): NP347-NP348.

17 Borkenstein AF, Borkenstein EM. Polarized glasses may help in symptomatic cases of intraocular lens glistenings. *Clin Optom* 2019;11:57-62.

18 Bharathi M, Senthil S. Cart-wheel pattern intraocular lens glistening. 2021.

19 Saylor DM, Coleman Richardson D, Dair BJ, Pollack SK. Osmotic cavitation of elastomeric intraocular lenses. *Acta Biomater* 2010;6(3): 1090-1098.

20 Philippaki E, O'Brart DP, Hull CC. Comparison of glistenings formation and their effect on forward light scatter between the Acrysof SN60WF and Eternity Natural Uni NW-60 intraocular lenses. *BMJ Open Ophthalmol* 2020;5(1):e000399.

21 Xi L, Liu Y, Zhao F, Chen C, Cheng B. Analysis of glistenings in hydrophobic acrylic intraocular lenses on visual performance. *Int J Ophthalmol* 2014;7(3):446-451.

22 Borghesi S, Colciago S, Zeri F, Scialdone A, Tavazzi S. *In vitro* glistening formation in IOLs: automated method for assessing the volumetric density and depth distribution of microvacuoles. *J Cataract Refract Surg* 2020;46(8):1178-1183.

23 Yildirim TM, Fang H, Schickhardt SK, Wang Q, Merz PR, Auffarth GU. Glistening formation in a new hydrophobic acrylic intraocular lens. *BMC Ophthalmol* 2020;20(1):186.

24 Yildirim TM, Schickhardt SK, Wang Q, Friedmann E, Khoramnia R, Auffarth GU. Quantitative evaluation of microvacuole formation in five intraocular lens models made of different hydrophobic materials. *PLoS One* 2021;16(4):e0250860.

25 Schweitzer C, Orignac I, Praud D, Chatoux O, Colin J. Glistening in glaucomatous eyes: visual performances and risk factors. *Acta Ophthalmol* 2014;92(6):529-534.

26 Jitpakdee P, Uyyanonvara B. Computer-aided detection and quantification in glistenings on intra-ocular lenses. *Multimed Tools Appl* 2017;76(18):18915-18928.

27 Chen WB, Li RY, Yu QJ, *et al*. Early detection of visual impairment in young children using a smartphone-based deep learning system. *Nat Med* 2023;29(2):493-503.

28 Kim SE, Logeswaran A, Kang S, Stanojcic N, Wickham L, Thomas P, Li JP O. Digital transformation in ophthalmic clinical care during the COVID-19 pandemic. *Asia Pac J Ophthalmol (Phila)* 2021;10(4): 381-387.

29 Wang T, Xia J, Li RY, *et al*. Intelligent cataract surgery supervision and evaluation via deep learning. *Int J Surg* 2022;104:106740.

30 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1):159-174.