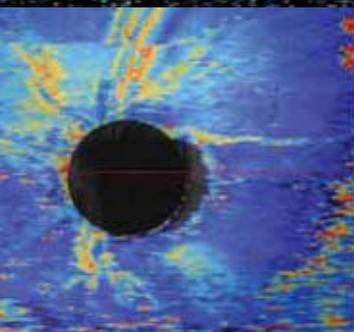
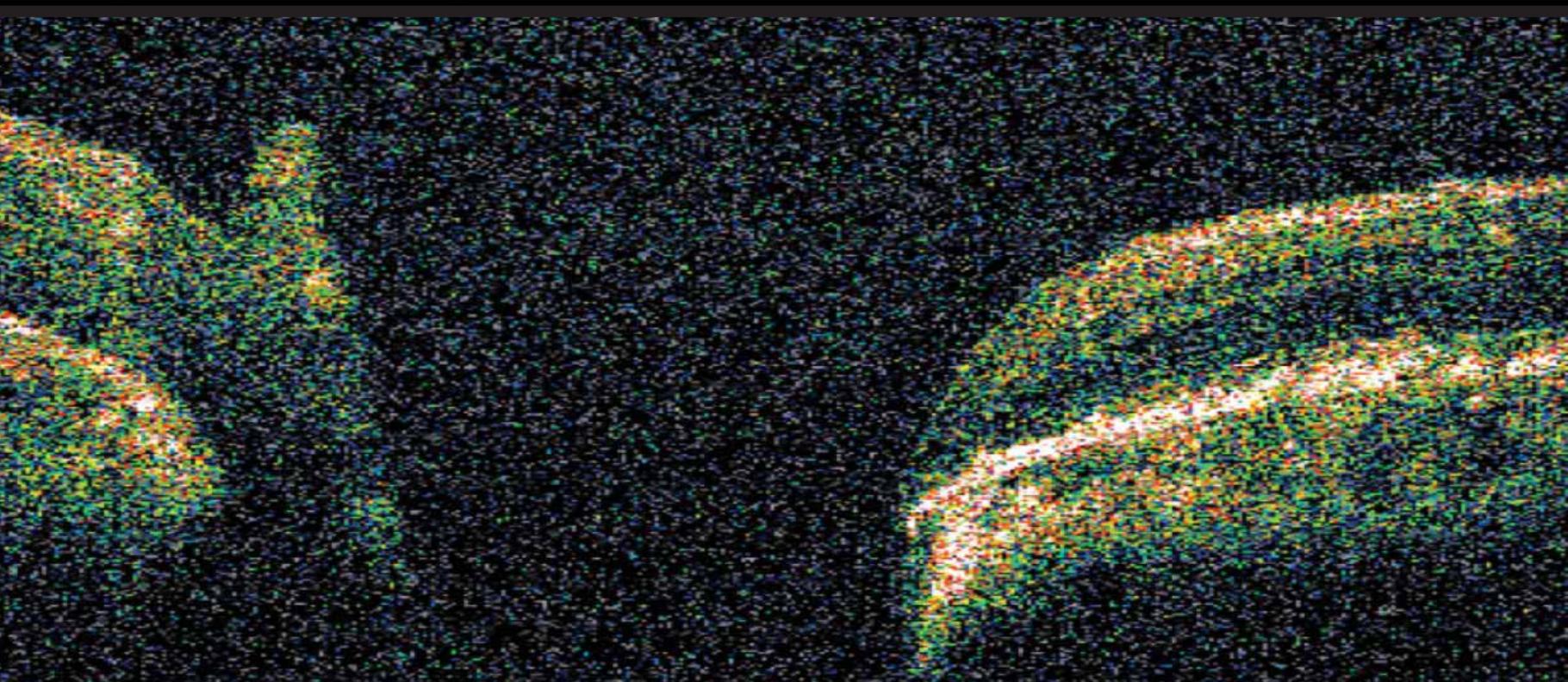
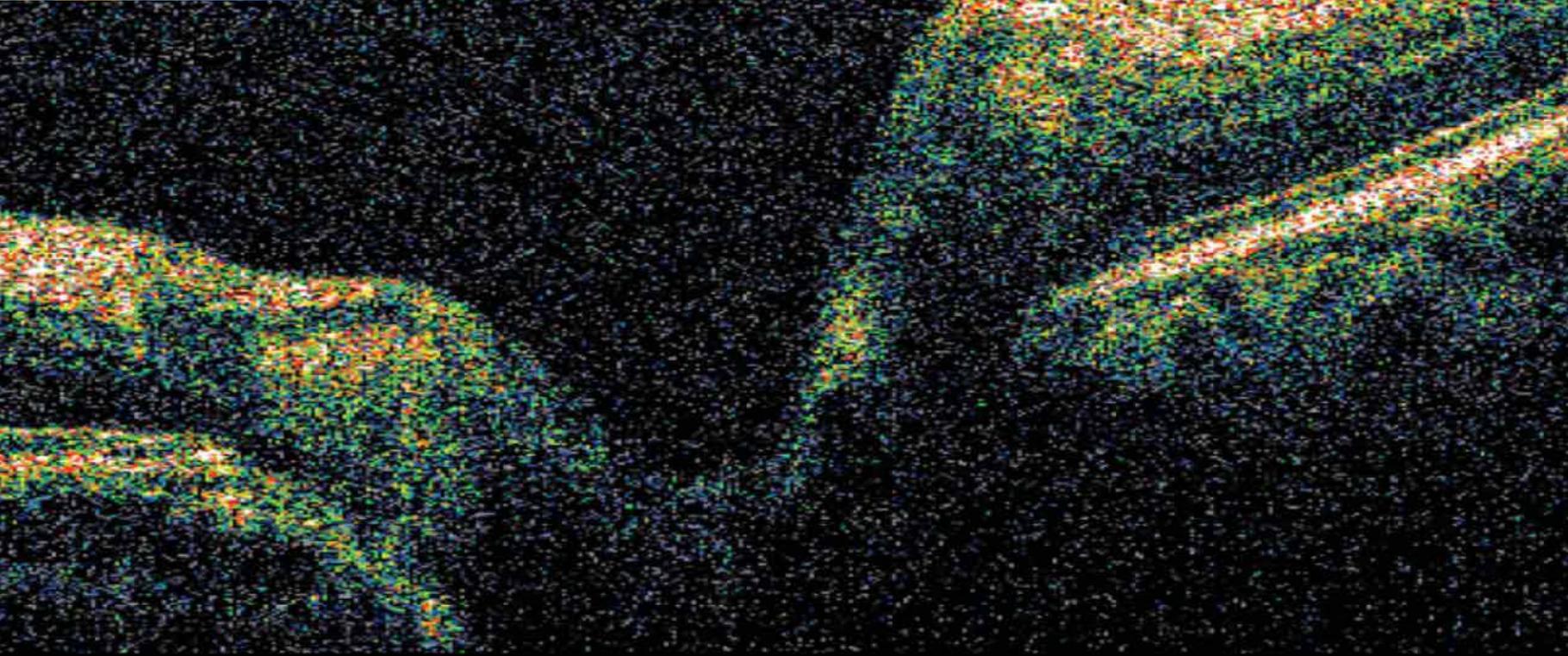
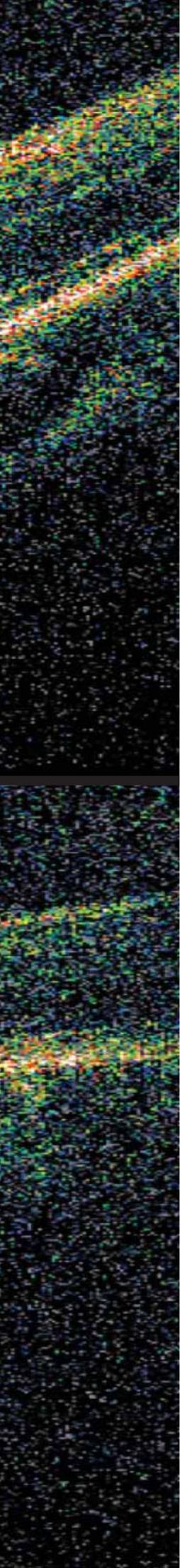


Joel Schuman has given physicians new tools for diagnosing and understanding glaucoma. These images were made by a prototype high-speed and ultrahigh resolution optical coherence tomography instrument, at a resolution of 3.5 microns—less than half the size of a red blood cell.



The indented structures in the images here are cross sections of optic nerves. The small inset images are the same optic nerves shown from another angle. In the healthy eye (above), you can see the bottom of the nerve “cup.” In the eye with glaucoma (below), the pit is so deep, you can’t see the bottom in the scan—too much tissue has been lost to glaucoma. The same deterioration is evident in the bottom left image. Blue indicates thin tissue.



JOEL SCHUMAN CAN SEE INTO YOUR FUTURE

BY MEGHAN HOLOHAN

# EYE ON GLAUCOMA

**A**m I going blind?  
Joel Schuman will tell me.  
Let me back up—you see, I can't see.  
Well, this isn't entirely true. I wear glasses or contacts.  
Without the advances of ultrathin lenses, I'd be the woman who wears the proverbial Coke-bottle glasses. Each time I go to my eye doctor, I'm told my eyes have worsened.

If I'm not wearing corrective lenses, I fumble around my house, unable to distinguish the difference between my cat and an end table. Everything looks like the same blurry blob.

I often wonder what life would be like if I couldn't see.

Maybe I'm melodramatic. I could just have poor eyesight, but if there's something more to my hazy vision, I want to know about it. And it's not every day that I'm offered insight into my future.

IMAGES | COURTESY SCHUMAN LAB

To be clear, I'm not a patient of Joel Schuman's. I'm getting to know him on an article assignment about important advances in glaucoma detection and how he helped make them happen. Schuman is chair of the University of Pittsburgh Department of Ophthalmology; he has offered me a tour of his lab full of tools for diagnosing eye disease. How could I refuse?

Almost immediately after my arrival at Schuman's lab, Bill Dilworth, the department's ophthalmologic imaging technician, shows up and asks if I want a test. Dilworth wears blue scrubs over his broad chest and has big hands; his hair is cut closely.

"Yes," I say without thought.

Dilworth wants to give me an exam on a machine that uses optical coherence tomography (OCT). The machine detects abnormalities years before traditional tests can find evidence of glaucoma. It is the most powerful tool available to clinicians, and Schuman was instrumental in its development.

I don't think anyone in my family ever had glaucoma; I'm younger than 40, and I

"Okay, you're going to see a dot in the right-hand corner. Keep looking at that," Dilworth says.

The black field looks like the background for Atari's Space Invaders, especially when red beams shoot across it. Red light flashes and dances as I struggle to keep my eye focused on a green target. I'm holding my breath because I want to focus so I can "pass" the test.

Now it looks like the red lines are vibrating. Where's that dot I should be looking at? It's hard to concentrate with red beams shooting all over the place.

Harder still if I think about what's actually happening.

Light beams are plunging through my eye tissue, examining the layers within. Red light vibrates and shoots across the screen; what is reminiscent of a video game is how Schuman has figured out how to scan for deep-set damage in my optic nerve.

As I hold my breath and watch lights, I hear Schuman talking to some grad students about their work, patiently listening to their concerns, giving them tips.

than 40, yet it does occur in children and young adults.

Gradual progression disguises the disease. Glaucoma's quarry may notice that she can't see out of the corners of her eye—she turns her head to observe something. Even on hazy days, she wears sunglasses because the light causes discomfort. You would think night would bring relief, yet it makes driving stressful. The halogen lights burn brightly, and she struggles to see the road and other cars. Fluorescent lights in the mall, her office, and the grocery store affect her ability to see.

This could easily be me. I don't keep my office lights on—they give me headaches and don't help me see better. And at 26, I have a hard time seeing at night.

As I continue to keep my eyes wide open, I ask whether the results will be different because I am wearing contact lenses. "Naw," Dilworth says.

OCT emits beams of infrared light (more specifically, low coherence waves; one of this year's winners of the Nobel Prize in Physics studied this phenomenon). By bouncing light off both the object of interest, in this case ocular tissue, and a reference point (usually a mirror), the machine creates a profile detailing the exact location of structures within the tissue. The OCT then makes a few other scanning maneuvers and in the end produces a scan of what's at

the back of the eye, including retinal or nerve damage. Because there's very little wave interference, the technology produces high-resolution images.

The technology uses light waves much like an ultrasound uses sound waves—the reflecting light waves create a picture of an internal structure. And as with ultrasound, OCT is safe for probing live organisms (like yours truly), without taking invasive measures.

What Schuman and Fujimoto accomplished with OCT allows clinicians to examine eye tissue without the subjectivity of what has been the gold standard in glaucoma detection technology—the visual field test. (In visual field tests, patients are asked to push a button when they see a light. Both the exam and the doctor's interpretation of the results are subjective, notes Schuman.)

If a doctor can detect damage with a visual field test, a patient has already lost 30 percent to 50 percent of her ocular nerve tissue. By that point, she may still not have a lot of trouble seeing.

## The machine detects abnormalities years before traditional tests find evidence of glaucoma. It is the most powerful tool available to clinicians, and Schuman was instrumental in its development.

don't suffer from a secondary disease known to cause glaucoma, so I'm not at high risk. Yet the "what-ifs" are anxiety inducing. What if there really is something wrong? What if Dilworth sees something other than glaucoma? Wait, can OCT see something other than signs of glaucoma?

If anyone can render an accurate verdict on questions concerning glaucoma, it is Joel Schuman. Throughout his career, he has been at the forefront of diagnostic testing for glaucoma. He also discovered the first molecular marker for the disease. The man has devoted his life to treating and curing glaucoma, and he is not satisfied with the current state of diagnostics and markers. Even though he is responsible for the development of the most powerful tool available for detecting glaucoma, he's determined to make it better.

Dilworth cleans off the eyepiece of a rectangular white machine. I place my forehead on the headrest to begin the exam. As he works, Schuman stands back, allowing Dilworth to run the show.

Shortly after he finished his own training in the early 1990s, Schuman, at Harvard University and then at Tufts University, partnered with James Fujimoto—a professor of engineering at Massachusetts Institute of Technology interested in the use of lasers in medicine. Schuman approached Fujimoto because he wanted to find a diagnostic technique that would identify glaucoma before the onset of often-debilitating symptoms. That's when they developed this OCT technology, which is about to reveal my visual future.

According to the Glaucoma Research Foundation, probably 3 million Americans suffer from glaucoma, yet only half of them know it. The disease is the leading cause of preventable blindness, but in its earliest stages people experience virtually no symptoms.

Glaucoma is characterized by damage to the optic nerve, usually because of high intraocular pressure. The disease causes blindness when nerve damage is so great that the brain and eye can no longer communicate.

It is most commonly found in people older

Alternatively, the OCT creates a cross-section of the eye, so that physicians can actually see damage done to the nerve fiber—the telltale sign of glaucoma. Commercially available OCTs can measure tissue at 10-micron resolution and detect nerve damage years before a visual field test can.

When Schuman first used OCT in Boston, physicians grumbled, *This thing only works in Boston*. Only expensive eye centers could use such sophisticated diagnostic equipment, many thought.

Schuman used the first commercial OCT in 1995; a decade later, 5,000 are in use in clinical and research settings, and he believes most of those machines were bought in the past few years. He dreams that one day, ophthalmologists worldwide will have OCTs in their offices. It has become the new gold standard for retinal disease and is now more widely sought out for glaucoma.

Why have some clinicians been slow to adopt OCT for glaucoma diagnostics? Some worry “abnormalities” that OCT users are seeing deep within patients’ eyes aren’t related to glaucoma. They suggest there isn’t enough information about what a normal eye looks like compared to an eye with glaucoma at such an early stage.

Who’s to say abnormalities detected by OCT are glaucoma related and not a result of normal wear and tear?

Schuman, that’s who.

He is confident that this machine is detecting glaucoma, and he has the data to back that claim.

Further, he knows that treatments for early glaucoma are both easier for the patient and more effective at preserving undamaged retinal nerves.

“The worse the disease, the harder it is to treat,” Schuman says.

“I would want to treat [patients] sooner rather than treating them too late.”

If Joel Schuman asks questions, he genuinely listens to the answers. He puts people at ease. In his few hours off, you might see the ophthalmologist with his children in the Apple Store or at a Black Eyed Peas concert. He keeps a guitar in his office. His other big hobby isn’t surprising for a man of vision: photography. There’s something about him that’s, well, kind of cool.

As an undergraduate at Columbia University, Schuman pursued a psychology degree. That’s when he became interested in

how people perceive objects. Soon questions of optical illusions captured his attention. Questions like, *Why does the moon look bigger when it rests on the horizon than when it’s overhead?* He started wondering why the retina itself seemingly played tricks on the mind. Inspired by his older brother, he attended medical school at Mount Sinai School of Medicine. He went on to cofound Tufts–New England Eye Center. (In addition to becoming vice chair and a professor of ophthalmology there, he served as an electrical engineering and computer science professor.)

When I am done with my OCT test, Dilworth waits while the computer processes the results of my scan. I blink and blink, now offered the freedom to do so. Dilworth waves me back to the computer screen behind the OCT, so I can look at some charts and graphs.

“You’re normal,” he declares, “you can go back to work and tell everyone you’re normal.”

“Well, you can tell them that your *eyes* are normal,” Schuman deadpans.

The tour continues. I take another eye test. This one resembles a firefight Luke Skywalker might have in mid-space. The tests become a jumble of alphabet soup—GDX, HRT, UBM. These are all machines Schuman brought to Pitt. Few hospitals or labs in the country have such sophisticated screening devices. There’s something that looks like a gauge to check air pressure in tires. Another contraption resembles headgear unlucky children with braces might have worn. And though the machines look clunky and the

tests remind me of sci-fi, they give Pitt docs the ability to diagnose eye disease more accurately and give Schuman other standards to test OCT results against.

Dilworth and Schuman grin each time they demonstrate a new machine. This feels like an engineer’s playground, yet Schuman does not think of himself as an engineer. He declares that he is a physician-scientist. He’s not interested in technology that doesn’t benefit patients.

And Schuman isn’t just known for his work on diagnostic technologies.

Ten years ago, while still at Tufts, Schuman was treating a patient who suffered from leukemia. The man—we’ll call him John Rudd—was in his 60s but not a prime candidate for glaucoma. Schuman wondered what



MARTHA RIAL

Schuman

it was about leukemia that caused Rudd to have glaucoma.

And, more urgently, he asked himself, *What causes glaucoma?* Schuman saw patient after patient with the haze of glaucoma setting in, but he had no answers for why they had the disease. That simply wouldn't do for Schuman—who is always looking to fill in the blanks. (Schuman is the kind of guy who needs to know how the DVD player works, his wife, Carole Schuman, reports.) So for years, he saved samples of eye tissue. He screened the tissue samples from his surgery patients (with their permission, of course) and compared them to eye samples from normal cadavers to see whether he could find a difference.

In most cases of glaucoma, the fluid in the eye does not drain into the body like it does in a healthy eye. By examining the trabecular meshwork—a network of channels that drain fluid from the eyes—Schuman learned there were basic differences between the meshwork in an eye with glaucoma and an eye without the disease.

## Schuman wondered what it was about leukemia that caused Rudd to have glaucoma.

Schuman started screening cells involved in the aqueous outflow of the eye. In every eye with glaucoma, a particular marker showed up—ELAM 1, or endothelial leukocyte adhesion molecule 1. It was never in eyes without the disease.

And he eventually figured out why Rudd had the disease: Leukemia cells cause basic changes in the trabecular meshwork that may be related to inflammation and healing.

Schuman's lab was the first to identify the marker that could indicate glaucoma at an early stage. He was able to decipher this with the help of a few students and a research associate. He knew they'd discovered something big but didn't have the time with his patient load to organize his data in a way that would be appropriate for publication.

Besides, he was more at ease in an OR than a lab. It was time that someone who knew her way around data came at the problem.

Enter molecular biologist Elizabeth Fini.

In 1995, Fini arrived at Tufts' medical school. The PhD always thought of herself as a student of wound-healing mechanisms, not someone particularly interested in ophthalmology. Although she came to the school to

research wound healing and the cornea, she often thought it was funny she was examining such a small entity when she could be studying a large organ like skin.

But Schuman talked her into sticking with the eye for a bit longer. Fini joined his project, and the amount of data astonished her. Hundreds of samples of the trabecular meshwork lined his freezer shelves. Schuman had harvested and collected the specimens for nearly a decade.

Fini watched Schuman in the OR, where the PhD took to heart the human component of their pursuit. She was inspired to dig deeper. Soon she was encouraging Schuman to think about the data in a different way, to try to understand the disease mechanism behind glaucoma. They eventually figured it out.

In the early stages of glaucoma, damaged cells lining the outflow encourage production of a molecule (NF-kappa B) that stimulates inflammatory cytokines such as IL-1 and ELAM-1. A damaged trabecular meshwork results in high intraocular pressure and optic nerve damage characteristic of the disease.

If a paper about a biological marker for glaucoma in itself is exciting, a paper reporting on a marker and a disease mechanism is outstanding.

Schuman and Fini's work landed the cover of the March 2001 issue of *Nature Medicine*. The abstract also appeared in *Nature*. Reviewers and reporters called to find out more.

After knowing about ELAM-1 for years, Schuman finally was able to reveal to the world a biological culprit behind glaucoma.

"Joel should be pretty proud of this," says Fini.

When asked how it felt to make that contribution, Schuman looks down and says, simply, "Great." Understanding the disease mechanism is a big step toward developing a better treatment. It means that maybe someday doctors like Schuman won't have to tell patients with glaucoma, *You can't drive anymore. Or, You're going to find it hard to continue your work as a painter.*

In 2002, Fini left Tufts for the University of Miami to become the scientific director of the Evelyn F. and William L. McKnight Vision Research Center and the Walter G. Ross

Chair in Ophthalmic Research. Schuman came to the University of Pittsburgh in 2003 to be the Eye and Ear Foundation Professor and chair of ophthalmology.

After I complete my tests, Schuman opens a door to what looks like a closet. Inside, the guts of a computer are splayed over a desktop. This is the future of OCT. Schuman says there are only two other machines of this caliber in the world: one in Fujimoto's lab at MIT and another at Tufts.

Massachusetts General Hospital, Duke University, the University of Miami, and the University of California, Davis, are each trying to develop an OCT prototype on this scale—which is 75 times faster and has three times clearer resolution than the instrument Dilworth used on me.

This prototype is designed to allow docs to see minute details of a living patient's eye, like how much oxygen and blood flow are present, in a way not possible using any other imaging technology. Schuman credits

the 15 members of his lab for doing "yeomen's work" to move this technology forward. He notes that colleague Gadi Wollstein, assistant professor of ophthalmology and director of Pitt's Ophthalmic Imaging Laboratories, has been the lead author and study designer on a number of "the most significant OCT studies over the past three years." Assistant professor of ophthalmology and bioengineering Hiroshi Ishikawa developed new algorithms for the OCT prototype. (Both men came to Pittsburgh from Boston with Schuman.) Larry Kagemann, research instructor of ophthalmology, joined the group recently after several years at Indiana University in the world's top ocular blood flow laboratory.

Schuman expects to detect a number of diseases with this new OCT.

But we'll have to watch for his lab's next big thing. At this point, Schuman is concentrating on getting the OCT prototype up and running smoothly.

"The cool thing is that we can provide cutting-edge diagnostics for patients as well as study the tools," Schuman says.

The cool thing is that Schuman is not done with being the first. ■