

## Summary

There have been significant advancements in retinal photography using portable handheld imaging devices. This study compared the agreement of single field macula centered versus two field macula and disc centered retinal images using three handheld fundus cameras with standard 7-field Early Treatment Diabetic Retinopathy Study (ETDRS) photography in detecting and grading the severity of diabetic retinopathy and diabetic macular edema. In this study, single field handheld mydriatic imaging did not meet the established standards for sensitivity (80%) and specificity (95%) in detecting and grading diabetic retinopathy and diabetic macular edema. Using two field retinal imaging, the ungradable rate is reduced by 20-53% and agreement with ETDRS photography is increased by 8 -30% compared to single field imaging. Although the addition of a second field improved agreement with ETDRS photos and increased sensitivity, not all devices met established standards. These data suggest the possible need for 2 fields and care in camera selection and understanding of sensitivity and specificity limitations.

## Purpose

To determine agreement of 1-field (1F, macula centered) and 2-field (2F, disc/macula) mydriatic handheld retinal imaging with standard ETDRS photography for DR/DME.

## Methods

- Prospective comparative instrument validation study for the detection and grading of diabetic retinopathy.
- Images acquired during the same visit were prospectively collected from adult diabetic patients at a tertiary care center.
- Two certified retinal imagers captured all images with handheld retinal cameras.
- Patients were excluded from the study if they had active periocular, ocular or intraocular infection at the time of examination and those with eye conditions like corneal opacities and dense cataracts that may obscure retinal imaging.
- Following standard imaging protocol, mydriatic macula-centered and disc-centered images were acquired using handheld retinal cameras [Aurora, field of view: 50° (AU) and Smartscope, 45° (SS) Optomed Oy, Finland), RV700, 60° (RV, Hill-rom Inc, Chicago,IL)] and followed by dilated 7-field standard ETDRS photography on the same visit.
- Images were independently evaluated at a centralized reading center by masked graders using ETDRS standard photographs and categorized using the international DR/DME classification system.
- Unweighted (K) and weighted (KW) kappa statistics assessed agreement for DR/DME. Sensitivity and specificity for any DR, referable DR [(refDR) moderate nonproliferative DR (NPDR) or worse, any DME or ungradable images] and vision threatening DR [(vtDR) severe NPDR or worse, center involving DME (ciDME) or ungradable images] were calculated..

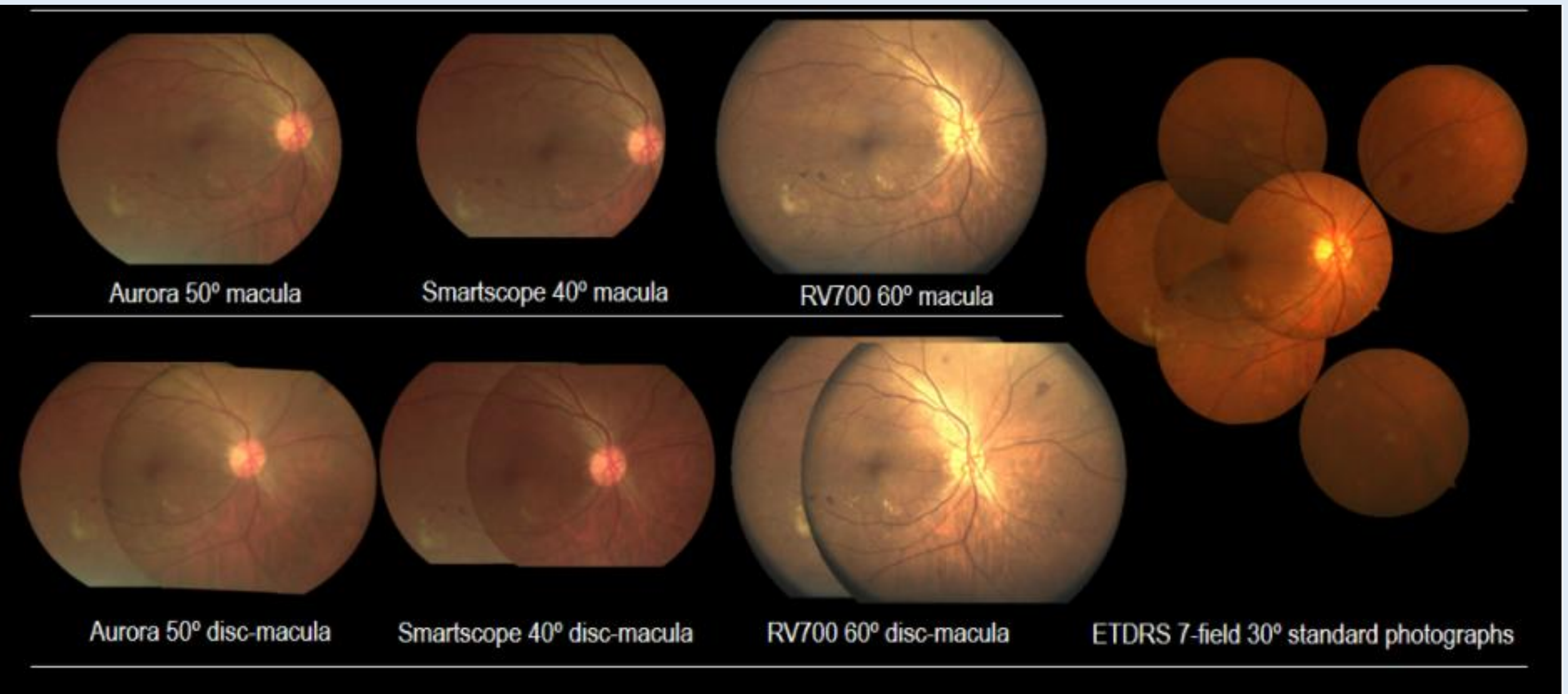


Figure 1. Comparison of Mydriatic 1-field and 2-field Mydriatic Handheld Retinal Images to ETDRS 7-field Fundus Photographs.

## Results

**Table1. Agreement of 1F and 2F handheld imaging with Early Treatment Diabetic Retinopathy Study (ETDRS) photography. K= unweighted Kappa, KW= weighted Kappa. refDR= referable DR. vtDR= vision threatening DR.**

	Threshold	Ungradable	K	Kw	Exact Agreement	Within 1-Step	Sensitivity	Specificity
<b>Aurora (AU)</b>								
<b>1-Field</b>	<b>Overall DR</b>	<b>2.23%</b>	<b>0.25</b>	<b>0.54</b>	<b>44.20%</b>	<b>81.25%</b>		
	<b>Any DR</b>		<b>0.58</b>				<b>0.76</b>	<b>0.99</b>
	<b>refDR</b>		<b>0.62</b>				<b>0.78</b>	<b>0.92</b>
	<b>vtDR</b>		<b>0.71</b>				<b>0.83</b>	<b>0.91</b>
<b>2-Field</b>	<b>Overall</b>	<b>1.79%</b>	<b>0.31</b>	<b>0.59</b>	<b>48.21%</b>	<b>85.71%</b>		
	<b>Any DR</b>		<b>0.61</b>				<b>0.78</b>	<b>0.99</b>
	<b>refDR</b>		<b>0.66</b>				<b>0.79</b>	<b>0.91</b>
	<b>vtDR</b>		<b>0.7</b>				<b>0.84</b>	<b>0.89</b>

<b>Smartscope (SS)</b>								
<b>1-Field</b>	<b>Overall DR</b>	<b>7.59%</b>	<b>0.27</b>	<b>0.51</b>	<b>41.96%</b>	<b>75.45%</b>		
	<b>Any DR</b>		<b>0.51</b>				<b>0.78</b>	<b>0.85</b>
	<b>refDR</b>		<b>0.65</b>				<b>0.78</b>	<b>0.92</b>
	<b>vtDR</b>		<b>0.61</b>				<b>0.75</b>	<b>0.92</b>
<b>2-Field</b>	<b>Overall</b>	<b>4.02%</b>	<b>0.35</b>	<b>0.59</b>	<b>49.11%</b>	<b>83.93%</b>		
	<b>Any DR</b>		<b>0.54</b>				<b>0.81</b>	<b>0.82</b>
	<b>refDR</b>		<b>0.67</b>				<b>0.80</b>	<b>91</b>
	<b>vtDR</b>		<b>0.66</b>				<b>0.8</b>	<b>0.91</b>

<b>RetinaVue700 (RV)</b>								
<b>1-Field</b>	<b>Overall DR</b>	<b>4.98%</b>	<b>0.52</b>	<b>0.77</b>	<b>60.63%</b>	<b>92.31%</b>		
	<b>Any DR</b>		<b>0.65</b>				<b>0.82</b>	<b>0.93</b>
	<b>refDR</b>		<b>0.86</b>				<b>0.91</b>	<b>0.95</b>
	<b>vtDR</b>		<b>0.78</b>				<b>0.91</b>	<b>0.90</b>
<b>2-Field</b>	<b>Overall</b>	<b>3.62%</b>	<b>0.56</b>	<b>0.75</b>	<b>63.11%</b>	<b>88.89%</b>		
	<b>Any DR</b>		<b>0.74</b>				<b>0.85</b>	<b>0.97</b>
	<b>refDR</b>		<b>0.84</b>				<b>0.88</b>	<b>0.97</b>
	<b>vtDR</b>		<b>0.77</b>				<b>0.90</b>	<b>0.89</b>

K = simple kappa statistic; K<sub>w</sub> = weighted kappa statistic, DR = diabetic retinopathy; refDR = referable DR [moderate nonproliferative DR (NPDR) or worse, any diabetic macular edema (DME) or ungradable images]; vtDR = vision threatening DR [severe NPDR or worse, center involving DME (ciDME) or ungradable images]  
Established minimum 80% sensitivity and 95% specificity rates for diabetic retinopathy screening devices.  
■ DR Thresholds that meet the established sensitivity and specificity rate  
■ DR Thresholds that did not meet the established sensitivity and specificity rate

## References

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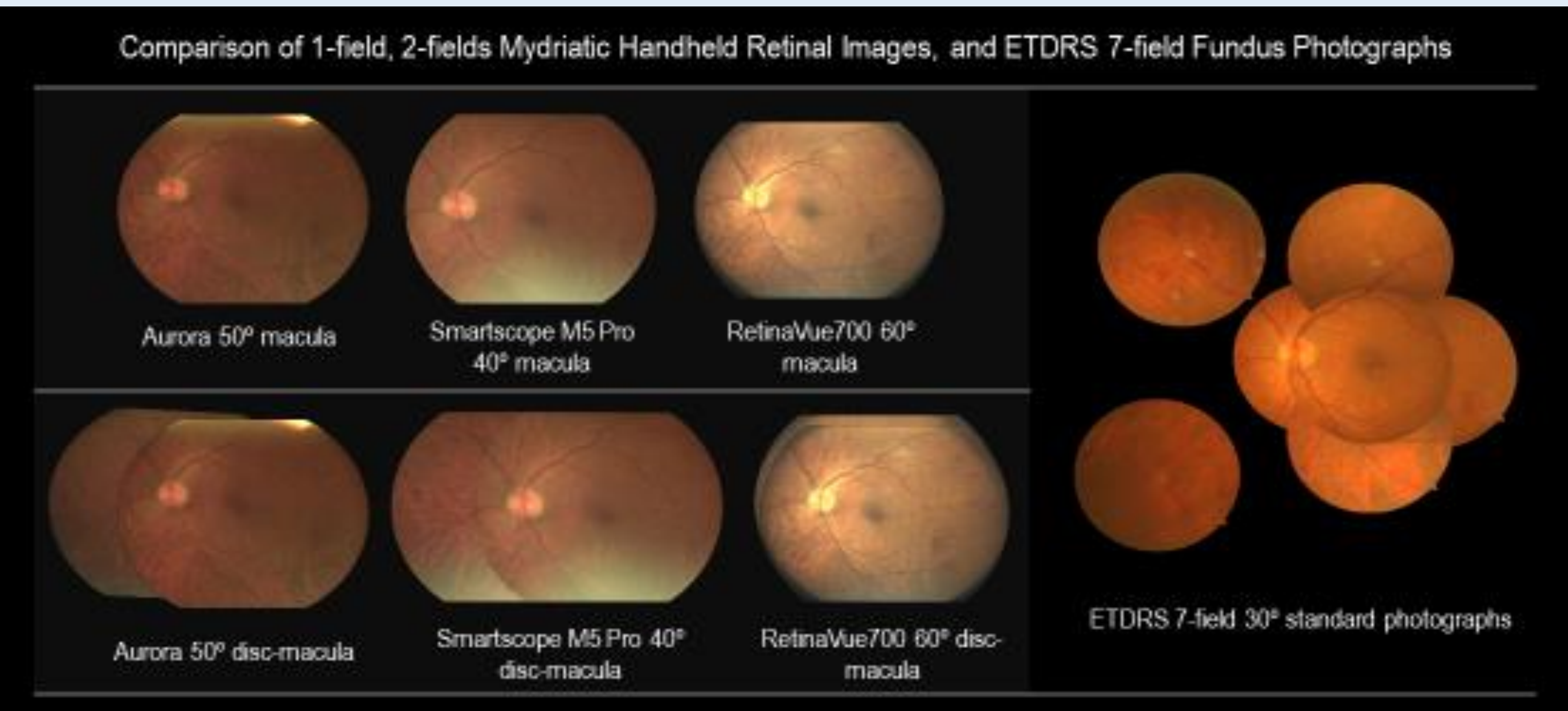


Figure 2. Representative montage of fundus photos showing false negative for presence of vision threatening compared to ETDRS standard 7-field 30° fundus photographs. On handheld retinal photography only mild or moderate nonproliferative diabetic retinopathy was identified. The corresponding ETDRS photography show severe diabetic retinopathy with multiple intraretinal microvascular abnormalities (IRMA) in supernonasal, temporal and inferotemporal macula.

- Images from 224 eyes of 116 patients with diabetes were evaluated. By ETDRS photos: no DR 33.04 eyes, mild NPDR 20.54%, moderate 14.29%, severe 11.61%, proliferate DR 20.54%; no DME 67.86%, DME 9.38%, CSME 17.41%, ungradable 5.36%.
- DME was ungradable in AU: 12.05%, SS: 13.39%, RV: 8%.
- A summary of the results is shown in table 1.
- With 2F imaging:
  - 1. DR ungradable rate decreased by 19.73% AU, 52.96% SS, 27.31% RV.
  - 2. Exact agreement of DR grading between handheld retinal imaging and ETDRS photos increased by 9.07% AU, 17.04% SS, 4.09%% RV.
  - 3. Kappa levels of agreement with ETDRS photos for DR increased by 24% for AU, 29.63% for SS and 7.69% for RV.
- With 1F or 2F imaging, only AU met thresholds for specificity for anyDR and vtDR.
- With 2F imaging, SS met thresholds for sensitivity but not specificity for any DR, refDR and vtDR
- With 2F imaging, RV improved specificity for any DR meeting the threshold of 95%

## Conclusions

- Handheld 1F imaging does not meet established standards for sensitivity (80%) and specificity (95%) in identifying DR and refDR.
- The acquisition of a second field in handheld imaging reduces the ungradable rate by 19.73%-52.96% and increases agreement with ETDRS by 7.69%-29.63%.
- The addition of a second field improves agreement with ETDRS photos and increases sensitivity but even with a second field not all devices meet established standards.
- These data suggest the possible need for 2 fields and care in camera selection and understanding of sensitivity and specificity limitations when using handheld imaging devices.

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# Comparison of Nonmydriatic Handheld Retinal Imaging with Early Treatment Diabetic Retinopathy Study (ETDRS) 7-Standard Field Photography for Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME)

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## Background

At the minimum an annual dilated eye examination within five years and at the time of diagnosis for types 1 and 2 diabetes mellitus (DM) are standard practice of care for persons with DM. The use of mydriatic drops in routine retinal evaluation may have a negative impact on a patient's lifestyle by temporarily decreasing visual acuity 1. The use of mydriasis may affect compliance to the screening examination and may put patients at risk for non-attendance. Handheld mobile retinal imaging devices in retinal evaluation may be more efficient to use than the standard tabletop fundus cameras due to its portability, accessibility and cost-effectiveness. However, image quality may be compromised due to lack of mydriasis. A study 2 suggested that mydriasis has a significant effect in the reduction of the proportion of ungradable photographs from 26% to 5%. In this study, nonmydriatic handheld retinal imaging is compared with Early Treatment Diabetic Retinopathy Study (ETDRS) standard 7-field 30° fundus photography for the evaluation of diabetic retinopathy and diabetic macular edema.

## Purpose

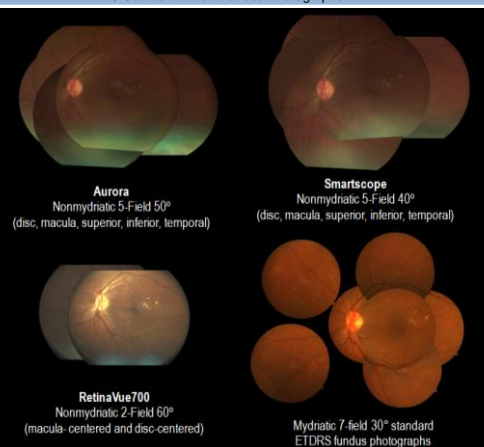
To compare nonmydriatic handheld retinal imaging with ETDRS standard 7-field 30° fundus photographs (ETDRS photos) for assessment of DR and DME severity.

## Methods

- Prospective, hospital-based, comparative instrument validation study for the detection and grading of diabetic retinopathy.
- Two certified retinal imagers-graders captured images from a total of 116 adult patients (225 eyes) who are clinically diagnosed to have DM and willing to undergo extensive imaging procedures.
- Patients who were excluded from the study include those who have active periocular, ocular or intraocular infection at the time of examination and those with eye conditions like corneal opacities and dense cataract since these may obscure the imaging of the retina.
- A 5-minute interval after taking photos from each camera was observed to help the pupil recover from light.
- Following a standard imaging protocol, nonmydriatic retinal images were taken using three handheld retinal cameras. Figure 1 presents a comparison of the different nonmydriatic handheld retinal images with standard ETDRS photos.
- Images taken using handheld retinal devices were compared to dilated stereoscopic ETDRS standard 7-field 30° fundus photographs (ETDRS photos).
- All images were evaluated at a centralized reading center using color-calibrated high resolution HD computer displays.
- Grading was performed independently by 4 graders (2 certified retinal image/graders, 1 ophthalmologist, 1 retina specialist) using international DR/DME classification.
- All differences were adjudicated by a senior retina specialist.
- Kappa statistics [Simple (K), weighted (KW)] assessed agreement for DR/ DME.
- Sensitivity/specificity for any DR, referable DR [(refDR) moderate nonproliferative DR (NPDR) or worse, any DME or ungradable images] and vision threatening DR [(vtDR) severe NPDR or worse, clinically significant DME (CSME) or ungradable images] were calculated.

- Images from 225 eyes of 116 patients with diabetes were evaluated. A summary of the cohort demographics and ETDRS DR severity is presented in Table 1.
- Agreement of clinical DR grading between handheld retinal and ETDRS photos are shown in table 2.
- Sensitivity/specificity for any DR, refDR and vtDR: AU, SS and RV had 69-97% specificity and 83-93% sensitivity for any DR, refDR and vtDR.
- Ungradable rate for DR/DME for AU: 34 (15.1%)/46 (20.4%); SS: 45 (20.0%)/51 (22.7%) and RV: 86 (38.2%)/90 (40.0%).
- Among the devices, AU (exact 55.6%; within 1-step 80.0%) had the highest agreement with ETDRS photos, higher than SS (51.6%; 75.6%) and RV (43.1%; 56.9%).
- 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 images were associated with a higher rate of refDR on corresponding ETDRS photos (AU: 2.1x, SS: 2.1x, and RV: 2.1x, p<0.0001).
- Ungradable images were associated with a vtDR on corresponding ETDRS photos (AU: 2.2x, SS: 2.1x, and RV: 2.4x, p<0.0001).

**Figure 1. Comparison of Nonmydriatic Handheld Retinal Images and ETDRS Standard 7-field Fundus Photographs.**



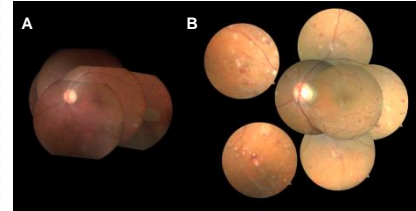
## Results

**Table 1. Baseline Characteristics**

Male sex	48 (41.4)
Age	56.8±10.5
Average A1c	7.3±1.6
Hypertension	65 (56.0)
Renal Disease	12 (10.3)
<b>ETDRS Diabetic Retinopathy severity</b>	
No DR	75 (33.3)
Mild NPDR	46 (20.4)
Moderate NPDR	32 (14.2)
Severe NPDR	26 (11.6)
PDR	46 (20.4)
<b>ETDRS Macular Edema</b>	
No DME	153 (68.0)
DME	21 (9.3)
Non-ciDME	11 (4.9)
ciDME	28 (12.4)

Count ± standard deviation or (%); ETDRS = Early Treatment Diabetic Retinopathy Study; DR = Diabetic Retinopathy; NPDR = Nonproliferative Diabetic Retinopathy; PDR = Proliferative Diabetic Retinopathy; DME = Diabetic Macular Edema; ciDME = Central-involved diabetic macular edema.

**Figure 2. Representative montage of fundus photos showing false negative for presence of vtDR compared to ETDRS standard 7-field 30° fundus photographs (ETDRS photos).**



**LEGEND = A and B:** False negative fundus photo for presence of vtDR. Graded as moderate NPDR on nonmydriatic handheld retinal imaging (A) but on ETDRS photos (B) were graded as PDR due to the presence of new vessels in ETDRS field 6 outside the fields captured by nonmydriatic imaging.

**Table 2. Comparison by Different Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME) Thresholds: Mydriatic ETDRS 7-Field Photographs Compared with Nonmydriatic Handheld Imaging Devices**

Device	Threshold	Ungradable Rate	K	K <sub>w</sub>	Exact Agreement	Within 1-Step	Sensitivity	Specificity	PPV	NPV
<b>Aurora (AU)</b>										
Overall		15.1%	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
<b>Smartscope (SS)</b>										
Overall		20.0%	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
<b>RetinaVue 700 (RV)</b>										
Overall		38.2%	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

■ DR Thresholds that did not meet the 80% sensitivity and 95% specificity rates ■ DR Thresholds that meet the published sensitivity and specificity rates

## Conclusions

- Compared to ETDRS standard photography, nonmydriatic handheld retinal imaging was able to achieve sensitivity of over 0.80 for identifying any DR, referable DR and vision threatening DR. However, specificity decreases with more severe disease.
- Despite a standardized protocol of image capture and evaluation, the ungradable rate of these devices varies from 15%-38%. Additionally, ungradable rate for DME varies from 20%-40% in all the handheld devices.
- In this cohort, a 2.1-fold increased risk of refDR among ungradable images. Risk of vtDR among ungradable images is 2.1-2.4x.
- Thus, although handheld nonmydriatic retinal devices are able to achieve substantial agreement with DR in some cases, additional methods may be needed to reduce ungradable rates and appropriately triage eyes that require specialized care.

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# Cost-effectiveness Analysis of Retinal Imaging Devices for Diabetic Retinopathy Screening



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## Background

One of the major complications of diabetes is vision loss due to a disease known as diabetic retinopathy (DR) that includes diabetic maculopathy affecting predominantly the center part of the back of the eye, the place of high acuity vision. The prevalence of diabetes-related blindness and visual impairment is lowest where continuous retinal evaluations for all persons with diabetes exist.

In the Philippines, DR examinations are usually done by dilated retinal examination by eyecare professionals. However, in-person retinal evaluation is not always possible due to the lack of trained personnel and suitable equipment. In response to this, the Philippine telecommunication and healthcare infrastructure is being developed to sustain centralized telemedicine programs using the optimal devices. The ultimate aim is to reduce blindness and visual impairment secondary to DR through a national DR screening program in the Philippines.

## Purpose

To estimate and compare the cost-effectiveness of mydriatic and nonmydriatic imaging devices for consideration in a community-based program for DR screening in the Philippines.

## Methods

A decision-analytic model was developed to simulate the costs and outcomes of each device [Aurora (AU), SmartScope (SS), RV700 (RV), InView (NV)] with dilation and without dilation of the pupil.

The key measures of effectiveness were determined by the devices' operating characteristics including positive and negative predictive values and rate of ungradable images. These parameters, as well as the distribution of patients with varying severity levels of DR, were obtained from a validation study performed in Manila involving images from 177 eyes of 92 patients with diabetes.

Associated costs of screening, referrals, panretinal laser photocoagulation for severe nonproliferative or proliferative DR, and corresponding cost of severe vision loss were estimated from the perspective of the patient.

Health outcomes were reported as quality-adjusted life years (QALYs) based on utility values assigned to vision threatening DR and vision loss. The primary outcome measure is reported as cost in Philippine Peso (PhP) per QALY gained.

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## Results

Figure 1. Costs and benefits of the devices (mydriatic, nonmydriatic and clinic-based ophthalmoscope)

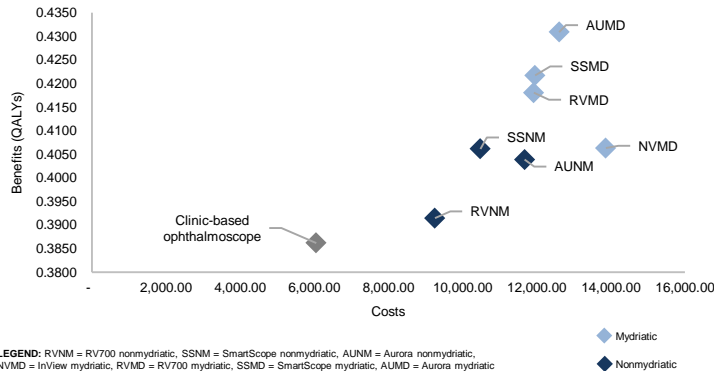


Table 2. Deterministic results of cost-effectiveness using incremental analysis versus comparator and dominance approach

	Total Cost (PhP)	Total Benefit (QALYs)	Incremental Cost	Incremental Benefit	ICER (vs comparator)	Dominance and Extended Dominance
<b>Mydriatic</b>						
AUMD	12,609.77	0.4309	6,558.62	0.04	146,647.76	71,207.86
SSMD	11,955.80	0.4217	5,904.65	0.04	166,142.51	-
RVMD	11,921.34	0.4180	5,870.20	0.03	184,268.43	Weakly Dominated
NVMD	13,865.86	0.4063	7,814.72	0.02	388,573.91	Strongly Dominated
<b>Nonmydriatic</b>						
AUNM	11,678.14	0.4039	5,626.99	0.02	318,187.58	Strongly Dominated
SSNM	10,478.67	0.4061	4,427.52	0.02	221,859.00	Weakly Dominated
RVNM	9,256.29	0.3915	3,205.14	0.01	606,485.99	Weakly Dominated
Clinic-based ophthalmoscope (comparator)	6,051.14	0.39				

LEGEND: RVNM = RV700 nonmydriatic, SSNM = SmartScope nonmydriatic, AUNM = Aurora nonmydriatic, NVMD = InView mydriatic, RVMD = RV700 mydriatic, SSMD = SmartScope mydriatic, AUMD = Aurora mydriatic. PhP = Philippine pesos, QALYs = quality-adjusted life year, ICER = incremental cost-effectiveness ratio.

Table 1. Parameters used

Parameter	Value	Reference
<b>Epidemiologic</b>		
Rate of DR	0.50	Yau GL, et al. 2017 <sup>4</sup>
Rate of vision threatening DR	0.15	Yau GL, et al. 2017 <sup>4</sup>
Panretinal laser photocoagulation (PRP) uptake	0.50	Hua W, et al. 2017 <sup>5</sup>
% with severe vision loss without PRP	0.26	Diabetic Retinopathy Study (1979) from AAO and VRSP DR Preferred Practice Patterns <sup>1</sup>
% with severe vision loss without PRP	0.11	

## Device operating characteristics

ARVO 2021 Abstract # 353717: Aquino LC, et al. Comparison of Nonmydriatic Handheld Retinal Imaging with Early Treatment Diabetic Retinopathy Study (ETDRS) 7-Standard Field Photography for Diabetic Retinopathy and Diabetic Macular Edema

ARVO 2021 Abstract #351893 Salongcay RP, et al. Comparison of Mydriatic Handheld Retinal Imaging with Early Treatment Diabetic Retinopathy Study (ETDRS) 7-Standard Field Photography for Diabetic Retinopathy and Diabetic Macular Edema

## Costs

Cost of screening (mydriatic)	250.00	Programme cost
Cost of screening (nonmydriatic)	260.00	Programme cost
Cost of clinic-based screening	1,500.00	Programme cost
Cost of referral for false positives	800.00	Programme cost
Cost of severe vision loss	109,632.00	Access Economics, 2010
Cost of panretinal laser photocoagulation	12,120.00	PhilHealth case rate, 2013
Philippine country-specific threshold	150,000	Department of Health, 2020

## Conclusions

The use of Aurora and SmartScope with pupil dilation yield good value for money based on their validity, and the reported ICER value falls below the country-specific threshold of 150,000 PhP, which shows great potential for being cost-effective in a community-based DR screening program.

A broader and more comprehensive analysis is warranted to account for societal costs when the devices are used in a larger-scale, relative to their individual and population-level benefits while considering other factors such as burden and treatment of disease, and health system capacity.

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# Intergrader Agreement for Diabetic Retinopathy (DR) using Hand-Held Retinal Imaging



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## Summary

There are several methods for assessing diabetic retinopathy (DR) severity that include the Early Treatment Diabetic Retinopathy Study (ETDRS) Severity Scale, and the International Classification for DR (ICDR). The ETDRS is considered the gold standard, while the ICDR scale is commonly used in teleophthalmology programs. Grading DR severity is a complex process that requires the identification and quantification of fine retinal features resulting in significant variability. The use of nonphysician graders and handheld retinal imaging add further complexity to this already difficult task.

In this study, we evaluated the use of handheld retinal imaging and nonphysician graders compared to ETDRS imaging and retinal specialists to assess DR severity. We show that following a structured program of grading certification, substantial over-all agreement for DR can be achieved across graders. However, compared to nonphysician graders, retina specialists remain the most reliable personnel to interpret handheld retinal images for DR. Among the nonphysician graders the ability to identify vision threatening disease was below 90% across all camera types. This suggests that in DR screening programs using hand-held retinal imaging, secondary grading of eyes with advanced disease by more experienced graders may be necessary to minimize unnecessary referrals that would otherwise decrease the effectiveness of screening programs.

## Purpose

To assess intergrader agreement when interpreting retinal images acquired with handheld retinal imaging devices for DR screening.

## Methods

- Mydriatic retinal images acquired using 3 hand-held retinal cameras [Aurora (AU), Smartscope (SS), RV700 (RV)] were compared with Early Treatment Diabetic Retinopathy Study 7-field standard photography (ETDRS photos).
- All handheld retinal images were independently evaluated by 2 grader-certified nonphysician staff and 1 retina specialist (RPS).
- The ETDRS photos were evaluated by a senior retina specialist (PSS). All graders had completed a structured certification program in DR assessment.
- Grading was performed using the International Classification for DR. Agreement was measured using kappa (k) statistics, multirater k across graders and sensitivity/specificity was calculated for vision threatening DR [(v)DR]: severe NPDR or worse).

## Results

Table 1 - Reliability indices for diabetic retinopathy severity compared to ETDRS 7-field standard fundus photographs

	Multirater Kappa (any DR)	Multirater Kappa (any DR)	Weighted Kappa	Sensitivity (vDR)	Specificity (vDR)	PPV (vDR)	NPV (vDR)
Aurora (AU)							
Grader 1	0.63 ± 0.03	0.72 ± 0.04	0.48±0.05	0.97	0.88	0.72	0.99
Grader 2			0.49±0.04	0.98	0.87	0.74	0.99
Retinal Sp.			0.78±0.03	0.95	0.96	0.88	0.98
Smartscope (SS)							
Grader 1	0.65 ± 0.02	0.71 ± 0.04	0.46±0.05	0.95	0.87	0.71	0.98
Grader 2			0.47±0.05	0.98	0.87	0.73	0.99
Retinal Sp.			0.72±0.04	0.92	0.97	0.91	0.97
RV-700 (RV)							
Grader 1	0.58 ± 0.02	0.74 ± 0.05	0.47±0.05	0.92	0.88	0.71	0.97
Grader 2			0.48±0.05	0.93	0.89	0.75	0.90
Retinal Sp.			0.70±0.03	0.85	0.96	0.85	0.96

DR = diabetic retinopathy; v)DR = vision threatening DR [severe NPDR or worse, center involving DME (ciDME) or ungradable images]; PPV = positive predictive value; NPV = negative predictive value.

DR Thresholds that do not meet minimum 80% sensitivity and 95% specificity rates

DR Thresholds that meet the minimum 80% sensitivity and 95% specificity rates

•Images from 177 eyes of 92 patients with diabetes were evaluated. Severity by ETDRS photos: no DR 40.1%, mild NPDR 19.2%, moderate 14.7%, severe 10.2%, proliferative DR 15.8%.

•Ungradable rate for DR was AU: 0%; SS: 4.5%; RV: 4.0%; and ETDRS: 0%. Results are presented in table 1.

•Multirater k for DR severity (0.58 – 0.65) and v)DR (0.71 – 0.74) was uniform across all devices.

•Agreement (k) for DR severity between ETDRS photos and graders was similar across nonphysician graders across devices (0.46 – 0.48) and highest with retina specialist evaluation across devices (0.70 -0.78).

•Sensitivity/specificity for v)DR on ETDRS photo for nonphysician graders was over 0.95 in all devices but specificity was 0.87-0.89.

•Retina specialist specificity for v)DR was 0.96-0.97.

## Conclusions

•In assessing DR severity, substantial over-all agreement (0.58-0.74) among all graders was achieved emphasizing the benefit of a structured program of grading certification.

•Retinal images obtained using all 3 handheld cameras achieved the highest agreement with ETDRS photos (0.70-0.78) when evaluated by a retinal specialist.

•Among the nonphysician graders for all devices, sensitivity for v)DR was over 90% but specificity remained 87-89%.

•These findings suggest that in DR screening programs using hand-held retinal imaging, secondary grading of eyes with v)DR by more experienced graders may be necessary to minimize unnecessary referrals that would otherwise decrease the effectiveness of screening programs.



# Comparison of Mydriatic Handheld Retinal Imaging with Early Treatment Diabetic Retinopathy Study (ETDRS) 7-Standard Field Photography for Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME)

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## Background

If left undetected and untreated, diabetic retinopathy and diabetic macular edema can lead to visual loss among people living with diabetes mellitus. Diabetic retinal complications remain one of the leading causes of blindness in the working age population worldwide. It is recommended that people with diabetes undergo regular clinical examination with an eye care professional or fundus (retina) photography to screen for the presence of diabetic retinopathy. However, this is not always possible especially in low resource settings where access to specialized eye care and/or equipment is limited. The use of portable handheld fundus cameras in such settings can potentially address this unmet need. In this study, the use of some handheld retinal imaging devices attained acceptable levels of agreement and met established standards for sensitivity and specificity in the detection of diabetic retinal disease and identified eyes requiring more specialized care.

## Purpose

To compare mydriatic handheld retinal imaging with standard ETDRS 7-field color 30-degree fundus photography (ETDRS photos) for assessment of DR and DME

## Methods

- Prospective, hospital-based, comparative instrument validation study for the detection and grading of diabetic retinopathy.
- Images acquired during the same visit were prospectively collected from adult diabetic patients at a tertiary center.
- Two certified retinal imagers-graders captured images from a total of 116 adult patients (225 eyes) who are clinically diagnosed to have DM and willing to undergo extensive imaging procedures.
- Patients who were excluded from the study include those who have active periorcular, ocular or intraocular infection at the time of examination and those with eye conditions like corneal opacities and dense cataracts that may obscure the imaging of the retina.
- Following a standard imaging protocol, mydriatic retinal images were acquired using dilated ETDRS 7-field photos and four handheld retinal cameras using a multi-field predefined imaging protocol (Figure 1)
- All images were evaluated at a centralized reading center using color-calibrated high resolution HD computer displays.
- Grading was performed independently by 4 graders (2 certified retinal image/graders, 1 ophthalmologist, 1 retina specialist) using international DR/DME classification. All differences were adjudicated by a senior retina specialist.
- Kappa statistics [simple (K), weighted (K<sub>w</sub>)] assessed agreement for DR/DME.
- Sensitivity/specificity for any DR, referable DR [(refDR) moderate nonproliferative DR (NPDR) or worse, any DME or ungradable images] and vision threatening DR [(vDR) severe NPDR or worse, clinically significant DME (CSME) or ungradable images] were calculated.

- Images from 225 eyes of 116 patients with diabetes were evaluated. A summary of the results is presented in Tables 1 and 2.
- Severity by ETDRS photos: DR – no DR 33.3%, mild NPDR 20.4%, moderate 14.2%, severe in 11.6%, proliferative DR 20.4%; DME: no DME 68.0%, DME 9.3%, cDME 17.3%, ungradable 5.3%.
- Agreement for DR was highest with the AU and RV (K<sub>w</sub> = 0.75) and lowest with NV (K<sub>w</sub> = 0.68). DME Agreement was highest for AU and RV (K<sub>w</sub> = 0.78).
- Agreement for DR Severity with ETDRS photos was highest with AU (65.8% exact, 93.8% 1-step).
- The established standard for sensitivity (0.80) was met by AU, SS and RV for anyDR, refDR and vDR, and specificity (0.95) was met by AU and RV for anyDR and refDR.
- The established standard for sensitivity (0.80) and specificity (0.95) was met by AU and RV for DME.

Table 1. Baseline Characteristics

Male sex	48 (41.4)	Count ± standard deviation or (n%); ETDRS = Early Treatment Diabetic Retinopathy Study; DR = diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; DME = diabetic macular edema; cDME = central-involved diabetic macular edema.
Age	56.8±10.5	
Average A1c	7.3±1.6	
Hypertension	65 (56.0)	
Renal Disease	12 (10.3)	
ETDRS Diabetic Retinopathy severity		
No DR	75 (33.3)	
Mild NPDR	46 (20.4)	
Moderate NPDR	32 (14.2)	
Severe NPDR	26 (11.6)	
PDR	46 (20.4)	
ETDRS Macular Edema		
No DME	153 (68.0)	
DME	21 (9.3)	
Non-cDME	11 (4.9)	
cDME	28 (12.4)	

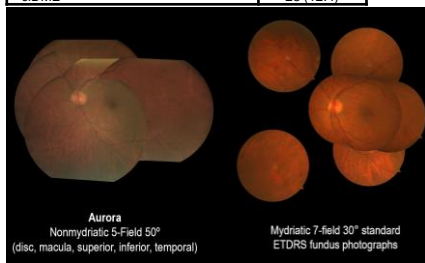


Figure 2. Retinal image montage of fundus photos showing false positive and false negative for presence of vDR compared to ETDRS standard 7-field 30° fundus photographs (ETDRS photos).

LEGEND = A and B: False negative fundus photo for the presence of vDR. Graded as moderate NPDR on mydriatic handheld retinal imaging (A) but were graded as severe NPDR on ETDRS photos (B) due to lesions on the superonasal and inferonasal quadrants not being captured on the handheld camera.

## Results

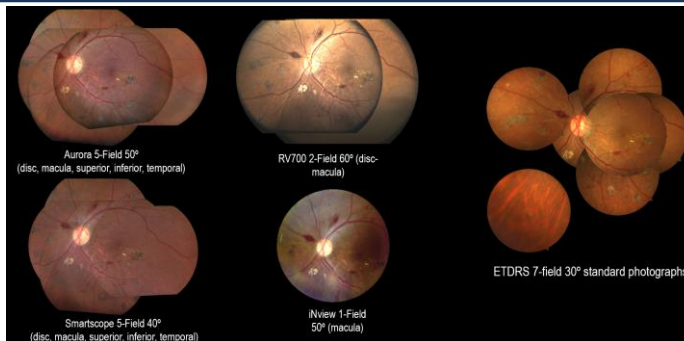


Figure 1. Comparison of Nonmydriatic Handheld Retinal Images and ETDRS Standard 7-field Fundus Photographs.

Table 2. Comparison by Different Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME) Thresholds: Mydriatic ETDRS 7-Field Photographs Compared with Mydriatic Handheld Imaging Devices

Device	Threshold	Ungradable Rate	K	K <sub>w</sub>	Exact Agreement	Within 1-Step	Sensitivity	Specificity	PPV	NPV
Aurora (AU)	Overall DR		0.55	0.75	65.8%	93.8%				
	Any DR	0%	0.78				0.86	0.97	0.98	0.77
	refDR		0.81				0.84	0.97	0.96	0.87
	vDR		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
Smart Scope (SS)	Overall DR		0.50	0.73	60.0%	90.7%				
	Any DR	3.6%	0.66				0.80	0.92	0.95	0.69
	refDR		0.79				0.87	0.92	0.91	0.89
	vDR		0.69				0.85	0.86	0.75	0.92
	DME	8.0%	0.63	0.77			0.75	1	1	0.91
RetinaVue 700 (RV)	Overall DR		0.56	0.75	63.1%	88.9%				
	Any DR	5.8%	0.74				0.83	0.97	0.98	0.73
	refDR		0.84				0.87	0.97	0.96	0.89
	vDR		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 (NV)	Overall DR		0.51	0.68	54.8%	75.1%				
	Any DR	33.8%	0.47				0.91	0.53	0.80	0.74
	refDR		0.43				0.91	0.54	0.64	0.86
	vDR		0.31				0.91	0.47	0.46	0.91
	DME	40.4%	0.83	0.91			*	*	*	*

\* Unreliable results due to high ungradable rate for DME

■ DR/DME Thresholds that did not meet the 80% sensitivity or 95% specificity rates

■ DR/DME Thresholds that meet the published sensitivity or specificity rates

## Conclusions

- Following a standardized protocol, handheld retinal imaging devices have substantial levels of agreement for both DR and DME, and meet standards for sensitivity and specificity in identifying any DR and refDR.
- The ungradable rate varies greatly, exceeding 30% even with pupil dilation in some devices.
- None of the handheld devices met the established 95% specificity for vDR, suggesting that lower thresholds for referral when handheld devices are used.

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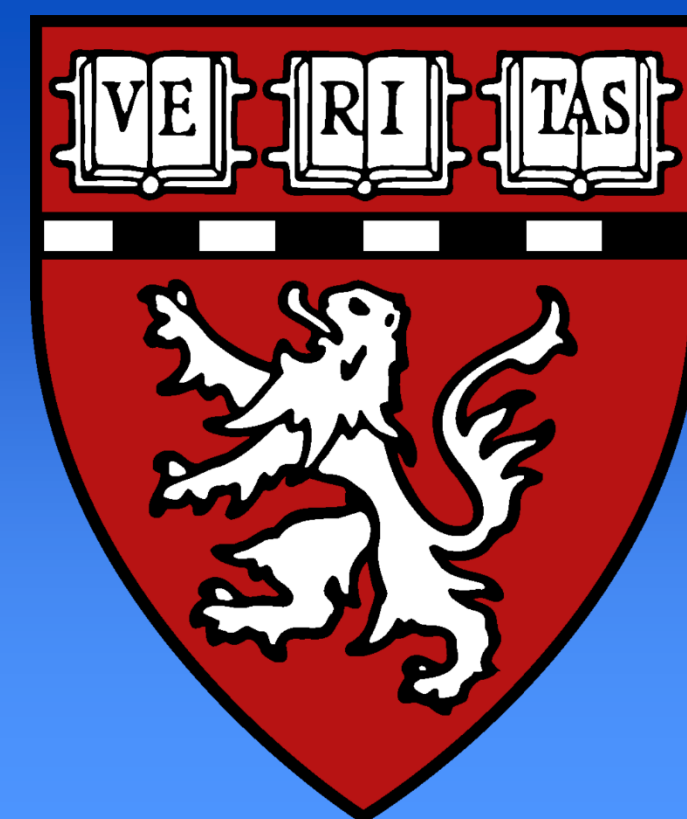




# Comparisons of Handheld Retinal Imaging Devices with Spectral Domain Optical Coherence Tomography (SDOCT) in the Identification of Macular Pathology

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## Lay Abstract

Handheld retinal imaging cameras are relatively inexpensive and highly portable devices that have the potential to greatly expand diabetic retinopathy screening programs.<sup>1</sup> However, it is essential that these devices accurately identify vision-threatening macular diseases.<sup>2</sup> Macular diseases such as diabetic macular edema (DME) that primarily affect central vision, remain a leading cause of visual loss in the diabetes population.<sup>3,4</sup> In this study, handheld retinal imaging was compared with gold standard diagnostic optical coherence tomography (SDOCT) imaging for the diagnosis of macular diseases. The data shows that without stereopsis, 37-46% of eyes without DME on handheld imaging will have DME on SDOCT, and 6-7% of the eyes with DME on handheld imaging will have no DME on SDOCT. These data clearly demonstrate the importance of SDOCT integration when using handheld retinal imaging cameras in order to improve detection of macular pathology and optimize appropriate referrals in large-scale DR screening programs.

## Purpose

To evaluate detection of diabetic macular pathology using monoscopic macula centered images using mydriatic handheld retinal imaging compared with spectral domain optical coherence tomography (SDOCT).

## Methods

- Single-site, prospective, clinic-based, comparative instrument validation study
  - Identification of macular pathology
  - Non-stereoscopic mydriatic 40°- 50° macula centered images compared to gold standard SDOCT
  - Acquired using handheld retinal imaging devices.
    - Optomed Aurora IQ (AU) (Optomed, Oulu, Finland)
    - Optomed Smartscope PRO (SS) (Optomed, Oulu, Finland)
    - Retinavue 700 Imager (RV) (Welch Allyn, New York, USA)
  - Cirrus 6000 SDOCT (Carl Zeiss Meditec Inc, Dublin, CA) macular scans.
  - All images were taken using a standardized protocol after pupillary dilation during the same visit.
- Eligibility: age ≥ 18 years, diagnosis of type 2 diabetes mellitus (DM), all severity levels of DR, [No DR to high-risk proliferative DR (PDR)].

## Results

Table 1: Baseline Characteristics

Male sex	48 (41.4)
Age	56.6 ± 10.5
Average A1c	7.3 ±1.56
Hypertension	65 (56)
Renal Disease	12 (10.3)
Diabetic retinopathy severity	
No DR	80 (35.5)
Mild NPDR	41 (18.2)
Moderate NPDR	24 (10.6)
Severe NPDR	34 (15.1)
PDR	46 (20.4)
Macular Edema	
CFP No DME	187 (83.1)
CFP Ci-DME	27 (12)
CFP Non-ciDME	11 (4.9)
OCT No DME	161 (75.2)
OCT Ci-DME	34 (15.9)
OCT Non-ciDME	19 (8.9)

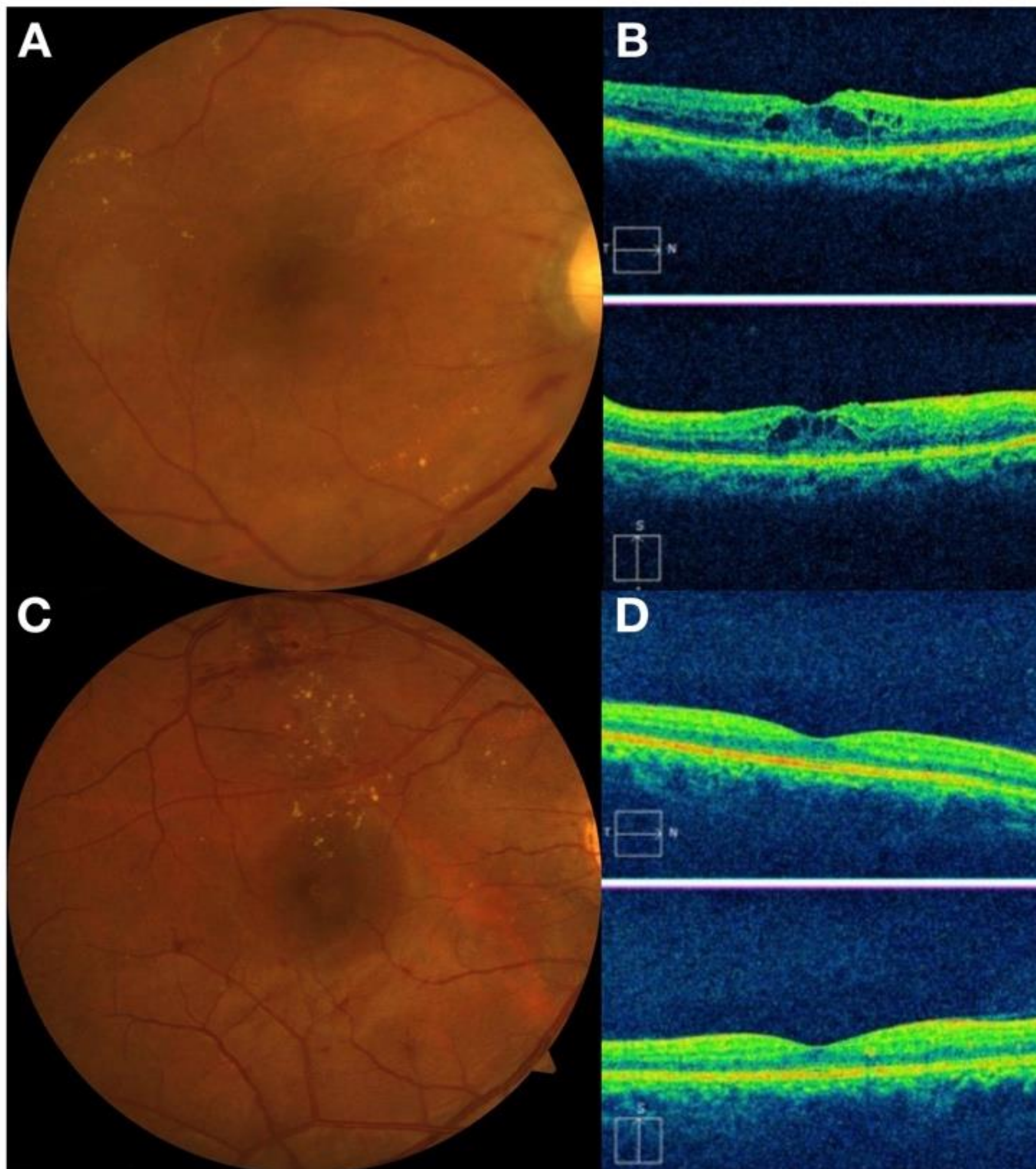
Count ± standard deviation or (n%); DR = Diabetic retinopathy; NPDR = Nonproliferative Diabetic Retinopathy; PDR = Proliferative Diabetic Retinopathy; CFP = Color Fundus Photo; OCT = Optical Coherence Tomography; Ci-DME = Central-involved diabetic macular edema; Non-ciDME = Non-central involved diabetic macular edema.

Table 2: Sensitivity and Specificity for Macular Pathology of Mydriatic Handheld Imaging Devices Compared with Spectral Domain Optical Coherence Tomography

Device	Macular Pathology	Sensitivity	Specificity	PPV	NPV
Aurora (AU), 3% ungradable					
	Any DME	0.54	0.94	0.72	0.88
	ciDME	0.64	0.95	0.62	0.95
	ERM	0.30	0.98	0.60	0.93
	Traction RD	0.50	1.00	1.00	0.97
	PED	0.33	1.00	0.50	0.99
Smartscope (SS), 7.3% ungradable					
	Any DME	0.63	0.93	0.71	0.90
	ciDME	0.52	0.96	0.63	0.94
	ERM	0.20	0.96	0.36	0.92
	Traction RD	0.50	1.00	1.00	0.97
	PED	0.33	0.99	0.33	0.99
RetinaVue 700 (RV), 9.1% ungradable					
	Any DME	0.60	0.93	0.69	0.90
	ciDME	0.50	0.96	0.59	0.95
	ERM	0.47	0.93	0.38	0.95
	Traction RD	0.50	0.99	0.86	0.97
	PED	0.33	1.00	1.00	0.99

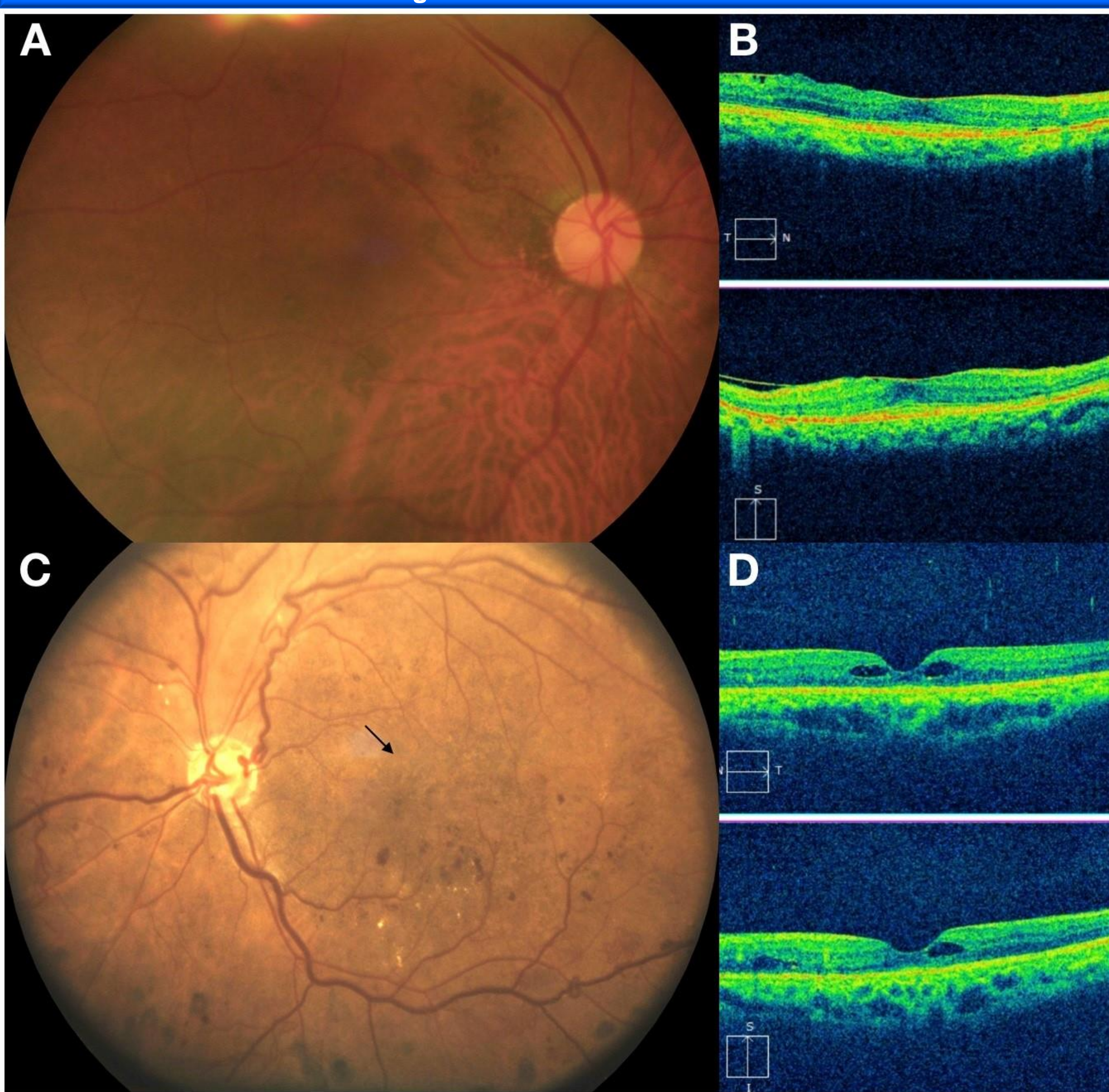
DME = Diabetic Macular Edema; ciDME = Central-Involved Diabetic Macular Edema; ERM = Epiretinal Membranes; RD = Retinal Detachment; PED = Pigment Epithelial Detachment; PPV = Positive Predictive Value; NPV = Negative Predictive Value; Ungradable = poor visualization > 50% of macula

Figure 1: Representative montage of monocular fundus photos from Smartscope handheld camera showing false positive and false negative for presence of DME compared to gold standard SDOCT.



Legend - A and B: False negative fundus photo for presence of DME. Graded as no DME on monocular fundus photo but on OCT shows presence of ci-DME. C and D: False positive fundus photo for presence of DME. Graded as ci-DME present on monocular fundus photo but on OCT shows no DME.

Figure 2: Representative montage of monocular fundus photos from Aurora (A) and RV700 (C) showing false negative and false positive for presence of ERM compared to gold standard SD-OCT.



Legend - A and B: False negative Aurora fundus photo for presence of ERM. Graded as no ERM on monocular fundus photo but on OCT shows presence of ERM. C and D: False positive RV700 fundus photo for presence of ERM. Arrow centered on macula shows subtle superficial retinal wrinkling and cellophane-like sheen graded as ERM. OCT shows no ERM, only presence of DME.

- Mean age was 56.6±10.8 years and 41.4% were male.
- Severity by standard ETDRS 7 field photography: No DR 35.5%, mild NPDR 18.2%, moderate 10.6%, severe 15.1%, proliferative 20.4%, ungradable for DR 0%; no DME 83.1%, non-ciDME 4.9%, ciDME 12.0%, ungradable for DME 0%.
- Gradable images by SDOCT (N=214, 95.1%) showed no DME in 75.2%, non-ciDME in 8.9%, ciDME in 15.9%.
- Epiretinal membranes (ERM) were the second most common pathology, present in 8.4% of eyes.
- Ungradable rate for images (poor visualization in >50% of the macula), was Aurora:3%, Smartscope:7.3%, Retinavue 700:9.1%.
- For DME/ciDME, sensitivity (0.54-0.63) and specificity (0.93-0.96) was similar across devices.
- For nondiabetic macular pathology across all devices, sensitivity was poor (0.2 – 0.5) but specificity was high (0.96 – 1.00)

## Conclusions

- Compared to SDOCT, handheld macular imaging attains high specificity but low sensitivity in identifying macular pathology.
- Without stereopsis, 37-46% of eyes without DME on handheld imaging will have DME on SDOCT, and 6-7% of eyes with DME on handheld imaging will have no DME on SDOCT. Additionally, 53-80% of eyes with macular ERM are missed without SDOCT imaging.
- This suggests that integration of SDOCT will substantially improve detection of macular pathology, leading to a higher percentage of appropriate referrals in large-scale DR screening programs.

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