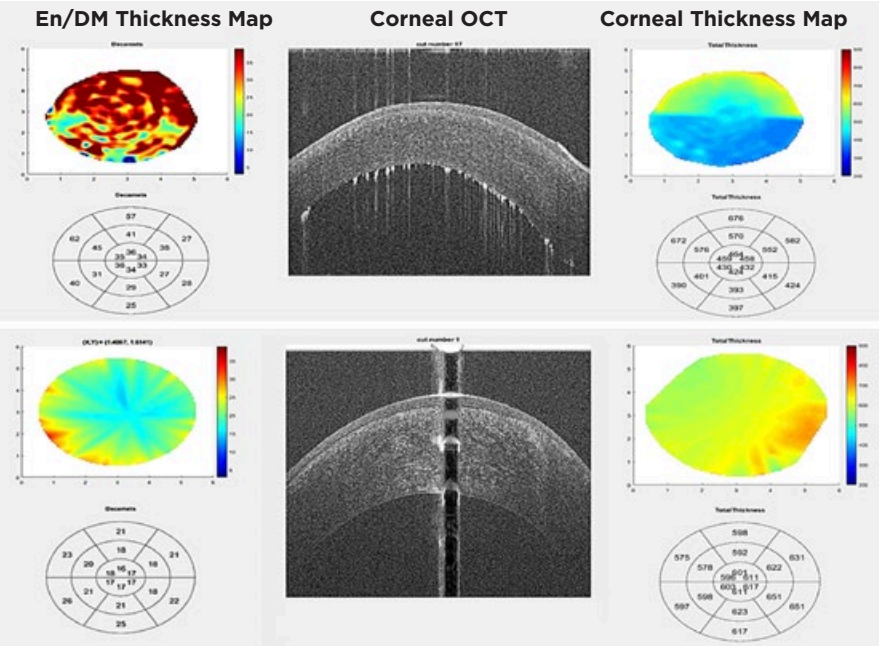
CORNEA

Graft Rejection Detected in Action



OPTICAL BIOPSY. *Corneal microlayer tomography of the endothelial/Descemet membrane display shows (top) active corneal graft rejection versus (bottom) a healthy graft. Differences in the thickness maps of the two grafts also are evident.*

UNIVERSITY OF MIAMI RESEARCHERS have developed an automatic algorithm that combines tomographic images of an in situ corneal graft into a 3-D model that can reveal an otherwise undetectable signal of graft rejection.

Results of their study showed that central thickening of the endothelial/Descemet membrane complex (En/DM) predicted graft rejection at least two months before the clinical diagnosis was made.[1] "Transplant surgeons are already using basement membrane to detect rejection in other organs, such as kidney and lung transplants, but they have to do it with a surgical biopsy. We demonstrated we can do it without having to do an invasive procedure, by doing an optical biopsy," said coauthor Mohamed F. Abou Shousha, MD, PhD.

Study findings. For this prospective trial in 60 high-risk cornea transplant patients, the researchers compared the performance of the OCT-based algorithm to the timing of rejection diagnoses made during five postoperative exams (at months 1, 3, 6, 9, and 12).

In eyes that did not develop rejection, analysis of the grafts' central 2 mm showed that the En/DM thickness was stable through 12 postoperative months. But when the En/DM thickness measured ≥18 µm, the risk ratio for clinical rejection was 6.89 (95% confidence interval [CI]: 2.03-23.4; p = 0.002). Once the En/DMT thickened further to 19 µm or greater, the risk of graft rejection increased by a factor of almost 10.

"The algorithm is detecting the microscopic changes that are happening on the endothelial/Descemet membrane, before rejection becomes clinically apparent," Dr. Abou Shousha said. "You can see the natural history of rejection rather than a 'snapshot' of the one time when the patient visits the physician and receives the diagnosis."

Mapping the microlayer. The researchers created a system to automatically and reproducibly measure corneal microlayer thickness by doing "optical microlayer tomography" with OCT, Dr. Abou Shousha said.

The group developed software that assembles a series of segmented OCT images, taken radially and centered on the corneal vertex, into color-coded 3-D maps of the layers. The maps are then analyzed, and the En/DM thickness is measured automatically.

What's next. Further research is needed, in order to demonstrate that the analytic system could be used with all OCT instruments, and FDA approval will be required before commercialization, Dr. Abou Shousha said.

He added that corneal transplant surgeons have told him they are eager to have it available because it could protect patients from going through corneal failure. "We know endothelial cells lost in a rejection episode will never be replaced. So predicting and diagnosing graft rejection early on is extremely important," Dr. Abou Shousha said. "What we have here is a method for diagnosing subclinical rejection that also would guide treatment decisions."

—Linda Roach

1 Eleiwa T et al. *Sci Rep.* 2021;11(1):14542.

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Mohamed Abou Shousha, MD, PhD

IMAGING

Refining Dx of Pentosan Polysulfate Maculopathy

TWO SEPARATE STUDIES OF PATIENTS who take pentosan polysulfate sodium have confirmed the drug's association with retinal toxicity at high cumulative dosages and demonstrated that multimodal imaging techniques can identify even mild cases of the condition.[1,2]

Indeed, multimodal imaging is essential both to detect damage from the drug and to distinguish the condition from age-related macular degeneration (AMD) and other maculopathies, the studies concluded.

Systemic treatment, macular toxicity. Since 1996, pentosan polysulfate (Elmiron) has been the only FDA-approved oral drug for treating interstitial cystitis. However, evidence of macular toxicity in patients who take the drug emerged in 2018. That study found that, typically, these patients had taken 300 mg daily for a decade or more.[3]

In one of the current studies, multimodal imaging of 105 suspected cases, which had been gathered by a Macula Society study group, confirmed pentosan polysulfate maculopathy in 74 patients. These patients had taken the drug for a median of 14 years (interquartile range [IQR], 10.2-18.9), and the median IQR dosage was 1,500 g (range, 900-2,400 g).[2]

A separate, prospective prevalence study examined 100 pentosan users with multimodal retinal imaging and detected drug-related maculopathy in 16% of cases.[1] "This study is the first prospective analysis showing that this drug is associated with retinal toxicity, that the prevalence is significant, and that the toxicity is dose-related," said coauthor David Sarraf, MD, at the University of California, Los Angeles. Dr. Sarraf added, "While there was a 16% prevalence of pentosan polysulfate maculopathy in general, if you look at the patients who had a cumulative dosage over 1,000 g, the prevalence rose to 40%, and for dosages over 1,500 g, it was 55%."

Imaging recommendations. In both studies, the researchers found that many eyes with pentosan maculopathy initially were misdiagnosed as having AMD. They recommended the following to detect signs in the retina and choroid characteristic of drug-induced damage:

Fundus photography, to identify

CATARACT

Surgery and RVO Risk

DOES CATARACT SURGERY REDUCE THE RISK OF RETinal vein occlusion (RVO)? A study of 4 million patients from the IRIS Registry yielded unexpected findings: First, cataract extraction did not appear to be protective against development of RVOs, despite its effect on intraocular pressure (IOP) reduction. Second, the presence of diabetic retinopathy (DR) emerged as the strongest predictor of RVO development.[1]

Power of big data. Both findings highlight the power of using large databases to explore questions that are impractical for randomized controlled trials. "Big data allows for even small effects to be teased out, so the finding that cataract surgery does not reduce the risk of RVOs despite lowering IOP was surprising," said Andrew Chen, MD, at the University of Washington, Seattle, a senior coauthor of the study.

Study design. To determine the risk of developing RVO, the researchers emulated randomized controlled trials with a machine learning model. Patients were classified as belonging to the treatment or control groups based on known risk factors for cataract development. This allowed the two groups of patients to be selected according to the same set of rules. Factors included age, sex, primary insurance type, and history of DR, glaucoma, and narrow angles.

Study findings. Of the 4 million patients, there were a total of 2,062 central RVO events within one year of undergoing uncomplicated cataract surgery—or, for 1:1 matched controls, one year from the baseline visit. Of these, 1,141 occurred in the surgery group, and 921 occurred in controls. In addition, there were 3,488 branch RVO events, with 1,942 in the surgery group and 1,547 in controls.

The bottom line: Although surgery did not prevent RVO development, the number of RVOs in both groups was relatively small, and the proportion of eyes that did not develop either type of RVO was greater than 99.8%.

DR risk. DR was the strongest predictor associated with developing central RVO (hazard ratio [HR] 2.79; $p < .001$) and branch RVO (HR 1.97; $p < .001$) after cataract surgery. "The magnitude of the increased risk associated with DR was not expected given the results from prior epidemiologic studies, such as the Blue Mountain Eye study," Dr. Chen said.

In discussing this discrepancy, the researchers noted that they relied on DR codes rather than systemic diabetes mellitus codes in their analysis. "Thus, we would have only considered diabetes cases severe enough to have ocular manifestations, unlike previous studies," they wrote.

Up next. Dr. Chen cautioned that relationships in a retrospective study do not imply causation. He called for future research that delves into the pathophysiology of the disease, noting that future versions of the IRIS Registry will include more variables that have been implicated as risk factors for RVOs, such as axial length. "We still do not fully understand the reason for why RVOs occur." *—Miriam Karmel*

1 Bagdasarova Y et al. *Ophthalmology Science.* Published online July 13, 2021.

Relevant financial disclosures—Dr. Chen: None.

macular hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelium (RPE) atrophy.

Fundus autofluorescence imaging, to identify a speckled pattern of hypo- and hyperautofluorescence centered around the macula and, in some cases, the disc as well.

OCT, to identify focal thickening or elevation of the RPE.

Near-infrared reflectance, to identify hyperreflective lesions of the RPE corresponding to focal thickening or elevation of the RPE with OCT. (This method may be the best way to detect some early cases, the authors said.)

Need to screen patients. Because of the dose correlation and because a few affected patients in the studies were asymptomatic, ophthalmologists should screen patients taking pentosan polysulfate at baseline and then annually after the cumulative dosage reaches 500 g, Dr. Sarraf said.

Nieraj Jain, MD, coauthor of the Macula Society study, said his study group suggests that ophthalmologists may consider screening annually from the time patients start taking the drug.

"Unfortunately, the macular damage doesn't appear to reverse once patients are off the drug, so early detection is important," said Dr. Jain, at Emory University in Atlanta. "And in most cases, it will be prudent for the affected patients to come off the drug."

Dr. Jain, who coauthored the original 2018 paper about this condition, said reports in journals appear to have informed many ophthalmologists about pentosan polysulfate maculopathy. Support also has come from advocacy groups that track new research about interstitial cystitis and discuss these issues online, he said. "The fascinating thing is that social media has helped us get the word out," Dr. Jain said. "Patients on this drug have been taking our paper to their ophthalmologists and asking, 'Do I have this?'" *—Linda Roach*

1 Wang D et al. *Am J Ophthalmol.* 2021;227:125-138.

2 Jain N et al., for the Macula Society Pentosan Polysulfate Maculopathy Study Group. *Ophthalmol Retina.* Published online July 20, 2021.

3 Pearce WA et al. *Ophthalmology.* 2018;125(11):1793-1802.

Relevant financial disclosures—Dr. Jain: None; Dr. Sarraf: Janssen: C.

RETINA

New Consensus on RRD Repair Risks

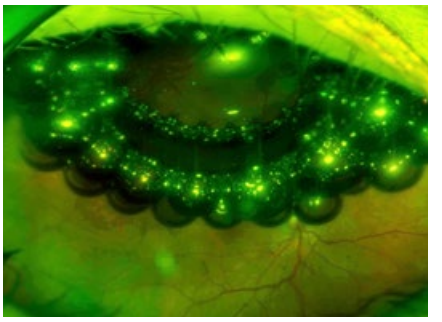
**IN A SYSTEMATIC REVIEW, THE COMplications of Retinal Detachment Surgery (CORDS) Study Group evaluated procedures for the repair of rhegmatogenous retinal detachment (RRD). They found that "the reporting of harms was inadequate and required improvement," said Noemi Lois, MD, PhD, at Queens University in Belfast, Northern Ireland. Even when the frequency of complications was recorded, the severity was rarely noted, making it difficult to compare different interventions.[1]

Clinical trials "are often good at presenting efficacy of new treatments tested, but they are not as good at reporting complications (harms) in a systematic and quantifiable manner," Dr. Lois said.

Classifying complications. The CORDS Study Group first developed a comprehensive list of 87 complications associated with retinal repair procedures, including general intra- and postoperative surgical complications as well as those specific to scleral buckling, pars plana vitrectomy (PPV), and pneumatic retinopexy. Seventy surgeons from 17 countries were invited to participate in ranking these harms; of these, 43 completed the process.[2]

Participants were asked to assign a score, ranging from 1 (no harm to patient or vision) to 10 (worst possible harm to patient or vision, e.g., permanent loss of vision or painful eye) for each item on the list. The study group then applied the Delphi method to compile the anonymous responses, present the summary results of the first round to the participants, and allow them to either maintain or modify their own rankings for the next round.

Achieving international consensus. The group reached consensus on 84 (97%) of the complications.[2] "It was very good indeed to see that this large group of surgeons from all continents graded complications in such a homogeneous manner and achieved consensus in only two rounds of the Delphi survey," said Dr. Lois. She added, "In my mind, this supports the generalizability of the CORDS results."



FISH EGGS. *The formation of gas bubbles (fish-egg phenomenon) during pneumatic retinopexy is included in the new classification system.*

Dr. Lois attributed the lack of consensus on the three remaining complications to the "very strict criteria we set" of an interquartile range (IQR) of ≤2 on a 10-point scale, while "many consensus studies set the consensus criteria at an IQR of ≤3 on a 9-point scale." The three outliers—suprachoroidal hemorrhage, not kissing and not involving the macula; subretinal infusion in the context of PPV; and early migration of the scleral buckle—each had an IQR of 2.75.

Looking ahead. To be useful, the classification must be easy for surgeons to consult, said Dr. Lois. "For this reason, we are working on an app that would be freely accessible through mobile phones and computers." This would "greatly facilitate [the classification's] introduction in clinical practice, not only for its use in clinical trials but also for auditing our surgical results." *—Peggy Denny*

1 Xu ZY et al; CORDS Study Group. *JAMA Ophthalmol.* Published online June 17, 2021.

2 Xu ZY et al *JAMA Ophthalmol.* 2021;139(8):857-864.

Relevant financial disclosures—Dr. Lois: None.

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