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# The Influence of Ultra-Widefield Fluorescein Angiography on the Diagnosis and Management of Diabetic Retinopathy

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## Abstract

**Purpose:** To study the influence of ultra-widefield fluorescein angiography (FA) on the diagnosis and management of diabetic retinopathy (DR). **Methods:** Ten experts in DR completed an online survey in which they were asked to diagnose and manage DR cases using different imaging modalities. Experts independently reviewed 20 cases of DR and provided a diagnosis and management plan for each case, first based on ultra-widefield color-free and red-free images alone and again with the corresponding ultra-widefield FA images. Experts were polled on their diagnostic confidence, use of FA in clinical practice, and opinions on the value of ultra-widefield FA. Based on the reference standard diagnosis, primary outcomes included diagnostic sensitivity and specificity with and without ultra-widefield FA. Secondary outcomes included intergrader agreement, expert confidence, management outcomes, and an analysis of experts' opinions on the clinical use of ultra-widefield FA. **Results:** Diagnostic sensitivity (95% CI) increased from 36% (29%-43%) to 69% (62%-75%) ($P < .05$) with ultra-widefield FA. Intergrader agreement (Fleiss kappa statistic, 0.29 [95% CI, 0.21-0.27] vs 0.44 [95% CI, 0.40-0.47]; $P < .05$) and expert confidence (38% vs 65%) also improved. In 39% of responses, management was changed from observation to treatment. Although 40% of experts did not request FA with the initial ultra-widefield color-free/red-free images, 80% found ultra-widefield FA clinically useful when provided. **Conclusions:** Diagnosis, treatment, and expert opinions on the use of FA all changed when a corresponding ultra-widefield FA was available. Incorporating FA into routine clinical practice may facilitate more accurate clinical decision-making.

## Keywords

diabetic retinopathy, fluorescein angiography, ultra-wide field imaging

## Introduction

Diabetic retinopathy (DR) is the leading cause of visual impairment and blindness among working-age individuals.[1] Early screening, diagnosis, and intervention are essential to prevent the progression of retinopathy and visual morbidity, with reports suggesting that these measures may reduce severe vision loss by up to 90%.[2,3]

The gold standard for diagnosing DR severity was established with the Early Treatment of Diabetic Retinopathy Study (ETDRS), which used 7-field 35 mm 30-degree color fundus photographs.[4] The ETDRS DR severity scale is critical for research but may be difficult to implement clinically because it can be complex and time-consuming. Subsequently, the International Clinical DR severity scale was proposed as a simplified method of obtaining a clinical diagnosis.[5]

The most common method for diagnosing DR is with a dilated fundus examination. However, as the number of patients with DR increases,[6] and as telemedicine screening programs become more prevalent, digital fundus photography plays a greater role in the diagnosis of DR.[7–12] Ultra-widefield fundus imaging, comprising an image that includes a greater than 100-degree field of view,[13] is helpful for the screening, diagnosis, and treatment of DR. It has an advantage over the 7-field standard ETDRS photographs because it only requires a single digital image.

Studies have shown that nonmydriatic ultra-widefield color fundus images compare favorably and are acquired more

rapidly than the dilated 7-field ETDRS photographs.[14–16] The larger field of view allows for greater sensitivity in detection of neovascularization (NV) everywhere.[17] The DRCR Retina Network validated the use of ultra-widefield imaging for clinical research,[18] and it is now used in clinical examinations and telemedicine.[19–21]

Fluorescein angiography (FA) has also been integral to the detection and management of DR, highlighting vascular leakage, capillary and large vessel nonperfusion, microaneurysms, and other vascular abnormalities that may be difficult to appreciate on fundoscopy or color fundus photography alone.[22] With the advent of ultra-widefield imaging, the visualization of far peripheral retinal perfusion beyond the field of view of traditional 7-field ETDRS photographs is now possible, allowing for greater detection of nonperfusion and NV everywhere.[23] The significance of these far peripheral lesions is not clear, but some studies suggest that patients with predominantly peripheral lesions and peripheral nonperfusion may have an increased risk of progression and development of proliferative DR (PDR).[24,25] The DRCR Retina Network is exploring the prognostic value of these peripheral findings in Protocol AA.[26]

Although FA is an excellent imaging modality for evaluating DR, it has limitations. FA can be invasive and time-consuming, carries a small risk of anaphylaxis and other adverse reactions, and may have lower resolution compared with other imaging devices.

The purpose of our study was to examine how the diagnosis and management of DR is influenced by ultra-widefield FA compared with ultra-widefield color fundus and red-free images alone. We also aimed to better understand the role of FA in current clinical practice. Primary outcomes included specificity and sensitivity of DR grading with and without the availability of ultra-widefield FA. Secondary outcomes included intergrader agreement, changes in management, and expert opinions on the use of ultra-widefield imaging in the diagnosis and management of DR.

## Methods

This study was conducted in accordance with the Health Insurance Portability and Accountability Act guidelines and conformed to the tenets of the Declaration of Helsinki. This study was granted an exemption by the Institutional Review Board at the University of Illinois at Chicago.

### *Image Acquisition*

De-identified ultra-widefield images from 16 treatment-naïve diabetic subjects (20 eyes) were included. Patients with diabetes without DR, with nonproliferative DR (NPDR), and with PDR were included. For each eye, we used the ultra-widefield color fundus/red-free images and both early and late phase ultra-widefield FA images. All images were captured with the Optos 200Tx or the Optos California (Optos PLC). As part of a quality check, the study investigators critically reviewed every image selected for each case. Inspecting images for excellent clarity, absence of artifact, and lack of ambiguity ensured that they could be accurately analyzed under optimal conditions.

### *Consensus Reference Standard Diagnosis*

A consensus reference standard diagnosis was established for each image set by combining the clinical diagnosis (as determined by indirect ophthalmoscopy) with the color fundus/red-free image-based diagnosis of multiple experienced readers (A.A.F., J.E.K., J.I.L.). Similar methods have been previously described by the authors (J.P.C., R.V.P.C.) for studies related to other retinal conditions.[27] The consensus reference standard diagnosis in the current study was defined as the diagnosis given by the majority of the 3 readers based on indirect ophthalmoscopy and color fundus/red-free images, as in previous studies. The rationale for this was that combining information from both clinical examinations and imaging data may provide the most accurate diagnosis. Diagnosis and grading of DR commonly involves a combination of indirect ophthalmoscopy and color fundus/red-free imaging data. The consensus reference standard diagnosis was used only for the purposes of this study and was considered the correct diagnosis and reference point for result analysis in the absence of other gold standard grading systems for DR.

### *Study Experts*

Eligible participants were defined as board-certified, fellowship-trained, practicing vitreoretinal specialists who routinely evaluate patients with DR and meet at least 1 of the following criteria: has served as a clinical investigator for a DRCR Retina Network clinical trial or has published at least 2 peer-reviewed

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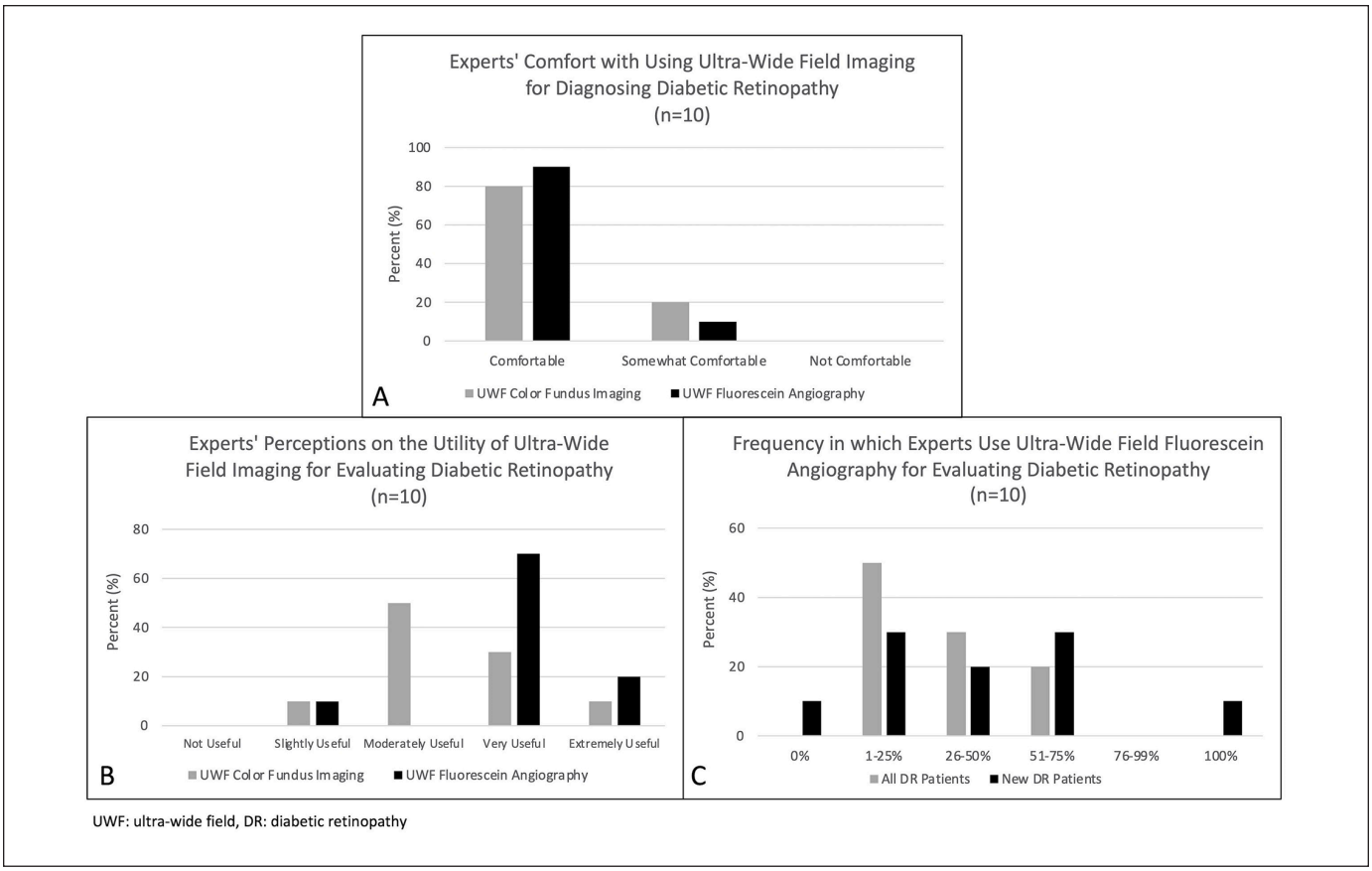



**Figure 1.** Experts' responses to the questions: (A) Rate your comfort in diagnosing diabetic retinopathy (DR) based on ultra-widefield color fundus photography and ultra-widefield fluorescein angiography (FA). (B) Rate how useful you find ultra-widefield color fundus and ultra-widefield FA for evaluating DR. (C) How often do you use ultra-widefield FA in your clinical practice to evaluate DR?

articles on DR. These participants are hereafter referred to in this study as experts.

## *Study Design*

Study experts were directed to a secure website developed by the authors (T.A., N.K.S., R.V.P.C.). Written consent was obtained. Baseline demographic data were collected, including type of fellowship training, years since completing fellowship, and level of comfort with reading color fundus and FA images (not comfortable, somewhat comfortable, or comfortable). We elicited how useful color fundus and FA images are for evaluating DR (not useful, slightly useful, moderately useful, very useful, or extremely useful), how often they use FA when evaluating patients with DR overall and with new patients with DR (0%, 1%-25%, 26%-50%, 51%-75%, or 75%-99% of the time), and any limitations to FA they experience. These results are shown in Figure 1.

Experts were presented with a series of 20 cases of DR. No demographic information was included. In Part I, the color fundus/red-free images were presented. The web-based platform supported magnification of all imaging. Experts were asked to diagnose each case sequentially based on these images alone. In Part II, each case was presented again in a new, random order. This image series included the corresponding ultra-widefield FA images (both early and late phase) in addition to the original ultra-widefield color fundus/red-free images.

For both Part I and Part II, experts were asked to grade the retinopathy (no DR, mild NPDR, moderate NPDR, severe NPDR, very severe NPDR, non-high-risk PDR, or high-risk PDR) and decide on a management plan (observation, treat with panretinal photocoagulation [PRP], treat with antivascular endothelial growth factor [anti-VEGF], or treat with both). Experts were asked to rate their confidence in identifying the correct diagnosis (not confident, somewhat confident, or confident), to recommend a time for follow-up (1 month, 2-3 months, 4-6 months, or 12 months), and answer questions regarding whether they would order an FA to obtain additional clinical information (Part I) or whether they found the FA provided clinically useful information (Part II) for diagnosis and management purposes (yes or no for both questions). Upon completion of each case, experts were unable to return to previous cases in either part of the study to review or alter their responses. The study methods are summarized in Figure 2.

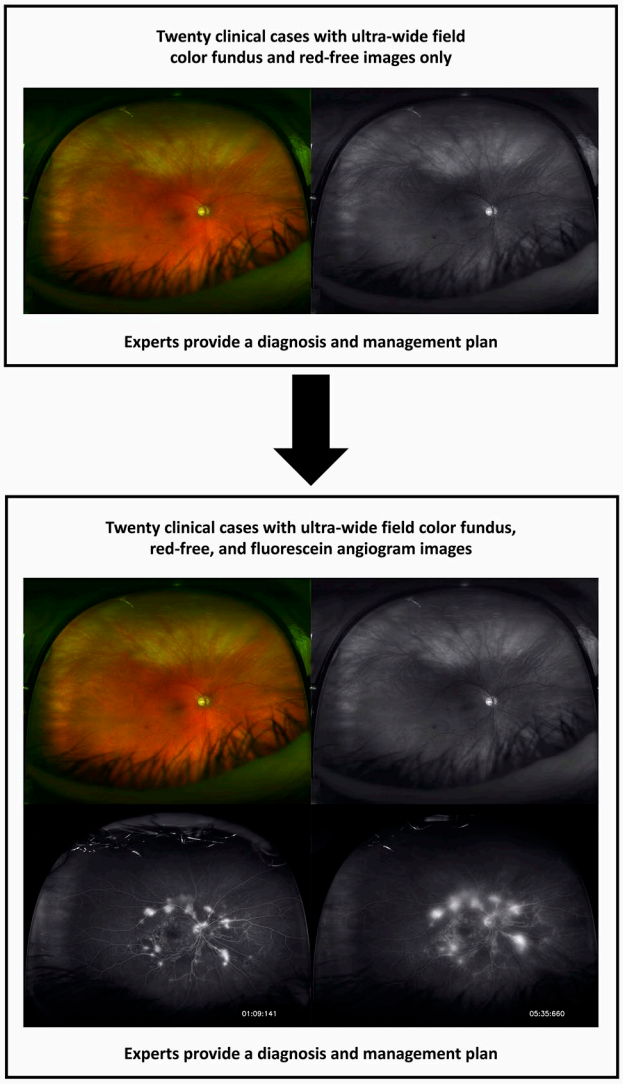



**Figure 2.** Survey study design presented to diabetic retinopathy experts. In Part I of the study, experts are presented with 20 clinical cases (color fundus and red-free images only) and are asked to provide the diagnosis, management plan, and recommended clinical follow-up. In Part II, experts are presented with the same cases in a new, random order with the addition of the corresponding fluorescein angiography. The experts are prompted again to provide the diagnosis, management, and recommended clinical follow-up. Experts are not able to see their previous responses from Part I.

### *Data Analysis*

Statistical analysis was performed using SPSS software (version 23, IBM Corp) unless otherwise mentioned. Diagnostic sensitivity and specificity were computed for each expert for Part I and Part II and compared with the consensus reference standard diagnosis. Diagnostic sensitivity and specificity were calculated overall for Part I and Part II and for subcategories of NPDR and PDR. The McNemar $\chi^2$ test was used to compare sensitivities and specificities.

Intergrader agreement was first analyzed with a Fleiss κ statistic to determine overall intergrader agreement for Part I and Part II. Using R (version 4.0, The R Foundation), the performance of individual experts was analyzed with a mean unweighted κ statistic. An unweighted Cohen's κ was calculated to measure chance-adjusted agreement for each head-to-head pairing of readers. Averages were taken to determine the mean unweighted κ for each reader overall, as well as for NDPR and PDR subcategories. The following accepted scale was used to interpret results: 0 to 0.20 indicated slight agreement, 0.21 to 0.40 indicated fair agreement, 0.41 to 0.60 indicated moderate agreement, 0.61 to 0.80 indicated substantial agreement, and 0.81 to 1.00 indicated near perfect agreement.[28] The average κ of all readers was then calculated for each category, and comparisons were made using a Wilcoxon sign-ranked test. The same test was used to determine if there were differences in the experts' confidence levels when providing a diagnosis with and without the ultra-widefield FA.

## Results

### *Diagnostic Sensitivity, Specificity, and Distribution of Expert Responses Based on Imaging Modality*

The diagnostic responses of the 10 experts to each of the 20 cases (in Part I and Part II) are shown in Figure 3. Overall, 20 cases ranged from no DR to high-risk PDR. Each graph shows the trend of increased diagnostic accuracy when the ultra-widefield FA was available compared with when ultra-widefield color fundus/red-free images were used alone. Experts agreed with the consensus reference standard diagnosis in 71 of 200 (35.5%) responses without the FA vs 137 of 200 (68.5%) responses with the FA ($P < .05$). Experts agreed with the consensus reference standard diagnosis for cases of PDR in 37 of 120 (30.8%) responses without the FA and 96 of 120 (80.0%) responses with the FA ($P < .05$). This coincides with the changes in diagnostic sensitivity and specificity when ultra-widefield FA was provided (Figure 4).

Experts altered their management choices when provided with ultra-widefield FA images. A total of 82 of 200 (43.0%) responses changed as a result of the availability of ultra-widefield FA. A majority of the treatment decision changes involved PDR cases (72/82 [87.8%] responses) where experts modified treatment recommendations from observation to PRP in 39 of 72 (54.2%) responses, observation to anti-VEGF therapy in 7 (9.7%) responses, and observation to both PRP and anti-VEGF therapy in 22 (30.5%) responses. The remaining 4 (5.6%) PDR case responses were changes from 1 intervention to another. Two case examples (non-high-risk and high-risk PDR) of diagnostic and management alterations based on ultra-widefield FA are displayed in Figure 5. NPDR cases represented 10 of 82 (12.2%)

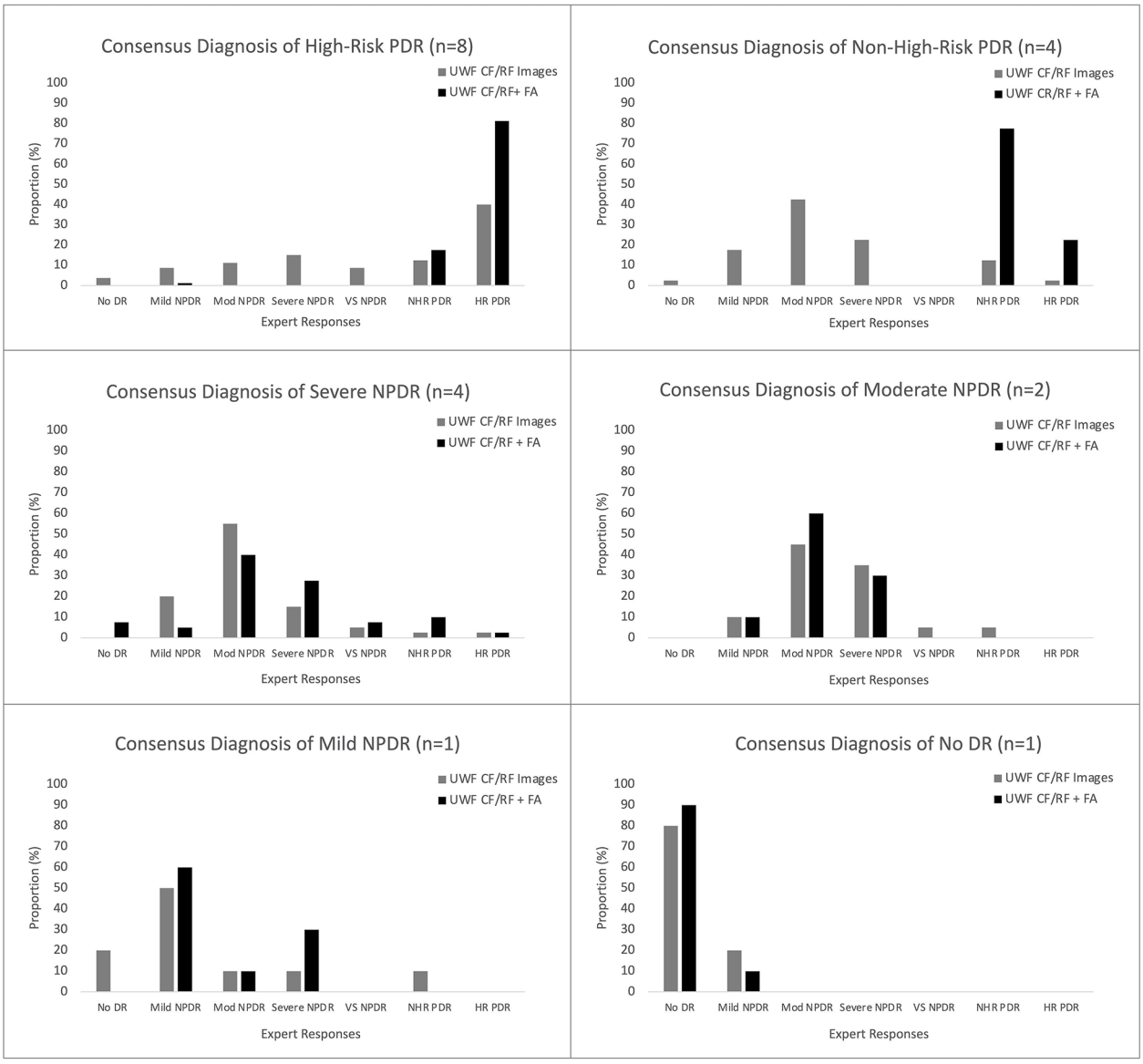



**Figure 3.** The 10 expert responses to each of the 20 presented cases. Cases are subdivided into different graphs based on their consensus reference standard diagnosis. The frequency with which experts selected each category of diabetic retinopathy (DR) based on the ultra-widefield color fundus and red-free images alone is compared with the addition of the corresponding ultra-widefield fluorescein angiography (FA). Increased diagnostic accuracy was more frequently associated with the use of ultra-widefield FA.

management change responses. All 10 were for severe NPDR cases, and 5 of 10 (50%) responses were to treat after the case was incorrectly diagnosed as PDR. No management changes occurred for no DR, mild NPDR, or moderate DR cases.

## *Intergrader Agreement*

In analyzing the intergrader agreement for grading of diabetic retinopathy, a Fleiss κ statistic was used for an overall comparison of intergrader agreement among all experts. The Fleiss κ statistic (95% CI) for ultra-widefield color fundus/red-free images alone was 0.24 (0.21-0.27) and increased to 0.44 (0.40-0.47) with the addition of ultra-widefield FA images ($P < .05$).

Mean intergrader agreement was calculated by averaging the unweighted Cohen's κ statistics of each expert compared with all other experts. Figure 6 displays a strip-plot of the mean unweighted κ for each expert in overall cases, as well as for NPDR and PDR cases, subcategorized into their agreement

| | Sensitivity (95% CI) | | *p* value | Specificity (95% CI) | | *p* value |
|---|---|---|---|---|---|---|
| DR Grade | UWF CF/RF Only | UWF CF/RF and FA | | UWF CF/RF Only | UWF CF/RF and FA | |
| All DR | 35.5% (28.9 –42.1%) | 68.5% (62.1 – 75.1%) | <0.05* | | | |
| NPDR | 42.5% (31.5 –54.1%) | 51.3% (39.8 –62.6%) | 0.32 | 30.8% (22.7 – 39.9%) | 80.0% (71.7 – 86.8%) | <0.05* |
| PDR | 30.8% (22.7 – 39.9%) | 80.0% (71.7 – 86.8%) | <0.05* | 42.5% (31.5 –54.1% | 51.3% (39.8 –62.6%) | 0.32 |

UWF: ultra-wide field, CF/RF: paired color fundus and red-free images, FA: fluorescein angiogram, CI: confidence interval, DR: diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy.
* statistically significant (p<0.05)

**Figure 4.** Differences in diagnostic sensitivity and specificity of experts when grading diabetic retinopathy cases with and without the corresponding ultra-widefield fluorescein angiography.

with ultra-widefield color fundus/red-free images alone and with the corresponding ultra-widefield FA images. Figure 6 also provides the averaged κ (95% CI) for all experts in each category.

### *Confidence of Clinical Diagnosis and Influence of Fluorescein Angiography*

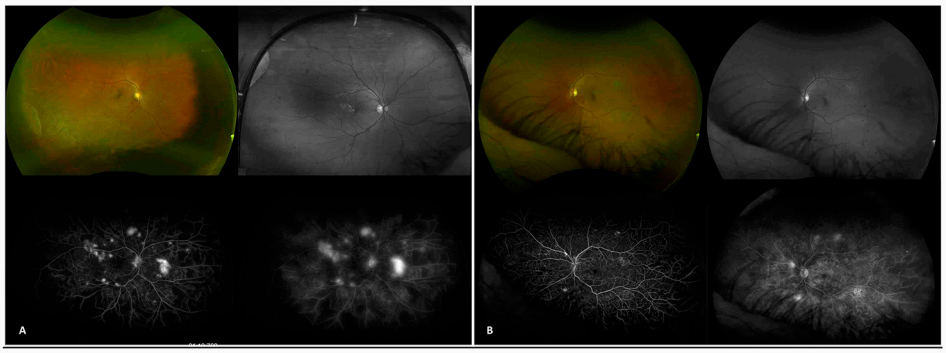
Overall, experts scored their subjective diagnostic confidence as "confident" in 64 of 200 (32.0%), "somewhat confident" in 110 (55.0%), and "not confident" in 26 (13.0%) when grading the ultra-widefield color fundus/red-free images alone. With the addition of ultra-widefield FA images, subjective confidence increased to "confident" in 133 of 200 (66.5%) and "somewhat confident" in 67 (33.5%) responses. None of the experts reported feeling "not confident" when grading the cases with availability of ultra-widefield FA. Experts felt significantly more "confident" and less "somewhat confident" or "not confident" with the addition of the ultra-widefield FA ($P < .05$ for all comparisons). A subgroup analysis of NPDR and PDR cases showed similar findings, reporting a statistically significant increase in diagnostic confidence when ultra-widefield FA was available ($P < .05$ for all comparisons).

After viewing the paired ultra-widefield color fundus/red-free images and answering questions regarding diagnosis and management in Part I, experts stated they would request an FA in 120 of 200 (60%) of the images. Although 40% of expert responses (80/200) stated they would not request an FA based on the ultra-widefield color fundus/red-free images in Part I, most experts found that ultra-widefield FA provided clinically useful information when it was presented in Part II (160/200 [80.0%] responses).

## Conclusions

This study examined whether diagnostic and management decisions were influenced by the inclusion of ultra-widefield FA as part of the image-based assessment for DR. The key findings of this study are as follows. Diagnostic sensitivity increased when ultra-widefield color fundus/red-free images and ultra-widefield FA images were reviewed in combination compared with when ultra-widefield color fundus/red-free images were reviewed alone. Intergrader agreement increased from "fair" to "moderate" with the addition of ultra-widefield FA. Subjective diagnostic confidence significantly improved with the addition of ultra-widefield FA. In conjunction with increased diagnostic sensitivity, particularly for PDR, management shifted toward a higher rate of treatment when ultra-widefield FA was included.

The increased diagnostic sensitivity was statistically significant overall (35% vs 69%, $P < .05$), as well as in cases of PDR (31% vs 80%, $P < .05$). The trend was similar, but not significant, in cases of NPDR (43% vs 51%, $P = .32$). In cases with a consensus reference standard diagnosis of non-high-risk PDR and high-risk PDR, ultra-widefield FA resulted in a shift toward fewer diagnoses of NPDR and more diagnoses of non-high-risk PDR and high-risk PDR (Figure 3). The greater diagnostic sensitivity for PDR with ultra-widefield FA likely reflects the angiogram's ability to highlight fibrovascular proliferation and NV that may be less apparent on color fundus photography alone.[29] The ability of ultra-widefield FA to highlight these and other vascular abnormalities has also been shown to be a beneficial tool for evaluating conditions such as uveitis and pediatric retinal diseases.[30–34] The use of ultra-widefield FA in the diagnosis and management of DR has been reported, but a direct comparison of FA vs color fundus/red-free images was last made in 1987, before the advent of ultra-widefield imaging.[22,23,29]



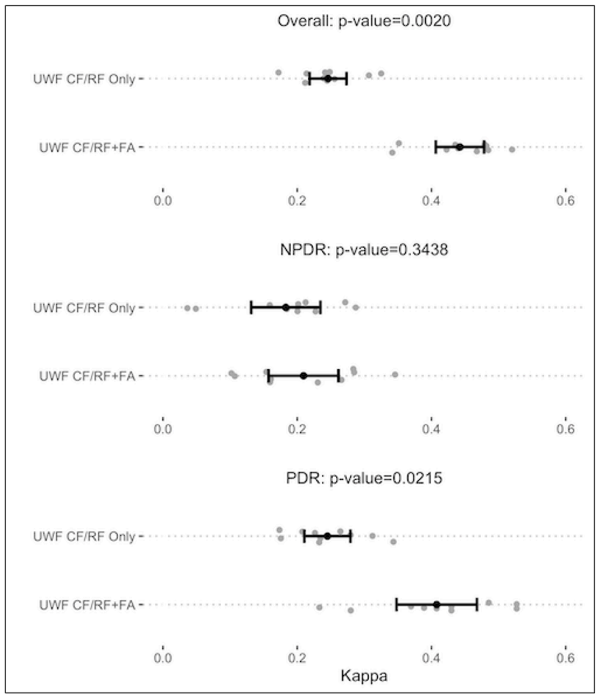

| Diagnostic Responses | UWF CF/RF Only | | UWF CF/RF and FA | |
|---|---|---|---|---|
| | **Case A** *HR PDR* | **Case B** *NHR PDR* | **Case A** *HR PDR* | **Case B** *NHR PDR* |
| HR PDR | 10% | - | 50% | 20% |
| NHR PDR | 10% | - | 40% | 80% |
| NPDR | 80% | 100% | 10% | - |

| Management Responses | UWF CF/RF Only | | UWF CF/RF and FA | |
|---|---|---|---|---|
| | **Case A** *HR PDR* | **Case B** *NHR PDR* | **Case A** *HR PDR* | **Case B** *NHR PDR* |
| Observe | 70% | 100% | - | - |
| PRP | 10% | - | 50% | 56% |
| Anti-VEGF | 10% | - | 20% | 11% |
| PRP & anti-VEGF | 10% | - | 30% | 33% |

UWF: ultra-wide field, CF/RF: paired color fundus and red-free images, FA: fluorescein angiogram, NPDR: non-proliferative diabetic retinopathy, NHR PDR: non-high-risk proliferative diabetic retinopathy, HR PDR: high-risk proliferative diabetic retinopathy, PRP: panretinal photocoagulation, Anti-VEGF: anti-vascular endothelial growth factor.

**Figure 5.** (A) A case of high-risk proliferative diabetic retinopathy (PDR) and (B) a case of non-high-risk PDR are shown. In (A), with ultra-widefield color fundus and red-free images alone, most experts (80%) selected a diagnosis of nonproliferative diabetic retinopathy (NPDR, 50% severe NPDR and 30% very severe NPDR). With the addition of ultra-widefield fluorescein angiography (FA), 90% of experts selected a diagnosis of PDR (40% non-high-risk PDR and 50% high-risk PDR). In (B), 80% of experts diagnosed the case as moderate NPDR with ultra-widefield color fundus/red-free images alone. None of the experts selected a diagnosis of proliferative disease. With the addition of FA, all experts changed their diagnosis to PDR (80% non-high-risk PDR and 20% high-risk PDR). With this change in diagnosis, management also changed in both cases. In (A), 70% of experts elected to observe the patient based on ultra-widefield color fundus/red-free images alone. With the addition of the ultra-widefield FA, 100% of experts treated the patient with either panretinal photocoagulation (PRP) (50%), antivascular endothelial growth factor (anti-VEGF) (20%), or both (30%). In (B), 100% of experts elected to observe based on color fundus/red-free photos alone. With the addition of ultra-widefield FA, 90% elected to treat the patient with PRP (56%), anti-VEGF (11%), or both (33%). When polling the experts, 100% found ultra-widefield FA useful for diagnosis and management in both cases.

Despite the overall increased diagnostic sensitivity when the consensus reference standard diagnosis was severe NPDR, experts were more likely to diagnose these cases as PDR with the addition of ultra-widefield FA (Figure 3). Previous reports have demonstrated a more severe assessment of DR with ultra-widefield imaging, as the wider field of view displays additional peripheral pathology previously unavailable with the standard 7-field ETDRS images.[17,24] The clinical significance of peripheral vascular leakage and nonperfusion often seen on ultra-widefield FA in cases of NPDR and PDR is under investigation.[26] Marcus et al,[35] for the DRCR Retina Network Protocol AA, reported on the enhanced ability of FA to identify predominantly peripheral lesions indicative of disease severity and predictive of disease progression compared with color fundus photography. At the 4-year follow-up, there was a statistically significant increased risk of disease worsening per the ETDRS Severity Scale if findings were noted on FA.[35] In addition, the DRCR Retina Network further identified that retinal nonperfusion, specifically, on ultra-widefield FA, is also a statistically significant indicator of disease worsening.[36] These findings may explain the increased likelihood of experts to diagnose PDR in our severe NPDR cases with ultra-widefield FA compared with ultra-widefield color fundus/red-free images alone.




UWF: ultra-wide field, CF/RF: paired color fundus and red-free images, FA: fluorescein angiogram, NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy.

**Figure 6.** Intergrader agreement measured as the unweighted kappa statistic. Each expert was compared with all other experts. This strip-plot displays the mean unweighted kappa statistic for a single expert (open circle) for each category. The average unweighted kappa statistic across all experts is displayed as a closed circle. The whiskers denote the 95% CI. The nonparametric sign test was used to determine statistical significance when comparing mean unweighted kappa statistics for paired ultra-widefield color fundus and red-free images alone vs the paired color fundus and red-free images with the corresponding fluorescein angiogram. $P < .05$ is considered significant.

Cases of moderate and severe NPDR had a higher diagnostic sensitivity with ultra-widefield FA compared with ultra-widefield color fundus/red-free images alone. While this trend did not reach statistical significance, it demonstrates the ability of ultra-widefield FA to accentuate the presence of microaneurysms, intraretinal microvascular abnormalities, and venous beading used in the grading of NPDR (Figure 3).

In our study, there was "fair" intergrader agreement among the 10 experts when diagnosing DR category based on ultra-widefield color fundus/red-free imaging. Previous studies using 7 standard field photos have demonstrated "substantial" agreement among nonophthalmologists in identifying hemorrhages, microaneurysms, hard exudates, and NV everywhere. Features including venous beading, intraretinal microvascular abnormalities, and NV of the disc had "moderate" agreement based on weighted κ values.[4] Similarly, Bursell et al[37] examined intergrader agreement between 2 graders using standard field photos and found "near perfect" agreement for hemorrhages or microaneurysms, "substantial" agreement for intraretinal microvascular abnormalities and NV of the disc, and "moderate" agreement for venous beading, hard exudates, and NV everywhere. Of note, in our study, there was only 30.8% agreement among experts when diagnosing cases of PDR using color fundus/red-free images alone. Grauslund et al[38] reported similar findings in a small study of 2 experts examining 45-degree color fundus photographs for lesions suggestive of DR. The authors calculated the intraclass correlation coefficient to understand the level of agreement among the 2 experts. This study was conducted via a virtual platform. There was high agreement when identifying microaneurysms (0.81), hemorrhages (0.83), and hard exudates (0.91); however, there was notably very low agreement when identifying NV (0.07).[38] While a larger sample size would allow for a higher-powered study and improved generalizability, these findings shed light on the difficulty of identifying NV on color fundus photographs alone. This corresponds with the findings in our study. Future work, including a larger sample size of retina specialists, should focus on examining the agreement on diagnosis of DR category based on ultra-widefield color fundus/red-free imaging.

When supplementing ultra-widefield color fundus/red-free images with ultra-widefield FA, increased intergrader agreement was seen among the experts in this study. The Fleiss κ statistic increased from 0.24 to 0.44 with the addition of ultra-widefield FA ($P < .05$). Using a widely accepted scale for κ interpretation, agreement increased from "fair" to "moderate."[28] The mean unweighted κ statistics for each expert also showed a trend toward their individual improvement with the addition of ultra-widefield FA (Figure 6). Ultra-widefield FA may be a useful adjunct to improve diagnostic agreement among DR examiners for image-based diagnosis. Similarly, Klufas et al[39] conducted a study that compared experts' diagnoses of retinopathy of prematurity (ROP) cases with a consensus reference standard diagnosis before and after the presentation of the corresponding FA. With the inclusion of FA, there were statistically significant increases in sensitivity when identifying advanced disease and in intergrader agreement for cases requiring treatment. FA is able to capture severe disease more clearly and may play an integral role in timely diagnosis and management. Looking forward, less invasive imaging techniques such as widefield and ultra-widefield optical coherence tomography (OCT) angiography (OCTA) could be a possible alternative to ultra-widefield FA. However, these devices are not widely available, and the role of ultra-widefield OCTA in DR management is currently not well established.[40–46] In the growing world of telemedicine, determining the most accurate method of obtaining a diagnosis with digital imaging may be critical to optimize patient outcomes.[6–12]

Concomitant with improved intergrader agreement, experts also reported increased confidence in their diagnoses with the ultra-widefield FA compared with ultra-widefield color fundus/red-free images alone (32% vs 66.5%, $P < .05$). However, despite an increased diagnostic sensitivity, improved intergrader agreement, and increased diagnostic confidence, 40% of experts reported they would not obtain an FA based on the ultra-widefield

color fundus/red-free images presented in Part I. Additionally, most experts (80%) reported using FA for the management of DR less than 50% of the time in their own clinical practice. The rate of FA use was reportedly slightly increased when experts were asked specifically about new patients presenting with DR. The potential limitations to FA may hinder its routine usage in practice. Experts reported well-known limitations, including risks to the patient (anaphylaxis, nausea, discomfort), additional time and cost, disruption to clinic flow, media opacities or eyelashes obstructing the image, and the invasive nature of the procedure. In our study, 40% of experts would not obtain an FA based on the ultra-widefield color fundus/red-free images. If experts have the impression that FA is not necessary for clinical diagnosis and management, this may also contribute to its underuse.

Moreover, experts modified their management plan in 82 of 200 (41%) responses, with management toward a higher rate of treatment when ultra-widefield FA was included. A majority of these responses were cases of PDR (82.9%) that were graded as less severe (or NPDR) with ultra-widefield color fundus/red-free images alone. These results suggest that FA provides clinically relevant information that leads to modifications in the diagnosis and management of patients with DR. Interestingly, our experts agreed with this statement. Despite 40% reporting they would not order an FA based on the color fundus images in Part I, 80% of responses indicated that the FA, when presented in Part II, offered clinically useful information. Likewise, in the study on the use of FA for the diagnosis of ROP, more than 25% of management plans changed from observation to treating with laser or anti-VEGF therapy.[39]

The current study evaluates the impact of ultra-widefield FA on the diagnosis and management of DR compared with color fundus/red-free images alone. A majority of the literature on ultra-widefield FA focuses on the presence and prognostic value of the peripheral diabetic changes previously not visible on FA when the ETDRS grading scale was established. Wessel et al[23] reported ultra-widefield FA reveals approximately 4 times more retinal nonperfusion and 2 times more NV everywhere than the standard 7-field ETDRS FA photographs. Talks et al[17] demonstrated that approximately 11.7% of patients have peripheral NV everywhere outside of the standard 7-field ETDRS photographs. The clinical significance of the peripheral lesions are not well understood and are under investigation with the DRCR Retina Network Protocol AA.[26] Our study, alternatively, aims to understand the role of ultra-widefield FA in the diagnosis and management of DR compared with using color fundus/red-free images alone.

There are several potential limitations to this study. Experts were asked to diagnose and manage DR based on digital color fundus/red-free and FA images. Consequently, this study analyzes the impact of ultra-widefield FA on DR diagnosis by imaging alone, not the impact of ultra-widefield FA on DR diagnosis in the clinical setting. It does not reflect a real-life clinical encounter because patient information was not provided, and there was no opportunity for experts to perform a dilated fundus examination. Some studies have suggested, however, that ultra-widefield imaging is comparable to retinal photography and clinical examination.[14,47,48]

The cases selected were chosen for their excellent image quality, which may not reflect the reality of most clinical encounters. However, all images presented were required to be of equivalent quality to minimize any potential confounding variables when evaluated by the experts. No postimage processing was performed to alter any of the images. There was a lack of multimodal imaging, such as OCT, along with variability between experts' comfort with reading ultra-widefield color fundus, red-free, and FA images. All experts were, however, selected to participate based on the criteria that defined them as having adequate experience in the management of DR. The consensus reference standard diagnosis used in this study was established based on consensus from 3 experienced readers and was based on indirect ophthalmoscopy and color fundus/red-free imaging data. However, it is possible that the consensus reference standard diagnosis may not be completely accurate and DR may have been underdetected or undergraded.

Experts were presented with ultra-widefield color fundus/red-free images in Part I and ultra-widefield FA images in Part II. Part II immediately followed Part I, so experts had the option of completing the entire study in 1 sitting. In clinical practice, images are typically presented sequentially in a short amount of time. The aim of the current study was for images to resemble those in real-life practice. It is also possible experts left the study open on their devices and completed it after an unknown period of time.

This study contributes to the body of knowledge related to ultra-widefield imaging and DR. The findings show that ultra-widefield FA may improve the sensitivity of DR grading, particularly for PDR. The improvement in diagnostic accuracy may affect management outcomes with the potential to reduce the risk of progression and subsequent visual morbidity. The roles of ultra-widefield imaging and FA for the diagnosis and management of DR in the era of multimodal imaging and telemedicine continue to evolve. Further studies are needed to understand the optimal use of ultra-widefield FA in DR and assess how these results from expert image graders compare with nonexpert graders.

## Authors' Note

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## Ethical Approval

This study was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) guidelines and conformed to the tenets of the Declaration of Helsinki. This study was granted an exemption by the Institutional Review Board at the University of Illinois at Chicago.

## Statement of Informed Consent

Written informed consent was obtained from all subjects before the study.

## Declaration of Conflicting Interests

Dr. Kim is a consultant for Heidelberg Engineering and Optos. None of the other authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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