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# American Society of Retina Specialists Clinical Practice Guidelines on Multimodal Imaging for Retinal Disease

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## Abstract

**Purpose:** Advancements in retinal imaging have augmented our understanding of the pathology and structure–function relationships of retinal disease. No single diagnostic test is sufficient; rather, diagnostic and management strategies increasingly involve the synthesis of multiple imaging modalities. **Methods:** This literature review and editorial offer practical clinical guidelines for how the retina specialist can use multimodal imaging to manage retinal conditions. **Results:** Various imaging modalities offer information on different aspects of retinal structure and function. For example, optical coherence tomography (OCT) and B-scan ultrasonography can provide insights into the microstructural anatomy; fluorescein angiography (FA), indocyanine green angiography (ICGA), and OCT angiography (OCTA) can reveal vascular integrity and perfusion status; and near-infrared reflectance and fundus autofluorescence (FAF) can characterize molecular components within tissues. Managing retinal vascular diseases often includes fundus photography, OCT, OCTA, and FA to evaluate for macular edema, retinal ischemia, and the secondary complications of neovascularization (NV). OCT and FAF play a key role in diagnosing and treating maculopathies. FA, OCTA, and ICGA can help identify macular NV, posterior uveitis, and choroidal venous insufficiency, which guides treatment strategies. Finally, OCT and B-scan ultrasonography can help with preoperative planning and prognostication in vitreoretinal surgical conditions. **Conclusions:** Today, the retina specialist has access to numerous retinal imaging modalities that can augment the clinical examination to help diagnose and manage retinal conditions. Understanding the capabilities and limitations of each modality is critical to maximizing its clinical utility.

## Keywords

fluorescein angiography, fundus autofluorescence, fundus photography, indocyanine green angiography, macular degeneration, multimodal imaging, optical coherence tomography, optical coherence tomography angiography, posterior uveitis, retinal vascular disease, retinal dystrophy, ultra-widefield imaging, vitreoretinal surgery

## Introduction

Since the capture of the first retinal photograph in 1885 by Howe and Starr and the subsequent publication of a human retinal image by Jackman and Webster in 1886, retinal imaging has developed rapidly over the past century.[1,2] Although fundus photography was initially appealing as a way to avoid close proximity to a patient with the ophthalmoscope during an era when infectious diseases were rampant (a concern reminiscent of recent challenges with COVID-19), advances in retinal imaging also augmented our understanding of retinal conditions.[3]

The invention of fundus photography laid the foundation for the development of fluorescein angiography (FA), which enabled dynamic in vivo visualization of retinal vasculature and associated pathology. The introduction of optical coherence tomography (OCT) followed and revolutionized retinal care because it allowed for tomographic optical sectioning of the retina and high-resolution 3-dimensional representations of the retinal tissue.

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At present, the retina specialist has access to numerous imaging modalities to help diagnose and manage retinal conditions. To mention a few, OCT, adaptive optics, and B-scan ultrasonography can provide insights into the microstructural anatomy; FA, indocyanine green angiography (ICGA), and OCT angiography (OCTA) can reveal vascular integrity and perfusion status; near-infrared reflectance and fundus autofluorescence (FAF) can characterize retinal pigment epithelium (RPE) and outer retinal dysfunction; while electroretinography and microperimetry help characterize visual function. Advancements in retinal imaging and visio-physiologic testing have augmented our understanding of retinal disease and fostered numerous insights into the pathology and structure–function relationships of retinal disease.

The modern retina specialist can gain a better understanding of retinal conditions by synthesizing the various types of data gleaned from multimodal imaging. Although color fundus photography and OCT may be the more commonly used tools in many clinics, no single imaging modality defines the standard of care of retinal practice. Depending on the complexity of the initial presentation of each patient, one or multiple imaging modalities may be helpful to narrow a differential diagnosis and determine a management plan. Furthermore, if a clinical course is unexpected or the treatment inadequate, repeated multimodal imaging evaluations may be necessary to identify nuanced features that can better explain unexpected outcomes and responses.

Last, evaluation of the fellow eye is key, especially in managing chronic, bilateral, or systemic conditions such as age-related macular degeneration (AMD) or diabetic retinopathy (DR). For example, retrospective studies of patients monitored by OCT found that one half of patients with unilateral diabetic macular edema (DME) and 20% to 30% of patients with unilateral exudative AMD develop fellow-eye involvement over 2 years.[4–7] The fellow eye often has a decreased treatment burden and better visual outcomes than the initial eye, which may be attributed to more frequent surveillance and early diagnosis and treatment.[7]

Following are some practical guidelines to consider toward making the most of the more commonly available multimodal imaging in the approach to diagnosing and treating medical and surgical retinal diseases. This review is not exhaustive but rather is designed to provide practical guidance to the practicing clinician.

## Retinal Vascular Disease

With the increasing prevalence of hypertension, diabetes, and obesity, retinal vascular diseases such as DR and retinal arterial and venous occlusions are common diagnoses in a retina clinic. Vision loss can occur from macular edema, retinal ischemia, and the secondary complications of neovascularization (NV). Retinal imaging has proven invaluable in the assessment of these parameters, risk stratification, and disease management.

### *Fundus Photography*

Color fundus photography is an integral part of the quantitative grading of DR. The Early Treatment Diabetic Retinopathy Study and the Diabetic Retinopathy Study laid the groundwork for the Diabetic Retinopathy Severity Scale, which portended a risk for progression to proliferative disease and associated severe vision loss based on 7 standard overlapping fields covering 75 degrees of the posterior pole.[8,9]

The more recent development of high-resolution ultra-widefield color imaging has enabled visualization of up to 200 degrees of the retinal surface with a single image capture in some cases. Studies have shown agreement in DR severity grading with ultra-widefield photography compared with both standard 7-field photography and clinical examination.[10,11] Similarly, widefield fundus photography can be useful in documenting clinical findings in other retinal vascular conditions, such as the presence of a Hollenhorst plaque, retinal hemorrhages in a vein occlusion, or NV.

Moreover, ultra-widefield imaging in DR can help screen for predominantly peripheral lesions because more than one half of retinopathy may be located outside the standard 7-field region limited to the posterior pole. Clinicians have studied the diabetic phenotype of eyes with predominantly peripheral lesions relative to those in which the majority of diabetic changes are within the 7 standard fields of view. Eyes with predominantly peripheral lesions were 3.2 times more likely to progress 2 or more steps on the Diabetic Retinopathy Severity Scale and 4.7 times more likely to progress to proliferative DR than eyes without predominantly peripheral lesions.[12,13]

### *Fluorescein Angiography*

In conjunction with fundus photography, ultra-widefield FA is helpful when assessing vascular nonperfusion and permeability. Ultra-widefield FA can be used to identify DR grading features that may not be obvious on color fundus photography or clinical examination (eg, subtle NV elsewhere), classify a retinal vein occlusion (RVO) as ischemic or nonischemic, and help identify the cause of peripheral ischemia. Recent DRCR Retina Network Protocol AA studies show the benefit of ultra-widefield FA in addition to ultra-widefield photography in identifying nonperfusion and predominantly peripheral lesions whose presence on ultra-widefield FA have been associated with a greater risk for progressive DR.[13,14] By identifying the presence of retinal NV or ischemia, ultra-widefield FA allows for better identification of patients who would benefit from panretinal laser photocoagulation, antivascular endothelial growth factor (anti-VEGF) therapy, or both (Figure 1). In addition, repeat ultra-widefield FA may provide an understanding of disease progression and alter decision-making if there is progressive ischemia or NV.[15]

In addition, although OCT has largely driven the monitoring and clinical decision-making for treating macular edema (eg, in diabetes or RVOs), FA can be useful in certain cases to guide

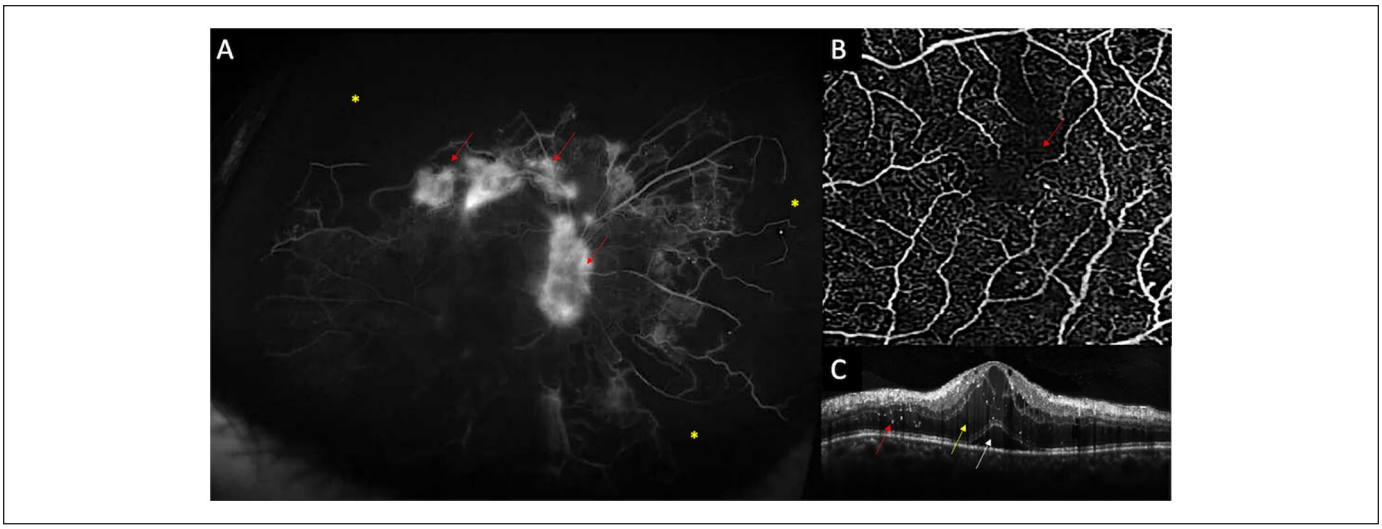


**Figure 1.** Multimodal imaging of diabetic retinopathy (DR). (A) Ultra-widefield fluorescein angiography shows extensive peripheral nonperfusion (asterisks) and peripheral and disc neovascularization (red arrows) in proliferative DR. (B) Optical coherence tomography (OCT) angiography of the macular superficial capillary plexus shows an enlarged and irregular foveal avascular zone (red arrow) seen in diabetic macular ischemia. (C) OCT of diabetic macular edema with subretinal fluid (white arrow), intraretinal fluid (yellow arrow), and hyperreflective dots (red arrow). (*Images courtesy of Yasha S. Modi, MD.*)

focal laser treatment in place of or in addition to anti-VEGF treatment. Leaking microaneurysms can be highlighted on FA as potential laser targets. Conversely, in cases of anatomic treatment response without corresponding functional visual improvement, FA can assess macular ischemia as the cause of poor visual recovery.

## *Optical Coherence Tomography*

OCT is the gold standard in assessing macular structure. With regard to the evaluation of macular edema, OCT has fostered the replacement of the definition of clinically significant macular edema with center-involving macular edema as one of many possible indications for anti-VEGF therapy in DR.[16] In addition to B-scan raster scans through the macula that can detect the presence of intraretinal fluid (IRF) and subretinal fluid (SRF), en face thickness "heat maps" can also be used to determine whether there is interval change in macular thickening that developed between visits that warrants a change in management. Once a treatment protocol (fixed, treat-and-extend, pro re nata) for macular edema has been initiated, a decrease in volumetric fluid helps confirm a positive response to treatment. OCT systems often are equipped with change analysis software platforms that can assist with this trend analysis. For example, OCT images can be registered, which synchronizes raster scans to the same anatomic location at every visit for micron-level comparisons between visits. These software enhancements can be used to tailor treatment intervals, enabling individualized therapy.

If visual outcomes are not correlating with the extent of macular edema, OCT may be able to provide insight into structural abnormalities that might affect visual function. For example, evidence of previous ischemic events can be recognized by inner retinal thinning, which can help with visual prognostication. Other prognosticators of a poor visual outcome include disorganization of the retinal inner layers, hyperreflective foci or hard exudates, and disorganization and loss of the outer retinal layers (ellipsoid zone [EZ] or external limiting membrane [ELM]).[17] These parameters may collectively provide clinicians with invaluable information related to the visual prognosis, which can be helpful in counseling patients and informing management decisions.

On the other hand, acute retinal ischemia can also be appreciated on OCT as hyperreflectivity and thickening of specific retinal layers; some of these ischemic events are best seen on OCT vs other imaging modalities or clinical examination. In the case of an acute retinal arterial occlusion, hyperreflectivity and thickening of the inner retinal layers are evident in the corresponding vascular territory. Newer and higher resolution OCT machines have also helped identify ischemia in the intermediate and deep capillary plexuses, as in the case of paracentral acute middle maculopathy (PAMM) or acute macular neuroretinopathy (AMN), in which hyperreflective bands can often be readily appreciated in the inner nuclear layer (INL) and outer nuclear layer (ONL), respectively[18] (Figure 2). Similarly, areas of inner retinal, INL, or ONL thinning may suggest previous episodes of any of these ischemic events. These can be all important signs of vascular risk factors that might prompt a neurovascular workup with the goal of preventing further ischemic episodes. Conversely, isolated vascular anomalies, such as perifoveal exudative vascular anomalous complex, have been identified as isolated vascular abnormalities. At present, no systemic association has been identified, although recognition of this entity is important given that these lesions are frequently unresponsive to anti-VEGF and may spontaneously resolve.[19]

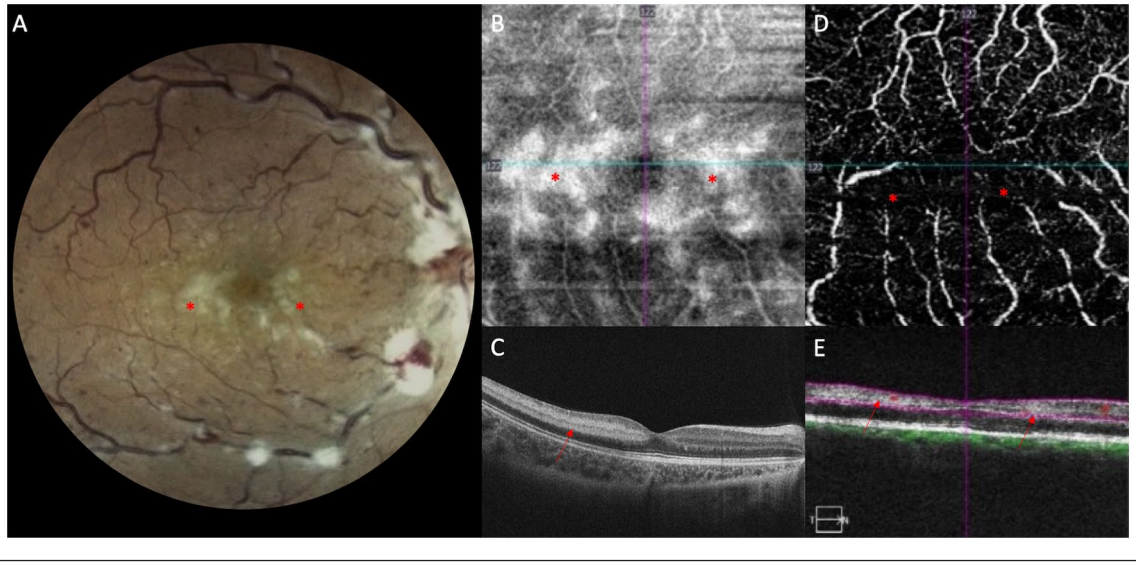


**Figure 2.** Multimodal imaging of paracentral acute middle maculopathy (PAMM). (A) Color fundus photograph of an eye with central retinal vein occlusion also shows patchy whitish parafoveal lesions deeper in the retina (red asterisks) that appear smoother in contour and grayer than cotton-wool spots. (B) En face optical coherence tomography (OCT) shows thickening of the superficial retina corresponding to the lesions (red asterisks) seen on the fundus photograph. (C) Cross-sectional OCT in PAMM shows placoid areas of hyperreflective bands (red arrow) and thickening of the inner nuclear layer. (D) En face OCT angiography of the macular superficial capillary plexus shows capillary nonperfusion in the PAMM lesions (red asterisks). (E) Structural OCT angiography segmenting the superficial capillary plexus shows flow voids in the PAMM lesions (red arrows). (*Images courtesy of Peter Weseley, MD.*)

### *Optical Coherence Tomography Angiography*

OCTA has the advantages of being noninvasive and allowing rapid image acquisition relative to dye-based FA, providing an excellent alternative for patients who cannot tolerate FA. OCTA can also reproduce the retinal microvasculature in remarkable detail and in a depth-resolved manner. Therefore, OCTA can evaluate macular ischemia and NV in a manner similar to that of FA; however, OCTA also has a clear advantage over FA in terms of evaluating the deep retinal vasculature within the macula. One example where this can be particularly helpful is in cases of unexplained scotomas. OCTA can be used to detect focal ischemic events in the deep retinal capillary beds to diagnose PAMM and AMN, especially in cases in which the correlating clinical or OCT findings may be subtle. Another case for using OCTA is in macular telangiectasia type 2, where it can reveal the diagnostic features of temporal thinning, capillary rarefaction in the superficial vascular plexus, dilation and telangiectasias of the deep capillary plexus, and outer retinal capillary invasion.[20] OCTA can be a useful imaging modality to monitor the progression of the nonproliferative stage to proliferation with NV.[21]

The quality of the OCTA maps is highly dependent on the accuracy of segmentation and frequently requires manual input to produce a reliable result. This can be time-consuming and impractical in a busy clinic. OCTA interpretation can also be plagued by image artifacts, such as blink/motion artifacts and projection artifacts (where blood flow of superficial layers is projected onto deeper layers, creating a false-positive signal). Adequate patient coaching, dilation, and corneal lubrication can help reduce motion and improve image quality. Software advances can also improve image processing to reduce artifacts and improve accurate segmentation. Moreover, OCTA does not assess leakage and at present is still limited in terms of the peripheral field of view compared with ultra-widefield FA. Although recent research directions include performing quantitative analysis of microvascular health and establishing associations with visually significant OCT parameters, large multicenter studies would likely be required to establish further clinical utility.

## Outer Retinal Diseases

### *Optical Coherence Tomography*

OCT revolutionized the identification, diagnosis, classification, and understanding of diseases involving the outer retina, RPE, and underlying choroid. The cross-sectional images of the retina can achieve near-histologic resolution, which allows localization of structural changes. As a result, our understanding of AMD, central serous chorioretinopathy (CSC), inherited retinal disorders, and toxic maculopathies have benefited greatly.

In early or intermediate AMD, OCT is instrumental in monitoring for progression to geographic atrophy (GA) or neovascular AMD (nAMD). Various drusen subtypes and OCT biomarkers have been identified as conveying an additional risk for conversion into advanced AMD, including cuticular drusen, drusen volume, subretinal drusenoid deposits, drusenoid

pigment epithelial detachments (PEDs), RPE thickening, hyperreflective foci, vitelliform changes, disruption of the ELM and EZ, choroidal thinning, among many others.[22–24] At the moment, close monitoring of patients with intermediate AMD is recommended. For advanced AMD with GA, color fundus photography represented the gold standard for diagnosis, with well-demarcated borders and depigmentation corresponding to loss of the outer RPE and RPE. However, obtaining good-quality fundus photographs to detect subtle changes in GA and with sufficient contrast to quantify lesion size can be challenging. OCT is much more sensitive in identifying GA as the loss of outer retinal layers and RPE. Recent consensus nomenclature meetings define GA on OCT as complete RPE and complete outer retinal atrophy (cRORA) with corresponding choroidal hypertransmission of 250 μm or greater.[25] Hypertransmission on en face OCT can be quantified to measure the GA area. With new and upcoming therapeutics for GA, imaging will become vital in identifying which patients may benefit most from treatment. Continued research regarding earlier OCT, near-infrared reflectance, and FAF biomarkers for impending GA will help clinicians assess the severity of non-nAMD as well as counsel patients.

In exudative AMD, similar to DME, the use of OCT has largely overtaken the use of FA and ICGA for the identification of macular NV (MNV). Exudative AMD is suspected when a "double-layer sign" of an irregular PED suggestive of MNV is associated with exudation via IRF/SRF on OCT. Rather than FA-guided laser evaluation, modern treatment paradigms include OCT criteria for the presence of fluid or subretinal hyperreflective material (SHRM) and central foveal thickness to determine whether to observe, treat with anti-VEGF injections, extend visit intervals, or a combination. Exudation and PEDs corresponding to MNV are often readily evident, and any PED suspicious for MNV without exudation (nonexudative MNV) on OCT can be further investigated with FA, ICGA, or OCTA.

MNV subtypes were initially characterized based on ophthalmoscopy, FA, and ICGA findings as occult, classic, or retinochoroidal anastomoses/retinal angiomatous proliferation (RAP).[25–29] Since then, OCT has allowed for easier identification of these MNV subtypes (now referred to as types 1, 2, and 3), which can prognosticate visual responses to anti-VEGF therapy for exudative AMD.[30] On OCT, type 1 MNV, located between the Bruch membrane and RPE, corresponds to a fibrovascular RPE detachment and is often accompanied by SRF. Type 2 MNV proliferates above the RPE in the subretinal space and often presents as SHRM, exhibiting concomitant intraretinal cystoid fluid and SRF. Last, RAP, now classified as type 3 MNV, presents initially with predominantly IRF; it is important to note that type 3 lesions classically develop from the retinal circulation and are therefore not initially choroidal NV (CNV).

There are implications for treatment strategies based on MNV type. With regular anti-VEGF therapy, maturation of a type 1 MNV can be seen and could be protective against macular atrophy.[31] In the post hoc analysis of the HARBOR study of ranibizumab in AMD, type 2 MNV led to worse visual outcomes 24 months after anti-VEGF therapy was initiated because of subretinal fibrosis and atrophy, while patients with type 1 MNV had the best mean visual acuity (VA).[32] Type 3 MNV is less likely to present with a large subretinal hemorrhage and in general responds well to intravitreal injections on a pro re nata regimen.[33,34] Of note, cross-sectional OCT is not ideal for visualizing blood; thus, the presence of a hemorrhage in nAMD is better ascertained with a clinical examination or fundus photography.

OCT has also improved our understanding of the role of the choroid in retinal diseases, in particular with the development of enhanced depth imaging that enables visualization of the full thickness of the choroid and posterior sclera.[35] As a result, increased choroidal thickness (pachychoroid) and an increased choroidal vascularity index have been found to be associated with CSC, a disease attributed to increased hydrostatic pressure and permeability in the choroid.[36] The pachychoroid disease spectrum has been described to include pachychoroid pigment epitheliopathy (with associated pachydrusen), focal choroidal excavation, peripapillary CNV, and polypoidal choroidal vasculopathy (PCV).[37] OCT can aid clinicians in determining the diagnosis and treatment in patients with pachychoroid disease and AMD. Increased choroidal thickness noted on OCT can be a valuable diagnostic marker of CSC.

In cases of newly diagnosed SRF, multimodal imaging with OCT, OCTA, and FA or ICGA can be helpful in determining whether exudation is the result of leakage from CSC or NV secondary to AMD, CSC, peripapillary CNV, or PCV. For example, OCTA can help screen for the presence of any NV, and corresponding B-scan OCT can confirm increased choroidal thickness. FA can help in CSC cases by identifying leaks that could be potential therapeutic targets for laser photocoagulation or photodynamic therapy (PDT). ICGA can help confirm dilation, anastomoses, and asymmetry of the vortex veins suggestive of pachychoroid disease and highlight any aneurysmal dilations indicative of PCV.[38]

In addition, because OCT imaging has enabled near-histological correlation of outer retinal structures, our understanding of structure–function relationships in the outer retina has improved. Visual potential can be better ascertained by evaluating the health and recovery of the photoreceptor signals (particularly in the EZ). OCT can play a key role in detecting early outer retinal/RPE involvement in macular dystrophies and screening for medication-related or toxic maculopathies (eg, hydroxychloroquine toxicity) and inflammatory conditions, including white-dot syndromes. Correlating OCT structural changes with the functional changes gleaned from near-infrared reflectance or FAF as well as psychovisual testing (visual fields, electroretinograms [ERGs]) can help narrow the differential on potential etiologies of challenging cases.

## *Near-Infrared Reflectance and Fundus Autofluorescence*

Near-infrared reflectance is a noninvasive, contactless, and rapid in vivo imaging technique for visualizing alterations in

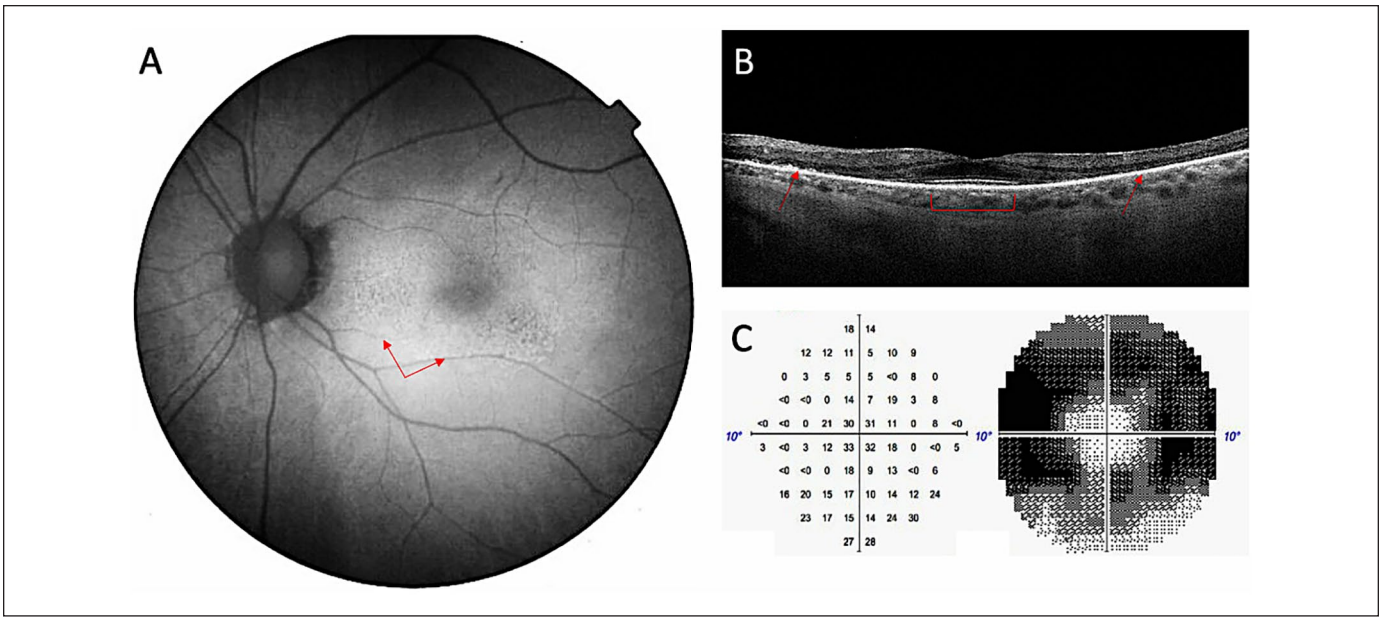


**Figure 3.** Multimodal imaging of hydroxychloroquine toxicity. (A) Fundus autofluorescence of the left eye with stippled hyperautofluorescence and hypoautofluorescence in the parafoveal region (red arrows). (B) Corresponding optical coherence tomography with extensive parafoveal ellipsoid zone loss and retinal pigment epithelial irregularity (red arrows) and a central preserved island of outer retinal structures subfoveally (red bracket). (C) 10-2 Humphrey visual field testing shows a dense paracentral scotoma resulting from the parafoveal photoreceptor disruption. (*Images courtesy of Kenneth J. Wald, MD.*)

the photoreceptor layer, RPE, and choroid. Most images are acquired simultaneously with cross-sectional spectral-domain OCT (SD-OCT) in routine clinical practice. Changes in the reflection and absorption of light through retinal tissues enhance visualization of structures beneath the RPE and melanin.[39] Images often correlate with blue-light FAF; however, near-infrared reflectance can better reveal sub-RPE lesions because of the greater absorbance of shorter wavelengths (480 nm) by melanin and lipofuscin granules at the RPE level. Therefore, highly reflective structures at the subretinal and sub-RPE level are enhanced and better recognized. For instance, hyperreflective crystalline deposits representing cholesterol crystals appear as intensely reflective plaques, while calcifications or calcified drusen are appreciated as roundish lesions with a glistening appearance. The glistening appearance is also characteristic of crystalline deposits in Bietti crystalline dystrophy. Such similarities in reflectance between inherited retinal dystrophies and age-related changes can also be seen in retinitis punctata albescens and reticular pseudodrusen. Conversely, AMN and PAMM, which may have "normal" clinical examinations, show hyporeflective globules on near-infrared reflectance that might be missed on clinical examination or even OCT.

FAF has also gained traction over the past decade in both research and clinical settings because of its ability to map naturally and pathologically occurring fluorophores in the RPE. Unlike FA, FAF does not require an injection of a fluorescein dye to image the retina but rather uses the fluorescent properties of lipofuscin within the RPE to create an image. Because many outer retinal pathologies often lead to RPE dysfunction and an accumulation of lipofuscin, abnormal patterns of autofluorescence on FAF imaging can act as markers for outer retinal disease. It is important to know that different systems use different wavelengths; for example, the excitation wavelengths are 488 nm (blue) in the Heidelberg Engineering system, 535 nm to 585 nm (green) in the Topcon Healthcare system, and 532 or 634 nm (green) in the Optos system.[40]

Hyperautofluorescence can reflect increased levels of lipofuscin/compounds with similar autofluorescent spectra or increased transmission of fluorescence. Some notable causes of hyperautofluorescence include RPE dysfunction leading to accumulation of lipofuscin (vitelliform lesions, certain drusen), blood breakdown products, optic disc drusen, or increased transmission of fluorescence from loss of macular photopigment with photoreceptor attenuation (eg, multiple evanescent white-dot syndrome [MEWDS]). Hypoautofluorescence is caused by decreased lipofuscin levels, decreased RPE density, or blockage of fluorescence. These can include RPE atrophy or tears, acute intraretinal or subretinal hemorrhage, fibrosis, or media opacities.[41,42] As a result, FAF is extremely useful in identifying hereditary macular diseases that have specific autofluorescence patterns, such as hyperautofluorescent flecks in Stargardt disease or vitelliform lesions in bestrophinopathies. Similarly, FAF is also useful for monitoring drug toxicities such as hydroxychloroquine-associated maculopathy (hyperautofluorescent parafoveal ring corresponding to photoreceptor damage, as in Figure 3) and for monitoring disease activity in white-dot syndromes (multifocal hyperautofluorescent spots or rings in MEWDS) or uveitis (hyperautofluorescent plaques in syphilitic placoid chorioretinitis corresponding to nodular thickening of RPE on OCT).[40,42]

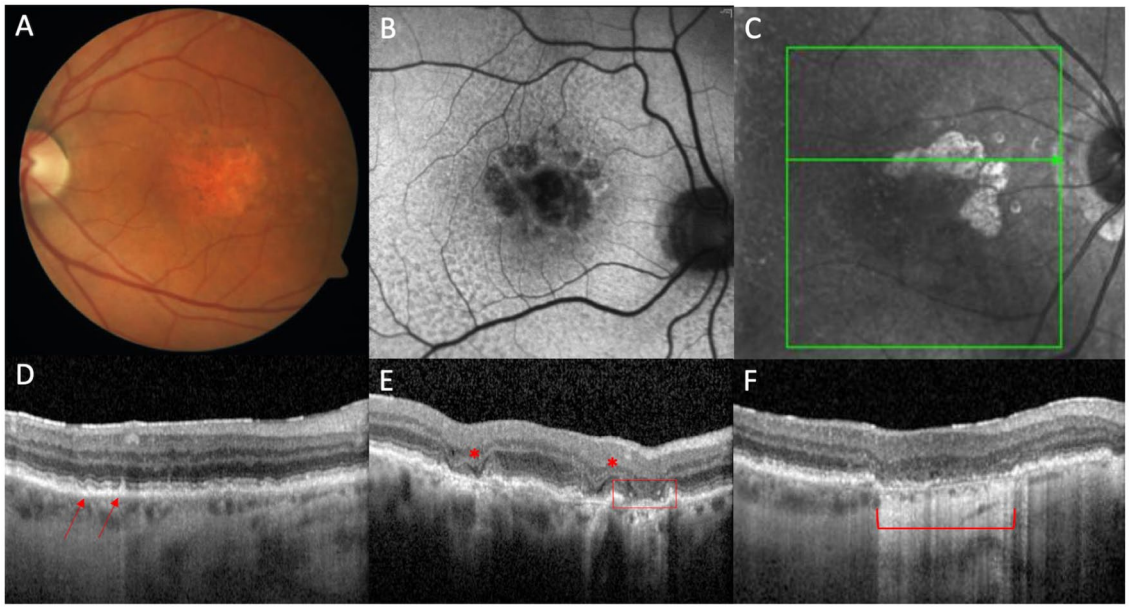


**Figure 4.** Multimodal imaging of non-neovascular age-related macular degeneration (AMD). (A) Color fundus photograph is notable for drusen and a central hypopigmented area with sharply defined borders revealing underlying choroidal vasculature indicative of geographic atrophy (GA) resulting from AMD. (B) Fundus autofluorescence shows darkly hypoautofluorescent lesions corresponding to retinal pigment epithelium (RPE) loss in GA and stippled autofluorescence from drusen. (C) Near-infrared reflectance imaging with hyperreflective lesions of GA corresponding to complete RPE and outer retinal atrophy with choroidal hypertransmission signal seen on OCT in panel F (red bracket). (D and E) Optical coherence tomography shows features predictive of AMD progression to GA, including reticular pseudodrusen (red arrows), subsidence of the outer nuclear layer (red asterisks), and hyperreflective foci (within red box). (*Images courtesy of Joel A. Pearlman, MD, PhD.*)

FAF and near-infrared reflectance imaging are often used in conjunction with structural modalities and visio-physiological testing (microperimetry, ERG) to better correlate the structural and functional changes. As such, FAF and near-infrared reflectance are helpful in "mystery cases" to pick up visual dysfunction in patients with symptomatic vision loss but no obvious structural changes on clinical examination or OCT. Through multimodal imaging, multiple new pathologies have been identified, such as pentosan polysulfate sodium maculopathy.[43] Fundus photography, FAF, near-infrared reflectance, OCT, and OCTA are all useful imaging modalities to establish a diagnosis of pentosan polysulfate sodium maculopathy. Clinical manifestations may be subtle, and changes may not be as evident on clinical examination or fundus photography. However, OCT imaging can reveal nodular thickening at the level of the RPE that colocalizes with macular pigment clumps that are hyperautofluorescent on FAF and hyperreflective on near-infrared reflectance imaging. FAF and near-infrared reflectance can show more dramatic changes of a striking, densely packed array of hyperautofluorescent, hypoautofluorescent, and hyperreflective spots. Changes on near-infrared reflectance are highly sensitive compared with those seen using other imaging modalities, and the reticular pattern can be used as a way to differentiate it from other causes, including AMD or inherited retinal disorders.

One of the most important applications of FAF and near-infrared reflectance imaging in the current era may be in monitoring GA in AMD. Cross-sectional OCT is highly sensitive for identifying the extent of photoreceptor degeneration, RPE loss, and choroidal hypertransmission that develops to become GA. In cases in which cRORA has been identified as GA on OCT, the GA area and rate of growth can be quantified on FAF, near-infrared reflectance imaging, or en face OCT. This has been a key outcome measure to monitor progression and responses to treatment in clinical trials, which will likely translate into clinical practice.

With the recent approval of complement inhibitor therapy for GA, FAF or near-infrared reflectance imaging is handy in identifying patients most likely to benefit from this therapy.[44] Near-infrared reflectance imaging can provide a surrogate GA area measurement approximated by the area that corresponds to choroidal hypertransmission.[43] This area, when quantified, correlates very closely with the area of hypoautofluorescence of FAF in GA patients.[45,46] Combining multimodal imaging of GA helps prognosticate atrophy growth and corresponding visual loss (Figure 4). For example, these prognosticating factors include reticular pseudodrusen on OCT, choriocapillaris atrophy on OCTA, junctional hyperautofluorescence seen on FAF which may correspond to photoreceptor loss or sick RPE at the edge of the atrophic area, and rapid progression of GA size over time, highlighting the importance of longitudinal imaging.[47–49]

The addition of artificial intelligence (AI) and convolutional neural network applications to OCT and FAF have been shown to predict growth of GA lesions.[50–52] However, a major limitation is that the current algorithms poorly predict the

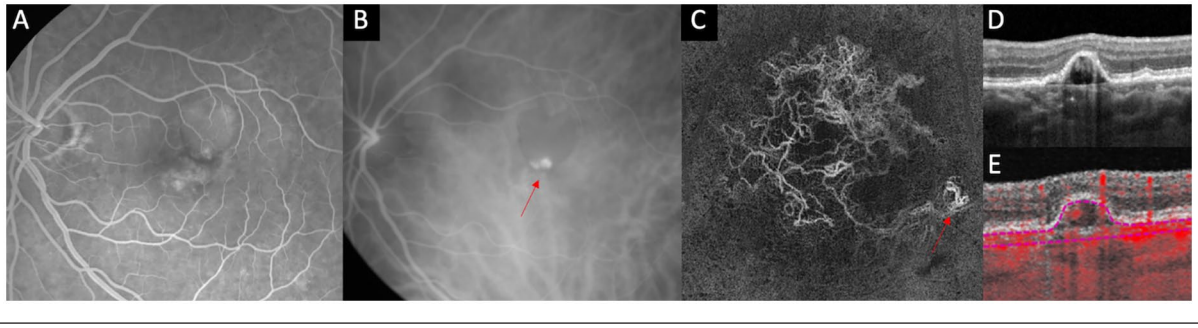


**Figure 5.** Multimodal imaging of polypoidal choroidal vasculopathy. (A) Fluorescein angiography shows ill-defined late staining of a pigment epithelial defect (PED) and leakage in the central macula. (B) Corresponding indocyanine green angiography better highlights the focal hyperfluorescent spot of the polypoidal lesion (red arrow). (C) En face optical coherence tomography angiography (OCTA) of the macula shows a large choroidal neovascular network with a terminal aneurysmal dilation consistent with the polyp (red arrow). Corresponding OCT (D) and cross-sectional OCTA (E) with flow overlay through the polyp show a fibrovascular PED with flow through the hyperreflective lesions within the PED. (*Images courtesy of Michael Engelbert, MD, PhD.*)

directionality of progression (eg, toward the fovea).[53] Further advancements in this area may lead to additional clinical tools to prognosticate vision-threatening GA progression.

## *Optical Coherence Tomography Angiography, Fluorescein Angiography, and Indocyanine Green Angiography*

Perhaps one of the most valuable uses of OCTA in the clinic today is the detection of CNV in AMD.[54] OCT and OCTA are best interpreted together, first by interpreting a B-scan OCT and OCTA with flow overlay and second with en face OCTA. PEDs in AMD can be categorized on OCT based on the morphology of the PED and the reflectivity characteristics of the sub-RPE material as drusenoid (smooth with homogenous, moderately hyperreflective material), serous (abrupt, oval-shaped elevations with homogenous hyporeflective space), hemorrhagic (large elevations with hyperreflective material, often with a notch at the base suggestive of a polypoidal lesion), or fibrovascular (irregular elevations with heterogeneous reflectivity). Corresponding OCTA can confirm the presence of MNV. Often PCV will present with recurrent large hemorrhagic PED or subretinal bleeds, where the hyperreflective blood may obscure visualization of the NV in the sub-RPE layers. In these cases, ICGA can be very useful. Although it has a more limited role than FA in the clinic, it has advantages in capturing choroidal circulation. In ICGA, the dye is more protein-bound than fluorescein, meaning that less leakage is visible on the angiogram. In addition, the longer wavelength can better penetrate the RPE and blood.[55] As a result, polypoidal lesions and the branching vascular network typical of PCV can be clearly seen on ICGA.[56] Although the PLANET trial showed that intravitreal aflibercept monotherapy is effective for treating PCV, 15% of PCV patients required rescue PDT. Multimodal imaging can help reveal the polyps in these cases for targeted PDT[57,58] (Figure 5).

In typical exudative AMD with IRF or SRF on OCT, en face OCTA can be highly sensitive and specific in confirming and visualizing MNV, including type 3 MNV. Longitudinal imaging of type 3 NV showed that OCTA could detect changes in the deep vascular complex even before the presence of exudation on structural OCT. OCTA also enabled the distinction of hyperreflective vascular structures of type 3 NV from hyperreflective foci of RPE migration.[59]

Moreover, not all fluid/hyporeflective spaces on OCT denote exudation from MNV in AMD; OCTA can also be helpful in these scenarios to evaluate for the presence of active MNV. Some hyporeflective intraretinal or subretinal spaces can instead represent degenerative cavitation of retinal structures resulting from cell loss or a geometric gap at the base of a PED from the retina draping over a PED or drusen. Difficult to distinguish by appearance on OCT, degenerative intraretinal cystoid fluid can be characterized by its nonresponsiveness to anti-VEGF treatment. Exudative intraretinal cystoid fluid typically shows rapid improvement or even resolution during initial monthly dosing, while degenerative cysts may not respond during this phase. They can also be found over areas of advanced RPE loss (disciform scar or GA). In addition, outer retinal tubulations might be mistaken for intraretinal cysts as round or ovoid hyporeflective spaces with hyperreflective borders at the ONL on OCT; however, they are a distinct sign of photoreceptor rearrangement seen in various chronic degeneration retinal disorders, most commonly in AMD.[60] These lesions do not require treatment.

Next, in nonexudative AMD, OCTA has been used in GA to note choriocapillaris flow voids. Serial OCTA in GA cases can show increased flow voids as a harbinger of progressive GA but are not yet predictive of the direction of GA growth.[61,62] OCTA has also helped identify nonexudative neovascular disease in which subclinical MNV is present without exudation. In a prospective study by de Oliveira Dias et al,[63] subclinical MNV was prevalent in 14.4% of eyes defined by OCT as intermediate AMD or advanced atrophic AMD and were 15.2 times more likely to progress to exudation at 1 year than those without any CNV. OCTA and ICGA are highly sensitive in

identifying nonexudative MNV, while FA may not reveal these lesions if there is no leakage. Therefore, if a suspicious lesion is seen on OCT (manifesting as the double-layer sign), OCTA or ICGA is recommended to rule out the presence of MNV.[64] Treatment is often not indicated in these cases given that clinical trials, including the PRO-CON and PREVENT studies failed to show a benefit of quarterly anti-VEGF therapy relative to sham.[65,66] Even so, these patients may warrant closer follow-up.

In addition, OCTA, FA, and ICGA can be useful in evaluating choroidal changes in neoplastic and inflammatory conditions. OCTA can detect CNV in secondary cases, such as in myopia, CSC, and uveitis. ICGA can help diagnose choroidal vascular abnormalities, as aforementioned in CSC and PCV, and certain choroidal tumors, such as choroidal hemangioma with late washout of the fluorescent dye from the circumscribed hemangioma.[67] OCTA and ICGA can also be used together to diagnose and treat inflammatory conditions, in which choroidal granulomas and choriocapillaris flow deficits can be seen in cases such as tubercular and sarcoid granulomas. FA and ICGA may be critical for distinguishing between CSC and Vogt-Koyanagi-Harada (VKH) disease, which can both present with multifocal serous retinal detachments (RDs) but often have distinct management approaches of avoiding vs initiating steroid therapy, respectively. OCT may reveal a thickened choroid in both conditions. However, FA classically shows an expansile dot or smokestack in acute CSC, whereas in VKH, there is a classic starry-sky pattern with multiple pinpoint leaks. ICGA will also reveal multifocal hypofluorescent spots in VKH, which are absent in CSC.[68]

## Surgical Vitreoretinal Disease

In surgical vitreoretinal diseases, imaging may be essential in confirming the diagnosis and guiding preoperative prognostication, surgical planning, and postoperative care delivery. Much of this is related to understanding the key anatomic relationships involving the vitreoretinal interface. As such, key imaging modalities in surgical planning include fundus photography, OCT, and B-scan ultrasonography, all of which can provide insights into the 3-dimensional relationship between the posterior hyaloid and the retina.

OCT is vital to our understanding of the progression of various macular diseases. In cases of vitreomacular traction, full-thickness or lamellar macular hole (MH), and epiretinal membrane (ERM), OCT highlights abnormal anterior–posterior traction of the posterior hyaloid face onto the macular surface and guides surgical planning techniques to relieve that traction via vitrectomy or vitreolysis. Important OCT prognostic factors in MH surgery include hole size and stage, presence of cystoid edema, concurrent retinal pathologies, and the status of the outer retinal layers at the edge of the hole.[69] In these cases, it is also important to notice the hyaloid status of the fellow eye, which will require serial monitoring because there is a 15% risk for MH development in the contralateral eye. For ERM, because the majority of membranes remain stable with observation over 5 years, OCT biomarkers in conjunction with functional complaints can help signal when to intervene with surgery. Signs, including the presence of ectopic inner foveal layers, inward deflection of the ONL, progressive attenuation of the ELM and EZ, the presence of the cotton-ball sign, schisis of the retinal fiber layer, ILM dehiscence, and increasing central retinal thickness, are markers associated with the progression of worsening vision but also have a likelihood of improving after surgery.[70,71] Despite favorable outcomes with surgery, 10% to 20% of patients will have unchanged or worse vision postoperatively.[72–74] For example, ganglion cell layer thinning by 10% can be seen after membrane peeling, which can correspond to worse postoperative visual outcomes, especially in patients with preexisting glaucoma or ERMs where retinal nerve fiber layer (RNFL) schisis or inner retinal clefts were present preoperatively.[71,73] Second, the duration of ERM symptoms is inversely correlated with visual outcomes and corresponds to the baseline integrity of the EZ.[74]

These concepts also apply to myopic traction maculopathy in which serial OCT can be used to determine the timing of surgery, usually when VA drops with progressive foveoschisis and associated foveal detachment. High-density raster scans or radial scans can help identify small MH formation in cases in which surgical repair will also be indicated. Other cases of retinoschisis, such as optic pit or optic disc coloboma, can often be visualized on macular OCT, especially in conjunction with OCT of the optic nerve, where the pit can be visualized. En face OCT can also show the extent of schisis due to optic pit or optic colobomas. Postoperatively, serial OCT can be used to track hole closure or normalization of the foveal contour and associated photoreceptor reconstitution to allow for visual recovery. Through OCT, the consequences of surgical intervention can be identified as well, such as dimpling of the nerve fiber layer (termed *peel-induced maculopathy* or *dissociated optic nerve fiber layer*), ganglion cell thinning, and in some cases, phototoxicity. Much is yet to be learned about how to optimize surgical techniques in macular surgery to optimize visual gains.

OCT can also be helpful in the management of peripheral pathology. Diagnosing a posterior vitreous detachment (PVD) can often be supported with traditional OCT, and swept-source OCT (SS-OCT) may add additional value.[75] However, because SS-OCT is not yet widely available, clinical examination combined with SD-OCT of the RNFL and macula can help confirm the presence of PVD.[76] Although widefield fundus photography and OCT cannot replace a scleral depressed examination to rule out retinal breaks, they can be helpful adjunctive imaging modalities. Widefield fundus photographs can often identify peripheral retinal breaks, and OCT may often reveal hyperreflective dots in the vitreous cavity that may represent vitreous hemorrhage or pigment, raising suspicion for the presence of a retinal break.[76]

In cases of RD, OCT can be used to document the preoperative PVD and foveal status and aid in counseling patients on the visual prognosis after RD repair. In addition, when an RD may be difficult to discern from peripheral retinoschisis or schisis-detachment by clinical examination, peripheral OCT scans can

help identify schisis, inner and outer retinal breaks, and the presence of SRF.

Recently, through the use of FAF, the concept of retinal displacement was developed, where "retinal vessel printings" or "ghost vessels" were seen superior and parallel to retinal vessels after RD surgery.[77] Studies have since suggested that these findings may correlate with patients' postoperative complaints of diplopia or metamorphopsia. The findings on FAF are thought to represent increased metabolic activity of RPE cells previously hidden by retinal vessels. Studies have raised questions on whether surgical techniques (vitrectomy, pneumatic retinopexy, scleral buckle) and use of adjunctive tools (gas or oil tamponade, drainage retinotomy, perfluorocarbon liquid) to flatten the retina may put patients at higher risk for retinal displacement.[78] This demonstrates how imaging advancements continue to influence surgeon decision-making and pursuits to attain better functional outcomes for patients.

Finally, in cases of tractional RDs, a combination of fundus photographs, OCT, and B-scan ultrasonography can help delineate the hyaloid location at the disc as well as in the peripheral retina. Vitreoschisis can be better appreciated on OCT, as can focal tractional pegs within the posterior pole, as in the case of diabetic tractional detachments. FA or OCTA of the vitreoretinal interface can be used to evaluate for NV.[79] Close evaluation of these surgical planes of the various ERMs can aid in identifying the initial approach for segmentation and delamination. Intraoperative OCT has been shown to be valuable for surgeons in visualizing surgical planes, peeling membranes without the use of dyes, locating retinal breaks, and identifying the location and volume of therapeutic injections in the subretinal space (as in tissue plasminogen activator or gene therapy). Performance enhancements may contribute to increased use of intraoperative OCT.[80]

## Future Directions

Future advances in retinal practice will likely involve deeper integration of AI as a valuable toolkit to the retina physician. The development of deep learning models has provided precise image recognition and classification in the medical field, and this has been especially so in retinal imaging.

In recent years, many studies have used AI-based image interpretation of OCT and fundus photographs in DR, AMD, and retinopathy of prematurity to screen for and prognosticate disease severity as well as predict treatment outcomes.[81–83] This, combined with imaging and infrastructural advances, has the potential to allow for more widespread implementation of telemedicine for remote or home monitoring of retinal diseases as well to serve as an adjunct tool in retinal surgery. Potential advantages of applying AI-assisted image interpretation are assisting clinical decision-making for earlier detection and better clinical outcomes and removing barriers to healthcare access. Although continued work is still needed to improve on these AI models that can transform AI from a research tool to a clinical tool, AI and telemedicine together hold promise to drastically change the future landscape of retinal practice.

## Conclusions

Modern retina specialists, and their patients, are fortunate to have many imaging modalities at their disposal. Understanding the capabilities and limitations of each modality is critical to maximizing its clinical utility. In combination with a comprehensive clinical evaluation, multimodal retinal imaging is indispensable for the diagnosis and ongoing management of many retinal pathologies. As future research fosters the development of improved imaging technology and expands clinical applications, our understanding of retinal disease will continue to flourish, with the promise of offering better sight to our patients.

### Ethical Approval

Ethical approval was not required for this study.

### Statement of Informed Consent

Informed consent was not required for this study.

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