AMERICAN ACADEMY OF OPHTHALMOLOGY®

Comparison of Handheld Retinal Imaging with ETDRS 7-Standard Field Photography for Diabetic Retinopathy and Diabetic Macular Edema

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Purpose: To compare nonmydriatic (NM) and mydriatic (MD) handheld retinal imaging with standard ETDRS 7-field color fundus photography (ETDRS photographs) for the assessment of diabetic retinopathy (DR) and diabetic macular edema (DME).

Design: Prospective, comparative, instrument validation study.

Subjects: A total of 225 eyes from 116 patients with diabetes mellitus.

Methods: Following a standardized protocol, NM and MD images were acquired using handheld retinal cameras (NM images: Aurora, Smartscope, and RetinaVue-700; MD images: Aurora, Smartscope, RetinaVue-700, and iNview) and dilated ETDRS photographs. Grading was performed at a centralized reading center using the International Clinical Classification for DR and DME. Kappa statistics (simple [K], weighted [Kw]) assessed the level of agreement for DR and DME. Sensitivity and specificity were calculated for any DR, referable DR (refDR), and vision-threatening DR (vtDR).

Main Outcome Measures: Agreement for DR and DME; sensitivity and specificity for any DR, refDR, and vtDR; ungradable rates.

Results: Severity by ETDRS photographs: no DR, 33.3%; mild nonproliferative DR, 20.4%; moderate DR, 14.2%; severe DR, 11.6%; proliferative DR, 20.4%; no DME, 68.0%; DME, 9.3%; non-center involving clinically significant DME, 4.9%; center-involving clinically significant DME, 12.4%; and ungradable, 5.3%. For NM handheld retinal imaging, Kw was 0.70 to 0.73 for DR and 0.76 to 0.83 for DME. For MD handheld retinal imaging, Kw was 0.68 to 0.75 for DR and 0.77 to 0.91 for DME. Thresholds for sensitivity (0.80) and specificity (0.95) were met by NM images acquired using Smartscope and MD images acquired using Aurora and RetinaVue-700 cameras for any DR and by MD images acquired using Aurora and RetinaVue-700 cameras for refDR. Thresholds for sensitivity and specificity were met by MD images acquired using Aurora and RetinaVue-700 for DME. Nonmydriatic and MD ungradable rates for DR were 15.1% to 38.3% and 0% to 33.8%, respectively.

Conclusions: Following standardized protocols, NM and MD handheld retinal imaging devices have substantial agreement levels for DR and DME. With mydriasis, not all handheld retinal imaging devices meet standards for sensitivity and specificity in identifying any DR and refDR. None of the handheld devices met the established 95% specificity for vtDR, suggesting that lower referral thresholds should be used if handheld devices must be utilized. When using handheld devices, the ungradable rate is significantly reduced with mydriasis and DME sensitivity thresholds are only achieved following dilation. *Ophthalmology Retina 2022;■:1–9 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

Diabetic retinopathy (DR) remains one of the leading causes of vision loss worldwide.[1–3] In the last 30 years, it is estimated that DR-related blindness has increased by 68%, mainly in low-to-middle income countries because of increasing populations and prevalence of diabetes mellitus (DM).[2–4] Fortunately, 95% of DR-related blindness is preventable through cost-effective and evidence-based strategies.[1] Regular DR screening is recommended for people with DM to identify high-risk DR characteristics, which can lead to vision loss if left untreated. This is performed

https://doi.org/10.1016/j.oret.2022.03.002
ISSN 2468-6530/22

through clinical eye examinations by a trained eye care professional or using fundus photography with remote evaluation via teleophthalmology.[5,6]

The deployment of widescale teleophthalmology DR screening programs (DRSPs) reduces the burden of DR by enabling access to timely referral and treatment.[7] The national DRSP in the United Kingdom is considered one of the most successful globally, with 2.14 million people with DM screened between 2015 and 2016, an uptake of 82.8%.[8] The UK DRSP has an identified target population, highly trained personnel, and referral pathways, and utilizes validated fundus cameras and teleophthalmology principles to deliver care.[8,9] However, such widescale programs are not always possible, especially in low resource settings due to the lack of skilled eye care personnel, appropriate screening equipment and infrastructure, and the high cost of services.[10,11] The use of mobile handheld fundus cameras in such settings can potentially address this unmet need.

Mobile handheld fundus cameras have the potential to broaden the reach of DRSPs because of their portability and lower costs, enabling such devices to be deployed in a wider geographic area and reaching a diverse patient population.[12] These devices can potentially be placed in strategic community locations that are easily accessible, which can lead to increased patient participation in surveillance. Handheld retinal imaging devices are in various stages of development. They are typically integrated into a smartphone or mobile computing platform. Most are in the very early stages of adoption. These devices provide a limited field of view 5° to 60°. Because these devices will be used to guide diagnosis and treatment, they will need rigorous validation to assess agreement with the standard of care and to evaluate which one attains adequate levels of sensitivity and specificity for the detection of DR.

The aim of this study was to evaluate whether mydriatic (MD) and nonmydriatic (NM) handheld retinal imaging may be used reliably to assess DR and diabetic macular edema (DME) when compared with standard ETDRS 7-field color 30° fundus photography.

Methods

Population and Sample

This was a single-site, prospective, cross-sectional, multidevice instrument validation study for the detection and grading of DR and DME. A total of 225 eyes from 116 patients were included in the study. The inclusion criteria were as follows: (1) patients known or diagnosed to have DM type 1 or 2; (2) those aged 18 years or older; and (3) those willing to undergo the study retinal imaging procedures. The exclusion criteria were as follows: (1) the presence of media haze, such as corneal opacities or dense cataracts, that precludes adequate view of the fundus; (2) contraindication to pupil dilation, including any history or evidence of hypersensitivity to MD eye drops; and (3) the presence of active periocular, ocular, or intraocular infection or inflammation at the time of examination. Retinal images acquired during the same visit were collected from the study participants.

The study design was compliant with the ethical standards stated in the 1964 Declaration of Helsinki. The study protocol was approved by the institutional review board of The Medical City. Informed consent was obtained from all study participants.

Imaging Protocol

All participants underwent fundus photography using 4 handheld retinal cameras—iNview (Volk Optical Inc), RetinaVue 700 (Welch Allyn), Smartscope (Optomed Ltd), and Aurora (Optomed Ltd)—and a standard ETDRS 7-field fundus camera (Visucam; Carl Zeiss Meditec, Inc). Nonmydriatic multifield retinal images were acquired using 3 handheld devices—RetinaVue 700 (RVNM) 2-field (macula-centered and disc-centered) 60° photographs, Smartscope (SSNM) 5-field (disc, macula, superior, inferior, and temporal) 40° photographs, and Aurora (AUNM) 5-field (disc, macula, superior, inferior, and temporal) 50° photographs.

The sequence of NM imaging was based on device availability and was usually random. A 5-minute interval was observed after taking photographs from each camera to help the pupil recover from light. One handheld camera (iNview) was not included in the NM data set analysis, as it failed to capture gradable NM images. After NM imaging, participants underwent pupil dilation using 1 drop of tropicamide 0.5% + phenylephrine 0.5% eyedrops, and MD retinal images were acquired using all 4 handheld devices (iNview [NVMD], single-field 50° photographs; RetinaVue 700 [RVMD], 2-field [macula-centered and disc-centered] 60° photographs; Smartscope [SSMD], 5-field [disc, macula, superior, inferior, and temporal] 40° photographs; and Aurora [AUMD], 5-field [disc, macula, superior, inferior, and temporal] 50° photographs) and standard 7-field 30° ETDRS photography. The sequence of MD imaging was based on device availability and was generally random.

Figure 1 compares the different NM retinal images with standard ETDRS photographs, and Figure 2 compares MD retinal images with standard ETDRS photographs. Retinal imager-graders who underwent training and certification (Gloucestershire Retinal Education Group, Gloucestershire Hospitals NHS Foundation Trust) acquired all handheld retinal images, and all ETDRS photographs were acquired by clinical trials certified ophthalmic photographers. Before the start of the acquisition of images for the study, the retinal imager-graders trained with the handheld imaging protocol by acquiring over 500 images from >50 patients and volunteers. All collected images were anonymized and stored in a secure location.

Grading Protocol

The images were evaluated at a centralized reading center using high-resolution, high-definition LCD computer displays, which were regularly color-calibrated to a color temperature of 6500 K and gamma setting of 2.2 (Spyder4PRO; Datacolor). Grading was performed independently by 4 masked trained graders (2 certified retinal image graders [L.C.A. and C.G.S.], 1 ophthalmologist [A.V.S], and 1 retina specialist [R.P.S.]). Diabetic retinal lesions, including hemorrhages and microaneurysms, venous beading, intraretinal microvascular abnormalities, new vessels, vitreous or preretinal hemorrhage, and presence of retinal tractional membranes were evaluated.

Using the international clinical classification for DR,[13] DR severity was assessed as no DR, mild nonproliferative DR, moderate nonproliferative DR, severe nonproliferative DR, proliferative DR, or ungradable. Diabetic macular edema severity was assessed as no DME, DME not clinically significant, noncenter–involving clinically significant DME (defined as retinal thickening at least 1 disc area in size within 1 disc diameter from the foveal center), center-involving clinically significant DME (defined as retinal thickening or exudates within 200 μm

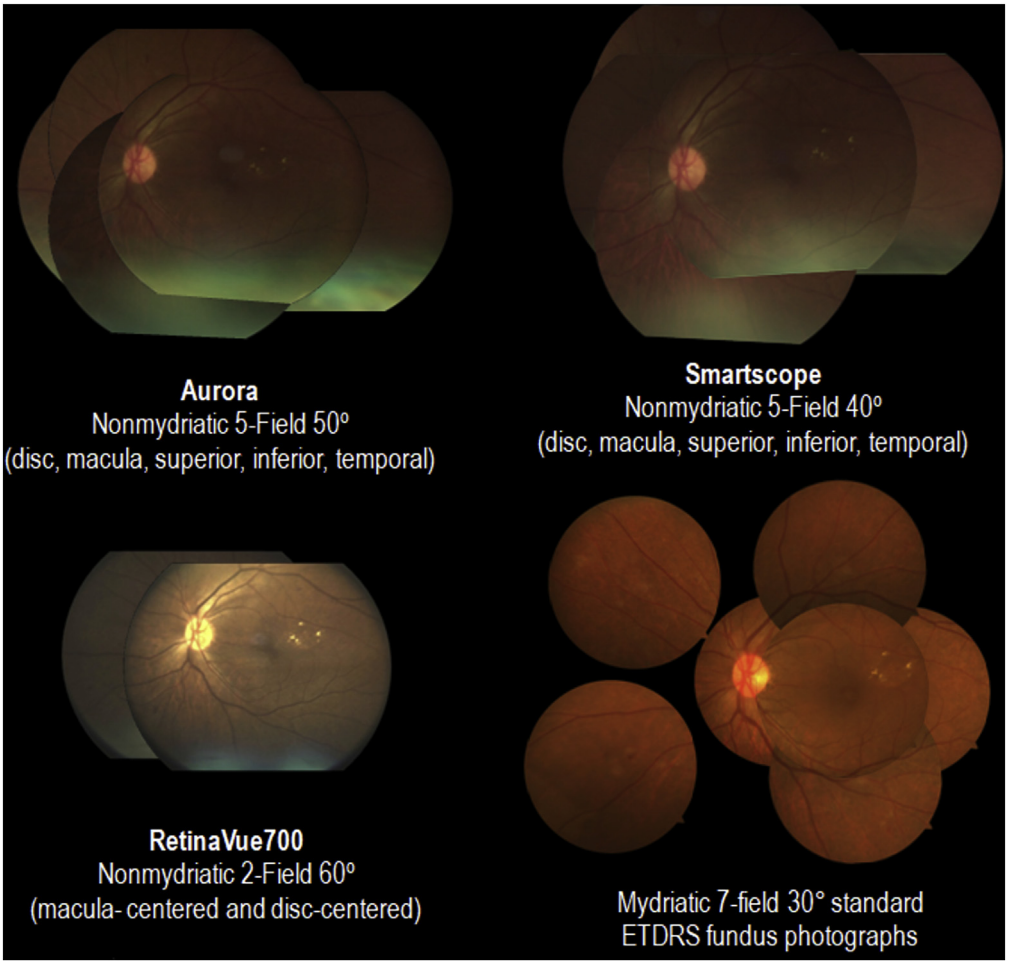

Figure 1. Comparison of nonmydriatic handheld retinal images and ETDRS standard 7-field fundus photographs.

from the foveal center), or ungradable. Referable DR (refDR) was defined as moderate nonproliferative DR or worse, any DME, or ungradable images), and vision-threatening DR (vtDR) was defined as severe nonproliferative DR or worse, clinically significant DME, or ungradable images Disagreements were adjudicated by a senior retina specialist (P.S.S.), and the adjudicate grade was considered the final assessment.

Statistical Analysis

Both simple (K) and weighted (Kw) kappa were used to assess the level of agreement between the images from the handheld retinal camera and ETDRS photographs. For multilevel categories (DR and DME severity), linear weights were used to estimate Kw statistics. The strength of agreement beyond chance alone was determined using the Landis and Koch interpretation of K statistics (0.20: slight agreement; 0.21−0.40: fair agreement; 0.41−0.60: moderate agreement; 0.61−0.80: substantial agreement; and 0.81−1.00: almost perfect agreement). Sensitivities and specificities for anyDR, refDR, and vtDR were calculated. Established sensitivity and specificity thresholds of 0.80 and 0.95,[14] respectively, were used to determine whether the devices met the current suggested clinical use standards. Statistical analysis was performed using SAS software version 9.4 (SAS, Inc).

Results

Of the 116 enrolled participants, 48 (41.4%) were men and 68 (58.6%) were women. The mean age was 58.6 (standard deviation [SD] ±10.5) years, and the mean hemoglobin A1c was 7.3 (± 1.6). Diabetic retinopathy severity by ETDRS photographs was as follows: no DR, 75 (33.3%) eyes; mild nonproliferative DR, 46 (20.4%) eyes; moderate nonproliferative DR, 32 (14.2%) eyes; severe nonproliferative DR, 26 (11.6%) eyes; and proliferative DR, 46 (20.4%) eyes. No eye was assessed to be ungradable for DR on ETDRS photographs. Moreover, DME severity by ETDRS photographs was as follows: no DME, 153 (68.0%) eyes; DME, 21 (9.3%) eyes; noncenter−involving clinically significant DME, 11 (4.9%) eyes; center-involving clinically significant DME, 28 (12.4%) eyes; and ungradable, 12 (5.3%) eyes. The baseline characteristics of patients and DR/DME severity by ETDRS photographs are summarized in Table 1.

Table 2 summarizes the agreement rates, ungradable rates, sensitivity, and specificity of NM and MD handheld retinal imaging for DR and DME. Agreement for DR was the highest with MD devices AUMD and RVMD. For any DR, the established standards for sensitivities and specificities were met by SSNM, AUMD, and RVMD; for refDR, they were met by

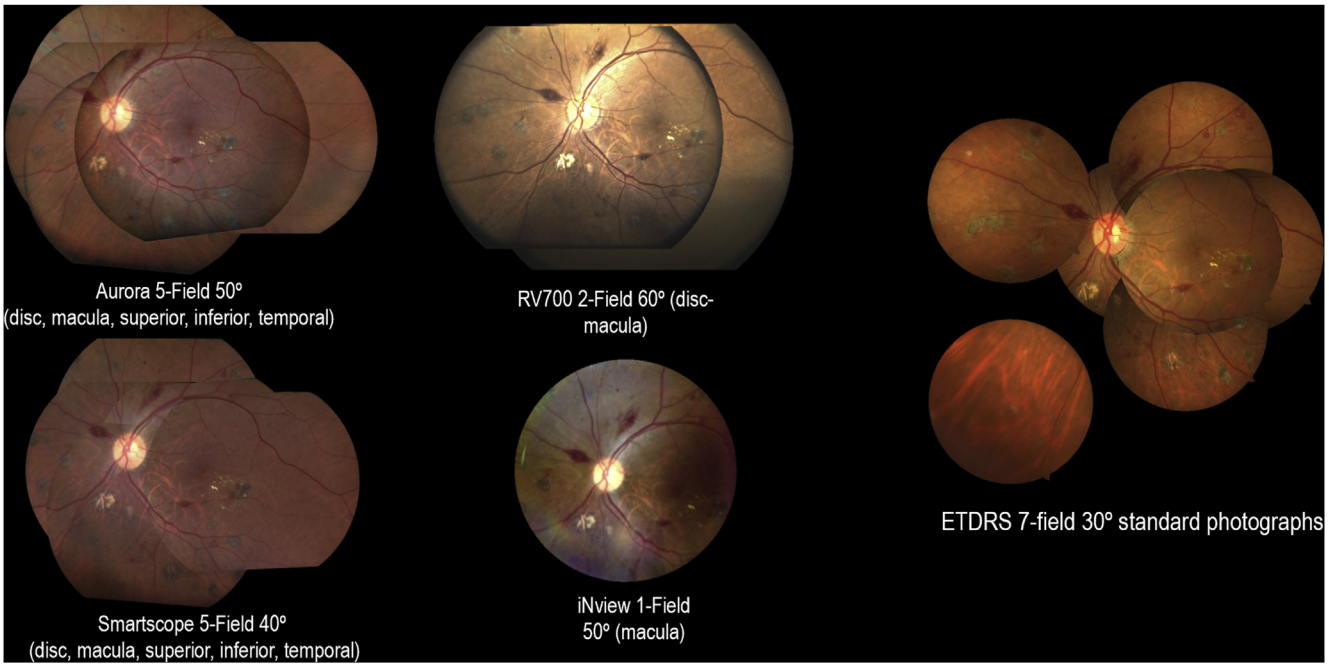

Figure 2. Comparison of mydriatic handheld retinal images and ETDRS standard 7-field fundus photographs.

AUMD and RVMD. For DME, the established standards for sensitivities and specificities were met by AUMD and RVMD. None of the handheld devices met the sensitivity and specificity thresholds for vtDR. With pupil dilation, the ungradable rates decreased by 82% to 100% for DR and by 65% to 82% for DME; exact agreement with ETDRS photographs increased by 16% to 46% (Table 3).

All NM retinal images obtained using handheld devices exhibited substantial agreement levels for DR when compared with ETDRS photographs. All devices had weighted agreement of over 0.70; DME agreement was substantial for AUNM ($K_W = 0.76$) and near perfect for SSNM ($K_W = 0.83$) and RVNM ($K_W = 0.81$). Sensitivity and specificity for any DR, refDR, and vtDR were as follows: AUNM, 0.89/0.97, 0.87/0.92, 0.83/0.86; SSNM, 0.80/0.96, 0.89/0.89, 0.88/0.81; and RVNM, 0.89/0.88, 0.93/0.76, 0.88/0.69. Sensitivity for identifying DME across all devices was below 0.80 (0.65 to 0.76) but specificity approached 1.00 (0.99 to 1.00). Ungradable rates for DR/DME were as follows: AUNM, 34 (15.1%)/46 (20.4%); SSNM, 45 (20.0%)/51 (22.7%); and RVNM, 86 (38.2%)/90 (40.0%). The cross tabulations on DR and DME severity for each device after NM imaging are presented in Tables S1–S3 (available at www.ophthalmologyretina.org).

Similarly, all MD retinal images obtained using handheld devices exhibited substantial agreement levels for DR compared with ETDRS photographs. Among the MD handheld retinal images, agreement for DR was the highest with the AUMD ($K_W = 0.75$; exact 65.8%), higher than RVMD ($K_W = 0.75$; 63.1%), SSMD ($K_W = 0.73$; 60.0%), and NVMD ($K_W = 0.68$; 54.8%). Diabetic macular edema agreement was substantial for AUMD ($K_W = 0.78$), SSMD ($K_W = 0.77$), and RVMD ($K_W = 0.78$), and near perfect for NVMD ($K_W = 0.91$). Sensitivity and specificity for any DR, refDR, and vtDR were as follows: AUMD, 0.86/0.97, 0.84/0.97, 0.81/0.92; SSMD, 0.80/0.92, 0.87/0.92, 0.85/0.86; RVMD, 0.83/0.97, 0.87/0.97, 0.89/0.89; and NVMD, 0.91/0.53, 0.91/0.54, 0.91/0.47. Sensitivity and specificity for DME were as follows: AUMD, 0.80/0.99; SSMD, 0.75/1.00; and RVMD, 0.87/0.98. The iNview device (NVMD) had an ungradable rate of 40.4% for DME, even with pupil dilation, making sensitivity and specificity calculations unreliable. The cross tabulations on DR and DME severity for each device after MD imaging are presented in Tables S4–S7 (available at www.ophthalmologyretina.org).

Discussion

In the present study, compared with ETDRS photographs, not all handheld retinal imaging devices attained substantial levels of agreement, met established standards for sensitivities and specificities in the detection of diabetic retinal disease, or identified eyes requiring more specialized care. Furthermore, without the use of mydriasis, certain handheld devices do not meet established standards for varying DR referral thresholds, thus limiting their NM usefulness. It should be noted that the minimum standard of specificity for vtDR was not met by any device tested, suggesting that lower thresholds of referral are warranted when handheld devices are used.

Among the devices evaluated, the MD images captured with Aurora and RetinaVue-700 cameras achieved the highest agreement rates for DR. When images were acquired with mydriasis, these 2 devices also achieved the established sensitivity and specificity standards for any DR, refDR, and DME. The MD ungradable rates between the 2 devices, however, are substantially different (AUMD: DR, 0%, DME, 3.6%; RVMD: DR, 15.1%, DME, 8.0%).

The future of retinal imaging for DR screening should start to move away from the tertiary medical center. The use of handheld retinal imaging devices in teleophthalmology

Table 1. Baseline Characteristics and DR/DME Severity by ETDRS Photographs

	Value ± SD or (%)
Male sex	48 (41.4)
Age, yrs	56.8 ± 10.5
Average A1c	7.3 ± 1.6
Hypertension	65 (56.0)
Renal disease	12 (10.3)
Diabetic retinopathy severity by ETDRS photographs	
No DR	75 (33.3)
Mild NPDR	46 (20.4)
Moderate NPDR	32 (14.2)
Severe NPDR	26 (11.6)
PDR	46 (20.4)
Ungradable	0
DME severity by ETDRS photographs	
No DME	153 (68.0)
DME	21 (9.3)
Non−ciDME	11 (4.9)
ciDME	28 (12.4)
Ungradable	12 (5.3)

ciDME = center-involving clinically significant diabetic macular edema; DME = diabetic macular edema; DR = diabetic retinopathy; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SD = standard deviation.

DRSPs is an innovative strategy that can provide a uniquely suited means to broaden the reach and increase the adoption of DRSPs, particularly in low-resource settings and hard-to-reach populations.

Using this strategy, retinal images obtained using mobile imaging devices are sent electronically and evaluated at a centralized reading center, and the findings are sent back to the screening sites and to the patient. Diabetic retinopathy screening programs utilizing teleophthalmology and digital retinal imaging are proven to increase the identification of referable disease, including treatment-requiring DR.[6,15,16] In addition, DR assessment using this strategy is faster and more convenient for both patients and clinicians, decreasing the burden on busy eye clinics by ensuring that only patients with referable disease attend face-to-face appointments.

To fully integrate handheld retinal cameras in the planning of a DRSP, however, they should first be validated against the gold standard for the detection and classification of DR, as only approved devices can be deployed in the screening program. Identifying mobile devices that achieve good agreement, sensitivity, and specificity values against ETDRS standard 7-field photography is, therefore, vital. A protocol regarding the need for pupil dilation when using these devices also needs to be established. The current study evaluated multiple handheld retinal imaging devices head-to-head in both MD and NM settings with direct comparison to the ETDRS standard 7-field photographs.

A prior study by Xiao et al[17] reported that retinal images from handheld and standard cameras reached high levels of agreement (K = 0.79−1.00) for DR and DME diagnosis at all levels of retinopathy. They reported that there was no significant difference in the detection of refDR between 2-field photography (macula and disc-centered) using a tabletop camera and MD handheld retinal imaging. However, there have been very limited published data on a standardized comparison of handheld retinal cameras and the gold standard stereoscopic ETDRS 7-field photography. A study by Rajalakshmi et al[18] compared a smartphone-based retinal imaging device with standard 7-field photography for the detection of DR and reported that the sensitivities and specificities of such a portable imaging system were 92.7% and 98.4% for any DR and 87.9% and 94.9% for vtDR.

Multiple previous studies have compared handheld retinal cameras with clinical dilated eye examinations. A study by Zhang et al[19] reported that handheld retinal imaging had high sensitivity of 64% to 88% and acceptable specificity of 71% to 90% for assessing vtDR compared with clinical examination. The study by Sengupta et al[20] reported similar results. Using a handheld retinal camera, the sensitivity was 82% to 88% and the specificity was 99% for detecting vtDR compared with dilated fundus examination.[20] In another study, the sensitivity and specificity for detecting any DR were 93.1% to 94.3% and 89.1% to 94.5%, respectively, when using a smartphone-based retinal imaging device compared with clinical examination by a retina specialist.[21] A recent meta-analysis of the diagnostic accuracy of smartphone-based handheld retinal imaging found pooled sensitivities and specificities of 87% (95% confidence interval [CI] , 74%−94%) and 94% (95% CI, 81%−98%) for any DR; 79% (95% CI, 63%−89%) and 93% (95% CI, 82%−97%) for DME; and 91% (95% CI, 86%−94%) and 89% (95% CI, 56%−98%) for refDR.[22]

Clearly, DR screening using mobile retinal cameras is an efficient method for identifying eyes at risk of visual loss from DR. Not only do handheld retinal imaging devices exhibit adequate levels of accuracy in detecting DR but also their portability, less space requirements, minimal power consumption, cheaper costs, and ease of use make them cost-effective alternatives to standard fundus cameras in widescale DRSP implementation, even in remote areas, thereby contributing to decreasing the burden on the health care system.[23]

However, none of the handheld devices met the established 95% specificity threshold for vision-threatening DR, suggesting that lower thresholds for referral should be utilized if handheld cameras must be used. Based on our data, handheld devices do not have the adequate specificity to base referrals on vtDR and may potentially increase unnecessary referrals. When using handheld devices in a DR screening program, the need for referral to more specialized care should be set at moderate nonproliferative DR or more severe levels, any level of DME, or ungradable images.

A study by Piyasena et al[24] found that handheld NM retinal imaging (with pupil dilation for ungradable images) has a sensitivity of 88.7% to 92.5% and a specificity of 94.9% to 96.4% when compared with MD biomicroscopy by a retinologist. In their study, the ungradable rates for DR and DME decreased from 43.4% to 12.8% after mydriasis when using handheld retinal cameras. It is well

Table 2. Agreement, Sensitivity, Specificity, PPV, and NPV of Handheld Retinal Images for DR and DME

Device	Ungradable Rate	Threshold	K	K_w	Exact Agreement	Within 1-Step	Sensitivity	Specificity	PPV	NPV
Nonmydriatic										
Aurora (AUNM)										
DR	15.1%	Overall	0.52	0.73	55.6%	80.0%				
		Any DR	0.69				0.79*	0.97†	0.98	0.69
		refDR	0.79				0.87†	0.92*	0.90	0.89
		vtDR	0.67				0.83†	0.86*	0.75	0.91
DME	20.4%		0.63	0.76			0.65*	1.00†	1.00	0.91
Smartscope (SSNM)										
DR	20.0%	Overall	0.50	0.72	51.6%	75.6%				
		Any DR	0.70				0.80†	0.96†	0.98	0.70
		refDR	0.78				0.89†	0.89*	0.88	0.90
		vtDR	0.64				0.88†	0.81*	0.69	0.93
DME	22.7%		0.72	0.83			0.72*	1.00†	1.00	0.93
RetinaVue700 (RVNM)										
DR	38.2%	Overall	0.54	0.70	43.1%	56.9%				
		Any DR	0.73				0.89†	0.88*	0.94	0.77
		refDR	0.68				0.93†	0.76*	0.79	0.92
		vtDR	0.50				0.88†	0.69*	0.62	0.91
DME	40.0%		0.72	0.81			0.76*	0.99†	0.95	0.95
Mydriatic										
Aurora (AUMD)										
DR	0%	Overall	0.55	0.75	65.8%	93.8%				
		Any DR	0.78				0.86†	0.97†	0.98	0.77
		refDR	0.81				0.84†	0.97†	0.96	0.87
		vtDR	0.74				0.81†	0.92*	0.84	0.91
DME	3.6%		0.67	0.78			0.80†	0.99†	0.96	0.93
Smartscope (SSMD)										
DR	3.6%	Overall	0.50	0.73	60.0%	90.7%				
		Any DR	0.66				0.80†	0.92*	0.95	0.69
		refDR	0.79				0.87†	0.92*	0.91	0.89
		vtDR	0.69				0.85†	0.86*	0.75	0.92
DME	8.0%		0.63	0.77			0.75*	1.00†	1.00	0.91
RetinaVue 700 (RVMD)										
DR	5.8%	Overall	0.56	0.75	63.1%	88.9%				
		Any DR	0.74				0.83†	0.97†	0.98	0.73
		refDR	0.84				0.87†	0.97†	0.96	0.89
		vtDR	0.77				0.89†	0.89*	0.81	0.94
DME	8.0%		0.67	0.78			0.87†	0.98†	0.94	0.95
iNview (NVMD)										
DR	33.8%	Overall	0.51	0.68	54.8%	75.1%				
		Any DR	0.47				0.91†	0.53*	0.80	0.74
		refDR	0.43				0.91†	0.54*	0.64	0.86
		vtDR	0.31				0.91†	0.47*	0.46	0.91
DME	40.4%		0.83	0.91			‡	‡	‡	‡

AUMD = Aurora mydriatic; AUNM = Aurora nonmydriatic; DME = diabetic macular edema; DR = diabetic retinopathy; K = kappa value; K_W = weighted kappa; NPV = negative predictive value; NVMD = iNview mydriatic; PPV = positive predictive value; refDR = referable DR; RVMD = RetinaVue-700 mydriatic; RVNM = RetinaVue-700 nonmydriatic; SSMD = Smartscope mydriatic; SSNM = Smartscope nonmydriatic; vtDR = vision-threatening DR.

*DR/DME thresholds that did not meet the 80% sensitivity or 95% specificity rates.

†DR/DME thresholds that met the 80% sensitivity or 95% specificity rates.

‡Unreliable results because of high ungradable rate for DME.

recognized that mydriasis improves image quality and increases agreement with the identification of disease.[25] This contrasts with previous studies using tabletop fundus cameras, which found that while mydriasis reduces the technical failure rate, it does not substantially affect the sensitivity and specificity of DR detection.[26,27] Possible reasons for this may include differences in the imaging protocol (imaging device used, number of fields taken, etc) and differences in technology (magnification, field of view, image resolution, illumination, etc) between tabletop and handheld devices.

Because patients with ungradable images are graded as having referable disease and need to be referred for in-person consults, imaging protocols with high ungradable rates diminish the efficiency and value of DRSPs.[6,28] In our study, ungradable images were associated with a higher rate of

Table 3. Change in Ungradable Rate and Exact Agreement for DR/DME with Pupil Dilation

	Nonmydriatic Ungradable Rate	Mydriatic Ungradable Rate	% Reduction in Ungradable Rate	Nonmydriatic Exact Agreement for DR	Mydriatic Exact Agreement for DR	% Increase in Exact Agreement
DR						
Aurora	15.1%	0	100%	55.6%	65.8%	18.3%
Smartscope	20.0%	3.6%	82.0%	51.6%	60.0%	16.3%
RetinaVue 700	38.2%	5.8%	84.8%	43.1%	63.1%	46.4%
DME						
Aurora	20.4%	3.6%	82.3%			
Smartscope	22.7%	8.0%	64.8%			
RetinaVue 700	40.0%	8.0%	80.0%			

DME = diabetic macular edema; DR = diabetic retinopathy.

refDR (Aurora, 2.1×; Smartscope, 2.1×; RetinaVue, 2.1×; $P < 0.0001$) and vtDR (Aurora, 2.2×; Smartscope, 2.1×; RetinaVue, 2.4×; $P < 0.0001$) when compared with ETDRS photographs. It is important to remember that the incidence of cataracts among people with DM is more frequent due to older age and as a consequence of the disease.[29] Hence, DRSPs utilizing handheld cameras need to have a defined protocol for pupil dilation, when necessary, to reduce ungradable rates. Queiroz et al[30] proposed the evaluation of the anterior segment when using handheld retinal cameras for DR grading, specifically to determine whether cataracts are the cause of ungradable fundus images and having a referral pathway for such cases. When deploying a teleophthalmology DRSP in a population with predominantly dark iris pigmentation, previous studies reported that pupil dilation can improve the image quality and decrease ungradable rates.[31,32]

In the present study, we report that pupil dilation significantly decreases ungradable rates for DR and DME and increases exact agreement for DR severity when using handheld retinal imaging devices. Additionally, the sensitivity threshold for DME was only achieved with mydriasis, suggesting that pupil dilation enhances DME evaluation. Mydriasis is generally considered safe, and in published literature, the incidence of angle closure after pupil dilation for DR screening is between 0.03% and 0.003%.[33–35]

However, it is also crucial to consider that nondilation of pupils is a factor in patients' acceptance of teleophthalmology DRSPs.[36] This is most relevant for developed countries or in communities with easy access to care and may not be applicable in settings where DR screening or treatment services are not readily available. For instance, patients from resource-limited communities in low-to-middle income countries may prefer pupil dilation (and more adequate image evaluation) over attending an in-person consultation at specialized eye care centers (with subsequent travel costs and lost wages) due to ungradable images. In remote communities, attending a community-based screening may be the only opportunity for DR evaluation.

Balancing the issue of image ungradable rates vis-à-vis program acceptance is critical for the scalability of the DRSP. Incorporating mydriasis into the imaging protocol is dependent not only on the imaging device and image quality but also on the screening program's operational simplicity and population-specific factors. A pragmatic approach that includes pupil dilation in the imaging protocol for DR screening is more suitable when using handheld cameras, especially in community or remote settings.

Our results are limited to the mobile imaging devices included in the study, specifically only those devices that were commercially available in the Philippines before the start of the study. Other handheld cameras will also need to be validated before they can be utilized in population-based DR screening. Intergrader variability was minimized by evaluating all the images in a centralized reading center with standardized display settings and direct adjudication by a senior retina specialist.

This study had only a moderately large sample size with well-defined and detailed imaging and grading protocols. The ETDRS standard 7-field, considered the gold standard for identifying DR, was used as the reference for comparison. The effect of the imaging protocol, specifically the number of fields used per device, is the subject of a separate analysis. Looking forward, the integration of artificial intelligence algorithms for automated image grading in teleophthalmology DRSPs using handheld retinal imaging will also need to be explored to permit more rapid, but still accurate, identification of DR and to ensure long-term sustainability.

In this study, we demonstrated that following a standardized protocol, both NM and MD handheld retinal imaging devices have substantial levels of agreement with ETDRS 7-field photography for both DR and DME. With mydriasis, not all handheld retinal imaging devices met the standards for sensitivity and specificity in identifying any DR and refDR. None of the handheld devices met the established 95% specificity for vtDR, suggesting that lower thresholds are needed for a referral if handheld devices must be used. Furthermore, without pupillary dilation, certain handheld devices did not meet the established standards for the identification of varying DR referral thresholds, which may limit NM use.

Overall, certain handheld retinal imaging devices, when used following a standard protocol with pupil dilation, can achieve substantial agreement with standard photography

and may be useful in settings where traditional means of retinal evaluation are not possible. These findings will be helpful to clinicians and public health managers in planning for a DRSP.

Acknowledgments. The authors thank Lloyd Paul Aiello, MD, PhD (Beetham Eye Institute, Joslin Diabetes Center, Department of Ophthalmology, Harvard Medical School) for his valuable contributions in the review, discussion, and editing of the scientific content of the paper.

Footnotes and Disclosures

Originally received: December 12, 2021.
Final revision: March 2, 2022.
Accepted: March 3, 2022.
Available online: ■■■. Manuscript no. ORET-D-21-00707R2.

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Presented virtually at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, May 3, 2021, online, and at the European Society of Retina Specialists (EURETINA) Annual Meeting 2021, September 9, 2021, online.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): J.K.S.: Financial support − Adaptive Sensory Technologies, Boehringer Ingelheim, Kalvista, Optovue, Boston Micromachines, Roche, outside of the submitted work; Personal Fees − Boehringer Ingelheim, Novo Nordisk, Kalvista, Roche, Novartis, Merck, outside of the submitted work.

T.P.: Personal Fees − Novartis, Bayer, Roche, Heidelberg, Optos, outside of the submitted work; Financial support − Optomed.

P.S.S.: Research support − Optomed, Hillrom, Optos; Personal fees - Optomed, Optos.

Research is funded jointly by the United Kingdom Medical Research Council (58 Victoria Embankment, London EC4Y 0DS, UK) and the Philippine Council for Health Research and Development (Saliksik Building, DOST Compound, Gen Santos Ave, Bicutan, Taguig City 1631, Philippines) through the Newton-Agham Grant. Grant Title: The UK − Philippines Remote Retinal Evaluation Collaboration in Health: Diabetic Retinopathy (REACH-DR) Project (Project Reference: MR/R025630/1). The funding agencies have no role in the design or conduct of this research.

HUMAN SUBJECTS: Human subjects were included in this study. The institutional review board of The Medical City approved the study. All research complied with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were used in this study.

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Obtained funding: Peto, Silva

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Abbreviations and Acronyms:
AUMD = Aurora mydriatic; **AUNM** = Aurora nonmydriatic; **CI** = confidence interval; **DM** = diabetes mellitus; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRSP** = diabetic retinoptahy screening program; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **MD** = mydriatic; **NM** = nonmydriatic; **NVMD** = iNview mydriatic; **refDR** = referable diabetic retinopathy; **RVMD** = RetinaVue-700 mydriatic; **RVNM** = RetinaVue-700 nonmydriatic; **SSMD** = Smartscope mydriatic; **SSNM** = Smartscope nonmydriatic; **vtDR** = vision-threatening diabetic retinopathy.

Keywords:
Diabetic retinopathy, Diabetic retinopathy screening, Handheld retinal imaging, Instrument validation, Mobile fundus camera, Teleophthalmology.

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