Screening for Diabetic Retinopathy: 1 and 3 Nonmydriatic 45-degree Digital Fundus Photographs vs 7 Standard Early Treatment Diabetic Retinopathy Study Fields

STELA VUJOSEVIC, ELISA BENETTI, FRANCESCA MASSIGNAN, ELISABETTA PILOTTO, MONICA VARANO, FABIANO CAVARZERAN, ANGELO AVOGARO, AND EDOARDO MIDENA

• PURPOSE: To evaluate if simple- or multiple-field digital color nonmydriatic (NM) retinal images can replace 7 standard stereoscopic fundus photographs in the screening of diabetic retinopathy (DR).

• DESIGN: Prospective, masked, comparative case series.

• METHODS: One hundred and eight eyes of 55 diabetics were studied to determine single lesions and to grade clinical levels of DR and diabetic macular edema (DME) using both 1 and 3 NM digital color retinal images compared with the Early Treatment Diabetic Retinopathy Study (ETDRS) 7 standard 35-mm stereoscopic color fundus photographs (7F-ETDRS). All eyes underwent NM 45-degree field images of 1 central field (1F-NM), NM 45-degree field images of 3 fields (3F-NM), and, after pupil dilatation, 30-degree 7F-ETDRS photography. Images were analyzed by 2 independent, masked retinal specialists (S.V. and E.B.), lesion-by-lesion according to the ETDRS protocol and for clinical severity level of DR and DME according to the international classification of DR.

• RESULTS: Using 7F-ETDRS as the gold standard, agreement was substantial for grading clinical levels of DR and DME ($\kappa = 0.69$ and $\kappa = 0.75$) vs 3F-NM; moderate for DR level ($\kappa = 0.56$) and substantial for DME ($\kappa = 0.66$) vs 1F-NM; almost perfect for detecting presence or absence of DR ($\kappa = 0.88$) vs both 1F-NM and 3F-NM; and almost perfect for presence or absence of DME ($\kappa = 0.97$) vs 3F-NM and substantial ($\kappa = 0.75$) vs 1F-NM. Sensitivity and specificity for detecting referable levels of DR were 82% and 92%, respectively, for 3F-NM and 71% and 96%, respectively, for 1F-NM.

• CONCLUSIONS: Three color 45-degree NM fundus fields may be an effective tool in a screening setting to determine critical levels of DR and DME for prompt specialist referral. One central 45-degree image is sufficient to determine absence or presence of DR and DME, but not for grading it. (Am J Ophthalmol 2009;148: 111–118. © 2009 by Elsevier Inc. All rights reserved.)

DIABETIC RETINOPATHY (DR) IS ONE OF THE LEADING causes of adult blindness in industrialized and some developing countries, despite the availability of different treatments that at least postpone diabetes-related visual loss.[1–3] This is mainly because DR is diagnosed and treated too late, when visually threatening conditions already have developed. In the effort to detect DR early, before visual loss, the American Diabetes Association and the American Academy of Ophthalmology formulated guidelines for DR screening, recommending annual fundus examination for all diabetic patients.[4,5] But less than half of the patients with diabetes mellitus (DM) receive recommended screening because of different socioeconomic, geographic, and cultural factors.[6,7] Thus, there is a clear and growing need for innovative population-based strategies for easy DR detection. One of the major problems is related to the technique or technology used to screen DR. Ophthalmoscopy has major limitations: low sensitivity (below critical value) even when performed by ophthalmologists, it must be a mydriatic procedure and is a subjective procedure, and it does not allow for final documentation.[8] Stereoscopic, mydriatic (7 fields) 30-degree retinal photography (the gold standard in clinical trials) is time consuming and expensive and currently may be considered just the standard for comparing any newly developed technique.[9,10]

The introduction and improvement of nonmydriatic (NM) fundus examination has overcome the inconvenience and risks of mydriasis, with good technical results.[8,11–13] Unfortunately, there is no agreement about the number of NM fields to detect and grade DR reliably, and this represents a current limitation to the widespread, standardized application of this technology.

The aim of this study was to evaluate whether NM 45-degree field images of 3 fields (3F-NM), of 1 field (1F-NM), or both may be used reliably for DR grading and screening when compared with Early Treatment Diabetic Retinopathy Study (ETDRS) 7 standard-field 35-mm

Accepted for publication Feb 10, 2009.

From the Fondazione G.B. Bietti per l'Oftalmologia, IRCCS (Istituto di Ricovero e Cura a Carattere Scientificio), Roma, Italy (S.V., M.V., E.M.); the Department of Ophthalmology, University of Padova (E.B., F.M., E.P., F.C., E.M.); and the Division of Metabolic Diseases, University of Padova (A.A.), Padova, Italy.

Inquiries to Edoardo Midena, Department of Ophthalmology, University of Padova, Via Giustiniani 2, Padova, Italy; e-mail: edoardo.midena@unipd.it

0002-9394/09/$36.00
doi:10.1016/j.ajo.2009.02.031

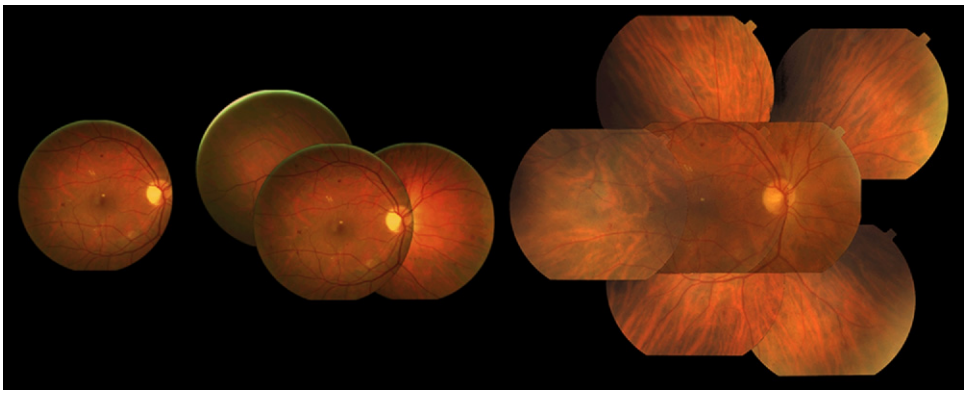

FIGURE. (Left) One and (Middle) 3 nonmydriatic 45-degree color fundus fields and (Right) 7 mydriatic Early Treatment Diabetic Retinopathy Study 30-degree color fundus fields of the same patient with moderate nonproliferative diabetic retinopathy (DR) and moderate diabetic macular edema (DME) according to the International Clinical DR and DME Disease Severity Scales.

stereoscopic 30-degree color fundus photography (7F-ETDRS).

METHODS

IN THIS SINGLE-CENTER, MASKED, COMPARATIVE STUDY, patients were recruited from the Diabetes Clinic at the Division of Metabolic Diseases from University of Padova. One hundred and eight eligible eyes of 55 consecutive patients with DM (type 1 and 2) who were referred for a regular fundus screening examination at the Diabetes Clinic and who agreed to participate were enrolled in this study. Exclusion criteria were: age less than 18 years, media opacities precluding fundus examination, and eyes that had undergone previous panretinal laser photocoagulation. Informed consent was obtained from all subjects after explanation of the purpose of this study.

Three NM 45-degree fundus photographs were obtained from all patients by a trained nurse with an NM retinography device (Nidek, Gamagori, Japan) characterized by image resolution of 1392 × 1040 pixels. Photographs were obtained in an standardized fashion and consisted of: field 1 (central), centered on the macula; field 2 (nasal), centered on the nasal margin of the optic disc; field 3 (temporal), centered superiorly and temporally from the macula, recalling field 3 of the Joslin Vision Network.[11] Thereafter, with adequate pupil dilation, patients underwent 7 stereoscopic 30-degree fundus photography according to the ETDRS protocol using a Topcon TRC 50IA fundus camera (Topcon, Tokyo, Japan) on Kodachrome slide (Kodak Professional Ektachrome E100G; Kodak Spa, Milano, Italy) transparency film by a certified photographer.[14]

• **IMAGE FORMAT, LABELING, AND GRADING:** Each included eye had 3 subsets of fundus color photographs: 1 NM digital 45-degree central field (1F-NM), 3 NM digital 45-degree fields (3F-NM), and 7 mydriatic film-based 30-degree stereoscopic fields (7F-ETDRS; Figure). Each fundus subset of images was assigned randomly a different number in a masked fashion with respect to the graders. Digital images were saved in JPEG format on hard disc and their grading was performed on a 17-inch monitor with standardized contrast and brightness. Color stereoscopic 30-degree fundus slides were mounted in transparent slide holders in stereo pairs, and the grading was performed using a Donaldson stereoscopic viewer. All images were graded independently in a masked fashion by 2 retinal specialists (S.V. and E.B.) trained in grading. In case of disagreement, adjudication was given by third party.

• **DETAILED GRADING SCHEME:** Stereoscopic 30-degree fundus color photographs were graded lesion by lesion according to the ETDRS protocol.[14] The following lesions were graded: microaneurysms (Micro); hemorrhages, microaneurysms, or both (HE + Micro); hard exudate (Ex); cotton wool spots (CWS); intraretinal microvascular abnormalities (IRMA); venous beading (VB); venous narrowing (VN); venous loops, reduplication, or both (VL); new vessels elsewhere (NVE); preretinal hemorrhage (PHE); vitreous hemorrhage (VH); retinal detachment (RD); new vessels on the disc (NVD); papillary swelling (PS); hard exudate rings (Ex-ring); macular thickening size (< 1 disc diameter [DD]; MTS); macular thickness (< 1 DD; MT); hard exudates within 1 DD of the center of the macula (Ex < 1 DD); hard exudates at the center of the macula (ExC); cystoid spaces (CME); clinically significant macular edema (CSME); new vessels or fibrous proliferations on or within 1 DD of the disc (NV < 1 DD); new vessels or fibrous proliferations in the center (NVC); epiretinal membrane (ERM); retinal hemorrhages in the center (RHEC); preretinal hemorrhages in the center (PHEC); and plaque hard exudates (Ex-plaque). Each lesion was assigned a number according to its presence or absence (0, lesion absent; 1, presence questionable) and gravity of the lesion (2 to 5). Number 8 meant that image was not gradable. CSME was graded as: 0, absent; 1,

TABLE 1. Intragrader and Intergrader Lesion-by-Lesion Grading According to the Early Treatment Diabetic Retinopathy Study Protocol on Seven Mydriatic Stereoscopic 30-Degree Fundus Photographs, Three Nonmydriatic Fundus Photographs, and One Nonmydriatic Central Fundus Photograph for Diabetic Retinopathy Screening

	Intragrader Agreement			Intergrader Agreement		
	7F-ETDRS	3F-NM	1F-NM	7F-ETDRS	3F-NM	1F-NM
Perfect ($\kappa = 1$)	PHE, VHE, NVD, PS, Ex-center, NV < 1 DD, ERM, PHEC	Ex, PHE, VN, VHE, RD, PS, MT, CME, NV < 1 DD, NVC, ERM, RHEC, PRHEC, Ex-plaque	PHE, VHE, RD, PS, NV < 1 DD, ERM, PRHEC, VN, NVE, NVD, NVC	VHE, RD, PS, CME, NV < 1 DD, NVC, PHEC	VN, PHE, VHE, RD, PS, CME, NV < 1 DD, PHEC	VN, VHE, RD, PS, MT, CME, NV < 1 DD, NVC, PHEC
Almost perfect ($0.8 < \kappa < 1$)	Micro, MT, CSME, RHEC	HE + Micro, NVE		PHE, NVD		Micro, ERM
Substantial ($0.6 < \kappa \leq 0.8$)	MTS	Ex < 1 DD	HE + Micro, Ex, IRMA, Ex-ring	Micro, HE + Micro, Ex, CWS, IRMA, HE < 1 DD, NVE, CSME, ERM	Micro, HE + Micro, Ex, NVD, Ex-center, NVC, Ex-plaque, Ex < 1 DD	HE + Micro, Ex, NVD, Ex < 1 DD
Moderate ($0.4 < \kappa < 0.8$)			Ex-center			

CSME = clinically significant macular edema; CWS = cotton wool spots; DD = disc diameter; ERM = epiretinal membrane; EX = hard exudates; Ex center = hard exudates at the center of the macula; Ex plaque = plaque hard exudates; Ex ring = hard exudate rings; Ex < 1 DD = hard exudates within 1 DD of the center of the macula; IRMA = intraretinal microvascular abnormalities; M + He = microaneurysms, hemorrhages, or both; MCE = cystoid spaces; Micro = microaneurysms; MT = macular thickness (< 1 DD); MTS = macular thickening size (< 1 DD); NVC = new vessels/fibrous proliferations in the center; NVD = new vessels on the disc; NVE = new vessels elsewhere; NV < 1 DD = new vessels or fibrous proliferations on or within 1 DD of the disc; PHE = preretinal hemorrhage; PHEC = preretinal hemorrhages in the center; PS = papillary swelling; RD = retinal detachment; RHEC = retinal hemorrhages in the center; VHE = vitreous hemorrhage; VN = venous narrowings.

The Table shows just significant results (power 80%; $\alpha = 0.05$; $\beta = 0.2$); minimum agreement, $\kappa > 0.4$ (confidence interval, > 0.4).

questionable; 2, thickening of 1 DD or more; and 3, thickening or hard exudates situated at less than 500 μm from the center of the macula. Thereafter, for each eye, a complessive DR level and CSME were assigned according to the ETDRS protocol.[15]

The same grading scheme was used for grading 1 NM and 3 NM 45-degree color photographs on a lesion-by-lesion basis as that described for 7 stereoscopic fundus fields. The overall level of DR and DME were evaluated according to the international classification proposed by the American Academy of Ophthalmology, which uses 5 levels of DR and 4 levels of DME.[16] To compare the results obtained from grading overall DR level with 7 mydriatic stereoscopic fields using standard ETDRS protocol and 1 NM and 3 NM fields using the international classification, the ETDRS classification was converted into the international classification.[16]

To verify the consistency of our data for each individual technique, intragrader and intergrader agreement for both single lesions and overall DR and DME grading levels were performed.

• STATISTICAL METHODS: *Sample Size*. κ Values lower than 0.40 were considered clinically unacceptable for the aim of the study. The hypothesis of significant reliability index κ of more than 0.40 when the expected value is approximately 0.70 and the proportion of positive ratings made on dichotomous classification of DR (present or absent) is 70% was verified according to a two-tailed test with $P = .05$. The sample size of 108 eyes was determined as the minimum number of observations required to guarantee a statistical power of 80%. The null hypothesis that κ is no more than 0.40 was retained only if 0.40 was included within the confidence interval (CI).

Reliability Indexes. The intertechnique agreement between 3 NM fields and 7 ETDRS fields (gold standard) in evaluating clinical levels of DR was the principal reliability index of the study. The κ statistic, a measure of intermethod reliability that adjusts for agreement by chance, and its 95% CI were calculated.[17] κ Statistics were computed also for DME and for single lesions. DR and DME were analyzed according to the 5-level and 4-level classification, respectively, as well as according to its presence or absence. Clinically relevant classifications were compared separately for the 2 methods. The κ statistics for presence and absence of any characteristics were calculated. To understand better the results, other indexes were computed besides κ statistics.

TABLE 2. Intermethod Agreement in the Evaluation of Clinical Levels of Diabetic Retinopathy According to the Early Treatment Diabetic Retinopathy Study Protocol on Seven Mydriatic Stereoscopic 30-Degree Fundus Photographs, Three Nonmydriatic Fundus Photographs, and One Nonmydriatic Central Fundus Photograph for Diabetic Retinopathy Screening

Diabetic Retinopathy	P_0	SE	SP	κ (95% CI)	P_{pos}	P_{neg}
3-Fields vs 7-fields method						
DR absent	0.99	1.00	0.99	0.88 (0.66 to 1.00)	0.89	0.99
nPDR mild	0.97	0.78	0.99	0.81 (0.60 to 1.00)	0.82	0.98
nPDR moderate	0.85	0.87	0.84	0.69 (0.55 to 0.83)	0.81	0.88
nPDR severe	0.82	0.66	0.89	0.55 (0.37 to 0.73)	0.67	0.88
PDR	0.92	0.73	0.98	0.76 (0.61 to 0.91)	0.81	0.95
Referable/no referable	0.87	0.82	0.92	0.74 (0.61 to 0.87)	0.87	0.87
Overall[a]	0.99	0.99	1.00	0.88 (0.66 to 1.00)	0.99	0.89
Overall[b]	0.78	n.a.	n.a.	0.69 (0.58 to 0.80)	n.a.	n.a.
1-Field vs 7-fields method						
DR absent	0.99	1.00	0.99	0.88 (0.66 to 1.00)	0.89	0.99
nPDR mild	0.93	0.67	0.96	0.60 (0.32 to 0.87)	0.63	0.96
nPDR moderate	0.80	0.87	0.75	0.59 (0.44 to 0.74)	0.76	0.83
nPDR severe	0.77	0.52	0.86	0.39 (0.19 to 0.59)	0.55	0.84
PDR	0.88	0.54	0.99	0.62 (0.43 to 0.80)	0.68	0.93
Referable/no referable	0.83	0.71	0.96	0.67 (0.53 to 0.80)	0.81	0.85
Overall[a]	0.99	0.99	1.00	0.88 (0.66 to 1.00)	0.99	0.89
Overall[b]	0.68	n.a.	n.a.	0.56 (0.44 to 0.68)	n.a.	n.a.
1-Field vs 3-fields method						
DR absent[c]	1.00	1.00	1.00	1.00	1.00	1.00
nPDR mild	0.96	0.87	0.97	0.76 (0.53 to 0.99)	0.78	0.98
nPDR moderate	0.89	0.93	0.86	0.78 (0.66 to 0.89)	0.87	0.90
nPDR severe	0.91	0.79	0.95	0.75 (0.61 to 0.90)	0.81	0.94
PDR	0.94	0.71	1.00	0.80 (0.65 to 0.95)	0.83	0.97
Referable/no referable	0.93	0.84	1.00	0.85 (0.75 to 0.95)	0.91	0.94
Overall[a,c]	1.00	1.00	1.00	1.00	1.00	1.00
Overall[b]	0.85	n.a.	n.a.	0.79 (0.69 to 0.89)	n.a.	n.a.

CI = confidence interval; DR = diabetic retinopathy; n.a. = not applicable; nPDR = nonproliferative diabetic retinopathy; ρ = proportional agreement by chance; PDR = proliferative diabetic retinopathy; SE = sensitivity considering 7-field method as gold-standard; SP = specificity considering 7-field method as gold standard.

[a]Classified as absent or present.

[b]Classified as absent, mild, moderate, severe, or proliferative.

[c]No discordant pairs.

Intergrader and intragrader agreement also were computed. All statistical analyses were performed with SAS/STAT software version 9.13 (SAS Institute, Cary, North Carolina, USA).

RESULTS

OF 55 ENROLLED PATIENTS, 22 WERE FEMALES AND 33 males (mean age ± standard deviation [SD], 57.1 ± 13.3 years; range, 20 to 85 years). Eighteen patients (32.7%) had type 1 DM (mean duration ± SD, 23.3 ± 11.4 years), and 37 (67.3%) had type 2 DM (mean duration ± SD, 15.8 ± 7.8 years). Mean age ± SD of patients with type 1 DM was 43.3 ± 10.8 years, whereas it was 61.7 ± 5.6 years for patients with type 2 DM. Mean HbA1c was 7.5 ± 1.9%.

Significant results of intragrader and intergrader agreement for lesion-by-lesion analysis according to the ETDRS protocol on 7F-ETDRS 30-degree fundus photographs, 3F-NM 45-degree photographs, and 1F-NM 45-degree photographs are shown in detail in Table 1. Significant results were considered in case of $\kappa > 0.4$ and with inferior limit of the CI > 0.4.

Intragrader agreement for DR and DME levels according to the international classification was substantial (κ = 0.76 and κ = 0.70 for both) on 7F-ETDRS; was almost perfect (κ = 0.86) and substantial (κ = 0.69) for 3F-NM photographs; and was substantial (κ = 0.75 and κ = 0.85, for both) for 1F-NM photographs.

Intergrader agreement for DR and DME levels according to the international classification was almost perfect (κ = 0.92) and substantial (κ = 0.62) on 7F-ETDRS photographs; was almost perfect (κ = 0.83) and substantial (κ =

TABLE 3. Intermethod Agreement in the Evaluation of Clinical Levels of Diabetic Macular Edema According to the Early Treatment Diabetic Retinopathy Study Protocol on 7 Mydriatic Stereoscopic 30-Degree Fundus Photographs, 3 Nonmydriatic Fundus Photographs, and 1 Nonmydriatic Central Fundus Photograph for Diabetic Retinopathy Screening

Macular Edema	P_0	SE	SP	κ (95% CI)	P_{pos}	P_{neg}
3-Fields vs 7-fields method						
Absent	0.86	0.97	0.83	0.82 (0.71 to 0.93)	0.93	0.89
Mild	0.89	0.50	0.95	0.48 (0.22 to 0.73)	0.54	0.94
Moderate	0.95	0.80	0.97	0.74 (0.52 to 0.96)	0.76	0.97
Severe	0.96	0.76	1.00	0.85 (0.70 to 0.99)	0.87	0.98
Referable/no referable	0.92	0.83	0.97	0.82 (0.71 to 0.93)	0.89	0.93
Overall[a]	0.86	n.a.	n.a.	0.75 (0.64 to 0.86)	n.a.	n.a.
1-Field vs 7-fields method						
Absent	0.88	0.91	0.83	0.75 (0.62 to 0.87)	0.90	0.84
Mild	0.88	0.43	0.95	0.41 (0.15 to 0.67)	0.48	0.93
Moderate	0.91	0.80	0.92	0.56 (0.33 to 0.80)	0.62	0.95
Severe	0.94	0.71	0.99	0.77 (0.59 to 0.94)	0.80	0.97
Referable/no referable	0.88	0.83	0.91	0.75 (0.62 to 0.87)	0.84	0.90
Overall[a]	0.81	n.a.	n.a.	0.66 (0.54 to 0.78)	n.a.	n.a.
1-Field vs 3-fields method						
Absent	0.92	0.89	0.89	0.76 (0.63 to 0.89)	0.91	0.85
Mild	0.90	0.50	0.95	0.46 (0.20 to 0.73)	0.52	0.94
Moderate	0.90	0.73	0.92	0.54 (0.30 to 0.78)	0.59	0.94
Severe	0.98	0.92	0.99	0.91 (0.79 to 1.00)	0.92	0.99
Referable/no referable	0.92	0.89	0.89	0.76 (0.63 to 0.89)	0.85	0.91
Overall[a]	0.83	n.a.	n.a.	0.70 (0.58 to 0.82)	n.a.	n.a.

CI = confidence interval; n.a. = not applicable; SE = sensitivity considering Early Treatment Diabetic Retinopathy Study as gold standard; SP = specificity considering Early Treatment Diabetic Retinopathy Study as gold standard.

[a]Classified as absent, mild, moderate, or severe.

0.62) for 3F-NM photographs; and was almost perfect (κ = 0.82) and moderate (κ = 0.53) for 1F-NM photographs.

Intermethod agreement for lesion-by-lesion grading on 1F-NM vs 3F-NM photography was substantial for Micro, Micro + He, Ex, NVE, PHE, VHE, RD, NVD, Ex-ring, Ex < 1 DD, Ex-center, NV < 1 DD, NV center, RHEC, PHEC, and Ex-plaque. Agreement was substantial and significant for IRMA, MTS, and MT when evaluating its presence or absence, but it was not statistically significant when evaluating the severity level. Agreement was not statistically significant for CWS, VB, VN, VL, PS, MCE, CSME, and MER (data not shown).

Intermethod agreement (κ) for assessing DR and DME levels were: 0.69 and 0.75, respectively, for 3F-NM vs 7F-ETDRS; 0.56 and 0.66, respectively, for 1F-NM vs 7F-ETDRS; and 0.79 and 0.70, respectively, for 1F-NM vs 3F-N. Intermethod agreement for assessing the absence or presence of any level of DR and DME were: 0.88 and 0.82 for 3F-NM vs 7F-ETDRS; 0.88 and 0.75 for 1F-NM vs 7F-ETDRS; and 1.00 and 0.76 for 1F-NM vs 3F-NM. Intermethod agreement for assessing the presence of referable or not referable disease (cut-off for referable disease was set for severe nonproliferative DR, proliferative DR, and presence of any level of DME) were: 0.74 and 0.85 for 3F-NM vs 7F-ETDRS; 0.67 and 0.77 for 1F-NM vs 7F-ETDRS; and 0.85 and 0.91 for 1F-NM vs 3F-NM (Tables 2 and 3).

DISCUSSION

BECAUSE OF THE DRAMATICALLY INCREASING PREVALence of DM in the world (the so-called diabetes epidemic), DR will remain one of the major causes of permanent visual loss in the world.[18] This occurs mainly because DR remains undetected and laser treatment is performed when irreversible visual loss is already established.[19] Moreover, evaluating diabetic patients for DR meets the main principles for screening services: retinopathy is an important health problem with a recognizable presymptomatic state; treatment for patients with recognizable disease is considered to be safe and effective; and the economic impact of early detection and treatment is cost-effective and may result in cost-savings.[20,21]

To identify patients reliably who are at risk for visual loss, annual dilated retinal examination is recommended and is considered the standard of care.[5] Unfortunately, using this traditional approach to detect DR, only approximately half of all diabetic patients in the United States receive the recommended annual screening for DR and, by extension, access to effective treatment.[22,23] Thus, new strategies for early DR detection are mandatory. Mydriatic and NM color retinal photography has shown better sensitivity in screening DR than direct and indirect ophthalmoscopy.[24,25] Pugh and associates found that dilated

direct and indirect ophthalmoscopy performed by an ophthalmologist have 33% sensitivity and 99% specificity, whereas single-field 45-degree NM retinal photography and 3F-NM 45-degree retinal photography (using color slide film) have 61% sensitivity and 85% specificity and 81% sensitivity and 97% specificity, respectively.[25] Harding and associates found that the sensitivity in detecting sight-threatening DR by mydriatic photography (color slide film) was 89%, and it was significantly better that of than direct ophthalmoscopy (65%).[25] Digital retinal photography also has shown the same results in grading DR compared with color slide film.[26] Therefore, the most promising screening technique seems to be digital NM retinal imaging. This technology has significantly improved patients' access to DR screening in Europe and Australia.[27] But apart from some minor purely technical issues, no general agreement exists about the number of NM 45-degree retinal fields to be captured to screen and grade DR adequately.

This study compares, for the first time, 1 and 3 NM digital retinal fields with standard ETDRS 7 fields, the gold standard in DR grading. Images were examined to identify single lesions, overall DR, and DME levels, as well as referable and nonreferable levels of DR and DME. Intragrader and intergrader agreement for DR and DME levels were substantial or almost perfect for most of the evaluated parameters. These results underline the reliability of NM techniques used in screening and grading settings and confirms the importance of digital images over ophthalmoscopic examination in screening and grading DR.

Unfortunately, direct comparisons between this study and previous reports is difficult, and sometimes impossible, because previous studies did not compare different numbers of NM fields vs standard ETDRS 7 fields. Notwithstanding, the analysis limited to comparable data from other reports documents that our intermethod agreement for DR level on 3F-NM vs 7F-ETDRS shows similar results to those obtained, for example, by the Joslin Vision Network ($\kappa = 0.69$ vs $\kappa = 0.65$, respectively), although these authors used stereoscopic 3F-NM 45-degree photography and slightly different retinal areas.[11]

Two recent studies evaluated sensitivity and specificity of 1 and 3 fundus field photographs for referral DR and compared them with ophthalmoscopic examination.[28,29] These results cannot be compared directly with ours, because we used 7 ETDRS photographs as a reference, but their data may be useful in this discussion. According to Murgatroyd and associates, sensitivity and specificity for detecting referable DR using 1F-NM photography was 77% and 95%, respectively, whereas they were 83% and 93% when using dilated 3-field photography.[28] Aptel and associates found that sensitivity and specificity of digital photography for detection of DR were, respectively, 77% and 99% using single-field NM and 92% and 97%, respectively, using 3-field NM. The latter authors also found that sensitivity was greater for detection of some specific retinal lesions (HE, nerve fiber layer hemorrhage, and VB) and was lower for microaneurysms, dot-blot hemorrhage, CWS, and IRMA because of different contrast definition of retinal findings that might have influenced the ability to detect them.[29] Both studies concluded that mydriasis did not significantly influence image grading. Grading of NM retinal fields has reached a sort of informal consensus.

The major clinical value of screening DR is to detect referable cases because a delay in full ophthalmic examination and treatment may lead to permanent visual loss. According to our results, sensitivity and specificity for detecting referable DR were 71% and 96%, respectively; for referable DME, they were 83% and 91% on 1F-NM 45-degree photography; and they were 82% and 92%, and 83% and 97%, respectively, when 3F-NM was used. A recent report by the American Academy of Ophthalmology indicates that 1 central field fundus photograph can serve as a screening tool for DR, although it is not a substitute for a comprehensive ophthalmic examination.[8] Our results showed 71% sensitivity for detecting referable levels of DR with a 1F-NM 45-degree photograph, a value considered lower (<80%) than requested targets for an effective screening program.[30] Therefore, 1-NM 45-degree central-field photography is probably not suitable for a community-based screening program where referable DR and DME need to be determined based on different severity levels, whereas 3F-NM 45-degree color photography seems to be a valid method for detecting referable DR and DME levels.[31]

This research has some limitations: studied eyes were not examined by ophthalmoscopy, and the 2 retinal field technique was not included. But ophthalmoscopy has a recognized lower value to detect and grade DR than any photographic technique, as previously reported.[12,13,25] The 3 NM retinal fields technique is the most common photographic method to quantify DR using more than 1 field, whereas the 2 retina field technique has limited application. We concentrated our efforts in comparing the most commonly used techniques vs the gold standard photographic approach.

Because visual loss resulting from diabetes may be efficiently prevented by early detection of DR, diabetic population screening of DR remains a major goal in the era of diabetes epidemics. Grading of NM fundus photographs should be considered the new standard in approaching DR screening. More possibilities will be offered after extensive research on less expensive and smaller retinal NM cameras and on the automatic grading of DR using a validated number of retinal fields.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN DESIGN AND conduct of study (S.V., E.M.); collection, management, analysis, and interpretation of data (E.B., F.M., M.V., F.C.); statistical expertise (F.C.); provision of materials and patients (A.A.); and preparation, review, or approval of the manuscript (S.V., E.M., E.P., M.V.). The study was conducted in accordance with the tenets of the Declaration of Helsinki and with the approval of the Institutional Ethical Committee, Comitato Etico dell'Azienda Ospedaliera, Universita' degli Studi di Padova.

REFERENCES

1. King H, Aubert RE, Hermann WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates and projections. Diabetes Care 1998;21:1414–1431.
2. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 1995;102:647–661.
3. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS Report No. 9. Ophthalmology 1991;98:766–785.
4. American College of Physicians, American Diabetes Association, and American Academy of Ophthalmology. Screening guidelines for diabetic retinopathy. Ann Intern Med 1992;116:683–685.
5. Fong DS, Aiello L, Gardner TW, et al, American Diabetes Association. Retinopathy in diabetes. Diabetes Care 2004; 27:S84–S87.
6. Harris EL, Sherman SH, Georgopoulos A. Black-white differences in risk of developing retinopathy among individuals with type 2 diabetes. Diabetes Care 1999;22:779–783.
7. Varma R, Macias GL, Torres M, et al, the Los Angeles Latino Eye Study Group. Prevalence of diabetic retinopathy in adult Latinos: the Los Angeles Latino Eye Study. Ophthalmology 2004;111:1298–1306.
8. 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.
9. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report No. 1. Arch Ophthalmol 1985;103:1796–1806.
10. Moss SE, Meuer SM, Klein R, Hubbard LD, Brothers RJ, Klein BE. Are seven standard photographic fields necessary for classification of diabetic retinopathy? Invest Ophthalmol Vis Sci 1989;30:823–828.
11. Bursell SE, Cavallaro JD, Cavallaro AA. Stereo nonmydriatic digital-video color retinal imaging compared with Early Treatment Diabetic Retinopathy Study seven standard field 35-mm stereo color photos for determining level of diabetic retinopathy. Ophthalmology 2001;108:572–585.
12. Scanlon PH, Malhotra R, Greenwood RH, et al. Comparison of 2 reference standards in validating 2 field mydriatic digital photography as a method of screening for diabetic retinopathy. Br J Ophthalmology 2003;87:1258–1263.
13. 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.
14. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS Report No. 10. Ophthalmology 1991;98: 786–806.
15. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS Report No. 12. Ophthalmology 1991;98: 823–833.
16. Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scale. Ophthalmology 2003;110:1677–1682.
17. Altman DG. Practical statistics for medical research. London, England: Chapman & Hall/CRC, 1991:1–611.
18. Saaddine JB, Honeycutt AA, Narayan KM, et al. Projection of diabetic retinopathy and other major eye diseases among people with diabetes mellitus: United States, 2005–2050. Arch Ophthalmol 2008;126:1740–1747.
19. Bresnick GH, Mukamel DB, Dickinson JC, Cole DR. A screening approach to the surveillance of patients with diabetes for the presence of vision-threatening retinopathy. Ophthalmology 2000;107:19–24.
20. Cavallerano JD, Aiello LP, Cavallerano AA, et al, Joslin Vision Network Clinical Team. Nonmydriatic digital imaging alternative for annual retinal examination in persons with previously documented no or mild diabetic retinopathy. Am J Ophthalmol 2005;140:667–673.
21. Hildebrand PL. Discovering optimal telemedicine strategies for evaluating diabetic retinopathy. Am J Ophthalmol 2005; 140:703–704.
22. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;348:2635–2645.
23. 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.
24. Pugh JA, Jacobson JM, van Heuven WA, et al. Screening for diabetic retinopathy. The wide-angle camera. Diabetes Care 1993;16:889–895.
25. Harding SP, Broadbent DM, Neoh C, et al. Sensitivity and specificity of photography and direct ophthalmoscopy in screening for sight threatening eye disease: the Liverpool Diabetic Eye Study. BMJ 1995:311:1131–1135.
26. Rudnisky CJ, Tennant MT, Weis E, et al. Web-based grading of compressed stereoscopic digital photography versus standard slide film photography for the diagnosis of diabetic retinopathy. Ophthalmology 2007;114:1748–1754.
27. Taylor CR, Merin LM, Salunga AM, et al. Improving diabetic retinopathy screening ratios using telemedicine-based digital retinal imaging technology: the Vine Hill Study. Diabetes Care 2007;30:574–578.

28. Murgatroyd H, Ellingford A, Cox A, et al. Effect of mydriasis and different field strategies on digital image screening of diabetic eye disease. Br J Ophthalmol 2004;88:920–924.
29. Aptel F, Denis P, Rouberol F, Thivolet C. Screening of diabetic retinopathy: effect of field number and mydriasis on sensitivity and specificity of digital fundus photography. Diabetes Metab 2008;34:290–293.
30. British Diabetic Association. Retinal photographic screening for diabetic eye disease. A British Diabetic Association Report. London, England: British Diabetic Association, 1997.
31. Scanlon P. The English national screening programme for sight-threatening diabetic retinopathy. J Med Screen 2008;15:1–4.

AJO History of Ophthalmology Series

The Golden Eye

In the ruins of "The Burnt City", an ancient community near the border of Afghanistan, recently found in Iran what is probably the first artificial eye ever, dating from about 2800 to 2900 BC. The hemispherical structure is a bit larger than one inch in diameter, made of bitumen (a type of asphalt) and animal fat. It is inscribed with ray-like lines, a pupil, possibly an iris, etc., and was evidently gilded at one time. It was found lying within the orbit of the intact skull of an uncommonly tall (5'10" to 6'00") woman with an africanoid skull who died in her late 20's. The prosthesis was held in place during life by strings passing through 2 small holes and tied behind the head, much like an eye patch. The golden eye might have promoted the contemporary view that she had occult powers.

Provided by Jay M. Enoch, PhD, of the Cogan Ophthalmic History Society.