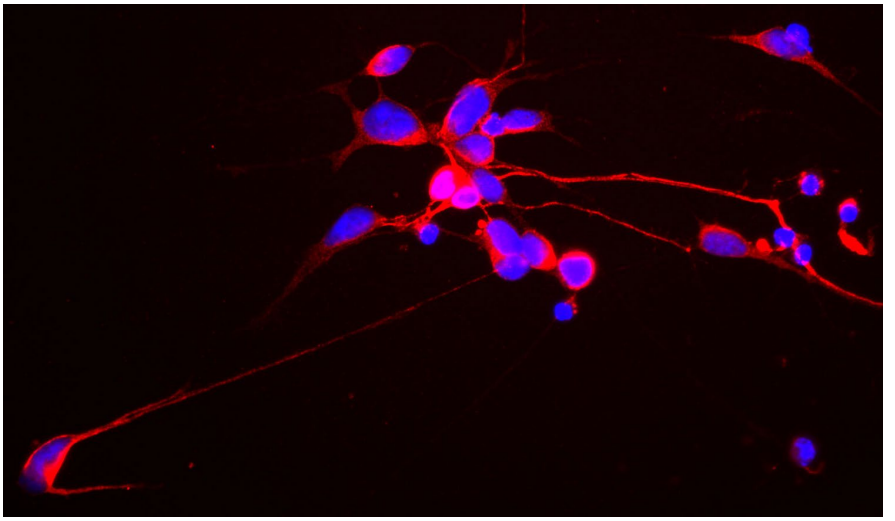
News in Review

COMMENTARY AND PERSPECTIVE



BIOMARKER. *Human neuronal cells show fibrillar staining for NfL (red). Cell nuclei of some non-neuronal cells are also evident (blue).*

Pete Shuster / NIH

NEURODEGENERATION

Protein in Vitreous Suggests Alzheimer Disease

SCIENTISTS AT BOSTON UNIVERSITY have detected another way in which the eye might serve as a window into the body's health—this time via a neurodegenerative molecule's presence in the vitreous at levels that correlate positively with levels of known biomarkers for Alzheimer disease (AD).[1]

The protein, neurofilament light chain (NfL), is a structural component of axons that is released into cytoplasm when axons degenerate. It has been identified in the cerebrospinal fluid and blood and appears to have potential as a screening tool and prognostic indicator in several neurological diseases, including multiple sclerosis.

Evaluating vitreous samples. In an earlier study, the Boston researchers found that amyloid-beta and tau proteins (biomarkers associated with AD) were present in vitreous—and that they positively correlated with patients' scores on mental tests.[2]

For this study, the researchers looked for NfL, testing the vitreous from 77 patients (mean age, 56.2 years) who underwent planned vitrectomy. NfL was detected in all 77 vitreous samples, and NfL levels were positively associated with increased vitreous levels of amyloid-beta and t-tau, but not with p-tau181. They also were significantly associated with select inflammatory cytokines and vascular proteins—and they were not affected by other ocular conditions or by systemic diseases like hypertension and hyperlipidemia.[1]

Next up: sampling the aqueous. At this point, vitreous sampling is still too risky and expensive to be used as a screening tool to detect AD proteins, said Manju L. Subramanian, MD, the principal investigator. As for next steps, the Boston group has begun an NIH-funded study to determine whether NfL can be detected in aqueous. The researchers eventually hope to evaluate tear secretions, because tear testing would be even less invasive with fewer risks and low cost, making it an ideal screening tool, she said.

Why not use OCT to detect AD? Some researchers favor evaluating the eye with optical coherence tomography (OCT) to look for structural signs of AD. However, this can be problematic, Dr. Subramanian noted. "There are some ocular findings on OCT that can indicate a patient may have Alzheimer disease. But the data are conflicting, and there are a lot of local eye conditions that impact OCT measurements, such as diabetes, age-related macular degeneration, and glaucoma. And for those patients OCT testing may not work that well."

Looking ahead. Further studies are needed to understand the sources of NfL in vitreous and to validate NfL levels in eye fluid and correlate them with other established biomarkers of neurodegeneration, Dr. Subramanian said.

Nonetheless, the results of this study suggest that NfL in vitreous might eventually prove to be a biomarker that physicians could use to screen for AD or to evaluate its progress, she said. "As an optical system, the eye allows us to actually visualize brain tissue. So if the eye can potentially be used as a diagnostic test for systemic diseases like Alzheimer, then the ophthalmologist might be playing a role in diagnosing neurodegenerative diseases in the future."

—Linda Roach

1 Subramanian ML et al. *Alzheimers Res Ther.* 2020;12(1):111.

2 Wright et al. *J Alzheimers Dis.* 2019;68(4):1429-1438.

Relevant financial disclosures—Dr. Subramanian: None.

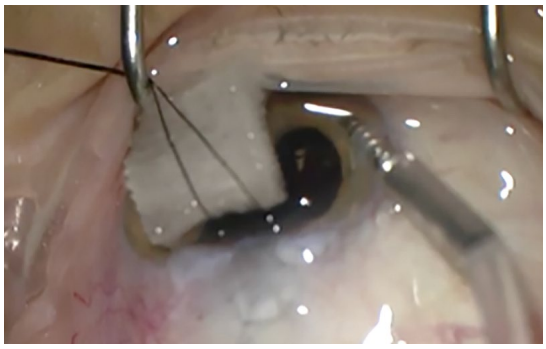
GLAUCOMA

Reoperations After Trabeculectomy

UNPLANNED RETURN TO THE OR following trabeculectomy surgery was more common than expected, according to researchers at the Wilmer Eye Institute in Baltimore.[1] In a retrospective case-control study, the researchers found that nearly one in 10 treated eyes required an unplanned reoperation within 180 days, while one in five underwent reoperation at any time up to three years.

This higher than expected rate of return "highlights the importance of reporting such data so that clinicians and patients have a better understanding of the risks and postoperative course after trabeculectomy," said coauthor Michael V. Boland, MD, PhD.

Two calculations. The findings are based on clinical data from 881 eyes that had undergone trabeculectomy from January 2014 to December 2016. Each eye was randomly matched to a control patient who had surgery near the same time. Reoperation and control eyes did not differ with regard to a number of factors, including mean follow-up, age at surgery, type of glaucoma, history of either prior incisional or glaucoma surgery, mean baseline intraocular pressure (IOP), and mean number of pre-op glaucoma eyedrops. The reoperation rate was 9.5% (84 eyes) up to 180 days post-trabeculectomy and 23.3% (205 eyes) up to a mean of three years.



BLEB NEEDLING. *Most reoperations following unplanned return to the OR required bleb needling.*

A second analysis excluded bleb needling to account for significant differences in surgeons' preferences for where to perform this procedure. One surgeon performed a large number of these procedures in the OR, while others performed bleb needling in the clinic. Given that the latter group was not identified by billing records, this biased the results. The return to OR

DRUG DELIVERY

Steroid-Eluting Contacts Show Promise

PATIENTS WHO HAVE DIFFICULTY COMPLYING WITH dosing schedules for their corticosteroid eyedrops might one day have an easier time of it, thanks to a steroid-eluting contact lens that is showing promise during preclinical testing.[1]

Sandwiched inside a hydrogel contact lens (DexaLens, TherOptix; formerly known as Dex-Lens), a polymer ring containing dexamethasone delivered the medication continuously and effectively onto rabbit corneas for up to seven days.

If these early results are borne out in human studies, the steroid-eluting contact lens "might be able to address any ocular inflammatory condition that you would typically treat with steroids. That includes uveitis, post-traumatic corneal injury, postcorneal transplant inflammation, and postcataract surgery," said Joseph B. Ciolino, MD, at Massachusetts Eye and Ear/Harvard Medical School in Boston.

Design. The contact lenses that the researchers used are made from methafilcon, a biocompatible hydrogel that is commonly used in bandage contact lenses. Encapsulated in the periphery of the lenses is a ring-shaped dexamethasone-polymer film. The central lens is clear, to allow light into the eye.

Results in rabbits. In a previous animal study, Dr. Ciolino and his colleagues found that the medication released by the contact lens onto the cornea diffused into the posterior segment and was able to inhibit VEGF-induced retinal vascular leakage.[2]

In this study,[1] the treatment inhibited suture-induced corneal neovascularization and inflammation for seven days and, in a five-day lipopolysaccharide-induced uveitis model, anterior uveitis. These outcomes were "similar to that of hourly-administered dexamethasone eyedrops," the researchers noted.[1]

In a secondary ocular irritation analysis, samples of drug concentration in the test animals' retinas showed that it peaked two days after lens insertion and averaged 4,353 ng/g. That finding compared to an average of 21 ng/g in the retina after administration of eight hourly doses of commercial 1.0% dexamethasone eyedrops.

Cautious optimism. "The steroid-eluting contact lens is a technology that ophthalmologists should consider as a promising potential therapeutic because it can deliver steroid to the eye in a sustained manner. In doing so, it eliminates patient adherence as part of the treatment equation. It may be able to eliminate the need for steroid injections," Dr. Ciolino said.

However, as he pointed out, "We will have to perform human studies to better understand whether [the contacts] can be more effective than steroid eyedrops."

—Linda Roach

1 Bengani LC et al. *Acta Biomater.* 2020;116:149-161.
2 Ross AE et al. *Biomaterials*. 2019;217:119285.

Relevant financial disclosures—Dr. Ciolino: TherOptix: C,O,P.

Michael V. Boland, MD, PhD

rate in this second analysis fell to 6.5% (57 eyes) at 180 days and 13.6% (120 eyes) at any time.

Reasons for reoperation. In the earlier post-op period, the most common reasons for return to the OR were bleb leak, choroidal effusion, and persistently elevated IOP despite medical therapy. These cases typically resulted in bleb revision, choroidal drainage, and intraoperative bleb needling procedures.

At any time, the most common reason for return to the OR by far was persistently elevated IOP despite medical therapy. In these cases, reoperation typically involved bleb needling or a new glaucoma surgery, such as a tube shunt. Factors that were not associated with return to the OR included maximum IOP prior to trabeculectomy, preoperative use of oral glaucoma medications, and combined cataract-trabeculectomy surgery.

Similar outcomes. Although those returning to the OR used more topical medications and underwent more surgeries than controls (sometimes multiple surgeries), outcomes between the two groups were similar. For instance, mean IOP, proportion of eyes meeting target IOP, and change in visual acuity following the original trabeculectomy were comparable.

Still, a return to the OR is far from optimal, Dr. Boland said. "Accordingly, these analyses of reoperation after trabeculectomy are important in helping to set appropriate expectations for patients and providers alike."

—Miriam Karmel

1 Cardakli N et al. *Am J Ophthalmol.* 2020;219:132-140.

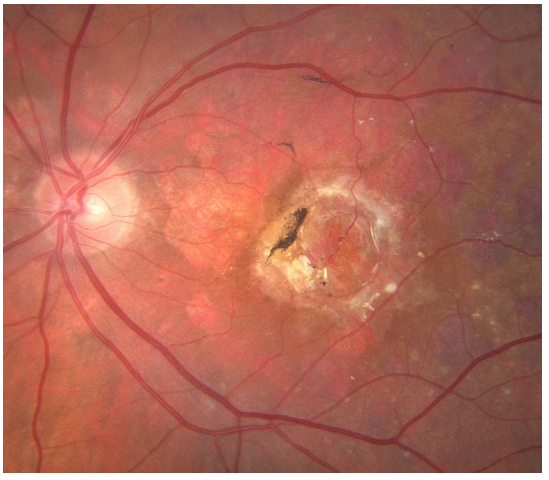
Relevant financial disclosures—Dr. Boland: Carl Zeiss Meditec: C.

RETINA

AI Flags Risk Factors for AMD Progression

RESEARCHERS HAVE HARNESSED artificial intelligence (AI) to create a reliable prediction model for progression to atrophic and/or neovascular age-related macular degeneration (AMD).[1] The AI algorithm identified nine risk factors from a larger set of phenotypic, genetic, and lifestyle predictors.

"The model could be used for patients showing some early signs of AMD, to identify those most at risk of progression to advanced AMD," said Cécile Delcourt, PhD, at the Université de Bordeaux in France. It also has implications for making recommendations to patients regarding their lifestyle and the frequency of follow-up visits. Moreover, it might be used for testing or adopting new therapies or interventions and for patient selection in clinical trials, she said.



WHO'S AT RISK? *The nine identified risk factors for progression of dry and/or wet AMD included dietary, genetic risk, and AREDS scores. The patient in this image had neovascular AMD.*

Data from two population-based cohort studies. The prediction algorithm was trained using data from 3,838 participants from the Rotterdam Study 1. These patients did not have advanced AMD at baseline and were age 55 or older. During a mean follow-up of 10.8 years, 108 incident cases of advanced AMD were detected.

The model was validated using 362 participants from the ALIENOR study, who were age 73 or older. During a median follow-up of 6.5 years, 33 incident cases of AMD were diagnosed.

Machine-selected variables. The four strongest risk factors for progression were genetic risk score, the score from AREDS (Age-Related Eye Disease Study), presence of intermediate drusen, and age.

These were followed in importance by smoking, pulse pressure, presence of retinal hyperpigmentation, education, and the Mediterranean diet score. Of note, pulse pressure and the Mediterranean diet have not appeared in earlier prediction models.

Three risk categories. The algorithm also estimated the cumulative incidence of advanced AMD, categorizing risk as low, intermediate, or high. In both the training and validation cohorts, incidence in the high-risk group increased steeply from baseline. The low- and intermediate-risk cohorts showed lower incidence rates across all time points.

Waiting for approval. The prediction model, which will be available to clinicians via www.macutest.net, is awaiting FDA approval in the United States and CE marking for Europe. Putting it into practice will require three steps: 1) The ophthalmologist will need to enter clinical exam findings, such as presence of drusen and retinal pigmentary abnormalities; 2) the patient must supply lifestyle information; and 3) a genetic sample should be taken, with results directly entered into the system. "The genetic test is performed only once," Dr. Delcourt said, "but the ophthalmological and lifestyle information can be filled in at each visit to monitor the risk evolution."

Because genetic testing is not currently available in routine ophthalmology practices, there is an alternative model that excludes the genetic risk score, with comparable results, she said.

—Miriam Karmel

1 Ajana S et al. *Ophthalmology*. Published online Sept. 2, 2020.

Relevant financial disclosures—Dr. Delcourt: None.

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