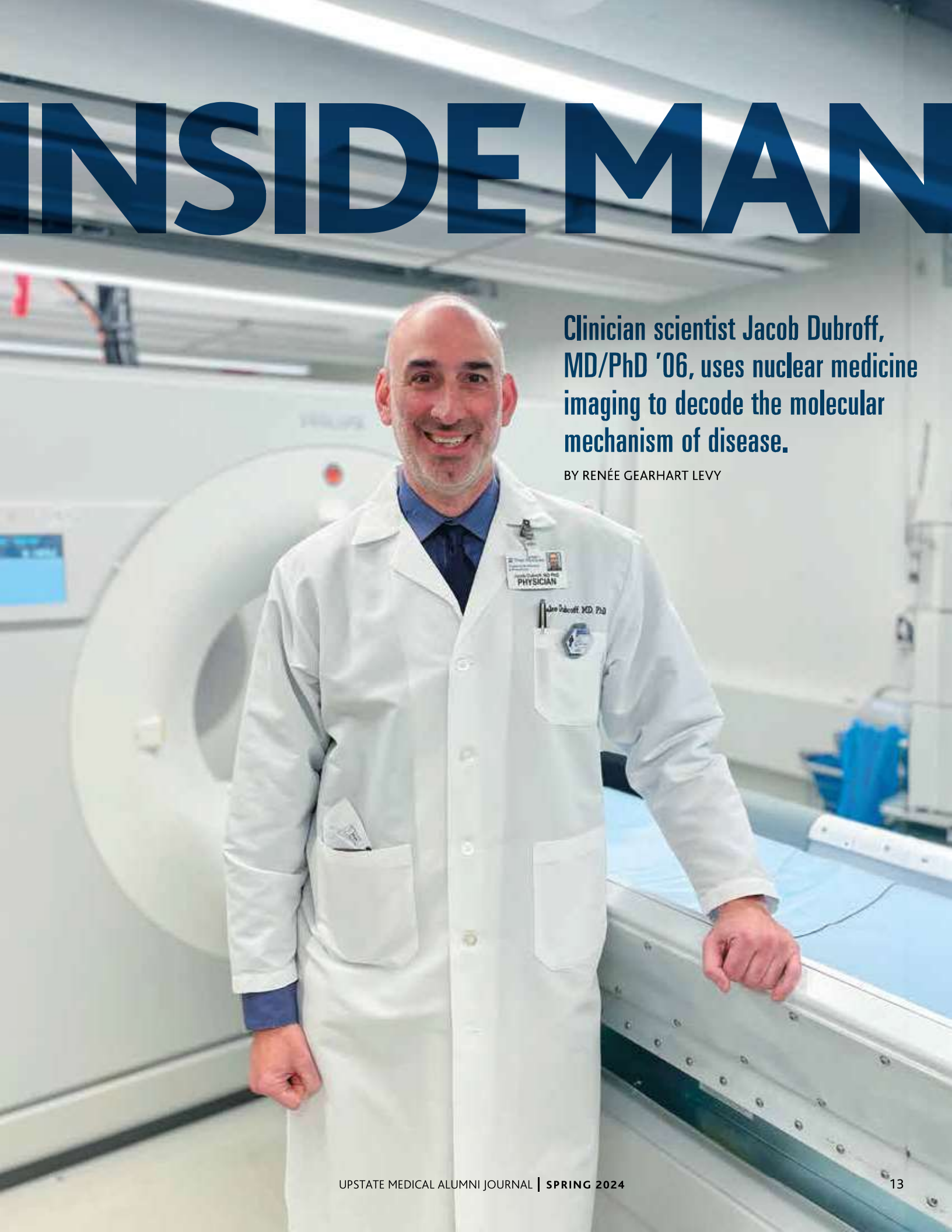
INSIDE MAN



Clinician scientist Jacob Dubroff, MD/PhD '06, uses nuclear medicine imaging to decode the molecular mechanism of disease.

BY RENÉE GEARHART LEVY

It's well-established that smoking cigarettes causes lung cancer. Many people who want to quit their cigarette habit turn to e-cigarettes, believing that vaping is less harmful. But research by Jacob Dubroff, MD/PhD '06, published last year in the *Journal of Nuclear Medicine* showed that e-cigarette users have greater lung inflammation than cigarette smokers and non-smokers, a unique inflammatory response that is different from cigarette smoking in younger, otherwise healthy individuals.

"It's a different beast altogether in terms of the inflammation happening inside the body," says Dr. Dubroff, a nuclear medicine specialist at the University of Pennsylvania Perelman School of Medicine and senior author on the study. "I fully expected the cigarette smokers to have more inflammation than anyone else."

In the first of its kind study, Dubroff used Positron Emission Tomography (PET) utilizing a novel radiotracer to compare lung inflammation between cigarette and e-cigarette users and a control group who had never smoked or vaped. "Inflammation in the lungs is difficult to identify early, and particularly to measure and to compare different types of behaviors," he says of the technology used. "The findings suggest molecular imaging may be uniquely poised to detect and measure the potential pathophysiologic harms associated with e-cigarettes, which have been touted as a safer vehicle for nicotine compared to traditional combustible cigarettes."

The idea for the study was germinated by earlier research using PET/CT to study brain receptor activity in cigarette smokers.

"Between the decriminalization of marijuana and the increase in vaping, it became more challenging to find people who only smoked cigarettes," Dubroff says.

With studies reporting that up to 40 percent of teenagers have tried e-cigarettes—and with two teenaged sons of his own—Dubroff became interested in studying the effects of vaping. He found a clinical partner, psychologist Reagan Wetherill, PhD, who was interested in the behavioral aspect, and received support for the pilot study from the National Institute of Drug Abuse, the National Heart, Lung, and Blood Institute.

"We know that e-cigarette usage has increased dramatically, particularly among adolescents and young adults. This could be a new population of patients that get cancer or other types of lung disease 20 years from now," he says. "We don't know, because we don't have the years of evidence on this behavior like we do with combustible cigarettes."

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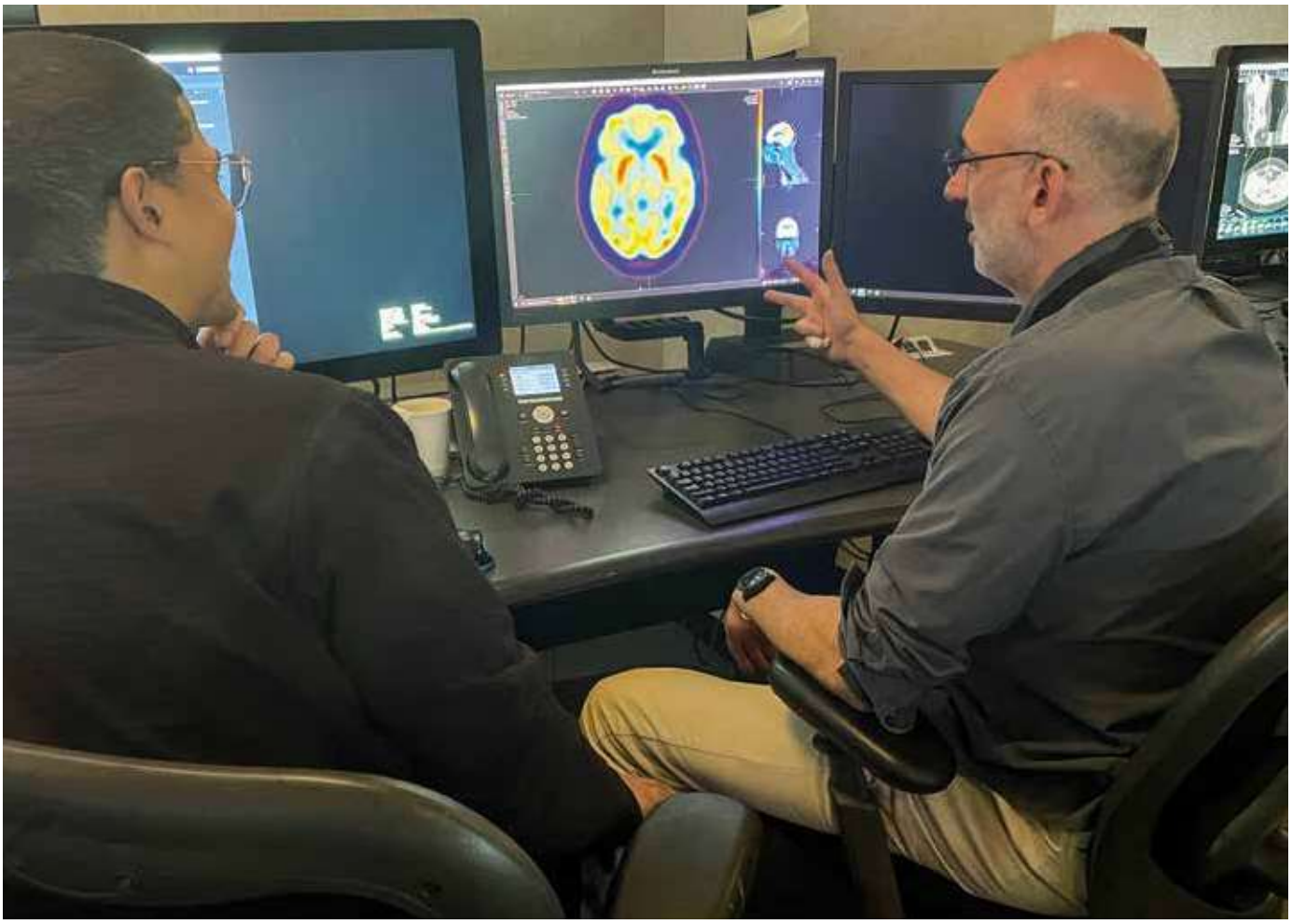
Dubroff has also conducted brain scans of e-cigarette and combustible cigarette users, unpublished research he's also excited about. "We're getting some really interesting insights," he says.

As a clinician scientist, Dubroff splits his time between patient testing—conducting nuclear stress tests, oncology scans, neuroscience imaging, and scans to detect infection—and research. Dubroff uses PET to better understand the molecular mechanisms behind conditions ranging from nicotine addiction and opioid use disorder to neurodegenerative diseases such as Alzheimer's and Parkinson's. His many publications include articles on imaging in addiction, cardiac sarcoidosis, pulmonary embolism in pregnancy, and various forms of dementia, among others.

"It's an exciting field making incredible advances with the continued development of more sensitive instrumentation that allows us to see smaller things that may have escaped us previously," he says. "There's always something new coming down the pipe."



Dr. Dubroff teaches a resident how to evaluate a brain FDG-PET study for a patient with memory complaints.

HOW SCIENCE IS MADE

Dubroff's first hands-on exposure with medical research began in the lab of Charles Hodge, MD, HS '74, former chair of the Department of Neurosurgery at Upstate Medical University. Dr. Hodge was a friend of Dubroff's father, Lewis Dubroff, MD, PhD, a Syracuse dermatologist. The younger Dubroff had just finished his first year as a biomedical engineering major at the University of Pennsylvania, and Hodge needed assistance with research using the new field of functional MRI technology (fMRI).

Hodge was conducting human studies using fMRI and Dubroff learned to process the complicated data from the brain imaging. "It was really neat to be doing that as an undergraduate," he says. "I don't know if that could even happen today."

The experience of working in Hodge's lab—which he did for three summers—had a profound impact. Being immersed in the research environment made Dubroff realize that understanding how research ideas develop was an important aspect in thinking about science. As a result, he picked up a second undergraduate major in the history and sociology of science at Penn's College of Arts and Sciences. He also began working on fMRI research at Children's Hospital of Philadelphia. "I used to scan my friends," he says.

Dubroff became more interested in medical research and its clinical applications than in engineering. His father had earned an MD/PhD, and although he had not conducted research in many years, felt his clinical work benefited from that scientific foundation. Dubroff enrolled in Upstate's MD/PhD program, where Hodge continued as a mentor. He completed his PhD in neuroscience, focusing his dissertation on brain plasticity under thesis advisor James McCasland, PhD, professor emeritus of neurobiology.

Although fascinated by the brain, Dubroff wasn't sure of his clinical direction. Neither neurosurgery or neurology seemed the right fit. And while he had imaging experience, radiology wasn't quite right either. "The people were really smart, but they weren't interested in the same kinds of questions I was," he recalls.

Dubroff spent a lot of time down in the stacks in the basement of the Health Sciences Library, reading papers and journal articles. "I started reading about nuclear medicine and this new modality called PET/CT used for brain imaging that was just coming out," he recalls. "I wasn't interested in all areas of radiology, but I was definitely interested in this."

He wondered if it was possible to only practice nuclear medicine and do research and was lucky to find a residency program at his alma mater, University of Pennsylvania, that would train him to do exactly that.

DRIVEN BY TECHNOLOGY

In the mid-1980s, there were only around 20 PET scanners nationwide and those were largely experimental. With the advent of PET/CT, researchers began redoing imaging trials to determine which modality was most effective. "What they found was that when you put the function of the PET scan on top of the anatomy of the CT scan, the PET/CT, you have a more accurate study," he says. "It actually changes the staging of a lot of cancers and can change how you manage a patient."

In other words, PET/CT was revolutionizing the field. As he was finishing his chief residency year, Dubroff had the opportunity to work with Caryn Lerman, PhD, emeritus professor of psychiatry at Penn and current director of the University of Southern California Norris Comprehensive Cancer Center, who was doing research on smoking behavior and needed a research partner to do imaging studies of the brain.

Although he hadn't previously worked in the area of addiction, Dubroff recognized smoking-related cancers as leading killers that were preventable. The prospect of a study that could impact that—and involved brain activity—was appealing.

Lerman had found that people metabolize nicotine at different rates, largely through a pathway in the liver. People who metabolize nicotine more slowly were also more successful at quitting smoking. Now she and Dubroff wanted to see what role brain receptors for nicotine played.

"We found that people with slower metabolism of nicotine—those most likely to be able to quit—also had fewer brain receptors available in the imaging studies," he says. "Perhaps the reason some smoking cessation therapies work or don't work is based on genetics and just how well your liver metabolizes nicotine."

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Since 2019, Dubroff has been part of the Penn PET Addiction Center of Excellence (PACE), created by psychiatry and radiology researchers to combine clinical research on opioid use disorder with PET neuroimaging in hopes of yielding mechanism-level discoveries for translating basic addiction science to the clinical care of patients suffering from opioid use disorder.

Dubroff says those efforts benefit from continuous advances in the radiochemistry of tracers and in the scanners themselves. "A

Dr. Dubroff during a press appearance explaining the results of his e-cigarette study.

typical PET scanner has a ring of 18–20 inches. We slide the patient through the ring to take different pictures," he explains. At PACE, Dubroff has access to a whole-body PET machine. "Instead of just looking at one spot and taking the static image, we can do dynamic imaging, acquiring data over time and looking at the whole body at the same time."

He's in the process of trying to figure out the best way to use these advancements in imaging and radiochemistry to help curb the epidemic of opioid overdose deaths. "We're approaching 80,000 deaths annually to opioid overdose, significantly exceeding traffic accidents and many kinds of cancer," he says.

Dubroff is studying whole-body scans of patients with opiate use disorder who are undergoing medication-assisted therapy, such as buprenorphine, with scans of non-opiate users. "Similar to the way the liver metabolizes nicotine, I'm looking to see whether there may be something physiologically that makes some people respond to opiates differently than others by how they metabolize synthetic opioid," he says.

At present, there are more questions than answers. "There's just so much data," he says. "We're trying to focus in on identifying what is the really important question that will allow us to understand this disease process. You can only do research if you have money, so we want to have the right question to pitch for funding."

A DRIVE TOWARD DISCOVERY

When Dubroff is not with a patient, conducting scans, or analyzing data, you might find him on the basketball court. At 6'6, it's not surprising he gravitated toward the sport growing up. After playing on his high school team, he was able to walk on to the University of Pennsylvania team as an undergrad and continues to play pick-up games with other former players at the historic Palestra, which is only a block from his clinic.

At the Penn School of Medicine, there's an annual spring faculty vs. medical student basketball game, a tradition Dubroff looks forward to. "I've been in that game for over a decade. The medical students stay the same age but each year I'm older," he says. "It's a fun, frustrating challenge."

He enjoys sharing his expertise with medical students, residents, and fellows in nuclear imaging off the court as well. "There's never a day that I don't have a trainee in some capacity," says Dubroff, who was honored as Nuclear Radiology Fellowship Teacher of the Year in 2020.

The biggest selling point for his field: the continuing potential for advancement that keeps things exciting. "Less than two years ago, a new tracer for prostate cancer was approved and was a game changer in terms of how we manage a lot of prostate cancer now," he says.

And then there's Alzheimer's disease. "Ten years ago, a patient suspected of having Alzheimer's could barely get a PET scan; it was considered experimental," he says. "Now there's a test to identify amyloid using PET. It's commercial and covered by Medicaid, and it's going to drive who gets what therapy."

With so many new developments, there's no room to rest on one's laurels. "As new tools develop, we gain a better understanding of what's going on in the body, and that leads directly to better patient care," he says. "I feel very lucky to be in a place where there's so much innovation and cooperation in terms of trying to figure out how to take care of patients. It just gets more exciting for me." ■