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Comparison of ETDRS 7-Field to 4-Widefield Digital Imaging in the Evaluation of Diabetic Retinopathy Severity

Barbara A. Blodi[1], Amitha Domalpally[1,2], Ashley H. Tjaden[2], Nancy Barrett[1], Emily Y. Chew[3], William C. Knowler[4], Christine G. Lee[5], Xavier Pi-Sunyer[6], Amisha Wallia[7], Neil H. White[8], and Marinella Temprosa[2]

[1] Wisconsin Reading Center, Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[2] Biostatistics Center and Department of Biostatistics and Bioinformatics, Milken Institute School of Public Health, The George Washington University, Rockville, MD, USA
[3] Division of Epidemiology and Clinical Applications, Clinical Trials Branch, National Eye Institute, National Institutes of Health, Bethesda, MD, USA
[4] Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, AZ, USA
[5] Division of Diabetes, Endocrinology and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA
[6] Columbia University Irving Medical Center, New York, NY, USA
[7] Division of Endocrinology, Metabolism and Molecular Medicine, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[8] Division of Endocrinology and Diabetes, Department of Pediatrics, Washington University in St. Louis, St. Louis, MO, USA

Correspondence: Amitha Domalpally, DPP Coordinating Center, The Biostatistics Center, Milken Institute School of Public Health, The George Washington University, 6110 Executive Boulevard, Suite 750, Rockville, MD 20852, USA.
e-mail: domalpally@wisc.edu, dppmail@bsc.gwu.edu

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Purpose: To compare Early Treatment Diabetic Retinopathy Study (ETDRS) severity levels between two digital fundus imaging protocols for research studies of diabetic retinopathy: the gold standard 7-field (7F) imaging and the more recent 4-widefield (4W) imaging.

Methods: Two hundred twenty-two participants enrolled in the Diabetes Prevention Program Outcomes Study underwent concurrent 7F and 4W imaging. The ETDRS levels from 220 paired gradable images were determined by masked graders. Each image was graded by two independent graders with adjudication by a senior grader, if necessary. Percent agreement between graders and between imaging protocols was evaluated with kappa statistics and weighted kappa statistics.

Results: Of 220 gradable eyes, diabetic retinopathy was seen in 11.8%; this was mild in 10.4% and more than mild in 1.4% using 7F imaging. The ETDRS levels showed exact agreement of 95% between 7F and 4W imaging (weighted kappa 0.86). Intergrader agreement for each modality had exact agreement of 89% (weighted kappa of 0.73) for 7F and 91% (weighted kappa 0.77) for 4W.

Conclusions: There is substantial agreement in the ETDRS severity level between the 7F and 4W digital imaging protocols, demonstrating that the two imaging protocols are interchangeable. Both 4W and 7F digital imaging protocols can be used for assessing ETDRS levels, even in populations with minimal diabetic retinopathy.

Translational Relevance: The 4W protocol requires fewer images than the 7F, is more comfortable for the patients, is easier for photographic capture, and provides diabetic retinopathy data that is equivalent to the 7F imaging protocol.

Introduction

Diabetic retinopathy (DR) includes a wide range of pathologic clinical features in the retina including microaneurysms, hemorrhage, intraretinal microvascular abnormalities, venous beading, fibrosis and neovascularization.[1] In the Early Treatment Diabetic Retinopathy Study (EDTRS), these features were assessed from 35-mm film fundus photographs taken annually on all participants.[2] In the ETDRS, the fundus photograph acquisition protocol was standardized and required that sites have both certified photographers and certified fundus camera systems. Photographers were required to use an imaging protocol of seven stereoscopic pairs of overlapping 30° fields to map out the macula and mid-peripheral retina. These standard 7-field (7F) photographs were analyzed for DR features, allowing the ETDRS research group to develop a multi-step DR severity scale (ETDRS scale) that correlates well with retinopathy progression.[1] The ETDRS scale has been employed in a number of epidemiological studies and clinical trials to monitor retinopathy.[3–7]

In the 1990s, retina specialists began switching from film-based to digital fundus cameras in clinical practice. Digital cameras provided the option of using a 45° to 60° wide-angle capture in addition to the 30° to 35° field of view of the retina. The 45° to 60° "widefield" photographs allowed the photographer to map out an area equivalent to seven fields with fewer images. This led to the development of the 4-widefield (4W) imaging protocol, which requires only four stereoscopic pairs of photographs to map out approximately the same area of the fundus as the seven standard fields (Fig. 1).

With the phasing out of film photography and with improvements in the resolution of digital imaging, researchers have reported on the accuracy of digital images compared with film-based fundus photographs.[8] In 2011, the Diabetic Retinopathy Clinical Research (DRCR) network compared 7F film fundus photographs to both digital 7F and digital 4W fundus photographs in eyes with DR. Graders independently evaluated the ETDRS levels obtained from both film and digital images; agreement was rated as "nearly perfect" based on the weighted kappa statistic of 0.82. The DRCR research group, however, did not design the study to compare agreement between the digital 7F and the digital 4W. The goal of this study was to compare the accuracy of grading DR between two digital photographic protocols, specifically the newer 4W imaging protocol versus the standard 7F imaging protocol.

Methods

The Diabetes Prevention Program Outcomes Study (DPPOS) is a clinical study investigating the long-term effect of lifestyle and metformin interventions in the Diabetes Prevention Program (DPP).[9–11] The DPP was a multicenter randomized controlled trial that enrolled 3234 adults at high risk of developing type 2 diabetes between 1996 and 1999. DPP enrollment was based on having impaired glucose tolerance (plasma glucose 140–199 mg/dL after a 75-g oral glucose load), elevated fasting blood glucose (fasting plasma glucose 95–125 mg/dL), and elevated body mass index. Participants were randomly assigned to placebo ($n = 1082$),

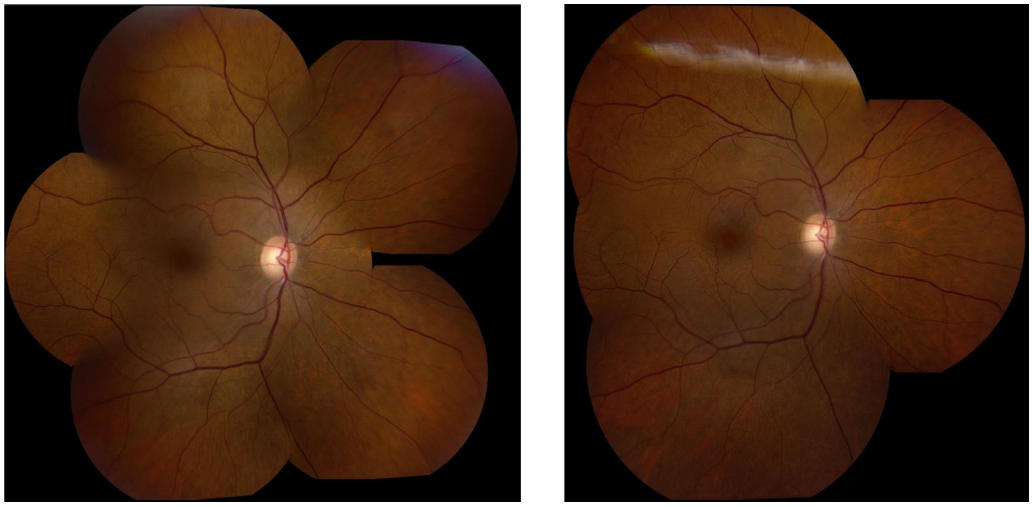

Figure 1. A montage of individual images using the 7-field protocol (*left*) and the 4-widefield protocol (*right*). The area of retina covered in the image is similar between the two imaging protocols. The difference is in additional nasal field coverage in the 4-widefield protocol.

850 mg metformin twice daily ($n = 1{,}073$), or intensive lifestyle intervention ($n = 1079$). The DPPOS is the long-term follow-up of the DPP cohort and includes 2779 (86%) of the original cohort.[9] Written informed consent was obtained from all participants, and both the DPP and the DPPOS study protocols and Health Insurance Portability and Accountability Act of 1996–compliant informed consents were approved by each clinical center's institutional review board. The study complied with all tenets of the Declaration of Helsinki, and DPPOS is registered on ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT00038727).

After an average of 20 years of follow-up, DPPOS participants underwent 7F imaging in both eyes in 2018 as part of the standard imaging protocol. This comparison study was conducted by DPPOS at a subset of eight clinical sites in the United States with a goal of enrolling at least 200 participants to undergo both 7F and 4W imaging at that follow-up visit. To help ensure a wide range of DR, the sample was enriched with participants graded to have retinopathy at the previous visit, at 15 years of follow-up.[12] A separate informed consent was obtained for the additional 7F imaging.

Photography

After pupillary dilation, 7F and 4W digital photographs were taken by a certified DPPOS photographer using a certified camera system. The 4W digital photographs were taken of both eyes as part of the DPPOS protocol. An additional set of 7F photographs was taken for one eye. In both the 7F and 4W photography protocols, the photographers are required to manually reposition the camera to obtain each field of view in stereoscopic pairs of images. Figure 2 shows the 7F images for 30° 7F imaging capture and 45° to 60° 4W imaging capture. In brief, the 7F imaging protocol requires the following fields: disc (Field 1M), macula (Field 2M), temporal to macula (Field 3M), and four peripheral fields (F4–F7). The 4W imaging includes the following fields: nasal to the optic disc (Field 1W), just temporal to the center of the macula (Field 2W), superior temporal to the macula (Field 4W), and inferior temporal to the macula (Field 5W). Images were de-identified and exported to the reading center according to the DPPOS study protocol.

Grading

Fundus photographs were evaluated by six certified graders at the Fundus Photograph Reading Center, University of Wisconsin. All graders were masked to clinical data and treatment assignment. The graders in this study were certified in the grading of DR and had over 18 years of experience in assessing the ETDRS DR severity scale. Image quality for all 7F and 4W photographs was assessed by the graders based on their ability to see the prespecified features of DR and provide an ETDRS level. Fundus photographs were considered ungradable if image quality prevented assessment of ETDRS level and could be due to either a technical or patient-related issue, or both.

DR level was graded in all eyes according to the ETDRS scale and recoded into 12 steps.[1] The 12-step classification is as follows: DR absent (levels 10 and 12), questionable DR (levels 14, 15, and 20), mild non-proliferative DR (level 35), moderate non-proliferative DR (level 43), moderately severe non-proliferative DR (level 47), severe non-proliferative DR (level 53), mild proliferative DR (level 61), moderate proliferative DR

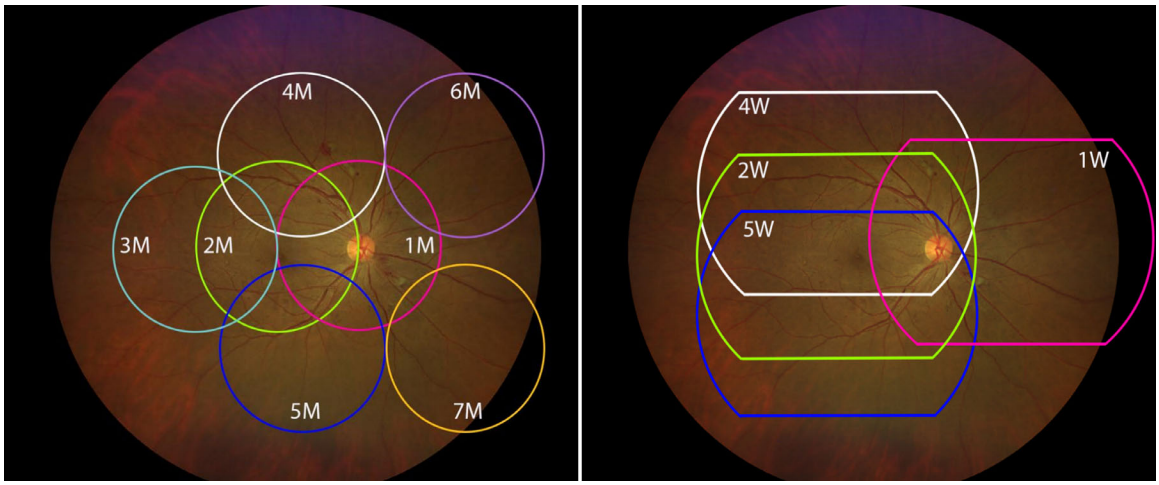

Figure 2. 7F and 4W imaging protocols. *Colored regions* represent individual fields of view captured. The 7F stereo imaging has seven stereo pairs (i.e. 14 images), and the 4W stereo protocol has eight images per eye.

(level 65), high-risk proliferative DR (levels 71 and 75), and advanced proliferative DR (levels 81 and 85).

Graders used handheld stereoscopic viewers to view the images on high-resolution monitors calibrated for color balance every month. Evaluation of the 7F images and 4W images were performed by different graders. The grader reviewed all fields and then assigned the DR level based on the most severe lesions in the eye. In assessing the DR level, the grader was allowed to optimize the color, contrast, and illumination of any image.

Each set of images was graded independently by two graders, masked to each other's reads. Following the ETDRS grading protocol, adjudication by a senior grader occurred if there was any discrepancy between two graders of one or more steps on the DR severity scale. The adjudicator's grade was considered the final grade of record. If adjudication was not required, the first grader's evaluation was considered the final grade of record.

Statistical Analysis

Statistical comparison of DR levels between the 7F and 4W imaging protocols utilized the final grade of record. The ETDRS level was cross-tabulated, and agreement was analyzed using percent agreement (exact agreement and agreement within one step), kappa statistic, and weighted kappa statistic. Weights were specified as 1 for exact agreement, 0.75 for one step of disagreement, and 0 for all other disagreements.[1] Based on the qualitative interpretation by Landis and Koch,[13] the weighted kappa statistics were grouped as poor, weak, fair, moderate, and almost perfect agreement. Eyes with ungradable ETDRS levels ($n = 2$) were excluded from the analysis. Inter-grader reproducibility was calculated between the two graders' evaluations before adjudication within each imaging protocol to assess uniformity between graders. Because the 4W and 7F images were graded by different graders, intra-grader reproducibility is not available. Reproducibility was assessed by percent agreement and kappa statistics, as well. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Two hundred twenty-two participants had images submitted using both 7F and 4W imaging protocols in one eye. Of these, two eyes were excluded due to ungradable ETDRS level; two of the 4W images (<1%) and one 7F image (<1%) were ungradable. The study participants' baseline characteristics are described in Table 1.

Table 1. Participant Characteristics at Visit ($N = 222$)

Characteristic	
Treatment group, *n* (%)	
Placebo	85 (38.3)
Metformin	74 (33.3)
Intensive lifestyle change	63 (28.4)
Age at visit (y), mean ± SD	68.1 ± 8.9
Sex, *n* (%)	
Male	49 (22.1)
Female	173 (77.9)
Race/ethnicity, *n* (%)	
Non-Hispanic white	121 (54.5)
Hispanic	41 (18.5)
Non-Hispanic black	31 (14.0)
American Indian	23 (10.4)
Asian	6 (2.7)
Diabetes status, *n* (%)	
No	72 (32.4)
Yes	150 (67.6)
Diabetes duration (y), mean ± SD	13.4 ± 5.1
Study eye, *n* (%)	
Right	93 (41.9)
Left	129 (58.1)

Based on the grading of the 7F photographs of 220 eyes, DR was present in 26 eyes (11.8%); 23 eyes (10.4 %) had mild DR (less than or equal to Level 35) and three eyes (1.4 %) had more than mild DR (Level 43 or greater). With 4W grading, 23 eyes (10.5%) had DR; 20 eyes (9.1%) had mild DR only and three eyes (1.4%) had more than mild DR. Rates of DR were not significantly different between the two sets of images ($P = 0.3173$). There were no eyes with proliferative DR, and only one eye in either group had clinically significant macular edema. The distribution of DR levels is shown in Table 2. In eyes with early DR (microaneurysms only), microaneurysm counts were done from all fields.

The stepwise conversion of ETDRS levels is shown in Table 2. Comparison of the DR severity level between the 7F and 4W imaging protocols in the same eye at the same visit revealed exact agreement in 95% of eyes and agreement within one step in 99.5% of eyes. The weighted kappa for DR severity level was 0.86 (range, 0.75–0.97), which falls in the "near-perfect" agreement category (Fig. 3, Table 3). Microaneurysm counts were done in all eyes in level 20 (early DR category). There were no differences in microaneurysm counts among the three categories

Table 2. Distribution of ETDRS Severity Levels, Clinically Significant Macular Edema, and Microaneurysm Counts Between the 4-Widefield and 7-Field Imaging Protocols

	4W		7F	
Variable	*n*	%	*n*	%
Diabetic retinopathy severity (ETDRS levels)				
Steps				
1 Absent (10, 12)	197	88.74	195	87.84
2 Questionable (14A, 14B, 14C, 14Z, 15)	5	2.23	5	2.26
2 Microaneurysms only (20)	10	4.54	12	5.42
3 Mild non-proliferative (35A, 35B, 35C, 35D, 35E, 35F)	5	2.25	6	2.70
4 Moderate non-proliferative (43A, 43B)	2	0.90	1	0.45
5 Moderately severe non-proliferative (47A, 47B, 47C, 47D)	0	0	1	0.45
6 Severe non-proliferative (53A, 53B, 53C, 53D, 53E)	1	0.45	1	0.45
90 Cannot grade	2	0.90	1	0.45
Clinically significant macular edema				
Absent	217	97.75	218	98.20
Questionable	2	0.90	0	0
Definite	1	0.45	2	0.90
Cannot grade	2	0.90	2	0.90
Microaneurysm counts				
Absent	201	90.54	192	86.49
Questionable	3	1.35	7	3.15
1	4	1.8	7	3.15
2	2	0.9	2	0.9
3	0	0	1	0.45
4	1	0.45	1	0.45
5	0	0	1	0.45
6	0	0	1	0.45
10	1	0.45	0	0
11+	5	2.25	6	2.7
Not applicable	4	1.8	2	0.9
Cannot grade	1	0.45	2	0.9

of absent/questionable, one to 10, and more than 11 (kappa = 0.68; range, 0.49–0.87).

Intergrader agreement was assessed using the ETDRS levels assigned by each of the two graders prior to adjudication for each set of images. Among the 220 eyes where an ETDRS level was assigned by both graders, exact agreement was 89%, one-step agreement was 99.1% with weighted kappa = 0.73 (95% confidence interval [CI], 0.61–0.86) for the 7F images. Because adjudication was done on all eyes that did not meet exact agreement, the adjudication rate in the 7F images was 11%. With 4W images, two eyes were marked as ungradable by both graders. The intergrader agreement on 220 eyes showed exact agreement in 91% and one-step agreement in 99.1%, with a weighted kappa = 0.77 (95% CI, 0.64–0.89) in the 4W images. The adjudication rate for the 4W images was 9%.

Discussion

In this subset of DPPOS participants, we assessed the agreement of reading center graders in grading DR level when viewing digital color fundus photographs using both the 7F and the 4W imaging protocols. Agreement between the two imaging protocols was substantial and demonstrates that the two imaging protocols provide equivalent information in determining DR level. The advantages to the 4W protocol are that the procedure takes less time than the

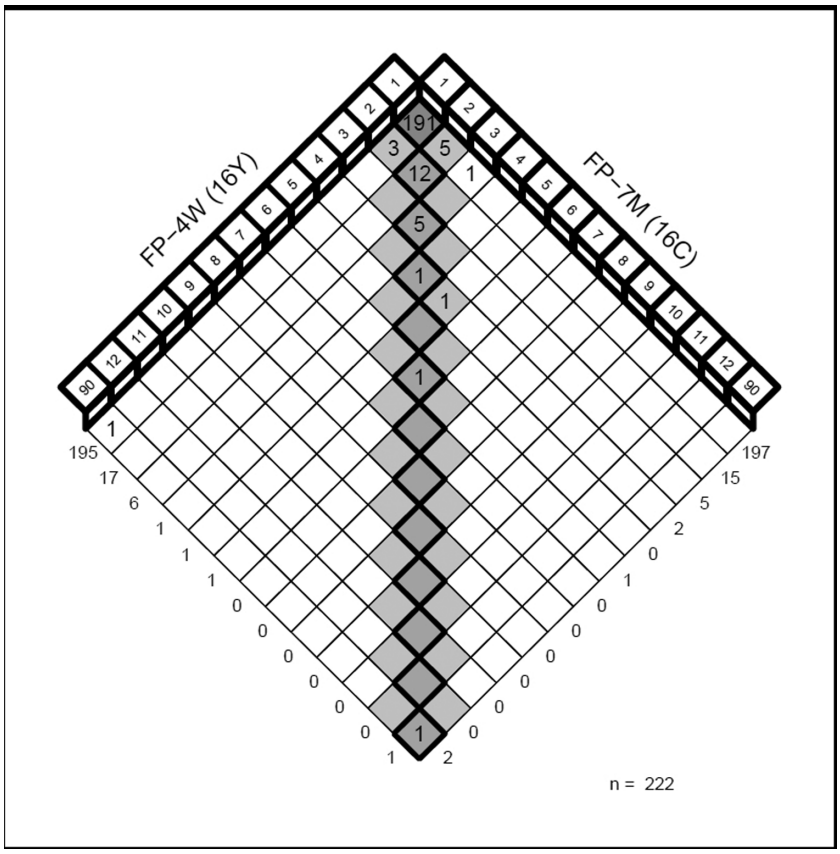

Figure 3. Cross-tabulation showing agreement for steps of the ETDRS severity scale between the 4W and 7F imaging protocols. *Dark boxes* represent perfect agreement, and *gray boxes* represent one-step differences.

Table 3. Comparison of ETDRS Severity Levels and Agreement Rates Between the 4W and 7F Imaging Protocols

	Complete Agreement	Within One Step	Within Two Steps	Weighted Kappa (CI)
Comparison of ETDRS level (n = 220)				
4W vs. 7F	95.5%	99.5%	100%	0.84 (0.64–0.91); near-perfect agreement
Intergrader Agreement (ETDRS Level)				
4W	91%	99.1%	100%	0.77 (0.64–0.89); substantial agreement
7F	89%	99.1%	99.5%	0.73 (0.61–0.86); substantial agreement

7F protocol and the patient is more comfortable with fewer photographs being taken per eye.

The severity and progression of DR have been strongly associated with HbA1c levels.[14–18] However, there is variability in the reporting of DR prevalence among studies for a similar range of HbA1c; this can be attributed to variability in definitions and detection methods for retinopathy.[15] The DPPOS has utilized a retinopathy assessment based on 7F stereoscopic fundus photography evaluated at a reading center using a definition of ETDRS score of ≥20 in either eye, or treatment of retinopathy with laser photocoagulation or intravitreal injections.[12] The DPPOS fundus imaging protocol switched from 7F to 4W due to technological imaging advances in the 16th year of the DPPOS study. The current study was undertaken to test the implications of fields of imaging (7F vs. 4W) on the ETDRS scale, particularly in populations with early DR changes. The 7F and 4W images cover an area difference of about 10%, particularly in the nasal fields (Fig. 1). In epidemiological and screening studies where incident retinopathy is an important outcome, variability in the detection of isolated early DR lesions can affect study outcomes.[14] Between the 7F and 4W imaging protocols, the 95% and 99% levels of exact and within one-step agreement, as well as the weighted

kappa of 0.86, are near perfect. This high level of agreement shows that the 7F and 4W imaging protocols are interchangeable and do not alter the assessment of ETDRS levels.

Previously published data from the DRCR network showed comparable results for the agreement rate of ETDRS level when comparing 7F film images to 4W digital images: 83% exact agreement and 93% agreement within one step with a weighted kappa of 0.85 in 48 eyes.[8] The DRCR network study had a wider distribution of ETDRS levels compared with the current study, with 91% more than mild retinopathy, whereas the current study only had 1.4% more than mild retinopathy. In 194 DRCR eyes with no DR on 7F imaging, microaneurysms were visible on 4W imaging in three eyes (1.5%). Among 17 eyes labeled as early DR (microaneurysms only) by 7F imaging, five eyes were labeled as no DR on 4W. A post hoc review of these images showed that differences in the detection of early DR changes were mostly due to photograph quality issues and not due to a difference in field of view.

Diabetic retinopathy progression is generally monitored in each eye as the development of proliferative DR or two-step change in one eye on the ETDRS scale. However, in epidemiological studies, such outcomes have a low incidence due to most participants presenting with no or minimal DR.[4] In such studies, microaneurysm counts have been considered an early important measure of progression.[19] In a population-based study by Klein et al.,[20] using 7F imaging, eyes with $\geq$3 microaneurysms at baseline were 2.3 times more likely to progress to proliferative DR over 10 years compared with those with fewer microaneurysms. Differences in field of imaging can affect the detection and count of microaneurysms; in a study comparing 200° ultrawide field images to standard 7F imaging, microaneurysm counts increased by 49.8% when regions outside the 7F were considered.[21] Therefore, it is important to confirm any changes to outcome parameters such as microaneurysm counts due to modifications in the field of imaging and the additional views of the nasal field offered with 4W imaging. In the current study, the microaneurysm counts were comparable in those eyes with confirmed microaneurysms using 7F imaging and 4W imaging. Microaneurysms were seen with 7F imaging in five eyes, but not with 4W. A review of these images revealed that the discrepancies were within field 2 (macular region) and image focus as a reason for the disagreement. A change in the imaging protocol does not appear to account for a significant change in microaneurysm counts in this study.

Intergrader agreement within each imaging modality was excellent, indicating that both methods are equally good for the evaluation of DR. Agreement rates in the current study are better than those in DRCR network studies, with 70% exact agreement and 91% within one step (weighted kappa = 0.81). This is possibly due to the difference in DR severity distribution, as DRCR studies have a wider distribution. The low adjudication rate of 9% to 11% between the two imaging protocols is another measure of intergrader agreement.

The strengths of this study are the inclusion of a large number of high-quality digital retinal photographs taken by both imaging protocols on the same day and by certified photographers of the well-described DPPOS participants from several clinical sites. Detailed assessments of ETDRS levels and microaneurysm counts were carried out by certified graders with robust quality control. Limitations of this study include a more limited distribution of DR than in other studies.

In this subset of the DPPOS study, participants were imaged with both imaging protocols (7F and 4W), and both sets of fundus photographs were analyzed using the ETDRS severity scale. Agreement between 4W and 7F digital imaging protocols is an important finding for clinical research, as the 4W protocol provides for retinal mapping with fewer images per eye, thus making the procedure less burdensome for the patient and less time consuming for the photographer.

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