Smartphone-Based Dilated Fundus Photography and Near Visual Acuity Testing as Inexpensive Screening Tools to Detect Referral Warranted Diabetic Eye Disease

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Purpose: To compare clinical assessment of diabetic eye disease by standard dilated examination with data gathered using a smartphone-based store-and-forward teleophthalmology platform.

Methods: 100 eyes of 50 adult patients with diabetes from a health care safety-net ophthalmology clinic. All patients underwent comprehensive ophthalmic examination. Concurrently, a smartphone was used to estimate near visual acuity and capture anterior and dilated posterior segment photographs, which underwent masked, standardized review. Quantitative comparison of clinic and smartphone-based data using descriptive, kappa, Bland-Altman, and receiver operating characteristic analyses was performed.

Results: Smartphone visual acuity was successfully measured in all eyes. Anterior and posterior segment photography was of sufficient quality to grade in 96 and 98 eyes, respectively. There was good correlation between clinical Snellen and smartphone visual acuity measurements (rho = 0.91). Smartphone-acquired fundus photographs demonstrated 91% sensitivity and 99% specificity to detect moderate nonproliferative and worse diabetic retinopathy, with good agreement between clinic and photograph grades (kappa = 0.91 ± 0.1, $P < 0.001$; AUROC = 0.97, 95% confidence interval, 0.93–1).

Conclusion: The authors report a smartphone-based telemedicine system that demonstrated sensitivity and specificity to detect referral-warranted diabetic eye disease as a proof-of-concept. Additional studies are warranted to evaluate this approach to expanding screening for diabetic retinopathy.

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Approximately 387 million individuals worldwide and 29.1 million Americans are affected by diabetes mellitus.[1,2] Diabetic retinopathy (DR) and diabetic macular edema are common ophthalmic sequela of diabetes, resulting from variable degrees of retinal capillary hyperpermeability and nonperfusion. Subsequent retinal ischemia and neovascularization may result in proliferative diabetic retinopathy (PDR).

The prevalence of retinopathy among patients with diabetes has been estimated to be 28.5%, and diabetes is the leading cause of blindness in adults in the United States.[3] If detected and treated in a timely fashion, blindness from progression of DR can be averted.[4,5] Nevertheless, rates of screening for DR remain low, particularly in the health care safety-net setting, perhaps related to insufficient provider availability, poor adherence to regular examinations, and cost to the patient.[6–8]

The gold standard for diagnosing DR, as defined by the Early Treatment of Diabetic Retinopathy Study (ETDRS), is 7-field stereoscopic-dilated fundus photographs graded by the modified Airlie House classification protocol.[9] Unfortunately, its implementation is logistically difficult, requiring specially trained photographers, specialized film processing and archiving, and dissemination of film to an outside ophthalmologist. The use of single-field digital fundus photography in telemedicine has shown promise in screening for DR,

particularly in primary care and safety-net settings[10–15]; however, these fundus camera systems are costly, ranging from several thousand to more than $10,000 each.

At the time of this study, more than 30,000 patients were receiving clinical care for diabetes at Santa Clara Valley Medical Center (SCVMC). This safety-net health care system, which predominantly serves uninsured and underinsured patients, has a reported 30.3% prevalence of DR or diabetic macular edema, with a disproportionate burden of disease affecting patients of Latino ethnicity.[16] Patients in this setting are at high risk for experiencing health and health care disparities. Therefore, improving access to screening, surveillance, and treatment of DR represents an important goal in this population; however, the large patient load presents a challenge for traditional models of patient care delivery. This study supports the use of a portable smartphone-based telemedicine system as one part of a comprehensive infrastructure to screen for and treat diabetes and diabetic eye disease.

Methods

Patient Enrollment

This was a prospective, single institutional comparative series of 100 eyes in 50 participants undergoing ophthalmic screening for diabetic eye disease using standard in-clinic methods compared with a smartphone-assisted telemedicine method. As the prevalence of DR in our population based on our nonmydriatic fundus photography program was 17%,[17] this study of 100 eyes had 80% power to detect a roughly 10% disparity (<5.3% or >26% prevalence) in detection of DR between the screening methods. Participants in the study were consecutively recruited from February 2014 to September 2014 for a single visit evaluation by two methods of screening. Patients enrolled constituted a subset of patients presenting to a scheduled monthly clinic dedicated to screening patients for diabetic eye disease. Patients were referred to this clinic by their primary care provider or the SCVMC diabetes clinic. As such, adult patients with a diagnosis of diabetes who provided proper informed consent were included in the study. The study was prospectively approved by the SCVMC Institutional Review Board, adhered to the tenets of the Declaration of Helsinki, and was HIPAA-compliant.

Ophthalmic Examination

All patients underwent comprehensive ophthalmic examination, including spectacle-corrected distance visual acuity on conventional Snellen charts, slitlamp examination, and dilated ophthalmoscopy. Concurrently, patients underwent smartphone-assisted acquisition of spectacle-corrected near visual acuity and anterior/posterior segment photography. After technician-administered Snellen visual acuity measurement, smartphone-assisted measurement was made of near visual acuity. This was patient self-administered and involved single letter discrimination on a high-contrast background using forced multiple choice at 14 inches, as previously described.[18] The smartphone photograph capture system consisted of an iPhone 5s (Apple Inc, Cupertino, CA) camera phone (8 megapixel resolution), Paxos Scope anterior and posterior segment hardware adapters with external light-emitting diode illumination (Figure 1; Stanford University, Palo Alto, CA; described in further detail previously[19,20]), and a beta version of the Paxos Scope mobile application, previously called SightBook (Figure 2; DigiSight Technologies, Inc, San Francisco, CA).

Both eyes of all patients were dilated with 1 drop each of 2.5% phenylephrine and 1% tropicamide after visual acuity measurement. Anterior segment photography was performed using the anterior segment adapter before and after pharmacologic dilation.[20] Briefly, the adapter containing a macro lens and external light source was attached to the phone. Then, the patient was instructed to fixate on a target straight ahead with eyes wide open, whereas the phone held in landscape orientation was brought straight-on to within 2 inches of the patient's orbital rim until iris

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Fig. 1. Photograph of Paxos Scope posterior segment adapter. The iPhone 5S (Apple Inc, Cupertino, CA) with external light-emitting diode (LED) illumination was attached to the Paxos Scope posterior segment adapter (Stanford University, Palo Alto, CA), which was fitted with a Digital ClearField indirect ophthalmoscopy lens (Volk Optical, Inc, Mentor,OH) as shown.

details, and specifically the pupillary margin were in focus. Fundus photography was performed using a Volk Digital ClearField lens (Volk Optical, Inc, Mentor, OH) mounted on the posterior segment adapter to capture views including the optic nerve and macula spanning approximately 45°.[19] Briefly, the anterior segment adapter with integral light and posterior segment adapter holding the indirect lens were attached to the phone. Similar to indirect ophthalmoscopy, the patient was then instructed to fixate straight ahead, whereas the phone-adapter complex was stabilized with fingers braced on the patient's brow and cheek, and with the axis formed by the indirect lens and camera directed nasally toward the optic nerve. Once the optic nerve was sufficiently in focus, the view was tilted temporally so that more of the macula could be captured.

Visual acuity data and participant photographs were automatically uploaded to a secure, HIPAA-compliant, cloud-based server (www.digisight.net) at the time of visit for remote grading in a store-and-forward telemedicine method.

Photograph Grading and Statistical Analysis

Visual acuities were converted from distance Snellen or near Snellen equivalent to ETDRS letters.[21] Pertinent clinical examination findings were abstracted from the medical record. Smartphone-acquired anterior segment photographs were evaluated for quality (able to grade or not) and the presence or absence of iris neovascularization. Other significant examination findings were also noted, including cataract or corneal opacity. Smartphone-acquired posterior segment photographs were graded for photograph quality and severity of DR (none, mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, PDR, or unable to grade), based on the International Clinical Classification for Diabetic Retinopathy (ICDR) disease severity scale.[22] The presence of hard exudates was used as a surrogate marker for possible macular edema.

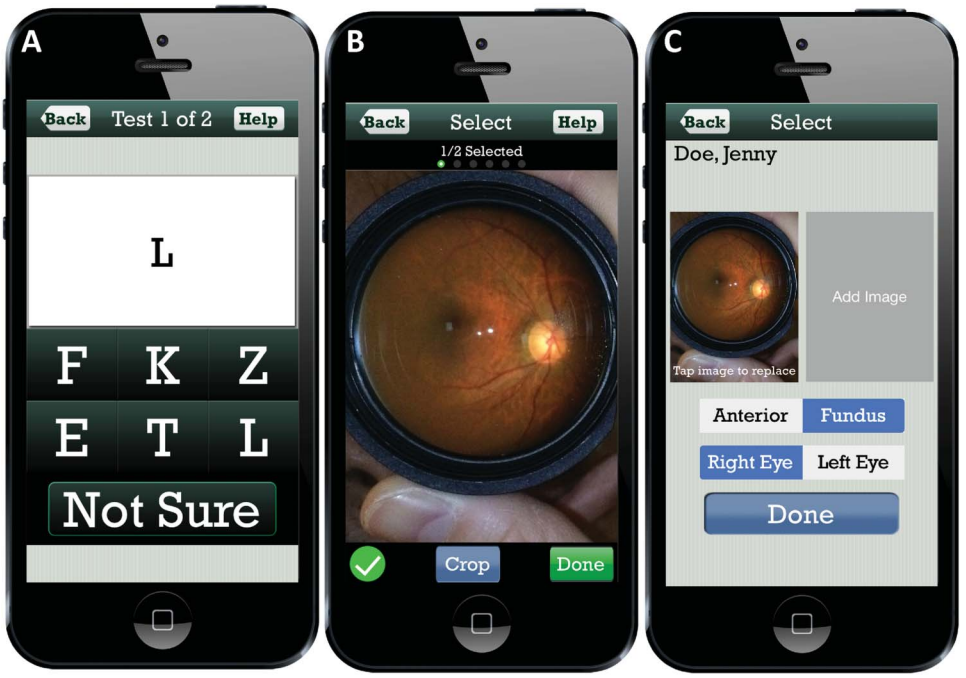

Fig. 2. In-app screenshots of Paxos Scope telemedicine app. **A.** The visual acuity measurement function used an interactive multiple forced choice alphabet letter match. **B** and **C.** The app acquired and securely uploaded anterior segment and dilated posterior segment photographs for subsequent grading. Burst photograph mode on the smartphone captured a series of images for immediate review and selection for upload to the patient's chart on the secure, Health Insurance Portability and Accountability Act (HIPAA)-compliant DigiSight telemedicine platform (DigiSight Technologies, Inc, San Francisco, CA).

Comparisons of clinic-acquired and smartphone-acquired data were performed using Stata (StataCorp, College Station, TX) to calculate descriptive, correlation, kappa, Bland–Altman, and receiver operating characteristic analyses. Where possible, analyses were clustered by patient to account for the correlation between fellow eyes of a single patient. Numeric values are reported as mean ± standard deviation, unless otherwise noted.

Results

Demographics

Table 1 details demographic data for the 50 consecutive participants enrolled in this study. The participants had a mean age of 60.5 ± 10.6 years and a mean duration of diabetes of 11.9 ± 8.4 years. The racial demographic of the enrolled patients was 46% Asian, 34% Latino, 6% Black, and 4% White. For the 43 (86%) patients whose hemoglobin A1c level within 6 months was available, it averaged 8.0 ± 1.5%. A total of 27 (54%) patients had not been previously screened for DR, and 10 (20%) had a previous diagnosis of any DR.

Visual Acuity

The mean distance spectacle-corrected visual acuity was 69 ± 13 letters (Snellen equivalent 20/40; median 70, IQR 65–80 ETDRS letters), and the near spectacle corrected visual acuity measured with the smartphone application also was 69 ± 13 letters (Snellen equivalent 20/40; median 70, IQR 65–75 ETDRS letters) (Table 2). A paired *t*-test demonstrated no difference between the two methods, with a *P* value of 0.45. The Pearson correlation coefficient was 0.91, indicating good correlation between the two measures. A Bland–Altman plot comparing the two methods of visual acuity measurement (Figure 3) demonstrated a bias near 0, indicating no systematic difference between the two measures and 95% limits of agreement of ±5 ETDRS letters (Snellen equivalent, 1 line) for the two methods of visual acuity measurement.

Table 1. Participant Demographics

Participant Demographics	
Number of Patients	50
Age (mean ± SD)	60.5 ± 10.6 years
Sex (% female)	58
Duration of DM (mean ± SD)	11.9 ± 18.4 years
Hemoglobin A1c	8 ± 1.5%
Race (%)	
White	4
Latino	34
Asian	46
Black	6
Other	10
Number of patients presenting for new screening	27 (54%)
Number of patients with a previous diagnosis of diabetic retinopathy	10 (20%)

Fifty patients (100 eyes) were enrolled in this study, with a racial distribution representative of our local population. Duration of diabetes was quite variable, ranging from 1 to 34 years.
SD, standard deviation; DM, diabetes mellitus.

Photograph Quality

Figure 4 demonstrates representative matched anterior and posterior segment photographs captured using the smartphone app and presented for grading. A total of 96 of 100 captured anterior segment photographs were judged of sufficient quality (eyelids open and image focused on iris) to evaluate for neovascularization of the iris. The most common causes for decreased photograph quality included insufficient lid opening, glare, and poor image focus. For 58 eyes, a single posterior segment photograph was sufficient to evaluate for DR within the macula (judged at the time of photograph acquisition). For 40 eyes, multiple photographs (2.3 ± 1.2) were required to obtain sufficient field of view, focus, or illumination. For 2 eyes, no gradable photograph could be captured. The most common causes for decreased photograph quality included media opacity (cataract), poor dilation, and poor image focus.

Anterior Segment Grading

Anterior segment photographs were graded by two masked reviewers (RTC and BCT). No eyes were

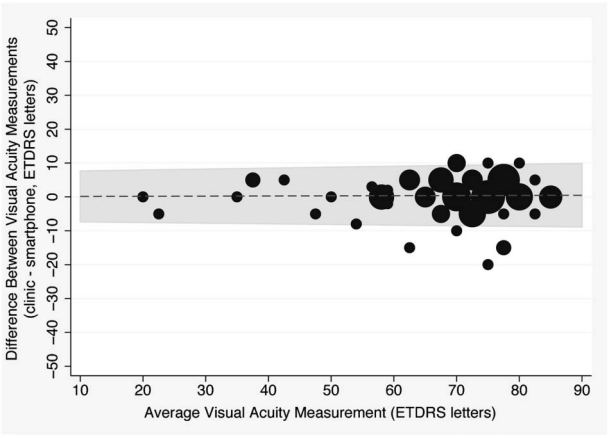

Fig. 3. Visual acuity comparison: Bland–Altman plot. The average (x-axis) and difference (y-axis) between the standard Snellen and smartphone-acquired visual acuity measurements are shown on a Bland–Altman plot. The bias (discrepancy between the two methods), illustrated by the dotted line, was near 0. The limits of agreement (shaded gray area) were narrow, ±5 early treatment of diabetic retinopathy (ETDRS) letters for most points.

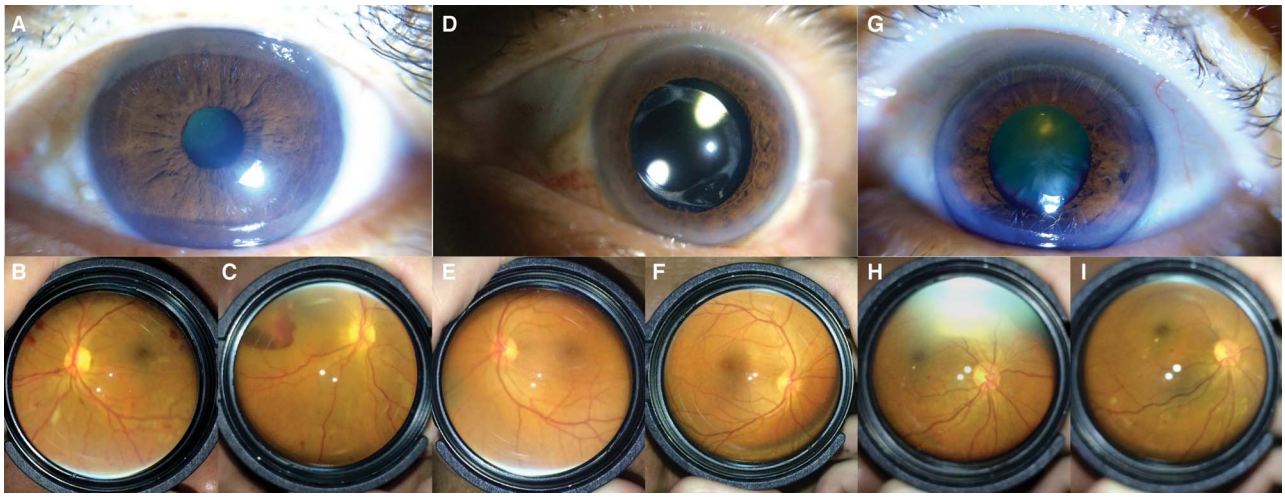

Fig. 4. Representative anterior and fundus photographs acquired by Smartphone. **A.** Anterior segment photograph of the left eye demonstrating no iris neovascularization and a nasal pinguecula. **B.** Fundus photograph of the right eye demonstrating microaneurysms and dot-blot and flame hemorrhages in all 4 quadrants, consistent with severe NPDR. Other findings included a cotton wool spot superonasal to the disc. **C.** Fundus photograph of the left eye with scattered microaneurysms, dot-blot hemorrhages, and a large preretinal hemorrhage obscuring the macula, consistent with proliferative diabetic retinopathy (PDR). **D.** Anterior segment photograph of the left eye demonstrating no iris neovascularization. Other findings included nasal pinguecula, arcus, and pseudophakia. Photography after pharmacologic dilation allowed for better visualization of the intraocular lens. **E** and **F.** Fundus photographs of the right and left eyes demonstrating no diabetic retinopathy. **G.** Anterior segment photograph of the left eye demonstrating no iris neovascularization. Other findings included arcus and cataract with both nuclear and cortical opacities. Photography after pharmacologic dilation allowed for better visualization of the cataract. **H** and **I.** Fundus photographs of the left eye demonstrating few microaneurysms, dot-blot hemorrhages, and exudates, consistent with mild nonproliferative diabetic retinopathy (NPDR). Because of glare related to the cataract (top right), two fundus images were acquired.

found to have neovascularization of the iris by either clinical or photographic grading. Other pertinent anterior segment findings included cataract (32 eyes), intraocular lens (7 eyes), pterygium/pinguecula (7 eyes), arcus (6 eyes), conjunctival melanosis (4 eyes), corneal opacity (1 eye), peripheral iridotomy (1 eye), eyelid papilloma (1 eye), and trabeculectomy (1 eye).

Posterior Segment Grading

Fundus photographs were graded by two masked reviewers (CKP and BCT) and scored on a 6-point scale: no retinopathy, mild NPDR, moderate NPDR, severe NPDR, PDR, and unable to grade. Consensus between the 2 reviewers was good, with 88% agreement and a kappa of 0.70. When the photograph grade assigned by the two reviewers differed by only 1 level, the more severe grade was assigned. If the difference was more than 1 level, a third reviewer (MSB) adjudicated the final photograph grade. This was necessary in 1 case. The clinical grade was assigned based on masked abstraction of the documented clinical examination findings. Table 3 is a frequency table comparing the clinical and final photographic grades. Table 4 displays these data dichotomized for no referral (no retinopathy or mild NPDR) or referral (moderate or severe NPDR, PDR, or unable to grade). When dichotomized in this way, the kappa value was 0.91 ± 0.1 ($P < 0.001$), indicating good agreement between the clinical and photographic measures. Using clinical grade as the reference to detect referral-warranted retinopathy, photograph grade was found to be 91% sensitive and 99% specific, with a 95% positive predictive value and a 98% negative predictive value. A Bland–Altman plot (Figure 5) demonstrated a bias near 0 and the 95% limits of agreement within ± 1 ICDR level for grading either

Table 2. Visual Acuity Comparison

	BSCVA at Distance (Snellen)	BSCVA at Near (smartphone)	
Mean ± SEM (converted ETDRS letters)	69 ± 1.3	69 ± 1.3	$P = 0.45$, paired t-test
Median (IQR, converted ETDRS letters)	70 (65–80)	70 (65–75)	
Correlation			r = 0.91 ($P < 0.001$)

Visual acuity measurements obtained using Snellen and smartphone methods demonstrate similar mean and range, and good correlation (r = 0.91).

BSCVA, visual acuity measured with spectacle correction; SEM, standard error of the mean; ETDRS, early treatment of diabetic retinopathy study; IQR, interquartile range.

Table 3. Comparison of Retinopathy Grading

Grade of Diabetic Retinopathy (Clinical Examination)	Grade of Diabetic Retinopathy (Smartphone)						
	None	Mild	Mod	Severe	PDR	U	Total
None	71	0	0	0	0	1	72
Mild	6	0	1	0	0	0	7
Mod	1	1	6	0	0	1	9
Severe	0	0	0	4	0	0	4
PDR	0	0	0	0	8	0	8
U	0	0	0	0	0	0	0
Total	78	1	7	4	8	2	100

This is a frequency table comparing the grade of retinopathy as ascertained by clinical examination and smartphone photograph. The outlined boxes indicate exact agreement. Kappa (κ) = 0.76 ± 0.06, $P < 0.001$. The two ungradeable photograph series were due to poor dilation and cataract.

None, no diabetic retinopathy; Mild, mild nonproliferative diabetic retinopathy (NPDR); Mod, moderate NPDR; Severe, severe NPDR; PDR, proliferative diabetic retinopathy; U, unable to grade.

by clinical examination or photograph. A receiver-operating characteristic curve (Figure 6) demonstrated an area under the ROC curve of 0.97 (95% confidence interval, 0.93–1). Other pertinent posterior segment findings included optic nerve cupping (11 eyes), peripapillary atrophy (4 eyes), and myelinated nerve fiber layer (1 eye).

Discussion

To our knowledge, this is the first smartphone-based system that integrates visual function testing (acuity) and structural findings (smartphone photography) to screen for diabetic eye disease.

Smartphone-acquired near visual acuity measurement with this system demonstrated good correlation with Snellen distance visual acuity acquired in a standard clinic setting. This confirms findings by others using the DigiSight visual acuity testing application in similar settings to measure and follow visual acuity in patients with diabetes[18] and age-related macular degeneration (Yu SY, Yang JH, Kim Y, Kwak HW, Blumenkranz MS. Reliability of Smartphone-Based Electronic Visual Acuity Testing. Poster presented at: ARVO Annual Meeting Abstracts; Orlando, FL; 2014).

With diabetes in particular, increased severity of DR and macular edema have been shown to be associated with lower levels of visual acuity.[23,24] Similarly, in our cohort, there was a statistically significant trend toward decreasing visual acuity with increasingly severe photograph grades of retinopathy ($P = 0.046$, test for trend across ordered groups). Furthermore, the Diabetic Retinopathy Clinical Research Network Protocol T study demonstrated a difference in the relative effectiveness of different anti-VEGF agents to treat diabetic macular edema that varied with initial visual acuity. Eyes having 20/50 or worse vision did not respond as well to ranibizumab and bevacizumab, compared with aflibercept, whereas eyes having 20/40 or better vision responded similarly.[25] Thus, detecting early decreases in visual acuity in patients with DR may be useful in combination with fundus imaging to guide treatment decision making. Future studies may evaluate the

Table 4. Dichotomized Comparison of Retinopathy Grading

Grade of Diabetic Retinopathy (Clinical Examination)		Grade of Diabetic Retinopathy (smartphone)						
		No Referral		Referral				
		None	Mild	Mod	Severe	PDR	U	Total
No referral	None	77			2			79
Referral	Mild Mod Severe PDR U	2			19			21
Total		79			21			100

This is a frequency table comparing the grade of retinopathy as ascertained by clinical examination and smartphone photograph, dichotomized for referral if retinopathy was greater than moderate NPDR. Kappa (κ) = 0.91 ± 0.1, $P < 0.001$. Sensitivity 91%, specificity 99%, PPV 95%, NPV 98%.

None, no diabetic retinopathy; Mild, mild nonproliferative diabetic retinopathy (NPDR); Mod, moderate NPDR; Severe, severe NPDR; PDR, proliferative.

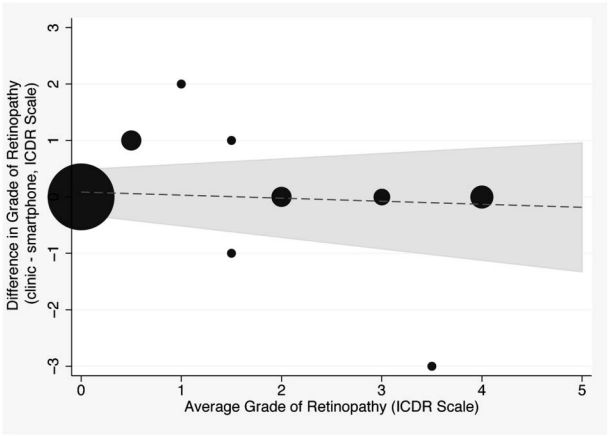

Fig. 5. Retinopathy grading comparison: Bland–Altman plot. The average (x-axis) and difference (y-axis) between the standard clinic and smartphone-acquired photograph grades of diabetic retinopathy are shown on a Bland–Altman plot. The bias (discrepancy between the two methods), illustrated by the dotted line, was near 0. The limits of agreement (shaded gray area) were narrow, $<\pm$ 1 international clinical diabetic retinopathy (ICDR) level for most points. The outlier near the x-axis indicates the two ungradeable photograph series.

potential role for serial visual function monitoring in the out-of-office setting, as has been performed for age-related macular degeneration.[26]

Anterior and posterior segment photographs acquired using this system demonstrated good agreement with the clinical examination. Many investigators have previously reported the successful incorporation of fundus photography as part of a telemedicine approach to screen for DR and diabetic macular edema.[11,27–33] These groups have used mydriatic or nonmydriatic fundus photography with a fixed in-clinic fundus camera and sometimes a dedicated reading center to grade

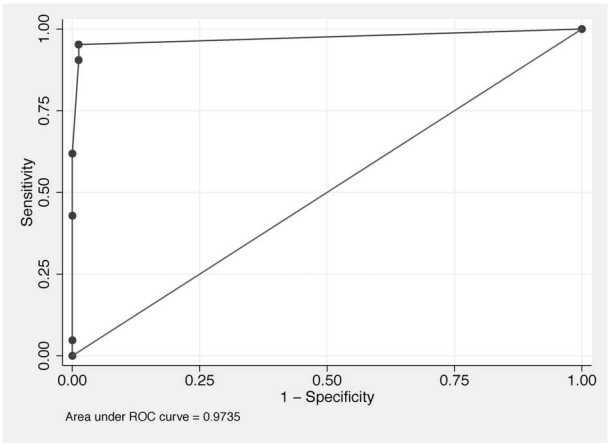

Fig. 6. Retinopathy grading comparison: Receiver operating characteristic. Compared to the gold standard clinic grade of diabetic retinopathy, the sensitivity and 1-specificity of smartphone-acquired photograph grade of diabetic retinopathy are shown on a receiver operating characteristic curve. The area under the receiver operating characteristic (AUROC) was high, 0.97 (95% confidence interval, 0.93–1).

photographs remotely.[34] This study reports on the use of a portable smartphone-based system to acquire nonmydriatic anterior segment, and mydriatic anterior and posterior segment photographs. These photographs were subsequently remotely graded on the DigiSight secure web site (https://www.digisight.net), where graders logged in and could view the photographs uploaded through the smartphone at the time of examination. Based on the good agreement between acquired fundus photographs and clinical examination in our study, and also the aim to identify referral-warranted diabetic eye disease, this platform is potentially consistent with a validation category 2 telehealth system for DR (using the International Clinical Diabetic Retinopathy scale), as described by the American Telemedicine Association (ATA).[35]

Clinical examination was used as the standard for comparison with photography, as in previous similar studies.[36,37] Other studies have directly compared ophthalmoscopy and 7-field ETDRS fundus photography with a 30° fundus camera, the gold standard in determining the severity of DR, and found agreement within 1 step in 34 to 86% of cases and kappa value for concordance ranging from 0.4 to 0.75.[38–40] Our findings in this study, without dichotomizing for moderate NPDR or worse disease, indicated 90% agreement with a kappa of 0.76, consistent with these previous data. Disagreements were rarely of clinical significance and occurred most often in cases of early retinopathy. Although most patients screened did not have retinopathy detectable on photography or by clinical examination, this is true for most studies on the efficacy of screening tests. Our power analysis indicated that there was sufficient enrollment to detect a difference if it did exist between the clinical examination and this novel screening system.

Some studies have indicated that standard in-clinic fundus photography may have higher sensitivity and specificity than clinical examination to detect small-to-moderate changes in DR over time.[41] Future studies comparing smartphone-based technologies to standard in-clinic fundus photography may be of interest.

As in previous telemedicine studies, patients with at least moderate NPDR were considered to require referral for full ophthalmic examination to evaluate more closely for diabetic eye disease requiring urgent ophthalmic intervention.[27,28]

In this study, the sensitivity and specificity of fundus photographs to detect referral-warranted diabetic eye disease were 91% and 99%, respectively, in line with findings of a systematic review by the American Academy of Ophthalmology, which also concluded that "single-field fundus photography can be used as a screening tool to identify patients with

DR who require referral for ophthalmic evaluation and management."[42]

The adapter system used a phone's native camera with coaxial light-emitting diode illumination in combination with an indirect ophthalmoscopy lens. With this system, a dilated pupil was required to obtain a 45° field of view necessary to adequately view the entire posterior pole for grading purposes. This requirement for pharmacologic dilation may limit generalized use of this system by photographers who are not comfortable dilating patients. Other challenges included occasional patient eye movement and poor fixation, which increased the difficulty of acquiring a centered and focused image. Thus, acquiring a single posterior pole photograph was more feasible than acquiring 7 standard 30° ETDRS fields. Currently, many telemedicine screening clinics use nonmydriatic imaging systems, which offer the advantage of avoiding the need for dilation, though at a much higher expense. The specific advantages of the system described herein are the very low incremental cost of equipment (low-cost plastic adapters combining existing practitioner-owned smartphone, low-cost smartphone application, and lens), direct wireless connectivity to a secure database through the phone, and concomitant structure and function data acquisition (photographs and visual acuity). A recent report demonstrated validation of a similar smartphone-assisted direct ophthalmoscopy-based system for fundus imaging.[43] The narrow field-of-view inherent to direct ophthalmoscopy techniques required the authors to pan across the posterior pole using the smartphone's video mode, resulting in longer examination times and decreased resolution (1080p, or approximately 2 megapixels) compared with a single wider field-of-view photograph (8 megapixels) that can be acquired using the smartphone's photograph mode.

In this study, all data and photographs were collected by an ophthalmologist using the smartphone telemedicine system. As fundus photograph capture using this system mimics indirect ophthalmoscopy, the implication is that an ophthalmologist would have greater ease applying this practiced skill. Future studies will need to be performed to evaluate the training required for a technician to capture high-quality data, because one of the important potential applications for this technology will be performing ophthalmic screening in underserved areas without adequate access to ophthalmic care. Indeed, in our own safety-net hospital, this may have a role in the primary care or out-of-office settings to screen for eye disease.

During a pilot period enrolling 10 patients over 2 clinic sessions not included in this study, data from seven patients were not able to be successfully uploaded because of technical issues with the beta version of the software. These issues were subsequently resolved, permitting successful execution of the study in 50 consecutive patients without incident. Collaboration between study physicians and the software development team was useful in optimizing the software platform and workflow plan, highlighting the need for partnerships with telehealth information services providers. Future work will include additional modifications to hardware and software integration to improve reliability of data, quality of photographs, ease of use, and nonmydriatic image capture. Further testing of this portable teleophthalmology system in other settings will likely be of interest, as it has now been FDA-registered as a Class II 510(k) exempt device.

An important caveat of this study was its implementation in a relatively small, clinic-based population. As such, the proportion of eyes presenting with referral-warranted disease was low (21%), and additional studies, enrolling more patients with more severe retinopathy, will be crucial to assess the sensitivity and specificity of this approach to screening for diabetic eye disease.

Using low-cost adapters and existing lenses, this study demonstrates the potential utility of smartphone mobile telemedicine to screen for referral-warranted diabetic eye disease. Our study suggests that there is a good correlation with findings on a standard clinical ophthalmic examination, making it potentially comparable with a category 2 ATA telehealth system. To our knowledge, this is the first mobile system to integrate ophthalmic structural and visual function data in the evaluation of diabetic eye disease. The portability of this system may be of particular use in underserved areas without adequate access to ophthalmic care. Future studies are necessary to further evaluate the feasibility of expanding screening for diabetic eye disease using smartphone technologies.

Key words: diabetic retinopathy, smartphone, telemedicine.

References

1. Control CfD, Prevention. National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States. Atlanta, GA: US Department of Health and Human Services 2014; 2014.
2. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311–321.
3. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. JAMA 2010;304: 649–656.
4. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early treatment diabetic retinopathy study research group. Ophthalmology 1991;98:766–785.
5. Chew EY, Ferris FL III, Csaky KG, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic

retinopathy: the early treatment diabetic retinopathy follow-up study. Ophthalmology 2003;110:1683–1689.
6. Brechner RJ, Cowie CC, Howie LJ, et al. Ophthalmic examination among adults with diagnosed diabetes mellitus. JAMA 1993;270:1714–1718.
7. Lee PP, Feldman ZW, Ostermann J, et al. Longitudinal rates of annual eye examinations of persons with diabetes and chronic eye diseases. Ophthalmology 2003;110:1952–1959.
8. Wylie-Rosett J, Basch C, Walker EA, et al. Ophthalmic referral rates for patients with diabetes in primary-care clinics located in disadvantaged urban communities. J Diabetes Complications 1995;9:49–54.
9. Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie House classification. ETDRS report number 10. Early treatment diabetic retinopathy study research group. Ophthalmology 1991;98:786–806.
10. Conlin PR, Fisch BM, Orcutt JC, et al. Framework for a national teleretinal imaging program to screen for diabetic retinopathy in Veterans Health Administration patients. J Rehabil Res Dev 2006;43:741–748.
11. Ogunyemi O, George S, Patty L, et al. Teleretinal screening for diabetic retinopathy in six Los Angeles urban safety-net clinics: final study results. AMIA Annu Symp Proc 2013;2013:1082–1088.
12. Ogunyemi O, Terrien E, Eccles A, et al. Teleretinal screening for diabetic retinopathy in six Los Angeles urban safety-net clinics: initial findings. AMIA Annu Symp Proc 2011;2011: 1027–1035.
13. Zimmer-Galler I, Zeimer R. Results of implementation of the DigiScope for diabetic retinopathy assessment in the primary care environment. Telemed J E Health 2006;12:89–98.
14. Chabouis A, Berdugo M, Meas T, et al. Benefits of Ophdiat, a telemedical network to screen for diabetic retinopathy: a retrospective study in five reference hospital centres. Diabetes Metab 2009;35:228–232.
15. Cuadros J, Bresnick G. EyePACS: an adaptable telemedicine system for diabetic retinopathy screening. J Diabetes Sci Technol 2009;3:509–516.
16. Day S, Ko M. Diabetic retinopathy in a multi-ethnic population in Santa Clara County, California. Poster presented at: ARVO Annual Meeting Abstracts; Fort Lauderdale, Florida. May 6, 2012.
17. Toy B, Aguinaldo A, Egbert J, et al. Non-mydriatic fundus camera screening for diabetic retinopathy in a Northern California safety-net setting. Paper presented at: ARVO Annual Meeting Abstracts; Seattle, Washington. May 5, 2013.
18. Tsui I, Drexler A, Stanton AL, et al. Pilot study using Mobile health to coordinate the diabetic patient, diabetologist, and ophthalmologist. J Diabetes Sci Technol 2014;8:845–849.
19. Myung D, Jais A, He L, et al. 3D printed smartphone indirect lens adapter for rapid, high quality retinal imaging. J Mob Technol Med 2014;3:9–15.
20. Myung D, Jais A, He L, Chang RT. Simple, low-cost smartphone adapter for rapid, high quality ocular anterior segment imaging: a photo diary. J Mob Technol Med 2014;3:2–8.
21. Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94:91–96.
22. Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–1682.
23. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. Ophthalmology 1984;91:1–9.
24. Klein R, Lee KE, Gangnon RE, Klein BE. The 25-year incidence of visual impairment in type 1 diabetes mellitus the wisconsin epidemiologic study of diabetic retinopathy. Ophthalmology 2010;117:63–70.
25. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015;372:1193–1203.
26. Chew EY, Clemons TE, Bressler SB, et al. Randomized trial of a home monitoring system for early detection of choroidal neovascularization home monitoring of the Eye (HOME) study. Ophthalmology 2014;121:535–544.
27. Massin P, Aubert JP, Erginay A, et al. Screening for diabetic retinopathy: the first telemedical approach in a primary care setting in France. Diabetes Metab 2004;30:451–457.
28. Choremis J, Chow DR. Use of telemedicine in screening for diabetic retinopathy. Can J Ophthalmol 2003;38:575–579.
29. Mansberger SL, Gleitsmann K, Gardiner S, et al. Comparing the effectiveness of telemedicine and traditional surveillance in providing diabetic retinopathy screening examinations: a randomized controlled trial. Telemed J E Health 2013;19:942–948.
30. Chin EK, Ventura BV, See KY, et al. Nonmydriatic fundus photography for teleophthalmology diabetic retinopathy screening in rural and urban clinics. Telemed J E Health 2014;20:102–108.
31. Garg S, Jani PD, Kshirsagar AV, et al. Telemedicine and retinal imaging for improving diabetic retinopathy evaluation. Arch Intern Med 2012;172:1677–1678.
32. Liesenfeld B, Kohner E, Piehlmeier W, et al. A telemedical approach to the screening of diabetic retinopathy: digital fundus photography. Diabetes Care 2000;23:345–348.
33. Peng J, Zou H, Wang W, et al. Implementation and first-year screening results of an ocular telehealth system for diabetic retinopathy in China. BMC Health Serv Res 2011;11:250.
34. Sanchez CR, Silva PS, Cavallerano JD, et al. Ocular telemedicine for diabetic retinopathy and the Joslin Vision Network. Semin Ophthalmol 2010;25:218–224.
35. Li HK, Horton M, Bursell SE, et al. Telehealth Practice Recommendations for Diabetic Retinopathy, second edition. Telemed J E Health 2011;17:814–837.
36. Ahmed J, Ward TP, Bursell SE, et al. The sensitivity and specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. Diabetes Care 2006;29:2205–2209.
37. Scanlon PH, Malhotra R, Thomas G, et al. The effectiveness of screening for diabetic retinopathy by digital imaging photography and technician ophthalmoscopy. Diabet Med 2003;20:467–474.
38. Lin DY, Blumenkranz MS, Brothers RJ, Grosvenor DM. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpretation for diabetic retinopathy screening: a comparison with ophthalmoscopy and standardized mydriatic color photography. Am J Ophthalmol 2002;134:204–213.
39. Emanuele N, Klein R, Moritz T, et al. Comparison of dilated fundus examinations with seven-field stereo fundus photographs in the veterans affairs diabetes trial. J Diabetes Complications 2009;23:323–329.
40. Moss SE, Klein R, Kessler SD, Richie KA. Comparison between ophthalmoscopy and fundus photography in determining severity of diabetic retinopathy. Ophthalmology 1985;92:62–67.
41. Gangaputra S, Lovato JF, Hubbard L, et al. Comparison of standardized clinical classification with fundus photograph grading for the assessment of diabetic retinopathy and diabetic macular edema severity. Retina 2013;33:1393–1399.
42. Williams GA, Scott IU, Haller JA, et al. Single-field fundus photography for diabetic retinopathy screening: a report by the American Academy of Ophthalmology. Ophthalmology 2004; 111:1055–1062.
43. Russo A, Morescalchi F, Costagliola C, et al. Comparison of smartphone ophthalmoscopy with slit-lamp biomicroscopy for grading diabetic retinopathy. Am J Ophthalmol 2015;159:360–364.