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ILLUMINATING RETINAL PATHOLOGIES

Modern imaging for examining chorioretinal disease.

Until recently, retinal specialists relied on fundus photography and optical coherence tomography (OCT) to see the retina and diseases that affect it. When NIDEK introduced the Mirante Scanning Laser Ophthalmoscope, which marries high-definition OCT and SLO with ultra-widefield imaging, clinicians gained valuable new tools for imaging and diagnostics. Additionally, the company has introduced a successor to its RS-3000 Advance 2. The RS-1 Glauvas combines a very high scanning speed, a wider imaging area, and new Structural Normality Map (SN Map) that makes use of deep learning (DL) technology to help physicians glean even more diagnostic information.

At a recent symposium, three renowned retinal specialists—Maria Cristina Savastano, MD, PhD, at the Università Cattolica del Sacro Cuore in Rome; Thomas Ach, MD, MSc, FEBO, at University Hospital Bonn in Germany; and Taiji Sakamoto, MD, PhD, at Kagoshima University in Japan—shared how they are using the Mirante, MP-3, and new RS-1 Glauvas in their clinics to diagnose and follow retinal pathologies.

– Nadia K. Waheed, MD, MPH

Multimodal Images in Retinal Dystrophies

Maria Cristina Savastano, MD, PhD

Healthy photoreceptors in the retina have a high rate of turnover (apoptosis). In retinal dystrophies, the turnover generally occurs in the inner segment of the photoreceptor. When the dystrophy involves the cones or rods, most of the damage is related to an alteration in metabolism in the inner segment, which controls regulated necrosis and autophagy.

The Mirante makes it possible to detect retinal dystrophy and study its effects via multimodal imaging: OCT, OCT angiography, and fundus autofluorescence (FAF) in standard field; and multicolor, angiograph, and Retro mode in ultra-wide field. In my clinical research, I have found the Mirante device to have the following benefits: (1) a fast and safe examination for patients, especially for those who have compromised mobility; (2) it safely stores patient data; and (3) it allows me to easily share data and compare differential diagnoses with colleagues.

The Role of Multimodal Imaging in Retinal Dystrophy

The main utility of multimodal imaging in retinal dystrophy is to differentiate a diseased retina from a healthy one. Visual comparisons are very helpful in both diagnosing and tracking the progression of dystrophies. For example, in an eye with retinitis pigmentosa (Figure 1), the Mirante revealed that the area of the retinal pigment epithelium (RPE) was totally interrupted, and the ellipsoid zone was preserved in the foveal region, whereas the outer retina was absent all around the perifoveal region, while the inner part was preserved. By comparing the image of the healthy eye to those of the pathological eye, we can clearly delineate the interruption of the ellipsoid zone, or it can be segmented outside of the linear aspect.

Figure 2 shows the same eye imaged with color SLO, blue fundus

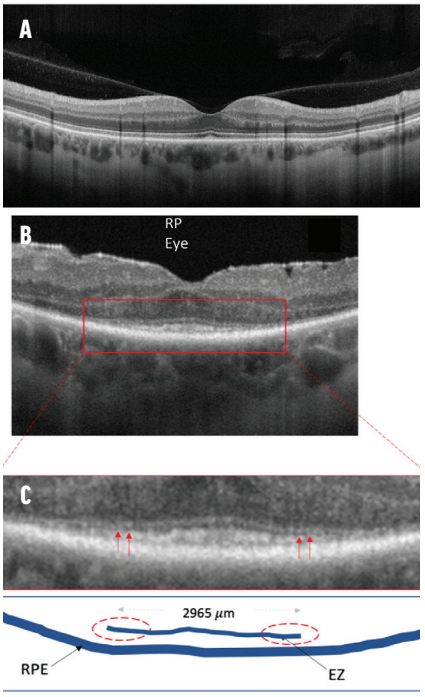

Figure 1. Multimodal imaging, available with the Mirante, enables clinicians to compare eyes with pathology to those with healthy ocular structures. By using the image of the patient's healthy eye as a reference (A), it is easy to see the diseased area of the eye affected by retinitis pigmentosa (B, C).

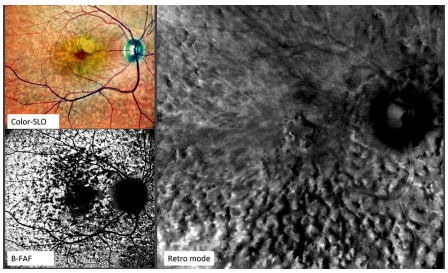

Figure 2. The same eye with retinitis pigmentosa as seen with the Mirante's other imaging modalities.

autofluorescence (B-FAF), and Retro mode on the Mirante.

I particularly like that Retro mode imaging provides information about the area of the retina near the sclera. This is new information that I could not access previously. In fact, Retro mode may show evidence of changes in this area of the eye before it is visible on autofluorescence.

Figure 3 shows an eye with Stargardt disease, which affects the foveal region of the RPE and the ellipsoid zone. The ellipsoid zone is completely destroyed, and the foveal and parafoveal areas are only partially preserved. Using the color fundus imaging, Retro mode, and B-FAF, we can see that the involvement is much larger and extends over the arcades. With the Mirante's broad imaging capabilities, we can collect more information about the stages of Stargardt disease.

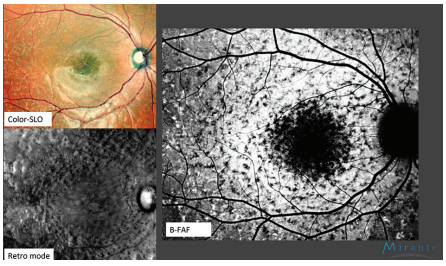

Figure 3. The Mirante's color fundus, Retro mode, and B-FAF imaging revealed that this patient's Stargardt disease had spread beyond the arcades. The various imaging options on the Mirante enable Dr. Savastano and her team to track the stages of the disease over time.

Making the Correct Diagnosis

Multimodal imaging on the Mirante is very helpful in making accurate diagnoses. In a case of early-stage Best disease, for example, the Mirante confirmed the diagnosis that we had detected with genetic information. Not only was the fovea involved, but the situation was diffused at the posterior pole, too.

In another case of a patient with X-linked disease, my team and I used the Mirante to visually confirm that the retinoschisis has affected both eyes. With en face imaging (Figure 4), we could see the petaloid aspect, which was useful in making the diagnosis.

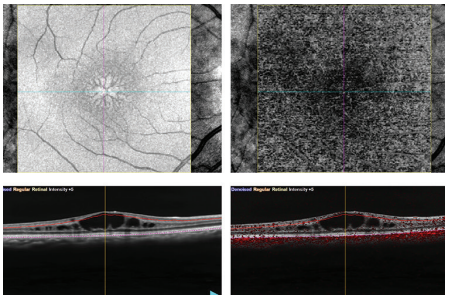

Figure 4. *En face* imaging with the Mirante helped Prof. Savastano to diagnose bilateral X-linked disease.

The Mirante proved very useful in diagnosing a case of Masquerade syndrome. The patient was referred to us with a diagnosis of retinal dystrophy, but after taking a thorough medical history and then observing the other new aspects at the posterior pole in the periphery, we changed our opinion to avitaminosis A (we confirmed the diagnosis with genetic testing, as well). The Mirante's wide-field imaging was particularly helpful in this case, because we didn't observe any alteration of pigmentation in the periphery (Figure 5).

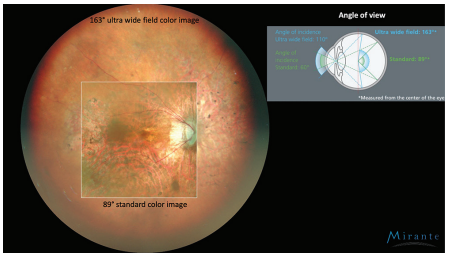

Figure 5. A diagnosis of avitaminosis A.

Using Mirante in the Clinic to Track Disease Progression

In the clinic, I tend to use the color fundus exam, autofluorescence, and OCT routinely on every patient, because with these three types of imaging, I can follow patients' ocular health over time. I also find Retro mode imaging very useful, mainly for detecting the exact extension of atrophy in the RPE or in the ellipsoid zone. Retro mode makes it easy to follow the evolution of atrophy over time. Furthermore, the autofluorescence function gives me the ability to outline atrophy in eyes with dystrophy.

CLINICAL USES FOR RETRO MODE

Maria Cristina Savastano, MD, PhD; Thomas Ach, MD, MSc, FEBO; and Taiji Sakamoto, MD, PhD, describe why they like using the Mirante Scanning Laser Ophthalmoscope in Retro mode in their clinics.

Dr. Savastano: There are some retinal diseases for which I find Retro mode especially useful, such as retinitis pigmentosa and Stargardt disease. With Stargardt disease, Retro mode provides fantastic information in pseudo 3D, whereby it is sometimes possible to delineate the atrophy and see the defect of the neuroepithelium in the center and periphery of the fovea.

Dr. Ach: I specifically like to use Retro mode when it comes to detecting material that is deposited in the outer retina (subretinal drusen or drusen deposits). Retro mode creates beautiful pseudo 3D images, maybe better than in optical coherence tomography (OCT), because you can image all the angles at once, instead of scanning through a lot of OCT images.

Dr. Sakamoto: I was surprised to see how clearly the Mirante could visualize the diseased areas of the retina. It is very useful, especially when it comes to the distribution across the fundus.

Using Mirante for the Detection of Subretinal Drusenoid Deposits: Linking Structure to Function

Thomas Ach, MD, MSc, FEBO

This article discusses sub-retinal pigment epithelium (RPE) drusen, material that is outside the RPE's basement membrane, and RPE subretinal drusenoid deposits (SDDs) in the subretinal space between the photoreceptors and the RPE. The presence of SDDs in an eye indicates an increased risk of progression to late-stage age-related macular degeneration (AMD) and geographic atrophy (GA), in addition to sub-RPE soft drusen and pigmentary changes.

In an eye with SDD and sub-RPE drusen, which entity contributes to the progression of AMD? To answer this question, my colleagues and I conducted several quantitative analyses of the number and distribution of SDDs and sub-RPE drusen using Retro mode imaging on the Mirante. We took this approach because a limited number of studies discuss the number or distribution of SDDs. Linking their structure with function is still an academic challenge.

Retro Mode

Our first study included 75 patients with intermediate AMD who were attending annual follow-up examinations. We examined these patients using Retro mode imaging and multicolor imaging, both on the Mirante (Figure 1).

My colleagues and I used customized FIJI plugins on the Mirante that allowed us to register and align the Mirante multimodal images and manually annotate all the sub-RPE drusen and SDDs (Figure 2).

This was validated by OCT to be sure that the deposits we saw were linked to an SDD or linked to a sub-RPE drusen.

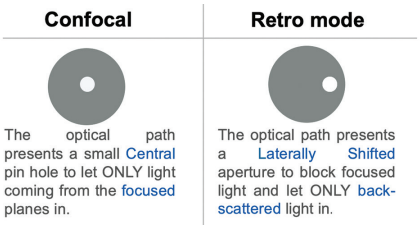

Figure 1. The central pinhole of a traditional confocal microscope lets light enter through the center only (the focused plane) and blocks all other light. In Retro mode imaging, the optical pathway is shifted laterally, which blocks focused light and only lets in back-scattered light. Retro mode illuminates the back of the eye and produces pseudo-3D images.

Results

Out of the original 75 AMD patients, 30 were eligible for inclusion in the study. The mean number of sub-RPE drusen (mean ± STD) was 74 ± 76 (range: 1-232), and the average SDD count (mean ± STD) was 1014 ± 849 (range: 107–3858). The sub-RPE drusen were mostly located within the central subfield or the first ring of the ETDRS grid, at between 1.5- and 3-mm eccentricity. SDDs were mostly located 4 to 5 mm outside the fovea (Figure 3). We have found the difference in distribution across the fundus between sub-RPE drusen and SDDs, though we are unsure of the reason.

Further Analysis

There was a second question my colleagues and I wanted to answer: can the Mirante also detect different stages of SDDs? By comparing the Retro mode images to the structural images on OCT, we confirmed that even the early stages of deposits are detectable with Retro mode. We were able to correlate stage 1 and stage 2 SDDs with the deposits we saw with Retro mode, with high specificity.

My team and I feel that Retro mode imaging on the Mirante adds a valuable aspect to our multimodal imaging capabilities in the clinic. With it, we can detect the early stages of these deposits. Although other groups have shown a high specificity for SDD detection using Retro mode,[1] the literature is inconclusive when it comes to SDDs and their impact on visual function. We still don't know whether the number, density, and location of SDDs are important. As clinicians, we must remember that not every AMD-affected eye shows SDDs, and there are eyes with SDDs but no other AMD lesions.

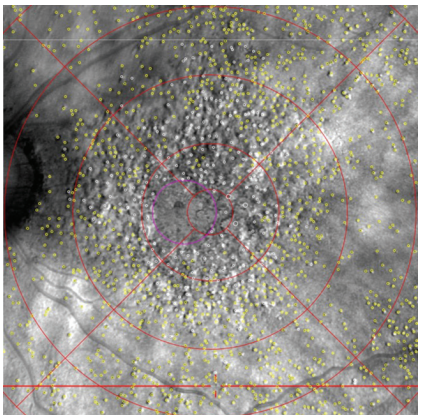

Figure 2. Customized FIJI plugins allow registration and alignment of Mirante multimodal images, and the ability to manually annotate sub-RPE drusen and SDDs. Zooming in allows the user to map the location of deposits, which can be done using a modified ETDRS grid that extends toward the periphery (radius: 0.5-1.5, 3-4, 5-6, >6-mm).

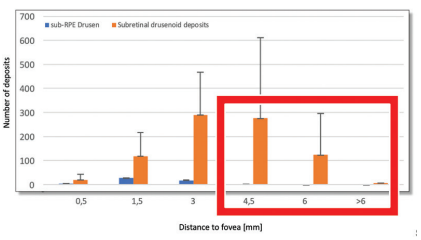

Figure 3. There was significant distribution of SDDs across the posterior pole at a distance of 4 mm or more from the fovea.

Correlating Structure and Function

I believe that clinical trials for AMD treatments need to add more functional endpoints, not only structural ones, and we also need longitudinal studies to learn more about how both structure and function change over time in these eyes.

For this purpose, my colleagues and I longitudinally analyzed the impact of structural phenotypes on spatially resolved retinal function in eyes with intermediate AMD. We included

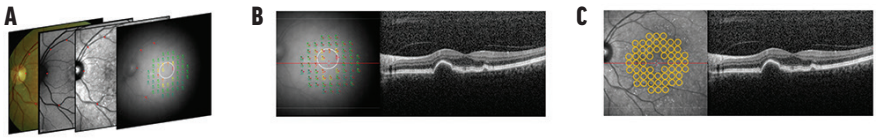

Figure 4 A-C. Dr. Ach's team was able to register the Mirante's structural image data to *en-face* FCP imaging. The qualitative grading provided data on the presence of sub-RPE drusen, SDDs, hyperreflective foci,RPE detachment, vitelliform material, and refractile deposits. The quantitative grading provided data on changes in the retinal layer thickness (as z-scores to controls). The team also noted the development of iRORA/cRORA lesions. (Reprinted with permission from: Saßmannshausen M, Döngelci S, Vaisband M, et al. Spatially resolved association of structural biomarkers on retinal function in non-exudative age-related macular degeneration over 4 years. *Invest. Ophthalmol. Vis. Sci.* 2024;65(4):45. https://doi.org/10.1167/iovs.65.4.45.)

51 eyes of 45 patients with predominant sub-RPE drusen, plus 27 healthy eyes as controls. We excluded eyes with any neovascularization. We applied multimodal imaging with the Mirante, and we also used the NIDEK MP-1S for fundus-controlled perimetry to test mesopic and scotopic function in these eyes. We followed these patients for 7 years at annual visits.

We looked at the structural changes on OCT to locate specific AMD lesions, and then we superimposed these with the fundus-controlled perimetry grid to learn more about lesion and function at those specific places. We then conducted a standardized point-wise grading of the structural biomarkers, looking not only for SDDs and hypervector foci sub-RPE drusen, but also at what's going on in lesions like iRORA and the cRORA lesions (Figure 4).

It was very obvious that, in eyes that have sub-RPE drusen at the fundus, over time, there was a significant decline in mesopic and scotopic function. We did not find a significant change in the presence of SDDs. However, the presence of all these other biomarkers at baseline—pigment epithelium detachment, hyperreflective foci, and iRORA lesions—were all highly correlated with a decline in function over time (Table 1).

In this study, at baseline, eyes with intermediate AMD were examined by mesopic and scotopic fundus-controlled perimetry. In the follow-up, changes began to emerge in the central macula. Drusen disappear, atrophy develops, and we see a significant decline in function, not only at the very center but also at the temporal part of the macula.

Table 1. The impact of structural biomarkers on point-wise retinal sensitivity.

	Mesopic sensitivity			Scotopic sensitivity		
Parameter	Coefficient Estimates [in dB]	SE	*P* value	Coefficient Estimates [in dB]	SE	*P* value
(Intercept)	5.454	1.43	0.0004	2.846	1.992	0.158
Age (years)	-0.098	0.0203	<0.0001	-0.068	0.028	0.019
Presence Sub-RPE Drusen	-0.206	0.057	0.0003	-0.199	0.064	0.002
Presence of SDD	-0.446	0.239	0.062	-0.465	0.271	0.087
Presence of PED	-1.621	0.153	<0.0001	-1.363	0.174	<0.0001
Presence of HRF	-1.161	0.198	<0.0001	-0.929	0.224	<0.0001
Presence of Vitelliform Material	-0.45	0.303	0.138	-0.167	0.344	0.627
Presence of Refractile Deposits	-0.185	0.353	0.600	-0.081	0.401	0.841
Presence of iRORA	-0.785	-0.238	<0.0001	-0.913	0.270	0.0007
Development of cRORA	-0.882	0.372	0.018	-0.338	0.422	0.423

Table adapted from: Saßmannshausen M, Döngelci S, Vaisband M, et al. Spatially resolved association of structural biomarkers on retinal function in non-exudative age-related macular degeneration over 4 years. *Invest Ophthalmol Vis Sci.* 2024;65(4):45.

SUMMARY

My colleagues and I think that multimodal imaging is absolutely worth conducting in AMD patients routinely, including at follow-up visits. Retro mode imaging, in particular, makes it easy to see and quantify lesions, and now we must track them over time to learn more about how they change and how their changes affect ocular structure and function. We showed some evidence that there is a spatial association between various AMD biomarkers and function—the presence of SDDs, retinal pigment epithelial detachment, and hyperreflective foci had the strongest association with functional decline.

We also found that patients experience functional decline even before any kind of atrophy occurs in the eye. Thus, we don't need to wait until we see cRORA lesions; cone- and rod-mediated functional decline precedes the manifestation of retinal atrophy.

1. Cozzi M, Monteduro D, Parrulli S, et al. Sensitivity and specificity of multimodal imaging in characterizing drusen. *Ophthalmol Retina.* 2020;4:987-995.

Next-Generation AI: Wayfinding AI for Retinal Diseases

Taiji Sakamoto, MD, PhD

As clinicians, Artificial Intelligence (AI) is creating the opportunity to improve the accuracy and efficiency of our daily operations. NIDEK built the new RS-1 Glauvas, which is a successor of the RS-3000 Advance 2, to capitalize on the deep-learning (DL) capabilities that AI offers. The RS-1 is the world's first 250-kHz SD-OCT device that provides high functionality as well as precision analytics based on DL. It is designed to speed up clinical workflow without compromising diagnostic reliability. To achieve this goal, it performs in five key areas: operability, glaucoma, vasculature, retina, and analytics (Figure 1). In terms of the application of DL in optical coherence tomography (OCT), this machine has segmentation, abnormality detection, and B-scan denoising.

1. **Rapid operability.** The RS-1 reduces the burden on both the examiner and the examinee through its high-speed imaging of 250,000 A-scans per second, 3D auto-alignment/high-sensitivity SLO, and combo capture sequences, which are preset scanning patterns based on target diseases or a facility's examination routine.
2. **Glaucoma.** The device has a function to measure axial length and applies OCT Analysis Correction Parameter to correct to the actual scan size and switch NDB or long axial length NDB automatically based on the axial length. (The value of the axial length is obtained based on the results of the OCT image capture and differs from the actual measured value of the axial length).
3. **Vascular.** The RS-1 enables vascular evaluation in three key ways: a wide-field SLO, a fast OCT-A, and a wide OCT-A at a maximum of 12 mm x 12 mm. Again, these functions speed up vascular assessment in the clinic.
4. **Retina.** The RS-1 offers denoised B-scan from a single shot and the retinal map scan captures both the macular and disc areas in a single shot. The combination of these functions gives clinicians the ability to detect an array of retinal abnormalities in high quality.
5. **Analytics.** The new OCT viewer reduces segmentation errors via a new segmentation algorithm based on deep learning. The Structural Normality Map (SN Map) feature detects subtle changes in retinal structures and clearly indicates where clinicians should focus their attention with the heat map.

"Wayfinding" AI Versus "Diagnostic" AI

Practitioners know that AI has been used for diagnosing retinal diseases since 2018, when the US FDA approved the first AI-based diagnostic machine for screening diabetic retinopathy. The main shortcoming of diagnostic AI, though, is that we are not sure how its thinking process works, or how it arrives at its decisions. In an article published in 2021 in the *Journal of the American Medical Association*, Adler-Milstein, Chen, and Dhaliwal proposed that we physicians need "wayfinding" AI rather than "diagnostic" AI, because we will not accept a machine-generated diagnosis if the process of determination is unclear.[1]

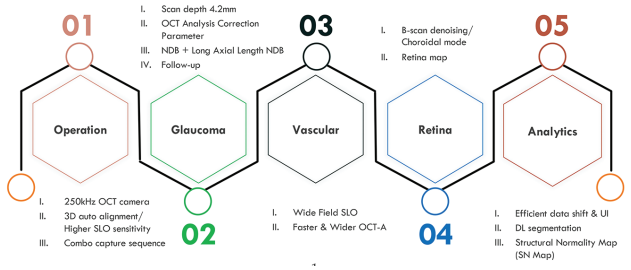

Figure 1. The RS-1 was designed to make clinical workflow more efficient without compromising diagnostic reliability. It offers five key functions.

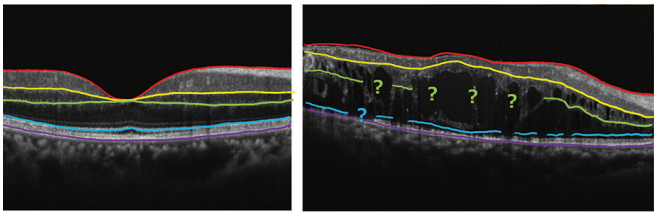

Figure 2. Each line is composed of pixels. Each pixel has an "entropy" value.

So, my colleagues and I at Kagoshima University worked with NIDEK to develop the RS-1's SN Map feature that offers wayfinding capabilities. Instead of giving a diagnosis, this device provides additional information for us to make a final diagnosis.

Structural abnormalities make retinal layer segmentation difficult for OCT imaging. The probability of this uncertainty level can be calculated by pixel when using entropy. By expressing its uncertainty in numerical value using entropy (Figure 2), we could visualize the degrees of each layer's abnormalities on a heat map.

CASE EXAMPLES

A case of simple diabetic retinopathy illustrates the clinical utility of wayfinding AI. We found that the patient had SDR from the OCT B-scan image, but our wayfinding machine indicated several abnormal structures in the inner retina (Figure 3).

In another example of prediabetic retinopathy, the SN Map shows that abnormal structures are distributed throughout the inner and outer retina (Figure 4).

Our practice receives many patients with epiretinal membrane (ERM), a condition that has a wide spectrum of severity from mild to severe. The trick is to decide when to operate on an ERM.

A 67-year-old male patient came to our office with symptoms of metamorphopsia. An OCT image showed the presence of typical wet AMD. When I ran his images through

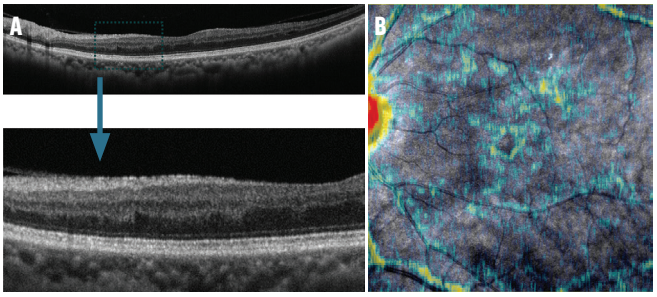

Figure 3. An indication of DRIL in the OCT image is an important detail for the physician (A). On the SN Map, the distribution of the disorganization of retinal inner layers becomes instantly visible (B).

our wayfinding machine, I could see a hotspot in the outer retinal structure, as one would expect with metamorphopsia. However, when I scanned the inner retina, there were some strange signals on the ILM. Looking back to the original OCT, I could see the ERM. It did not require immediate treatment, but our machine advised me that there was something wrong.

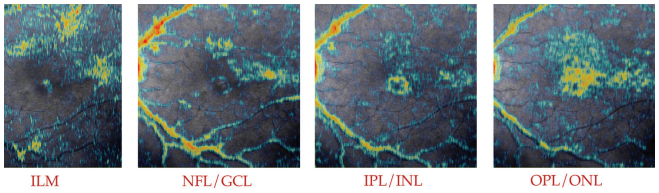

Figure 4. In this eye with prediabetic retinopathy, even simple DR shows signs of abnormal structure spread across the retina. These would be difficult to see with fundus photography or B-mode OCT.

Wayfinding AI Better Suited to the Clinic

The accuracy and power of diagnostic AI is getting stronger and stronger, but it can't explain why or how the machine reached its final diagnosis. As a clinician, I prefer to use wayfinding AI. Wayfinding AI will not replace a doctor's knowledge and experience; I would call it a *robot-assisted diagnosing process*. Or, we can use the term that Audrey Tang, Taiwan's Digital Minister, coined: *assistive intelligence*. This device can be a reliable diagnostic assistant in our clinics. ■

1. Adler-Milstein J, Chen JH, Dhaliwal G. Next-generation artificial intelligence for diagnosis: from predicting diagnostic labels to "wayfinding." *J Am Med Assoc.* 2021;326(24):2467-2468.

Product/model name of RS-3000 Advance 2: Optical Coherence Tomography RS-3000 Advance. RS-1 and RS-3000 Advance 2 are not cleared by the FDA for distribution in the United States.

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