The Retinal Disease Screening Study: Prospective Comparison of Nonmydriatic Fundus Photography and Optical Coherence Tomography for Detection of Retinal Irregularities

Yanling Ouyang,^{1,2,4} Florian M. Heussen,^{1,2,4} Pearse A. Keane,³ Srinivas R. Sadda,¹ and Alexander C. Walsh¹

PURPOSE. To compare the sensitivity of volume scanning with optical coherence tomography (OCT) to nonmydriatic color fundus photography (FP) for the detection of retinal irregularities in asymptomatic populations.

METHODS. Asymptomatic subjects without known ocular disease were recruited over a 6-month period. For each eye, two undilated 45° fundus images and four undilated volume OCT image sets covering the macula and optic nerve were obtained. Color images were evaluated for irregularities both inside and outside the area covered by OCT. OCT image sets were evaluated for internal limiting membrane irregularities, abnormal retinal thickness, hyper/hyporeflective features, and photoreceptor/retinal pigment epithelium (RPE) irregularities. Detection sensitivities were compared and false-negative cases were analyzed.

RESULTS. A total of 284 eyes (144 subjects) were included, with a mean age of 38.1 years (range 18–77). Among 253 eyes (135 subjects) with gradable images from both FP and OCTs, the detection sensitivities for OCT were higher (96.2% infield and 85.7% in full field) than for FP (19.9% infield and 43.8% in full field) for all irregularities evaluated in the study (including epiretinal irregularities, abnormal retinal thickness, intraretinal hyperreflective/hyporeflective features, and photoreceptor/RPE irregularities). Overall, the presence of definite irregularities on either fundus imaging or OCT by eye in this

asymptomatic population was 42.6% (121/284), with 39.4% (112/284) of eyes having RPE irregularities such as drusen.

CONCLUSIONS. For detection of a variety of retinal irregularities evaluated in the current study, volume OCT scanning was more sensitive than nonmydriatic retinal photography in our asymptomatic individuals. OCT detected clinically relevant disease features, such as subretinal fluid, that were missed by FP, and had a lower ungradable image rate. It is likely that OCT will be added to photography screening in the near future for chorioretinal disease. (*Invest Ophthalmol Vis Sci.* 2013; 54:1460–1468) DOI:10.1167/iops.12-10727

Chorioretinal diseases, in particular diabetic retinopathy and age-related macular degeneration (AMD), remain as leading causes of visual loss in the developed world.¹ In many cases, visual loss is preventable if the condition can be identified and treated at an early stage in its progression.² Conversely, delays in diagnosis and treatment are known to adversely affect outcomes; such delays often occur due to the relatively asymptomatic nature of these diseases in their earliest stages.³ Thus, a rationale exists for the provision of chorioretinal disease screening; and screening programs have been established for conditions such as diabetic retinopathy—the national diabetic retinopathy-screening program in the United Kingdom is a prime example.⁴ For other conditions, such as AMD, screening approaches have not yet been initiated, in large part due to the paucity of treatment options and the inability to intervene in early-stage disease progression.⁵ However, with recent rapid progress in potential treatment for early-stage AMD,⁶ as well as advances in telemedicine and health informatics, effective screening methods for this and other chorioretinal diseases will soon be required.

Several potential approaches exist for the screening of chorioretinal disease. These include application of clinical examination techniques performed by trained health care professionals, such as direct ophthalmoscopy or slit-lamp biomicroscopy.^{7–9} Other options include fundus imaging techniques such as color photography and fluorescein angiography.^{10–12} Ultimately, a realistic screening approach depends firstly on the sensitivity and specificity of the chosen method, but then on safety, cost-effectiveness, and logistical considerations. Currently, nonmydriatic color fundus photography (FP) possesses the optimal combination of these factors, in particular for screening of diabetic retinopathy.^{13,14} However, the emergence of a new modality in recent years, optical coherence tomography (OCT),¹⁵ may present an opportunity to increase screening efficacy and to extend screening range.

From the ¹Doheny Eye Institute and Department of Ophthalmology, Keck School of Medicine of the University of Southern California, Los Angeles, California; the ²Department of Ophthalmology, Charité, University Medicine, Berlin, Germany; and the ³NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and the UCL Institute of Ophthalmology, London, United Kingdom.

⁴These authors contributed equally to the work presented here and should therefore be regarded as equivalent authors.

Supported in part by the Deutsche Forschungsgemeinschaft (DFG Grant He 6094/1-1), NIH Grant EY03040, NEI Grant R01 EY014375, Research to Prevent Blindness, and the Department of Health's NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and the UCL Institute of Ophthalmology. The authors alone are responsible for the content and writing of the paper.

Submitted for publication August 7, 2012; revised October 14 and November 19, 2012; accepted December 12, 2012.

Disclosure: **Y. Ouyang**, None; **F.M. Heussen**, None; **P.A. Keane**, None; **S.R. Sadda**, Carl Zeiss Meditec (F), Optos (F), Optovue, Inc. (F), Heidelberg Engineering (C), P; **A.C. Walsh**, Heidelberg Engineering (C), P

Corresponding author: Srinivas R. Sadda, Doheny Eye Institute, 1450 San Pablo Street, Los Angeles, CA 90033; ssadda@doheny.org.

OCT devices provide high-resolution cross-sectional images of the neurosensory retina in a rapid, easy, and noninvasive manner.¹⁶ In 2006, the commercial release of spectral-domain OCT systems permitted, for the first time, dense volume scanning of the macula. As a result of this capability, small retinal lesions are less likely to be missed, and accurate correlation of OCT findings with other fundus images is more easily achieved. Consequently, OCT has emerged as a potential candidate for chorioretinal disease screening, with pilot studies in diseases such as diabetic retinopathy.¹⁷ Recent advances in OCT technology, such as the development of binocular OCT systems, may also be well suited to provision of screening.¹⁸ Furthermore, OCT has recently been incorporated into a number of large population-based epidemiological studies, such as the UK Biobank and European EPIC studies,^{19,20} which involve tens of thousands of participants. A significant need exists, therefore, to determine the sensitivity of OCT for the detection of retinal irregularities in asymptomatic individuals. In the Retinal Disease Screening Study described in this report, we evaluate these parameters and compare them to those obtained with the established screening standard of nonmydriatic FP.

METHODS

Data Collection

In this study, asymptomatic subjects (i.e., family members of patients) were prospectively recruited at a satellite retina subspecialty clinic of the Doheny Eye Institute from June 5, 2009, to December 21, 2009. Written informed consent was obtained from all subjects. Approval for data collection and analysis was obtained from the Institutional Review Board of the University of Southern California. The research adhered to the tenets set forth in the Declaration of Helsinki.

Information about age, sex, ethnicity, history of recent-onset ocular symptoms, ophthalmologic diseases or eye surgeries, and family history of eye diseases was gathered before the ophthalmic examinations. A technician was specifically trained for the purposes of this study to perform undilated FP and OCT imaging of the optic nerve and central retina. For each eye, four raster volume (three-dimensional) OCT (3D-OCT) scans were obtained covering the macula and optic nerve head (OPN) ($1 \times 512 \times 128$ centering at macula only; $1 \times 512 \times 128$ and $1 \times 1024 \times 64$ for macula and temporal side of OPN; and $1 \times 512 \times 128$ centering at OPN only) using the Topcon 3D OCT-1000 (Topcon Co., Tokyo, Japan). This OCT system acquires 18,000 A-scans per second with an axial resolution of 6 μm . Using the 3D-OCT raster scan protocol, the complete data set is acquired in fewer than 3.7 seconds. Additionally, a pair of color images (one centered at OPN and one centered at macula), each with a field of view of 45° , were acquired using the same instrument. To optimize color image quality, these fundus images were acquired at a separate time from when the OCT images were captured. Raw color fundus and OCT data were then exported from the device for review at an image reading center.

Grading Methodology

Two graders (FMH, ACW), certified for assessment of color fundus at the Doheny Image Reading Center (DIRC), evaluated each set of fundus images for each eye independently. In FP, all irregularities were assessed using both macular-centered and OPN-centered images for each eye as a means of optimizing findings. FP-based irregularities included epiretinal membrane (ERM), macular hole (MH), cystoid macular edema (CME), retinal atrophy, hard exudates, hemorrhage, microaneurysms, intraretinal microvascular abnormalities (IRMA), cotton-wool spots, intraretinal pigment migration, subretinal fluid (SRF), macular edema (non-CME), drusen, RPE atrophy, retinal pigment epithelium detachment (PED), and choroidal neovascularization

(CNV)/subretinal fibrosis (SRFibrosis). Since peripapillary chorioretinal atrophy (PPA) and pigmentary changes represent relatively common clinical findings,^{21–23} neither was considered abnormal for the purposes of the current study. The presence/absence of each irregularity was then graded as definitely present (Y), questionably present (Q), absent (N), or cannot grade (CG). In order to compare findings with OCT images, areas of the fundus captured by OCT scans were defined as “infield”; regions not captured by OCT scanning were defined as “outfield.” The entirety of the fundus area captured, irrespective of OCT scanning, was defined as the “full field.”

Two graders (YO, ACW), certified for the assessment of OCT images at the DIRC, evaluated each OCT image set for each eye independently. OCT image sets were assessed using a previously described and validated spectral-domain OCT reading center software program (3D-OCTOR).²⁴ For each eye, all four sets of OCT images were assessed together to optimize detection of irregularities. OCT-based irregularities included internal limiting membrane (ILM) irregularity, increased retinal thickness, decreased retinal thickness, retinal hyperreflective features, retinal hyporefective features, photoreceptor inner segment–outer segment (IS-OS) irregularity, and RPE irregularity. For each case, the irregularity was recorded as Y, Q, N, or CG. As mentioned above, PPA is relatively common and thus was considered a normal finding. Despite this, however, other photoreceptor/RPE irregularities, such as juxtapapillary PED, were defined as abnormal. All findings from OCT image sets were regarded as infield for this study.

Since FP-based irregularities and OCT-based irregularities differ (e.g., intraretinal pigment migration on the FP appears as hyperreflective foci on the OCT), a schema of corresponding findings was developed based on prior reading center experience. Specifically, the consistency or “equivalence” of observed features between color images and OCT was predefined as follows in order to facilitate comparative analyses: ILM irregularity (OCT) was deemed to be consistent with or equivalent to ERM and/or MH (FP); abnormal retinal thickness (OCT) to macular edema and/or retinal atrophy (FP); hyperreflective foci (OCT) to hard exudates, and/or hemorrhage, and/or microaneurysms, and/or IRMA, and/or cotton-wool spots, and/or pigment migration (FP); hyporefective features (OCT) to SRF and/or CME (FP); and photoreceptor/RPE irregularity (OCT) to drusen, and/or RPE atrophy, and/or PED, and/or CNV (FP).

Statistical Analysis

To compare the ability to detect retinal/choroidal irregularities by FP and OCT, two main methods were used based on different ground truth. Firstly, findings from infield fundus images were set as ground truth. Numbers of eyes with irregularities that were missed by OCT were organized by FP-based irregularity categories. In this way, failure of OCT to detect the irregularities that were observed by infield fundus photos was analyzed. Secondly, the ground truth for each case was determined by merging the findings from both methods to generate the maximal possible level of detection for each finding. The sensitivity of each imaging method, for the detection of each irregularity, was then calculated as the proportion of true positives correctly identified as such ($\text{sensitivity} = \text{true positives} / [\text{true positives} + \text{false negatives (FN)}]$). Similarly, the specificity = $\text{true negatives} / (\text{true negatives} + \text{false positives})$. A previously published method using partial credits was chosen to transform data with Q grades.²⁵ For example, in a case in which the ground truth is Y but the grade is Q, a value of 0.5 is added to the true-positive column (implying that the modality is half correct), and a value of 0.5 is added to the false-negative column (implying that the modality is half incorrect). In a case in which the ground truth is Q and the adjudicated grade is N for CME, the modality receives partial credit for a negative answer (true negative = 0.5), since the ground truth grade is uncertain; however, the modality also receives partial credit for a FN, since the ground truth indicates that there is a chance that CME is present. If, in this case, the modality grade is Q (which agrees with the ground truth), the modality is given partial credit both for a true positive and for a true negative, since the two grades show

TABLE 1. Demographic Characteristics in the Study

Women:men	86:57 (59.7%:39.6%)*
Mean age, y (range)	38.1 (18–77)
Right eye:left eye	141:143 (50.4%:49.6%)
Race	
Hispanic or Latino	50%
White (non-Hispanic)	20.8%
Asian	18.1%
Black or African American	4.2%
Others or unknown	6.9%

* Out of 144 subjects included in the study, one was documented with unknown sex.

equal uncertainty regarding the existence of CME. As described above, irregularities assessed as CG in either color fundus or OCT image sets were excluded.

Intergrader reproducibility for each retinal/choroidal irregularity evaluated in the study was calculated by kappa value.

Commercially available software (SPSS, version 13; Statacorp LP, College Station, TX) was used for processing all statistical analysis. All *P* values were two-sided and were considered statistically significant when they were less than 0.05.

RESULTS

Characteristics of the Study Population

A total of 158 subjects were enrolled in this study. Twenty-eight eyes, from 16 subjects, failed to complete OCT and/or color fundus photographic examinations. Two subjects reported eye problems of recent onset and were then excluded. As a result, 284 eyes, from 144 subjects, met the inclusion criteria for the study. Demographic characteristics are shown in Table 1.

All OCT images included in the study met reading center criteria for sufficient image quality, with the exception of four OCT image sets. For FP, 10.6% (30/284) of macula-centered images and 3.2% (9/284) of OPN-centered images lacked sufficient image quality. As a result, 6.9% of fundus images included in the study were ungradable, and 57.9% had some type of image artifact, compared to 0.4% of the OCT images included. In total, 253 eyes (135 subjects) with gradable images from both FP and OCTs covering the fields of both macula and OPN were included in the sensitivity and specificity analyses.

Detection of Irregularities in Eyes with Gradable OCT and FP Images

Grading results for each retinal irregularity assessed in the study are summarized in Table 2.

Detection of Irregularities by OCT with Use of Infield Findings Observed by FP as Ground Truth. As shown in Table 3, a total of 25.5 retinal/choroidal irregularities were observed by infield FP in our asymptomatic subjects. With use

of these findings as ground truth, OCT failed to detect 1 eye with questionable ERM, 1 eye with questionable intraretinal hemorrhage (Fig. 1F), 1 eye with questionable abnormal vasculatures (Fig. 1E), 16 eyes with definite drusen (small hard drusen) (Figs. 3D1, 3D2), 1 eye with questionable PED, 1 eye with definite RPE atrophy, and 1 eye with questionable RPE atrophy (Fig. 3D3).

Sensitivities of OCT and FP with Use of Maximum Findings as Ground Truth. Sensitivities of FP and OCT with use of findings from both FP and OCT as ground truth are reported in Table 4.

Irregularities of the ILM were found infield in 4.8% of eyes (Y for 2.8%, or 7/253; Q for 2.0%, or 5/253) and outfield in an additional 0.4% of eyes (Q for 1 eye). The sensitivity for FP was 31.6% infield and 40.0% in full field. All FN cases were graded as ERM (Y for 4 eyes and Q for 5 eyes) by OCT. In contrast, the sensitivity for OCT examination was two to three times higher (94.7% infield, 90.0% in full field) than for FP, with a total number of FN of 0.5 infield and 1.0 in full field. For the single infield FN case for OCT, an ERM was graded as Q due to the suspicion of abnormal traction on retinal vessels as seen on fundus photographic images, while no abnormal membrane was seen on OCT. The additional outfield FN case was graded as a questionable ERM.

Abnormal retinal thickness was found infield in 2.0% of eyes (Y for 1.2%, or 3/253; Q for 0.8%, or 2/253) and none in outfield. The sensitivity for FP was 12.5% for both infield and full field, with 3.5 FNs. Each of these FN cases was graded as retinal edema (Y for 3 eyes and Q for 1 eye) on OCT. In turn, OCT managed to detect 100% of all eyes with abnormal retinal thicknesses.

Intraretinal hyperreflective features, including intraretinal hyperreflective foci seen by OCT and exudates, cotton-wool spots, aneurysms, hemorrhage, and pigment migration seen by FP, were also studied. These features were detected infield in 22.2% of eyes and were observed in 48.1% of the eyes in full field. On fundus images in all the study eyes, no cotton-wool spots, or aneurysms were observed. However, infield hemorrhage (one case for Q), exudates (one case for Y), abnormal vessels (one case for Q), and outfield pigment (Y for 3 and Q for 3 eyes), were detected. With OCT, an additional 10 (Y for 4 and Q for 6) eyes with hyperreflective foci were identified. Among these, 3 eyes (1 graded as Y, 2 as Q) had hyperreflective foci in the outer nuclear layer in several adjacent OCT B-scans, while 7 eyes (3 graded as Y, 4 as Q) had foci in the inner retina on OCT. Hyperreflective foci in the outer nuclear layer on OCT were likely to represent pigment migration; in the inner retina, with evidence of retina edema or cystoid changes in the same or adjacent OCT B-scans, they were likely to represent exudates. However, since this interpretation is hypothetical without histopathological confirmation, instead of the terms “pigment migration” or “exudates”, the terms “questionable pigment migration” or “questionable exudates” were used in this study. The sensitivity of OCT was 88.9% infield and 59.3% in full field. The FN cases infield are shown in Figure 1E (Q for

TABLE 2. Original Grading Results for Retinal/Choroidal Irregularities Observed by Nonmydriatic FP and 3D-OCT

	Epiretinal Irregularities, <i>n</i> (%)			Retinal/Subretinal Irregularities, <i>n</i> (%)			RPE/Choroidal Irregularities, <i>n</i> (%)		
	FPI	FPP	OCT	FPI	FPP	OCT	FPI	FPP	OCT
Y	2 (0.8%)	3 (1.2%)	7 (2.8%)	1 (0.4%)	4 (1.6%)	19 (7.5%)	12 (4.7%)	30 (11.9%)	89 (35.2%)
Q	2 (0.8%)	2 (0.8%)	4 (1.6%)	2 (0.8%)	5 (2.0%)	7 (2.8%)	14 (5.5%)	40 (15.8%)	33 (13.0%)
N	249 (98.4%)	248 (98.0%)	242 (95.7%)	250 (98.8%)	244 (96.4%)	227 (89.7%)	227 (89.7%)	183 (72.3 %)	131 (51.8%)
Total	253	253	253	253	253	253	253	253	253

FPI, FP infield; FPP, FP in full field.

TABLE 3. Grading Results for Infield Retinal Irregularities Seen by Nonmydriatic FP but Missed by 3D-OCT

Abnormal Findings	Eyes with Irregularities Seen by Infield FP		Eyes with Irregularities Missed by 3D-OCT
	<i>n</i> (Y/Q)	Total <i>n</i> (<i>n</i> = Y + Q/2)	Total <i>n</i>
Epiretinal irregularities			
ERM	2/2	3	0.5
Macular hole	0/1	0.5	0
Retinal/Subretinal irregularities			
Macular edema (non-CME)	0/1	0.5	0
Exudate	1/0	1	0
Hemorrhage	0/1	0.5	0.5
Aneurysms	0/0	0	0
Abnormal vasculatures	0/1	0.5	0.5
Cotton-wool spot(s)	0/0	0	0
SRF/CME	0/0	0	0
Pigment migration	0/0	0	0
RPE/Choroidal irregularities			
Drusen	11/12	17	16
CNV/SRFibrosis/PED	0/1	0.5	0.5
RPE atrophy	1/2	2	1.5

FIGURE 1. Examples of false-negative cases for hyperreflective foci on nonmydriatic FP and 3D-OCT. (A-C) Color images graded as absent for pigmentary changes in the macula and OCT B-scans with definite/questionable hyperreflective foci (*circle*) in the outer nuclear layer in the same eye. (D) Color images graded as absent for exudates and OCT B-scans showed questionable hyperreflective foci (*circle*) in the inner retina in the same eye. (E) Color images of one eye graded as questionable abnormal retinal vessels (*arrows*). (F) Color image of one eye graded as questionable intraretinal hemorrhage (*circle*) and B-scan without visible chorioretinal changes in the corresponding area (*circle*).

FIGURE 2. Examples of false-negative cases for hyporeflective features for nonmydriatic FP and 3D-OCT. (A) Color image graded as present for ERM but absent for CME. OCT B-scan showed ERM (*small arrows*) and CME (*big arrow*). False negative for FP was calculated as 1.0 for hyporeflective features. (B) Color image graded as absent for CME and OCT B-scan with intraretinal hyporeflective feature (*arrow*) and adjacent questionable hyperreflective foci (*circle*). (C) Color image graded as absent for SRF and photoreceptor/RPE irregularities and OCT B-scan with photoreceptor/RPE irregularities and hyporeflective features (*arrow*). (D) Color image graded as absent for SRF and OCT B-scan with SRF (*arrow*).

abnormal vessel by FP) and Figure 1F (Q for hemorrhage by FP).

For intraretinal hyporeflective features, detection sensitivities were 100% for OCT and 0% for color fundus images, both infield and in full field. A total of 7 (1 Y for SRF; 3 Y and 3 Q for CME) eyes with SRF or CME were missed on FP (Fig. 2).

Photoreceptor/RPE irregularities were detected in full field FP in a total of 27.7% of eyes (70/253, Y for 30 eyes and Q for 40 eyes). Within this category, 15.4% of study eyes (Y for 4.0% or 10/253, Q for 11.5% or 29/253) had small hard drusen graded as outfield. As a result, the detection sensitivities for FP were 17.4% infield and 40.3% in full field, and for OCT were 96.3% infield and 85.1% in full field. The sensitivity of OCT was statistically higher than that of color fundus images either infield or in full field ($P < 0.05$). FN cases for OCT infield are illustrated in Figure 3. Seven (Y for 3 and Q for 4) eyes were graded as drusen by color images, with a single additional eye graded as questionable atrophy. For FN cases missed by color photography, no visible choroidal/RPE atrophy was found except for the peripapillary region, which was not considered abnormal as discussed previously. As a result, these FN cases were all assessed as drusen or PED. For the same reason as discussed above for the hyperreflective foci, the term “questionable drusen/PED” was used to categorize these findings observed by OCT.

Overall, as shown in Table 4, when considering both definite and questionable grades, the detection sensitivities for OCT were higher (96.2% infield and 85.7% in full field) than for FP (19.9% infield and 43.8% in full field) for irregularities evaluated in the study. For each type of feature, the sensitivities of OCT were greater than those of nonmydriatic FP. With regard to overall detection of retinal irregularities, at least one form of irregularity was detected in 32.0% of eyes (81/253) from 44.4% of subjects (60/135) by color fundus imaging and in 52.6% of eyes (133/253) from 68.9% of subjects (93/135) by OCT. When the two techniques were combined, 54.9% of all

eligible eyes (139/253) from 71.1% of participants (96/135) were shown to have retinal irregularities. When considering only definite grades (i.e., excluding questionable findings), the presence of any irregularity by eye, on either fundus imaging or OCT, was 41.5% (105/253).

Detection of Irregularities by OCT in Eyes with Ungradable FP

For 31 eyes from 23 subjects with ungradable FP, OCT imaging identified an additional 5 (Y for 4 and Q for 1) eyes with ILM irregularities, 2 (Y for 1 and Q for 1) eyes with intraretinal hyperreflective foci, and 3 (Y for 2 and Q for 1) eyes with intraretinal hyporeflective features. Photoreceptor/RPE irregularities were found in 18 (Y for 13 and Q for 5) eyes. In total, 21 (Y for 16 and Q for 5) of these 31 eyes with ungradable FP had at least one type of irregularity evident on OCT imaging. Overall, the presence of definite irregularities on either fundus imaging or OCT (i.e., in full field) by eye in this asymptomatic population was 42.6% (121/284), with 39.4% (112/284) of eyes having photoreceptor/RPE irregularities such as drusen.

Intergrader Reproducibilities for Retinal/Choroidal Irregularities

Almost perfect agreement indicated by kappa values²⁶ was achieved for intergrader reliabilities on most OCT-based parameters (ILM irregularity: 0.973; increased retinal thickness: 1.000; decreased retinal thickness: 1.000; retinal hyperreflective foci: 0.856; IS-OS irregularity: 0.894; RPE irregularity: 0.952), with the exception of the retinal hyporeflective features (kappa = 0.396). For FP-based irregularities, intergrader reproducibility was also between substantial agreement (hemorrhage: 0.666) and almost perfect agreement (hard exudates: 1.000).

FIGURE 3. Examples of false-negative cases for photoreceptor/RPE irregularities for nonmydriatic FP and 3D-OCT. (A1–A3) Color image graded as absent for retinal PED and OCT B-scan with PED. (B1–B3) Color image graded as absent for drusen or PED and OCT B-scan with definite photoreceptor/RPE irregularities in the macula but absent in the peripapillary region. (C1–C3) Color image graded as absent for PED and OCT B-scan with definite PED in the peripapillary region and absent photoreceptor/RPE irregularities in the macula. (D1, D2) Color images graded with definite and questionable small drusen without visible photoreceptor/RPE irregularities detected by OCT. (D3) Color image graded as questionable atrophy and OCT B-scan without visible photoreceptor/RPE irregularities detected by OCT.

DISCUSSION

For detection of a variety of retinal irregularities evaluated in the current study, the sensitivity of volume OCT scanning was found to be higher than that of nonmydriatic FP of the posterior pole for our asymptomatic subjects, although OCT failed to detect small hard drusen, intraretinal hemorrhage, or abnormal retinal vessels in some cases. Even when areas not covered by OCT were included, FP still detected fewer irregularities than OCT. Furthermore, the percentage of ungradable image sets was much lower with OCT. Finally,

potentially clinically relevant disease features, such as SRF, CME, and PED, were detected in this study with a much higher frequency than was anticipated for an asymptomatic population.

Screening methods for chorioretinal diseases, such as clinical examination and FP, all possess important shortcomings. Photographic screening has been widely advocated, with a detection sensitivity for diabetic retinopathy twice as high through a dilated pupil than for an undilated pupil.²⁵ However, concern about the risk of precipitating acute glaucoma and the associated waiting time for dilatation are important potential

TABLE 4. Comparison of Sensitivities of Nonmydriatic FP to 3D-OCT with Use of Findings from Both FP and OCT as Ground Truth

	FP				3D-OCT			
	Ground Truth		Sensitivities		Eyes with Irregularities Missed by FP		Eyes with Irregularities Missed by 3D-OCT	
	Infield <i>n</i> (Y/Q)	Full Field <i>n</i> (Y/Q)	Infield Field	Full Field	Infield <i>n</i> (Y/Q)	Full Field	Infield <i>n</i> (Y/Q)	Full Field <i>n</i> (Y/Q)
ILM irregularity	7/5	7/6	31.6%	40.0%	4/5	ERM	0/1	0/2
Abnormal thickness	3/2	3/2	12.5%	12.5%	3/1	Retinal edema	-	-
Hyperreflective foci	5/8	8/11	22.2%	48.1%	4/6	Pigment/exudates?	0/2	3/5
Hyporefective features	4/3	4/3	0%	0%	4/3	SRF/CME	-	-
Photoreceptor/RPE irregularity	92/35	99/50	17.4%	40.3%	33/11	Drusen?/PED?	3/5	11/30
Total	111/53	121/72	19.9%	43.8%	48/26		3/8	14/37

* Represents that the sensitivity of OCT is statistically higher than that of FP ($P < 0.05$).

limitations of this approach.²⁷ As a result, nonmydriatic photographic screening has been advocated for in many previous reports.^{28–30} A recent study suggested that, in the setting of a large elderly cohort, nondilated 45° digital retinal imaging was an excellent method for fundus examination with the advantages of being fast, noninvasive, and reliable in the detection of AMD.²⁷ However, previous studies have reported disappointing results for the nonmydriatic detection of sight-threatening disease, with detection sensitivities ranging from 41% to 67%.³¹

With the advent of OCT imaging, high-quality cross-sectional images of the neurosensory retina can be acquired without pupil dilatation in a matter of seconds. As a result, volume scanning with OCT has potential as a method for screening for chorioretinal disease. In our study, a much higher sensitivity of OCT for detection of a variety of retinal irregularities was found in comparison with nonmydriatic photography. This finding was consistent for each individual retinal abnormal feature studied.

Volume scanning with OCT failed to detect small hard drusen, chorioretinal atrophy/depigmentation, hemorrhage, abnormal retinal vessels, and ERM in some cases. Of note, the single case with ERM noted by FP that OCT failed to identify may actually be a false positive. In this case, ERM was graded as Q on FP due to the suspicion of traction on a focal area of the retinal vasculature. In addition, failure to detect an area of abnormal retinal vasculature by OCT was perhaps unsurprising given the limitations of current technology; in the near future, advances in OCT technology are likely to address this shortcoming by allowing enhanced vascular mapping and quantification of retinal blood flow.³²

With respect to the failure of OCT to detect some areas of chorioretinal depigmentation, a threshold of depigmentation and atrophy may be required before there is sufficient transmission of light to the underlying choroid to be evident on OCT.

The main retinal irregularity that OCT scanning failed to detect, however, was small, hard drusen—a common finding in healthy young and middle-aged subjects, with some studies reporting a prevalence as high as 95.5%.^{33,34} Of note, although we used a combined ground truth of FP and OCT, the prevalence of photoreceptor/RPE irregularities (such as drusen) found in our study was only 39.4% by eye, a figure far lower than that reported in previous studies.³⁴ Since the volume scanning protocol we used for OCT image acquisition was 512 A-scans $\times$ 128 B-scans over an area of 6 $\times$ 6 mm, the distance between adjacent B-scans was 47.2 μ m. As a result, irregularity smaller than this will commonly be missed. Furthermore, our study used nonmydriatic two-field FP, so it is perhaps understandable that a lower prevalence of small hard drusen was seen than in studies employing seven-field stereoscopic photographs. However, as small hard drusen are common and not considered visually significant, this failing may not be serious for screening purposes.

In a single eye, an area of intraretinal hemorrhage was detected on nonmydriatic FP, but not on OCT. Since hemorrhage is an important finding in eyes with diabetic retinopathy, inability to detect hemorrhage may be a major limitation for OCT in the screening of diabetic retinopathy and other chorioretinal diseases. However, as there was only a single case in the current study, it remains unclear whether this result will be applicable in a broader context. Future studies are suggested to further validate OCT as a screening tool for diabetic retinopathy or other retinal vascular diseases.

In contrast to OCT, nonmydriatic FP failed to detect SRF and CME in all positive cases; all of these are potentially vision-threatening irregularities that may require early ophthalmic referral and treatment. Nonmydriatic fundus images also failed

to detect instances of ERM and abnormal retinal thickness, which may both be signs of chronic ocular disease. In addition, FP failed to detect many cases of intraretinal pigment migration and exudates, which are potentially early signs of AMD or diabetic retinopathy. The majority of FN cases for FP, however, were with respect to photoreceptor/RPE irregularities. In particular, FP was relatively insensitive for the detection of PED, a major finding of intermediate and advanced stages of AMD. In some of these cases, the PED may contain a fibrovascular component warranting urgent referral and treatment. Recent advances in OCT software algorithms may allow identification and referral of patients with high-risk features.³⁵ As a result, even with current commercial OCT platforms, volume scanning with OCT may be already applicable to AMD screening.

In this study, we used a nonmydriatic fundus methodology applied by the European Community-funded Concerted Action Programme into the epidemiology and prevention of diabetes (EURODIAB), in which two 45° photographs were taken as grading standards for the assessment of diabetic retinopathy.¹² Accordingly, four sets of OCT images in the region between macula and optic nerve were obtained in our study. This approach was chosen to increase the likelihood of detection of small lesions. All the images can be taken by a technician and sent to the tertiary referral center for grading, which is a cost-effective approach for screening purposes.³¹ In our study, the technician was newly trained and was able to obtain sufficient OCT images in nearly all cases; this was not the case for the nonmydriatic FP. Significantly, volume scanning with OCT led to detection of retinal irregularities in many of the eyes in which FP images were ungradable.

Our study has a number of limitations. We used the findings from color images or the combined findings from the color fundus images and the OCT as the reference standard (i.e., a final, “true” clinical diagnosis was not made). In addition, our method for calculating sensitivities—in particular the use of partial credit for questionable grades—means that our results are not directly comparable to those of many previous screening studies. Moreover, we did not specifically document the reason for unobtainable images from 28 eyes of our study population. Finally, we used Topcon 3D OCT-1000 for the purposes of this study. Recently, this device has been supplanted by the introduction of Topcon 3D OCT-2000. This newer model incorporates a digital fundus camera with considerably higher resolution (12.3 megapixels versus 3.15 megapixels) and thus could potentially provide increased detection sensitivity for a variety of retinal irregularities.

In conclusion, the results of our study suggest that, for detection of a variety of retinal irregularities evaluated in the current study, volume OCT scanning was more sensitive than nonmydriatic retinal photography in our asymptomatic individuals. OCT detected clinically relevant disease features that were missed by FP, and had a lower ungradable image rate. It is likely that OCT will be added to photographic screening in the near future for chorioretinal disease. The potential for OCT as a screening tool for chorioretinal disease warrants further study.

References

- Klein R, Klein BE, Moss SE. Visual impairment in diabetes. *Ophthalmology*. 1984;91:1-9.
- Bailey CC, Sparrow JM, Grey RH, Cheng H. The National Diabetic Retinopathy Laser Treatment Audit. III. Clinical outcomes. *Eye (Lond)*. 1999;13(pt 2):151-159.
- Lim JH, Wickremasinghe SS, Xie J, et al. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. *Am J Ophthalmol*. 2012;153:678-686.
- NHS Diabetic Eye Screening Programme. Available at: <http://diabeticeye.screening.nhs.uk>. Accessed March 20, 2012.
- Jain S, Hamada S, Membrey WL, Chong V. Screening for age-related macular degeneration using nonstereo digital fundus photographs. *Eye (Lond)*. 2006;20:471-475.
- Zarbin MA, Rosenfeld PJ. Pathway-based therapies for age-related macular degeneration: an integrated survey of emerging treatment alternatives. *Retina*. 2010;30:1350-1367.
- Eggertsen R, Kalm H, Blohmé G. The value of screening for retinopathy and microalbuminuria in patients with type 2 diabetes in primary health care. *Scand J Prim Health Care*. 1993;11:135-140.
- Wang F, Tielsch JM, Ford DE, Quigley HA, Whelton PK. Evaluation of screening schemes for eye disease in a primary care setting. *Ophthalmic Epidemiol*. 1998;5:69-82.
- Nathan DM, Fogel HA, Godine JE, et al. Role of diabetologist in evaluating diabetic retinopathy. *Diabetes Care*. 1991;14:26-33.
- Friberg TR, Rehkopf PG, Warnicki JW, Eller AW. Use of directly acquired digital fundus and fluorescein angiographic images in the diagnosis of retinal disease. *Retina*. 1987;7:246-251.
- Razvi FM, Kritzing EE, Tsaloumas MD, Ryder RE. Use of oral fluorescein angiography in the diagnosis of macular oedema within a diabetic retinopathy screening programme. *Diabet Med*. 2001;18:1003-1006.
- Aldington SJ, Kohner EM, Meuer S, Klein R, Sjølie AK. Methodology for retinal photography and assessment of diabetic retinopathy: the EURODIAB IDDM complications study. *Diabetologia*. 1995;38:437-444.
- Beynat J, Charles A, Astruc K, et al. Screening for diabetic retinopathy in a rural French population with a mobile nonmydriatic camera. *Diabetes Metab*. 2009;35:49-56.
- Minuto N, Emmanuele V, Vannati M, et al. Retinopathy screening in patients with type 1 diabetes diagnosed in young age using a nonmydriatic digital stereoscopic retinal imaging. *J Endocrinol Invest*. 2012;35:389-394.
- Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254:1178-1181.
- Keane PA, Sadda SR. Imaging chorioretinal vascular disease. *Eye (Lond)*. 2010;24:422-427.
- Mackenzie S, Schmermer C, Charnley A, et al. SDOCT imaging to identify macular pathology in patients diagnosed with diabetic maculopathy by a digital photographic retinal screening programme. *PloS One*. 2011;6:e14811.
- Walsh AC. Binocular optical coherence tomography. *Ophthalmic Surg Lasers Imaging*. 2011;42:S95-S105.
- UK Biobank. Available at: <http://www.ukbiobank.ac.uk/>. Accessed March 20, 2012.
- EPIC Project. Available at: <http://epic.iarc.fr/>. Accessed March 20, 2012.
- Wang Y, Xu L, Zhang L, Yang H, Ma Y, Jonas JB. Peripapillary atrophy in elderly Chinese in rural and urban Beijing. *Eye (Lond)*. 2008;22:261-266.
- Healey PR, Mitchell P, Gilbert CE, et al. The inheritance of peripapillary atrophy. *Invest Ophthalmol Vis Sci*. 2007;48:2529-2534.
- Curcio CA, Saunders PL, Younger PW, Malek G. Peripapillary chorioretinal atrophy: Bruch's membrane changes and photoreceptor loss. *Ophthalmology*. 2000;107:334-343.
- Ouyang Y, Heussen FM, Mokwa N, et al. Spatial distribution of posterior pole choroidal thickness by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2011;52:7019-7026.
- Ouyang Y, Keane PA, Sadda SR, Walsh AC. Detection of cystoid macular edema with three-dimensional optical coherence tomography versus fluorescein angiography. *Invest Ophthalmol Vis Sci*. 2010;51:5213-5218.

26. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33:159-174.
27. Hancox J, Murdoch I, Parmar D. Changes in intraocular pressure following diagnostic mydriasis with cyclopentolate 1%. *Eye (Lond)*. 2002;16:562-566.
28. Aung KZ, Robman L, Chong EWT, English DR, Giles GG, Guymer RH. Non-mydratic digital macular photography: how good is the second eye photograph? *Ophthalmic Epidemiol*. 2009;16:254-261.
29. Vleming EN, Castro M, López-Molina MI, Teus MA. Use of non-mydratic retinography to determine the prevalence of diabetic retinopathy in diabetic patients [in Spanish]. *Arch Soc Esp Ophthalmol*. 2009;84:231-236.
30. Delcourt C, Massin P, Rosilio M. Epidemiology of diabetic retinopathy: expected vs reported prevalence of cases in the French population. *Diabetes Metab*. 2009;35:431-438.
31. Buxton MJ, Sculpher MJ, Ferguson BA, et al. Screening for treatable diabetic retinopathy: a comparison of different methods. *Diabet Med*. 1991;8:371-377.
32. Fingler J, Zawadzki RJ, Werner JS, Schwartz D, Fraser SE. Volumetric microvascular imaging of human retina using optical coherence tomography with a novel motion contrast technique. *Opt Exp*. 2009;17:22190-22200.
33. Munch IC, Sander B, Kessel L, et al. Heredity of small hard drusen in twins aged 20-46 years. *Invest Ophthalmol Vis Sci*. 2007;48:833-838.
34. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology*. 1992;99:933-943.
35. Lee SY, Stetson PF, Ruiz-Garcia H, Heussen FM, Sadda SR. Automated characterization of pigment epithelial detachment by optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53:164-170.