DETECTION OF CLINICALLY UNSUSPECTED RETINAL NEOVASCULARIZATION WITH WIDE-FIELD OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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Purpose: To evaluate wide-field optical coherence tomography angiography (OCTA) for detection of clinically unsuspected neovascularization (NV) in diabetic retinopathy (DR).

Methods: This prospective observational single-center study included adult patients with a clinical diagnosis of nonproliferative DR. Participants underwent a clinical examination, standard 7-field color photography, and OCTA with commercial and prototype swept-source devices. The wide-field OCTA was achieved by montaging five 6 × 10-mm scans from a prototype device into a 25 × 10-mm image and three 6 × 6-mm scans from a commercial device into a 15 × 6-mm image. A masked grader determined the retinopathy severity from color photographs. Two trained readers examined conventional and wide-field OCTA images for the presence of NV.

Results: Of 27 participants, photographic grading found 13 mild, 7 moderate, and 7 severe nonproliferative DR. Conventional 6 × 6-mm OCTA detected NV in 2 eyes (7%) and none with 3 × 3-mm scans. Both prototype and commercial wide-field OCTA detected NV in two additional eyes. The mean area of NV was 0.38 mm^2 (range 0.17–0.54 mm^2). All eyes with OCTA-detected NV were photographically graded as severe nonproliferative DR.

Conclusion: Wide-field OCTA can detect small NV not seen on clinical examination or color photographs and may improve the clinical evaluation of DR.

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Diabetic retinopathy (DR) is a leading cause of vision loss in working age population.[1,2] In DR, capillary damage from hyperglycemia can cause nonperfusion, hyperpermeability, neovascularization (NV), retinal edema, vitreous hemorrhage, traction retinal detachment, and vision loss. Retinal NV is a key clinical feature that predicts a risk of severe vision loss and requires sensitive detection and timely treatment to reduce the risk.[3] The standard of care for detecting NV is a careful dilated ophthalmoscopy or color fundus photography and fluorescein angiography (FA) when occult NV is suspected.[3] Among conventional methods, FA is considered as the most sensitive for detecting NV.[4] However, according to American Academy of Ophthalmology Preferred Practice Patterns on diabetic retinopathy,[5] routine use of FA is not indicated. It is usually recommended for the following situations: "to guide laser treatment of clinically significant macular edema, to evaluate unexplained visual loss, and to identify suspected by clinically obscure retinal neovascularization."

Optical coherence tomography angiography (OCTA) is a novel technique that can provide clinically useful quantitative and qualitative information in DR.[6–15] The currently available OCTA systems, however, have a limited field of view, typically 3 × 3 mm or 6 × 6 mm. Many NV lesions occur outside this area, limiting the sensitivity of OCTA to diagnose proliferative DR.[16] The current study evaluates the value of wide-field OCTA (WF-OCTA) versus conventional OCTA for detection of clinically unsuspected NV in DR.

Methods

The institutional review board of Oregon Health Science University approved this prospective clinical

observational single-center study, which complies with the Health Insurance Portability and Accountability Act of 1996, and adheres to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the participants.

The study team recruited patients from the retina clinic of an academic center with a clinical diagnosis of nonproliferative DR (NPDR) of any severity without other significant concurrent ocular pathology. Eyes with significant media opacity or poor vision that precludes fixation were excluded. When both eyes of the same patient were eligible for study, one eye was randomly selected for inclusion.

All participants underwent comprehensive ophthalmic clinical examinations including standard Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity, intraocular pressure, slit-lamp biomicroscopy, and indirect binocular ophthalmoscopy. Imaging procedures included standard 7-field ETDRS color fundus photographs, a commercial 70-kHz spectral domain OCT (RTVue-XR; Optovue, Fremont, CA) with 840-nm central wavelength and a 200-kHz experimental swept-source OCT device using 1.4-mW light source at 1,050 nm. Fluorescein angiography was performed when the treating physician determined it was clinically necessary.

The commercial system first acquired conventional OCTA volumetric scans of 3×3 mm and 6×6 mm centered at the fovea with 400×400 sampling density. Two repeated B-scans at the same location were acquired and processed by the commercial version of the split-spectrum amplitude-decorrelation angiography. Each scan consisted of two orthogonal acquisitions in horizontal and vertical priority directions registered into a single volumetric data cube by the proprietary software.[17] Retinal layers were segmented by a directional graph search algorithm, generating a superficial vascular angiogram and a vitreous angiogram by projecting the maximum flow signal located within ganglion cell complex layer and vitreous layer, respectively.[18] To acquire a wider field of view, 2 additional 6×6-mm scans centered on the disk and temporal to the fovea were performed, generating a 15×6-mm montage using the three 6×6-mm angiograms.[19]

To obtain WF-OCTA using the high-speed prototype swept-source OCT, five 6×10 mm with 850×400 sampling density were captured, centered on the fovea, the disk, the midpoint between the disk and the macula, nasal to the disk and temporal to the macula. Each scan was repeated at the same location. A regression-based algorithm[20] was applied to remove the bulk motion contribution to flow signal three-dimensionally. After superficial vascular angiograms and vitreous angiograms were generated, a parallel strip registration algorithm[21] was applied to remove microsaccadic artifact by merging two en face angiograms acquired on the same region. Then, five individual-registered, motion-free angiograms were montaged into an ultra-WF view (25×10-mm).

An experienced retinal specialist (T.S.H.), masked from OCTA images, determined the severity of DR based on 7-field ETDRS color fundus photographs according to the International Clinical Diabetic Retinopathy Disease Severity Scale.[22] Masked from clinical information, two trained graders (Q.S.Y. and Y.G.) evaluated WF-OCTA and conventional OCTA qualitatively for vascular abnormalities using customized algorithm as reported previously.[21,23,24] Flow signal detected in the vitreous slab was considered retinal NV. Finally, a panel (T.S.H., Q.S.Y., Y.J., Y.G., and J.W.) performed a side-by-side comparison of the prototype WF-OCTA images and montaged commercial multifield OCTA images, conventional 6×6-mm macular OCTA images, and color fundus photographs to determine whether the NV detected by OCTA is clearly recognizable as such on color photographs.

Statistical analysis was conducted using Statistical Package for Social Sciences software (SPSS for Windows, version 25.0; IBM SPSS, Inc, Chicago, IL). Descriptive statistics that included mean, standard deviation (SD), range, and percentages were presented where appropriate. The McNemar test was used to compare the sensitivity of detection of retinal NV of prototype WF-OCTA system and macular 6×6-mm scan with commercially available OCTA system. The chi-square test was used to compare the percentage of eyes treated with anti–vascular endothelial growth

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All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Oregon Health & Science University (OHSU) and Y. Jia and D. Huang have a significant financial interest in Optovue, Inc, a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU. No other disclosures were reported.

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Table 1. Clinical Characteristics of the Study Participants

Parameters	Eyes With NV on WF-OCTA	Eyes Without NV	Combined
Photographic retinopathy severity			
Mild NPDR	0	13	13
Moderate NPDR	0	7	7
Severe NPDR	4	3	7
Total	4	23	27
Age mean ± SD (range), years	64.5 ± 7.9 (56–73)	63.9 ± 13.6 (25–78)	64.0 ± 12.8 (25–78)
Female (%)	1 (25)	10 (43)	11 (41)
Type I diabetes (%)	0 (0)	4 (17)	4 (15)
Laterality (right/left)	2/2	13/10	15/12
logMAR visual acuity ± SD (Snellen ± SD)	0.13 ± 0.15 (20/26 ± 20/77)	0.17 ± 0.17 (20/28 ± 20/24)	0.16 ± 0.16 (20/24 ± 20/24)
Pseudophakia (%)	2 (50)	12 (52)	14 (52)
Eyes with anti-VEGF treatment >60 days prior (%)	3 (75)	3 (13)	6 (22)
Eyes with anti-VEGF treatment within 60 days (%)	0 (0)	6 (26)	6 (22)

logMAR, logarithm of the minimum angle of resolution.

factor (anti-VEGF) between eyes with and without retinal NV. The Mann–Whitney test was used to compare the nonperfusion area in the superficial plexus between eyes with and without retinal NV. All *P* values were 2-sided and considered statistically significant if the value was less than 0.05.

Results

Twenty-seven patients with NPDR were enrolled, including 13 mild, 7 moderate, and 7 severe NPDR. The participant characteristics are summarized in Table 1. The swept-source OCT WF-OCTA and

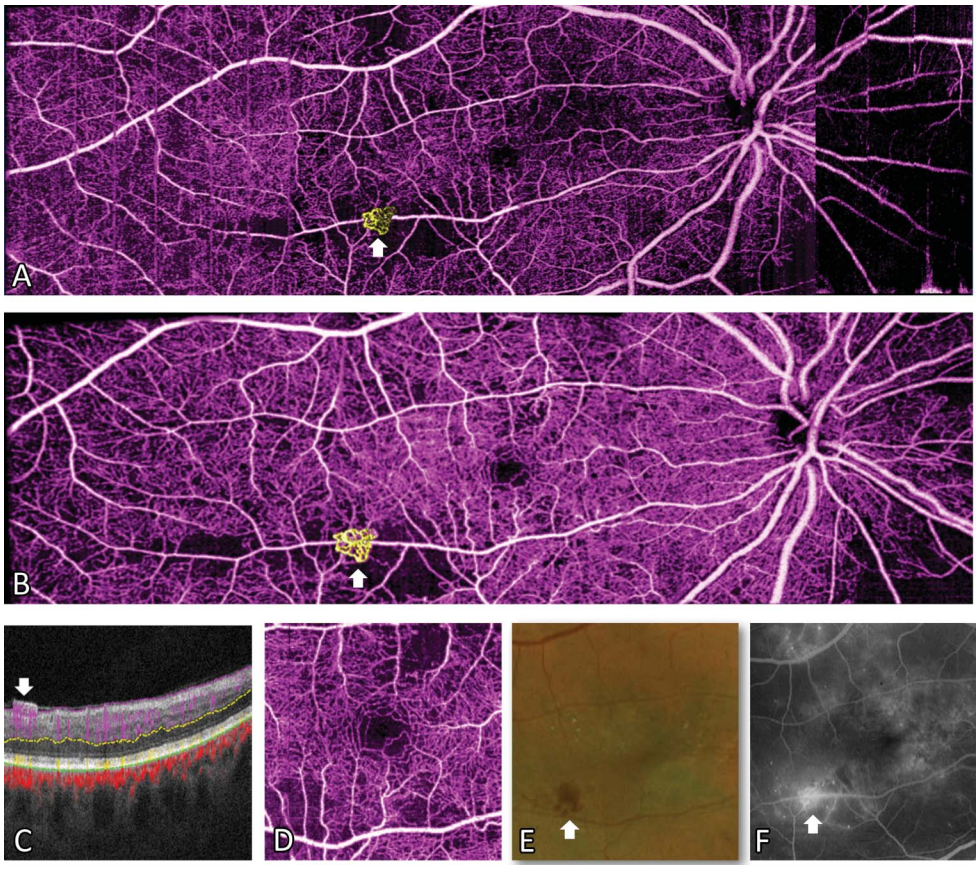

Fig. 1. The prototype WF-OCTA (**A**) shows a frond of NV (arrow) on the inferotemporal arcade. Magenta indicates the retinal slab, and yellow indicates the vitreous slab. The montage of 3 commercial 6 × 6-mm scans (**B**) and cross-sectional angiogram (**C**) with flow signal indicated in magenta also demonstrate the NV (arrows). This is outside the field of the central macular 3 × 3-mm scan (**D**). On the color photograph (**E**), the area of the NV looks like a retinal hemorrhage without a distinct vascular pattern (arrow). Fluorescein angiography (**F**) demonstrates profuse leakage from the NV (arrow).

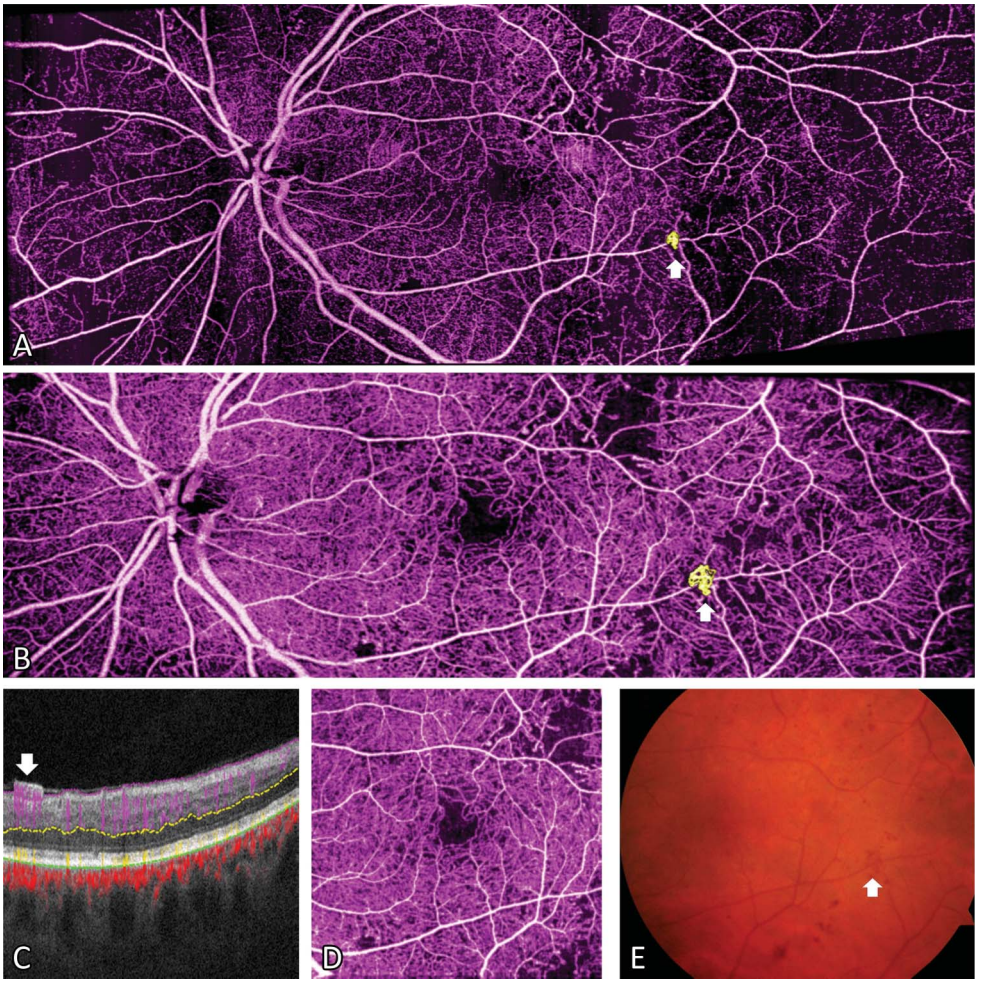

Fig. 2. The prototype WF-OCTA (**A**) reveals NV (arrow) along the inferotemporal arcade with an area of 0.26 mm^2. Magenta indicates the retinal slab, and yellow indicates the vitreous slab. The montage of 3 commercial 6 × 6-mm scans (**B**) and cross-sectional angiogram (**C**) with flow signal indicated in magenta also demonstrate the NV (arrow), which was not detected with central 6 × 6-mm (**D**) scan. On the color fundus photograph (**E**), the area of NV looks like a retinal hemorrhage (arrow).

montaged spectral domain OCT WF-OCTA detected retinal NV in 4 eyes (4/27, 15%), while the conventional OCTA 6 × 6-mm central scan detected NV in 2 eyes (2/27, 7%) (McNemar test, $P = 0.50$). The 3 × 3-mm scans did not detect NV in any eyes (Figures 1–4).

Of the four eyes with detected NV, 2 were graded by the clinician as moderate NPDR, but all were graded as severe NPDR based on the 7-field color photographs. Three of the 4 eyes (75%) with NV detected on OCTA had a history of intravitreal anti-VEGF injections greater than 2 months before the study visit for diabetic macular edema compared with 3 of 23 eyes (13%) without detected NV (chi-square test, $P = 0.03$). Six patients without detected NV had received an anti-VEGF injection within 60 days of the study visit.

The mean area of NV was small at 0.38 mm^2 (range 0.17–0.54 mm). There was no significant difference in the nonperfusion area in the superficial vascular plexus between eyes with NV and without NV both on macular central 6 × 6-mm ($P = 0.19$, Mann–Whitney test) and 3 × 3-mm ($P = 0.13$) scans.

When examined side-by-side, the areas of NV clearly seen on OCTA were difficult to identify on color photographs (Figures 1–4) even when the exact locations were known. When an FA was obtained (Figure 1), the area of NV showed characteristic leakage. However, the vessel details were not distinct on FA due to the leakage compared with OCTA.

Discussion

In this study, OCTA detected subtle retinal NV in eyes with DR that experienced clinicians did not suspect. Four of seven eyes photographically graded as severe NPDR had small tufts of NV on OCTA. Even when we re-examined the photographs after seeing the OCTA demonstrating the NV, we could not identify the vessels on the color photographs. Compared with the conventional OCTA, WF-OCTA identified more eyes with NV. The ability to detect NV more unambiguously compared with clinical examination or color photographs can be a significant

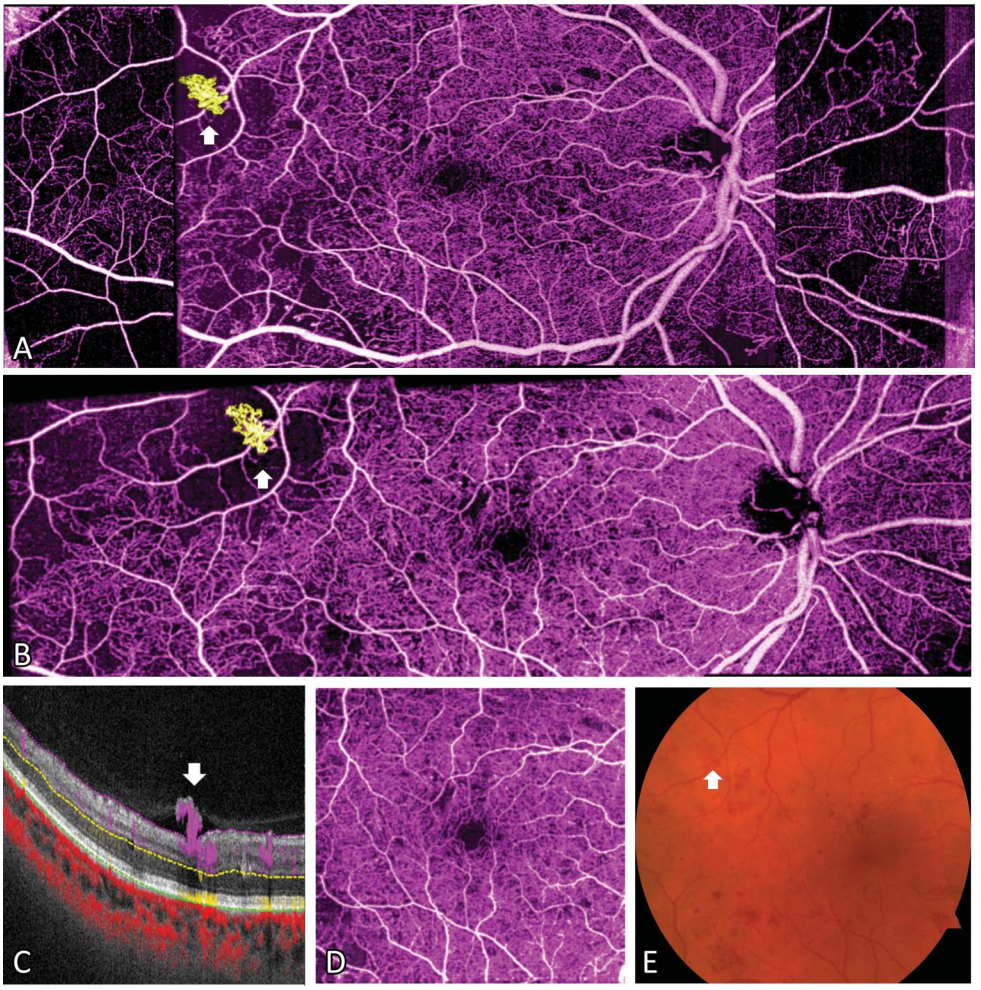

Fig. 3. Both prototype WF-OCTA (**A**) and WF-OCTA from montaging scans from commercial device (**B**) revealed NV (arrows) along the superotemporal arcade with an area of 0.54 mm^2. Magenta indicates the retinal slab, and yellow indicates the vitreous slab. The cross-sectional angiogram through the lesion (**C**) demonstrates the flow signal in magenta (arrow). The NV was outside the field of view for the central 6 × 6-mm (**D**) scans. On the color fundus photograph (**E**), it is difficult to identify the NV (arrow).

improvement in the management of DR. Because OCTA is faster and safer compared with FA, it may be more suitable for routine use in DR management.

Three of the four eyes that had clinically unsuspected NV had a distant history of anti-VEGF treatment. The eyes on discontinuous treatment schedule for diabetic macular edema, such as Diabetic Retinopathy Clinical Research Network pro re nata protocol,[25] where VEGF is intermittently suppressed may be at a particularly high risk of developing NV that clinicians may have low suspicion for, as the focus of management decision is macular edema. This may be particularly true of Year 2 or 3 of anti-VEGF treatment for DME, where the number of injection and surveillance visits may be less frequent.[26] Optical coherence tomography angiography provides an objective screening tool for NV that can be safely used on routine basis in patients undergoing anti-VEGF treatment for diabetic macular edema.

It is possible that in the eyes with the history of anti-VEGF injections, the NV may have been easier to detect before treatment and became more difficult to detect clinically with treatment. However, if the NV was present before treatment, it remained clinically unsuspected and undetected by retinal specialists, supporting the idea that a noninvasive routine screening method for NV in the setting of no specific suspicion for NV may be helpful.

Furthermore, various authors have reported that anti-VEGF treatment can significantly reduce or mask the clinical findings of DR while not eliminating the risk of progression to proliferative disease.[27,28] This may further decrease the clinician's suspicion for NV. In the cases presented in this study, even with the appropriate clinical suspicion, we do not believe that the clinicians would have been able to make a definite diagnosis of NV based on examination and or have had an indication to pursue additional diagnostic testing to do so. Therefore, it may be reasonable to consider the routine use of a safe and inexpensive ancillary test that can augment the sensitivity to detect NV in patients undergoing anti-VEGF treatment for DME or those clinically graded as severe NPDR.

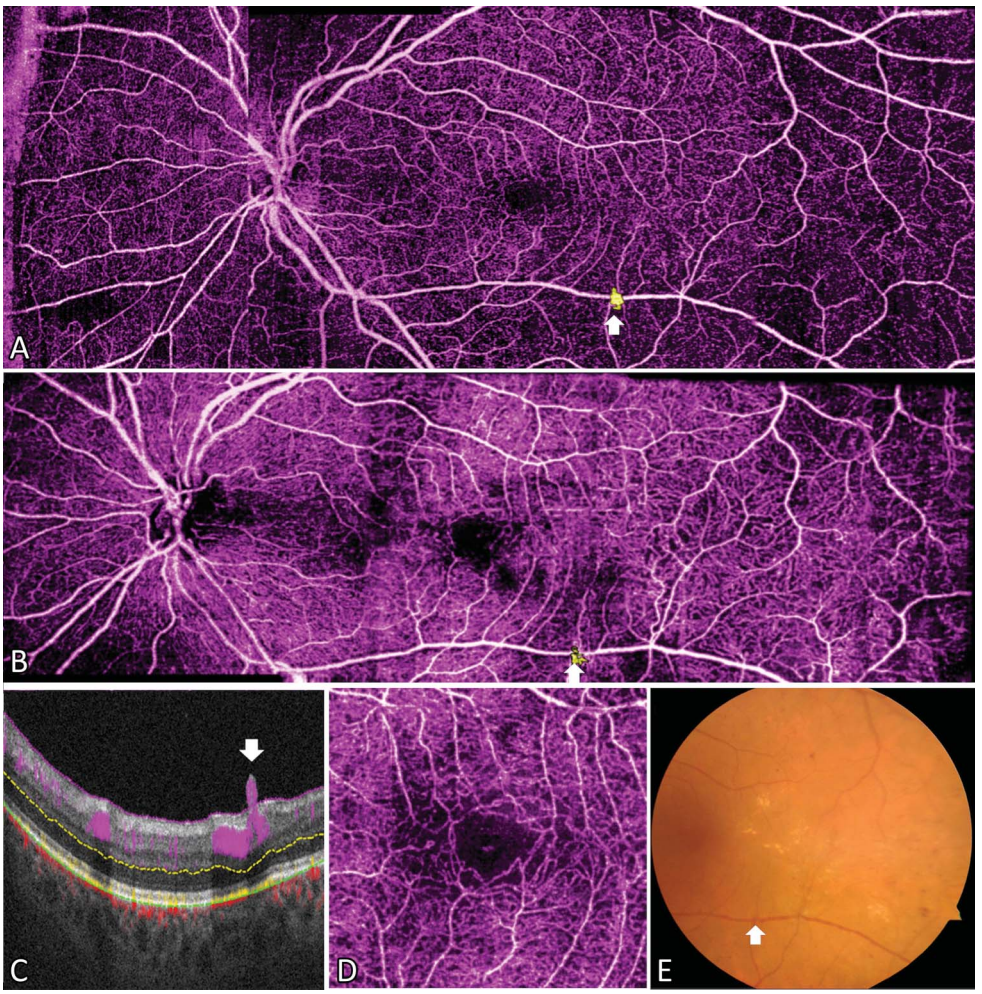

Fig. 4. Wide-field OCTA from prototype (**A**) and commercial (**B**) devices revealed retinal NV (arrows) along the inferotemporal arcade with an area of 0.17 mm^2. Magenta indicates the retinal slab, and yellow indicates the vitreous slab. The cross-sectional angiogram through the lesion (**C**) demonstrates the flow signal in magenta (arrow). The small frond was not detected on the central macular 3 × 3-mm scan (**D**). The color photograph (**E**) does not reveal the retinal NV (arrow).

Although OCTA is well suited for routine surveillance, the reimbursement structure in the United States disincentivizes its use. Optical coherence tomography angiography is currently not separately billable in addition to structural OCT. The absence of separate reimbursement may discourage clinicians from routine utilization of resources and time for the procedure. The recognition and reimbursement of OCTA as a separate procedure may be necessary for appropriate incentivization of best practices.

Wide-field OCTA used in this study clearly improved on detection of NV over conventional OCTA but does not yet match the currently available ultra-WF angiographic modalities. In the evaluation of DR, several studies have demonstrated the advantages of WF modalities.[16,29] Sawada et al reported that 12 × 12-mm WF-OCTA may be comparable with ultra-WF FA in detecting nonperfusion or NV.[10] The field of view used in this study is comparable at 90 mm^2 and 250 mm^2 versus 144 mm^2 used by Sawada et al, and all improve significantly on the conventional 36 mm^2 of 6 × 6-mm scans. Further improvement in technology to extend the field of view of OCTA will likely improve its utility in the evaluation of DR.

Limitations of this study include the small patient population and nonoptimized image quality in the prototype WF-OCTA. Fluorescein angiography was not available for every case, which would have been necessary to determine the sensitivity and specificity of OCTA for detection of NV. Furthermore, the study was not designed to determine whether there would be meaningful benefit to the patients from detecting small fronds of NV not visible on clinical examination.

In conclusion, OCTA with extended fields of view can unambiguously detect NV missed in clinical examination and fundus photographs. This technology has the potential of making the determination of proliferative stage of disease more reliable and objective. Because OCTA is safer, faster, and less expensive than FA, it may be more suitable for routine surveillance for NV, particularly in severe NPDR or eyes undergoing anti-VEGF treatment for DME. Both technological maturation and reimbursement changes

may be necessary for adoption of WF-OCTA for routine use in DR.

Key words: anti–vascular endothelial growth factor, diabetic retinopathy, optical coherence tomography angiography.

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