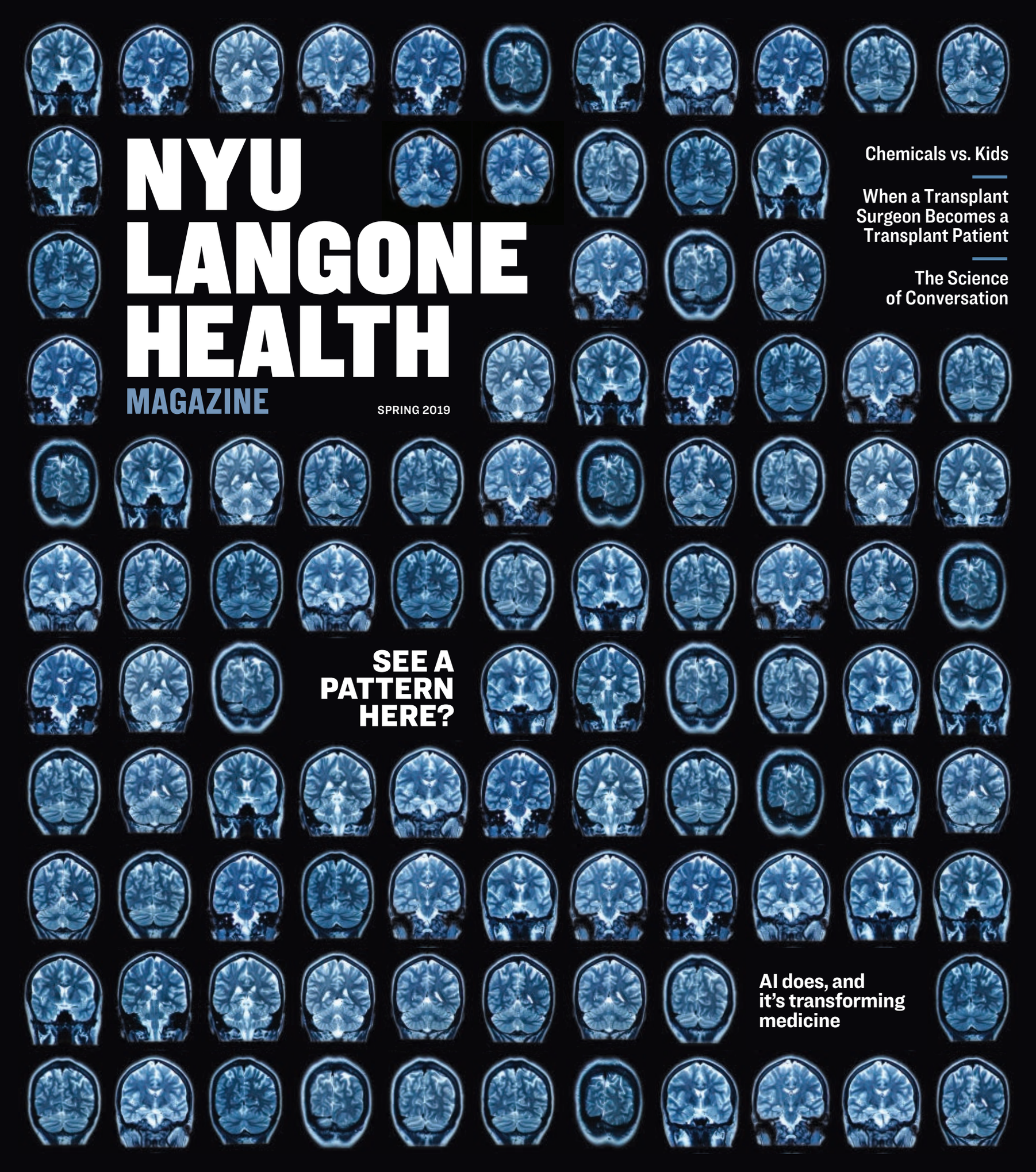

NYU LANGONE HEALTH

MAGAZINE

SPRING 2019

Chemicals vs. Kids

When a Transplant Surgeon Becomes a Transplant Patient

The Science of Conversation

SEE A PATTERN HERE?

AI does, and it's transforming medicine

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A Pattern of Trailblazing

Message from the Dean and CEO

JULIANA THOMAS

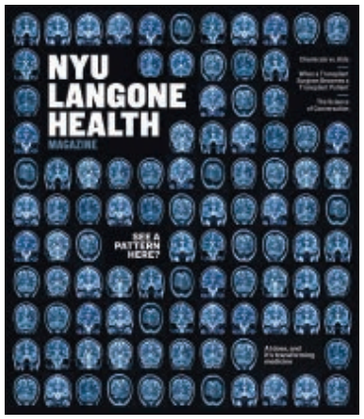
TEN YEARS AGO, NYU Langone Health became the first healthcare institution in New York City to implement "digital medicine" throughout its enterprise when it rolled out Epic, a state-of-the-art electronic medical record system that has eliminated paper and enhanced vigilance. Nationwide, one in five medical professionals report that their own system has saved the life of one or more patients. But there's certainly room for improvement. Each year in the US, an estimated 10 million medical errors occur, and as many as 12 million outpatients are misdiagnosed.

As you'll read in this issue, artificial intelligence, or AI, promises to revolutionize medicine by elevating the quality and safety of patient care. The more than 1 million medical records stored in NYU Langone's database, when stripped of any identifying patient information, provide a rich trove for our clinicians and researchers, and a host of them are mining this data to make better, safer decisions (page 14).

You'll also learn about two impressive trailblazers. Robert Montgomery, MD, DPhil, director of NYU Langone's Transplant Institute, has long been a pioneering surgeon, but recently he became a pioneering patient as well. Having established a protocol that enables transplant patients to accept organs from hepatitis C–positive donors, he became a recipient himself when he underwent a heart transplant last fall (page 26). Leonardo Trasande, MD, a pediatrician and epidemiologist, is spearheading several ambitious clinical studies to better understand the link between chronic exposure to everyday chemicals and childhood development (page 44).

To borrow a phrase from the cover story, "See a pattern here?" I do. These articles and others in this issue remind us that our community is fortunate to have many innovative, exceptional people. In different ways, they are making their mark by advancing medicine and improving healthcare.

Robert I. Grossman, MD, Saul J. Farber Dean and CEO



NYU Langone Health

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BRAD TRENT

Features


MATCH RESULTS
Congratulations, you have matched!

Scope

EMBRACING A FUTURE IN MEDICINE

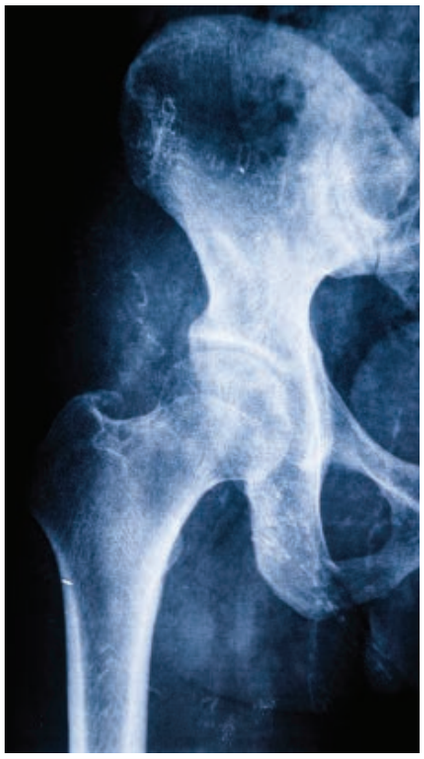
FOR NYU SCHOOL OF MEDICINE student Kimberly Khouri, this year's Match Day event on March 15—when fourth-year medical students nationwide learn their residency placements—was doubly gratifying. She matched not only to the specialty of her choice, but also to a program she describes as "a dream come true." This fall, she'll assume one of three coveted residency spots in plastic surgery at Harvard Medical School, which serves Boston's finest teaching hospitals. Khouri, who spent last July at Harvard for a subinternship, looks forward to the diversity of cases that makes the program "a mecca of medicine." A first-generation American, she is a second-generation physician: her father, a plastic surgeon, is from Lebanon, and her mother, a dermatologist, is from Cuba. "I am extremely grateful to my parents, siblings, mentors, and friends who have supported me along the way," says Khouri. "This is their dream come true, as well."

Photograph by **Joshua Bright**

Stat

9,500

Number of surgeries performed annually at NYU Langone Health's Sports Medicine Center.



A Game-Changing Surgery Scores Big

When a hip injury jeopardized Madison Packer's career as a pro hockey player, her team physician got her back on the ice and performing like a champion.

By Thomas Ranieri

Madison Packer has never been one to let obstacles get in her way. A forward on the Metropolitan Riveters, one of the four founding franchises of the National Women's Hockey League (NWHL), she started playing hockey at age three, joining boys' teams on which she played until her freshman year of high school. In her senior year, the Detroit native blew out her right knee. Nevertheless, a year after reconstructive surgery, as a freshman at the University of Wisconsin, she helped the Badgers win the 2011 NCAA Women's Ice Hockey Tournament.

Packer started with the Riveters in 2015, their first season. The following season, an opponent caught Packer from behind, causing her to fall awkwardly to her knees and tear the labrum in her right hip. She finished the year, but when a cortisone shot failed to ease her pain, Packer announced her retirement. The team's head physician, Guillem Gonzalez-Lomas, MD, assistant professor of orthopedic surgery, reassured her, however, that her playing days might well continue.

Dr. Gonzalez-Lomas is one of several physicians at NYU Langone Health's Hockey Center in the Department of Orthopedic Surgery. As part of NYU Langone's bustling Sports Medicine Center, the practice treats not only professional athletes, but also those who play recreationally, in youth leagues, and on college teams. Dr. Gonzalez-Lomas was a hockey player himself during his school days. "He appreciates the mental side of the game," says Packer. Dr. Gonzalez-Lomas believes that for elite athletes, sport is an important part of their identity, and they should stop playing on their own terms, not because they're forced out by an injury. "I felt that because Madison was very fit and tremendously motivated," he says, "it was just a matter of fixing a fixable problem."

In June 2017, Dr. Gonzalez-Lomas performed arthroscopic surgery on Packer's right hip. Through two small incisions, he inserted pencil-size instruments into the joint, reattached the torn labrum to the pelvic socket, contoured the rim of the femur, and restored the seal around the joint. "High-level athletes are able to play through a lot of pain," he says, "so by the time you operate on them, the repairs are a little more complex. This was the case with Madison because she had played through her injury."

The day after surgery, Packer says she felt like a new person, and she began riding a stationary bike for two hours a day—instead of the 30 minutes her surgeon had prescribed. By December, she was competing again. "The fixed hip feels better than the other one," she says. "I have a phenomenal surgeon."

Dr. Gonzalez-Lomas told Packer that, once again, she could play her heart out. She did just that. In 2018, the Riveters won their first NWHL championship, defeating the Buffalo Beauts in a dramatic 1–0 victory. Packer led the league in goals and was named an MVP finalist. The Riveters tweeted a photo of her holding the Isobel Cup aloft, with the words: "Retirement is the last thing on Madison Packer's mind."

MICHELLE JAY (RIGHT); ISTOCK.COM/FEELLIFE

A champion on both the collegiate and professional levels, Madison Packer is known for her power and tenacity. Dr. Guillem Gonzalez-Lomas, her surgeon at NYU Langone, describes her as “a born leader—on and off the ice.”

Getting a Word in Edgewise

An NYU School of Medicine study of duetting Alston's singing mice reveals brain centers that can coordinate conversations with split-second precision.

By Bahar Gholipour

Waiting your turn in a conversation is not just polite—it's an extreme exercise in timekeeping. It typically takes only a fifth of a second, or about half as long as a blink, for people to respond to another speaker. Anything shorter, you are talking over someone. Anything longer, you risk creating an awkward pause. "If you ever want to experience it for yourself, try waiting a full second in between conversational turns. It is extremely painful," says Michael Long, PhD, associate professor of neuroscience and physiology at NYU Langone Health's Neuroscience Institute.

However, awkward silences rarely happen, and in fact, we have often formulated our response before the other speaker finishes. Given the tight window for switching turns, it's a wonder that people don't interrupt each other more often. To find out what enables such precise turn-taking, Dr. Long has spent a long time listening to loud chirps of Alston's singing mice. These musical creatures, native to Costa Rica's cloud forest, sing to each other to announce themselves, entice mates, and negotiate territories. Barring occasional blunders, the mice are greatly skilled at waiting for each other to finish before immediately responding with their own song. "They're quite considerate," Dr. Long says.

In a new study published in *Science*, Dr. Long and colleagues found that the mice divide the task load between two brain regions. One area produces the songs unique to each mouse. "It's what allows them to get up on their hind legs and sing out who they are to the world: 'I am Ralph the mouse,' " Dr. Long says. Another area, called the orofacial motor cortex, or OMC, is the maestro orchestrating the mice's conversational duets. When the researchers slowed neural activity by mildly cooling the OMC, the mice produced a longer song. When the OMC was turned off entirely, the animals started to sing over each other.

"This is the first demonstration of the brain mechanisms behind coordinated vocal turn-taking in any mammal," says Dr. Long, who is now looking for similar mechanisms in humans. What he finds may offer a new

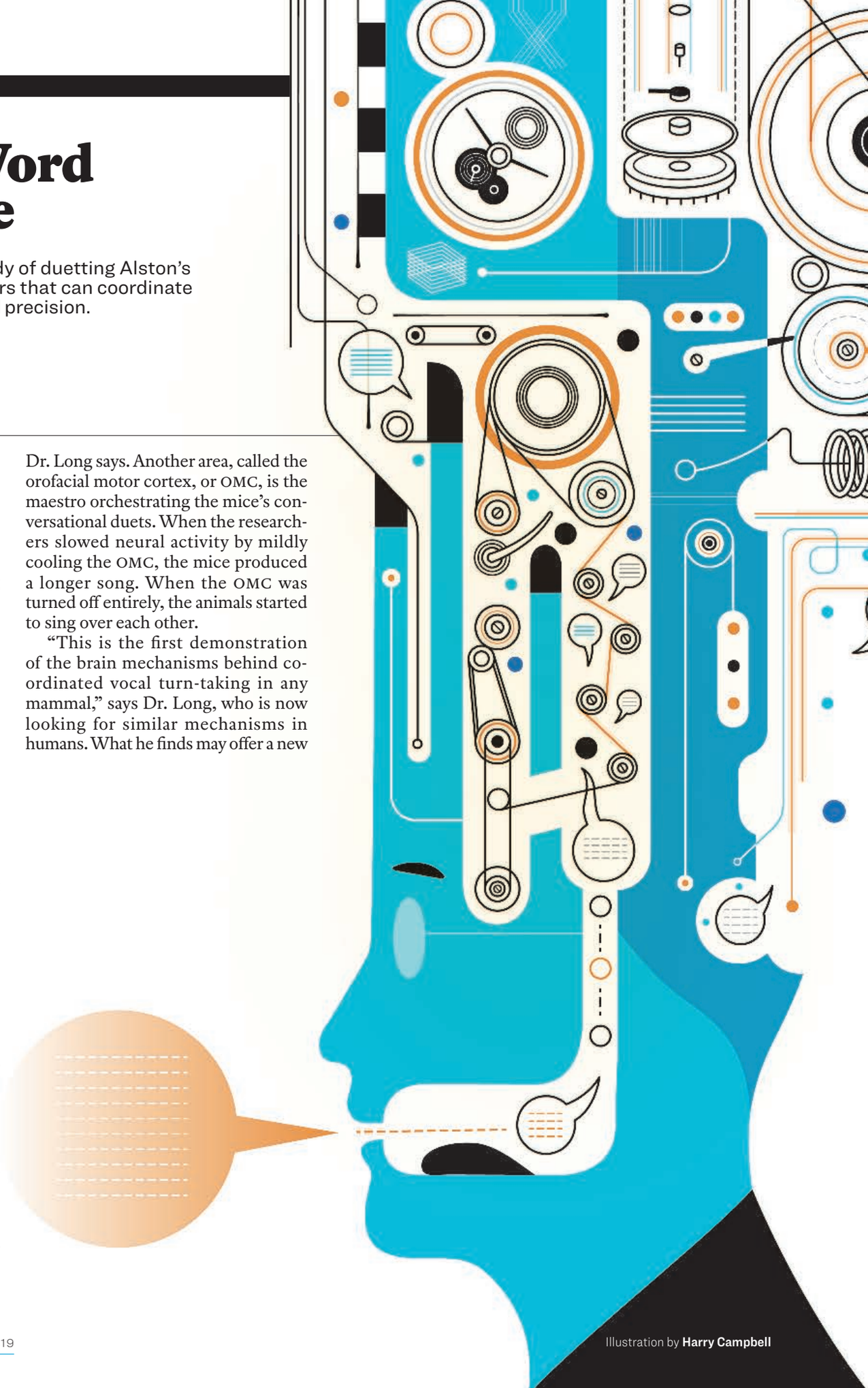
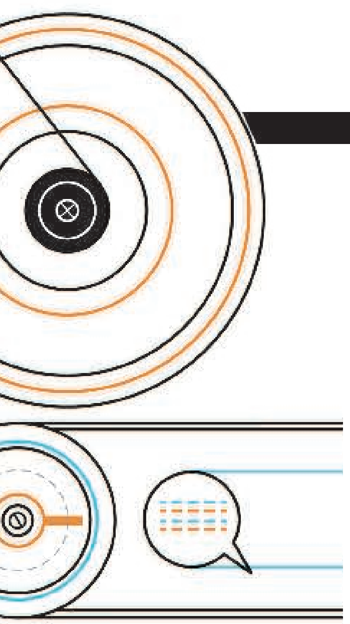
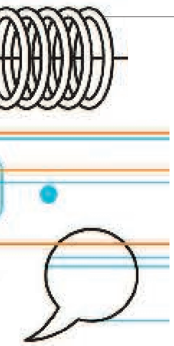


Illustration by **Harry Campbell**



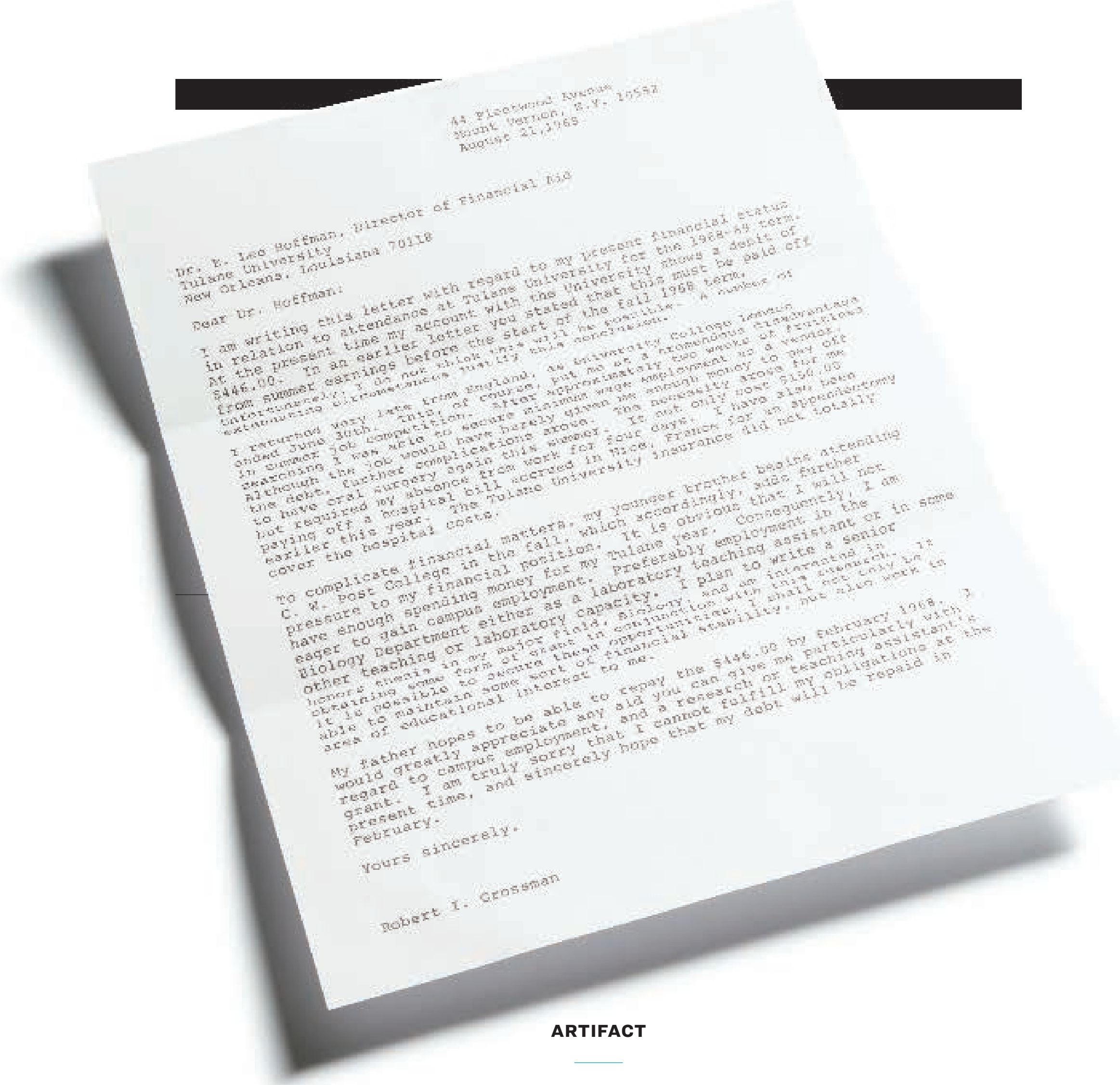


way of understanding communication problems in autism or stroke-related language deficits. Precise timing is a central component to speech, and not just in conversations. To produce just one word, the brain needs to orchestrate over a hundred speech-involved muscles on a 20-millisecond timescale.

Before studying social communication in singing mice, Dr. Long's laboratory had focused on another musical prodigy, the zebra finch. In 2008, Dr. Long and his colleagues showed that the pace of the birds' songs relies on a small area in their brains; when the area is cooled, the birds sing in slow motion. In a collaboration with neurosurgeons that was published in 2016, Dr. Long found humans, too, have an internal metronome: an area that, when cooled in people undergoing brain surgery, slows speech. "Instead of saying 'Monday,' they'd say 'Mooondaaaay,' " Dr. Long says.

Carrying on a conversation adds another layer of complexity to this sophisticated clockwork. It's the leap between learning to hit a tennis ball over the net and competing against another player, or learning to play the violin and performing with others in an orchestra. Although we practice conversation every day, "it's an exceptionally impressive act when we take a step back and see just how much skill is involved," Dr. Long says.

Just like any complex skill, conversational turn-taking is probably something humans hone through practice. "Even these mice can get in sync much better when they have known each other for a while," Dr. Long says.



44 Fleetwood Avenue
Mount Vernon, N.Y. 10552
August 21,1968

Dr. E. Leo Hoffman, Director of Financial Aid
Tulane University
New Orleans, Louisiana 70118

Dear Dr. Hoffman:

I am writing this letter with regard to my present financial status in relation to attendance at Tulane University for the 1968-69 term. At the present time my account with the University shows a debit of $446.00. In an earlier letter you stated that this must be paid off from summer earnings before the start of the fall 1968 term. Unfortunately, I do not think this will be possible. A number of extenuating circumstances justify this conclusion.

I returned very late from England, as University College London ended June 30th. This, of course, put me at a tremendous disadvantage in summer job competition. After approximately two weeks of fruitless searching I was able to secure minimum wage employment as a vendor. Although the job would have barely given me enough money to pay off the debt, further complications arose. The necessity arose for me to have oral surgery again this summer. It not only cost $150.00 but required my absence from work for four days. I have also been paying off a hospital bill accrued in Nice, France for an appendectomy earlier this year. The Tulane University insurance did not totally cover the hospital costs.

To complicate financial matters, my younger brother begins attending C. W. Post College in the fall, which accordingly, adds further pressure to my financial position. It is obvious that I will not have enough spending money for my Tulane year. Consequently, I am eager to gain campus employment. Preferably employment in the Biology Department either as a laboratory teaching assistant or in some other teaching or laboratory capacity. I plan to write a senior honors thesis in my major field, Biology, and am interested in obtaining some form of grant in conjunction with this research. If it is possible to secure these opportunities, I shall not only be able to maintain some sort of financial stability, but also work in area of educational interest to me.

My father hopes to be able to repay the $446.00 by February 1968. I would greatly appreciate any aid you can give me particularly with regard to campus employment, and a research or teaching assistant's grant. I am truly sorry that I cannot fulfill my obligations at the present time, and sincerely hope that my debt will be repaid in February.

Yours sincerely,

Robert I. Grossman

ARTIFACT

In Debt and Indebted

In August 1968, the average cost of a loaf of bread was 22¢; a new car, $3,407; and a new home, $25,000. But for Robert I. Grossman, then an undergraduate at Tulane University in New Orleans, the only amount that really mattered was $446. That was the sum of his debt for tuition, and until it was paid off, he would not be able to begin the fall semester. Writing to the director of financial aid in a letter shown here, he explained that "I do not think this will be possible," citing a number of extenuating circumstances that had set him back financially. He expressed hope that he would be able to repay the debt in February, after obtaining employment on campus. In response, the university granted him assistance, enabling him to complete his undergraduate education, enroll in medical school, and ultimately become the Saul J. Farber Dean and CEO of NYU Langone Health. Dean Grossman's experience as an impoverished student not only left him with a lasting impression, but also shaped his view that a medical school has "a moral obligation to help aspiring doctors fulfill their desire to serve humanity, unencumbered by overwhelming debt." At last year's White Coat Ceremony on August 16, he recounted his personal story to 102 incoming medical students who had gathered to mark the formal start of their own journey to become physicians. He shared their joy as they heard some historic news: NYU School of Medicine would become, from that point on, a tuition-free medical school for all MD students.

"No one is truly a self-made person," he reminded the students, as their family members looked on. "Everyone is connected in some way to individuals who have aided their careers or other aspects of their lives. One person can make a dramatic difference in another's life journey."

Photograph by **Devin Jarvis**

Stat

30,000

The number of genetic experiments that can be run daily—with 100% accuracy—in the GenomeFoundry@ISG thanks to robots. That's 10 times the number humans can handle.

Jef Boeke, PhD, (above) and Andrew Martin

Photograph by **Chris Payne**

By Nicole Dyer

Inside a DNA Factory

At GenomeFoundry@ISG, researchers employ robots, computers, and their own brain power to reengineer genes.

We love to quiz kids on what they want to be when they grow up, but these days, it's not exactly a fair question. By some estimates, up to 65% of grade-schoolers will ultimately have jobs that don't exist today. How do young people prepare for a constantly evolving marketplace? "That's a tough one," says Jef Boeke, PhD, director of the Institute for Systems Genetics at NYU Langone Health. Dr. Boeke himself is a pioneer in a field that barely existed two decades ago: synthetic biology, an emerging discipline employing industrial robots and computers (like the ones seen here) to reengineer DNA in living organisms. The potential applications are vast—everything from manufacturing new medicine and producing biofuels to cleaning up hazardous waste and advancing our understanding of genetics.

But as a kid, Dr. Boeke had his heart set on becoming a scuba diver. "I read all the magazines, memorized the decompression tables, and even bought all the gear," he recalls. So he was crushed when, in high school, he flunked an open-water certification exam because of a "tooth squeeze," an excruciating toothache induced by pressure changes. "It was one of the great disappointments of my life," he says.

He reoriented and, in college, gravitated toward biochemistry, where he began experimenting with chemical approaches to manipulating DNA. Fast-forward to the present, and Dr. Boeke now belongs to an elite international corps of synthetic biologists ("engineers trapped in the bodies of geneticists," as he says) working together to build a multicellular organism from the ground up, starting with the 16 chromosomes in baker's yeast. In 2017, Dr. Boeke's team graced the cover of *Science* with a historic package of papers documenting their progress: six fully reengineered yeast chromosomes so far.

His state-of-the-art laboratory, called the GenomeFoundry@ISG, wouldn't run without Andrew Martin, a scientific technologist. Part lab manager, part MacGyver, Martin not only specs out all the rarified equipment needed to splice, dice, and analyze DNA with factory-like efficiency, but he also serves as the resident troubleshooter. "People come to me all the time and ask, 'Hey, can you fix this or that?' " says Martin. "I love it."

Beyond that, he finds the lab's fast-paced progress thrilling. "Researchers used to be able to manipulate 1, 2, maybe 10 genes at a time," Martin explains. "At the GenomeFoundry, they can work on thousands of genes at once. The robots free up scientists to use more of their brains and less of their hands."

The Mystery of the Missing Rejection

Of the 40 face transplants performed worldwide since the procedure debuted in 2005, only two patients—both at NYU Langone Health—have yet to experience an acute rejection episode.

By Thomas Ranieri

In the months after 24-year-old Cameron Underwood of Yuba City, California, became the second person to receive a face transplant at NYU Langone Health early last year, something unexpected happened: nothing. Transplant patients are at greatest risk for an acute rejection episode during the first few months after surgery because the immune system may attack the donor's tissue. The skin is highly immunogenic—that is, likely to elicit an immune response—so face transplant recipients are believed to be even more susceptible to acute rejection than recipients of solid organs. But nearly a year and a half after Underwood's surgery, he has yet to experience this problem. The same is true for NYU Langone's first face transplant patient, Patrick Hardison, a firefighter from Mississippi, whose surgery was performed four years ago when he was 41 years old.

A definitive explanation for why both men have escaped the threat of tissue rejection is still unclear, but Eduardo D. Rodriguez, MD, DDS, chair of the Hansjörg Wyss Department of Plastic Surgery, who led the surgical teams for both face transplants, and Bruce Gelb, MD, director of the transplant unit, who devised the antirejection protocol, have an intriguing hypothesis. If it's confirmed, their novel approach to heading off acute rejections could change the standard of care for face transplant recipients everywhere and greatly improve these patients' quality of life.

Most face transplant recipients prior to Patrick Hardison had received a standard combination of steroids and antithymocyte globulin, a T cell–depleting agent, prior to surgery to tamp down the immune system. Surprisingly, the regimen had failed to prevent acute rejection in even a single patient. So, in 2015, when Patrick Hardison was preparing for surgery, Dr. Gelb, assistant professor of surgery, knew he had to try something different. Seeking a way to delay rejection for at least one year, Dr. Gelb turned to another immunosuppressant, rituximab, which is commonly used in high-risk kidney transplants. Unlike the T cell–killing agent, rituximab also kills B cells, some of which linger in the transplanted skin. "There was little downside to trying it," Dr. Gelb recalls, "so we administered a single dose to Patrick Hardison the day after surgery."

The fates—and faces—of Cameron Underwood (above right) and his donor, Will Fisher (above left), merged on January 5, 2018. At right, portraits spanning from March 2017 to November 2018 chronicle Underwood's transformation after a self-inflicted gunshot wound.

When Hardison went more than two years without an acute rejection episode or even a spike in antibody levels, the doctors began to rethink what had happened—or didn't happen. "A light bulb went on," says Dr. Gelb. "We suspect that rituximab removes some of the immunogenic cells from the donor's tissue. Adding that drug, while slowly reducing the immunosuppressants used for maintenance, may well account for our results."

Drs. Gelb and Rodriguez decided on the same protocol for Underwood, but with a different rationale. "For Patrick, our aim was to reduce the risk of rejection," notes Dr. Gelb, "but for Cameron, it was to prevent rejection entirely. Our initial results were unexpected, but they drove our plan the second time around."

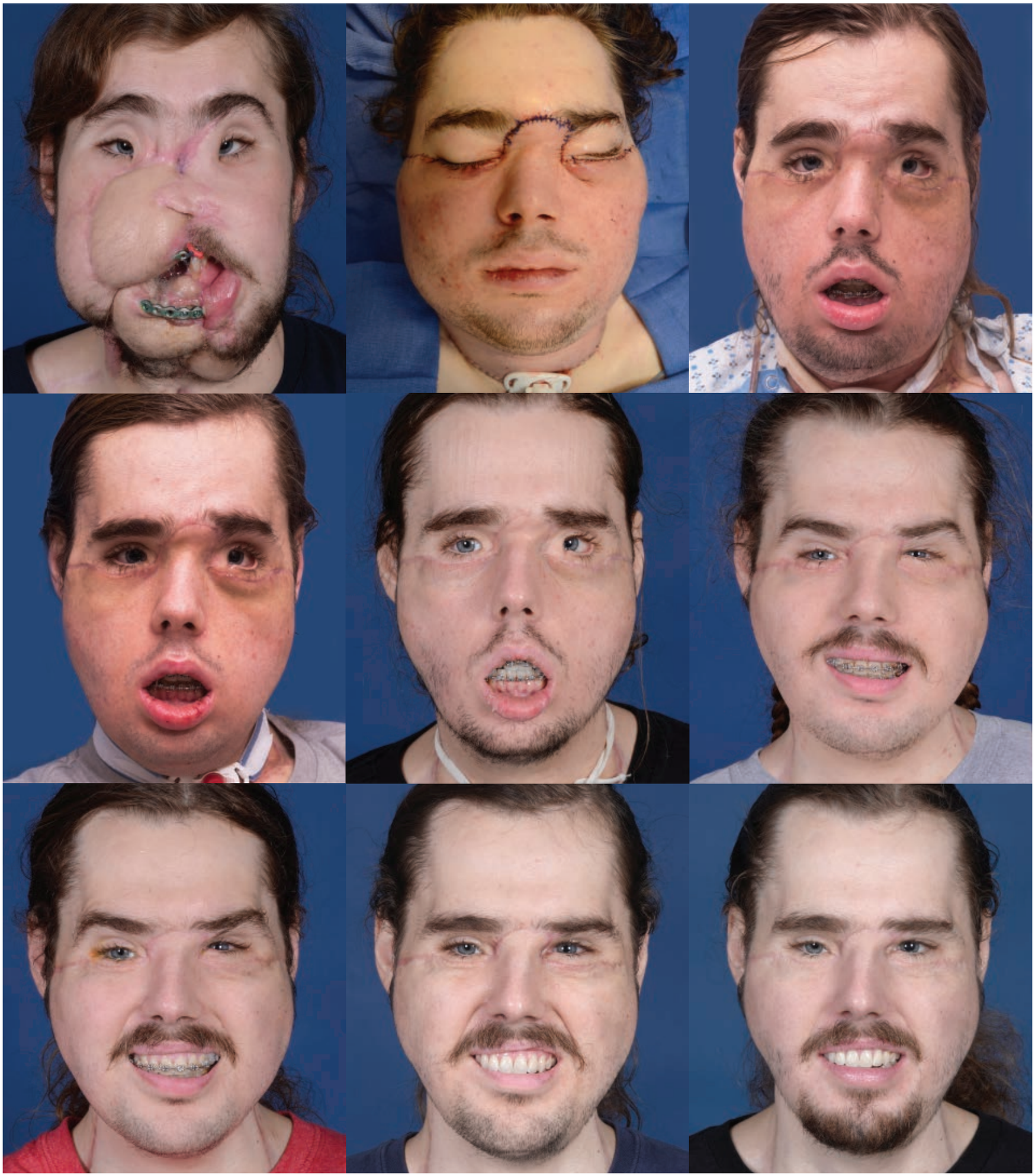
Dr. Gelb cautions that two successful outcomes do not constitute proof that rituximab is a game changer. But "given that the previous rate of rejection was 100%," he notes, "it's exceptionally promising."

The lifelong regimen of immunosuppressants prescribed for face transplant patients is known to have life-threatening risks, including malignancies, organ damage, and virulent infections. The first recipient of a face transplant lived for 10 years, but Dr. Gelb acknowledges that with so few cases performed, life expectancy can't really be estimated. What is known, however, is that preventing an acute rejection episode avoids high doses of the drugs needed to treat it.

"We now know that face transplants are technologically possible," says Dr. Rodriguez, the Helen L. Kimmel Professor of Reconstructive Plastic Surgery. "What we hope for at this point is that these patients can have longevity with their new faces."

COURTESY OF THE FISHER FAMILY (LEFT); COURTESY OF THE UNDERWOOD FAMILY (RIGHT)

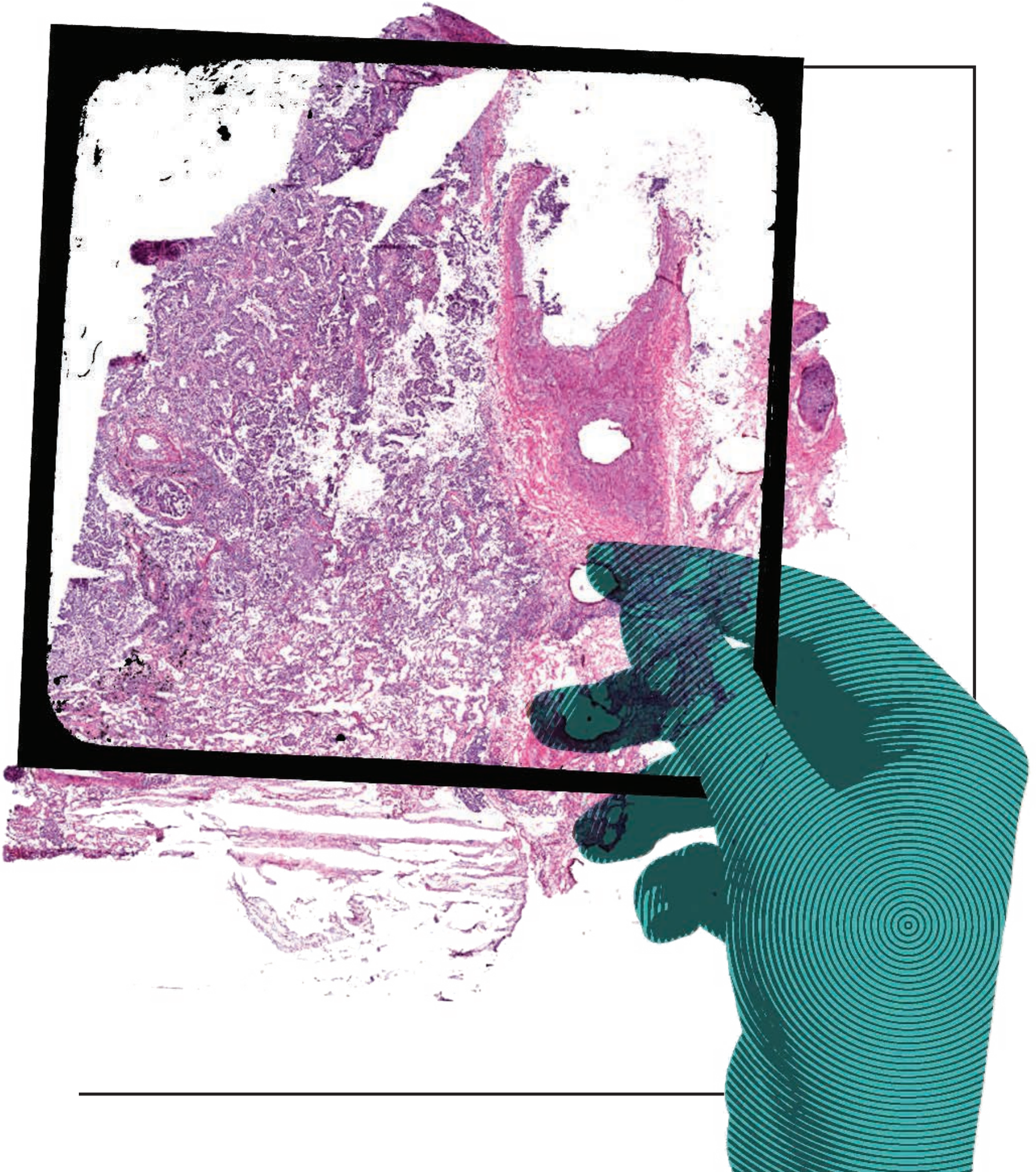
Photographs (right) by **Mary Spano**



An inside look at NYU Langone's latest efforts to harness the pattern-seeking power of **AI**.

WHAT ARTIFICIAL INTELLIGENCE CAN SEE THAT WE CAN'T—AND HOW IT'S IMPROVING MEDICINE

BY DAVID FREEDMAN ILLUSTRATIONS BY ANDY MARTIN



"Delaying the start of cancer treatment is never good. Using AI, we will soon be able to instantly determine cancer subtypes and possibly the mutational profile to start targeted therapies sooner."

ARISTOTELIS TSIRIGOS, PHD, ASSOCIATE PROFESSOR OF PATHOLOGY AT NYU LANGONE'S LAURA AND ISAAC PERLMUTTER CANCER CENTER

One day in 2017, computational biologist Aristotelis Tsirigos, PhD, strolled into the kitchen near his office in NYU Langone Health's molecular pathology lab to grab a cup of coffee, and met a new faculty member. When Dr. Tsirigos introduced himself as director of clinical informatics, his new colleague, Narges Razavian, PhD, perked up. She was also a computer scientist, albeit one with a slightly different focus. While Dr. Tsirigos was applying genomic data to uncover some of the complex cellular processes underlying disease, Dr. Razavian, assistant professor of population health and of radiology, was experimenting with ways to use artificial intelligence, or AI, in the clinic as a diagnostic tool. But like most researchers at the intersection of AI and medicine, her big challenge was finding enough patient data to properly train her software to recognize the telltale markers of pathology. As it happened, pulling together large databases of patient data was one of Dr. Tsirigos's specialties—and so a fruitful partnership was born.

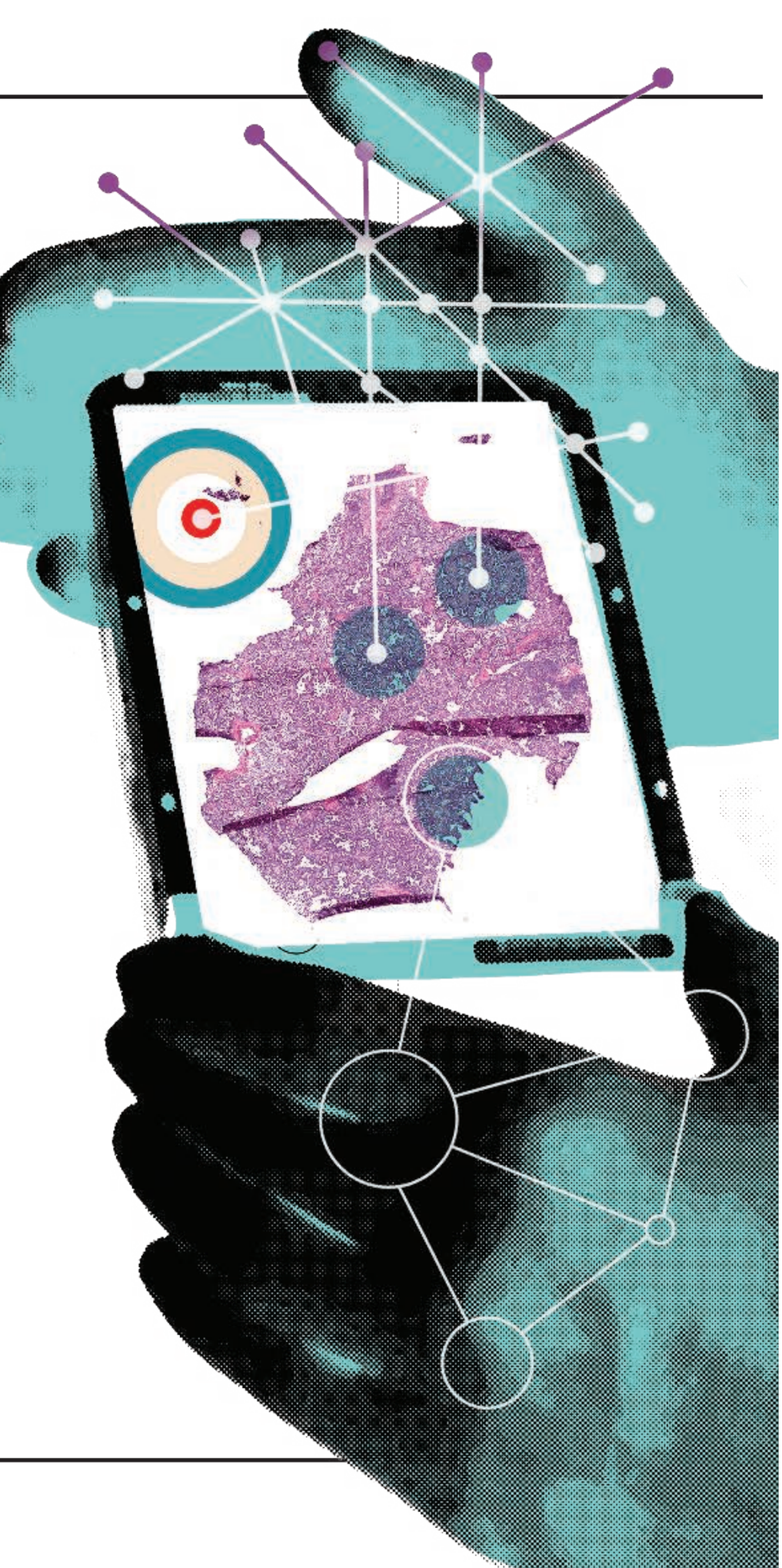
The result of that serendipitous encounter is an experimental AI program that can automatically diagnose two of the most common types of lung cancer with 97% accuracy, a rate that bests human pathologists. Even more remarkable, the system has taught itself to identify specific genetic mutations associated with lung cancer by analyzing pathology images alone—a process that ordinarily relies on expensive genetic tests and can take weeks. "Delaying the start of cancer treatment is never good," says Dr. Tsirigos, associate professor of pathology at NYU Langone's Laura and Isaac Perlmutter Cancer Center. "Using AI, we will soon be able to instantly determine cancer subtypes and possibly the mutational profile to start targeted therapies sooner."

Last September, Dr. Tsirigos and Dr. Razavian published their work online in *Nature Medicine*. Their paper, along with hundreds of others published in recent years chronicling the rapid ascent of AI in medicine, signals a looming paradigm shift in which intelligent machines are poised to make healthcare safer and more efficient. It's a prospect that could dramatically reduce the estimated 10 million medical errors that occur every year in the US, all while mitigating harmful delays and unnecessary testing. "The partnership between human clinician and machine can potentially be remarkably richer than either one alone," says Daniel K. Sodickson, MD, PhD, vice chair for research in the Department of Radiology and director of the Center for Advanced Imaging Innovation and Research.

AI is already helping gastroenterologists to spot hidden polyps during colonoscopies, ophthalmologists to diagnose retinal pathologies from eye scans, and psychiatrists to identify post-traumatic stress disorder from voice recordings. Some experimental AI systems are scanning electronic medical records and flagging undiagnosed conditions like heart failure and diabetes. Indeed, machine-learning algorithms are now 150 times as fast as humans in finding signs of stroke and other neurological events in CT scans.

What's more, the machines will only get faster as developers gain access to more clinical data. The so-called "neural networks" that power AI learn to make decisions autonomously by searching for patterns in vast pools of data—the more data, the better. Indeed, last February, the federal government launched a program called the American AI Initiative to facilitate data sharing among federal agencies and universities. The hope is to spur the development of machine-learning software in the US to keep pace with AI advances in China, where the absence of privacy laws gives the government unhindered access to hundreds of millions of medical records.

Among the many reasons AI projects are booming at NYU Langone is that researchers benefit from the medical center's trove of medical records stored in Epic, its electronic health records database. Stripped of any information that might reveal patients' identities, these records, along with medical scans, pathology reports, and even voice recordings, are now powering numerous projects intended to leverage neural networks for clinical good. Some look to be especially useful for diagnostic screening, for prompting a closer look at cases when a system's decision is at odds with a clinician's, and for flagging risks and problems that sometimes fly under the radar. With computers backing up clinicians rather than replacing them, patients are likely to end up with better diagnoses and treatment decisions, potentially at lower cost. "The system can support what we do or help us pay more attention to something we may have overlooked," says Leora Horwitz, MD, associate professor of population health and of medicine, and director of the Center for Healthcare Innovation and Delivery Science, who is helping to develop several machine-learning systems at NYU Langone. "But we still have to rely on our experience and what we see in the patient."



THE MUSCLE BEHIND AI'S BRAINY INSIGHTS

Meet NYU Langone's New High-Performance Computers, Big Purple and Skynet.

Artificial intelligence is all well and good until it melts the computers. Just ask Daniel K. Sodickson, MD, PhD, vice chair for research in the Department of Radiology. He recalls the day one of his radiology projects churned through so many X-rays that it burned out multiple hard drives on NYU Langone Health's old high-performance computer system. "We overworked it so much that the circuits actually started smoking," Dr. Sodickson says.

That problem is long gone. Last year, NYU Langone invested in two new, more powerful high-performance computing systems: Big Purple, which fuels AI projects like the lung cancer diagnosis algorithm of Aristotelis Tsirigos, PhD (see page 22); and Skynet for image-intensive radiology projects like Dr. Sodickson's fastMRI collaboration with Facebook (see page 24).

The two systems share physical space in a secure 5,500-square-foot data center with backup power and cooling systems in Piscataway, New Jersey. Both are configured to protect confidential patient data while crunching millions of data-hogging graphics. "A single MRI can have 65 million pixels of information, and our research involves tens of thousands of imaging studies, so you can see how the data add up," says Yvonne Lui, MD, associate chair for artificial intelligence in the Department of Radiology. Big Purple is capable of 18 quadrillion floating point operations per second, or petaflops, and Skynet is close behind at 17 petaflops. While these numbers can't compete with the 200-petaflop speed of Summit, the Department of Energy's top-ranked supercomputer, both high-performance computers are among the fastest at any academic medical center, says Martin Ossowski, PhD, director of high-performance computing at NYU Langone.

Skynet (a tongue-in-cheek nod to the humanity-hating AI in *The Terminator*) has already reduced the time required to train a typical neural network to perform a complex task from days or weeks to hours. Big Purple, meanwhile, runs AI algorithms at roughly twice the speed of its predecessor while also supporting the non-AI work of more than 700 researchers across the institution. "Big Purple and Skynet are a quantum leap forward for NYU Langone," says Dr. Sodickson. "Many AI projects we are doing now simply wouldn't be possible without them."

What happens to the brain after a concussion? AI may be the only way to find the answer.

Concussions are an ever-growing concern to those who suffer head trauma. They're also a concern to doctors trying to determine if a hit to the head has actually resulted in a concussion. Making a correct diagnosis is critical to keeping the patient out of harm's way long enough for them to recover. "If the impact isn't caught on camera or closely witnessed, we have to rely on the patient's own report and memory of the incident," says **YVONNE W. LUI, MD**, associate professor of radiology and associate chair for artificial intelligence in the Department of Radiology. "But self-reporting by concussion victims is almost by definition incomplete. Sometimes, all they can tell you is that they don't remember what happened, but their head hurts."

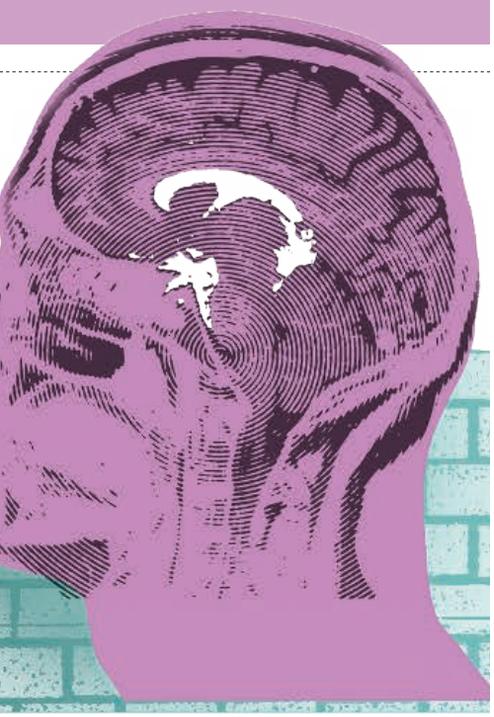
What physicians need is a more quantitative measurement of physical and metabolic changes in the brain after an impact, explains Dr. Lui. It's easy enough to scan the brain with a CT or MRI, but physicians don't really know what to look for in the resulting images. "Sometimes, the scan looks completely normal, even after someone's head has bounced on the ground hard," she says. "If it's a football player, he may end up back in the game in the fourth quarter. But it's hard to believe nothing has happened to his brain." More than 1.7 million Americans are diagnosed with a concussion each year, but Dr. Lui suspects that many of these traumas go undiagnosed, leaving patients at risk for more serious damage.

To provide a more quantitative diagnostic technique, Dr. Lui collaborated with Yao Wang, PhD, of the NYU Tandon School of Engineering, and they've developed an AI program that has learned to detect changes in patches of white matter throughout the brain. White matter, which is composed of nerve fibers that connect different parts of the brain and nervous system, stands out in scans and, in many cases, shows signs of alteration after head trauma. By allowing the software to study the results of some 200 research MRI brain scans of patients who experienced head trauma, along with physicians' determinations of whether or not a concussion occurred, the software learned to find patterns in the white matter that seem to be associated with concussion.

When the program analyzed the scans without the benefit of a corresponding clinician diagnosis, it arrived at the correct diagnosis 87% of the time. "Because of the uncertainties of diagnosing concussion, that's as high a rate of accuracy as we could expect," says Dr. Lui.

Beyond the potential clinical benefits of her system, Dr. Lui has applied an ingenious solution to the perennial data shortage that hampers many AI projects. Her project was limited to some 200 scans of suspected concussions. That may sound like a lot, but AI systems often require tens of thousands of cases to build reliable accuracy. To get the most out of the low number of samples, Dr. Lui took advantage of the fact that concussion damage to white matter is typically scattered throughout different parts of the brain. She divided individual scans into hundreds of pieces, with each patch serving as a unique sample of white matter. In this way, she could feed the system what equated to more than 100,000 samples. The approach seemed to work well for concussions and may prove a useful strategy for other AI systems in medicine. "A lot of cutting-edge AI research in medicine lacks access to, say, 50,000 samples," says Dr. Lui. "This approach may be a way to get meaningful results from smaller data sets in some other imaging applications."

Of course, any AI system is only as good as the data it churns,



and Dr. Lui recognizes that her own program must evolve as quickly as the science. "I hope and expect that within five years or so, we'll have a wholly different way of diagnosing concussion," says Dr. Lui. When the field gets to that point, she adds, the next generation of AI systems like hers will be ready to step in and learn from more and better case examples. "I think these systems will be able to recognize not only structural changes in the brain, but also metabolic changes that are harder to detect," she says. "That could help take the uncertainty out of diagnosing concussions."

Can a computer have a "Eureka!" moment?

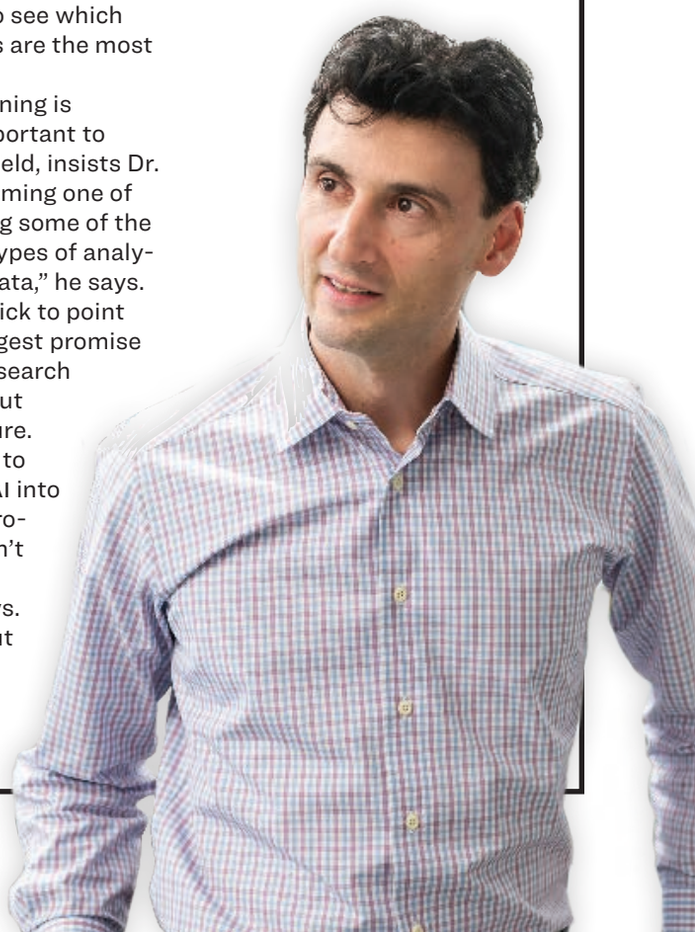
Understanding how genes behave in different cells and tissue types throughout the body is breathtakingly complex, but it's critically important to advancing our basic understanding of human biology. While basic-science researchers have become adept at identifying gene activity among large clusters of cells, pinpointing activity within individual cells has always been elusive. That is, until Moana tackled the challenge.

Moana is a machine-learning program that can infer the gene behavior of a lone cell by churning through massive databases of gene-related data extracted from larger cell clusters. The system (named after the favorite movie character of the daughter of one of the program's developers) recently emerged from NYU Langone's Institute for Computational Medicine. The institute's goal is to focus the power of advanced computing on basic medical research that's becoming ever more dependent on enormous sets of gene and other data. "There are amazing discoveries to be made in new large-scale data sets," says **ITAI YANAI, PHD,** the institute's inaugural director and professor of biochemistry and molecular pharmacology. "It's become central to medicine, even if you can't see it walking through the hospital corridors."

Whereas researchers were previously limited to investigating the impact of a single gene at a time on disease or development, Dr. Yanai's work has allowed sifting through whole strings of genes to pick out the most important patterns. "Not only can we look at all the genes," he says, "but we can track them to an individual cell to see which particular genes are the most important."

Machine learning is increasingly important to advancing the field, insists Dr. Yanai. "It's becoming one of the keys to doing some of the most complex types of analysis on a ton of data," he says. But he's also quick to point out that the biggest promise of AI in basic research is still floating out there in the future. "What we'd like to do is integrate AI into the discovery process, but we don't know how to do that yet," he says. "Can it figure out something new that we didn't even know to look for? We don't know yet if it can actually make novel discoveries."

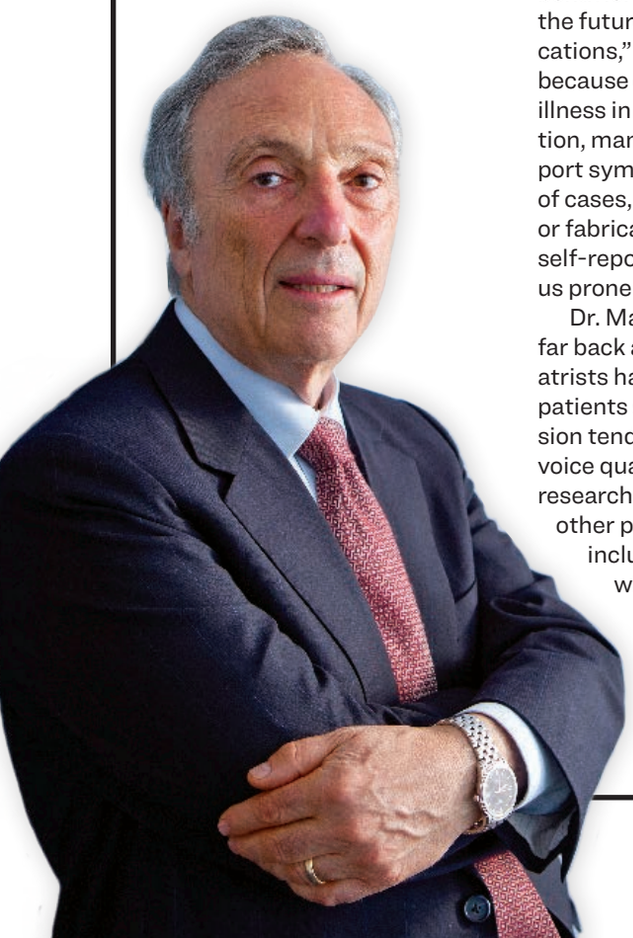
For now, basic-research discoveries will have to be made the old-fashioned way, but programs like Moana can at least crunch through the mountains of data that those new discoveries will undoubtedly spawn.



Hearing the signs of trauma in a patient's voice

In the 1980s, as speech-recognition software began hitting the market, psychiatrist **CHARLES R. MARMAR, MD,** was quick to adopt the technology. "I used one of the earliest consumer versions," says Dr. Marmar, the Lucius N. Littauer Professor of Psychiatry and chair of the Department of Psychiatry.

It's no wonder, then, that Dr. Marmar would think of enlisting voice-processing technology as a way to apply machine learning to one of the thorniest diagnostic challenges in modern psychiatry: post-traumatic stress disorder, or PTSD, a potentially debilitating psychiatric condition affecting one in 13 adults in the US. In spite of its impact, PTSD remains an elusive diagnosis. "Normally, it's done by interviewing patients and asking about nightmares, flashbacks, startle reactions, perceiving the world as dangerous, risk-taking behaviors, and being fearful of the future, among other indications," says Dr. Marmar. "But because of the stigma of mental illness in much of the population, many patients underreport symptoms. In a minority of cases, they may dramatize or fabricate them. Reliance on self-reported symptoms leaves us prone to error."



Dr. Marmar knew that as far back as the 1800s, psychiatrists had established that patients suffering from depression tend to have recognizable voice qualities. Since then, research has suggested that other psychiatric conditions, including PTSD, may carry with them unique vocal characteristics. Detecting those traits has always been a matter of the clinician's subjective perception in patient interviews. But seeing that machine learning was making inroads into all sorts of diagnostic challenges, Dr. Marmar considered the possibility that a machine-learning program could do the detection.

Dr. Marmar started researching the question and immediately ran into a statistical dilemma. "Classically, you need 10 subjects for each variable you examine," he explains. "But there are 40,000 variables in speech, which means I'd need 400,000 speech samples." For his research, Dr. Marmar only had access to 150 voice samples from the US military veterans who were serving as research subjects. But help came from the nonprofit research group SRI International, makers of the iPhone's personal assistant, Siri, which had developed new analysis techniques to study a large number of features in samples from a small number of subjects. In the end, their machine-learning software highlighted 18 vocal characteristics that helped distinguish between people with or without PTSD, coming to the same diagnostic conclusion as a clinician 89% of the time.

Eventually, a voice sample as short as five minutes will be needed to make a determination, and the sample could be recorded on a smartphone. "Right now, a patient has to spend 90 minutes with a psychiatrist just for an initial intake interview," Dr. Marmar says. "This software could make the process less burdensome to those patients." While it wouldn't provide the final word on who does or doesn't have PTSD, it could suggest which

patients may be most in need of a full diagnostic interview. "It's not meant to replace a clinical interview," explains Dr. Marmar. "But it could become an important element of the diagnostic process." In particular, he says, the program could be ideal for screening large populations that might be at higher risk for PTSD, including military personnel and first responders.

Dr. Marmar says that it's possible his system or another one like it might eventually be expanded and modified to screen for other psychiatric disorders, including depression, schizophrenia, and bipolar disorder. That could lead to an important improvement in medicine's ability to ensure that patients who most need psychiatric help are seen by a clinician.

▸ COLORECTAL CANCER

A second set of eyes for scoping out precancerous lesions

Colonoscopies prevent thousands of cancer deaths every year, but even the most skilled gastroenterologists can miss a potentially deadly polyp growing flush against the colon wall or nestled within its nooks and crannies. In fact, according to one large study published in 2017, one in eight suspicious growths are missed during the procedure. **SETH GROSS, MD**, director of clinical care and quality in the Division of Gastroenterology and Hepatology at NYU Langone, believes artificial intelligence may soon deliver a powerful solution. "Some of these polyps can be very subtle in appearance," notes Dr. Gross, associate professor of medicine. "If AI can help us with a second set of eyes when we're looking for them, that could save lives."

Dr. Gross has long embraced new technology in his clinical practice. He was among the first gastroenterologists in the country to use a 360-degree endoscope in clinical practice. Recognizing the vast potential of AI to improve outcomes for his patients, last year, he began using an experimental machine-learning program from a Chinese company that's trained on thousands of colonoscopy images to distinguish between healthy and diseased colons. During a colonoscopy, the software scans the same real-time monitor image that Dr. Gross sees and draws boxes around any parts of the image it deems a potential lesion. "That focuses my attention on a specific part of the image, so I can take a closer look," he says. He also provides feedback to help the company improve its software.

Is the system spotting polyps that Dr. Gross might not have found himself, or that a different practitioner might have missed? To answer that question, in June he will kick off the first multicenter clinical trial of the system to compare the rate at which precancerous polyps are found with and without the AI software. Anything that leads to even a small improvement in polyp detection is well worth pursuing, he notes. "When we find and remove a precancerous polyp, we've just interrupted one pathway to colon cancer," Dr. Gross says.

If the system proves helpful, says Dr. Gross, it will likely be made available widely to the field in a commercial version within two years. Along the way, he adds, it will probably be extended to assist with endoscopies intended to spot precancerous tissues in the stomach and esophagus, such as those associated with Barrett's esophagus, a condition related to reflux disease. "The software will continue to improve and get better at dealing with nuances in the appearance of lesions on different tissue surfaces," he says. "I think we're just seeing the tip of the iceberg in what AI systems like this can do for us in this field."

Giving pathologists supervision to diagnose lung cancer faster and more precisely

When they decided to collaborate on an AI project to diagnose lung cancer, **DR. ARISTOTELIS TSIRIGOS** and **DR. NARGES RAZAVIAN** both understood it was important to let physicians tell them where they needed help from AI, not the other way around. "We needed to hear about the big questions they want answered, and what matters most to patients," says Dr. Tsirigos, associate professor of pathology at NYU Langone's Laura and Isaac Perlmutter Cancer Center.

What they heard back was that patients who get a cancer diagnosis often want reassurance that their clinician has made the right call. "A patient may think their doctor is the best in the world," he says. "But they know cancer is complex, and they often have some doubts about what they're hearing from the doctor." The apprehension is well founded. The National Academy of Medicine estimates that as many as 10% of patient deaths can be attributed to misdiagnosis, and false positives can suggest that cancer is present when it isn't.

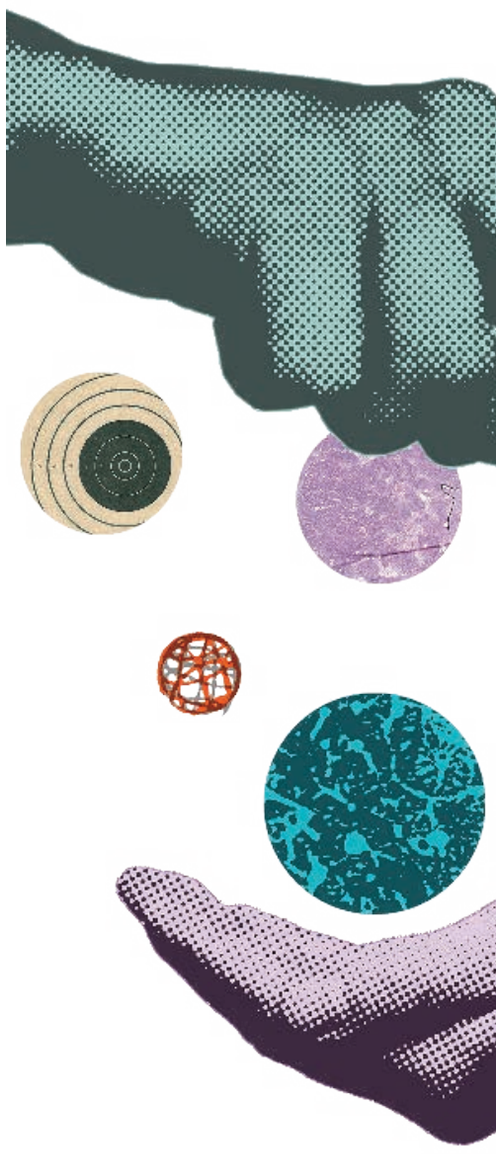
The researchers thought that machine learning could provide physicians with another set of eyes, so to speak, to wring correct diagnoses out of images. So they "trained" their AI system by feeding it images to which pathologists had already attached their diagnoses. This allowed the system to determine which sort of visual data in the image, such as texture, color, density, and the distance between cells, tended to be associated with which diagnosis.

Not only could their system distinguish between two of the most common types of lung cancer with 97% accuracy, but it was also able to correctly classify 83% of the tumors that pathologists had misclassified.

There was also a surprise: the system taught itself to identify six mutations linked to the most common form of lung cancer, adenocarcinoma. That's something human pathologists could never do from images. Identifying these mutations is critical for determining the best course of treatment for this rapidly metastasizing cancer, but normally it can be done only through DNA sequencing of a biopsy, a costly process that can take weeks.

What's more, no one really knows how the machine learned this skill. "From our findings, it seems the machine may be flagging subtle changes in a tumor's appearance," says Dr. Tsirigos. "But, really, we have no idea how it's recognizing the mutations." Right now, the software isn't always accurate in labeling the mutations, but if the accuracy can be pushed to 90%, the researchers plan to seek FDA approval to use the technology clinically and eventually adapt it to other types of cancer, such as melanoma.

Dr. Tsirigos estimates a three-year time frame before some version of the software rolls out in clinical use at NYU Langone and perhaps elsewhere, but he stresses that it will never serve as the sole source of diagnosis. "The goal is to at least help the doctors by providing a quick second opinion," says Dr. Tsirigos. "We can't even imagine that the doctor would ever be out of the loop."



Spotting hospital patients who require an extra level of vigilance

More than 90% of hospitals in the US now rely on electronic medical records. Digitization offers huge benefits: different care providers within a system can access the same patient record, creating opportunities to streamline care, and patients can review their medications and care plan. Indeed, electronic medical records have been shown to reduce costs and save lives. The downside, however, for both doctor and patient alike, is that care providers increasingly find themselves spending more time facing their computer screen than their patients.

LEORA HORWITZ, MD, and her colleagues in the predictive analytics unit at the Center for Healthcare Innovation and Delivery Science see AI as the perfect tool to help alleviate that burden. At the same time, it can perform tasks that are beyond the reach of human cognition, like finding hidden patterns in a sea of clinical records. "Patients can have problems, whether diagnosed or undiagnosed, that may seem small but aren't," says Dr. Horwitz. "Our AI system can help clinicians prioritize those problems."

The predictive analytics unit has already rolled out systems designed to comb through medical records and flag patients who are at higher risk for a range of conditions. One system looks for the telltale signs of potential heart failure, such as rapid heart rate and weight gain from accumulating fluid. Then, it analyzes a list of the patient's health challenges. If heart failure isn't on the list, the software flags that risk on the patient's electronic medical record. "Normally, heart failure is on the problem list for patients who are at high risk for the disease," says Dr. Horwitz. "But if the patient is new to our system, the records may not yet have transferred in, and clinicians may be focusing on other, more immediate medical issues." Almost all patients at risk for heart failure are eventually identified by clinicians, she notes, but the software provides a second line of defense.

Another system scrutinizes the medications, lab results, and clinical history of hospitalized patients with kidney disease to predict which ones are most likely to suffer kidney failure and require immediate dialysis. Under ordinary circumstances, dialysis patients undergo a surgical procedure to interconnect an artery and vein in their arm, forming a strong section of blood vessel, called a fistula, that can safely connect to a dialysis machine. Without a fistula, they are at higher risk of infection and clotting. With the AI system, an alert could help clinicians decide to schedule a patient for dialysis before the need becomes urgent, allowing enough time to place a fistula.

Dr. Horwitz emphasizes that the unit's efforts are not intended to offload any responsibilities from clinicians, but rather to augment their decision making. "In the torrent of data that clinicians are exposed to today, it's so easy for something to be overlooked," she explains. "We're building systems that bring some of that data to the top, so that clinicians can do what they think is appropriate with it."

Tapping Facebook's burgeoning AI expertise to make MRIs speedier and more comfortable

A few years ago, **DANIEL SODICKSON, MD, PHD,** received a message from a colleague who suggested a partnership with Facebook. His associate was familiar with the research of **FLORIAN KNOLL, PHD**, assistant professor in the Department of Radiology, who was using machine-learning systems to dramatically reduce the time it takes to capture an MRI image. He said Facebook was looking to support AI-related projects that would do some good in the world and thought it might be a good match, recalls Dr. Sodickson, vice chair for research in the Department of Radiology.

That call led to an ongoing collaboration between NYU Langone's Department of Radiology and the Facebook AI Research (FAIR) unit. The result is "fastMRI," an initiative that promises to make MRIs far more convenient and accessible to patients worldwide, and benefit NYU Langone patients before the end of this year.

An MRI machine transforms raw radio-signals generated by a magnetic field into sharp, detailed images of water-filled tissue and cartilage, including organs, that may not come through clearly in an X-ray. The downside is that it requires a patient to lie still inside a narrow tube for 15 minutes to an hour. For many patients, especially children, the elderly, and people who are claustrophobic, anxious, or in discomfort, remaining still for that long can be nearly impossible. Some may require sedation, while others simply refuse to get an MRI. The long imaging time also raises costs by limiting the number of patients who can be scanned in a day—one reason many rural regions can't make MRIs broadly available to patients. "Speeding up MRIs can open them up to new populations," says Dr. Sodickson.

Early on, he and his colleagues, including Michael P. Recht, MD, the Louis Marx Professor of Radiology and chair of the Department of Radiology, and Yvonne W. Lui, MD, associate professor of radiology and associate chair for artificial intelligence in the Department of Radiology, envisioned a way to apply AI to achieve those higher speeds: capture less raw data and use AI to fill in the gaps by inferring what's missing. The AI program knows how to flesh out the image in the same way you might know how to fill in gaps in an image of a traffic sign partially obscured by tree branches: by relying on extensive familiarity with the complete object.

To familiarize the program with MRI images, researchers from NYU Langone and Facebook's FAIR team fed the software the images from the fully anonymized knee scans from 1,000 patient exams. Since each scan generates multiple images, the total number of images provided to the system topped 1.5 million. Along with the images, the program was also given snippets of the radio-signal data that generated them. The system then "learned" how the sharp, detailed images could be derived from the fast-scan data. Achieving the current speed-up of a factor of five involves taking only one-fifth as much raw signal data, yet the software fills in the gaps so well that radiologists can't tell the results apart from those of full scans.

Facebook's FAIR group has been essential to the effort, notes Dr. Sodickson. "We have some truly top-notch experts here at NYU Langone, but it's very difficult to stay on top of every aspect of the burgeoning AI field," he says. "Besides helping to design and run the process of 'training' the system to fill in the missing data in the images, Facebook's experts also hunted down advances in AI algorithms for other applications that helped improve the results." (Facebook provided assistance

with no expectation that the company would benefit, or that NYU Langone would share any identifiable patient data.)

The AI-enhanced MRIs Dr. Sodickson and his colleagues hope to roll out this year are five times faster than current conventional MRIs, but he says the fastMRI team hopes to eventually improve the scanning speed by a factor of 10. "Our progress has been steady," he says.

▸ HEARING

Making things clear with cochlear implants

In 2015, **SUSAN WALTZMAN, PHD,** and colleagues invited a physician-scientist from Belgium to speak at an NYU Langone conference on programming cochlear implants. Dr. Waltzman, codirector of the Cochlear Implant Center, wanted to hear more about AI-based software the Belgian group had developed to make the devices easier to tune.

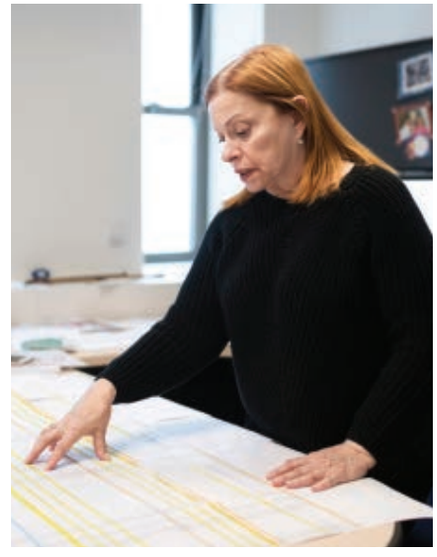
The researchers were struck by what they heard. "We were all impressed by the potential for this technology to dramatically improve programming methods," says Dr. Waltzman, the Marica F. Vilcek Professor of Otolaryngology–Head and Neck Surgery.

More than 40,000 adults and 25,000 children in the US have cochlear implants. The device picks up sounds and transmits them as electrical signals to implanted electrodes that stimulate the auditory nerve in the inner ear. Because the damage to the auditory nerve varies from person to person, every cochlear implant must be individually programmed to provide the best outcome. To do that, an audiologist usually tries different settings on the implant, noting the patient's response. "There hasn't been a standardized, objective method, and patients may not always end up with the desired result," Dr. Waltzman says. In addition, patients who receive an implant can return 10 times or more in the first year for adjustments.

To reduce that burden, Dr. Waltzman and colleagues embarked on a multicenter clinical trial of the new AI-based technique. In this study of 100 patients, an AI program ties into the implant to monitor the signals received by the auditory nerve. Based on a large database of information from previous cochlear implant patients, the software knows what the optimal received signals should be to produce the ideal result for a given patient. The AI software autoadjusts the way the implant converts sounds to signals until it achieves the best match.

The trial started in early 2018 and will end this September. Dr. Waltzman points out that among patients in the trial who previously experienced the conventional implant-tuning procedure, more than three-quarters reported preferring the technique. For patients getting a new implant, the new approach has cut the number of required readjustment visits in the first year by more than half.

Dr. Waltzman expects the new process to become widely available late this year, adding that the NYU Cochlear Implant Center is already making it available to cochlear implant patients outside the trial who have not done as well as expected with their implants. "We've been using the same approach for more than 30 years," she says. "It's very exciting to be able to offer better outcomes, a better patient experience, and fewer visits to the center."



The Life and Death and Life of Dr. Robert Montgomery

A pioneering transplant surgeon becomes a pioneering transplant patient.

BY KENNETH MILLER PHOTOGRAPHS BY BRAD TRENT

Transplant surgeon Robert Montgomery, MD, became a pioneer in his field despite a rare, progressive cardiac condition that would prove fatal without a heart transplant.

One night in September 2018, transplant surgeon Dr. Robert Montgomery died.

Again.

He was sitting on a hotel bed in Matera, Italy, where he had traveled for a medical conference, and was about to get undressed when the palpitations hit. He shouted to his wife, who ran in from the bathroom just as his face hit the stone floor, blood spraying from a gash in his cheek. His heart stopped. Then, after 60 long seconds, the cardiac defibrillator implanted in his chest delivered the shock that brought him back to life.

Dr. Montgomery's wife, Denyce Graves, struggled to keep her own heart rate in check as she helped him back to bed and pressed a washcloth to his wound. This was not the first time the 58-year-old professor of surgery and director of NYU Langone Health's Transplant Institute had died and been revived; he'd endured several such episodes during the past three decades. But it happened again as the couple waited for an ambulance, and twice more at the tiny local hospital. The staff there, he quickly realized, were ill equipped to treat his condition. The next morning—against medical advice—he signed himself out and flew home with his wife and a physician friend, who carried syringes full of resuscitation medications supplied by the worried Italian ER doctors.

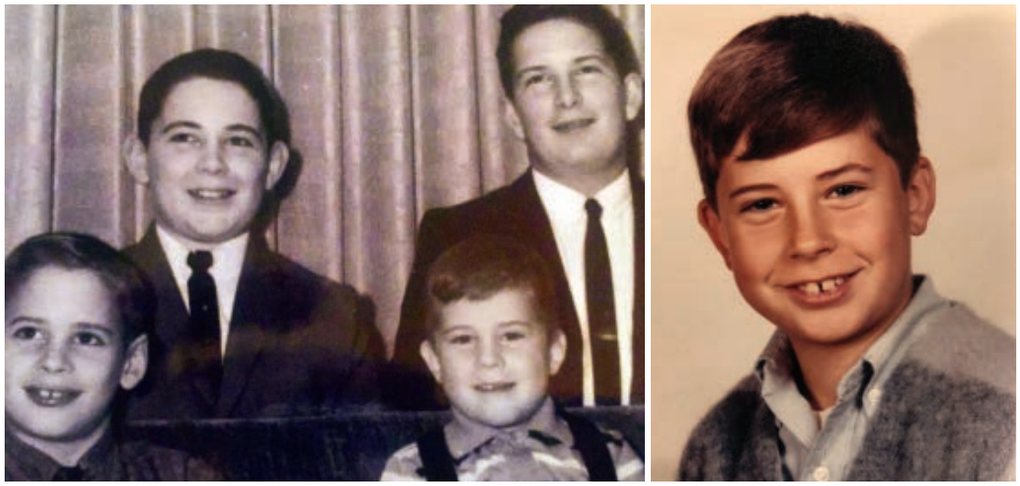
In New York, Dr. Montgomery met with the heads of NYU Langone's heart transplant team: Nader Moazami, MD, surgical director of heart transplantation and mechanical circulatory support, and professor of cardiothoracic surgery; and Alex Reyentovich, MD, medical director of the Heart Transplant Program and associate professor of medicine. Until recently, neither had known that their boss had a disorder that might make him their patient. Dr. Montgomery suffered from familial dilated cardiomyopathy, a rare, progressive disease of the heart muscle that weakens its pumping ability and causes dangerous arrhythmias. He'd managed to become a renowned kidney transplant surgeon nonetheless, keeping his illness at bay with medications, electronic implants, and sheer willpower. Yet, over the past year, a string of terrifying incidents, of which this was only the latest, had shown that he would need more to survive. "We all agreed he was in serious trouble," Dr. Moazami recalls.

Although his life-threatening symptoms qualified him for priority status on the transplant list, Dr. Montgomery knew how difficult it could be to get a new heart. His uncommon size (six feet one) and in-demand blood type (O) made him a tough match. Moreover, as with every other organ, there simply weren't enough to go around. In 2018, some 114,000 Americans needed an organ transplant, but only 36,500 received one; each day, an average of 20 patients died while waiting. About 4,000 people were desperate for a heart, but fewer than half that many hearts became available.

Under Dr. Montgomery's leadership, however, the Transplant Institute has been pioneering innovative protocols aimed at improving those numbers. Among the most promising is the use of organs infected with hepatitis C (HCV). The deadly virus, carried by an estimated 3.2 million Americans, attacks the liver, typically causing no symptoms until the damage is severe. New antiviral medications, introduced over the past five years, have made HCV curable in up to 98% of cases, without the grueling side effects of older, less effective drugs. If the virus is detected early, these newer therapies can often eliminate the need for a liver transplant. A growing body of research suggests that they can also make it safe to transplant organs of all types

Heart transplant surgeon Dr. Nader Moazami (right) with his boss and patient, fellow transplant surgeon Dr. Robert Montgomery.

As a young boy growing up in Philadelphia, slow to read and wildly energetic, Montgomery's heedless behavior got him kicked out of parochial school. "The nuns used to say, 'Bobby doesn't believe the rules apply to him,' " he recalls.



A progressive cardiac condition affected three of the four Montgomery brothers. From left to right: Lawrence had a heart transplant in 1996 at age 39; Richard succumbed to the disease in 1987 at age 35; Robert, now 59, received a heart transplant in January; and John, now 69, is unaffected. Far right: Dr. Montgomery, age 8.

COURTESY OF THE MONTGOMERY FAMILY

ROBERT MONTGOMERY'S comfort with risk emerged early, but it took a tragedy to harness it for a larger purpose. As a young boy growing up in Philadelphia, slow to read and wildly energetic, his heedless behavior got him kicked out of parochial school. "The nuns used to say, 'Bobby doesn't believe the rules apply to him,' " he recalls. Then, when he was 13, his father, a mechanical engineer in the aerospace industry, was diagnosed with cardiomyopathy, which doctors mistakenly attributed to a viral infection. His condition deteriorated rapidly, and he suffered three cardiac arrests over the next two years. The last one left him in a chronic vegetative state for several months before his death, at 52.

With his three older brothers away at college and his mother reeling from the loss, 16-year-old Bobby had to grow up quickly. He discovered a passion for medical science, particularly organ transplantation—fueled, in part, by frustration over his father's inability to obtain a new heart. (At the time, 50 was considered too old to qualify.) During his premed studies at St. Lawrence University, he spent a summer doing aid work in Africa. After graduation, he returned to the continent on a fellowship to study the interface between Western and traditional medicine. The close personal bonds between African healers and their patients would inform his own approach to doctoring. "He's incredibly caring toward his patients," says Brigitte Sullivan, executive director of the Transplant Institute.

He went on to medical school at the University of Rochester, and then to Johns Hopkins for his residency. One night during his internship, he received a call from his sister-in-law: one of his older brothers had died of cardiac arrest at 35 while waterskiing. Suspecting that an inherited disorder was the culprit, Dr. Montgomery sent tissue samples from his brother's and father's hearts to his old pathology professor, who confirmed his fears. He decided to undergo tests himself. On the treadmill, his heartbeat

from HCV+ donors.

Because HCV is most commonly transmitted through shared needles, using these organs may be one way for some good to come out of America's devastating opioid epidemic, which killed more than 49,000 overdose victims in 2017. Almost 1,500 HCV+ organs were transplanted last year—triple the number for 2013. Still, they constituted just 4% of total transplants, and most were implanted in people who were already HCV+. (Overdose-death donors as a whole now account for over 13% of solid organ transplants, up from 1% in 2000.) Only a handful of transplant programs have adopted them, and many potential recipients remain unwilling to accept them. As a result, more than 40% of donated HCV+ organs are discarded.

Dr. Montgomery, for his part, had no hesitation. As he often told his patients, any transplant requires weighing the risks against the potential rewards. "I'll take any heart you can find," he told his team. "I don't care if the donor has a needle in their arm."

In 24 Hours, One Life Lost, Another Saved

SEPTEMBER 20-21, 2018

THURSDAY

3:35 am

Transplant surgeon Dr. Nader Moazami receives word that a donor heart is available from an overdose victim in their 20s.

4:00 am

Dr. Moazami notifies his patient, Dr. Robert Montgomery, that a compatible donor has been found for him.

7:45 am

Transplant surgeon Zachary Kon, MD, takes a chartered plane from Teterboro Airport in New Jersey to a neighboring state to procure the donor heart.

9:57 am

Dr. Montgomery is prepped in OR #8 in the Kimmel Pavilion, just across from the OR in which he himself performs surgery.

11:12 am

Dr. Moazami and fellow surgeon Deane Smith, MD, make the first incision and start removing the tangle of wires and capacitors from Dr. Montgomery's old implants.

12:35 pm

Dr. Kon removes the donor heart and places it in a sterile plastic bag containing a preservative solution that will keep it viable for the next six hours.

went wild, and he almost passed out.

So, in 1989, Dr. Montgomery became the first practicing surgeon in the world to receive an implantable cardiac defibrillator—a device that had just been developed at Johns Hopkins. In those days, the procedure required open-heart surgery. A generator the size of a soda can was placed in his abdomen, powering a pair of large capacitors attached to the outside of his heart. The apparatus made it painful to wear a belt—but worse, it threatened to dash his dreams of becoming a transplant surgeon. (He'd decided to focus on abdominal organs, because heart surgeons of that era typically performed transplants only as a sideline.) "We'd like you to take a few years off and do some research," his chair of surgery told him. "Let's see how this thing progresses."

Dr. Montgomery, in 2009, speaking with family members of a patient who underwent kidney surgery at the Johns Hopkins Transplant Center in Baltimore, Maryland. As the center's director, he gained a reputation for his trailblazing efforts to get more organs to people who needed them.

With his pregnant first wife, Dr. Montgomery set off for the University of Oxford to pursue a doctorate in molecular immunology. Soon after arriving, he heard a crash outside his apartment. Running to the street, he found a car turned upside-down with a baby strapped inside and a woman screaming on the pavement. He climbed in through the window and extricated the baby. Then, he felt a blow like a baseball bat slamming against his chest as his defibrillator discharged, triggered by his racing heartbeat.

At that moment, he realized that he could never resume his surgical career, in which steadiness under pressure was the most basic job requirement, unless he learned to control his response to stress. "I had to completely remodel my brain and not allow my body to react," he explains. Like a self-taught Zen master, he began to monitor his emotions and his flow of adrenaline, forcing himself to grow calmer as a situation grew more challenging.

In 1992, having earned his doctorate, Dr. Montgomery returned to Johns Hopkins and was cleared to finish his training in general surgery and later in multiorgan transplantation. During his surgical fellowship, he helped develop the first laparoscopic kidney procurement technique. The innovation made recovery easier for donors, facilitating donations of live-donor kidneys, which last much longer than those from cadavers. By 2003, he'd become director of the transplant program at Johns Hopkins, where he gained a reputation as a trailblazer in efforts to get more organs to people who needed them.

One of his innovations was the "domino" kidney transplant, which occurs when several people who need transplants have friends or relatives who are willing to donate but aren't compatible; a chain of surgeries is arranged in which each would-be donor is matched with a compatible recipient, with "altruistic" donors, who are willing to give a kidney to anyone, filling in the gaps. An eight-way swap in 2010 landed Dr. Montgomery in the *Guinness Book of World Records*. He also helped develop a protocol combining kidney and bone marrow transplants to prevent rejection of donor organs in immune-incompatible patients and eliminate the need for immunosuppressive therapy. He was

ALGERINA PERNA/BALTIMORE SUN/MCT VIA GETTY IMAGES

2:00 pm — Dr. Kon returns to Teterboro Airport, and then takes an ambulance to NYU Langone.

2:08 pm — The surgeons place Dr. Montgomery on a heart-lung bypass machine and begin removing his diseased heart.

2:26 pm — Dr. Kon delivers the donor heart to the OR.

2:46 pm — Dr. Moazami places the donor heart in Dr. Montgomery's chest and starts connecting it to his circulatory system.

4:01 pm — Dr. Moazami shocks the new heart to make it start beating again.

6:27 pm — Dr. Montgomery recovers in the cardiac intensive care unit. He becomes one of 35 patients at NYU Langone—and one of 3,408 people in the US—to receive a heart transplant in 2018.

FRIDAY **2:30** pm — Dr. Montgomery leaves his hospital bed, assisted by his wife Denyce Graves.

also among the first transplant surgeons to promote the idea of using HCV+ organs, after the new generation of antivirals proved capable of quickly clearing the virus.

Recruited to NYU Langone in March 2016 to found the Transplant Institute, Dr. Montgomery (along with Brigitte Sullivan, who accompanied him from Johns Hopkins as executive director) brought together transplant specialists from all disciplines under one roof, enabling them to pool skills and insights without the territorial barriers found at many institutions. A slew of new hires from across the country enhanced the institute's capabilities. The kidney transplant program soon added a pediatric group. Dr. Moazami, who formerly headed the heart transplant program at the Cleveland Clinic, where he helped develop a range of novel surgical and device-based approaches to heart failure, led NYU Langone's first heart transplant procedure in January 2018. The institute's first lung transplant followed just weeks later, and its first pancreas transplant some months after that.

Dr. Montgomery also launched several initiatives to identify potential donors more swiftly and to ensure that potentially viable organs often rejected for transplantation didn't go to waste (including those infected with HCV or HIV). Within two years of his arrival, NYU Langone had increased the number of organ transplants from fewer than 50 to more than 280. Its heart transplant rate, or the number of transplants each year divided by the number of patients on the waiting list, was five times the average for the New York region. Its wait times for all organs was the shortest—an average of 36.3 days for a heart, versus 66.1 across the metropolitan area.

However, when Dr. Montgomery went on the waiting list in September 2018, those statistics were scant comfort. No one could say whether he would survive long enough to benefit from his own breakthroughs.

As Dr. Montgomery waited in a patient room at the Helen L. and Martin S. Kimmel Pavilion, tethered to vital signs monitors, he had time to reflect on his vulnerability—something he had largely avoided doing during the course of his extraordinarily active life. From the day he was diagnosed, he'd been determined to prove that his illness could not defeat him. Yet, he'd never known when the next crisis would hit. His antiarrhythmia medication had ruined his thyroid. His defibrillator's batteries needed replacing every few years, requiring major surgery. When the leads wore out, they began triggering shocks whenever he lifted his kids. He'd eventually gotten a smaller, more modern device installed, but much of the old hardware remained in his chest.

To defy his disease, Dr. Montgomery had taken up strenuous pastimes in exotic places—bow hunting in Argentina, fly-fishing in Tanzania. Even there, however, escape was only provisional. In 2012, researchers supported by his family's charitable foundation had isolated the genetic mutation responsible for his type of cardiomyopathy. Dr. Montgomery's older son and daughter, as well as his late brother's two daughters, proved to have it, and all were implanted with defibrillators. (Another brother had already undergone a heart transplant and is still healthy at 62; the remaining brother is not affected.) Later that year, Dr. Montgomery was on a mountain in the Andes when his defibrillator went off, knocking him facedown in the snow. His son helped him hike to safety. From that point on, he rode in the jeep instead of climbing, but he refused to give up his adventurous trips. "I had to set an example for the rest of the family," he says. "I wanted them to know you could have this and still live a full life."

But his resistance had begun to fail. In 2017, back in Argentina, he contracted a drug-resistant strain of pneumonia. Near death, he was placed on a ventilator. Luis Angel, MD, professor of medicine and of cardiothoracic surgery, and medical director of the Lung Transplant Program, flew down and rushed him to NYU Langone, where he spent weeks recovering. That October, he went into cardiac arrest while watching a Broadway show with his family. This time, his implanted device initially failed, and he needed prolonged CPR before he came back to life. Afterward, his defibrillator was modified to administer a stronger shock, and he was fitted with a pacemaker. Then came the incident in Italy.

Now, here he was, yearning for a reprieve like so many of his patients over the decades. In the future, he thought, he could tell them truthfully that he knew how they felt.


"Every patient is a VIP in my mind. They're all someone's father, mother, husband, wife, son, daughter."
NADER MOAZAMI, MD

"To me, it's a thrill to do research that can have an impact around the world. Anything I can contribute, as a doctor or a patient, I'm all in."

ROBERT MONTGOMERY, MD, DPHIL

Dr. Montgomery receives a visit from his son, John, and daughter, Elizabeth. Both children inherited their father's heart condition and rely on implantable defibrillators to safeguard against sudden cardiac arrest. Bottom: Dr. Montgomery with Drs. Alex Reyentovich (left) and Nader Moazami.

THE HOPED-FOR CALL came at 4:00 a.m. on September 20, just five days after he was admitted to NYU Langone. "We have a donor," said Dr. Moazami. "Heroin overdose, in their 20s, hepatitis C+."

Dr. Montgomery didn't pause. "Let's go," he said.

Within a few hours, Zachary Kon, MD, assistant professor of cardiothoracic surgery and surgical director of the Lung Transplant Program, was in a neighboring state, procuring the donor's heart and preparing it for transport. Meanwhile, Dr. Moazami was in an OR at NYU Langone with Deane Smith, MD, assistant professor of cardiothoracic surgery and associate director of heart transplant and mechanical circulatory support, opening Dr. Montgomery's chest. It took an hour to remove the tangle of wires and capacitors that remained from his old implants. Around 2:00 p.m., when Dr. Kon's chartered plane landed at Teterboro Airport, the two surgeons placed their patient on a heart-lung bypass machine and began to carefully remove his heart.

By the time Dr. Kon walked in, with the donor organ in a wheeled cooler, his colleagues were ready to begin the transplant. For Dr. Moazami, the fact that the man under his knife was not only his boss but also his friend was not a particular cause for anxiety. "Every patient is a VIP in my mind," he says. "They're all someone's father, mother, husband, wife, son, daughter. And I was confident in our team." It also helped that he had smuggled himself out of Iran as a teenager, made it through college and medical training on his own, and held the hearts of hundreds of other men and women in his hands. Like Dr. Montgomery, he had trained himself to respond to stress with intense calm.

At 2:46 p.m., Dr. Moazami lifted the new heart—healthy and strong, despite the virus that lurked in its cells—and placed it in the recipient's thoracic cavity. At 6:09 p.m., nearly seven hours after the surgery began, he and Dr. Smith were closing up the incision. "Good job, everyone," Dr. Moazami said. "Thanks for everything you've done."

Afterward, one of the nurses approached him with tears in her eyes. "Dr. Montgomery did my daughter's kidney transplant," she said. "I hope he'll be all right."

TOP: COURTESY OF THE MONTGOMERY FAMILY; BOTTOM: CAITLIN OCHS

CAITLIN OCHS

Dr. Montgomery visits a transplant patient recovering from surgery just a few months after his own transplant surgery.

He was all right. Although his new heart had some rhythm problems at first, they were resolved with medication. Dr. Montgomery went home 10 days later. By then, he'd tested positive for HCV, as expected, and a course of medication had cleared the virus. Less than a week after his discharge, he returned to work half-time. "You can't slow him down," says Dr. Reyentovich, who had suggested that he wait longer. Soon, Dr. Montgomery was back to his usual long hours at the office. He even began doing cardio exercises as part of his recovery program at Rusk Rehabilitation. "For the first time in years, I can get on a treadmill and run," he marvels.

However, eight months after his surgery, Dr. Montgomery's life has not quite returned to normal. Like most transplant recipients, he takes a triple-drug immunosuppressant cocktail to ward off rejection; a dozen more medications each day to prevent infections, to which the immunosuppressants make him vulnerable; and pills to prevent coronary artery disease in his new heart. He'll be on some version of this regimen, with periodic biopsies to make sure it's working, forever. (The median survival for a transplanted heart is at least 12 years.) One of the immunosuppressants causes a hand tremor—a minor annoyance for most patients, but not for a surgeon. The effect typically wears off after a few months, but if it doesn't, he plans to switch to a different drug.

Still, Dr. Montgomery is eager to pick up the scalpel again as soon as safety allows. He's grateful for the gift in his chest, provided by a grieving family, and he's glad for the chance to prove that the risk he took in accepting it can benefit many people other than himself. Everyone who receives an HCV+ organ at NYU Langone (about half of all heart recipients) does so as part of a clinical trial—one that, so far, has shown striking results. "No transplant patient has failed to respond to the hepatitis C therapy we've given," says Ira Jacobson, MD, professor of medicine and director of hepatology, who led pivotal early studies of the new antivirals and helped design the Transplant Institute's treatment protocols. "The virus is suppressed very quickly."

"To me, it's a thrill to do research that can have an impact around the world," Dr. Montgomery says. "Anything I can contribute, as a doctor or a patient, I'm all in."

IMMUNOTHERAPY FOR

BY KAREN HOPKIN

PHOTOGRAPHS BY JONATHAN KOZOWYK

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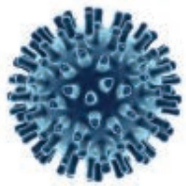
HIV

At NYU School of Medicine, researchers are closing in on a therapeutic vaccine that could one day yield a functional cure for a global epidemic.



In the mid 1990s,

as the first wave of life-extending therapies for HIV began to reach the clinic, microbiologist Nathaniel "Ned" Landau, PhD, was puzzling over why some people infected with the virus never fell ill, even without medications, while others seemed immune to infection altogether. As a young scientist at the Aaron Diamond AIDS Research Center in New York City, he'd been studying how HIV slips into CD4 helper T cells—immune cells whose job is to rally other immune cells to fight off infections. It was clear that HIV grabs onto CD4 cells by attaching to a receptor protein on their surface, but that recognition was not enough. The virus needed another trick to fully infiltrate the cell.

The mystery went unsolved until 1996 when, in an unprecedented episode of academic confluence, Dr. Landau and his research partner, Dan Littman, MD, PhD, now the Helen L. and Martin S. Kimmel Professor of Molecular Immunology at NYU School of Medicine, announced the discovery of a second CD4 receptor, called CCR5, that also mediates HIV entry. The scientists tied five other labs in a nationwide race to publish their findings first, collectively confirming an ingenious two-step locking mechanism that permits HIV to ease its way inside the immune cells.

The discovery ignited a wave of excitement in the research world, but its clinical implications were even more stunning. Within months, Dr. Landau and another Aaron Diamond colleague, Richard Koup, MD, revealed that a mutation in the gene encoding the CCR5 coreceptor could confer immunity to HIV infection. Some of the patients who appeared immune to HIV, they found, were in fact missing the gene responsible for the CCR5 coreceptor. Remarkably, even people with only one copy of the defective gene had an edge over HIV: while they were still vulnerable to infection, they tended to stay healthier longer than those who did not have the mutation.

Disabling CCR5, it turns out, is not the only ticket to taking advantage of basic biological mechanisms to thwart HIV. "That discovery led to lots of research to try to understand whether other things can make people resistant to HIV infection and how the body fights against HIV in general," Dr. Landau says.

Nearly three decades later, Dr. Landau, now a profes-

For the past two decades, Nathaniel "Ned" Landau, PhD, has sought to understand the immunological secrets of people infected with HIV who naturally suppress the virus without the aid of medications.

Dr. Landau examines a plate of "Vero cells," a lineage isolated from an African green monkey in 1962 and commonly used to study viral replication.

sor of microbiology at NYU School of Medicine, is zeroing in on a therapeutic vaccine he hopes will supercharge the immune system's fighting force: the killer T cells that, once activated, can take down the virus. Indeed, a small number of people infected with HIV—fewer than 1%—do just that. For reasons still unclear, these so-called elite controllers are able to naturally suppress HIV replication. A vaccine that mimics this ability to hold HIV in check could effectively transform the 37 million people worldwide currently living with HIV into elite controllers. "If we can develop a vaccine that will program an infected person's immune system to act like that of an elite controller, so that they have a strong T cell response and suppress the virus, we might enable patients to come off their lifelong medications and be functionally cured," says Dr. Landau.

Last year, in support of his innovative efforts, Dr. Landau received an Avant-Garde Award for HIV/AIDS research from the National Institute on Drug Abuse, part of the National Institutes of Health. The five-year grant, which provides $4.2 million in funding, will allow his team to expand testing of their therapeutic vaccine to nonhuman primates over the next couple of years.

Although the basis of a therapeutic vaccine involves mimicking the virus-suppressing skills of elite controllers, it's not entirely clear how most elite suppressors themselves manage to keep HIV down. "That's been one of the important questions in AIDS research for many years," says Dr. Landau. Elite suppressors don't harbor a weaker strain of HIV. "Their CD4 T cells are vulnerable to infection, as far as we can tell," explains Dr. Landau. "They're not intrinsically resistant, like people who lack CCR5."

Instead, the killer T cells of elite suppressors—the immune cells that take cues from T cells to kill off infections—show a naturally vigorous response to HIV. "Perhaps they were previously exposed to something that caused a similar T cell response," says Dr. Landau. "Or maybe it's

“If we can develop a vaccine that will program an infected person’s immune system to act like that of an elite controller, we might enable patients to come off their lifelong medications and be functionally cured.”

Nathaniel Landau, PhD, professor of microbiology at NYU School of Medicine

something in their genes. It’s not really understood. But what we do know is that these people exist. The virus never fully clears in these patients, but it remains controlled.”

By hindering viral replication, antiretroviral medications essentially do the same thing, and they have improved over the years. In the early days, “you had to take something like 15 pills a day, and they made you nauseated, depleted your bone marrow, and were very toxic,” Dr. Landau says. “Now, there are combination therapies that are as simple as one pill once a day, and overall, they are much better tolerated.”

Even so, each drug component comes with its own toxicity: some affect the kidneys; others, the bones. It’s not uncommon for patients to switch drug regimens due to side effects. Furthermore, taking one pill a day is not as foolproof as it sounds. If you miss a dose, the virus could develop resistance, which could then render a whole class of medications ineffective.

Globally, access to care remains a major challenge. “In the US, we’re fortunate,” Dr. Landau says, “but there are many places throughout the world where medications and clinics aren’t readily available.” A therapeutic vaccine wouldn’t eliminate every single copy of the virus hidden in the body, but it would represent a functional cure. “It would be so much better than having to take a daily regimen of medications for the rest of your life and dealing with all of the side effects that can come with it,” says Dr. Landau.

A vaccine that prevents HIV infection continues to be a goal, albeit an elusive one. “There’s been a tremendous effort,” says Dr. Landau, “but it hasn’t worked so far.” A 2007 trial for a vaccine developed by the pharmaceutical company Merck, for example, was halted prematurely when volunteers who received the experimental treatment proved more susceptible to HIV infection than those who did not. “Whether a preventative vaccine will be possible remains to be seen,” says Dr. Landau.

The Landau Lab’s approach to a therapeutic vaccine centers on dendritic cells—a frontline player in the battle against in-

An estimated 66% of adults in East and Southern Africa take anti-HIV medications every day.

TINA STALLARD/GETTY IMAGES (TOP)

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The Great Vaccine Boom

Flu, malaria, HIV—NYU Langone's new Vaccine Center builds on a groundswell of research to eradicate deadly infectious diseases.

Most children in the US receive 35 vaccination shots by their fifth birthday. (Cue the crying.) That may sound like a lot, but public health experts believe we need even more—a lot more. The current roster of routine childhood vaccines in the US protects against 16 infectious diseases, and the World Health Organization estimates that overall, vaccines save 2.5 million lives each year. Yet an even larger number of people die annually from malaria, tuberculosis, and HIV/AIDs combined.

The good news is that there are a historic number of experimental vaccines in the pipeline—270 and counting—aimed at preventing these three global killers, along with 51 other infectious diseases. The new Vaccine Center at NYU Langone Health, launched this year by Mark Mulligan, MD, a nationally renowned infectious disease investigator recently recruited from Emory University, will build on this extraordinary momentum through a combination of basic research and clinical trials.

"Vaccine research is of the highest importance to humankind," says Dr. Mulligan, the Jeffrey P. Bergstein Professor of Medicine and director of the Division of Infectious Diseases and Immunology. "We still lack vaccines for many long-standing diseases, and new threats like Zika and Ebola continue to emerge. The center's mission is to discover new vaccines to protect and restore human health."

Dr. Mulligan's own lab will focus on developing a universal influenza vaccine, a national priority to contain one of the deadliest infectious diseases in the US, accounting for 80,000 deaths last season alone. The Holy Grail, he says, is a single shot, perhaps with a booster every 5 to 10 years, that inoculates against all influenza strains and eliminates the annual hit-or-miss scramble to predict dominant strains for each flu season.

The center will also investigate therapeutic vaccines—like the one Nathaniel Landau, PhD, professor of microbiology, is developing against HIV—that train the body's immune system to fight existing infections. It's a fast-growing strategy now being explored to treat everything from Alzheimer's disease to diabetes, but cancer tops the list: currently nearly half of the vaccines in clinical trials target cancer—a trend that Dr. Mulligan, professor of medicine and microbiology, believes will only grow. "Cancer vaccines are an exciting field, reinvigorated in the new era of immunotherapy, and we will recruit researchers and collaborate with investigators and clinicians to develop them," says Dr. Mulligan.

fection, and the "brains" of the immune system. These cells patrol the body and, when they encounter a marauding virus or bacterium, ingest the invader, chop it up, and then display these fragments like flyers that allow other immune cells to recognize the infection. "Dendritic cells educate T cells," explains Dr. Landau, "saying, in effect, 'This is what HIV looks like. Your job is to kill any cells infected with HIV.' "

The insidious trick of HIV is to compromise the ability of helper T cells to call the killer T cells to action. It's like disabling the body's 911. To get around this impairment, Dr. Landau is targeting the dendritic cells, artificially arming them with fragments of HIV to present to killer T cells and equipping them with some of the stimulatory chemicals that would normally be provided by helper T cells. Vaccination with such engineered dendritic cells should allow those infected with HIV to activate their killer T cells and produce a targeted immune response. "The idea is to reinforce the immune system so that it can control replication of the virus," says Dr. Landau.

Preliminary attempts by other labs to produce dendritic-based therapeutic vaccines have met with some success. "Two published clinical trials did show a short-term immune response," notes Dr. Landau. "But then the virus rebounded." That may be because these studies mixed synthetic preparations of viral fragments with dendritic cells before injecting these cells into patients. In such a preparation, the dendritic cells may present antigen fragments for a short time, but ultimately, the antigens get lost.

In the approach adopted by the Landau Lab, the dendritic cells are engineered with a gene that encodes a segment of HIV protein. These engineered dendritic cells are thus armed with a blueprint that allows them to continually produce the viral antigen they need to alert killer T cells to be on the lookout for HIV.

So far, the approach has worked well in a test tube. There, the engineered dendritic cells were able to stimulate human killer T cells and instruct them to recognize HIV, doing an end run around hobbled helper T cells. What's more, the vaccine was able to coax dormant HIV hidden inside helper T cells to reveal itself. That observation was particularly promising, says Dr. Landau, because "if you can wake up

"Their approach takes advantage of how the body naturally detects retroviruses like HIV. It's absolutely essential."

Dan Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology and a Howard Hughes Medical Institute investigator

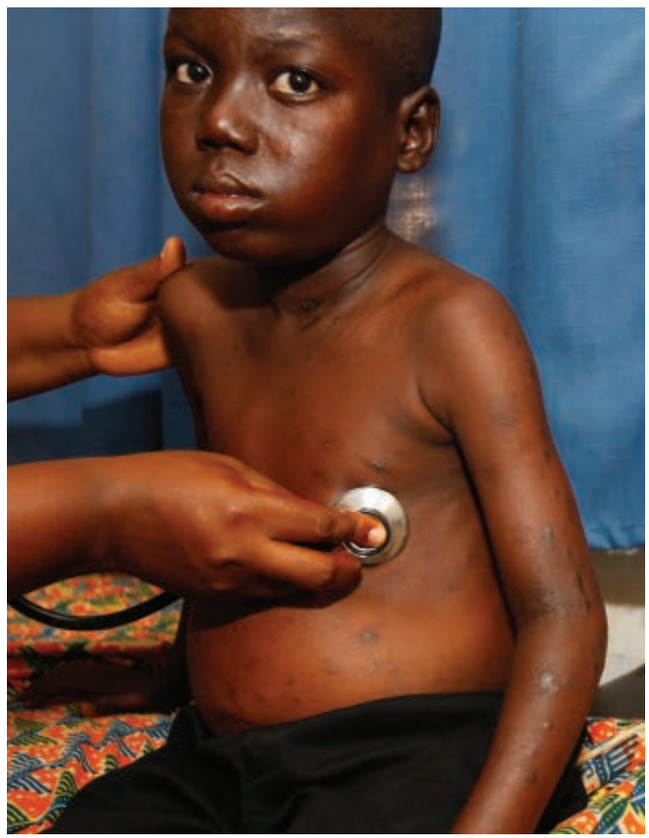
latently infected cells and allow them to be recognized by T cells, the immune system can clear them." Eliminating these latent HIV-infected cells depletes the viral reservoir, lessening the likelihood that one of these stowaway viruses can reawaken later, when the immune system may be unprepared, and ignite an explosion of replication that could lead to AIDS.

"Their approach takes advantage of how the body naturally detects retroviruses like HIV," says Dr. Littman, a Howard Hughes Medical Institute investigator. You need to have this hard-wired, innate mechanism, he explains, to mount a strong adaptive response, which includes the activation of both helper and killer T cells, as well as the production of antibodies that recognize the virus. "That's the part that a lot of people working on HIV had ignored for the first couple of decades of research in the field," he adds, "but it's absolutely essential. This project bridges that gap."

Dr. Landau recently began collaborating with a team at the University of California, Los Angeles, to hone their vaccine in mice. In preliminary tests, he and his collaborators found that their dendritic cells restrained viral replication. "But the suppression lasted only about two months before the virus came back," says Dr. Landau. "We think the T cells were getting exhausted"—activating the natural "checkpoint" mechanisms they use to shut themselves down once an infection has been eliminated, thereby preventing a runaway immune reaction. "But if you have a chronic infection, you don't want those T cells to get turned off," he explains. "You want to keep them active." Now, the researchers are arming their dendritic cells with proteins that inhibit those checkpoints to keep killer T cells on their toes—the same strategy that's used in a number of cancer immunotherapies.

While the current focus of this collaborative research is HIV, its promise extends beyond this one disease. "The cool thing about the research is that it has a number of potential applications," notes Jeffrey Weiser, MD, the Jan T. Vilcek Professor of Molecular Pathogenesis and chair of the Department of Microbiology, who is involved in the launch of NYU Langone's new Vaccine Center (see page 42). "You can reprogram dendritic cells for a lot of different immune responses—to other infectious diseases and even to cancer."

Indeed, Dr. Landau has found that reprogrammed dendritic cells can protect mice injected with melanoma cells from developing cancer. "We hope this is going to be a nice addition to the story," he says. "It's definitely going to be a big focus in our lab. At the end of the day, if you really want to make a breakthrough in HIV/AIDS, or any disease, you need bold new ideas."



BSIP/GETTYIMAGES

A young HIV patient in Togo, a small country in West Africa. More than 90% of the world's HIV-positive children live in Africa, and globally 120,000 children die each year from AIDS-related illnesses.

A Pediatrician's Crusade against Chemical Saboteurs

Dr. Leonardo Trasande is exposing the everyday chemicals that may cause children a lifetime of harm.

BY BRYN NELSON

ILLUSTRATIONS BY CHAD HAGEN PHOTOGRAPHS BY TONY LUONG

In

the winter of 1944, at the tail end of World War II, Nazi troops cut off food supplies to the western provinces of the Netherlands, creating a widespread famine that killed nearly 20,000 people. Conditions improved dramatically when the war ended a year later, but the health implications of the humanitarian crisis would be felt for generations. In what is considered one of the most startling paradoxes in medicine, children born to women who survived on meager rations during the Dutch Hunger Winter, as the period is now known, tended to be the same weight at birth as those born to unaffected mothers, but they became heavier as adults. They were also more prone to heart disease, obesity, diabetes, and early death.

The phenomenon raised a profound and perplexing question: How could the environment in the womb leave such a dramatic and lasting mark on human health and longevity? Studies of the Dutch children, as well as other major investigations from Japan, Scandinavia, and elsewhere have since begun to tease out the answers. Harsh conditions during a critical early window of human development, evidence suggests, may trigger a survival mechanism called a thrifty phenotype. The hypothesis posits that hormonal changes in the developing fetus can help it adapt to unfavorable conditions, such as by converting calories into fat instead of protein or sugar to maximize energy when food is scarce. Later in life, though, the adaptation can become a threat: continuing to readily convert calories into fat, even when food is abundant, can predispose someone to obesity and diabetes.

As it turns out, starvation isn't the only condition that can reconfigure the body's metabolic and hormonal wiring early in life. Leonardo Trasande, MD, MPP, vice chair for research in the Department of Pediatrics at NYU Langone Health, is among a growing cadre of scientists who believe that chronic exposure to the chemicals found in numerous everyday sources, such as plastics, flame retardants, pesticides, and air pollution, can trigger the same phenomenon and may be fueling the rising rates of diseases like obesity and diabetes. "We suspect the thrifty phenotype can occur in a subtler fashion and impact children through early chemical exposures," says Dr. Trasande, director of the Division of Environmental Pediatrics, and professor of pediatrics, environmental medicine, and population health.

Equal parts physician, researcher, and policy expert, Dr. Trasande has spent the past two decades painstakingly documenting the threat and burden of environmental toxins on human health, and the economic cost of failing to prevent related diseases, all while advocating for reforms to mitigate their damage. His concerns about the health hazards of hormone-disrupting chemicals have been echoed by the World Health Organization, the International Federation of

KNOW YOUR CHEMICAL HAZARDS

Phthalates, aka Plasticizers

WHY THEY EXIST

Phthalates belong to a class of chemicals that make plastics more flexible and act as industrial solvents.

WHERE THEY'RE FOUND

In many plastics that are soft and squeezable, including detergent bottles, raincoats, plastic bags and packaging, inflatable toys, food-grade plastic tubing, medical tubing, and blood-storage containers. They're also common in soaps, shampoos, cosmetics, and nail polish. Look for the recycling code 3 on plastic containers or the ingredient "fragrance" on labels of hygiene products.

WHY THEY'RE SUSPECT

Phthalates cause genital birth defects and impaired reproductive function in male mice, and they alter the function of protein receptors involved in sugar and fat metabolism. The CDC has found detectable levels of phthalate metabolites in the general population, with higher levels in those who use more personal care products such as cosmetics, body washes, and shampoos. More than 1,000 population-wide studies have linked exposures in humans to neurodevelopmental issues, low IQ, infertility, and asthma, among other health problems.

Dr. Leonardo Trasande has earned an international reputation for his expertise and leadership in the burgeoning field of pediatric environmental health.

KNOW YOUR CHEMICAL HAZARDS

Bisphenols, aka BPA, BPS, BPF, BPP

WHY THEY EXIST

This class of chemicals is used to harden plastics and prevent corrosion in aluminum cans.

WHERE THEY'RE FOUND

Canned foods, beverage containers, toys, dental sealants, thermal paper receipts, and pipes. Products marketed as "BPA-free" are often replaced with other bisphenols within the same class.

WHY THEY'RE SUSPECT

BPA exposure causes infertility and hormonal dysfunction in research animals. In women, higher BPA levels have been linked to fewer egg follicles. Population-wide studies have linked BPA to early puberty, breast cancer, and childhood obesity and neurological disorders. In addition, the chemical makes fat cells bigger and disrupts a protein that protects against heart disease.

Gynecology and Obstetrics, the Endocrine Society, and the American Academy of Pediatrics.

Even as the evidence mounts, however, the challenge of protecting society from a pervasive threat hiding in plain sight can seem insurmountable. Synthetic chemicals lurk just about everywhere: in our soil and food supply, in cosmetics and hygiene products, in furniture and clothing, and even in medical equipment (think IV bags, tubing, and pill bottles). Since 2004, the world has produced more than 4 billion metric tons of plastic alone.

Dr. Trasande, for his part, is undaunted by the scope and scale of the task before him. Supported by more than $40 million in federal funding, he and his colleagues at NYU School of Medicine are leading some of the most ambitious clinical studies yet to clarify the link between chemical exposure and childhood development. Beyond more research, his antidote turns on a public awareness campaign whose message is as persistent as the chemicals it seeks to oust. Dr. Trasande recently published a book to alert the public to the hazards of hormone-disrupting chemicals, which he considers an environmental challenge second only to climate change. "We can do a lot to protect everyone from 'lifestyle' diseases caused by things other than lifestyle," he says. "Our choices and habits matter."

In the relatively young field of pediatric environmental health, Dr. Trasande has rapidly earned an international reputation for his expertise and leadership. In 2014, he organized the Endocrine Disrupting Chemical Disease Burden Working Group, a cohort of nearly 30 international scientists who advise policymakers about the economic burden of medical conditions linked to these chemicals. Earlier this year, he was appointed director of NYU Langone's new Center for the Investigation of Environmental Hazards. The center, which complements the

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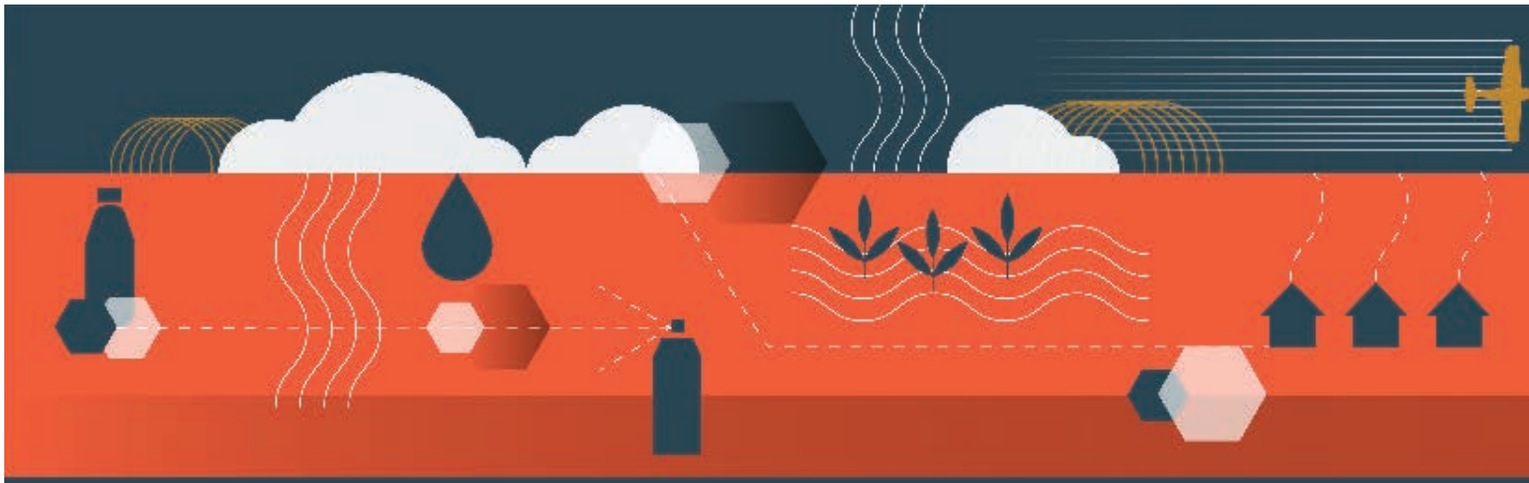
clinical care provided by Hassenfeld Children's Hospital, advances tools and technologies to help measure the effects of environmental exposure and translates research findings for the public. "I think he's a towering intellect—and a practical person," says Catherine Manno, MD, the Pat and John Rosenwald Professor of Pediatrics and chair of the Department of Pediatrics. "And those things together augur for a great contribution to public health."

DR. TRASANDE WAS first drawn to health policy during medical school at Harvard University in the 1990s. After completing his pediatric residency at Boston Children's Hospital and Boston Medical Center, he completed a legislative fellowship in then-Senator Hillary Rodham Clinton's office. Working on both child and environmental health policy, he realized that formulating sound medical guidance could fundamentally impact the health of not only individuals but entire populations. Since then, Dr. Trasande has increasingly focused on building the public health case against a group of chemicals known as endocrine disruptors, which



Seven Ways to Reduce Your Exposure to Everyday Chemicals

Beyond building a case for major policy changes in how chemicals are used and regulated, Dr. Trasande is educating consumers about how to reduce their own risk. Here, he offers some practical tips for protecting yourself and your loved ones from the downstream effects of environmental chemicals.

1. Don't microwave plastic containers, even those labeled "microwave safe," or put them in the dishwater. Discard plastic containers that are etched or scratched since heat and physical damage can cause chemicals to leach into food and liquids.

2. Avoid plastic containers labeled with the recycling numerals 3, 6, and 7, which pose the greatest health risk.

3. Eat organic produce, especially leafy greens and vegetables, to avoid pesticide exposure.

4. Limit exposure to canned foods and drinks, and thermal-paper receipts, all of which can shed bisphenols.

5. Avoid using synthetic pesticides on your own garden.

6. Limit the use of fragrances, cosmetics, and hygiene products made with synthetic chemicals. Phthalates commonly found in these products can be absorbed through the skin or inhaled.

7. Open windows for air circulation.

KNOW YOUR CHEMICAL HAZARDS

Organophosphate Pesticides

WHY THEY EXIST

These nerve agents are widely used to kill insect and other animal pests in agricultural fields and homes.

WHERE THEY'RE FOUND

Pesticides sprayed on crops and plants leach into the soil and water supply and can make their way to your kitchen. Pesticides used in homes have shown up in the cord blood of infants.

WHY THEY'RE SUSPECT

Organophosphates cause tumors and severe brain damage in research animals and have been linked to lymphoma and leukemia in humans. High exposure can cause nausea, vomiting, neuropathy, and seizures.

interfere with the function of hormones such as estrogen, androgen, and thyroid. "We know that hormones, in addition to performing important physiological functions, are crucial for shaping body mass," he says.

Dr. Trasande's work has been driven by the central hypothesis that early-life exposure to environmental chemicals, especially endocrine disruptors, alters our hormones in harmful ways, contributing to birth defects, developmental delays, obesity, diabetes, infertility, and cardiovascular and immunological diseases. He notes that while these chemicals have been shown to have long-lasting health implications for everyone, babies and young children are particularly vulnerable. "Pound for pound," says Dr. Trasande, "children are breathing more air, eating more food, and drinking more water, so they have greater exposure, and their organ systems are still developing."

For much of their research, Dr. Trasande and his investigators have zeroed in on four kinds of chemicals for which there is the strongest evidence of health effects: bisphenols, phthalates, organophosphate pesticides, and polycyclic aromatic hydrocarbons (PAHs). Bisphenols make plastics hard, and because they are used to prevent corrosion in aluminum cans, they are often present in canned foods. Phthalates increase the flexibility and durability of plastics and are often added to lotions, cosmetics, soaps, fragrances, food packaging, and other consumer products. Organophosphate pesticides are widely used to kill insect pests in agricultural fields and homes. PAHs are air pollutants found in everything from vehicle exhaust to charred meat.

Research in humans and lab animals has linked these endocrine disruptors to other potential consequences, as well. Bisphenol A (BPA), for example, makes fat cells bigger and disrupts the function of a protein that protects against

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heart disease, potentially contributing to cardiovascular risks. Phthalates can alter the function of protein receptors involved in sugar and fat metabolism, meaning that—like the thrifty phenotype—they may fundamentally reset the body's response to calories in food.

Given the pervasiveness of these chemicals, they often end up in household air and dust. Our reliance on products made from them could be coming at a steep cost. Evidence of the harm they pose has accrued primarily through epidemiological studies of hormone-deficient mothers or children and through toxicology studies of lab animals.

Epidemiological studies are notoriously challenging due to the near-impossibility of finding control populations that haven't been exposed to the ubiquitous chemicals and the sheer variety of other contributing factors that must be considered. Uncertainty remains over the cumulative effects of exposure to intermingling chemicals and over how best to assess the risks from chronic low-level exposures. Some skeptics have likewise questioned the validity of extending the results of toxicology experiments on animals to people, particularly as the scientific basis for new policies.

“Pound for pound, children are breathing more air, eating more food, and drinking more water, so they have greater exposure, and their organ systems are still developing.”

LEONARDO TRASANDE, MD, MPP, VICE CHAIR FOR RESEARCH IN THE DEPARTMENT OF PEDIATRICS AT NYU LANGONE HEALTH

Pediatrician Leonardo Trasande, MD, in Children’s Hall at Hassenfeld Children’s Hospital.

Although correlations between exposures and impairments don't prove that such chemicals are toxic, Dr. Trasande argues that most human and lab animal studies have consistently pointed in the same direction, strengthening the case for causation. In a 2015 study that measured children's and adolescents' exposure to phthalates found in processed foods, Dr. Trasande and his colleagues discovered that higher concentrations of phthalate in urine samples were associated with higher blood pressure. In a related study, his group linked some of the same chemicals to increased insulin resistance, which causes sugar to build up in the blood and can lead to diabetes.

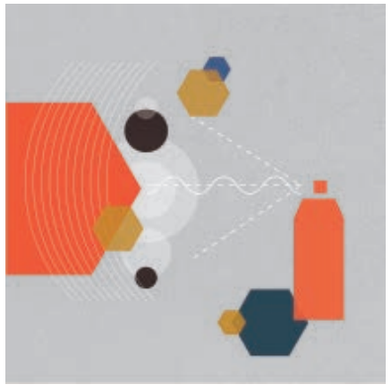
Among multiple studies that have sought to estimate the public health burden of endocrine-disrupting chemicals, Dr. Trasande and his colleagues have suggested that reproductive disorders account for billions of dollars in expenditures. In men, these chemicals were associated with major costs for disorders such as infertility, testicular cancer, and undescended testicles, while in women, they were linked to reproductive disorders such as fibroids and endometriosis.

In a major 2016 study, Dr. Trasande and his team conservatively estimated that exposure to endocrine disruptors accounted for total annual healthcare costs of $340 billion in the US (2.3% of the nation's gross domestic product) and $217 billion in Europe. They linked the lion's share of these costs to the effects of organophosphates on children's brain development. Even these huge expenditures are likely to be underestimated, Dr. Trasande explains, given that the researchers focused on only a small fraction of the chemicals sold commercially and their associated medical conditions. There are more than 85,000 such chemicals on the market, but limited screening efforts have identified about 1,000 as endocrine disruptors. "That's why we need to keep doing research," says Dr. Trasande. "There are substantial gaps."

IT'S ONE THING to study chemical exposures in mice or to comb existing data sets for associations. But how do we really know what's happening in humans? A few reviews of observational studies have yielded contradictory results, and experts agree that the field may never find a true "smoking gun" because of the impossibility of ethically testing the effects of potential toxins on people. "Causation is never certain," Dr. Trasande acknowledges. "The best we can do as scientists is to lay out the information, along with all the uncertainties, and interpret the probability of a scientific phenomenon."

To drill deeper, Dr. Trasande is spearheading some of the largest clinical investigations of endocrine disruptors to date. In 2016, he and his colleagues began tracking chemical exposures in women early in their pregnancy through a clinical study called CHES, for NYU Children's Health and Environment Study. CHES has since received substantial funding through a larger National Institutes of Health (NIH) program called Environmental influences on Child Health Outcomes, or ECHO. This research initiative is examining how maternal and pediatric exposure to a wide range of environmental factors prior to conception through early childhood can affect the health and development of children and adolescents. ECHO aims to enroll more than 50,000 children from dozens of study sites nationwide, providing a scale that Dr. Trasande says will represent the best opportunity yet to understand the effects of endocrine disruptors and other environmental exposures.

By the end of last year, Dr. Trasande's team had recruited more than 2,000 women and 1,100



KNOW YOUR CHEMICAL HAZARDS

Polycyclic Aromatic Hydrocarbons, aka PAHs

WHY THEY EXIST

They appear whenever we burn things. PAHs, a group of more than 100 chemicals, are the ubiquitous by-products of combustion.

WHERE THEY'RE FOUND

PAHs are released everywhere there's vehicle exhaust, charred meat from high-temperature cooking, cigarette smoke, fumes from asphalt roads, or smoke from burning coal, gasoline, trash, or wood.

WHY THEY'RE SUSPECT

Direct exposure to PAHs can irritate your eyes and lungs. Higher exposures among children have been linked to neurodevelopment problems like ADHD. Grilled, charred, and smoked meats have long been linked to cancer.

"Causation is never certain. The best we can do as scientists is to lay out the information, along with all the uncertainties, and interpret the probability of a scientific phenomenon."

DR. LEONARDO TRASANDE

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infants from Tisch Hospital, NYC Health + Hospitals/Bellevue, and NYU Langone Hospital–Brooklyn. Based on their success, they subsequently received a $40 million five-year NIH grant to ramp up their efforts. Some of that funding has gone toward amplifying existing collaborations with other institutions in the US and the Netherlands that are examining the effects of chemicals on infant development. Another portion of the grant has allowed Dr. Trasande and his colleagues to extend their CHES study window to include childhood exposures through age two and track some maternal exposures prior to pregnancy. Dr. Trasande and his colleagues are calling the new preconception phase Factors Influencing Reproductive Success and Time to pregnancy, or FIRST.

"While pregnancy matters, it may be exposures even before pregnancy that impact how the baby does," Dr. Trasande explains. The FIRST phase enrolls women who come in for regular gynecologic or well visits. If they become pregnant, they move on to the second phase, CHES prenatal. Researchers follow the women through their prenatal care and collect samples at 18 weeks or less, at 18 to 25 weeks, and again in the third trimester. The combined FIRST-CHES data bank will be one of only three in the world to contain prospective data from preconception through early childhood, and the only one to contain preconception semen samples from male partners.

ONE OF DR. TRASANDE'S overarching goals is to establish the threats posed by certain chemicals with enough evidence to guide people on how to better protect themselves and their children. But he acknowledges that personal choices can only go so far, given the pervasiveness of these chemicals in consumer products and the environment. Even if you can control what's in your home, you can't necessarily control what's in your school, workplace, or surrounding environment. For this reason, he and other researchers stress that change must also take place at the institutional level. "We have much more power as a society through our pocketbooks and wallets," Dr. Trasande says. "The ban on BPA in sippy cups and baby bottles occurred because consumers cried out to companies asking whether BPA was in these products."

Dr. Trasande hopes that his studies will help drive broader changes in public policy, as well, by characterizing and confirming the risks of specific chemicals and by identifying the most vulnerable populations, notably children. The key, he says, is to imagine childhood health and disease as a three-legged stool supported by environment, behavior, and genetics: any leg can affect another, and all three must be examined together. "If we incorporate better information about these influences into our studies," says Dr. Trasande, "we can unlock diseases and their origins."

As the lessons of the Dutch Hunger Winter suggest, revealing the true agents of disease and devising early ways to overcome them may help prevent a lifetime of avoidable illness.

POST

New People, Places, and Projects at NYU Langone Health

Faculty Conversation

REINVENTING A CANCER CENTER

Benjamin G. Neel, MD, PhD, guides Perlmutter Cancer Center to the top tier—and aims higher.

When Benjamin Neel, MD, PhD, joined NYU Langone Health in 2015 to lead the Laura and Isaac Perlmutter Cancer Center, he was tasked with propelling the center into the elite echelons of cancer research. It was a lofty mandate tailor-made for Dr. Neel, a renowned cancer biologist who had just spent the past eight years at the helm of the largest cancer research center in Canada, the Ontario Cancer Institute at Princess Margaret Cancer Centre. In his new role, he quickly set in motion a trifold strategy, bolstered by a $50 million gift from Laura and Isaac Perlmutter, to reinvigorate basic research, expand the center's clinical trials, and recruit a new wave of top-notch physician-scientists focused on cancer.

Just four years later, these investments are paying off. In February, Perlmutter Cancer Center earned comprehensive status from the National Cancer Institute ▸

Benjamin G. Neel, MD, PhD, director of Perlmutter Cancer Center, first trained his talents on cancer research 40 years ago after he lost his grandmother to the disease.

Photograph by **Jonathan Kozowyk**

(NCI), a prestigious designation shared by only 49 other cancer centers nationwide and accompanied by $20 million in funding over the next five years. We sat down with Dr. Neel to discuss this recent milestone, its implications for patients, and the most important actions you can take to mitigate your cancer risk.

The NCI describes its Cancer Centers Program as the anchor of the nation's cancer research efforts. What does its "comprehensive" designation mean for patients?

Comprehensive cancer centers are unique in that they offer full-service teams that can bridge the gap between basic science and clinical care. Ultimately, that means scientific insights and discoveries reach patients faster. Not only do patients benefit from a full complement of clinical services in one place—medical oncology, surgical oncology, radiation oncology—but they also have access to the latest experimental therapies. Unfortunately, for too many cancers, the best medicine is still a clinical trial.

How are Perlmutter and its patients benefiting from NYU Langone's continued growth?

NYU Langone's dramatic expansion in recent years into Brooklyn, Queens, and Long Island means that Perlmutter Cancer Center now reaches more people than ever before. We've seen patient volume increase 110% over the past five years. What's more, our enlarged footprint enables us to provide the highest-quality care to many patients who live in traditionally underserved areas. Sadly, minority groups have much poorer outcomes for almost every disease, including cancer. Among our priorities at Perlmutter is addressing these unacceptable health disparities.

You've recruited 30 distinguished cancer researchers and clinicians, many in leadership positions, since you joined NYU Langone. What's been the impact?

One benefit is that our growing roster of top physicians and scientists has markedly improved our collaborations with pharmaceutical companies, providing our patients with access to more cutting-edge clinical trials. When I arrived, it could take up to 250 days to launch a new clinical trial. Today, on average, it takes less than 95 days. Thanks to the leadership of Dan Cho, MD, who directs our Phase 1 Drug Development Program, we've gone from having two phase 1 clinical trials in 2015 to over 100 this year. Overall, the size of our clinical trials office has tripled since 2014.

Another huge benefit is enhanced clinical services. For example, with the recruitment of renowned hematologist-oncologist Ahmad Samer Al-Homsi, MD, director of the Blood and Bone Marrow Transplant Program, we've now built an elite team capable of tackling the most complex cases of blood cancer. This year, we're on track to perform more than 100 bone marrow transplants, most of them allogeneic, meaning that a patient receives stem cells from a donor instead of himself.

Did that shift help attract the $75 million donation from an anonymous donor to fund a new Center for Blood Cancers, announced in February?

I'm sure it helped. The Center for Blood Cancers (see page 62) will also have a new focus on advancing treatments for multiple myeloma, a blood cancer originating in the bone marrow that kills nearly 13,000 Americans each year. We've recruited two top experts in the field and plan to expand our multiple myeloma clinical trial efforts.

Perlmutter Cancer Center is now the third NCI-designated comprehensive cancer center in New York City. How does that concentration of expertise motivate you?

Scientific research has always been, in my opinion, the most collaborative enterprise in the US. That said, NYU Langone also competes with other research institutions. It's that tension between collaboration and competition that drives progress in research. The reality is that people in my lab work harder knowing that somebody else might be working on the same thing. I do, too. It's a good thing, a healthy thing. Humans

Perlmutter Cancer Center–Sunset Park in Brooklyn, slated to open next month, is part of NYU Langone Health's broader effort to bring comprehensive cancer care to more New Yorkers. "Cancer knows no boundaries," says Dr. Neel.

In the lab, Dr. Neel studies signaling pathways in cancer. He recently began a clinical trial investigating the impact of vitamin C on a form of preleukemia linked to mutations in an enzyme that regulates blood cells.

thrive on competition. But as scientists we also thrive on the exchange of information. So our researchers will always collaborate with their counterparts here in New York City and beyond.

Do you see personalized medicine as the future of cancer therapy?

No two cancers are the same. In some types of cancer, no two cancer cells are the same. But it's also true that no two humans are the same, even identical twins, and yet they still share common traits. Similarly, there are generally describable principles about cancers that apply to genetics and even the host response, which means you don't necessarily need individualized therapy for every patient. The truth is that we've made great progress in our understanding of cancer genetics. We know most of the genes that contribute to various types of tumors at the research level. What we haven't fully figured out is how to apply that knowledge clinically to best treat most cancers. That remains a very active area of our research.

You've said that if any of your family members or friends were diagnosed with cancer, you'd insist that they are treated at an academic medical center. Why?

I'd pretty much insist on that if they needed to be treated for anything more serious than a broken bone. In general, academic medical centers are better positioned to deliver state-of-the-art care. Part of that is because they encourage a culture of competitive exploration, so there's never really time to rest on your laurels. The day after we received an overall "outstanding" rating on the renewal of the NCI Cancer Center Support Grant, I was on to the next grant. There's a coterie of people whose raison d'etre is to push the boundaries of knowledge, and I think everyone benefits from that mind-set.

What can people do to reduce their cancer risk?

Obesity has surpassed cigarette smoking as the leading cause of cancer in the US. The number of people who smoke cigarettes, which used to be about 35% of the population, has been cut in half over the last 30 years to around 17%. That's an amazing success story. It's an incredible testament to public policy, and we need similar policies for obesity. As a community, I think we need to do a better job of communicating relative risk. We're unwilling to say, "Smoking is the single worst thing you can do for your health. It's like playing in traffic." Or, "Tanning beds are like cigarette smoking through your skin." That's pretty easy to communicate, but we don't lay it out that bluntly.

The truth is there are certain things that are just really, really bad for you because they substantially increase your cancer risk—smoking, obesity, excessive sun exposure, excessive drinking, a sedentary lifestyle. We know that up to 60% of all cancers are preventable. It's mind-boggling.

Of course, I'm very sympathetic to the challenges of behavioral change. I was a fat kid. I was fat all the way to medical school. There's no question that genes play a role in appetite control and obesity. But the rate of obesity is climbing too fast to attribute it to genetics alone. Environmental influences play a major role, and many of those variables can be controlled.

Do you have to work at keeping your weight down?

Constantly. I walk to work. I try to get to the gym four or five days a week. That's my goal. And I'm hungry all the time. It's hard.

What's the most common question laypeople ask you about cancer?

"When is there going to be a cure for cancer?" Of course, that question underscores a pervasive misperception about cancer, because cancer isn't one disease but many diseases. It's like asking, "When is there going to be a cure for infectious disease?" Everyone realizes that what we need to treat pneumonia is not what we need to treat a urinary tract infection.

Unfortunately, we're never going to wake up to the headline "Cancer cured!" The boring answer is that over the next decade, we'll continue to make steady, and occasionally, major, progress against many different forms of cancer. And that's our focus.

NEW FUNDING

THE SCIENCE

Seeking to Stem Pancreatic Cancer's Relentless Growth

HOW MUCH

$6.7 million

HOW LONG

Seven years

SOURCE

National Cancer Institute

LEAD INVESTIGATOR

▸ **Alec Kimmelman,** MD, PhD, the Anita Steckler and Joseph Steckler Chair of Radiation Oncology and professor of radiation oncology, Perlmutter Cancer Center

WHY IT MATTERS

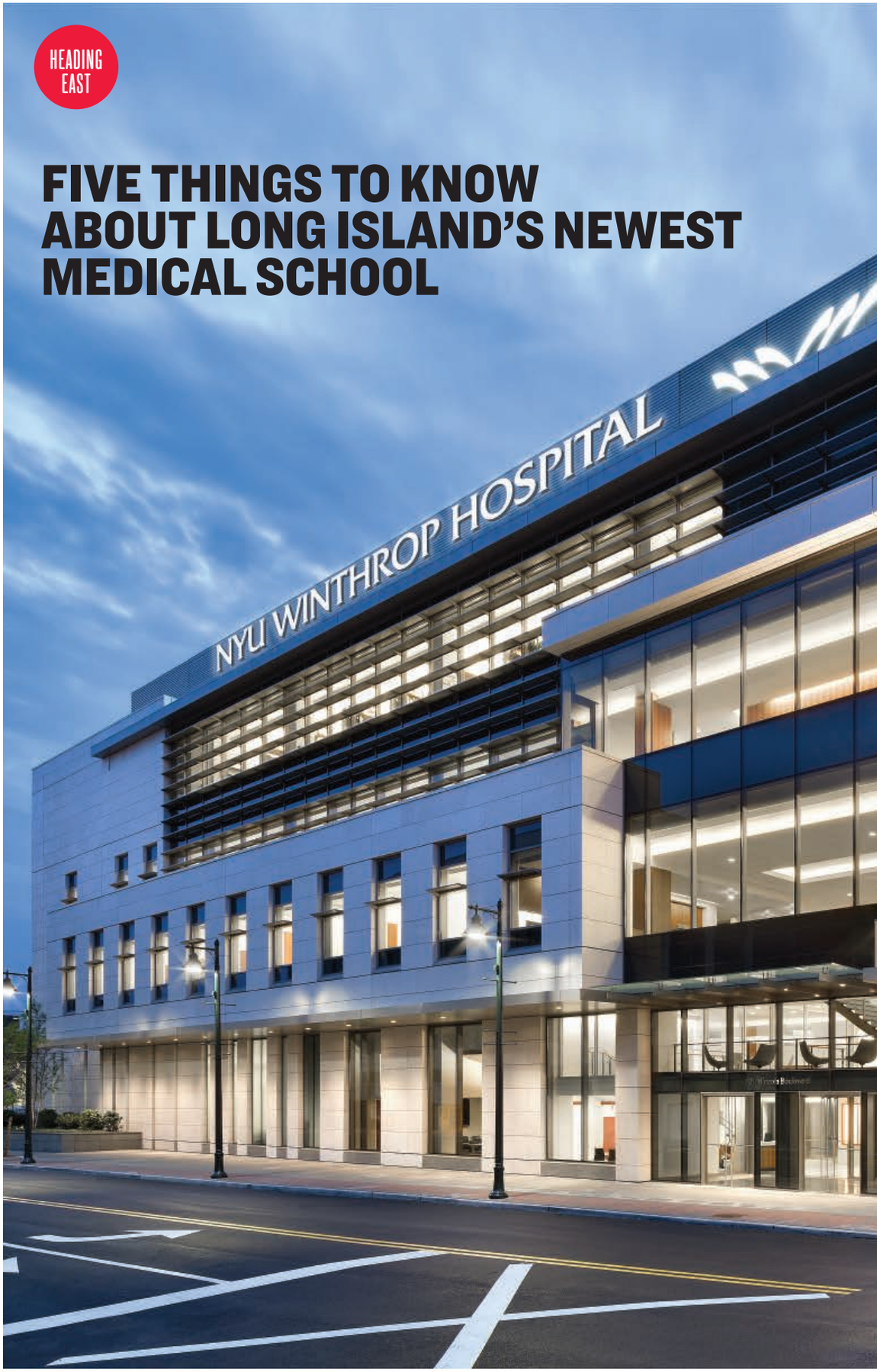
Pancreatic ductal adenocarcinoma (PDAC) kills more than 40,000 Americans annually, and just 20% of patients diagnosed with the disease live beyond a year. The cancer's signature oncogene, *KRAS*, endows it with a supernatural ability to proliferate in environments devoid of nutrients and oxygen, giving it a clear edge over cancer treatments. "It's one of the most metabolically plastic tumors, because it adapts to stress and rewires its metabolic pathways," says Dr. Kimmelman. "That's why even when you catch it early, patients still tend not to do very well."

WHAT IT FUNDS

This NCI Outstanding Investigator Award enables Dr. Kimmelman to build on his decade's worth of research on the adaptive metabolic processes of pancreatic cancer. These include PDAC's ability to derive nutrients from damaged or nonessential parts of its own cells (a scavenging phenomenon known as autophagy) and to induce stromal cells in the tumor microenvironment to secrete nutrients, such as amino acids, that can provide fuel. Dr. Kimmelman and his team plan to identify the metabolic dependencies of PDAC tumors by performing sophisticated screens in cell lines and mice. "We need to understand how these adaptive processes integrate with each other and how to target them," says Dr. Kimmelman. Although the main objective is to identify potential therapeutics that might stem PDAC's growth, Dr. Kimmelman adds that if his research uncovers a metabolite from the tumor that is secreted into the blood stream, "it could lead to an early detection test for pancreatic cancer."

HEADING EAST

FIVE THINGS TO KNOW ABOUT LONG ISLAND'S NEWEST MEDICAL SCHOOL



1 **TUITION COSTS $0.** A year after NYU School of Medicine launched the first top-ranked MD program to award full-tuition scholarships to all students, NYU Long Island School of Medicine launches this July on the campus of NYU Winthrop Hospital, in Mineola, New York, with the same full-scholarship model. Of the dozen medical programs nationwide specializing in primary care medicine, it's the only one that spares students the annual burden of tuition.

2 **PRIMARY CARE IS THE FOCUS.** With a national shortage of primary care physicians, the School is training future doctors who are committed to careers in internal and community medicine, pediatrics, OB/GYN, and general surgery. It received more than 2,400 applicants for 24 spots. The class size will grow to 40 by 2021.

3 **SCHOOL'S OUT IN THREE YEARS, NOT FOUR.** NYU Long Island School of Medicine will be the first medical school in the nation to offer an exclusive three-year MD program. Factoring in the tuition benefit, savings on cost-of-living expenses and the opportunity to begin practicing one year earlier, students stand to save $417,000.

4 **TALENT STAYS LOCAL.** Matriculated students receive conditional acceptance to an NYU Winthrop residency slot in primary care through the National Resident Matching Program. "There's a high correlation between where primary care doctors do their residency and where they wind up practicing," says founding dean Steven Shelov, MD.

5 **NYU LANGONE HEALTH IS FAMILY.** After the merger of NYU Langone Hospitals and NYU Winthrop Hospital this September, the new school will be affiliated with NYU Langone Health, a relationship that offers clinical experiences and future professional opportunities for its graduates. "NYU Long Island School of Medicine will serve a special role in the history of our institution as it prepares the next generation of physicians to meet the needs of our evolving healthcare system," says Robert I. Grossman, MD, Saul J. Farber Dean and CEO, NYU Langone Health.

Eric Sulman, MD, PhD

An international leader in malignancies of the central nervous system, Erik Sulman, MD, PhD, was recently appointed codirector of the Brain Tumor Center at NYU Langone Health's Perlmutter Cancer Center and vice chair for research in the Department of Radiation Oncology. Dr. Sulman, professor of radiation oncology, treats patients with brain and spinal cord tumors using Gamma Knife® radiosurgery and external beam radiation therapy. He also serves as the translational chair on many large clinical trials for developing and validating biomarkers, molecular predictors of treatment response, in patients with malignant tumors. Dr. Sulman joined NYU Langone Health from the University of Texas MD Anderson Cancer Center. He had worked there since his residency and research fellowship, and recently served as section chief of central nervous system and pediatric radiation oncology.

Vamsidhar Velcheti, MD

Vamsidhar Velcheti, MD, a nationally renowned clinician and researcher, has been appointed director of thoracic medical oncology at NYU Langone Health's Perlmutter Cancer Center. Dr. Velcheti broadens the depth and breadth of cutting-edge clinical trials for lung cancer patients at Perlmutter Cancer Center through his research on biomarkers to predict response to immunotherapy. He also serves as principal investigator of a multisite, National Institutes of Health–funded translational research project on early-stage lung cancer. Previously, Dr. Velcheti was associate director of the Center of Immuno-Oncology Research at Cleveland Clinic's Taussig Cancer Institute. After earning an MD at the Armed Forces Medical College in India, Dr. Velcheti completed a residency in internal medicine at Ochsner Medical Center in Louisiana and a fellowship in hematology and oncology at Yale University.

Reinvented Spaces

Grounded in Science

A once-flooded basement is reborn as the home of two high-tech facilities that advance biomedical research and surgical training.

When Superstorm Sandy unleashed its devastation on NYU Langone Health's main campus in October 2012, more than 15 million gallons of water surged through vents and other openings, filling basements and subbasements—all in about 30 minutes. In the depths of the Joan and Joel Smilow Research Center, located near the FDR Drive, a mix of water and fuel oil rose to a height of some seven feet, reaching the tops of doorways. The damage was so shocking that an administrator of the Federal Emergency Management Agency, upon surveying the damage, remarked to NYU Langone officials, "Don't look at this," he told them. "Think about what's next."

Robert I. Grossman, MD, the Saul J. Farber Dean and CEO, needed no encouragement to see light at the end of the submerged tunnels. "Even as the torrent of water was pouring into our campus," he told the class of 2013 at graduation, "I just knew we'd come out stronger."

To ensure that the entire basement would be impervious to future flooding, it was essentially reengineered to function like a vault. NYU Langone's office of Real Estate Development and Facilities devised a comprehensive flood mitigation system designed to withstand a 14-foot storm surge. Newly fortified and gut renovated, the Smilow basement is now home to two new state-of-the-art facilities that are advancing the frontiers of science and medicine—and fulfilling the most optimistic vision of NYU Langone's leadership.

The Surgical Education Training Center, made possible in part thanks to a gift from Swiss philanthropist and international businessman Hansjörg Wyss, provides a high-tech rehearsal studio for surgeons, enabling them to master procedures and techniques used in some of the most complex, pioneering operations attempted anywhere. The facility features a procedure room, complete with eight prosection stations, and an adjacent seminar room that can accommodate up to 140 visitors.

"To be a trailblazer for surgical procedures, NYU Langone must be an epicenter for training," says Eduardo D. Rodriguez, MD, DDS, the Helen L. Kimmel Professor of Reconstructive Plastic Surgery and chair of NYU Langone's Hansjörg Wyss Department of Plastic Surgery. "This model facility enables us to groom champions."

Its next-door neighbor, the Cryo-Electron Microscopy Lab, houses two massive microscopes that use subzero temperatures to capture proteins in a natural state and preserve features down to the atomic level. A suite of cameras can capture up to 1,000 high-resolution images within 24 hours, while NYU Langone's new supercomputer, Big Purple (see page 17) combines them into a single 3-D image.

"Setting up the facility was no small feat," says David Stokes, PhD, professor of cell biology, who launched the core facility. The larger scope weighs 7,220 pounds while the smaller one tips the scales at 5,264 pounds. The components were transported from the Netherlands on a 747 cargo plane, and then painstakingly assembled on vibration-control platforms, all in temperature-controlled rooms shielded by aluminum-lined walls to eliminate electromagnetic interference.

"Both spaces were meticulously designed to provide distinct, specialized environments," says Vicki Match Suna, AIA, senior vice president and vice dean for Real Estate Development and Facilities.

Photograph by **Rene Perez**

NEW FUNDING

THE SCIENCE

Can an Epilepsy Drug Curb Alcohol Cravings in People with PTSD?

HOW MUCH

$6 million

SOURCE

National Institute on Alcohol Abuse and Alcoholism

PRINCIPAL INVESTIGATOR

▸ **Charles R. Marmar,** MD, the Lucius N. Littauer Professor of Psychiatry, chair of the Department of Psychiatry, and director of the Steven and Alexandra Cohen Veterans Center

WHY IT MATTERS

People who abuse alcohol are more likely to develop PTSD after experiencing a traumatic event, and those with PTSD are more likely to abuse alcohol. Each syndrome tends to magnify the other, complicating treatment options. The urgent need for medications that address both conditions has led Dr. Marmar and his colleague Michael Bogenschutz, MD, professor of psychiatry, to topiramate, an anticonvulsant drug used to treat epilepsy and migraines. In early studies, the drug has shown promise as a remedy for alcohol abuse. Now, Dr. Marmar's team is among the first to study topiramate's effect on both disorders.

WHAT IT FUNDS

NYU Langone Health is the exclusive location for the 12-week clinical trial, which will recruit 150 volunteers diagnosed with both PTSD and alcohol abuse. "Our goal is to find out who topiramate works for and at what dosage, so we can take a personalized approach to treatment," says Dr. Marmar. Participants will begin with a minimal daily dose that is increased incrementally. At weekly visits, their blood will be tested to measure levels of two brain chemicals that regulate stress and anxiety: glutamate, which is increased in patients with alcohol dependency, and gamma-aminobutyric acid, which is decreased. Aside from tracking self-reported patient progress, the trial will use functional MRIs to measure changes in the brain as volunteers respond to alcohol cues, such as images of a glass of wine or a bottle of beer, before and after treatment. "We hope topiramate helps patients achieve better emotional and cognitive control, a reduced urge to drink, and fewer PTSD symptoms," says Dr. Marmar.

Transformational Gift Creates Dedicated Center for Blood Cancers

Thanks to a transformational philanthropic gift, NYU Langone Health's Laura and Isaac Perlmutter Cancer Center has established a new Center for Blood Cancers. The $75 million gift, made by an anonymous donor, supports the center's ongoing campaign to enhance its state-of-the-art research and clinical space. The center significantly expands patient services, bolsters new and existing research efforts, and enriches educational resources for students and faculty at NYU School of Medicine. "There is a pressing need for more research in the areas of early diagnosis and prevention of blood cancers," says Benjamin G. Neel, MD, PhD, director of Perlmutter Cancer Center. "This gift will help us as attract new talent, leaders, and added expertise to further our mission to prevent and treat these deadly diseases."

Unlike solid organ tumors, blood cancers originate in the bone marrow, where blood is produced, or in the lymphatic system, which protects us from infection. The most common forms—leukemia, lymphoma, and multiple myeloma—prevent the blood from fighting off infection or containing serious bleeding. Leukemia, found in the blood and bone marrow, is caused by the rapid production of abnormal white blood cells. Lymphoma strikes the lymphatic system, which removes excess fluids from the body and produces immune cells. Multiple myeloma, which affects antibody-producing plasma cells, prevents the normal production of cells in the bone marrow.

To advance Perlmutter Cancer Center's clinical and research programs in multiple myeloma—a disease for which there has been major progress during the past 15 years but still no cure—NYU Langone has recruited two nationally renowned hematology experts. Gareth Morgan, MD, PhD, has been appointed director of multiple myeloma research. He previously served as director of the Myeloma Institute and deputy director of the Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences (UAMS). While low-risk cases of multiple myeloma are largely treatable, Dr. Morgan focuses on developing targeted treatments for high-risk variants of the disease. His wife, Faith Davies, MD, has been named director of the Clinical Myeloma Program. At UAMS, she served as medical director of the Myeloma Institute. Dr. Davies directs a new inpatient facility in the Kimmel Pavilion for myeloma transplants. Her research focuses on genetic, biological, and radiological markers to improve patient outcomes through new drugs and technologies.

Blood cancers account for nearly 10% of all new cancer cases in the US each year, according to the National Foundation for Cancer Research. In 2018, more than 170,000 Americans were diagnosed with a form of blood cancer, and these diseases collectively claimed the lives of more than 58,000 people. More than 1,345,000 Americans are either living with blood cancer or in remission.

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In Memoriam
Frank C. Spencer, MD

1925–2018

Frank C. Spencer, MD, a pioneering cardiac surgeon who served as chair of the Department of Surgery at NYU Langone Health for more than 30 years, died on July 23, 2018. He was 92.

Dr. Spencer joined NYU Langone's faculty in 1966, when he was appointed the George David Stewart Professor of Surgery and chair of the Department of Surgery at the age of 41. Over the next three decades until his retirement in 1998, he pioneered techniques, such as coronary artery bypass grafting, that served as the basis for what is now modern cardiac surgery. Advances in the surgical treatment of coronary artery disease, valvular heart disease, myocardial preservation, mitral valve repair, and safe cardiopulmonary bypass have been attributed, in large part, to his efforts or those of surgeons he trained and mentored.

Born in 1925, Dr. Spencer grew up on a farm outside Haskell, Texas, a tiny town in the Panhandle. As a child who was educated at home and later in a two-room schoolhouse until he entered high school, he dreamed of becoming a physician like his paternal grandfather. At 15, he became the youngest freshman at North Texas State College, graduating in two and a half years. After being rejected by both medical schools in Texas due to his age, he applied to the one at Vanderbilt University in Nashville, Tennessee, which accepted him. He enrolled just before his 18th birthday and earned his MD in 1947. Elected to Alpha Omega Alpha, he was also honored as class valedictorian.

After completing his internship at Johns Hopkins Hospital in 1948, Dr. Spencer began his residency in the just-formed Department of Surgery at the University of California, Los Angeles, but his training was interrupted by service in the US Navy during the Korean War. Having learned how to perform arterial repairs during his surgical training, Dr. Spencer was dismayed to see soldiers with arterial injuries scheduled for amputation, as protocol dictated, rather than repair. Because rescue helicopters could swiftly transport the wounded to a mobile surgical hospital, Dr. Spencer saw an opportunity for more timely repairs. He sought permission to repair arteries, but when three weeks went by without a response, he assembled surgical teams in two medical units behind the combat zone. At the risk of being court-martialed for not following protocol, he spent the next nine months performing more than 150 arterial repairs, with a success rate of nearly 90%.

When a reporter interviewed Dr. Spencer about his unsanctioned limb-saving technique, news of his efforts traveled across the wire services, earning the 26-year-old surgeon widespread acclaim, as well as the navy's Legion of Merit Award for exemplary service. "Arterial repair in Korea benefited more people than anything I've ever done," Dr. Spencer recalled many years later. "Why did I do this? It was simply a reflex—do what's best for the patient."

After military service, Dr. Spencer completed his surgical training at Johns Hopkins, where he remained on the faculty for several years. Subsequently, he launched the cardiac surgery program at the University of Kentucky's School of Medicine. Dr. Spencer was one of only a handful of surgeons to be elected president of the American Association of Thoracic Surgery, the American College of Surgeons, and the American Surgical Association.

Dr. Spencer is survived by his daughters, Dr. Elizabeth Kay Spencer Crabb and Patricia Spencer, and grandchildren, Elizabeth and Adelaide Crabb.

"Running a lab involves guiding people through good times and not so good times. And it requires being curious, listening, trying to understand, and finding creative solutions."

WHO:

Dafna Bar-Sagi, PhD

Senior Vice President and Vice Dean for Science, Chief Scientific Officer

Professor, Department of Biochemistry and Molecular Pharmacology

Professor, Department of Medicine

Last spring, NYU Langone Health leader Dafna Bar-Sagi, PhD, spoke to first-year medical students about what she's learned during her career as a pioneering cancer researcher and executive leader at NYU Langone Health. The conversation was part of NYU School of Medicine's Leaders and Teams lecture series. Here, a few highlights.

• • •

Gratitude will take you far. My parents were Holocaust survivors, and their stories taught me never to take anything for granted. Human life is so, so precious. Be grateful for everything that comes your way and determined to do the most you can with it.

Think of everybody around you as a potential role model. All of us interact daily with people who are either colleagues or supervisors, who are so capable, so intelligent, so creative that it's a huge privilege to be around them. Every day I hear something that causes me to pause, consider how I think about things, and ask myself whether I need to recalibrate.

Women shouldn't feel obligated to take on everything. Because a minority of women hold leadership positions, we're asked to do a lot of things. That can detract from our ability to accomplish our goals. It's important to be gracious about the trust and the respect your peers are paying you by asking you to do certain things, but also to guard your own interest and make sure that you prioritize things in a way that allows you to proceed with your own career.

Good science requires leadership. Running a lab involves motivating people, guiding them through good times and not so good times. And it requires being curious about things, listening, trying to understand, and finding creative solutions.

It takes perseverance, too. Every research project I have done myself or lived through with the people in my lab has taken longer than expected. We might think a certain project will take three months, and it ends up taking three years. But that's part of the beauty of what we're doing. We let the science guide us through the journey of finding an answer to the question that we're pursuing.

Transparency is key to inspiring a team. It's wonderful when people have a clear-cut idea of the landscape and the motives behind how things are being done. I've always been a firm believer in disclosing whatever is possible so that everyone understands where they're coming from and where they're going to. No secrets.

Don't just talk the talk; walk the walk. To energize people to achieve your vision, you need to be positive, have a can-do attitude, and empower them by giving them the tools to succeed. Only then you can hold them accountable.

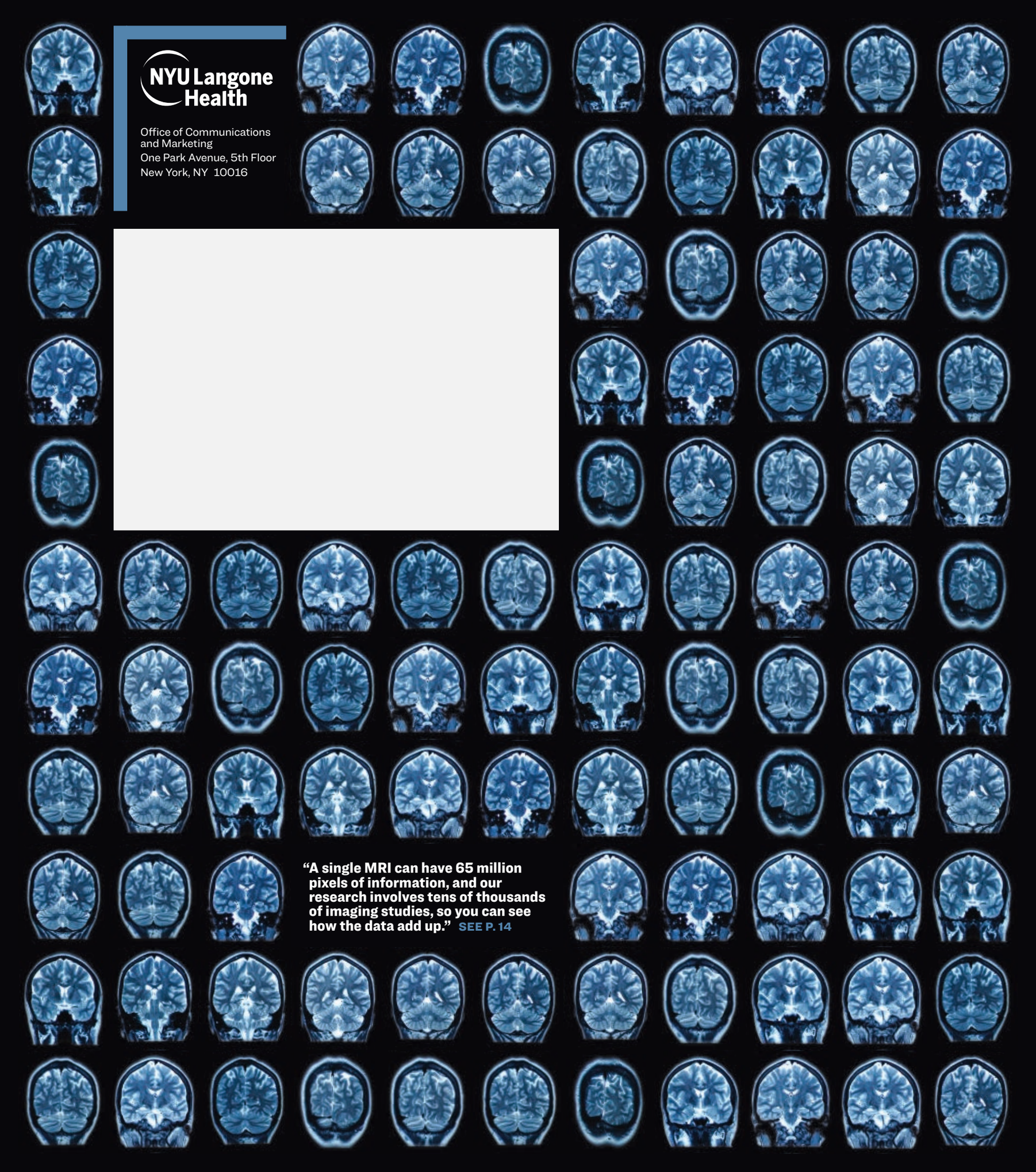
Live your career by these three principles. Work hard, no matter how smart or privileged you are. Seize the opportunity—there are so many amazing things you can learn from and take advantage of, so don't let them pass you by. Finally, look for someone you can relate to, either as a role model or a friend. To navigate through your professional career, you need a compass, someone you can always come to and count on.

Keep striving to improve. It's very easy to become comfortable when things are going well. But leaders don't get any particular points for that success because it's expected of them. That's why they were picked in the first place. Where you're really being tested is when things aren't going well—what you learn from these situations and how you correct them.

Bequests and other planned gifts to NYU School of Medicine, both large and small, have a resounding impact on our mission. Whether you want to give back to support scholarships or educational and research programs, our planned giving specialists will help you make a meaningful gift that is right for you. We deeply appreciate the generosity of all who support our future.

Contact us at (800) 422-4483 or plannedgiving@nyulangone.org

NYU School of Medicine



NYU Langone Health

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"A single MRI can have 65 million pixels of information, and our research involves tens of thousands of imaging studies, so you can see how the data add up." SEE P. 14