News in Review

COMMENTARY AND PERSPECTIVE

EARLY SCREENING. *A child undergoes an eye exam with a slit lamp biomicroscope.*

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DIABETES

AI Increases Screening for DR in Youth

AUTONOMOUS ARTIFICIAL INTELLI-gence (AI) diabetic eye exams can significantly improve completion rates for screenings that detect diabetic eye disease in young people, new research shows.

The study, published in *Nature Communications,* suggests that the new technology has the potential to close care gaps among individuals most at risk for diabetic eye disease, including individuals whose social determinants of health adversely affect their health.[1]

Generally, it's recommended that young people with diabetes get screened annually for diabetic eye disease, like diabetic retinopathy (DR), but these screenings involve a visit to an eye care professional, which often proves difficult for patients, the study authors wrote.

"In pediatric diabetes care, patients are seen by their diabetes team every three months, so when a referral to an eye care professional is made, it means another visit on top of these four visits per year," said study author and pediatric endocrinologist Risa Wolf, MD, Director of the Pediatric Diabetes Program and Associate Professor of Pediatrics at Johns Hopkins Children's Center in Baltimore.

"AI has made it much easier for patients to complete the diabetic eye exam when it is offered at the point of care in the diabetes care setting," she said.

Methodology and results. Dr. Wolf and her team enrolled 164 patients, ages 8 to 21, with diabetes. Of these, 83 received standard care and a referral to see an ophthalmologist or optometrist for an eye exam. The rest of the participants underwent a brief AI diabetic eye exam during a routine visit to their endocrinologist. They received the results in office. If DR was detected, the patient then received a referral for an eye exam with an eye care professional.

While 100% of the AI group was screened that day, only 22% of participants from the standard care group followed up with an eye exam by an ophthalmologist or optometrist within six months.

Growing crisis. DR is estimated to affect between 4% and 9% of young people with type 1 diabetes and between 4% and 15% of those with type 2 diabetes.

As diabetes among youth in the United States continues to grow, so does the risk of eye complications. Dr. Wolf said, "Recent research shows that at a median duration of diabetes of 12 years, up to 50% of youth with type 1 and type 2 diabetes have some form of diabetic retinopathy." The percentage of people aged 20 and under with type 2 diabetes is expected to increase by nearly 700% in the next four decades, and the number of youth with type 1 is expected to rise as much as 65%.[2]

Barriers to care. Some studies suggest only 35% to 72% of young people with diabetes undergo recommended eye screenings, the authors wrote.

Lisa S. Schocket, MD, Interim Chair and Chief of Vitreoretinal Surgery at the University of Maryland School of Medicine, in Baltimore, who was not involved with the research, said barriers to care include:

- **Lack of education.** Some patients do not understand that diabetes can lead to permanent vision loss.
- **Financial strain.** This can include transportation issues, parents having to take time off work, childcare issues, and cost of appointments.
- **Mistrust of providers.** Racial, ethnic, and cultural differences between physicians and patients can lead to mistrust and pose a significant barrier.

New solutions needed. To overcome these barriers, new strategies

are required to make sure patients get screened and receive proper treatment to prevent vision loss, said Dr. Schocket, adding that challenges come with this.

"Young diabetic patients in their 30s come to see me with severe disease at a point that I can sometimes still preserve their vision. I explain what we need to do to keep their vision and that without treatment they will progress to total loss of vision. But often, the patients decline treatment, or they have one treatment and don't come back until they have lost all their vision. We have excellent surgical techniques, but in far too many cases, patients are returning too late," she said.

Dr. Wolf said AI can help bridge this gap and get more people screened for diabetic eye disease. It takes about five minutes to take the photos and no pharmacologic dilation is required.

In a separate trial, the technology had a sensitivity of 87% and specificity of 90%.[3] Another prior study in youth indicated sensitivity of 86% and specificity of 79%.[4]

Limitations. In the AI arm of the study, 25 of the 81 patients scanned had signs of DR requiring an exam. Of these 25 patients, 16 (64%) followed through and saw an eye care provider, compared with 22% in the control arm. But despite being told the exam was positive and required referral, nine patients in the AI arm did not receive a dilated exam.

"I don't feel that AI is a panacea for this problem because if the patient does

TECHNOLOGY

Machine Learning for Detecting Cognitive Decline

RESEARCHERS FROM DUKE UNIVERSITY HAVE DEVEL-oped a machine learning model that shows promise for helping to detect early signs of cognitive decline.[1] The model, which combines OCT and OCT angiography (OCTA) images with quantitative data, differentiated individuals with normal cognition from those with mild cognitive impairment, according to findings in *Ophthalmology Science*.

Senior author Sharon Fekrat MD, FASRS, Professor of Ophthalmology and Neurology, at Duke University in Durham, North Carolina, said, "Our multidisciplinary team at Duke, iMIND, aims to use multimodal retinal and choroidal images to develop adjunctive diagnostic tools for neurodegenerative diseases."

Background. In recent years, various machine learning models have been investigated—including some that use MRI and positron emission tomography (PET) scans of the brain, or ophthalmic images—so that neurologists may one day be able to diagnose mild cognitive impairment and Alzheimer disease earlier and more easily.

Previously, the Duke team compared and analyzed numerical retinal imaging using traditional statistical methods, Dr. Fekrat said, but "we have not been able to document a statistically significant difference between most metrics in individuals with mild cognitive impairment and those with normal cognition thus far."

So, the goal of their current research was to develop a machine learning model—specifically a convolutional neural network (CNN)—that "may 'see' more than just the quantitative imaging metrics used in statistical analyses and thus, be able to differentiate persons with mild cognitive impairment from those with normal cognition," said Dr. Fekrat.

Methodology. The multimodal CNN used ganglion cell–inner plexiform layer (GC-IPL) thickness maps derived from the OCT scans, OCTA images centered on the macula, and quantitative data to predict the likelihood of mild cognitive impairment. To train, validate, and test the CNN, the researchers used images from 236 eyes in participants who were cognitively normal and 154 eyes of individuals who had mild cognitive impairment.

The machine learning model was able to identify individuals with mild cognitive impairment with a sensitivity of 79% and a specificity of 83%, Dr. Fekrat said.

The researchers intentionally excluded individuals with diabetes, glaucoma, and vitreoretinal diseases. "As we are still exploring the use of a CNN for neurodegenerative diseases, it is valuable to use high-quality images from individuals without these confounding comorbidities for our early work. This way, once we have a foundational understanding, we can start to better assess the impact of other ocular and systemic conditions," Dr. Fekrat explained.

Next steps. Dr. Fekrat expects future work to include imaging from a larger and more diverse patient population in terms of age, race, ethnicity, and comorbidities so that the model can "learn how to account for those demographics and conditions while still being able to differentiate mild cognitive impairment from normal cognition."

"We also have a CNN that can differentiate those with symptomatic Alzheimer from normal cognition using similar model inputs," she said. "We would like to be able to combine both of these models into one, so the model can sort patients into normal cognition, mild cognitive impairment, or Alzheimer disease."

Dr. Fekrat described the importance of developing a model that can differentiate dementia types—for example, Lewy body dementia, frontotemporal dementia, and Alzheimer disease.

"Earlier diagnosis along the 20-year Alzheimer disease continuum will allow more accurate enrollment of such individuals into clinical trials studying novel therapeutics," she said.

—Patricia Weiser, PharmD

1 Wisely CE et al. *Ophthalmol Sci.* 2023;4(1):100355.

Relevant financial disclosures—Dr. Fekrat: None.

not see the ophthalmologist, they will not receive treatment," Dr. Schocket said. "We need to focus on community engagement and education. We need to go out into the community to screen patients. Once patients are identified, we need to do a better job connecting them with care." —*Ashley Welch*

1 Wolf RM et al. *Nat Commun.* 2024;15:421.
2 Tönnies T et al. *Diabetes Care.* 2023;46(2):313–320.
3 Abràmoff M et al. *Digital Med.* 2018;1(39).
4 Wolf RM et al. *Diabetes Care.* 2021;44(3):781-787.
Relevant financial disclosures—Dr. Schocket: None; Dr. Wolf: None.

GLAUCOMA

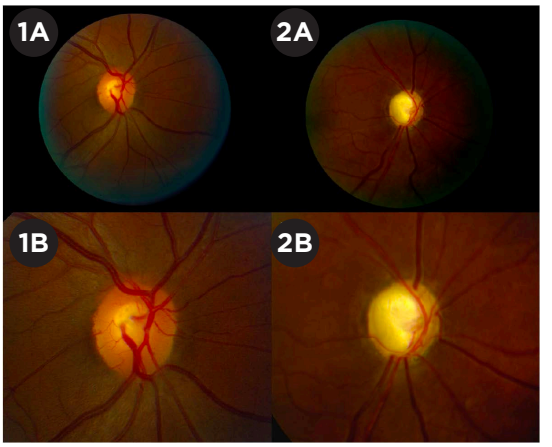
Gene Variants Linked to Glaucoma

A NEW ANALYSIS THAT FOCUSES ON individuals of African ancestry identified three gene variants that may be linked to why people of African descent are disproportionately affected by and blinded by glaucoma.[1] The study aimed to identify variants of pathophysiological importance to primary open-angle glaucoma (POAG) in individuals of African ancestry in order to gain insight into the genetics of the disease, said corresponding author Joan O'Brien, MD, Professor of Ophthalmology and Director of the Penn Center for Genetics of Complex Disease at the University of Pennsylvania Perelman School of Medicine in Philadelphia.

People of African ancestry are five times as likely as people of other ancestries to develop glaucoma and up to 15 times as likely to be blinded by it.[2]

Study details. The genome-wide association study published in *Cell* analyzed data from three African datasets that included 11,275 individuals —6,003 people with POAG and 5,272 controls. To conduct the analysis, the scientists used functionally informed fine-mapping, multiple trait co-localization, and in silico validation—experimental techniques performed via computer—to pinpoint the three genes.

"We detected 46 risk loci associated with POAG at genome-wide significance," Dr. O'Brien said, explaining that they then identified "two previously undescribed" gene variants: rs1666698, associated with gene *DBF4P2*, and rs34957764, which is tied to the *ROCK1P1* gene. Additionally, they spotlighted one previously associated variant, rs11824032, linked to the *ARHGEF12* gene, which is related to cup-to-disc ratio.



FUNDUSCOPIC VIEWS. *Fundus photographs of a healthy control eye (1A and 1B) and an eye with large cup-to-disc ratio (2A and 2B).*

Study significance. Any work that expands glaucoma research to include genetic analysis "is critical to understanding how high-risk populations are disproportionately affected by this blinding condition," said Carla Siegfried, MD, the Jacquelyn E. and Allan E. Kolker, MD, Distinguished Professor of Ophthalmology and Visual Sciences and Vice Chair for Diversity, Equity, and Professionalism at Washington University in St. Louis.

Because glaucoma is heritable, affecting families across generations and perpetuating associated morbidity and mortality, Dr. O'Brien said research must be inclusive, noting that most POAG research has relied on data from people of European ancestry.

"Only 2% of genetic studies have been conducted in individuals of African ancestry," she said. "We developed a polygenic risk score that was more predictive of disease risk than a polygenic risk score derived from a much larger predominantly European population."

Polygenic risk scores are important because they provide a measure of disease risk due to one's genes, said Dr. Siegfried. "Identifying risk loci within the whole genome associated with glaucoma risk is very exciting and enhances polygenic risk score analysis," she said.

Study limitations. While this may be the largest African ancestry genome-wide association study for POAG, it does not compare in size to similar studies using datasets of European ancestry individuals.

Next steps. "We are performing further studies using structural genomics, functional genomics, and transcriptomics to make these variants—and others that we discover using orthogonal platforms for analysis—robust," Dr. O'Brien said. "We will then develop a genetic test that identifies disease risk."

Identifying the genetics of heritable diseases in the populations that are most acutely affected will better enhance screening, diagnosis, and therapeutics development, she said, adding, "This is an unmet medical need because we do not understand glaucoma's pathophysiology, and many affected individuals see disease progression despite currently available treatments."

The scientific community hasn't often focused on population diversity in both genetic research and clinical trials, and scientists are only beginning to examine disparities in cellular physiology from subjects of different ancestral backgrounds, said Dr. Siegfried. The new findings—of risk variants in specific genes associated with tissue genetics—may help lead to further understanding of glaucoma pathophysiology and cellular function in trabecular meshwork and/or retinal ganglion cells, and she said, that "is even more exciting." —*Brian Mastroianni*

1 Verma SS et al. *Cell.* 2024;187:464-480.
2 Mamidipaka A et al. *Genes*. 2023;14(9):1809.
Relevant financial disclosures—Dr. O'Brien: None; Dr. Siegfried: None.

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