Retinal imaging and diagnostics

This special series is devoted to a broad range of breakthroughs in multimodal retinal imaging that will be of interest to all specialists, and to those in the many other disciplines that increasingly rely on imaging for research, diagnosis and clinical management. Thus, the topics themselves are not broad, but are developed in enough detail to bring a depth of understanding to the most enquiring mind, one that might consider further applications.

The imaging techniques range from the subcellular, as in Thomas Ach's beautiful catalog of the tiniest granules in the retinal pigment epithelium (RPE) by Structured Illumination Microscopy (SIM), to computer scientist Alauddin Bhuiyan's deep learning models for the detection of multiple diseases simultaneously through artificial intelligence (AI), automated retinal photography and telemedicine. Dr. Ach's work is foundational for understanding age-related macular degeneration (AMD) pathogenesis, and may ultimately lead to treatment in the clinic; Dr. Bhuiyan's creations are in the clinics now, and will likely transform the care of AMD and diabetic retinopathy (DR). With complementary functional testing, as described in Weitzman *et al*., this goal is even closer. Imaginative, easily interpretable images on an iPad become highly sensitive screening tests for many eye diseases. Back at the bench, the hyperspectral autofluorescence (AF) imaging of RPE by Tong and colleagues discovered the AF spectral signature for drusen and drusen precursors, detectable after excitation with blue light. A clinical hyperspectral camera employing this discovery is now being built for earliest detection of AMD.

A pair of other papers venture into the worlds of inherited retinal diseases (IRD) and crystalline retinopathies. These diseases are all relatively uncommon themselves, but both papers illustrate the power of new imaging modalities such as optical coherence tomography angiography (OCTA) and fundus autofluorescence (FAF) to provide critical diagnostic and mechanistic insights even in unexplored terrain. For example, Bietti crystalline dystrophy was described decades ago, but lacked pathogenetic mechanism. Now Kovac and colleagues have clearly defined functional defects of the choriocapillaris (CC) on OCTA underlying these deposits. Subretinal drusenoid deposits (SDD) in AMD are also associated with CC deficiency, underscoring the importance of such damaged perfusion. And importantly, as Georgiou and colleagues point out in their comprehensive imaging atlas of IRD, such insights are no longer just "academic". The notorious IRD of choroideremia, with dramatic findings on AF, is now in a phase 2/3 gene therapy trial.

The structure and prognosis of common retinal afflictions are also better understood with advanced retinal imaging. OCTA has visualized and quantified the retinal microcirculation and CC. In AMD, CC flow deficits worsen with progression, but Corradetti *et al*. now demonstrate that the CC may play a causative role in the pathogenesis of non-neovascular AMD, an important concept that has been widely debated. For retinal vein occlusion (RVO), Miere *et al*. applied the novel and fully automated OCTA parameters of vascular density (VD), skeletal density (SD) and fractal dimension (FD) to predict the visual outcome in RVO eyes, of major importance to patient and physician alike. Structure and function are also combined. In a study by Borrelli and Querques, where dynamic SD-OCT imaging in AMD patients with SDDs revealed abnormal photoreceptor shape changes following photobleaching that paralleled the known functional prolongation of dark adaptation in these eyes, offering clues to the cellular mechanism.

Here we present advanced retinal imaging techniques that are leading us to new understandings of disease processes that were currently inaccessible. From the molecular basis of RPE fluorescence, for translation into cameras for earliest detection of AMD, to remote retinal imaging coupled with AI in primary care settings, poised for major impact on public health, these imaging advances will continue to transform the care of blinding retinal diseases.

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