Augmented Intelligence

Harnessing AI for Glaucoma

A look at AI's potential benefits for glaucoma—as well as what is needed to move the field forward.

By Annie Stuart, Contributing Writer

WHILE TECHNOLOGY IS PROVIDing more valuable health information than ever before, health care efficiency is under increasing pressure from a multitude of factors, including the inability to analyze the never-ending flood of information that threatens to engulf researchers and clinicians alike.

Can artificial intelligence (AI) come to the rescue? "We need AI—especially given the aging population, increase in health care costs, and shortage of ophthalmologists," said Lama A. Al-Aswad, MD, MPH, at Envision Health Technologies and Visi Health Technologies in New York City.

While some ophthalmologists worry about technology and AI taking their jobs, Dr. Al-Aswad said, "the future is an augmented intelligence where we and machines work together to increase efficiency, enable personalized medicine, and improve patient outcomes."

Benefits for Patients and Physicians

Among its many benefits for the field of glaucoma, AI has the potential to help in screening, diagnosis, detection of progression, and prediction, said Felipe A. Medeiros, MD, PhD, at Duke University in Durham, North Carolina.

Screening in primary care settings. Louis R. Pasquale, MD, FARVO, considers the use of AI for glaucoma screening in a primary care setting to hold considerable potential. "This would involve acquiring and subjecting a nonmydriatic optic nerve photograph to an AI algorithm," said Dr. Pasquale, at Mount Sinai in New York City. In retina, for instance, some clinicians are already screening for diabetic retinopathy (DR) by applying the FDA-approved algorithms for the detection of DR, Dr. Pasquale noted.[1] Looking ahead, he said, "It seems natural that AI-guided glaucoma screening will be an early application to the field of glaucoma."

Many researchers are working on developing highly accurate AI models for this application, said Dr. Medeiros. "It's essential to have very high specificity in screening to avoid many false positives, which could overburden the health care system."

For instance, Dr. Medeiros and his colleagues trained an AI model to predict spectral-domain OCT measurements of retinal nerve fiber layer (RNFL) thickness using just simple fundus photographs.[2] "This results in a much more objective assessment of the photographs for detecting damage from glaucoma," he said.

Predicting function and progression. One area in which AI excels is in the analysis of complex imaging data, which could provide insights into a patient's visual function, said Dr. Medeiros. This could help identify patients with the fastest rates of functional loss, Dr. Pasquale said, and it might predict who might need glaucoma surgery, for example.

Using data collected from nearly 6,500 patients in the United Kingdom, David P. Crabb, PhD, and colleagues explored whether it was possible to use structural measures from OCTs and infrared

Jason S. Calhoun, COA

reflectance optic disc imaging to predict what a person's visual fields would look like.[3]

"We developed a policy-driven, deep learning model to decide what inputs were best to predict visual function," said Prof. Crabb, at City, University of London. He added that AI models can learn by consensus without being given any prior information. "We found we could quite accurately predict what people could see, which could be particularly helpful for patients who can't undergo visual function tests."

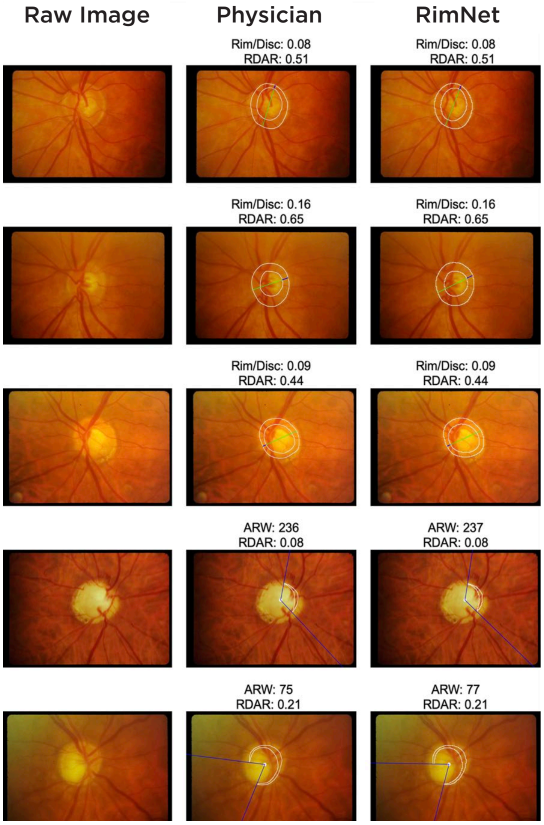
Increasing access, reducing costs. Joel S. Schuman, MD, FACS, at NYU Langone Health in New York City, also cited AI's potential to provide patient care before actual damage occurs and to reduce the cost of care. Using AI to identify early on those patients who are most likely to progress quickly will allow health care dollars and more intensive care to be directed where it's most needed, he said. "Using AI in this way helps address issues of equity, making excellent care more accessible to all," Dr. Schuman added.

Analyzing whole systems. In the future, AI may help take personalized medicine to the next level by looking at the interplay between the eye and the whole system—the body—in order to track disease progression, uncover how intervention affects disease, and aid with prognosis, said Dr. Al-Aswad.

Previous studies hint at the veracity of this approach, she noted. For instance, Dr. Al-Aswad said, "Using deep-learning models trained on data from nearly 285,000 patients, a Google Research study astonished the world by predicting from a retinal fundus photo the patient's gender, smoking status, age within two to three years, and systolic blood pressure within about 11 mm Hg." It even came close to the accuracy of the Framingham Risk Score, which estimates the 10-year risk of heart attack.[4]

Advancing research. AI can help the field of glaucoma not just through clinical decision-making but also through research, said Dr. Pasquale. He pointed to a study by Han et al., in which AI was used to classify a large fundus image repository to grade cup-disc ratio.[5] The researchers then compared these measurements across different genetically defined ancestry groups. The results add to our understanding of the genetic architecture for cup-disc ratio, which is "an important endophenotype for glaucoma," said Dr. Pasquale. He added that applying AI to other big data resources like metabolomics and proteomics datasets may lead to the discovery of new biomarkers for glaucoma.

Working with colleagues in neuro-ophthalmology, Dr. Pasquale and colleagues have also learned



RIM MEASUREMENT. *Researchers built an automated system known as RimNet for the purposes of direct rim identification in glaucomatous eyes and optic disc damage grading.*

that it is possible to use AI algorithms to detect structural and functional endpoints in randomized clinical trials, using data from previously published studies.[6] Given the accuracy of their machine learning approach, AI could reduce the need for expert graders, the researchers wrote. AI also could "supplant the need for designated reading centers in future glaucoma neuroprotection randomized clinical trials," Dr. Pasquale said. This would reduce costs and allow for more resources to be diverted to other investigations, he noted.

Saving vision. What if an algorithm was able to identify glaucoma patients who need drastic IOP lowering at the outset of clinical care? "A clinical trial that randomizes such patients to an aggressive IOP target—perhaps, an IOP lowering of 30% from untreated IOP—and ultimately shows that [such an] aggressive intervention saved vision would be impressive," Dr. Pasquale said.

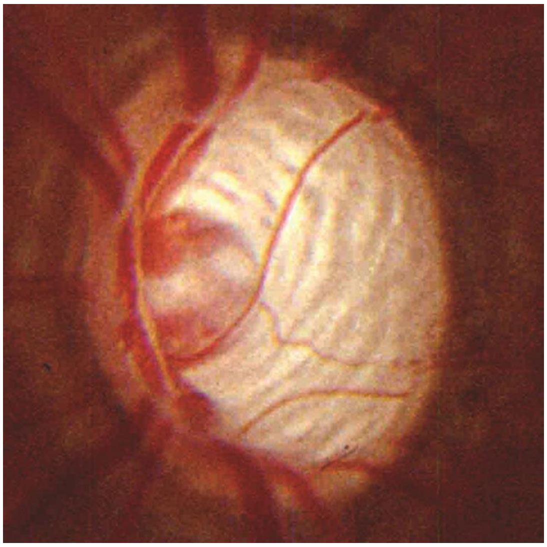
Special AI Challenges in Glaucoma

Despite many potential applications, the use of AI in glaucoma poses certain challenges, and much work is needed to bring its full potential to fruition.

No gold standard. "We are not ready for artificial intelligence in glaucoma, partly because we have not created consensus on the definition of glaucoma," said Dr. Al-Aswad. "For DR, we have a classic definition because we can easily diagnose it by looking at the fundus. But for glaucoma, there is no pathognomonic diagnostic test or symptoms. Instead, diagnosis is based on a constellation of symptoms, diagnostic tests, and longitudinal data." Further complicating matters is the heterogeneity of the disease among different populations.

"When ophthalmologists look at fundus photographs, they often can't confirm whether or not the patient has glaucoma," said Dr. Medeiros, noting that this can lead to overestimation or underestimation of disease. He added, "Most AI models are developed through a process called supervised learning, which requires a labeled dataset to diagnose the disease or detect change over time. In other words, training a deep learning model to detect glaucoma from photographs or identify progression from a series of tests is only as good as the gold standard used to train it." If such a gold standard is faulty, the deep learning model will also be, he said.

Working to create these standards is exceedingly important, agreed Dr. Schuman, and identifying and reaching consensus on features of early glaucoma remains problematic. "However, when looking at the thickness of the RNFL and corresponding visual field loss, we don't have such a hard time agreeing on what constitutes manifest glaucoma. Therefore, I think we could agree on the utility of AI algorithms for this population."



ADVANCED. *Striations of the lamina cribrosa in an optic nerve with severe glaucomatous damage.*

A slow-moving disease. Another challenge with glaucoma is that it is usually a slow-moving

Ethical and Legal Considerations

There are other factors related to AI to consider, not just for glaucoma, but also for ophthalmology—and medicine—at large.

Equity. One ethical problem to resolve is how to make AI equitable and generalizable to heterogeneous populations, said Dr. Pasquale. "We need to make a concerted effort to extend diagnostic capabilities in places where resources are not available to meet clinical needs."

Privacy. It is theoretically possible to reverse engineer a patient's identity from a retinal photo or OCT, Dr. Schuman pointed out. One solution would be to have individuals grant permission to use their data, possibly on an opt-out basis, he said. Federated learning, where each center holds on to its own information, is another potential solution.

Ownership. There is also the question of who owns the data, Dr. Schuman said. "The answer varies quite a bit depending upon who you're talking to." This can cause problems further down the line, said Prof. Crabb. "To improve care in National Health Service clinics, we got permission for our study to use data that were just gathering dust. But someone else might also use those data to develop intellectual property around an algorithm."

This brings up another thorny issue regarding who profits from AI implementation, said Dr. Pasquale. "AI algorithms are built using patient data, and patients paid for the data that were acquired to build [the algorithms]. Why should they not share in any profits generated from the use of those algorithms? At some point, patient advocacy groups may take up this issue and challenge entities that partake in for-profit AI ventures."

Liability. Some observers suggest that makers of AI may bear liability if patients encounter harm because of decision-making that is guided by a computer-based algorithm, said Dr. Pasquale. "I, for one, feel that the ultimate responsibility for medical care lies with the provider. Of course, the legal system may have the final word on this and other novel matters that will arise as AI is integrated into medical care."

Ultimately, Prof. Crabb said, responsibility for liability "has to lie with the people who are developing these algorithms and getting the intellectual property for these algorithms as well."

disease, making it difficult to observe over a short period of time, said Prof. Crabb. However, he said, if researchers can improve the measurements taken in trials using AI techniques, "I think that could make a big difference by speeding up clinical trials and potentially delivering evidence on new treatments." In fact, Prof. Crabb and his fellow researchers found that an AI model could identify patients at high risk of progression, thus reducing the number of participants or the length of the study needed to meet clinical trial endpoints.[7]

Data availability and quality. "We don't yet have large datasets that are diverse enough to cover all populations with glaucoma," said Dr. Al-Aswad. "That can create health disparities at scale."

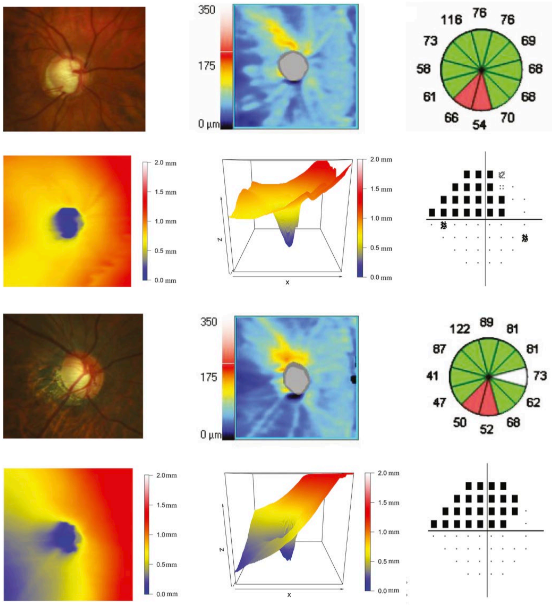
Once you develop a model, added Dr. Medeiros, it must be tested and validated externally on a separate population—one that is representative of the target population and doesn't introduce racial bias, for example.

In addition, data sharing is a key issue due to concerns about patient privacy, said Dr. Al-Aswad (see "Ethical and Legal Considerations," page 43). Along with other researchers, she is working on ways to share the algorithm instead. Under this approach, known as federated AI, "A lead institution creates an algorithm, which they share with participating institutions," she said. "The algorithm can learn from each institution and come back to the lead institution for further adjustment, perpetuating until the most robust model is developed."

Data transparency and interoperability. Standardizing image acquisition across different platforms remains a significant challenge, said Dr. Pasquale. Acquiring the raw information from the images also is very difficult and time consuming, as there is no Digital Imaging and Communications in Medicine (DICOM) standard for reporting images in ophthalmology, said Dr. Al-Aswad.

"In cardiology, an echocardiogram and all accompanying data, including volume, is transmitted in the report," she said. In contrast, Dr. Al-Aswad noted, "in ophthalmology, you need a special license to access the raw data from OCTs or visual fields." Going forward, it will be important for researchers to push for DICOM standard reporting to make any AI process much easier for training and validation, she said.

Workflow integration. Another challenge relates to how AI models will be used within routine clinical practice, said Dr. Medeiros. "Can AI help us with the interpretation of images right in our clinics? Potentially, yes. But there has been very little work done on creating clinical decision support systems that would allow these models to actually be integrated into practice and the EHR." If that doesn't happen, he said, clinicians may find



ASSESSING SHAPE. *In one study, Dr. Pasquale and colleagues used AI to assess shape patterns of the optic nerve and peripapillary RNFL and correlate those findings with VF loss.*

AI too cumbersome to use and will prefer the simpler tools that are more readily available.

Moreover, clinicians may need algorithms tailored to the specific populations they serve, said Dr. Pasquale. "We need to allow practitioners to fine-tune algorithms they may use in their offices," he said, explaining that methods that allow for code-free machine learning and automated machine learning would make this possible.

What's Needed to Move Forward

It will take some time, perhaps five years or more, before we start seeing real results with AI in the field of glaucoma, Dr. Medeiros said. He added that data collaboration, clear image standards, and clinical support systems are essential.

Defining glaucoma. Members of an FDA initiative called the Collaborative Community on Ophthalmic Imaging (CCOI) have published a number of papers relevant to glaucoma. In a recent paper, Drs. Al-Aswad, Medeiros, Schuman, and other participants in the CCOI glaucoma workgroup delved into the need for objective reference standards for glaucomatous optic neuropathy and its progression.[8] Dr. Medeiros emphasized, "We definitely want to develop AI models for screening that target people with moderate or advanced stages of disease. We don't really need to go after people with very early damage because it becomes too hard to distinguish them from those who simply have some normal variation in the appearance of the optic nerve. Then the specificity becomes very low."

Integrating data. In addition, Dr. Medeiros said, much work remains if comprehensive AI models are to be developed. Such models would integrate all available information about a patient—not only results of glaucoma testing but also details on their coexisting systemic disorders, their medications, and any relevant socioeconomic conditions. "This would allow us to create recommendation systems to provide guidance about the best treatment option for a specific patient, given everything that is known," he said.

For instance, Dr. Medeiros said, a systemic collection of data might reveal that it's best to proceed with surgery instead of eyedrops if a patient's overall health profile indicates that it's unlikely that the person will be able to adhere to an eyedrop regimen. Moreover, the merger of environmental exposure data and genetic information with imaging data will make for even more robust AI models of disease, said Dr. Pasquale.

Training. "We need to think more broadly and train the next generation" in the field of AI, said Dr. Al-Aswad. Efforts to do so are underway at multiple ophthalmology programs across the United States, including at NYU Langone, where Dr. Al-Aswad launched an innovations fellowship. And the NIH is providing significant support and guidance to researchers via its Bridge2AI program, which aims to expand the use of AI in biomedical and behavioral research—and will develop ethical practices for data generation and use.[9]

MORE ONLINE. For a list of AI terminology and suggested further reading, see this article online at aao.org/eyenet.

MONITORING. *An acquired optic disc pit located in the inferior temporal region. Note the absence of rim tissue.*

1 The DR algorithms approved at time of press are IDx-DR (Digital Diagnostics), EyeArt (Eyenuk), and AEYE-DS (AEYE Health).
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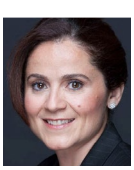
MEET THE EXPERTS



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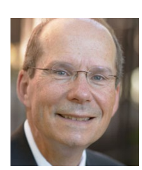

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