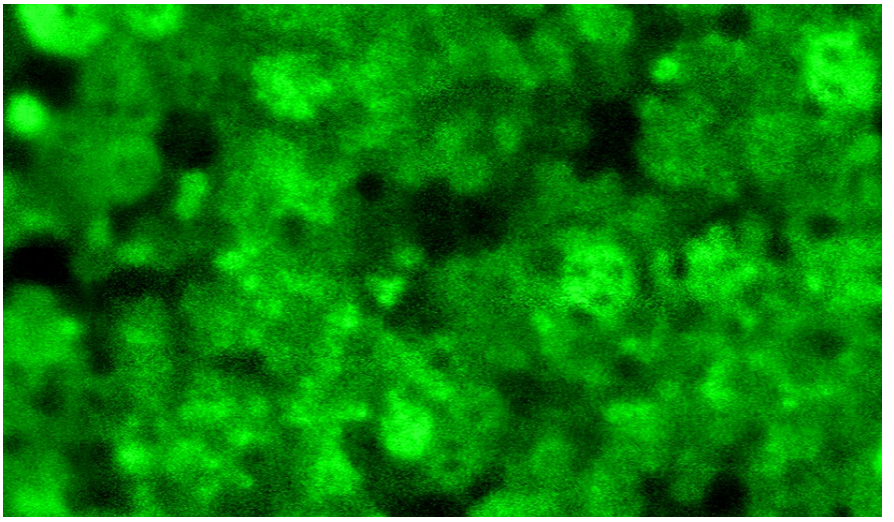
News in Review

COMMENTARY AND PERSPECTIVE



DISRUPTION. *NEI scientists visualized the RPE cell mosaic in the living human eye. Here, fluorescence imaging shows how cells are disrupted in choroideremia.*

Johnny Tam, PhD, NEI

RETINA

Adaptive Optics Sheds Light on Choroideremia

CHOROIDEREMIA IS A RARE BLINDING disease resulting from progressive retinal degeneration due to loss-of-function mutations in the gene *CHM*. Previously, little had been known about the cellular mechanisms underlying choroideremia owing to the limited resolution of current clinically available imaging techniques.

Now, NEI researchers have used advanced multimodal imaging to investigate cellular changes in the living human eye. They found that all subjects with pathogenic mutations in the *CHM* gene had subclinical structural changes in the retina and widespread enlarged retinal pigment epithelial (RPE) cells.[1]

"Using adaptive optics [AO], we were able to show that RPE cells were dramatically enlarged in choroideremia," said Johnny Tam, PhD, at the NEI. "Our study supports the notion that we should start thinking about choroideremia as an RPE-driven disease. When developing treatments for this disease, we should monitor the RPE layer before and after treatment, as this seems to be the most affected layer."

Multimodal imaging approach. AO allows researchers to "image in vivo at the cellular level, providing a higher clarity and resolution than current clinical imaging technologies," Dr. Tam said. Although it is not a new technology, "it has not made its way into routine clinical care because it is a complex technology to deploy."

In their multimodal approach, the NEI team used AO in concert with OCT and with indocyanine green (ICG) to assess the photoreceptor, RPE, and choriocapillaris layers at the cellular level.

The researchers also introduced a strategy for detecting enlarged RPE cells using conventional ophthalmic imaging instrumentation without AO. In this part of their study, late-phase ICG using routine scanning laser ophthalmoscopy revealed retinal structural changes similar to those seen with multimodal imaging, Dr. Tan said.

A structural surprise. In choroideremia, *CHM* mutations show an X-linked inheritance pattern. However, in this study, subclinical, widespread enlarged RPE cells were present not only in affected males but also in female carriers who carry only one chromosome with an altered *CHM* gene and do not show clinically significant vision impairment. This finding "was very surprising and unexpected," Dr. Tam noted.

With regard to the RPE cells, disruptions to the RPE layer in the fovea were greater than those in the photoreceptor or choriocapillaris layers. The research team was also able to show that some photoreceptors were fluorescently labeled, even though they were "structurally and functionally normal." This finding suggests that the integrity of the RPE blood barrier may be disrupted in choroideremia, which "allows some of the dye to get through and label the photoreceptors," Dr. Tam said.

Unanswered questions. What happens to enlarged RPE cells? "We would like to longitudinally follow enlarged RPE cells to see what happens to them throughout the natural course of the disease as well as during treatment," Dr. Tam said.

Bigger picture. "Until now, widespread changes in RPE cells were not easily detected using clinical imaging tools," Dr. Tam said. "Finding that RPE cells can be so dramatically affected changes the way we view choroideremia and other diseases that impact the RPE layer." *—Christos Evangelou, PhD*

1 Aguilera N et al. *Commun Biol.* 2022;5(1):893.

Relevant financial disclosures: Dr. Tam—None.

GLAUCOMA

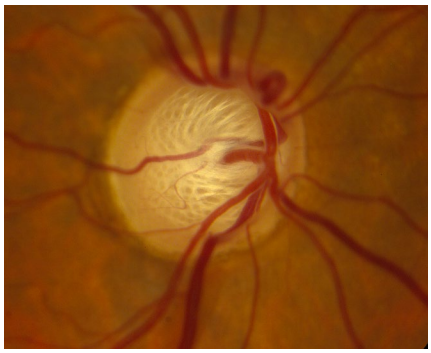
Smoking and RNFL Thinning in POAG

SMOKING IS ASSOCIATED WITH cataract and age-related macular degeneration, but its effect on glaucoma progression is still unknown. Researchers at the Hamilton Eye Center at the University of California San Diego have moved closer to establishing a link: in a recent study, they found that smoking intensity is associated with faster rates of retinal nerve fiber layer (RNFL) thinning in patients with primary open-angle glaucoma (POAG).[1]

The findings build on an earlier study by the San Diego researchers, which found that visual field progression in eyes of heavy smokers was 2.2 times greater than in eyes of patients with no smoking history,[2] said Sasan Moghimi, MD.

"The [latest] findings support [the hypothesis] that smoking severity might add information to the assessment of risk of glaucoma progression," said Dr. Moghimi. Moreover, they might be used to develop intervention strategies for this modifiable risk factor.

Looking at longitudinal progression. The researchers evaluated 314 patients (466 eyes) enrolled in two studies: the UCSD Diagnostic Innovations in Glaucoma Study (DIGS) and the multicenter African Descent and Glaucoma Evaluation Study (ADAGES). Patients received at least three years of follow-up and a minimum of five OCT imaging visits to measure RNFL thickness.



EVALUATING RISK. *Researchers have found a direct dose-response relationship between smoking and RNFL thinning in patients with POAG.*

Smoking intensity was calculated by pack-year, a standard measure of the

NEURO-OPHTHALMOLOGY

Predicting ION Risk After Cardiac Surgery

ISCHEMIC OPTIC NEUROPATHY (ION) IS A RARE BUT serious complication of cardiac surgery. Now, building on previous investigations into conditions that predispose patients to develop ION, researchers at the University of Illinois at Chicago have developed the first preoperative calculator that clinicians can use to estimate a patient's risk of perioperative ION.[1]

While the model has obvious implications for cardiac surgery, it also has relevance for ophthalmologists, said Steven Roth, MD, whose lab conducted the studies.

Creating a risk model. For this retrospective case-control study, the researchers considered hospital discharge records of more than 5 million patients in the National Inpatient Sample (NIS) who had undergone cardiac surgery. The researchers looked for procedure codes—including coronary artery bypass grafting, heart valve repair/replacement, and left ventricular assist device insertion—and found 771 cases of ION, for a rate of 1.4 per 10,000 patients.

ION risk factors used in the model included carotid artery stenosis, cataract, diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma, male sex, and prior stroke.

The findings. Patients were more likely to develop ION if they had AMD (OR = 4.45); carotid artery stenosis (OR, 3.17); cataract (OR, 9.78); DR (OR, 5.38); glaucoma (OR, 3.17); peripheral vascular disease (OR, 1.75); and stroke (OR, 2.66). The ORs for male sex and uncomplicated type 2 diabetes were lower (.69 and .55, respectively).

It's not clear why several of the highest risk factors were eye diseases, although glaucoma indicates an already compromised optic nerve, and these patients may be more susceptible to injury, Dr. Roth said. He added that "AMD was a surprise."

How it works. The risk calculator assigns integer point values for each preexisting comorbidity, which, when added together, generate a risk score for ION. For example, if a male patient has carotid artery stenosis and glaucoma, but no AMD or DR, his total score is 3, for an estimated .087% risk for ION. If a patient's score is 7—which would be the case for someone with a history of stroke, AMD, and cataract—ION risk would then rise to 1%.

Clinical implications. The researchers acknowledged that a risk prediction may not alter the patient's choice to proceed with surgery. However, it is reasonable to discuss risks and benefits with patients who have scores of 6 or 7, they said. Even a lower score warrants discussion if a patient expresses concern.

And although cardiologists are most likely to use the risk calculator, it could be beneficial for the patient to discuss their risk of developing ION with a specialist, such as a neuro-ophthalmologist, to better understand what's at stake, Dr. Roth said.

"ION after cardiac surgery is an underappreciated occurrence," Dr. Roth said. "While we are not advocating that the surgery be postponed, we are suggesting that the risk calculator [which appears in the published article] be used to provide informed consent to patients at higher risk of ION." *—Miriam Karmel*

1 Shah SH et al. *J Cardiothorac Vasc Anesth.* Published online Aug. 12, 2022.

Relevant financial disclosures: Dr. Roth—NIH: S.

Jason S. Calhoun, COA

amount a person smokes over time. For example, a 10 pack-year is equal to smoking two packs per day for five years, or five packs for two years.

Dose response. Of the 314 patients, 118 (38%) reported a history of smoking, with 55 reporting 0-10 pack-year, 25 reporting 10-20 pack-year, and 38 reporting 20 or more pack-year.

There was a direct dose-response relationship between smoking and RNFL thinning; each 10 pack-year was associated with .06 µm per year faster RNFL thinning. Overall, RNFL thinning increased significantly when smoking intensity exceeded 8 pack-year.

Race and other variables. The researchers also considered current alcohol consumption, which was self-reported by 136 patients (57.1%), and body mass index (mean, 27.9 kg/m^2). Neither variable significantly affected rates of RNFL thinning.

In addition, although patients of African descent experience a disproportionate burden of POAG, racial differences did not emerge as a factor in the effect of smoking intensity on the rate of RNFL thinning in this study. However, as the authors pointed out, additional research is needed to clarify the interplay between race, smoking cessation, and glaucoma progression.

A modifiable risk factor. "Assessment of progression in the presence of risk factors for structural change may help clinicians in customizing the intensity of glaucoma therapy in higher-risk patients," Dr. Moghimi said. He added that clinicians can recommend smoking cessation, particularly for patients who are heavy smokers, to slow down glaucoma progression.

Going forward. Future studies are needed to evaluate the impact of heavy smoking on RNFL thinning, the authors emphasized.

—Miriam Karmel

1 Nishida T et al. *Br J Ophthalmol.* Published online Sept. 13, 2022.

2 Mahmoudinezhad G et al. *Ophthalmology.* Published online June 23, 2022.

Relevant financial disclosures: Dr. Moghimi—None.

PEDIATRIC OPHTHALMOLOGY

Smartphone App Developed for Retinoblastoma

AN UNMET NEED EXISTS FOR EF-fective, low-cost screening tools for retinoblastoma, especially in regions with limited resources. To meet this need, researchers at the University of Michigan in Ann Arbor have developed the EyeScreen smartphone application.[1]

"This app is another step toward using artificial intelligence [AI] and machine learning in the field of ophthalmology," said Hakan Demirci, MD.

Need for early detection. Early detection and treatment of retinoblastoma are essential for improving a child's chances of survival. As Dr. Demirci noted, global mortality rates in retinoblastoma are disproportionate, with "higher death rates in lower-income parts of the world compared to higher-income regions."

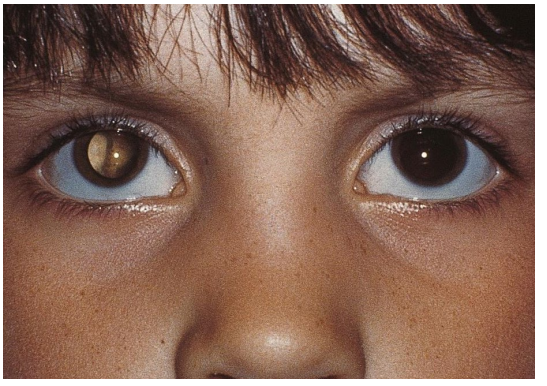
For instance, patients from high-income countries are diagnosed at a median age of 14.1 months, and less than 1% have metastasis. In contrast, those from low-income countries are diagnosed at a median age of 30.5 months, with 18.9% having metastasis.

Smartphone apps have been created previously to screen for leukocoria, the leading presenting sign of retinoblastoma, but they have limitations.[1] The EyeScreen app has been designed for Android devices, the most commonly used smartphones in the world, for real-time screening using multiple directions of gaze, Dr. Demirci said.

Study details. For this study, more than 4,000 images from 1,457 children were obtained using the EyeScreen app on Android smartphones at pediatric and ophthalmology clinics in Addis Ababa, Ethiopia. Eighty percent of the images were used to train a machine learning model to detect leukocoria; the remaining 20% were used to test the accuracy of the model. Analysis of the results showed 87% sensitivity and 73% specificity.

Using AI to guide screening. Dr. Demirci said that he thinks the app will be useful for multiple types of care providers, including physician extenders and pediatricians, throughout the world. Failure to detect leukocoria and other pupillary anomalies "can cause delays in diagnosis and treatment of retinoblastoma," even in higher-income countries, he said.

Coming soon. Dr. Demirci said the EyeScreen app is "very close" to being ready for use in clinical practice. He said that his team is trying to improve the model's sensitivity and specificity, in collaboration with Professor Elliott Soloway from University of Michigan's College of Electrical Engineering and Computer Science. They plan to "increase the availability of the app for other researchers and physicians around the world."



LEUKOCORIA. *Researchers hope that the app will facilitate early, accurate detection of leukocoria and other anomalies.*

The team is also working on adding new features to the app and developing it to potentially detect other eye problems. "Considering how cell phones are widely used everywhere, I think this will be a good step for further developments," he said.

—Patricia Weiser, PharmD

1 Bernard A et al. *Ophthalmology Science.* 2022; 2(3):100158.

Relevant financial disclosures: Dr. Demirci—None.

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