Automated Analysis of Angle Closure From Anterior Chamber Angle Images

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Submitted: May 21, 2014
Accepted: October 9, 2014

Citation: Baskaran M, Cheng J, Perera SA, Tun TA, Liu J, Aung T. Automated analysis of angle closure from anterior chamber angle images. *Invest Ophthalmol Vis Sci*. 2014;55:7669–7673. DOI:10.1167/iovs.14-14852

Purpose. To evaluate a novel software capable of automatically grading angle closure on EyeCam angle images in comparison with manual grading of images, with gonioscopy as the reference standard.

Methods. In this hospital-based, prospective study, subjects underwent gonioscopy by a single observer, and EyeCam imaging by a different operator. The anterior chamber angle in a quadrant was classified as closed if the posterior trabecular meshwork could not be seen. An eye was classified as having angle closure if there were two or more quadrants of closure. Automated grading of the angle images was performed using customized software. Agreement between the methods was ascertained by κ statistic and comparison of area under receiver operating characteristic curves (AUC).

Results. One hundred forty subjects (140 eyes) were included, most of whom were Chinese (102/140, 72.9%) and women (72/140, 51.5%). Angle closure was detected in 61 eyes (43.6%) with gonioscopy in comparison with 59 eyes (42.1%, $P = 0.73$) using manual grading, and 67 eyes (47.9%, $P = 0.24$) with automated grading of EyeCam images. The agreement for angle closure diagnosis between gonioscopy and both manual ($\kappa = 0.88$; 95% confidence interval [CI], 0.81–0.96) and automated grading of EyeCam images was good ($\kappa = 0.74$; 95% CI, 0.63–0.85). The AUC for detecting eyes with gonioscopic angle closure was comparable for manual and automated grading (AUC 0.974 vs. 0.954, $P = 0.31$) of EyeCam images.

Conclusions. Customized software for automated grading of EyeCam angle images was found to have good agreement with gonioscopy. Human observation of the EyeCam images may still be needed to avoid gross misclassification, especially in eyes with extensive angle closure.

Keywords: anterior chamber angle, gonioscopy, EyeCam, angle closure, automated grading

Gonioscopy is the established reference standard clinical method for angle evaluation.[1] Objective capture of gonioscopic views can be obtained with standard goniophotography or EyeCam (Clarity Medical Systems, Pleasanton, CA, USA) goniography.[2] Currently, grading of the documented images can be done only manually, but automated solutions are needed to enable clinician independent grading of the angle images.[2–4] In the absence of routine gonioscopy in clinical practice,[1] such automated angle image analysis potentially may serve as a surrogate for gonioscopy by a clinician.

EyeCam is the anterior segment module of Retcam (Clarity Medical Systems), a pediatric wide-angle fundus photography system.[5,6] We have previously evaluated the EyeCam in grading angle status[2] and in detecting the extent of angle opening after laser peripheral iridotomy (LPI).[3] Building on this, we have developed an automated software algorithm to classify open and closed angles in Eye Cam angle images.[7] Further, the algorithm can identify the specific quadrant from its orientation and provide a summary of the number of quadrants that are closed. This article aimed to test this software by comparing automated grading of EyeCam angle images with manual grading of images, with gonioscopy as the reference standard.

Methods

This prospective hospital-based study was approved by the ethics committee of Singapore Eye Research Institute. Written informed consent was obtained from every participant and the study was performed in accordance with the tenets of the Declaration of Helsinki.

Consecutive eligible subjects older than 40 years were recruited from a single glaucoma clinic at a Singapore hospital. After obtaining a detailed ophthalmic history, each subject underwent a standardized examination that included visual acuity assessment, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, and imaging with the EyeCam. Subjects with prior intraocular surgery or penetrating eye injury, or corneal disorders, such as corneal endothelial dystrophy, pterygium, or corneal scars that may preclude satisfactory imaging, were excluded from the study. Poor-quality images from EyeCam, with blurred angle details (even in one quadrant) were excluded from the study. Patients who had previously undergone LPI were not excluded.

Gonioscopy

Gonioscopy was performed in the dark in all cases by a single examiner with previous glaucoma fellowship training (SAP), who was masked to imaging findings. A 1-mm light beam was reduced to a narrow slit and the vertical beam was used for assessing superior and inferior angles and offset horizontally for nasal and temporal angles. Static gonioscopy was performed using a Goldmann 2-mirror lens (Ocular Instruments Inc., Bellevue, WA, USA) at high magnification (×16), with the eye in the primary position of gaze. The gonioscopy lens was tilted minimally to permit a view of the angle over the convexity of the iris, avoiding distortion of angle. Care was taken to avoid light falling on the pupil and to avoid inadvertent indentation during examination. The angle in each quadrant was graded as per the Scheie grading system according to the anatomical structures observed during gonioscopy.[8] The anterior chamber angle (ACA) was considered "closed" in that quadrant if the posterior pigmented trabecular meshwork (TM) could not be seen in the primary position without indentation (Scheie grade 3 or 4). The eye was classified as having angle closure if there were two or more quadrants of closure. Indentation gonioscopy was performed to ascertain angle structures in the presence of a pigmented Schwalbe's line.

EyeCam Angle Imaging

Image capture by EyeCam has been described in detail elsewhere.[3,4] This instrument is identical to the Retcam device used for retinal imaging.[5,6] In brief, EyeCam imaging was performed on participants in the supine position on a couch, in a darkened room. Images were captured by a single trained technician (TAT) in all four quadrants of the eye at least 20 minutes after the gonioscopy was performed, to avoid any distortion of angle status. After applying topical anesthetic eye drops (proparacaine hydrochloride 0.5% ophthalmic solution; Alcon Laboratories, Inc., Fort Worth, TX, USA), coupling gel was applied to the anesthetized eye before imaging proceeded with a 130° lens held next to the limbus. The illumination light was pointed at the angle rather than the pupil to minimize any pupillary dilatation. If the angle was not visible due to pronounced convexity of iris, the probe was moved anteriorly within 10° of the limbus to gain a view over the convexity of the iris. The illumination was adjusted using the foot pedal to avoid overexposure until the TM and/or the peripheral iris roll was clearly visible. Clear, still images were saved to the hard disk of the attached computer for subsequent grading.

Manual and Automated Grading of EyeCam Images

The resulting EyeCam images were randomly ordered and graded on a separate occasion, by a fellowship-trained glaucoma specialist (MB) who was masked to gonioscopic data. The methodology for grading the quality of EyeCam images and the method of grading the images have been described elsewhere.[3] The quality of images was graded from 1 to 4 based on the visibility of angle details. Only grade 1 and 2 images were included. Each quadrant was graded for anatomical structures observed in the ACA. As with gonioscopy, angle closure in a quadrant was defined as the inability to visualize the pigmented TM in that quadrant. An eye was considered to have angle closure if the pigmented TM was not visible in at least two quadrants. We have not reported on the presence of peripheral anterior synechiae (PAS) or iris processes because indentation was not possible using the EyeCam. Further classifications such as one-quadrant closure or more and three-quadrant closure or more were considered in the analysis.

Automated analysis was performed by AGATE (Version 1.0; Institute of Infocomm Research and Singapore Eye Research Institute, Singapore), a software program to analyze the angle images by quadrants and assign the classification as "open" or "closed" based on a training data set. The methodology for the program evaluation and the basis for the program were published earlier.[7,8] The method first determines the quadrant information from the image. Then it detects focal edges associated with angle structures. A circular Hough transform is applied to locate the iris surface. From the iris surface and the quadrant information, a focal region is calculated. Edges within the focal region are extracted and used to estimate the angle width profile. Finally, a classification between "open" and "closed" is given based on the angle width profile.

Reproducibility of Grading Methods

Intra- and interobserver reproducibility for EyeCam manual grading were analyzed in 40 randomly selected eyes by two observers masked to gonioscopic data and were found to be acceptable for two quadrants angle closure (first-order agreement coefficient statistics [AC1] between 0.57 and 0.63).[3]

Automated software (AGATE) reproducibility was excellent ($\kappa = 0.99$) for a sample of 30 eyes (120 images).

Statistical Analysis

One eye from each patient was randomly selected for analysis if both eyes were eligible for the study. The McNemar test was used to compare differences in the distribution of categorical variables between two related samples. Kappa statistic was used to assess the agreement between categorical variables and for reproducibility analysis. First-order agreement coefficient statistics were used to assess the agreement between graders in situations in which the prevalence of positive classifications may lead to inconsistent results. First-order agreement coefficient statistic results are interpreted in a similar manner to κ statistics.[9] Cochran's Q test was performed to test differences in proportions of two or three quadrants of angle closure among the three methods. Receiver operating characteristic (ROC) curves, with calculations of area under the curve (AUC) and 95% confidence intervals (CIs) were used as an index of each instrument's diagnostic performance for identifying eyes with angle closure, using gonioscopy as the reference standard. A P value less than 0.05 was considered statistically significant. The sample size calculation was based on comparison of sensitivities for matched groups in a diagnostic study, as reported by Beam et al.[10] With an estimated sensitivity of 82%, the number of subjects required was 78 in this study. Statistical analysis was performed using MedCalc version 12.3.0.0 (Mariakerke, Belgium). Venn diagrams to scale were generated for either two or three quadrants of angle closure to show overlap among the three methods.[11]

Results

Out of the 145 consecutive eligible subjects, five were excluded due to missing/poor-quality images. One hundred forty eyes were included for analysis using the automated software. The mean age of included subjects was 60.5 (SD 12.9) years with most being Chinese (102/140, 72.9%) and women (72/140, 51.5%). Five subjects had previously undergone LPI. Gonioscopic angle closure was noted in two

Table 1. Kappa Agreement of Manual and Automated Grading of EyeCam Angle Images Compared With Gonioscopy

	Agreement Between Methods					
	Manual vs. Gonioscopy, $n = 140$		Automated vs. Gonioscopy, $n = 140$		Manual vs. Automated, $n = 140$	
Definition of Closure	κ (95% CI)	AC1	κ (95% CI)	AC1	κ (95% CI)	AC1
One or more quadrants closed	0.87 (0.79–0.95)	0.87	0.50 (0.36–0.64)	0.50	0.57 (0.44–0.70)	0.57
Two or more quadrants closed*	0.88 (0.81–0.96)	0.89	0.74 (0.63–0.85)	0.74	0.68 (0.56–0.81)	0.69
Three or more quadrants closed†	0.76 (0.64–0.87)	0.79	0.78 (0.67–0.89)	0.82	0.79 (0.68–0.89)	0.81
Four quadrants closed	0.60 (0.44–0.76)	0.76	0.46 (0.28–0.65)	0.72	0.47 (0.29–0.65)	0.70
Superior quadrant closed	0.81 (0.71–0.91)	0.82	0.69 (0.57–0.81)	0.69	0.73 (0.62–0.84)	0.73
Inferior quadrant closed	0.88 (0.81–0.96)	0.89	0.65 (0.52–0.78)	0.67	0.58 (0.45–0.72)	0.62
Nasal quadrant closed	0.65 (0.51–0.79)	0.74	0.64 (0.50–0.78)	0.72	0.61 (0.47–0.75)	0.67
Temporal quadrant closed	0.67 (0.54–0.80)	0.73	0.37 (0.21–0.53)	0.41	0.48 (0.33–0.62)	0.50

κ, kappa statistic; AC1, first-order agreement coefficient statistic; Cochran's Q test: *$P = 0.12$, †$P = 0.28$.

quadrants or more among 61 eyes (43.6%) in comparison to 59 (42.1%, $P = 0.73$) using manual grading of angle images. Automated grading of angle images graded more angle closure eyes but was statistically insignificant in comparison to gonioscopy (67/140, 47.9%, $P = 0.24$).

Table 1 shows the agreement for various definitions of angle closure among the three methods. Generally, two- or three-quadrant closure definitions showed good agreement among methods. The temporal quadrant showed the least agreement with automated grading in comparison with gonioscopy. Manual versus automated grading comparison showed moderate to good agreement. Figure 1a shows a Venn diagram depicting eyes identified by each method for two-quadrant angle closure definition, with automated grading overestimating angle closure. Figure 1b shows a similar diagram for three-quadrant angle closure definition, suggesting slight overestimation by manual grading. However, this difference in agreement was not statistically significant for two (Cochran's Q test, manual versus automated, 0.88 vs. 0.74, $P = 0.12$) or three quadrants (0.76 vs. 0.78, $P = 0.28$) of angle closure among the methods. The agreement statistics did not change when subjects with previous LPI were removed from the analysis (data not shown). Table 2 shows that the AUC ROC is indistinguishable and very high for both methods in particular for the predominant two-quadrant definition of angle closure by gonioscopy. The AUC for two-quadrant closure (manual versus automated = 0.974 versus 0.954, $P = 0.31$) was slightly better than three-quadrant closure definition (manual versus automated = 0.927 vs. 0.94, $P = 0.67$), but this was not statistically significant.

Figures 2 and 3 depict EyeCam images showing discrepancy with gonioscopic diagnosis of open and closed angles respectively. The Figure 2A image was graded as closed on both manual and automated grading possibly due to a convex

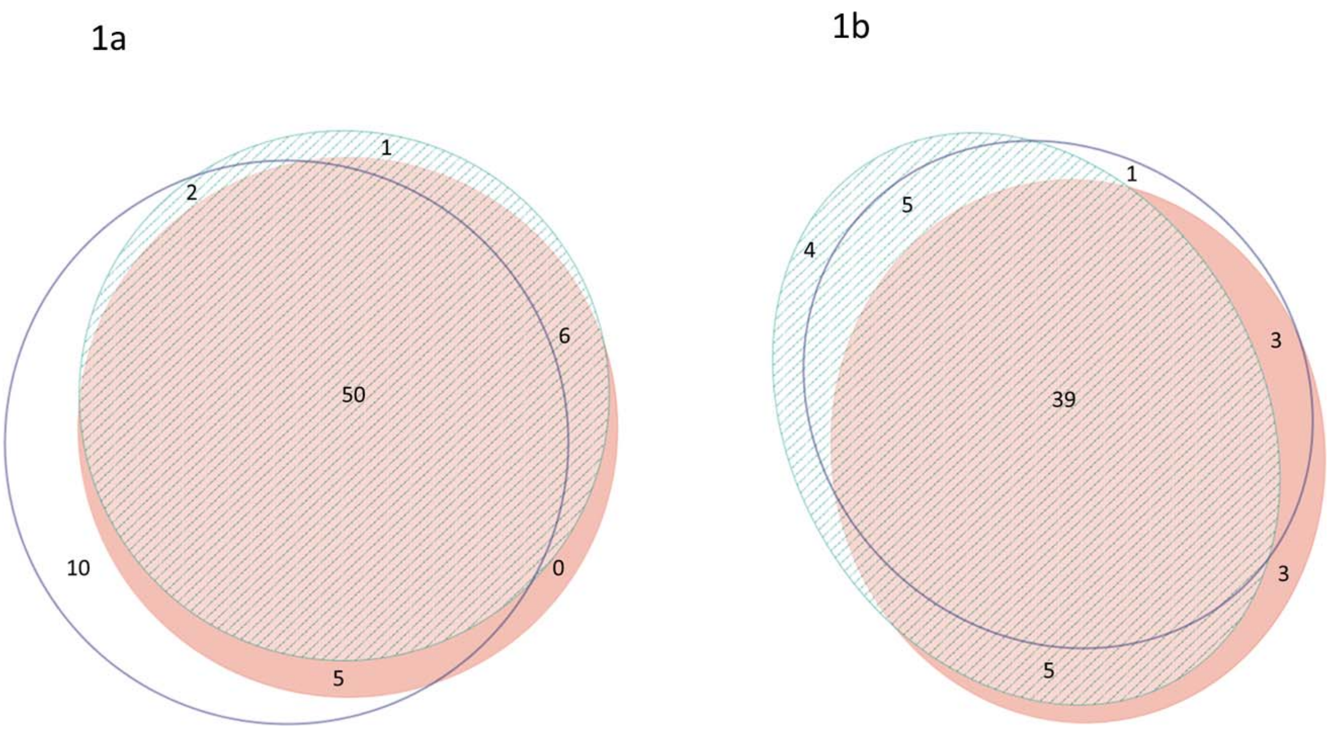

Figure 1. Venn diagrams showing the number of (**a**) two and (**b**) three quadrants closed angle detection by gonioscopy (*solid fill*), EyeCam manual (*stripes*) and automated (*empty*) grading methods, suggesting overestimation by the latter two methods.

Table 2. Receiver Operating Characteristic Curve Analysis to Compare Manual and With Gonioscopy for Various Definitions of Angle Closure

	Manual vs. Gonioscopy, $n = 140$			Automated vs. Gonioscopy, $n = 140$			
Definition of Closure	**AUC (95% CI)**	**Sensitivity**	**Specificity**	**AUC (95% CI)**	**Sensitivity**	**Specificity**	***P* Value***
One or more quadrants closed	0.955 (0.906–0.983)	0.92	0.95	0.923 (0.865–0.961)	0.95	0.55	0.266
Two or more quadrants closed	0.974 (0.933–0.994)	0.92	0.96	0.954 (0.905–0.982)	0.90	0.85	0.306
Three or more quadrants closed	0.927 (0.87–0.964)	0.88	0.89	0.94 (0.886–0.973)	0.84	0.93	0.665
Four quadrants closed	0.891 (0.828–0.938)	0.75	0.88	0.877 (0.811–0.926)	0.56	0.89	0.728

* Comparison of independent ROC curves between manual and automated grading of EyeCam angle images.

iris configuration. The Figures 2B and 2C images were graded as open on manual grading and gonioscopy but closed on automated grading, possibly due to the presence of a lightly pigmented TM or heavy TM pigmentation respectively, thus blurring the demarcation between TM and iris root. The Figure 3A image was graded as open on both gradings due to partial angle closure, whereas Figure 3B was graded as open with automated grading owing to the presence of pigmented Schwalbe's line. Overall misclassification rate with automated grading for angle assessment was 12.1% (17/140 eyes) with 7.9% false positives (i.e., 11 closed-angle eyes), whereas it was 5.7% (8/140 eyes) and 2.1% (3/140 eyes) with manual grading, respectively. Most open angles on gonioscopy had very light TM pigmentation (6/11) or dense pigmentation (4/11), leading to erroneous marking by automated grading as closed angles, whereas closed angles were marked as open if it was partial angle closure (3/6) or if the angle had a pigmented Schwalbe's line (3/6) in that quadrant. Another reason for error in automated grading was the presence of a convex iris, obscuring angle details and masquerading as closed angle.

Discussion

We report the clinical utility of the first automated software for goniophotographic angle assessment. The agreement of this software in comparison with gonioscopy was found to be very good for the two- and three-quadrant definitions of angle closure.

Several anterior segment imaging methods have been developed to address reproducibility and contact issues inherent in gonioscopic angle assessment. Although such techniques can quantitatively assess the anterior chamber angle, none can claim to completely replace gonioscopy for several reasons.[1] Assessing the distribution and degree of pigmentation in the TM, 360° circumferential angle view and detection of peripheral anterior synechiae are a few of the advantages with gonioscopy. Furthermore, the low specificity of these devices may limit their usefulness in screening for angle closure.[12] Reported practice patterns of ophthalmologists reveal only 50% use of gonioscopy in comprehensive eye examinations, and follow-up documentation of the angle is poor even among glaucomatologists.[13] To improve this, one must deconstruct gonioscopy into its constitutive parts. First, there is the technical aspect of image capture, followed by the interpretation and grading. Image capture can be done by EyeCam-fluent technicians, whereas the software algorithm in our study can fulfill the unmet need of interpretation and grading. This tool probably may be used for education and documentation of the angle and it can be easily adapted to goniophotography. Its uptake in screening for angle closure is unfortunately subject to other external factors, such as the cost and patient acceptability.

We have earlier examined the agreement between gonioscopy and manual assessment of angle images[3] using EyeCam, as well as in comparison with goniophotography and anterior segment optical coherence tomography (ASOCT).[14] Although ASOCT showed poor to fair agreement with manual EyeCam images, goniophotography shared better agreement and AUC for two- or three-quadrant angle closure.[2] This is unsurprising, in that they share similarities in acquisition and views. The misclassifications may stem from the fact that gonioscopy is far more versatile and one can use the corneal wedge to exactly identify the Schwalbe's line and evaluate the most open angle to correctly identify the angle anatomy for grading. Dynamic indentation adds another dimension in that it can differentiate between synechial and appositional closure and can help with discerning plateau iris and a prominent peripheral iris roll.

Individual quadrant angle closure diagnosis did not show very good agreement with gonioscopy for either manual or automated methods of EyeCam angle grading. This could be due to the nasal bridge obstructing the bulky probe, altering the angle view of the temporal quadrant. Misclassification of open or closed angles with either method was often due to heavy or light pigmentation and partial angle closure. In a

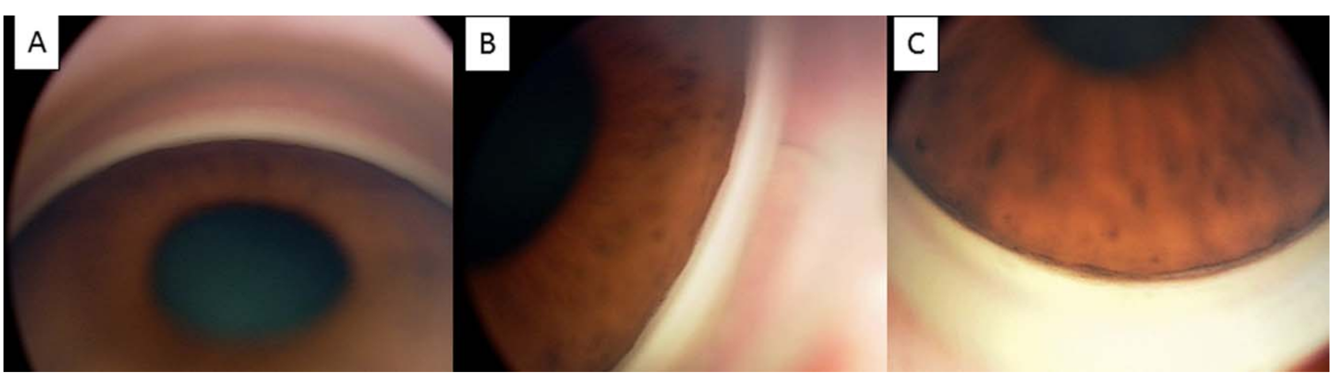

Figure 2. EyeCam images: misclassification into closed angles by automated grading method due to (**A**) convex iris, (**B**) lightly pigmented TM, and (**C**) heavy TM pigmentation.

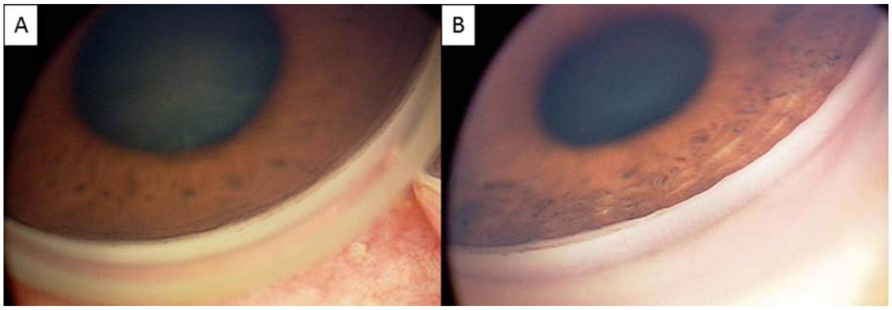

FIGURE 3. EyeCam images: misclassification into open angles by automated grading method due to (**A**) partial angle closure in that quadrant and (**B**) pigmented Schwalbe's line.

study of 291 subjects, including African American, "Far East" Asian, and Caucasian individuals, Oh et al[15] suggested that refractive error and racial origin may influence iris insertion, leading to variation in gonioscopic angle assessment. These limitations may have less bearing on EyeCam grading. Partial angle closure in a quadrant (which was misclassified by the software as open angles) in this study could be due to inclusion of subjects who have undergone LPI. Thus, the actual performance of the software may be better than reported, for as yet untreated angle closure subjects.

Our study had a few limitations. Gonioscopy was performed by a single observer and used the Scheie grading system. Misclassification error rates due to lightly pigmented angles or heavily pigmented TM may need to be addressed using better engineering methods, such as feature extraction techniques. These methods may identify angle structures irrespective of TM pigmentation and may improve the software algorithm in detecting angle closure. Until then, human observation of the images still may be needed to avoid gross misclassification, especially in eyes with extensive angle closure. Although inclusion of subjects who had previously undergone LPI in this study did not affect the overall results, it may be possible that the pigmentation released after LPI may have influenced the automated grading.

In summary, we evaluated a novel automated angle assessment software tool and reported very good diagnostic performance in comparison with gonioscopy. We believe that EyeCam imaging with automated angle assessment has potential to be a useful adjunct in clinical evaluation and documentation of the irido-corneal angle.

Acknowledgments

Supported by grants from the National Medical Research Council, Singapore; SingHealth; and Singapore National Eye Centre, Singapore.

Disclosure: **M. Baskaran**, None; **J. Cheng**, None; **S.A. Perera**, None; **T.A. Tun**, None; **J. Liu**, None; **T. Aung**, None

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