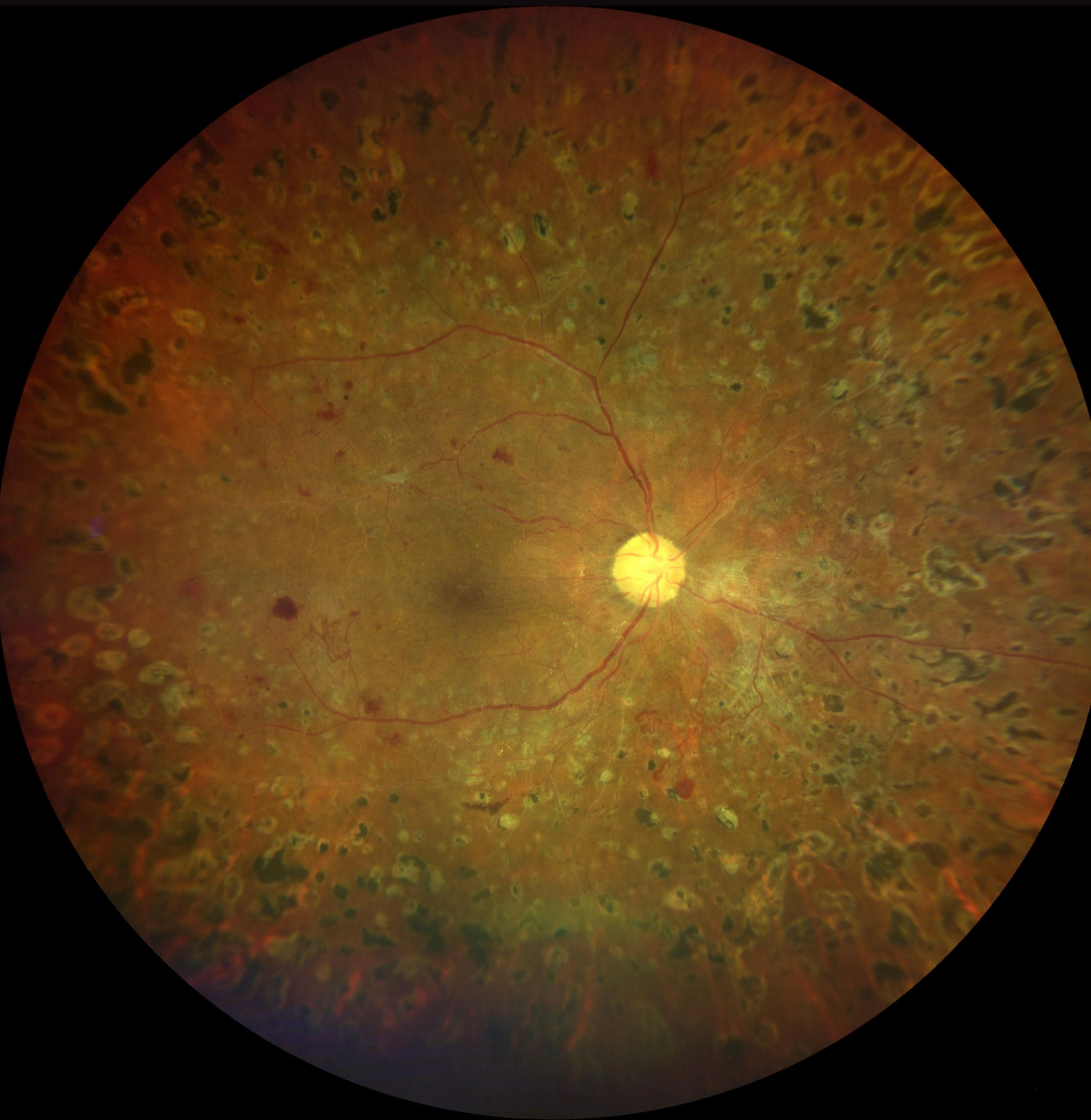

Diabetic Retinopathy

Screening, Treatment, and Trends

Creating an ocular biobank, reaching communities at risk, enhancing detection with AI, and pursuing better anti-VEGF agents are among the latest DR-fighting efforts.

By Ashley Welch, Contributing Writer

WHILE SIGNIFICANT ADVANCES have been made in recent decades to preserve sight and treat vision loss in patients with diabetic retinopathy (DR), gaps in care coupled with a growing global diabetes epidemic make it imperative to improve existing screening and treatments, say experts.

DR is all too common. It is the leading cause of blindness among working-age adults in the United States.[1] A meta-analysis estimated that across the globe, DR accounted for more than 2.6% of all cases of blindness in 2010.[2]

"Diabetic retinopathy is the most common vascular complication of diabetes, and we see it very frequently in patients who have been diagnosed with diabetes, usually by 10 or 15 years," said Jennifer K. Sun, MD, MPH, at Beetham Eye Institute at Joslin Diabetes Center in Boston.

Troubling Trends

Climbing cases. The diabetes epidemic continues to grow around the world and in the United States. In 2021, it is estimated that 529 million people globally were living with type 1 and type 2 diabetes. By 2050, that figure is expected to explode to 1.3 billion people.[3] In the United States, more than 37 million Americans, or about one in 10 people, have diabetes—more than 90% live with type 2 diabetes.[4] By 2060, that number is projected to triple.[5]

As the incidence of diabetes continues to grow, so does the risk of its complications, including DR. According to a recent study, 9.6 million Americans have DR—25% of people in the United States with diabetes. More than 1.8 million, or about 5% of Americans with diabetes, have vision-threatening advanced microvascular complications.[6]

"It's a huge public health issue and remains the leading cause of vision loss in many [high income] countries like the United States," Dr. Sun said.

Disparities in DR. As with many chronic illnesses, there are health disparities with DR. One cross-sectional study that included 778 participants (ages 45 to 85) and examined diabetic retinopathy in a multiethnic cohort in the United States found that the prevalence of any diabetic retinopathy and macular edema were significantly higher in Black participants (36.7% and 11.1%, respectively) and Hispanic participants (37.4%

DIAGNOSING WITH FUNDUSCOPY. *A fundus photo captures signs of proliferative diabetic retinopathy in a 57-year-old patient.*

and 10.7%) than in White (24.8% and 2.7%) and Chinese (25.7% and 8.9%) participants.[7]

According to the INSIGHT study, a U.S. study that involved four urban clinics and included mostly African-American (62.4%) and Hispanic (14.8%) patients, one in five study participants with diabetes came up positive for DR when screened for the condition. Almost half of participants had other ocular findings, the researchers reported.[8]

Improving DR Screening

A major barrier to reversing trends in diabetic retinopathy, and to closing the gap in racial disparities, is getting patients appropriately screened. The Academy's current *Diabetic Retinopathy Preb ferred Practice Pattern* guidelines recommend an annual dilated eye exam for patients with diabetes, beginning at the time of diagnosis for people with type 2 diabetes and five years after diagnosis for people with type 1 diabetes.[9] But only about half of patients who fall into those categories routinely get screened.[10]

"It's challenging because people can develop fairly advanced diabetic retinopathy without having any visual symptoms, and many patients don't understand that," Dr. Sun said.

In addition to gaps in patient education, other barriers to diagnosis and treatment include socioeconomic and geographic barriers and delayed referrals from primary care physicians. One study found that in the United States, annual eye exams are lower among Black (48.9%) and Hispanic (48.2%) people with diabetes compared with non-Hispanic White (55.6%) people with the condition.

Screening in the U.K. Some countries outside the United States have made substantial progress in lowering the prevalence of visual complications from diabetic retinopathy. In the United Kingdom, for example, routine screening in the primary care setting has reduced the risk of vision loss from diabetic retinopathy such that it is no longer a leading cause of blindness.

"The one payer system of health care provides the ability to conduct such complete DR screening," said Emily Y. Chew, MD, at the National Eye Institute in Bethesda, Maryland. "The lack of universal DR screening in the United States is a huge roadblock to reversing DR trends," she said.

Telehealth and remote screening. With new technological advances, efforts by medical centers and nonprofit organizations are helping to increase access to screening in the United States. The use of telemedicine skyrocketed during the COVID-19 pandemic and continues to be an integral part of health care in the United States. Experts say it can play an important role in getting more patients screened for DR.

The traditional approach for DR screening requires a referral from a primary care provider to an eye care professional. Many comprehensive ophthalmologists, who have close relationships with community primary care providers, conduct this annual exam. Dr. Sun said new methods of imaging the retina through undilated pupils allows primary care physicians—and even patients themselves—to capture retinal images using handheld devices, including smartphone attachments. These images can then be transmitted to an eye care professional or trained grader to see which patients should be referred for additional screening.

"That has really opened up the ability to create efficient and potentially cost-effective telemedicine programs that can help support the number of screening exams that are needed in the United States," Dr. Sun said.

Artificial intelligence. Although artificial intelligence (AI) is still new and evolving, machine learning and deep learning algorithms may play a key role in the future of diabetic retinopathy detection. To date, the FDA has approved three AI ale gorithms for the detection of diabetic retinopathy: IDx-DR, EyeArt, and AEYE Diagnostic Screening (AEYE-DS).[11]

"At this point, the [AI] programs are doing a kind of very general triage," Dr. Sun said. "They're diagnosing referable retinopathy, rather than specific stages of diabetic retinopathy severity, which is what we do in the clinics."

The technology behind AI algorithms and machine learning is complex, but the general idea is that instead of sending retinal images—fundus photography images, for example—to an ophthalmologist or trained human grader, AI-powered software can independently analyze these images to identify signs of DR so that patients can be referred for additional screening and potential intervention.

"AI will never replace ophthalmologists," said G. Atma Vemulakonda, MD, at the Palo Alto Medical Foundation in Palo Alto, California. "But rather it's a rough screen that can hopefully capture more at-risk patients and get them where they need to go."

In addition to helping with more efficient screening and diagnosis, this technology has the potential to free up clinicians' time to see more patients, Dr. Vemulakonda said.

Drug Delivery Advances

Improving screening for diabetic retinopathy is one piece of the puzzle, but new and improved DR treatments are also needed.

Better anti-VEGF drugs. While anti-VEGF injections are effective at preventing and treating vision loss in many people with advanced DR, they require frequent office visits for treatments and follow-ups, which contribute to high levels of patient nonadherence. Faricimab (Vabysmo) and brolucizumab (Beovu), for example, have been approved by the FDA to treat diabetic macular edema. To help improve patient adherence, other anti-VEGF therapies are currently in development that allow for longer intervals between follow-up treatments.[12]

"As the anti-VEGF agents become longer acting, this will take some of the concern around visit adherence and patient adherence to care out of the equation, because they don't need to be seen or treated as often," said Brian L. VanderBeek, MD, MPH, at the Hospital of the University of Pennsylvania.

There are also ongoing efforts to improve delivery systems for anti-VEGF agents, including the use of eye drops and a port delivery system—an ocular implant that would provide continuous anti-VEGF medication to treat DME.

Potential New Pathways

While anti-VEGF therapies have led to improvements in diabetic retinopathy management, they are not effective for everyone. "About 50% of our patients with diabetic macular edema being treated with anti-VEGFs don't get vision back to 20/20 or better or don't have full resolution of their DME," said Dr. Sun, who added that there is a lot of interest in finding new molecular pathways to target.

Fenofibrate. One area of research into a potential new therapy for diabetic retinopathy is affected, who have decades of disease ahead.

More research. To better understand exactly when and how diabetic retinopathy begins in young people, Dr. Rosenthal and colleagues are conducting preliminary research in children and teens with diabetes looking at retinal functioning—rather than structural changes—that may signal early signs of DR.

"In my practice, every once in a while, I see patients just out of adolescence or who have just finished college who come in with proliferative diabetic retinopathy," Dr. Rosenthal said. "That's really what motivates me to try to find when does this start? And then eventually, what can we do about it to intervene earlier?"

A Younger Generation at Risk for DR

As diabetes cases climb in those under age 18, ophthalmologists are concerned for related vision complications, including diabetic retinopathy.

One study projects a dramatic rise in type 2 diabetes among young people in the United States over the next four decades, with as many as 220,000 kids and adolescents under the age of 20 expected to have the disease in 2060. That represents a 673% increase from today's figure. Childhood obesity, the American diet, and lack of physical activity are cited as drivers of the type 2 diabetes epidemic in young people. The number of young people with type 1 diabetes could also climb as much as 65% in the same time frame.[1]

"This is certainly a cause for alarm because here we're talking about not just the working age population, but now kids, who have their whole life ahead of them," Dr. Vemulakonda said.

Signs. When it comes to DR incidence in young people, recent U.S.-based research indicated that 52% of youth with type 1 diabetes and 56% of those with type 2 diabetes experience retinal changes at 12.5 years' follow-up from diagnosis.[2] The study authors wrote that tight monitoring of glucose and blood pressure could help slow the development and progression of DR in young people with diabetes.

"Thankfully, most of these cases were not severe or end-stage," said Julie M. Rosenthal, MD, at the University of Michigan Kellogg Eye Center. The cases were mild or moderate, but she said it is still too many young people

EARLIER INTERVENTION. *Rising cases of diabetes in children and teens raises alarm bells for ophthalmologists.*

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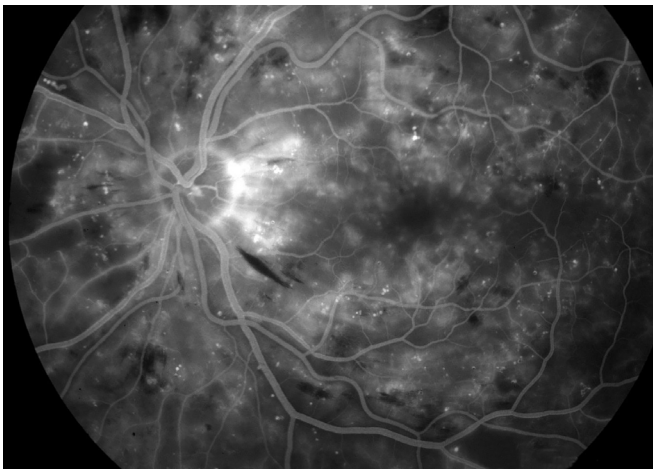
1 CDC. www.cdc.gov/media/releases/2022/p1229-future-diabetes-surge.html. Accessed Oct. 10, 2023.
2 Jensen ET. *Diabetes Care.* 2023;46(6):1252-1260.



DIABETES' TOLL ON VISION. *Fluorescein angiogram of an eye with severe nonproliferative diabetic retinopathy with extensive macular edema.*

fenofibrate, an oral medication approved by the FDA to treat abnormal blood lipid levels. This is being investigated because elevated triglycerides are often seen in persons with diabetes. Two large international clinical trials (FIELD and ACCORD) demonstrated a 30% reduction in the progression of DR with use of 160 to 200 mg/day of fenofibrate, said Dr. Chew.

"Fenofibrate is not commonly used in the treatment of DR. This may be due to the perception that these analyses [FIELD and ACCORD] were secondary analyses and would hence require additional clinical trials that test DR progression as primary outcomes to provide evidence for more widespread use," said Dr. Chew, who is involved in fenofibrate research.

There's also the question of who should be prescribing the medication to patients. "Physicians providing care for the systemic therapy of diabetes are not likely to be able to determine the level of diabetic retinopathy, while ophthalmologists may not be comfortable in prescribing systemic drugs that need monitoring," Dr. Chew said.

The Diabetic Retinopathy Clinical Research Retina Network is now conducting a controlled clinical trial of fenofibrate to evaluate the feasibila ity of ophthalmologists prescribing the drug with continued communication and monitoring from the primary care physician, and to see whether fenofibrate is beneficial for reducing the risk of DR progression using this treatment paradigm.[13]

"If this trial is successful in proving the importance of fenofibrate for the reduction of DR, this could be an important public health contribution," Dr. Chew said. "Such treatment may reduce the need for onerous and costly intravitreal therapies with anti-VEGF drugs, which carry a low risk of endophthalmitis."

Gene therapy. Another approach under consideration is gene therapy. With this intervention, a vector transports a gene to the eye that is designed to neutralize vascular endothelial growth factor. "So rather than doing all the injections in the office, you do one injection and then the body basically becomes an anti-VEGF factory," Dr. Vemulakonda said. Research into gene therapy for DR is still early, and trials are ongoing.[14]

Moonshot to End Blindness From DR Diseases

In order to reverse DR trends both nationally and globally, improved screening and treatments are needed. But what would it take to end vision loss from diabetes completely?

The Mary Tyler Moore Vision Initiative has lofty goals in this area. Best known for her work as an actress, Mary Tyler Moore, who died at age 80 in 2017, also lived with type 1 diabetes and was a fierce advocate. "As International Chairman of the Juvenile Diabetes Research Foundation [JDRF] from 1984 to 2017, Mary helped JDRF raise billions of dollars for their direct funding of research and billions more through her leading advocacy efforts in support of federal funding of diabetes research," said Mary's husband S. Robert Levine, MD. "Mary was optimistic and thought anything was possible. Her dream was to help find cures for diabetes and its complications."

Eventually, diabetic retinopathy robbed Mary of her vision, resulting in near-blindness and greatly reducing her independence. Though Mary did not live to see a cure, her legacy lives on through the Mary Tyler Moore Vision Initiative, founded by Dr. Levine in collaboration with the JDRF and the Elizabeth Weiser Caswell Diabetes Institute (CDI) and Kellogg Eye Center at the University of Michigan.

A biorepository dedicated to DR. To achieve the goal of a world without vision loss from diabetes, the Mary Tyler Moore Vision Initiative has developed a multiphase plan. A major element of the first phase is to create the world's first biorepository dedicated to diabetic retinal disease.

A significant barrier to DR research is the limited availability of human eye tissue, which cannot be safely biopsied from living patients. According to Dr. Levine, a biobank of postmortem tissue samples will provide a critical resource to accelerate the development of new interventions to pre-

serve and restore vision in people with diabetes. The initiative's aim is to collect and deeply analyze ocular tissues and fluids from over 250 donors per year over the next four years.

"We've started to collect from donors with both type 1 and type 2 diabetes," said Patrice E. Fort, PhD, MS, of the Mary Tyler Moore Vision Initiative Biorepository and Resource Center in Ann Arbor, Michigan. "These will then be age-, gender-, and race-matched with tissues from nondiabetic donors," he said.

The biobank data and samples will be shareable with academic and industry scientists in the DR research community to help drive a global collaborative effort to better understand the cellular and molecular basis of DR. Using these data and analyses, the Mary Tyler Moore Initiative plans to organize a consortium to identify new clinical endpoints and molecular targets for therapeutics development.

Another goal of the initiative is to develop a large retinal image bank for use by scientists that aggregates millions of digital images with functional measures and de-identified patient data collected from across diverse clinical settings. It would aim to improve AI-based diagnostics and address health care inequities.

"The idea is to crowdsource a cure," Dr. Levine said. "The data and the specimens have to get out into the community because you need to leverage the genius of everyone in the community to reach that goal."

1 CDC. www.cdc.gov/diabetes/managing/diabetes-vision-loss.html. Accessed Oct. 19, 2023.
2 Leasher JL et al. *Diabetes Care.* 2016;39(9):1643-1649.
3 Ong KL et al. *Lancet*. 2023;402(10397):203-234.
4 CDC. www.cdc.gov/diabetes/basics/type2.html. Accessed Oct. 19, 2023.
5 Lin J et al. *Popul Health Metr.* 2018;16:9.
6 Lundeen EA et al. *JAMA Ophthalmol.* 2023;141(8):747-754.
7 Wong TY et al. *Am J Ophthalmol.* 2006;141(3):446-455.
8 Owsley C et al. *JAMA Ophthalmol.* 2015;133(2): 174-181.
9 American Academy of Ophthalmology. *Diabetic Retinopathy Preferred Practice Pattern.* 2019. Available at aao.org/ppp.
10 https://health.gov/healthypeople/objectives-and-data/browse-objectives/diabetes/increase-proportion-adults-diabetes-who-have-yearly-eye-exam-d-04. Accessed Oct. 19, 2023.
11 Rajesh AE et al. *Diabetes Care.* 2023;46(10):1728-1739.
12 Shahzad H et al. *Syst Rev.* 2023;12:92.
13 JAEB Center for Health Research. https://public.jaeb.org/drcrnet/stdy/568. Accessed Oct. 10, 2023.
14 NIH. https://classic.clinicaltrials.gov/ct2/show/NCT05916391. Accessed Oct. 10, 2023.

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