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Smartphone-based anterior segment imaging: a comparative diagnostic accuracy study of a potential tool for blindness prevalence surveys

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Abstract

Purpose: to determine if smartphone photography could be a useful adjunct to blindness prevalence surveys by providing an accurate diagnosis of corneal opacity.

Methods: 174 patients with infectious keratitis who had undergone corneal culturing over the past 5 years were enrolled in a diagnostic accuracy study at an eye hospital in South India. Both eyes had an ophthalmologist-performed slit lamp examination, followed by anterior segment photography with a handheld digital single lens reflex (SLR) camera and a smartphone camera coupled to an external attachment that provided magnification and illumination. The diagnostic accuracy of photography was assessed relative to slit lamp examination.

Results: 90 of 174 enrolled participants had a corneal opacity in the cultured eye and no opacity in the contralateral eye, and did not have a penetrating keratoplasty or missing photographs. Relative to slit lamp examination, the sensitivity of corneal opacity diagnosis was 68% (95%CI

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DECLARATION OF INTEREST

Drs Fletcher and Maamari are co-inventors on patents owned by the University of California, Berkeley that pertain to CellScope technology. None of the intellectual property is directly related to the Corneal CellScope used in this study. None of the other authors have financial disclosures.

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58–77%) using the smartphone's default settings and 59% (95%CI 49–69%) using the SLR, and the specificity was 97% (95%CI 93–100%) for the smartphone and 97% (95%CI 92–100%) for the SLR. The sensitivity of smartphone-based corneal opacity diagnosis was higher for larger scars (81% for opacities 2mm in diameter or larger), more visually significant scars (100% for eyes with visual acuity worse than 20/400), and more recent scars (85% for eyes cultured in the past 12 months).

Conclusion: The diagnostic performance of a smartphone coupled to an external attachment, while somewhat variable, demonstrated high specificity and high sensitivity for all but the smallest opacities.

Keywords

corneal ulcer; telemedicine; smartphone; cornea; photography; diagnostic techniques, ophthalmological

INTRODUCTION

Corneal opacity is estimated to be the fifth-leading cause of blindness worldwide.[1] However, prevalence data on corneal opacity is more limited than that of other major causes of blindness such as cataract and refractive error.[2] Although methods like the Rapid Assessment of Avoidable Blindness (RAAB) can be used to assess causes of blindness in resource-limited settings, such methods rely on a skilled ophthalmic workforce with the clinical expertise necessary to identify a corneal opacity.[3] It might be preferrable to leverage technological advances to task-shift such prevalence surveys to less specialized workers, allowing eye care providers to focus on medical management and surgery.[4]

Low-cost smartphone attachments have been developed to image the anterior segment, but the diagnostic accuracy of such types of attachments has not been well characterized for specific corneal pathologies.[5–9] In the present study, the diagnostic accuracy of a 3D-printed smartphone attachment, the Corneal CellScope, was compared to handheld digital single lens reflex (SLR) photography to assess the potential for smartphone photography in large-scale blindness prevalence surveys. A handheld SLR was chosen as a comparator camera since it was the highest-quality camera that could plausibly be used for field studies. The SLR was thought a priori to be the closest thing to a reference standard for corneal photography, although formal diagnostic accuracy studies are lacking. The device was investigated previously for diagnosis of active corneal ulcers and found to have acceptable sensitivity and specificity.[10] However, corneal scars that remain after an ulcer has healed are fainter and thus more challenging to detect with an anterior segment imaging device. We performed the present study to establish the diagnostic performance of smartphone-based corneal photography specifically for corneal scars.

METHODS

Ethics.

Ethical approvals were obtained from the University of California, San Francisco and Aravind Eye Care System. Written informed consent was obtained from all participants. The study adhered to the Declaration of Helsinki.

Study Design.

A diagnostic accuracy study was performed to determine the accuracy of corneal photography for diagnosis of corneal opacity. A series of patients who had developed a corneal ulcer within the previous 5 years was examined with slit lamp bio-microscopy and had corneal photography performed with a digital single lens reflex (SLR) camera and smartphone camera. Photographs were graded in a masked fashion and diagnostic accuracy metrics calculated relative to a slit lamp reference standard.

Participants.

The population of interest consisted of individuals who had a corneal scar due to infectious keratitis over the previous 5 years. Patients who had undergone corneal scraping at Aravind Eye Hospital, Madurai, India from October 31, 2009 to October 30, 2014 were identified from the Microbiology Laboratory log. Patients residing near the hospital location, defined as the 9 contiguous districts surrounding Madurai, were eligible for inclusion. Patient names were listed in a random order stratified by time since corneal scraping, with patients scraped in the previous 12 months on one list and those scraped from 13 to 60 months ago on a second list. A study coordinator went in order through each enrollment list and telephoned patients to ask them to return to the hospital for the study, with the goal of enrolling 100 patients from each list.

Ophthalmology examination.

For the present study, visual acuity was assessed in each eye with tumbling E ETDRS Snellen vision charts. An ophthalmologist performed a comprehensive slit lamp examination of each eye, specifically noting the presence and size of corneal opacities, with size measured as the longest diameter and longest perpendicular width as described previously.[11]

Photography.

A Nikon D7100 camera and 105/2.8f macro lens were used for handheld SLR imaging (aperture priority mode, f/32, ISO 400, compulsory flash with strobe return, white balance set to flash). An LG Nexus 5 smartphone coupled to a custom-made external attachment (Corneal CellScope) was used for smartphone imaging. The design of the Corneal CellScope has been described in detail in a prior report, but in brief the attachment consisted of a 3D-printed housing, a +25-diopter lens, and 2 light emitting diode (LED) light sources to provide external illumination.[10] Images were captured in 3 ways: first using the default smartphone settings, then with the exposure set to +1, and finally with the high dynamic range (HDR) setting.

Photo-grading.

The photograph files were renamed with unique random numbers to remove any information about participant, camera, or camera setting. All images were reviewed in random order by 13 independent graders. Photo-graders were certified ophthalmic assistants from Nepal who had received training in grading anterior segment photographs for corneal opacities and were able to identify the presence or absence of a scar on a 50-image quiz with at least 80% accuracy relative to a panel of 3 cornea specialists. Graders assessed each image for the presence or absence of a corneal opacity, and whether their assessment was of high or low confidence. The grade assigned by the majority of the 13 photo-graders was used as a consensus grade for any particular image. To assess intra-rater reliability, the SLR and default smartphone images from both eyes of 43 randomly selected participants were relabeled and presented in a random order to each of the 13 photo-graders to grade a second time.

Statistical considerations.

Analyses of agreement were restricted to participants without a penetrating keratoplasty (PKP) and without missing data for any of the photo-modalities; analyses of diagnostic accuracy were further restricted to those participants with a slit lamp-diagnosed corneal opacity in the cultured eye and no corneal opacity in the non-cultured contralateral eye. Inter-rater agreement on the presence of corneal opacity was assessed with an intraclass correlation coefficient (ICC) calculated from a mixed effects logistic regression model of eye-level observations. Diagnostic accuracy metrics (e.g., sensitivity and specificity) for the various photography methods were determined for the consensus grade relative to the slit lamp examination reference standard. Subgroup analyses were performed based on (A) opacity size as determined from length and width measurements performed at the slit lamp examination for this study, with resulting geometric mean values categorized into groups, (B) best corrected visual acuity (BCVA) at the time of the study visit, categorized as mild/no visual impairment (BCVA of 20/60 or better), moderate/severe visual impairment (BCVA worse than 20/60 but better or equal to 20/400), or blindness (BCVA worse than 20/400), and (C) the time interval from corneal scraping to examination (e.g., 0–12 months, 12–24 months, or ≥ 24 months). Bootstrapped 95% confidence intervals (Cis) were calculates around estimates of diagnostic accuracy, with resampling of participants to account for cluster-correlated data (N=999 replications). A sample size of 200 participants would provide a 95% CI width of ±7% around the diagnostic accuracy estimate assuming three-quarters had unilateral opacity and assuming a sensitivity and specificity of 80%.

RESULTS

Of 11,684 patient records identified from the Microbiology Laboratory register with documentation of corneal scraping during the 5-year study period, we attempted to contact 1343 and eventually enrolled 174 (i.e., 89/348 with an ulcer in the previous 12 months, and 85/997 with ulcers older than 12 months; Figure 1). Demographic characteristics of participants and non-participants were similar (Supplemental Table 1). Of those enrolled, 31 participants were excluded from analyses of inter-rater agreement due to penetrating keratoplasty (N=20) or a missing photograph (N=11) in either eye, leaving 286 eyes from

143 participants. A further 53 participants were excluded from analyses of diagnostic accuracy because an opacity was observed in both (N=43) or neither (N=10) eye on slit lamp examination, leaving 180 eyes from 90 participants.

Each of the 13 photo-graders assessed images from all 4 camera modalities for all 286 eyes included in the agreement analyses. All images were judged to be of good quality by a majority of graders. The 13 graders demonstrated high intra- and inter-rater agreement for detection of corneal opacities from photographs, without substantial differences between camera settings (Table 1). Photo-grades from the 13 graders were subsequently combined into a single consensus diagnosis for each eye and each camera setting. The consensus opacity grades were similar for each of the 3 smartphone camera settings (ICC=0.99; Supplemental Table 2).

Both eyes of 90 participants were included in the accuracy analyses; each participant contributed one eye that had been cultured and was observed to have a scar on slit lamp examination (i.e., reference standard positive), as well as the contralateral eye that was not cultured and did not have an opacity (i.e., reference standard negative). When compared to this reference standard, the overall sensitivity of the consensus corneal opacity grade on smartphone photography ranged from 68–70% depending on the settings, and the specificity ranged from 96–97%. The positive predictive value was approximately 15% given a pre-test probability of 1%, but increased to approximately 70% at a pre-test probability of 10% (Figure 2). The negative predictive values remained above 90% over a range of plausible prevalence estimates.

As shown in Table 2, diagnostic accuracy was higher for larger opacities (sensitivity of 100% for opacites ≥ 6 mm with the default smartphone settings), visual impairment (sensitivity of 100% for blind eyes), and more recent ulcers (sensitivity 85% for those diagnosed in the past 12 months). Specificity remained high across all subgroups (Table 2). The particular smartphone settings (i.e., exposure levels or HDR setting) did not make much difference for estimates of sensitivity and specificity, although smartphone images tended to be slightly more sensitive than SLR images (Table 2).

Given the inherent importance of opacity size to diagnostic accuracy, eyes with an opacity were ordered from smallest to largest based on the slit lamp examination, and sensitivity estimated cumulatively along this ordered set of 90 opacities. This analysis showed that on average, smartphone sensitivity improved dramatically with increasing opacity size (Figure 3). Representative images of small and large scar sizes are shown for all four photo modalities in Figure 4. For example, consensus grades of the default smartphone photographs captured 55 of 68 eyes (81%, 95%CI 71–89%) with an opacity 2 mm in diameter or larger, and 42 of 46 eyes with an opacity 4 mm in diameter or larger (91%, 95%CI 83–98%). Separate assessments of each grader demonstrated variability, with notably lower sensitivity estimates across the range of scar sizes for several of the graders. A similar analysis performed to determine the relationship between time since culture and smartphone sensitivity found a weaker association, with less monotonicity over the range of elapsed time (Supplemental Figure 1).

DISCUSSION

This diagnostic accuracy study found that a smartphone coupled to an external attachment had variable sensitivity and specificity for detecting corneal opacities. The major factors that affected the diagnostic accuracy was the size of the opacity, although diagnostic accuracy also tended to be better for more recent corneal ulcers. Despite the observed variability, the smartphone used in this study was more sensitive than a handheld digital SLR camera for detection of corneal opacities across a range of stratified analyses.

Several other attempts have been made to quantify agreement between anterior segment photo-grading with clinical examination.[12,13] One of these studies found smartphone photography to be considerably less sensitive for corneal scars than for active corneal ulcers or abrasions.[13] However, that study did not use a smartphone attachment, so it is possible that the native camera was not able to capture images at high enough resolution at the level of magnification required to observe fainter corneal scars. The present study, which did use an attachment to improve magnification and illumination, found considerably higher sensitivity. It is likely that the native cameras on currently available smartphones have insufficient macro lens capabilities for capturing subtle corneal scarring, although it is notable that the sensitivity was not any better for the handheld digital SLR camera with macro lens. For the time being, an external attachment on a smartphone likely offers sufficient quality for telemedicine applications incorporating anterior segment imaging.

Stratified analyses revealed that false negative tests were primarily found in eyes with older, smaller, and less visually significant opacities. The effect of each of these factors is plausible. Corneal collagen lamellae remodel after stromal injury, restoring some transparency to the cornea.[14] A previous study of patients with large corneal scars due to bacterial keratitis found reductions in the density of the opacity over time.[15] Such remodeled scars would be expected to be more difficult to observe with the direct illumination employed by the corneal photography methods of this study. Moreover, small scars evident on slit lamp microscopy would be expected to be difficult to distinguish with certainty under the direct illumination of anterior segment photography, since these might be confused with flash artifacts, reflections, or iris markings. Although smartphone anterior segment imaging missed some corneal scars, it performed very well for the detection of even moderately sized opacities, and also performed well in eyes with visual impairment.

This study’s results suggest that smartphone photography might be considered as an adjunctive diagnostic tool for blindness prevalence surveys that assess cause of visual impairment. Such surveys require knowledgeable workers who can distinguish corneal opacity from cataract and other anterior segment pathology. But workers experienced in ophthalmic diagnosis can be hard to recruit, train, and retain. Smartphone photography could be a simple solution allowing a much less specialized workforce to capture diagnostic information with ease and at low cost—especially since most health surveillance data is currently collected on a smartphone anyway. Although smartphone photography may miss small opacities, such small opacities are unlikely to be visually significant, and thus photography should not bias cause-of-blindness data. To the contrary, recent meta-analyses of blindness surveys have omitted corneal opacity due to a lack of data, so including anterior

segment photography in prevalence surveys may actually give a truer picture of the causes of blindness in a population. [2] Anterior segment photographs may also be able to provide data on cataract and pseudophakia in a population, although further study is needed to explore the validity of smartphone photographs for these conditions.

One reason for conducting this study was to determine the optimal smartphone camera settings for capturing corneal pathology for a randomized trial employing smartphone corneal photography as an outcome measure.[16] We hypothesized that increasing the exposure might increase the sensitivity of anterior segment photography, since this might make subtle opacities more white. In practice, while the higher exposure setting did result in slightly higher sensitivity, the difference was not clinically meaningful relative to the other two settings, and thus we did not find strong evidence to support one smartphone setting above another. It is possible that the camera settings may be more important for other models of smartphone.

This study has limitations. The study was designed around corneal opacities, and thus the results cannot be extrapolated to other anterior segment pathology (e.g., cataract, pterygium). Moreover, none of the camera modalities image the posterior segment. A single SLR and smartphone camera were studied, and it is unclear whether other smartphones will perform as well, although it is reasonable to expect that more recent smartphones would generally have even better cameras than the smartphone used in this study. The eligibility for the study was based on a corneal scraping, so the results are likely only generalizable to patients with a corneal ulcer severe enough to present for care and undergo corneal cultures. The study's generalizability outside the Indian subcontinent is also unclear given the severity of corneal ulcers in this part of the world. Moreover, although a random sample of patients was recalled for the study, not all potential participants were willing or able to return for the study, and it is possible that participants had systematically different levels of scarring than nonparticipants. However, even if the distribution of severity of ulcers was different than other settings, this should not affect the fundamental conclusions of the study given the stratified analyses.

In summary, this study showed that the diagnostic accuracy of a smartphone coupled to an inexpensive external attachment providing magnification and illumination was good for moderately sized corneal opacities. The smartphone-CellScope device was on par with, or even better than, a handheld digital SLR camera for diagnosing corneal opacity—thus broadening the possibility of smartphone anterior segment imaging for public health surveillance. Diagnostic accuracy was best for larger, more visually significant, and more recent corneal scars, which are the very scars that most stakeholders would want to capture.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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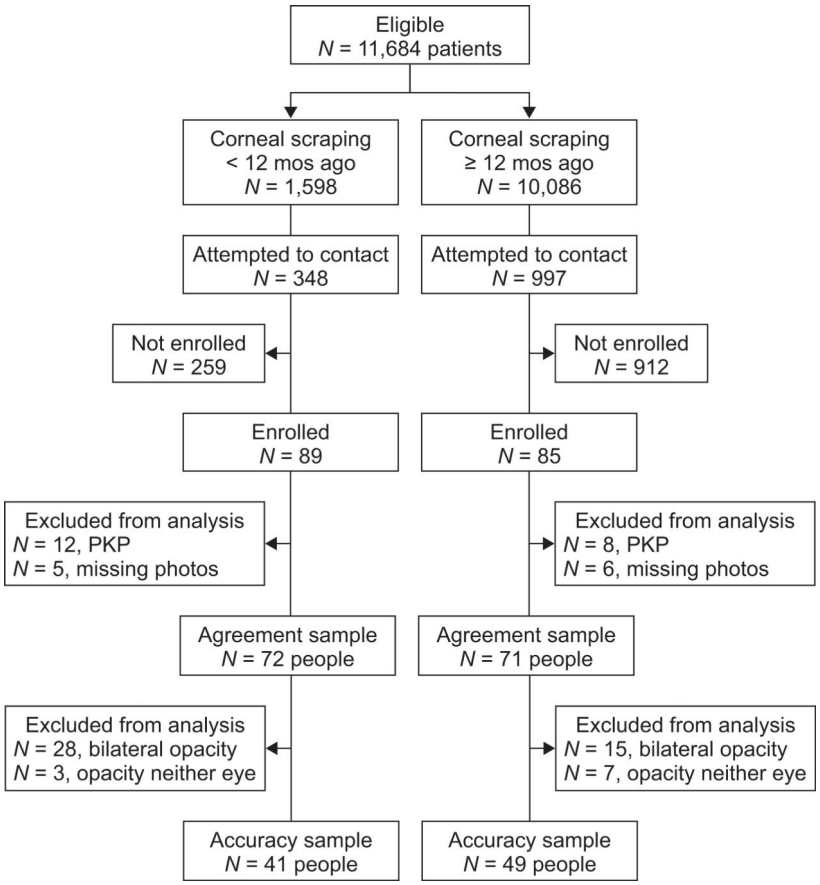

Figure 1. Study participant flow diagram.

Patients who had undergone corneal culturing during the previous 5 years were listed in random order. A coordinator went through the randomly ordered list, attempting to contact each person by telephone to request that they return for a follow-up visit. All numbers in the diagram refer to patients. PKP: penetrating keratoplasty.

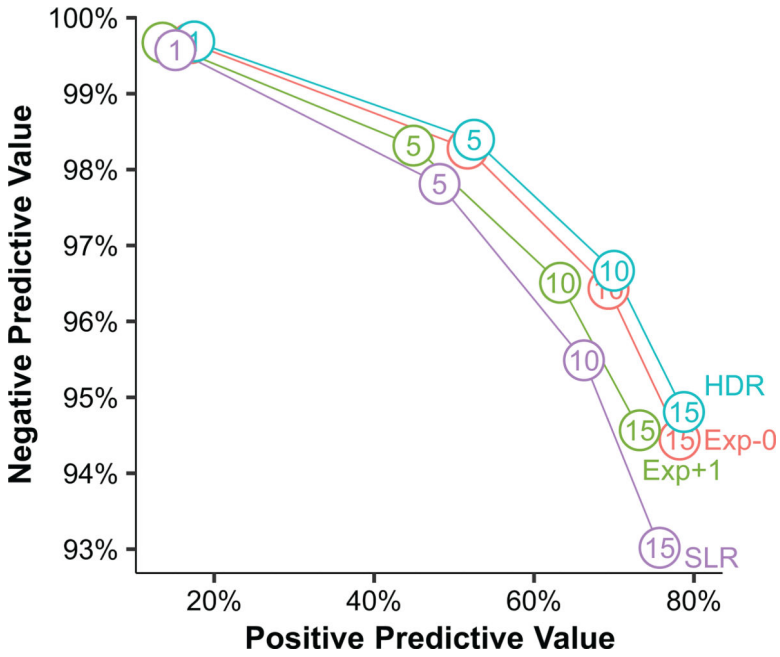

Figure 2. Positive and negative predictive values for photographic diagnosis of corneal opacity.

Each circle represents the performance of one of the camera modalities at a specific population prevalence or pre-test probability. Predictive values are shown for a prevalence of 1%, 5%, 10%, and 15%, with the prevalence assumption depicted inside the circle. Values in the upper right part of the plot optimize the positive and negative predictive values. Exp-0: default smartphone camera settings; Exp+1: smartphone +1 overexposure setting; HDR: smartphone high dynamic range setting; SLR: single lens reflex camera.

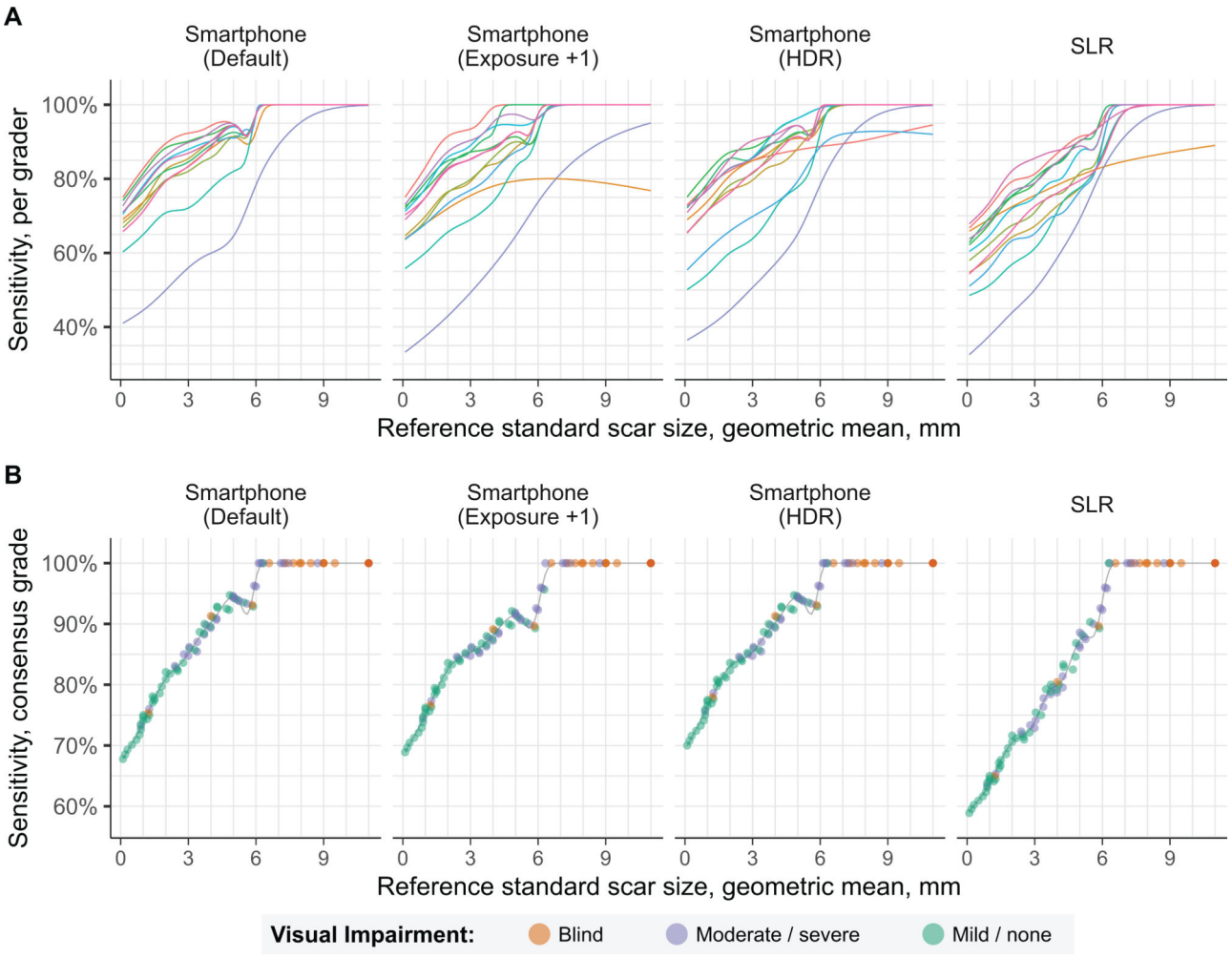

Figure 3. Cumulative estimates of sensitivity across the range of corneal scar size.

The 90 eyes with a reference standard opacity were ordered from smallest to largest based on the slit lamp examination, and sensitivity was estimated cumulatively along this ordered set of 90 opacities. Specifically, for each corneal opacity, the cumulative sensitivity was estimated including all eyes with the same or a larger scar size. Panel A shows the cumulative sensitivity for the individual 13 graders (each in a different color), and Panel B shows the cumulative sensitivity for the consensus grade. In panel B, each dot represents an eye; dots are colored according to their visual acuity status have some transparency in order to better depict overlying points.

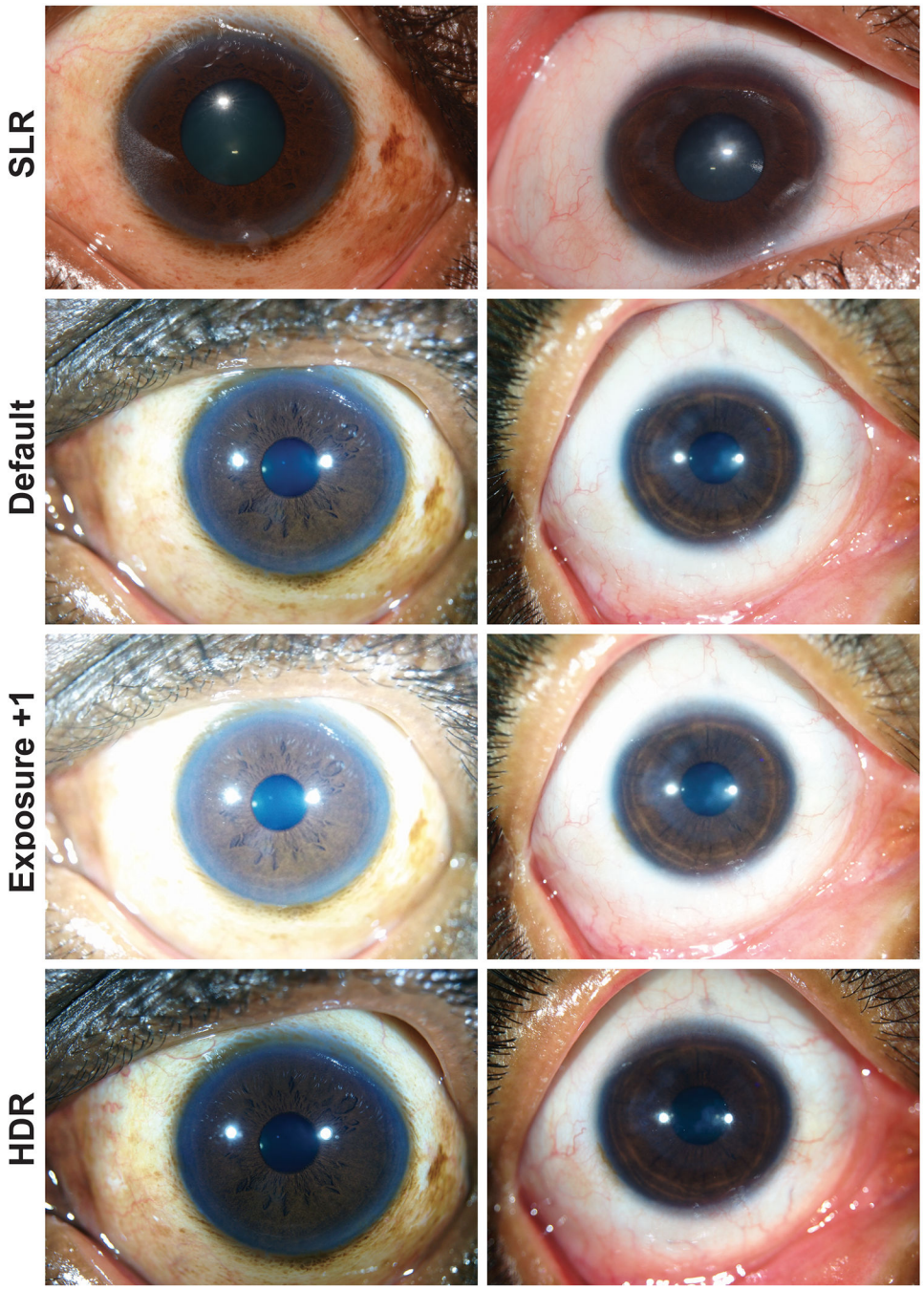

Figure 4. Representative images of corneal opacities from smartphone and single lens reflex (SLR) photography.

An eye was randomly selected from the lowest and highest quartiles of opacity size. The smaller opacity, with a geometric mean of 1.2 mm on slit lamp examination, is shown in the left column. The larger opacity, with a geometric mean of 11.0 mm on slit lamp examination, is shown in the right column. Images were not cropped or processed.

Table 1.

Inter-grader and intra-grader agreement using smartphone photography and single lens reflex (SLR) photography for detection of corneal opacities.

Thirteen masked graders assessed 4 sets of photographs from 286 unique eyes; a between-grader intraclass correlation coefficient (ICC) was calculated separately for each camera modality to determine inter-rater agreement. The same 13 graders assessed a duplicate SLR and default smartphone photograph for 42 eyes, and an ICC was calculated on these pairs of duplicate photographs to assess intra-rater reliability.

Camera setting	ICC (95% CI)
Inter-rater agreement (N=286 eyes)	
SLR	0.94 (0.91–0.99)
Smartphone – default	0.96 (0.92–0.99)
Smartphone – exposure +1	0.94 (0.89–0.96)
Smartphone – HDR	0.96 (0.93–0.99)
Intra-rater agreement (N=42 eyes)	
SLR	0.98 (0.95–1.00)
Smartphone – default	0.99 (0.97–1.00)

CI=confidence interval; ICC=intraclass correlation coefficient; SLR=single lens reflex camera

Table 2.
Diagnostic accuracy stratified by time since culture, visual impairment, and scar size.

Sensitivity and specificity are shown for single lens reflex (SLR) photography and smartphone photography for detection of corneal opacities compared to slit lamp examination gold standard. A Nexus 5 smartphone was coupled to a Corneal CellScope for smartphone photographs, using 3 different settings. Each column lists estimates for a different camera modality. Overall sensitivity and specificity is shown, along with estimates for subpopulations stratified by (A) time since the participant underwent corneal culture in the affected eye, (B) degree of visual impairment, and (C) opacity size.

			Smartphone		
Metric (95%CI)	**N**	**SLR**	**Default settings**	**Exposure +1**	**HDR**
SENSITIVITY					
Overall	90	59% (49–69%)	68% (58–77%)	69% (60–78%)	70% (60–79%)
Time since culture					
0–12 months	41	83% (70–94%)	85% (73–95%)	85% (73–95%)	85% (73–95%)
13–24 months	20	50% (27–71%)	65% (41–84%)	65% (41–84%)	65% (41–84%)
> 24 months	29	31% (15–48%)	45% (27–63%)	48% (31–65%)	52% (32–70%)
Visual impairment[a]					
Mild/none	42	45% (30–61%)	52% (38–68%)	52% (38–67%)	57% (42–72%)
Moderate/severe	28	50% (31–69%)	68% (49–84%)	71% (53–88%)	68% (49–84%)
Blind	20	100% (100–100%)	100% (100–100%)	100% (100–100%)	100% (100–100%)
Opacity size[b]					
<2 mm	22	23% (6–42%)	27% (9–46%)	27% (9–46%)	32% (12–52%)
2–3.9 mm	22	50% (30–70%)	59% (38–79%)	68% (48–86%)	64% (43–83%)
4–5.9 mm	21	62% (41–83%)	81% (62–96%)	81% (62–96%)	81% (62–96%)
≥ 6 mm	25	96% (86–100%)	100% (100–100%)	96% (88–100%)	100% (100–100%)
SPECIFICITY					
Overall	90	97% (92–100%)	97% (93–100%)	96% (91–99%)	97% (93–100%)
Time since culture					
0–12 months	41	95% (88–100%)	93% (84–100%)	90% (81–98%)	93% (84–100%)
13–24 months	20	100% (100–100%)	100% (100–100%)	100% (100–100%)	100% (100–100%)
> 24 months	29	97% (89–100%)	100% (100–100%)	100% (100–100%)	100% (100–100%)
Visual impairment[a]					
Mild/none	72	99% (96–100%)	99% (96–100%)	97% (93–100%)	99% (96–100%)
Moderate/severe	14	100% (100–100%)	100% (100–100%)	100% (100–100%)	100% (100–100%)
Blind	4	50% (0–100%)	50% (0–100%)	50% (0–100%)	50% (0–100%)

[a]Moderate-to-severe visual impairment defined as worse than Snellen 20/60 up to 20/400; blindness defined as worse than 20/400.

[b]No true negatives in this subset