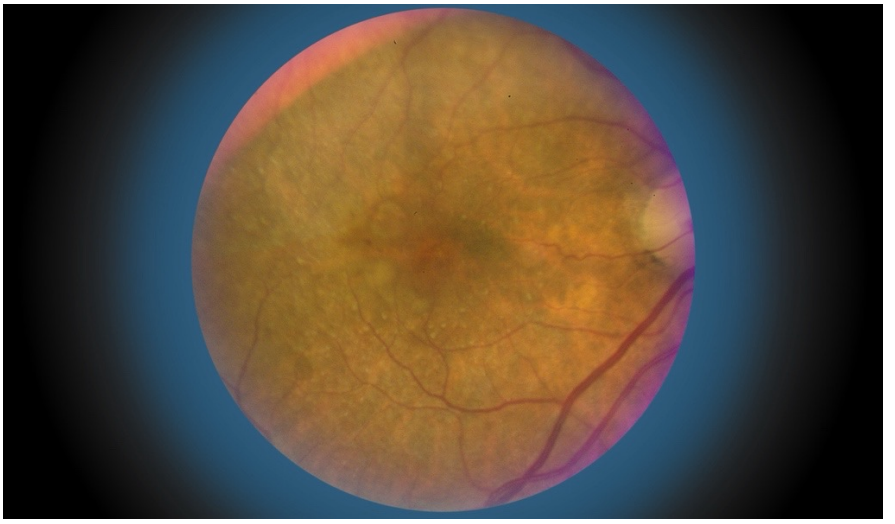


PARADOX. *Drusen, pigmentary changes, pigment epithelial detachments, edema, and scant hemorrhage in a patient with untreated neovascular AMD. Apolipoprotein-B100 may play a paradoxical protective role in some patients with the disease.*

Photo by Bob Moore, Wilmer Eye Institute / Image created by Alexander Sodhi

RETINA

Biomarkers Predict Anti-VEGF Response in AMD

ALTHOUGH ANTI-VEGF THERAPIES can improve visual acuity in many patients with neovascular age-related macular degeneration (AMD), predicting response to treatment remains a clinical challenge. Researchers from Johns Hopkins School of Medicine in Baltimore have found that aqueous biomarkers may help identify patients who might not require or benefit from lifelong anti-VEGF therapy.[1]

The study findings suggest that up to one-third of patients receiving anti-VEGF injections for AMD can be safely taken off treatment, thus sparing them any potential risks of repeated intraocular injections and the burden of frequent clinic visits, said coauthor Akrit Sodhi, MD, PhD.

Moreover, the results also suggest that apolipoprotein-B100 and other aqueous proteins that have been implicated in macular degeneration may, in fact, play a protective role in AMD, Dr. Sodhi added.

Study design. The researchers used an approach that they termed "treat-and-extend-pause/monitor," Dr. Sodhi said. Eyes with neovascular AMD had three consecutive monthly anti-VEGF injections, followed by a treat-and-extend protocol. If eyes remained quiescent, they were switched to treatment on a pro re nata basis. Proteomic assays were used to compare the levels of aqueous proteins between patients who responded well to therapy and those who did not.

Results. At the end of 12 and 24 months, 31% and 38% of eyes, respectively, were successfully weaned off of treatment.[1]

With regard to whether the aqueous fluid proteins could be used as a surrogate marker, approximately 170 proteins were found to correlate with patients' response to anti-VEGF therapy, Dr. Sodhi noted. He added that many of these proteins had been previously implicated in AMD pathogenesis.

An unexpected finding. "Perhaps the most surprising and exciting finding of the study is that apolipoprotein-B100 was found in higher levels in patients who required less frequent injections," Dr. Sodhi said. In contrast, prior data have suggested that apolipoprotein-B100 may contribute to AMD pathogenesis by driving dry macular degeneration.

Investigating further. To validate their finding, the researchers measured aqueous apolipoprotein-B100 levels in an independent cohort. "We found that aqueous apolipoprotein-B100 levels were higher in AMD eyes than in controls and lower in AMD eyes with choroidal neovascularization than in patients with dry AMD," Dr. Sodhi said. The researchers also studied mice that overexpress apolipoprotein-B100 in the part of the retina that plays a role in macular degeneration—and found that apolipoprotein-B100 overexpression protected the mice from laser-induced choroidal vascular lesions.

Looking ahead. Dr. Sodhi noted that further research is needed to elucidate the role of apolipoprotein-B100 in wet AMD. "We also want to conduct a prospective clinical trial to validate these potentially protective proteins as well as aqueous biomarkers that could predict the response to anti-VEGF therapy."

—Christos Evangelou, PhD

1 Cao X et al. *J Clin Invest.* 2022;132(2):e133369.

Relevant financial disclosures—Dr. Sodhi: NEI: S.

NEURO-OPHTHALMOLOGY

OCT Pins Down MOGAD and MS Diagnosis in ON

WHILE OPTIC NEURITIS (ON) CAN occur with both myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) and multiple sclerosis (MS), treatment of the two demyelinating diseases differs. Now, researchers have found that OCT can be used to determine whether a patient has MOGAD-ON or MS-ON.[1]

In the study, optic nerve edema was assessed with OCT-derived peripapillary retinal nerve fiber layer (pRNFL) thickness and shown to be more severe in eyes with MOGAD-ON than in eyes with MS-ON. Additionally, pRNFL thickening appears to be a sensitive biomarker for confirming MOGAD-ON, the researchers said.

"We were not too surprised to find that the pRNFL during an acute optic neuritis attack was much thicker in MOGAD compared to MS overall, but the degree that OCT differentiated the two entities was quite striking," said John J. Chen, MD, PhD, at the Mayo Clinic in Rochester, Minnesota.

Pathway to better outcomes. The findings can help guide acute treatment while the clinician awaits results of antibody testing, Dr. Chen said. "MOG antibody test results typically return in one to two weeks, which may be outside the window of opportunity for early steroids to influence outcomes." But based on this study, the presentation of optic neuritis with significant pRNFL thickening would be suggestive of MOGAD, and such a patient should be treated with early steroids, he said. This is in contrast to MS-ON, for which steroid treatment has been found to speed up recovery but does not change the ultimate outcome,[2] Dr. Chen added.

"It is likely even more important

CORNEA

Assessing Clinicians' Ability to Dx Infectious Keratitis

HOW WELL DO CORNEA SPECIALISTS DISTINGUISH bacterial from fungal keratitis? There is significant room for improvement, according to a comparison of human clinical performance and confirmed microbiologic data.[1]

"The average expert cornea clinician was only a little bit better than random chance when interpreting images of corneal ulcers," said lead author Travis K. Redd, MD, MPH, at the Casey Eye Institute in Portland, Oregon. However, there was considerable regional variation, with cornea experts in South India significantly outperforming their colleagues in other countries.

Grading the images. Sixty-six cornea specialists from 16 countries were asked to grade 100 corneal ulcer images from a clinical trial database at the Aravind Eye Care System in South India. The graders received no clinical or historical information but were told that half the cases had been microbiologically proven to be bacterial keratitis, the other half fungal. Ten images (five bacterial; five fungal) were presented twice to each grader for assessment of test-retest reliability.

Results showed that the experts' areas under the curve (AUC) were highly variable. These measures of the usefulness of a test ranged from 0.39 to 0.82, with a mean of 0.61. This means that some graders did worse than a coin toss at predicting the cause of infection, while others were reasonably accurate. The mean AUC figure suggests that the average expert cornea clinician was only a little better than random chance in interpreting the images, said Dr. Redd.

Regional variations. A subgroup analysis revealed that the clinicians who practice in India were more accurate in identifying fungal ulcers than their colleagues located elsewhere (76% vs. 49% accuracy rate, respectively). No comparable geographic difference was noted with bacterial ulcers.

The subgroup finding suggests a possible difference in the appearance of ulcers in different regions. Thus, familiarity with one's local ulcer morphology possibly confers better accuracy at predicting the underlying cause of infection, Dr. Redd said. Alternatively, the difference may be attributable to Indian experts' greater familiarity with fungal keratitis, which is less common in other regions, including the United States and Europe.

While additional studies are needed to compare expert performance, the finding emphasizes the importance of regionality in predicting etiology of corneal ulcers and has implications for designing an artificial model (AI) model, Dr. Redd said. "Careful regional evaluation will be required before these models can be implemented. AI models trained on data from one location may not generalize to other regions."

Building on the findings. The researchers recently published initial results of an AI model that demonstrated "superhuman performance, even surpassing the Indian experts in differentiating bacterial and fungal keratitis," said Dr. Redd.[2] Now they are working to incorporate clinical history and expert opinion into the model. They're also developing models to interpret smartphone images, which may allow for earlier initiation of antimicrobial therapy and improved visual outcomes for patients. *—Miriam Karmel*

1 Redd TK et al. *Ophthalmology*. 2022;129(2):227-229.
2 Redd TK et al. *Ophthalmol Science.* Published online Jan. 28, 2022.

Relevant financial disclosures—Dr. Redd: NEI: S; Research to Prevent Blindness: S.

to differentiate these entities when it comes to chronic treatment decisions," he said. "For the most part, traditional MS medications are not effective for patients with MOGAD and vice versa. OCT may be able to help confirm cases of MOGAD in the setting of low MOG antibody titer, which has recently been shown to be a false positive in up to 50% of cases."

In addition, it is important to have objective evidence of ON in clinical practice, Dr. Chen said, because patients often develop vague symptoms such as blurred vision and discomfort. "If a patient has these symptoms along with a significant increase in pRNFL thickness, we can be confident it is a true attack [of ON]." This is particularly the case with MOGAD, he said, "since every attack was associated with at least a 5 µm increase in pRNFL thickness."

Study specifics. This retrospective multicenter case series included 64 MOGAD patients (96 eyes) and 50 MS patients (51 eyes) who underwent OCT within two weeks of onset of ON symptoms. None of the study eyes had experienced a previous ON attack. Of the MOGAD patients, 29 (45%) had bilateral simultaneous ON, compared with one (2%) of the MS patients.

The median pRNFL thickness was 164 µm in MOGAD-ON eyes and 103 µm in MS-ON eyes ($p < 0.001$). A cutoff value of 118 µm provided a sensitivity of 74% and specificity of 82% for the optic neuritis being from MOGAD. Among 31 MOGAD eyes and 48 MS eyes with baseline or comparator data, there was a median pRNFL thickening of 45 µm and 7.5 µm, respectively ($p < 0.001$).

What's next? OCT-derived pRNFL thickening will be used in an upcoming clinical trial on MOGAD as one of the objective criteria to confirm an ON attack, Dr. Chen said.

—Patricia Weiser, PharmD

1 Chen JJ et al. *Mult Scler Relat Disord.* 2022;58:103525.

2 Beck RW, Gal RL. *Arch Ophthalmol.* 2008;126(7):994-995.

Relevant financial disclosures—Dr. Chen: None.

GENETICS

AI Quantifies Loss of Retinal Cells in Stargardt

NEI RESEARCHERS HAVE DEVELOPED and validated an artificial intelligence (AI)–based method that surpasses conventional approaches to analyzing structural changes in the retina related to *ABCA4*-associated retinopathy, the most common form of Stargardt disease.[1] Their model provides a framework for evaluating disease progression and appears to help control for the significant variability among patients for age of onset and spatial pattern of photoreceptor degeneration.

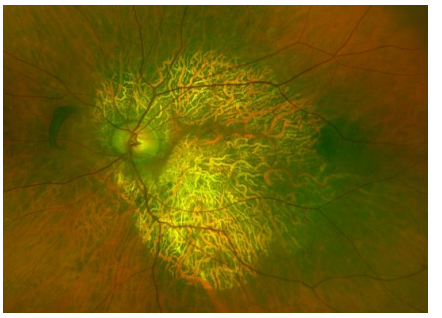
"Despite the apparent heterogeneity of patients with Stargardt disease, a simple additive model of allele severity, in conjunction with age, explains almost half of the between-patient variability in imaging-based severity," said lead author Maximilian Pfau, MD.

Homing in on the ellipsoid zone. The researchers used thickness maps of six retinal layers from OCT images of 132 eyes (66 patients) to train a deep-learning (DL) algorithm to quantify retinal degeneration over time. These images enabled the algorithm to detect patterns for quantifying and comparing loss of photoreceptors and layers of the retina that correlate *ABCA4* variants with a patient's phenotype.

Researchers focused their interest on ellipsoid zone (EZ) loss, a measure of severe photoreceptor degeneration. They also considered the outer nuclear layer beyond the areas of EZ loss. Finally, they compared measures of macula-wide photoreceptor loss, genotype, and age against the genetic data.

Outcomes. Photoreceptor losses followed predictable spatial and temporal patterns. Importantly, patients with *ABCA4*-associated retinopathy exhibited photoreceptor degeneration beyond the area of EZ loss. The researchers propose that this distant area may be the actual leading front of the disease.

The study also demonstrated different rates of retinal change among patients, with the age of loss dependent on genotype. Thus, the DL model generated a way of classifying the severity of 31 variants, including 16 variants not previously quantitatively analyzed for clinical severity.



SHEDDING LIGHT. *The presentations of Stargardt disease vary widely. Previous approaches to analyzing structural changes in the retina have not allowed researchers to correlate genetic variants with disparate disease characteristics.*

Avenues for further research. Although the prediction model works well for macula-wide loss of photoreceptors, the genetic determinants of foveal sparing in Stargardt are less clearly understood and warrant further investigation, Dr. Pfau said.

With regard to potential therapies, a clinical trial of oral metformin for Stargardt is now underway at the NEI, but it was initiated before this study was published. Dr. Pfau and his colleagues plan to apply the AI-based segmentation to investigate potential treatment effects of metformin on photoreceptors distant to the EZ loss boundary.

Other therapeutic approaches to prevent progression of photoreceptor loss are underway, Dr. Pfau said. However, these therapies will only slow the deterioration of vision, not improve it, and patients will want evidence of treatment effects. "Ultimately," he said, "it will be necessary to translate these photoreceptor loss maps to patient-relevant measures, such as reading ability and mobility." *—Miriam Karmel*

1 Pfau M et al. *JCI Insight.* 2022;7(2):e155373.

Relevant financial disclosures—Dr. Pfau: Apellis: C; Novartis: L.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.