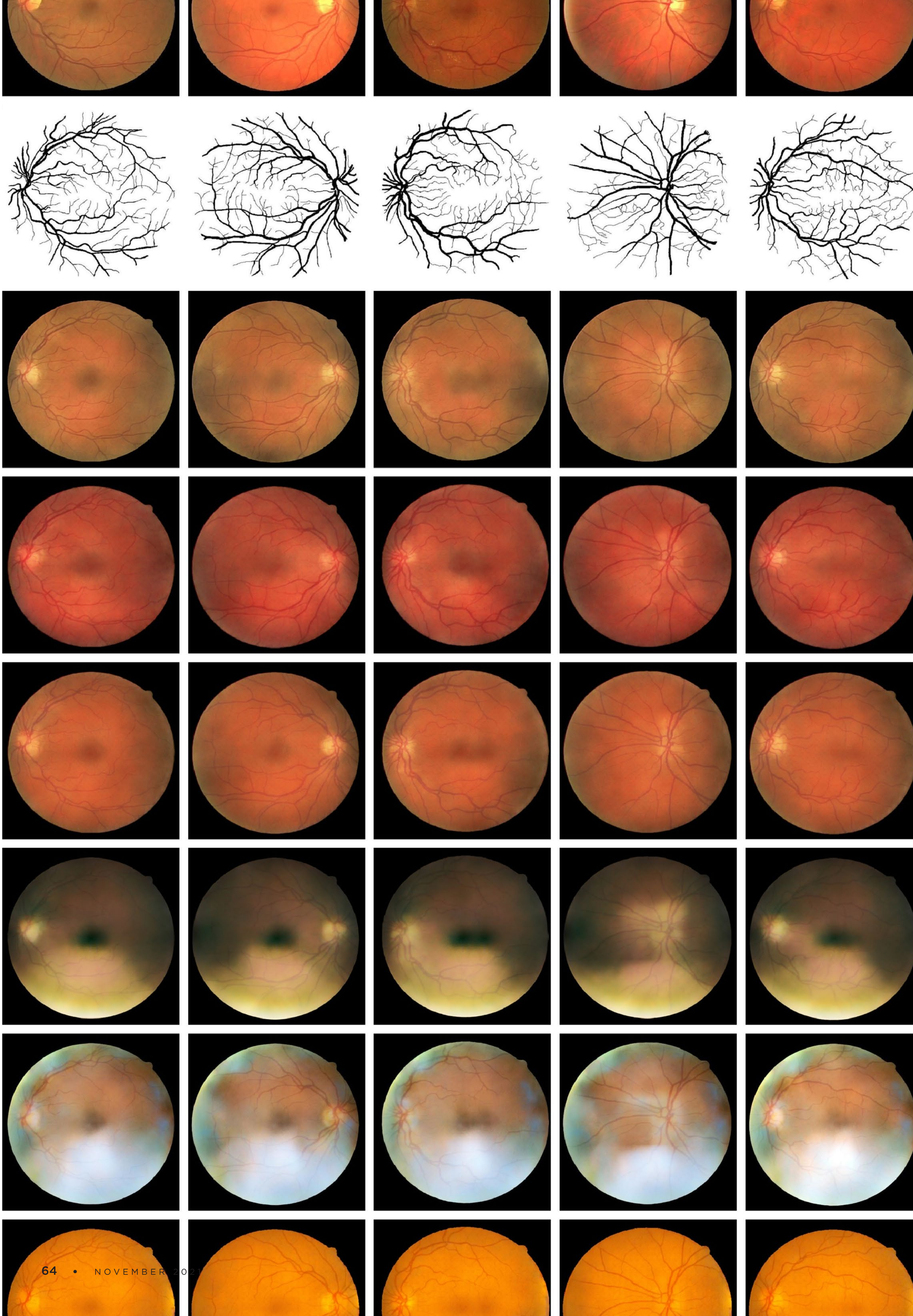


AI and the Retina: Finding Patterns of Systemic Disease

Whatever its future evolution—or revolution—the new field of oculomics is a force to be reckoned with.

By Rebecca Taylor, Contributing Writer

THE RETINA IS UNIQUE: IT'S THE ONLY human tissue allowing direct, noninvasive visualization of the central nervous system and microvascular circulation.[1] And retinal changes have been mapped to systemic disease, from vascular tortuosity for cardiovascular disease (CVD) to retinal cell layer thinning for neurological disease.[2,3]

"The retina is now considered a platform to study disorders in the central nervous system, since it's an accessible extension of the brain in terms of embryology, anatomy, and physiology," said Carol Y. Cheung, PhD, at the Chinese University of Hong Kong.

It's no surprise, then, that advances in OCT, OCT angiography (OCTA), and other imaging modalities would set the stage for new insights into the retina and systemic disease. What's radical is how these images are now being analyzed, with insights generated not only by clinicians but also by machines.

Deciphering the Oculome

A new term. As with "genome," the term "oculome" refers to a comprehensive, integrated understanding of the macroscopic, microscopic, and molecular features associated with health and disease—in this case, in the eye.

In 2020, a U.K. group referenced oculome, and the researchers added "oculomics," to refer to the blending of big data, artificial intelligence (AI), and ocular imaging to identify retinal biomarkers of systemic disease.[1] "One of our collaborators, Alastair Denniston, coined the term oculomics," said Pearse A. Keane, MD, FRCOphth, at Moorfields Eye Hospital and University College London. "Ophthalmology is at the forefront of AI and can be an exemplar for other medical specialties."

A new field. "Broadly speaking, oculomics is the utilization of measurements we obtain from the eye to establish a person's health status," said David Huang, MD, PhD, at Oregon Health & Science University in Portland.

For instance, Dr. Huang said, "With OCTA, we can look at blood flow down to the capillary level and see capillary dropout correlated with systemic health. With Doppler OCT, we can measure retinal blood flow, which is a reflection of carotid and systemic circulation."

Moreover, other approaches—including hyperspectral fundus imaging and visible wavelength OCT (vis-OCT)—are being used to measure markers of systemic health, such as retinal oximetry, Dr. Huang said.

And although the field of oculomics is new, awareness among ophthalmologists is growing

CLONED IMAGES. *This training set of retinal images was created by a generative adversarial network (GAN).*

rapidly as researchers publish their findings. "We are now using the eye to discover mechanisms of disease outside of the eye," said Tien Yin Wong, MD, MPH, PhD, at the Singapore National Eye Center and Duke-NUS Medical School in Singapore. "Well-cited articles have found that retinal vascular changes predicted stroke, were related to heart disease, and preceded the onset of high blood pressure and diabetes—all fundamental biology that the cardiovascular and metabolic disease folks are very excited about."

Building on Retinal Biomarkers

Fast, noninvasive, cost-effective ways to screen for and diagnose disease—and stratify risk to prioritize treatment—are key goals of oculomics research.[1] And leading research targets include such pressing population health issues as CVD and Alzheimer disease (AD).

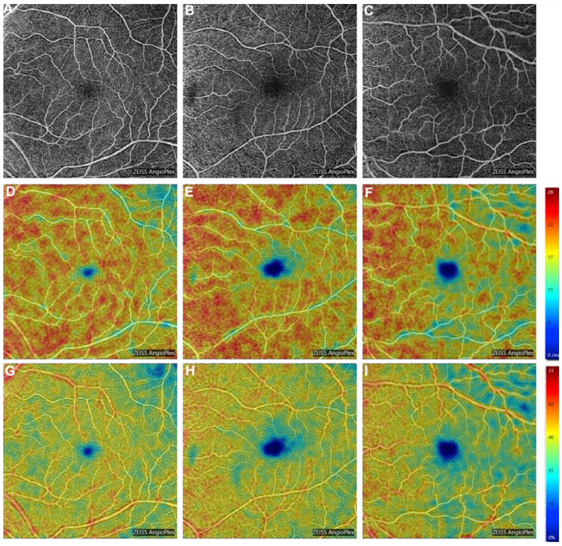
The power of a "retinal fingerprint." In a 2021 review article on retinal biomarkers in AD screening, Dr. Cheung and her colleagues proposed a useful definition of biomarker: an objective parameter of disease that helps predict, assess, or diagnose a condition and plan treatment.[4] AI has a unique capacity to identify retinal biomarkers, as it can automatically learn key features in scans, form a "retinal fingerprint" of a disease, and see unconventional features unnoticed by clinicians.[4]

Applications in cardiology. "Studies have shown that in addition to automatic eye disease detection, AI can estimate and identify a range of nonophthalmic conditions, such as chronic kidney disease, carotid artery atherosclerosis, and CVD risk factors such as blood pressure, body mass index, and hemoglobin A1c," said Dr. Cheung.

And Dr. Wong and his colleagues found that adding retinal parameters to a CVD risk model improved its predictive accuracy more than adding traditional chemical biomarkers, such as high-sensitivity C-reactive protein.[5]

Applications in neurology. Sharon Fekrat, MD, at Duke University in Durham, North Carolina, coauthored a systematic review of 14 OCTA studies that confirmed the link between a thinning retinal nerve fiber layer and reduced capillary density with cognitive impairment and risk of AD.[6]

"New OCTA software takes about 70,000 scans per second to allow visualization of the retinal microvasculature, with some vessels only 5 microns in diameter, which mirrors the cerebral vasculature," Dr. Fekrat said. She added, "Our research group at Duke, iMIND (for Eye Multimodal Imaging and Neurodegenerative Disease), published the first paper describing a convolutional neural network that used retinal images to differentiate individuals with AD from those with normal cognition. It successfully predicted Alzheimer dementia using multimodal images and patient data."[7] (See next page for more on convolutional neural networks.) The group is also investigating retinal biomarkers of Parkinson disease (image on page 68).



__ALZHEIMER.__ OCTA images of the superficial capillary plexus taken of (A) a control patient, (B) a patient with mild cognitive impairment, and (C) a patient with Alzheimer. Corresponding maps show (D-F) vessel density and (G-I) perfusion density in the same participants.

A Fast-Moving Field

"Three fundamental developments created the ground for this new field of oculomics," said Dr. Wong. "First, the collaboration with people outside of ophthalmology; second, the use of digital techniques that don't depend on clinical science; and third, working with computer scientists to quantify retinal changes."

Dr. Fekrat concurred: "As ophthalmologists, we're moving into an era where multidisciplinary work is often necessary to move this field forward, with rapid advances not only in imaging technology and diagnostics but also AI and computer engineering."

Ophthalmology's deep learning breakthroughs. Deep learning (DL), a form of AI, was inspired by the architecture of the cerebral cortex and uses mathematics to connect points in a multidimensional space similar to the brain's extensive synapses.[8] Because of this vast capacity, deep learning networks offer researchers enormous datasets that have been applied to work in robotics, human-machine interfaces, and digital imaging.[8]

The Google/Stanford paper. In health care, Google Research and Stanford School of Medicine published seminal research in *Nature Biomedical Engineering* in 2018. The researchers used a DL model to predict CVD risk factors from retinal photographs from more than 284,000 patients. This DL network used layers of mathematical computations to build an algorithm that "learned" to recognize patterns based on seeing multiple examples of something—in this case, retinal images of patients with CVD.[9]

Convolutional neural networks. This model of DL was optimized for digital images and has since produced diagnostic algorithms for diabetic retinopathy and other conditions with accuracy akin to human experts. This application has also successfully predicted a patient's age (within three years), sex, smoking status, and systolic blood pressure as well as adverse cardiac events.[9]

Code-free deep learning. Code-free deep learning (CFDL) models now process vast image datasets largely on their own.[2]

"That's the magic of it; that's why people are so excited," Dr. Keane said. "The model takes in all of the pixels and figures it out itself. It takes inputs in the form of vectors, so the retinal photograph simply becomes a 3-D grid of numbers."

It's a pattern-recognition game, at enormous scale—and it holds vast potential. For instance, a 2021 paper in *Nature Machine Intelligence* reported using CFDL to predict sex from retinal images after being trained on more than 84,000 scans. The model's accuracy was 86.5%, outperforming AI models built with human—aka "manual"—engineering.[2]

"It was jaw-dropping, because I've spent the last 20 years looking obsessively at retinal photographs, and I cannot begin to tell you whether it's a man or a woman—that's not something ophthalmologists can do," said Dr. Keane. "From those scans, the neural network could see that this is a woman, she's 58 years old, she smokes, and

Oculomics in Action

The AlzEye (Alzheimer-Eye) Study highlights the opportunities and challenges of oculomics research. Currently ongoing, this study uses the U.K.'s database of Hospital Episode Statistics (HES), a data record of every hospital admission and outcome.

From frustration to inspiration. "We can image almost every part of the eye with cellular-level resolution noninvasively, and at Moorfields we do about 1,000 OCT scans every day," said Dr. Keane. But at one point, he was frustrated by the dearth of experts to interpret those scans. As a result, he initiated a collaboration between Moorfields and the AI company DeepMind, whose parent company is Google, to find better ways to leverage those retinal images for health. "Global impact, that's what gets me excited," he said.

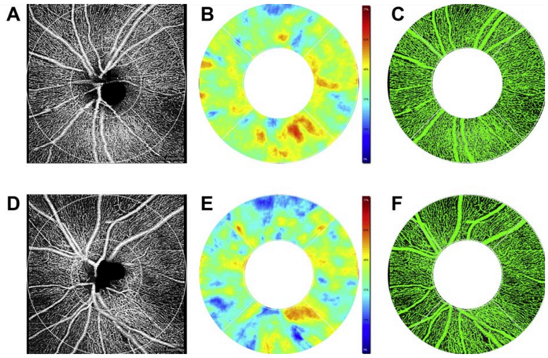
"On a train in 2017, I had the idea to take the millions of eye scans at Moorfields and link them with the HES database," said Dr. Keane. "It's taken us until now to get access to the data, make the linkage, and get the data ready to start the experiments."

How the team gained access to this data. "We did a lot of public engagement with patients with Alzheimer and eye disease, friends and family members of patients, Alzheimer's Research U.K., and Fight for Sight U.K.," Dr. Keane said. Their resulting linked database, he said, is the largest in the world.

"We have about 12,000 incident cases of myocardial infarction and about 12,000 incident cases of stroke," said Dr. Keane. "The Rotterdam study had 86 patients who had OCT scans who went on to develop Alzheimer, while we have about 15,000 patients who've gone on to develop Alzheimer and other causes of dementia, with about 6 million images associated with this cohort."

A potential oculomics application. "We might do an experiment such as, 'Can we train the deep learning model to predict heart attack on a retinal photograph?'" said Dr. Keane. "We'd create a training dataset with retinal images from 15,000 patients who developed a heart attack, plus a control group of images of patients without heart attack. We'd present the images to the neural network as if to say, 'Here's a retinal image of someone who went on to have a heart attack, and here's one of someone who didn't.'"

The researchers would then repeat the process thousands of times to train the neural network, Dr. Keane said. "Finally, we'd get a separate dataset the neural network had never seen, show it a scan, and ask, 'Will this patient have a heart attack?' It would give an output, and since we'd know the answer, we could tell whether it was accurate or not."



PARKINSON. *Peripapillary OCTA images of (A) a patient with Parkinson and (D) a control patient. A color-coded quantitative map of the capillary perfusion density was generated for each eye (B, E), and vessel trace maps identify areas of perfused vasculature (C, F).*

here's her estimated blood pressure and body mass index. There's a lot more information locked in the retinal photograph that, if we had tools like AI, we could retrieve."

Challenges and Unknowns

Lack of standardization. "One elephant in the room is the lack of standardization," said Dr. Fekrat. "If you do a study using a Zeiss machine but everyone else has Optovue, it's not an apples-to-apples comparison. Standardization is a big hurdle that's going to require multiple players to agree on a path forward."

Of note, both the NEI and the Academy have called for industry to standardize machines, segmentation algorithms, and analysis software.[10,11]

Questions of clinical utility. "My main concern is that clinical utility is unclear," said Dr. Cheung. "How to translate the current research to improve clinical management and how it benefits patients and other stakeholders in the health care system are still largely unknown."

"We have validated the automatic measurements, but the next part is more challenging," said Dr. Wong. On one hand, it's good that researchers from the National Heart, Lung, and Blood institute are interested, he said, "because the research tells them how hypertension, diabetes, and vascular disease develop." But on the other, he noted, "how are we going to use it for the patient, who's going to pay for it, and what does it really mean? This is the typical 'translational valley of death' for any discovery."

That begs the question: Who will "own" the oculomics field as it matures, ophthalmologists or internal medicine? "It's a very interesting question," said Dr. Wong. He voted for cardiologists and diabetologists, given their front-row seat in the CVD arena.

Shared data and privacy concerns. AI has already clashed with privacy in health care. "At first, there was a lot of excitement about using big data, but now there's a pullback we need to resolve," said Dr. Wong. Because eye images are now seen as "so individualized," he said, the ability to share data in ways the AI community needs has been halted. "The data are now locked under tight privacy concerns, and the burst of activity that started this has been clamped down."

"The only way we're going to move this field forward is to share data between institutions and countries, but now individuals claim that a retinal photo is protected health information, like a fingerprint," said Dr. Fekrat. "Note that when the COVID-19 pandemic hit, we witnessed the benefits and speed of worldwide collaboration, so if you drop the 'red tape' and let experts around the world do what they do best, you'll have answers fast."

"It's like any of the 'omics'—the 'omics' fields always raise concern," said Dr. Wong. Genomics is a prime example, he said: "If you do a full genome scan, what happens if there are five snips associated with cancer later in life?" Similarly, in the field of oculomics, he said, "If an OCT scan reveals data about systemic health that ophthalmologists have captured, what does it mean from the medical-legal side?"

Dr. Wong contrasted these current privacy concerns with research done earlier in his career. "Blood [samples] could be shared because, unless you're analyzing DNA, blood serum is not identifiable. But the retinal image is now classified as identifiable, which is a big step backward for oculomics. Companies such as Google have given up on U.S. data and gone to places where there's less regulation, such as India and Thailand."

GANs to the rescue? Even so, AI researchers remain undeterred and are investigating potential solutions to privacy concerns. "One exciting technology is to subtly modify unuseful parts of the retinal image so that it cannot be traced to the individual," said Dr. Wong. "A technique called generative adversarial networks, or GANs, artificially creates thousands or millions of images from one scan, with subtle differences, so AI can learn the patterns of disease from clones of one image." (For example, see page 64.)

The clinician's role. Finally, what role will the clinician play in this research? On a positive note, while the results of the 2021 study on the CFDL model showed that the model identified subtle variations and patterns in retinal scans unseen by human experts, the researchers concluded that clinicians are still needed to prepare usable image datasets and design AI experiments that are clinically relevant.[2]

In the Clinic: What's the ETA?

Ask five experts when oculomics might arrive in an ophthalmologist's office, and how it might be put into use, and you'll hear five different views:

Dr. Cheung. "First, we need evidence-based guidelines on the use and interpretation of oculomics. Second, we need more research on prospective validation and real-world implementation to demonstrate the clinical value, with appropriate infrastructure to make sure the clinical workflow is smooth, efficient, and effective."

Dr. Fekrat. "There are three ways you might use oculomics: You could use it for widespread screening, as an alternative to diagnosis in resource-poor settings, or as an adjunct to existing tests—for instance, as part of a diagnostic index."

Dr. Huang. "Oculomics could drive the use of OCT, OCTA, and Doppler OCT into the primary care office as well as to ophthalmology. OCT hardware isn't cheap, but it's cheaper than CT, MRI, or coronary angiography."

Dr. Keane. "It could be within five years, if everything goes beautifully. If we can predict a heart attack, for instance, we'd test the model on U.S. data, or Brazilian or African data, to see if it works in different populations, and eventually commercialize the neural network that had been trained."

Dr. Wong. "The oculomics story will take a decade, if not longer. The genomics story has been around without much progress in legislation or understanding what it means. Oculomics, frankly, will undergo several revolutions."

1 Wagner SK et al. *Trans Vis Sci Tech.* 2020;9(2):6.
2 Korot E et al. *Sci Rep.* 2021;11(1):10286.
3 Chan VTT et al. *Ophthalmology.* 2019;126(4):497-510.
4 Cheung CY et al. *J Neurol Neurosurg.* 2021;92(9):983-994.
5 Ho H et al. *Scientific Rep.* 2017;7:41492.
6 Rifai OM et al. *Alzheimers Dement* (Amst). 2021;13(1):e12149.
7 Wisely CE et al. *Br J Ophthalmol.* Published online Nov. 26, 2020.
8 Sejnowski TJ. *PNAS.* 2020;117(48):30033-30038.
9 Poplin R et al. *Nat Biomed Eng.* 2018;2(3):158-164.
10 www.nei.nih.gov/about/news-and-events/news/nei-joins-call-standardization-ophthalmic-imaging-devices. Accessed Aug. 31, 2021.
11 Lee AY et al. *Ophthalmology.* 2021;128(7):969-970.

Meet the Experts

Carol Y. Cheung, PhD Associate professor in the Department of Ophthalmology and Visual Sciences at the Chinese University of Hong Kong. *Relevant financial disclosures: The Bright Focus Foundation: S.*

Sharon Fekrat, MD, FACS, FASRS Vitreoretinal surgeon, professor of ophthalmology, and associate professor of surgery at Duke University School of Medicine in Durham, N.C. *Relevant financial disclosures: Alcon: P; The Alzheimer Drug Discovery Foundation: S.*

David Huang, MD, PhD Director of the COOL Lab (Center for Ophthalmic Optics and Lasers), associate director and director of research at Casey Eye Institute, and professor of ophthalmology and biomedical engineering at Oregon Health & Science University (OHSU), all in Portland, Ore. *Relevant financial disclosures: OHSU and Dr. Huang have significant financial interests in Optovue, a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU.*

Pearse A. Keane, MD, FRCOphth Professor of artificial medical intelligence at University College London. He is also U.K. Research and Innovation Future Leaders Fellow and a retina specialist at Moorfields Eye Hospital in London. *Relevant financial disclosures: Allergan: L; Apellis: C; Bayer: L; Big Picture Medical: O; DeepMind: C; Heidelberg Engineering: L; Novartis: C; Roche: C; Topcon: L.*

Tien Yin Wong, MD, MPH, PhD Medical director of the Singapore National Eye Centre. He is also vice dean and chair of the Ophthalmology and Visual Sciences Academic Clinical Program at Duke-NUS Medical School in Singapore. *Relevant financial disclosures: Bayer: C; Boehringer-Ingelheim: C; Eden Ophthalmic: C; EyRIS: P; Genentech: C; Iveric Bio: C; Merck: C; Novartis: C; Oxurion: C; plano: P; Roche: C; Samsung: C; Shanghai Henlius: C; Zhaoke Pharmaceutical: C.*

See disclosure key, page 12.