



# Comparison of Widefield Laser Ophthalmoscopy and ETDRS Retinal Area for Diabetic Retinopathy

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**Purpose:** To evaluate agreement of nonmydriatic confocal scanning laser ophthalmoscopy (SLO; EIDON [CenterVue]) and the 7-standard field ETDRS area on ultrawide-field (UWF) SLO imaging for identification of diabetic retinopathy (DR) severity.

**Design:** Single-site, prospective, comparative, instrument validation study.

**Participants:** One hundred ten eyes of 55 patients with diabetes mellitus were evaluated.

**Methods:** Each patient underwent nonmydriatic, nonsimultaneous stereoscopic imaging using the EIDON camera and 4 fields of 60° × 55° were acquired (macula centered, disc centered, temporal macula, superotemporal). Mydriatic UWF retinal images were acquired using a nonsimultaneous stereographic protocol with UWF imaging (California; Optos plc). Before grading, a standardized ETDRS 7-field image mask was applied to all UWF retinal images. Images from each device were graded independently by 2 masked graders using the ETDRS clinical DR classification. Any discrepancy in DR grading between the devices was adjudicated by a third grader.

**Main Outcome Measures:** κ Levels of agreement, sensitivity, and specificity for DR thresholds.

**Results:** Severity by ETDRS grading was as follows: no DR, 10.9%; mild nonproliferative DR (NPDR), 45.5%; moderate NPDR, 16.5%; severe NPDR, 11.8%; proliferative DR, 12.7%; high-risk proliferative DR, 2.7%; and ungradable, 0%. After adjudication, the level of DR identified on EIDON images agreed exactly with that of UWF ETDRS imaging in 87% of eyes (n = 96) and was within 1 step in 99.1% of eyes (n = 109) with a simple κ value of 0.8244 ± 0.0439 (95% confidence interval [CI], 0.7385–0.9104) and weighted (linear) κ value of 0.9041 ± 0.0257 (95% CI, 0.8537–0.9545). Sensitivity and specificity compared with ETDRS field grading for any DR were 0.96 and 0.75, for moderate NPDR or worse were 0.96 and 0.97, and for severe NPDR or worse were 0.91 and 1.00, respectively.

**Conclusions:** Nonmydriatic 4-field stereoscopic widefield imaging using the EIDON device was comparable with the DR severity identified within the ETDRS 7-standard field area of UWF images. Future studies will need to evaluate the applicability of this device as a clinical and research tool and the impact of different widefield coverage areas. *Ophthalmology Science* 2022;2:100190 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Diabetic retinopathy (DR) affects more than one-third of the population with diabetes mellitus and remains a leading cause of vision loss worldwide.<sup>1</sup> Access to appropriate diabetes eye care is highly variable and remains far from optimal, with DR surveillance rates of 60% to 70% in developed countries and substantially lower rates in less developed countries.<sup>2,3</sup> Methods to distribute quality eye care to virtually any location at a lower cost are highly desirable and would have significant public health care benefits.

The prevention of visual complications resulting from diabetes relies on the early identification and accurate assessment of DR severity to determine timely follow-up and to inform initiation of sight-preserving interventions.<sup>4</sup> Retinal evaluation and photography are integral components of clinical care for DR and telemedicine programs.<sup>5</sup> ETDRS 7-standard field 35-mm color 30° stereoscopic fundus photographs (ETDRS photography) are

the gold standard for determining severity of DR. However, ETDRS photography requires pupillary dilation and trained photographers.<sup>6</sup>

In the teleophthalmology programs for DR, the use of ultrawide-field (UWF) scanning laser ophthalmoscopy (SLO) has been shown to reduce the rate of ungradable nonmydriatic images by nearly 90%.<sup>7</sup> However, the substantial cost of current UWF confocal SLO retinal imaging devices (e.g., Optos; Optos, plc) can be a barrier to more widespread adoption. The EIDON (CenterVue) device combines the advantages of high-resolution confocal SLO without flood flash illumination color imaging at a substantially lower cost, albeit without the extended visualization provided by 200° UWF viewing of devices such as the Optos. The camera provides a resolution of 60 pixels/degree with an optical resolution on the retina of 15 μm. Each single exposure image is 60° (horizontal) by 55° (vertical) with a resulting visualized area more than 3-fold

larger than standard 30° fields. Multiple images can be acquired with SLO imaging, allowing an overall imaging area of up to 110° in programmable automatic mode as used in this study and 150° in manual mode. The addition of peripheral fields has been shown to increase both the sensitivity and specificity in the detection of referable DR.<sup>8</sup> Multiple-field protocols offer better stereopsis and increased visible retinal area, leading to improved screening accuracy compared with single-field protocols. This is particularly important in remote and underserved populations where access to care is limited and accurate triage of disease severity is critical to avoid unnecessary referrals or missing potentially vision-threatening disease.

An efficient, cost-effective, clinically validated, nonmydriatic method of retinal imaging would provide greater access to diabetic eye care, ranging from primary clinics to resource-poor settings worldwide, thus decreasing the risk of visual loss and preserving vision. In this study, we evaluated the EIDON device to rigorously assess agreement of DR severity within the ETDRS area as compared with the same area using a well-validated imaging system.

## Methods

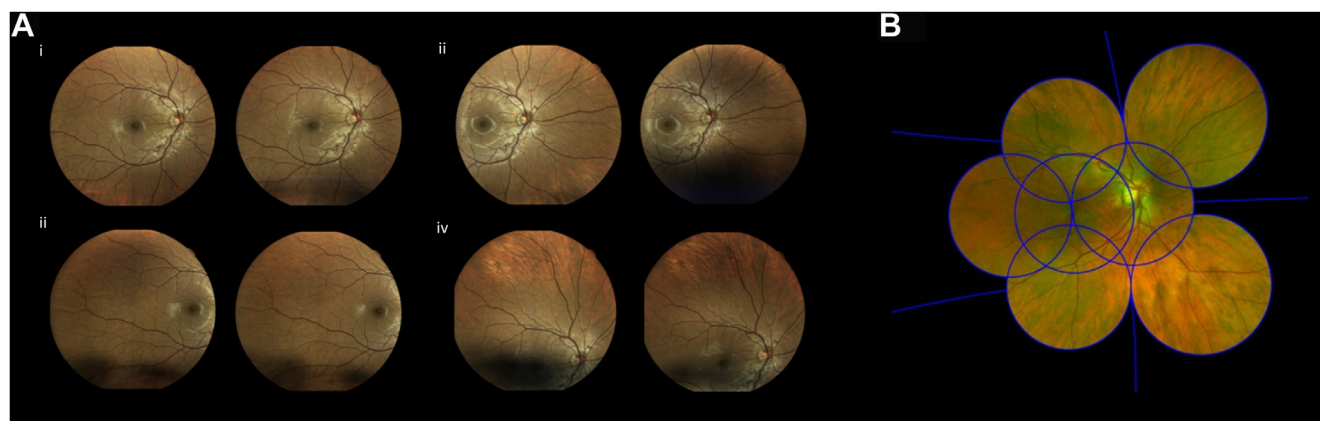
This was a single-center, masked, multireader study that evaluated the agreement in assessing severity of DR between EIDON images and the ETDRS 7-standard field area of UWF images. Participant eligibility was determined from medical record review of the most recently diagnosed clinical level of DR. Participants were selected sequentially to ensure adequate distribution of various DR severity levels, ranging from no DR (ETDRS level 10) to high-risk proliferative DR (ETDRS level 75).<sup>9</sup> The recruitment of patients was weighted toward those with mild to moderate levels of DR because more severe changes of DR would most likely be easier to identify. More than 80% of participants enrolled demonstrated documented DR on clinical examination, approximately 70% showed varying levels of nonproliferative DR (NPDR), 43.6% showed potentially sight-threatening DR (moderate NPDR or worse), and 5.4% showed proliferative DR.

All participants were recruited during regularly scheduled appointments from the clinic population of the Beetham Eye Institute

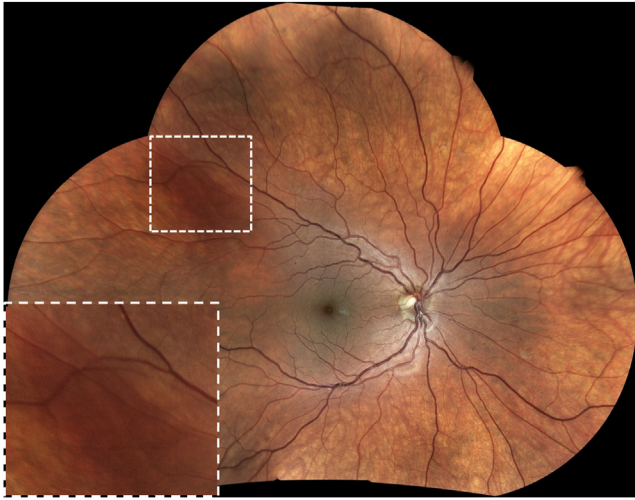
at the Joslin Diabetes Center, a tertiary eye care center specializing in diabetic eye disease. Inclusion criteria were age older than 18 years, type 1 or type 2 diabetes mellitus as defined by the American Diabetes Association,<sup>10</sup> and willingness to undergo UWF and EIDON imaging sessions. Exclusion criteria were a history of conditions in either eye that may preclude pupil dilation, use of eye drops (mydriatic or miotic) that would alter pupil size or reactivity, and known significant media opacities precluding adequate imaging of the retina. The research was conducted according to the tenets of the Declaration of Helsinki and received Joslin Committee of Human Studies review and approval. All enrolled participants signed a Joslin Committee of Human Studies approved consent form after explanation of the nature of the study.

Each participant underwent nonmydriatic retinal imaging using the EIDON camera with ophthalmic photographer-guided stereoscopic imaging of 4 EIDON fields (macula centered, disc centered, temporal macula, and superotemporal; Fig 1A). After EIDON imaging, pupils were dilated with 1% tropicamide and 2.5% phenylephrine hydrochloride. Ultrawide-field retinal images (Optos; Optos, plc) were acquired using a nonsimultaneous stereographic protocol previously described.<sup>11</sup> All images were uploaded to a secure cloud server database for image storage and retrieval. Before grading of the UWF images, a standardized ETDRS 7-standard field image mask was applied to all UWF retinal images that precluded evaluation of the retina outside this area (Fig 1B). With the EIDON device, only individual images were evaluated and assessed for DR severity. The EIDON montaged images were not evaluated in this study because of the possible distortion of montaging and edge errors that have been observed with this type of image processing (Fig 2).

In this study, each eye was assessed according to the ETDRS extension of the modified Airlie House classification of DR for the presence and severity of specific DR lesions.<sup>9</sup> A single independent masked reader (P.S.S.) experienced in evaluating nonmydriatic SLO images evaluated the EIDON images for the presence and severity of DR. A separate independent masked reader (M.A.) experienced in grading UWF and ETDRS retinal images evaluated the UWF ETDRS images for the same parameters. Agreement between graders at the Joslin Vision Network Retinal Reading Center with regard to grading DR level has been demonstrated to have substantial to almost perfect agreement (internal reading center quality control,  $\kappa = 0.80 \pm 0.13$ ,  $\kappa_w = 0.95 \pm 0.04$ ).<sup>12</sup> The retinal findings for both UWF ETDRS



**Figure 1.** A, Confocal widefield scanning laser ophthalmoscopy (EIDON) images. Four stereoscopic pairs, as follows: macula centered (i), disc centered (ii), temporal macula (iii), and superotemporal (iv). B, Ultrawide-field image with the ETDRS 7-field image mask applied.



**Figure 2.** Confocal widefield scanning laser ophthalmoscopy (EIDON) 4-image montage: macula centered, disc centered, temporal macula, and superotemporal. Inset shows a magnified view of an area in the superotemporal retina with artifactual retinal vessel duplication resulting from image montaging errors.

images and EIDON images were recorded on electronic medical record grading templates according to already established and validated grading protocols.<sup>11</sup> The ETDRS clinical level of DR was compared between EIDON and UWF ETDRS images.

The EIDON images were uploaded for access through the Axis image management system (Sonomed Escalon), which provides a digital interface for secure review of the retinal images. The UWF ETDRS images were uploaded into the Optos Advance image management system (Optos plc), which similarly provides a digital interface for secure review of the retinal images. All images were displayed on 27-inch, color-calibrated, high-definition LCD monitors (model VG278H; Asus) with Quadro 600 video cards (Nvidia). The primary display monitors are part of the Joslin Vision Network Reading Center and are calibrated biannually to a color temperature of 6500 K and a  $\gamma$  setting of 2.2 (i1Display, Gretag Macbeth; X-Rite Inc). All image graders were allowed to magnify and adjust the image color, contrast, brightness, and  $\gamma$  correction as desired.

### Retinal Image Discrepancy Adjudication

All UWF ETDRS and EIDON images that showed discrepancies in DR severity underwent a direct side-by-side comparison by an independent senior retinal grader (J.D.C.) to identify the source of discrepancy and to determine the preferred method in evaluating that eye. The final adjudicated level of DR was determined based on the adjudicated and side-by-side grading of both the EIDON and UWF ETDRS images. Image adjudications in image validation studies are an essential component and are necessary to standardize grader disagreements or errors.

### Statistical Analysis

Diabetic retinopathy severity derived from the UWF ETDRS images was considered the reference standard. Agreement of clinical ETDRS level of DR severity between EIDON and UWF ETDRS images was cross-tabulated, and both simple and weighted (linear scheme)  $\kappa$  statistics were calculated. Guidelines for interpretation were based on Landis and Koch as used in ETDRS report number

10: 0.0 to 0.2, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and 0.81 to 1.00, almost perfect agreement.<sup>13</sup> All statistical analyses were performed using SAS version 9.4 software (SAS, Inc).

## Results

One hundred ten eyes of 55 patients with diabetes mellitus were evaluated. The severity of DR derived from UWF ETDRS images compared with the EIDON images is shown in [Table 1](#) (after adjudication) and [Table 2](#) (before adjudication). By design, the prevalence of DR evaluated in this study did not reflect the generalized severity distribution of DR in the clinic, but rather was intentionally enriched with participants with DR so as to test the ability of the camera system to detect disease more rigorously. In this study, only 10.9% of participants (12 eyes) enrolled did not have DR, in contrast to general clinic population cohorts, which vary from 60 to 80% with no DR. None of the images acquired in this study were ungradable for DR.

After initial grading of EIDON and UWF ETDRS images, adjudication was required for 41 eyes (37.2%). After side-by-side adjudication, EIDON images were judged to be more accurate in 11 eyes (26.8%), UWF ETDRS images were more accurate in 10 eyes (24.4%), and the methods showed similar accuracy in 20 eyes (48.8%). For the 20 eyes with similarly accurate images, grader disagreement was the reason for the difference, which was distributed equivalently between EIDON images ( $n = 11$ ) or UWF ETDRS images ( $n = 9$ ). When either EIDON images ( $n = 11$ ) or UWF ETDRS images ( $n = 10$ ) were identified as the more accurate method, the major reason for the difference was suboptimal image quality of the other method (UWF,  $n = 6$ ; UWF ETDRS,  $n = 9$ ).

After adjudication, comparison between the level of DR identified on EIDON images agreed exactly with UWF ETDRS images in 87.3% of eyes ( $n = 96$ ) and was within 1 step in 99.1% of eyes ( $n = 109$ ), with a simple  $\kappa$  value of  $0.8244 \pm 0.0439$  (95% confidence interval [CI], 0.7385–0.9104) and weighted (linear)  $\kappa$  value of  $0.9041 \pm 0.0257$  (95% CI, 0.8537–0.9545; [Table 1](#)). Sensitivity and specificity compared with ETDRS field grading for any DR were 0.96 and 0.75, those for moderate NPDR or worse were 0.96 and 0.97, and those for severe NPDR or worse were 0.91 and 1.00, respectively.

## Discussion

This study assessed agreement between 4-field stereoscopic EIDON images and the retinal ETDRS area acquired using UWF imaging for determining DR severity in patients with type 1 or type 2 diabetes. In this cohort of eyes, EIDON images demonstrated substantial agreement with the clinical level of DR severity as compared with the ETDRS 7-standard field area acquired with dilated UWF imaging. The resolution of the EIDON images exceeded the minimum standards to identify diabetic retinal changes.<sup>14</sup> This

Table 1. Diabetic Retinopathy Severity Derived from EIDON and Ultrawide-field Treatment Diabetic Retinopathy Imaging before Reading Center Adjudication

Diabetic Retinopathy Level	Grading by Ultrawide-field ETDRS Imaging							Total by EIDON Imaging, No. (%)
	No Diabetic Retinopathy	Mild Nonproliferative Diabetic Retinopathy	Moderate Nonproliferative Diabetic Retinopathy	Severe Nonproliferative Diabetic Retinopathy	Proliferative Diabetic Retinopathy	Proliferative Diabetic Retinopathy with High-Risk Characteristics	Ungradable	
Grading by EIDON imaging								
No DR	9*	3†	0	0	0	0	0	12 (10.9)
Mild NPDR	3†	45*	2†	0	0	0	0	50 (45.5)
Moderate NPDR	0	1†	14*	0†	0	0	0	15 (13.6)
Severe NPDR	0	1	2†	11*	0†	0	0	14 (12.7)
PDR	0	0	0	2†	14*	0†	0	16 (14.6)
PDR with HRC	0	0	0	0	0†	3*	0	3 (2.7)
Ungradable	0	0	0	0	0	0†	0	0 (0)
Total by UWF ETDRS Imaging, no. (%)	12 (10.9)	50 (45.5)	18 (16.4)	13 (11.8)	14 (12.7)	3 (2.7)	0 (0)	110 (100)

DR = diabetic retinopathy; HRC = high-risk characteristics; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; UWF = ultrawide-field.

Simple  $\kappa$ , 0.8244 ± 0.0439 (95% confidence interval, 0.7385–0.9104). Weighted (linear)  $\kappa$ , 0.9041 ± 0.0257 (95% confidence interval, 0.8537–0.9545). Perfect agreement, 87.3% (n = 96); within 1 step, 99.1% (n = 109). Sensitivity and specificity: any DR, 0.96 and 0.75; moderate NPDR or worse, 0.96 and 0.97; and severe NPDR or worse, 0.91 and 1.00, respectively.

\*Indicates perfect agreement and † indicates within 1-step.

Table 2. Diabetic Retinopathy Severity Derived from EIDON and Ultrawide-field ETDRS Imaging before Reading Center Adjudication

Diabetic Retinopathy Level	Grading by Ultrawide-field ETDRS Imaging							Total by EIDON Imaging, No. (%)
	No Diabetic Retinopathy	Mild Nonproliferative Diabetic Retinopathy	Moderate Nonproliferative Diabetic Retinopathy	Severe Nonproliferative Diabetic Retinopathy	Proliferative Diabetic Retinopathy	Proliferative Diabetic Retinopathy with HRC	Ungradable	
Grading by EIDON images	*	†						
No DR	10*	3†	0	0	0	0	0	13 (11.8)
Mild NPDR	4†	36*	4†	0	0	0	0	44 (40)
Moderate NPDR	0	11†	6*	1†	0	0	0	18 (16.4)
Severe NPDR	0	2	5†	6*	3†	0	0	18 (14.6)
PDR	0	0	1	3†	11*	0†	0	15 (13.6)
PDR with HRC	0	0	1	0	3†	0*	0	4 (3.6)
Ungradable	0	0	0	0	0	0†	0	0 (0)
Total by UWF ETDRS imaging, no. (%)	13 (11.8)	53 (48.2)	17 (15.4)	10 (9.1)	17 (15.4)	0 (0)	0 (0)	110 (100)

DR = diabetic retinopathy; HRC = high-risk characteristics; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; UWF = ultrawide-field.

Simple  $\kappa$ , 0.4938 ± 0.0626 (95% confidence interval, 0.3711–0.6165). Weighted (linear)  $\kappa$ , 0.7074 ± 0.0411 (95% confidence interval, 0.6268–0.788). Perfect agreement, 62.7% (n = 69); within 1 step, 96.4% (n = 106). Sensitivity and specificity: any DR, 0.96 and 0.76; moderate NPDR or worse, 0.91 and 0.90; severe NPDR or worse, 0.96 and 0.89, respectively.



study did not evaluate any comparisons with regard to the retinal periphery, which also may influence substantially the risks and progression rates of DR.<sup>11,15</sup> Furthermore, grading variability is expected in clinical setting implementations of DR screening programs, emphasizing the importance of quality control and quality assurance programs to ensure standardization, particularly when new image methods are used.

As demonstrated in this study, high-quality retinal SLO images evaluated by experienced eye care providers can detect clinically significant DR successfully. The use of retinal imaging with remote reading by experts has substantial public health benefit in areas where qualified eye care professionals are not available and may enhance efficiency and potentially reduce costs when the expertise of ophthalmologists can be used preferentially for more complex cases and treatment. However, this study did not address retinal evaluation peripheral to the ETDRS area in terms of quality, nor in terms of differences in viewable area (EIDON, 110–150°; Optos, 200°), which are known to effect DR identification and risk of DR progression.<sup>11,15</sup>

## Footnotes and Disclosures

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**HUMAN SUBJECTS:** Human subjects were included in this study. The research was conducted according to the tenets of the Declaration of Helsinki and received Joslin Committee of Human Studies review and approval. All enrolled subjects signed a Joslin Committee of Human Studies approved consent form after explanation of the nature of the study.

In telehealth programs for DR, the imaging system is essential; however, it is only a single component of an entire system that includes substantial technical and operational infrastructure. All components of this system can affect outcomes of such a program. High-quality, lower-cost, nonmydriatic imaging is an important advance within these diabetic retinopathy screening programs. In this study, a lower-cost nonmydriatic 4-field stereoscopic imaging device compared favorably with the DR severity identified within the ETDRS area using validated dilated UWF ETDRS images. These results should be confirmed across diverse sites and broader diabetic populations to fully establish the applicability of EIDON imaging in both research and clinical settings.

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Conception and design: Silva

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Data collection: Ashraf, Hock, Cavallerano, Wang, Silva

Obtained funding: Silva, Wang

Overall responsibility: Ashraf, Hock, Cavallerano, Wang, Silva

Abbreviations and Acronyms:

**CI** = confidence interval; **DR** = diabetic retinopathy; **NPDR** = nonproliferative diabetic retinopathy; **SLO** = scanning laser ophthalmoscopy; **UWF** = ultrawide-field.

Keywords:

Diabetic retinopathy, EIDON, Scanning laser ophthalmoscope, Widefield retinal imaging.

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