

Comparison of a digital retinal imaging system designed for detection of diabetic retinopathy in the primary care physician's office to stereo seven-field color fundus photography

Rhett M. Schiffman, M.D., M.S., M.H.S.A.¹, Gordon Jacobsen M.S.¹, Julian J. Nussbaum, M.D.^{1,2}, Uday R. Desai M.D.¹, J. David Carey M.D.¹, David Glasser M.D.^{3,4}, Ingrid E. Zimmer-Galler M.D.⁴, Ran Zeimer, Ph.D.⁴, Morton F. Goldberg, M.D.⁴

Abstract

Many patients with diabetes do not receive the recommended annual dilated examination by an eye care professional. Because these patients visit their primary care physician regularly, a retinal risk assessment in the primary care setting could improve the screening rate for diabetic retinopathy. We evaluated the DigiScope as an imaging system to identify diabetic retinopathy requiring referral to an ophthalmologist. In a masked prospective study, 111 patients with diabetes, were imaged with the DigiScope and with seven-field stereo color fundus photography. The ability to obtain gradable images and to identify diabetic retinal lesions was compared. 85% of DigiScope and 88% of seven-field images were gradable. Agreement based on "no retinopathy" vs. "any retinopathy" was excellent (Kappa = 0.96). Agreement based on "microaneurysms or less retinopathy" vs. "retinal hemorrhages or worse retinopathy" was very good (Kappa = 0.83). The agreement between the DigiScope and seven-field photography indicates that the DigiScope may be useful to screen for diabetic retinopathy.

¹Eye Care Services, Henry Ford Health System, Detroit, MI

²Medical College of Georgia, Augusta, GA

³Patuxent Medical Group, Columbia, MD

⁴Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine, Baltimore, MD

Corresponding author:

Rhett M. Schiffman, M.D., M.S., M.H.S.A.
Allergan, Inc.
2525 Dupont Dr.
P.O. Box 19534
Irvine, CA 92623-9534
Phone: 714-246-4949
Fax: 714-246-4002
Email: rmschfmm@aol.com

Financial disclosure: Under an agreement between the EyeTel Imaging Corporation and the Johns Hopkins University, Dr. Zeimer is entitled to a share of sales royalty received by the University from EyeTel Imaging Corporation. Dr. Zeimer and the University own EyeTel Imaging Corporation stock, which under University policy, cannot be traded until 2 years after the first sale of FDA-approved products related to the research described in this consent form. The terms of this agreement have been reviewed and approved by the University in accordance with its conflict of interest policies. This research was supported by an unrestricted grant from EyeTel Imaging Inc. An abstract of the study has been published in IOVS 42(4):S741, 2001.

Introduction

In the United States, diabetic retinopathy is the leading cause of blindness among adults aged 20 to 74 years.¹ It is estimated that 75,000 new cases of macular edema, 65,000 cases of proliferative retinopathy and 8,000 cases of blindness develop each year.² Landmark prospective clinical trials such as the Diabetic Retinopathy Study (DRS)³ and Early Treatment Diabetic Retinopathy Research Study (ETDRS)⁴ have shown that timely treatment for diabetic retinopathy is highly effective in reducing the risk of serious vision loss due to diabetes. For this reason, screening has also been shown to be cost-effective⁵. Consequently, screening for diabetic eye disease is recommended by leading organizations and medical societies.^{6,7}

Despite these recommendations, the Wisconsin Epidemiologic Study of Diabetic Retinopathy revealed that out of over 2000 diabetic patients, 11% of type 1 patients with diabetes and 7% of type 2 patients with diabetes with high-risk proliferative diabetic retinopathy,

(and at risk for severe vision loss) had not been seen by an ophthalmologist within 2 years.¹ More recently, the Health Plan Employer Data and Information Set (HEDIS), the national report card for Health Maintenance Organizations, reported that only 45% of eligible patients with diabetes had eye examinations in the previous year.

Many of the barriers to proper eye care among patients with diabetes may be divided between factors related to the primary care provider and those related to the patient. Primary care providers frequently lack the skill and equipment necessary to perform screening eye examinations, may be unaware of the current recommendations, or simply do not educate diabetic patients appropriately.² Patients are often uninformed about their risk for development of eye disease and report a lack of perceived benefit to eye examinations as well as more logistical issues, such as high cost, not enough time, difficulty obtaining an appointment, lack of transportation, and no access to eye care providers.³ Although patients have reported that cost is a factor³, annual HEDIS reports continue to show low screening rates even in the managed care environment. Moreover, educational programs designed to show the importance of eye examinations demonstrated only marginal value, even when patients were provided with culturally relevant educational material.⁴ Because most patients with diabetes visit their primary care physician multiple times each year, screening in this setting may hold the greatest promise for bypassing most of these barriers and significantly increasing the screening rate.

HEDIS now accepts retinal photography for screening for diabetic retinopathy, provided the images are read by a qualified reading center under the direction of a retinal specialist. Successful diabetic retinopathy detection in the primary care setting requires an imaging system that has sufficient field of view and resolution to detect pathologic changes. ETDRS 30° stereo color seven standard field film photography is the current accepted gold standard for evaluating diabetic retinopathy, and any alternative system should be validated against this current standard. To be practical, available office staff must be able to operate the device and generate images that can be read at an expert reading center. The DigiScope, a new dedicated retinal imaging

system, was designed to meet these criteria. The DigiScope, previously described in detail,⁵ automatically centers on the pupil, illuminates, focuses, and estimates visual acuity. It encrypts patient and provider identifier information, creates JPEG 2000 images with 9:1 to 15:1 compression ratios, and transmits the information overnight or after office hours (at a rate of 6 minutes per patient via 56K modem,) to the Wilmer-EyeTel Reading Center for expert reading. The DigiScope used in this study imaged 15 slightly overlapping fields providing a 55 to 60° overall view centered on the macula. The DigiScope is designed to be operated by staff in the primary care environment with minimal training. Monochromatic images are obtained under red-free illumination, which maximizes contrast. The images are captured through a dilated pupil, as is required by HEDIS, and to maximize the number of gradable images.

The purpose of this prospective validation study was to determine how well the DigiScope retinal imaging system compares with the gold standard seven-field color stereo fundus photography in identifying diabetic patients with diabetic retinopathy requiring referral to an ophthalmologist for further evaluation. Additionally, patient preference for this modality was compared with that for gold standard retinal photographs.

Research Design and Methods

Study Design

The ability of the DigiScope to detect diabetic retinopathy requiring referral to an ophthalmologist, defined either as any retinopathy or as ETDRS level 20 or more severe retinopathy, was evaluated in a prospective, single-masked, randomized study in patients undergoing diabetic eye examinations. In random order, patients received retinal imaging with the DigiScope and with standard seven-field photography with a fundus camera in the same setting. The trial was conducted in compliance with Good Clinical Practices, investigational site Institutional Review Board Regulations, Sponsor and Investigator Obligations, Informed Consent Regulations, and the Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation in the study. The first patient was

enrolled in May 1999 and the last patient completed the study by April 2000.

Subjects

Male and female patients who were at least 18 years of age with type 1 or type 2 diabetes mellitus were consecutively recruited after a chart review to include the full spectrum of diabetic retinopathy. To generate a study population in which clinically relevant levels of diabetic retinopathy were represented, enrollment was continued for each of the following groups until approximately equal numbers of patients with no diabetic retinopathy, nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy, based on the clinical examination by an ophthalmologist and chart review, were enrolled. Once a given group had reached the desired size, new patients with the corresponding retinopathy level were excluded. A total of 111 patients were enrolled. All patients presented to an ophthalmology clinic for a diabetic eye examination by a board-certified ophthalmologist at either the Henry Ford Health System (Detroit MI), an ambulatory primary care and referral center; Associated Retinal Consultants (Livonia, MI), a private practice retinal specialty group; or Patuxent Medical Group (Columbia, MD), an ambulatory care group practice. Patients unwilling to give written informed consent or unwilling to have retinal imaging performed were excluded. No attempt was made to select patients based on type or duration of diabetes and patients were not excluded if other known ocular disease was present.

Study Protocol

All patients provided written informed consent and completed a questionnaire on sociodemographic information and medical history. Patients underwent a detailed eye examination in an ophthalmology setting including pupillary dilation with a standard protocol using a single drop of epinephrine 2.5% and tropicamide 1%. The subjects then received, in random order, retinal imaging with the DigiScope and standard seven-field stereo photography with a fundus camera taken by an ophthalmic photographer in the same setting. Following retinal imaging, patients completed a

three-item survey to assess their preference for the DigiScope or standard seven-field fundus photography.

Outcome Measures

Image Reading

The DigiScope images were transmitted to the Wilmer-EyeTel Reading Center at the Wilmer Eye Institute (Johns Hopkins University, Baltimore, MD). At the reading center, two retinal specialists read each DigiScope image nonstereoscopically in a masked fashion using standard ETDRS criteria (other than stereoscopic viewing). The same retinal specialists also read the seven-field stereo photographs stereoscopically in a masked fashion. In addition, one specialist re-graded a randomly selected sample of DigiScope images. Images were graded on a lesion-by-lesion basis to assess for the presence or absence of each of the following diabetic retinal lesions: retinal hemorrhages and microaneurysms, soft exudates, venous beading, intraretinal microvascular abnormalities, neovascularization of the disc, neovascularization elsewhere, fibrous proliferation, pre-retinal or vitreous hemorrhages, and hard exudates. Seven-field photographs were viewed stereoscopically and macular edema was graded as being present if macular thickening was noted based on ETDRS criteria. DigiScope images were not evaluated in stereo for this study, and were graded as having macular edema if hard exudates were present in the posterior pole using the location criteria of the ETDRS. DigiScope images (15 fields per eye) and seven-field photographs were designated as gradable or non-gradable. A field was defined as ungradable if the image was not adequate to allow determination that a diabetic lesion was present or absent with at least 50% confidence (due to media opacity, poor photographic quality, etc.). The field was considered gradable for a lesion if it was clearly identified in an unobscured part of the field. A study eye was strictly defined as ungradable if any single field of the study (15 fields per eye for DigiScope images and 7 fields per eye for stereo photographs) was ungradable. Patients were designated as requiring referral to an ophthalmologist based on the presence and severity of diabetic retinopathy, or if the study was ungradable, even if no retinopathy was

observed. The presence of any ungradable field (ungradable study) was a reason for referral of the patient, because significant pathology could not be ruled out in the ungradable field. While this criterion may increase the number of patients referred who do not have diabetic retinopathy, it minimizes patients not recommended for referral who may have important disease.

To define further the operating characteristics of the DigiScope, we computed agreement, sensitivity and specificity compared with the seven-field photographs for pairs of gradable images only. Since the DigiScope is currently intended only for diabetic retinopathy risk assessment purposes, the images were categorized by two levels: 1) no diabetic retinopathy vs. any diabetic retinopathy or 2) “microaneurysms (MA) or less retinopathy” (which corresponds to a modified ETDRS level 20⁶) vs. “retinal hemorrhages (RH) (which corresponds to a modified ETDRS level 35) or worse retinopathy”. MA or less retinopathy includes no diabetic abnormalities and microaneurysms only. RH or worse retinopathy includes retinal hemorrhages and more severe diabetic pathology. The first referral threshold was used to validate how well the DigiScope detects any diabetic retinal abnormalities compared to seven-field stereo photographs. The second referral threshold was selected (referral of patients for levels of retinopathy worse than very mild non proliferative disease) may be more appropriate since referral based on the presence of any diabetic retinopathy may result in an unnecessary high number of referrals. Grading that differed by any level between the two retina specialists was adjudicated by a third senior retina specialist. Agreement at the individual lesion level between DigiScope images and ETDRS photographs was also analyzed.

Agreement Analysis

Agreement between the DigiScope and the seven-field photographs with respect to the designation of individual lesions, gradable images, and level of retinopathy was measured with the Kappa statistic, which controls for chance agreement. Kappa values range from 0, indicating no agreement, to 1, indicating perfect agreement. Kappa values between 0.80 and 1.00 are

considered excellent, and Kappa values between 0.60 and 0.80 are considered substantial. Inter-rater agreement (between the two readers) was also measured for the DigiScope and fundus photographs separately, based on the unadjudicated results. Finally, intra-rater agreement was measured on the sample of randomly selected DigiScope images read a second time by one of the raters. Statistical testing of agreement was also done using McNemar’s test, which is based on the premise that disagreement between methods will be equally distributed.

Sensitivity and Specificity Analysis

The sensitivity and specificity of the DigiScope were calculated with the seven-field stereo photographs as the gold standard. In this case, sensitivity is the proportion of abnormal cases found with the standard fundus camera that was also detected by the DigiScope. Specificity is the proportion of normal cases found with the standard fundus camera that were also considered normal with the DigiScope. As with agreement, we calculated sensitivities and specificities for individual lesions and based on the two-referral thresholds: 1) no diabetic retinopathy vs. any diabetic retinopathy and 2) “MA or less retinopathy” vs. “RH or worse retinopathy”.

Patient Survey

The three-item survey of patient acceptability asked patients to rate comfort, time required, and preference for the DigiScope compared with standard fundus seven-field photography.

Statistical Analysis

Both eyes were imaged and where statistics for the right and left eyes are shown separately there are no statistical issues related to the correlation between eyes. Sample size was calculated to achieve a confidence interval of $\pm .10$ for Kappa. Data are represented as the mean \pm S.D. or mean with confidence intervals.

Table 1: Gradability of Images and Patient Referral

		Eyes with fully gradable image n (%)	Eyes with ≥ 1 ungradable field n (%)	Eyes warranting referral*** n (%)
Right Eye	DigiScope	94 (84.7)*	17 (15.3)	86 (77.5)
	Fundus camera	98 (88.3)	13 (11.7)	83 (74.8)
Left Eye	DigiScope	95 (85.6)**	16 (14.4)	86 (77.5)
	Fundus camera	98 (88.3)	13 (11.7)	81 (73.0)

*Kappa 0.85 (95% CI = 0.70 to 0.99), **Kappa 0.80 (95% CI = 0.63 to 0.97), ***Includes patients with any abnormalities or any ungradable fields

Table 2: Sensitivity and specificity of the DigiScope compared with seven-field stereo fundus photographs based on fully gradable images

No retinopathy vs. Any retinopathy							
Right Eye		Fundus camera		Left Eye		Fundus camera	
		Normal	Abnormal			Normal	Abnormal
DigiScope	Normal	22	1	DigiScope	Normal	23	0
	Abnormal	0	69		Abnormal	2	68
Kappa (95% CI)	0.97 (0.91–1.00)			Kappa (95% CI)	0.94 (0.87–1.00)		
Sensitivity (95% CI)	0.986 (0.92–1.00)			Sensitivity (95% CI)	1.00 (0.95–1.00)		
Specificity (95% CI)	1.00 (0.85–1.00)			Specificity (95% CI)	0.92 (0.74–0.99)		
MA or Better vs. RH or Worse							
Right Eye		Fundus camera		Left Eye		Fundus camera	
		MA or Better	RH or Worse			MA or Better	RH or Worse
DigiScope	MA or Better	25	3	DigiScope	MA or Better	27	1
	RH or Worse	6	60		RH or Worse	4	62
Kappa (95% CI)	0.78 (0.64–0.92)			Kappa (95% CI)	0.88 (0.77–0.98)		
Sensitivity (95% CI)	0.95 (0.87–0.99)			Sensitivity (95% CI)	0.98 (0.91–1.00)		
Specificity (95% CI)	0.81 (0.63–0.93)			Specificity (95% CI)	0.87 (0.70–0.96)		

Results

Patient demographics

A total of 111 patients with diabetes (222 eyes) were enrolled in and completed the study. The mean age was 57 ± 14 years (range: 18–99 years), and 59% of the patients were women. Fifty-nine percent of the patients were white, 39%

were black, and 3% were Hispanic. The mean time since diabetes was diagnosed was 19 ± 12 years (range: 1 year–49 years). Current diabetes therapy consisted of diet-control in 4% of patients, insulin in 58% of patients, oral medications in 31%, and insulin along with oral medications in 7% patients. The median Snellen acuity was 20/25 (range OU: 20/15-HM) in both eyes.

Outcome Measures

Gradable eyes and eyes warranting referral

The number of patients with gradable images, meaning all fields permitted a grading, is listed in Table 1. Most images from both the DigiScope (85%OD, 86%OS) and standard fundus camera (88%OU) were fully gradable. Images of 37 eyes were ungradable by at least one of the imaging modalities. Four eyes (2 OD and 2 OS) were gradable by DigiScope images and ungradable by fundus photographs. Eleven eyes (6 OD and 5 OS) were gradable by fundus photographs but not by the DigiScope. The excellent agreement (Kappa 0.85 OD, 0.80 OS) between the DigiScope and fundus camera with respect to which eyes were gradable indicates that imaging problems are not specific to the DigiScope. By definition, referral was recommended if one or more fields were ungradable. The number of patients warranting referral either because of any diabetic pathology or because of an ungradable image was

similar between the DigiScope (86 OU) and fundus camera (83 OD, 81 OS) and was very high in this population (Table 1).

Agreement and Sensitivity/Specificity Analysis

Agreement on no diabetic retinopathy vs. presence of any diabetic retinopathy was nearly perfect (Kappa 0.97 OD, 0.94 OS) (Table 2). This was reflected in very high sensitivities (0.99 OD, 1.00 OS) and specificities (1.00 OD, 0.92 OS). Agreement based on “MA or less retinopathy” vs. “RH or worse retinopathy” classification was very good to excellent (0.78 OD, 0.88 OS). The sensitivities (0.95 OD, 0.98 OS) and specificities (0.81 OD, 0.87 OS) were also quite high based on this classification. For right and left eyes combined, 1 eye was not referred by DigiScope but was referred based on photographic grading, and 2 eyes were referred by DigiScope but not by grading of photographs ($p=0.375$, no significant difference in % found abnormal).

Table 3: Agreement between DigiScope and Fundus camera as to presence or absence of different retinal pathologies, based on fully gradable images.

	Right Eye Kappa (95% CI)	Left Eye Kappa (95% CI)
Hemorrhages & Microaneurysms	0.70 (0.55–0.86) n = 62	0.77 (0.63–0.91) n = 62
Soft Exudates	0.76 (0.58–0.94) n = 15	0.80 (0.62–0.97) n = 14
Venous Beading	0.93 (0.79–1.00) n = 8	0.90 (0.72–1.00) n = 5
Intraretinal Microvascular Abnormalities	0.83 (0.69–0.97) n = 20	0.93 (0.83–1.00) n = 18
Neovascularization of Disc	1.00 (N.A.†) n = 2	1.0 (N.A.†) n = 4
Neovascularization Elsewhere	0.79 (0.50–1.00) n = 5	0.87 (0.73–1.00) n = 13
Fibrous Proliferation	0.84 (0.66–1.00) n = 10	0.94 (0.81–1.00) n = 8
Preretinal Hemorrhages	1.00 (N.A.†) n = 1	1.00 (N.A.†) n = 7
Hard Exudates/Macular edema	0.58 (0.41–0.75) n = 34	0.74 (0.61–0.88) n = 45

†N.A.: the confidence interval cannot be computed in this case

Table 4: Agreement between graders and between readings of one grader

Inter-grader Agreement				
	No retinopathy vs. Any		MA or better vs. RH or worse	
	<i>DigiScope</i>	Fundus camera	<i>DigiScope</i>	Fundus camera
Right Eye	0.94 (0.86–1.00)	0.91 (0.81–1.00)	0.76 (0.62–0.90)	0.77 (0.63–0.90)
Left Eye	0.91 (0.81–1.00)	0.91 (0.82–1.00)	0.67 (0.52–0.82)	0.76 (0.62–0.90)
Intra-grader Agreement				
	No retinopathy vs. Any		MA or better vs. RH or worse	
	DigiScope	Fundus camera	DigiScope	Fundus camera
Random Eyes	1.00 (N.A.†)	1.00 (N.A.†)	0.76 (0.32-1.00)	0.75 (0.31-1.00)

Values are Kappa (95% CI)

†N.A.: the confidence interval cannot be computed in this case.

Agreement by Pathology

Agreement with respect to the presence or absence of each of the individual diabetic retinal pathologies, not the level of pathology, is presented in Table 3. Agreement was good to excellent for each abnormality and was particularly good for the more severe diabetic retinal pathologies. In particular, based on fundus photographs, no cases of treatable disease were missed with the DigiScope. These findings demonstrate that the red-free DigiScope images are particularly useful for identifying vascular abnormalities.

Inter- and Intra-rater Agreement

Agreement between readers, before adjudication, was excellent (Kappa 0.91 – 0.94) for the no retinopathy vs. any diabetic retinopathy classification and substantial (Kappa 0.67 - 0.77) for the “MA or better retinopathy” vs. “RH or worse retinopathy” classification (Table 4). A sample of randomly selected images was re-read by one specialist and the agreement in readings was perfect for the normal vs. abnormal classification from DigiScope images and fundus photographs and substantial (Kappa 0.75 - 0.76) for the “MA or less retinopathy” vs. “RH or worse retinopathy” classification from DigiScope images and fundus photographs (Table 4).

Patient Survey

With respect to patient acceptability and preference, 83% felt that the DigiScope was more comfortable than standard fundus photography and 77% preferred the DigiScope procedure. Only 5% felt that the fundus camera was more comfortable and 6% preferred standard fundus photography. Approximately half of patients (47%) thought that the DigiScope required less time, while 36% thought both techniques required about the same amount of time.

Conclusions

This validation study demonstrates that the DigiScope retinal imaging system can successfully identify diabetic retinal abnormalities and has excellent agreement, sensitivity, and specificity with the current gold-standard seven-field color stereo fundus photography. The DigiScope detects diabetic retinopathy and appropriately promotes referral of patients to an eye care professional for comprehensive eye examinations. The DigiScope imaging system is not intended to replace the need for a comprehensive eye examination, but rather is designed to increase the number of patients with diabetes receiving the recommended eye care.

The need for referral based on DigiScope images was found to be nearly identical to that based on stereo fundus photography. In this

patient population, the rate of referral was high because the recruitment was designed to yield similar numbers of eyes at all levels of retinopathy regardless of the typical prevalence. In the primary care setting, where the DigiScope is intended to be used to assess patients with diabetes not currently receiving eye care, the prevalence of patients recommended for referral will most likely be lower. Further studies on the implementation of the DigiScope in the primary care setting are planned.

To obtain enough cases to study the agreement for each pathology the amount of diabetic retinal pathology in this study population was greater than expected in a typical primary care setting, and it is possible that the sensitivity was artificially increased. While this is a limitation of this study, it was minimized by the fact that there were a significant number of eyes without any pathology that were identified with each imaging method. The DigiScope was shown to be adequate both for identifying absence of pathology and the presence of any pathology.

Two thresholds for referral were evaluated in this study, the presence of any diabetic retinopathy and the presence of any level of retinopathy greater than very mild nonproliferative disease (ETDRS level 20). Ungradable cases were assigned for referral in both threshold schemes. Ideally, patients with diabetes with any retinopathy should be under the care of an ophthalmologist. In practice, referral based on the presence of any retinopathy, no matter how mild, may result in an unnecessarily high number of referrals. Referral of patients with diabetic retinopathy worse than ETDRS level 20 may be more practical. Therefore, this study evaluated a second threshold level of very mild nonproliferative diabetic retinopathy to reduce the number of unnecessary referrals. Other diabetic retinopathy surveillance systems, such as the Joslin Vision Network system and Inoveon Diabetic Retinopathy-3DT system (references 6,7), are designed for management of diabetic retinopathy, and patients with less severe levels of retinopathy may be monitored with future imaging. However, the DigiScope is designed to facilitate entry of diabetic patients into the eye care system rather than to serve as a disease management tool; therefore, patients with even low levels of retinopathy are intended to be

referred for a comprehensive eye examination with this system. The decision on the level of retinopathy requiring referral will depend on many factors such as cost, consensus in the medical community, and ease of access to an ophthalmologist. At this point, the authors prefer to be conservative and refer for low levels of retinopathy. The impact of actual subsequent visits to an ophthalmologist due to referrals based on DigiScope imaging also needs to be studied.

While the number of ungradable eyes was slightly higher with the DigiScope, there was excellent agreement between the DigiScope and conventional fundus photography with respect to which eyes were gradable. With the DigiScope system, referral criteria include patients for whom images are not obtainable or are not gradable. Ungradable images may include those due to ocular pathology that interferes with imaging (such as cataract), characteristics of older eyes such as smaller pupils, or equipment failure. Referral based on ungradable images may therefore increase the number of unnecessary referrals, but may also help ensure that patients with significant disease are not “missed”. For this study, a stringent definition of ungradable image was used; namely, if any field of the study was ungradable, the entire study was considered ungradable, and referral was advised. The percentage of ungradable images for the DigiScope is similar to other reported diabetic retinopathy screening, risk assessment, or surveillance systems, such as the Joslin Vision Network (12%), when using similar stringent definitions of gradable images. This study did not attempt to determine the extent of retinal pathology, if any, in eyes with ungradable images. While some eyes with ungradable images will be found to have no pathology, it is possible that other ocular pathology such as media opacity or poor fixation due to macular disease may lead to some ungradable images for which referral would be appropriate.

The agreement by individual pathology or retinal lesion was substantial to excellent in most cases. For this study, the presence or absence of individual retinal abnormalities was determined for each image, but grading into multiple ETDRS severity levels was not performed because the DigiScope is not designed to be used to diagnose specific levels of diabetic retinopathy beyond

determining need for referral. Comparison between the DigiScope and conventional fundus photography was based on adjudicated gradings within each method. Taken together, this increased the accuracy for each method prior to assessing agreement between modalities. The DigiScope performed exceptionally well for advanced disease, and no high-risk lesions (neovascularization of the disc, preretinal hemorrhage) were missed with DigiScope images. Using a definition of presence of hard exudates in the posterior pole, the DigiScope performed less well when grading for macular edema alone, but all cases in which macular edema was not identified on DigiScope images were classified as referrals due to the presence of other retinopathy. Therefore, using either of the referral levels in this study, all cases with macular edema should be identified correctly as referrals. The DigiScope was particularly effective in detecting early levels of pathology, including MAs and particularly RHs. The increased sensitivity for these lesions may be due to the better contrast provided by the DigiScopes monochromatic red-free light source compared to color photography. Finally, the comparison between DigiScope and conventional fundus photography yields the same Kappa as the intra-reader variability, which suggests that the methodology is no worse than any disagreement within readers.

Our findings are similar to those of other investigators who have evaluated the efficacy of screening protocols based on digital photography.^{7,8} They also found high degrees of sensitivity and specificity and concluded that remote imaging is a valuable tool to identify patients with diabetes needing referral to an eye care specialist. Such remote imaging systems are most often based on existing fundus cameras adapted for digital photography and communication with a reading center. The cost of this equipment, the need for a trained ophthalmic photographer, and reimbursement issues may be barriers to the widespread use of these systems. In contrast, the design of the DigiScope, which can be operated by existing office staff and has a low production cost, may make it better suited for implementation in the primary care setting.

It is encouraging that patients found the DigiScope more acceptable than seven-field photography with a conventional fundus camera. There is no risk to DigiScope imaging other than pupillary dilation, which is currently necessary to meet HEDIS requirements when using imaging to detect diabetic retinopathy. The main potential complication of pupillary dilation is the provocation of acute-angle closure glaucoma. A systematic review of the published literature from 1933 to 1999 revealed no reported cases of acute angle-closure glaucoma following mydriasis with tropicamide alone. The risk with long-acting or combined mydriatic agents is between 1 in 3,380 and 1 in 20,000, and the presence of chronic open-angle glaucoma constitutes no additional risk.⁹ Nevertheless, the personnel in settings where pupillary dilation is being performed need to be well informed about the symptoms of angle-closure glaucoma and the appropriate actions to take should such symptoms develop. In addition to being required by HEDIS, mydriasis increases the proportion of gradable images. Previously reported studies consistently show a higher percentage of ungradable images with nonmydriatic cameras compared to mydriatic cameras^{10,11}. Patients with diabetes may have smaller pupils in ambient light, and older patients have a higher incidence of cataracts and other media opacities, which may affect image quality if the pupils are not pharmacologically dilated.

This image validation study demonstrates that the DigiScope, when used as a remote diabetic retinopathy risk assessment system, has excellent agreement, sensitivity, and specificity compared with the “gold-standard” seven-field color stereo photography for identifying patients with any or low levels of diabetic retinopathy who should be under the care of an ophthalmologist. The DigiScope is not designed as a diabetic retinopathy disease management tool or to replace a comprehensive eye examination. Patients very well accept the DigiScope. The results indicate that the DigiScope may be useful for point-of-care retinal imaging to promote increased access to recommended diabetic eye care in patients with any or mild diabetic retinopathy. Further implementation studies will be performed in the primary care setting to assess outcome measures.

Figure Legends

Figure 1: Examination of an individual with the DigiScope. Note the touch pad screen used by the operator to control the instrument.

Figure 2: Coverage of the DigiScope versus ETDRS standard seven-field protocol. The circles indicate the ETDRS coverage of 96 degrees. The square represents the original DigiScope coverage of 59 degrees (diagonally). The 10 fields of the current DigiScope covering 71 degrees (diagonally) are also shown.

Figure 3: DigiScope image of a diabetic patient with proliferative retinopathy. RH: retinal hemorrhage, MA: microaneurysms, NVE: new vessels elsewhere, SE: soft exudates.

.
.

References

1. Moss SE, Klein R, Klein BE. Factors associated with having eye examinations in persons with diabetes. *Arch. Fam. Med.* 1995;4:529-534.
2. Schoenfeld ER, Greene JM, Wu SY, Leske MC. Patterns of adherence to diabetes vision care guidelines: baseline findings from the Diabetic Retinopathy Awareness Program. *Ophthalmology.* 2001;108:563-571.
3. National Center for Chronic Disease Prevention and Health Promotion of the Centers for Disease Control. The prevention and treatment of complications of diabetes. *A Guide for Primary Care Practitioners.* 1991;1-93.
4. Legorreta AP, Hasan MM, Peters AL, Pelletier KR, Leung KM. An intervention for enhancing compliance with screening recommendations for diabetic retinopathy. A bicoastal experience. *Diabetes Care.* 1997;20:520-523.
5. Zeimer R, Zou S, Meeder T, Quinn K, Vitale S. A fundus camera dedicated to the screening of diabetic retinopathy in the primary-care physician's office. *Invest Ophthalmol. Vis. Sci.* 2002;43:1581-1587.
6. 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.
7. Fransen SR, Leonard-Martin TC, Feuer WJ, Hildebrand PL. Clinical evaluation of patients with diabetic retinopathy: accuracy of the Inoveon diabetic retinopathy-3DT system. *Ophthalmology.* 2002;109:595-601.
8. Cavallerano AA, Cavallerano JD, Katalinic P, et al. Use of Joslin Vision Network digital-video nonmydriatic retinal imaging to assess diabetic retinopathy in a clinical program. *Retina.* 2003;23:215-223.
9. Pandit RJ and Taylor R. Mydriasis and glaucoma: exploding the myth. A systematic review. *Diabet. Med.* 2000;17:693-699.
10. Lim JJ, Labree L, Nichols T, Cardenas I. A comparison of digital nonmydriatic fundus imaging with standard 35-millimeter slides for diabetic retinopathy. *Ophthalmology.* 2000;107:866-870.
11. Klein R, Klein BEK, Neider MW, et al. Diabetic retinopathy as detected using ophthalmoscopy, a nonmydriatic camera and a standard fundus camera. *Ophthalmology.* 1985;92:485-491.