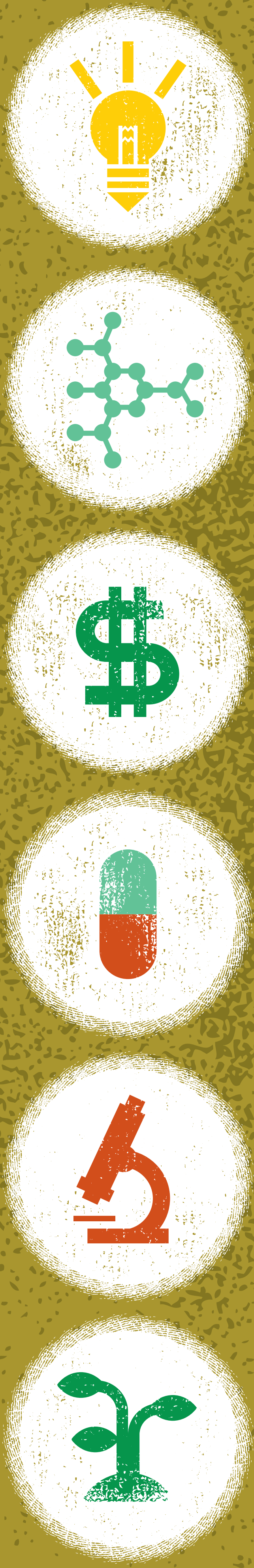
yale medicine magazine

TECHNOLOGY

A tool for treatment

Summer 2019



Features

summer 2019 departments

COVER AND THIS SPREAD: MATTHEW DALEY ILLUSTRATIONS

from the editor

Technology, the subject of this issue, means change. And change is often good and bad—more of the former, one hopes, than the latter.

Yale Medicine Magazine (YMM) used to receive physical correspondence from readers, for example. That correspondence would be printed on this page. Later, physical correspondence was replaced by emails. More recently still, physical correspondence has almost entirely disappeared, which might be considered bad. That correspondence still occurs, though—in real time, via social media. It includes many more and varied voices than in the past, which is good ... but almost none of that dialogue is suitable for print (definitely bad).

Writers, thinkers, and scientists have been considering the ethical ramifications of technological advances for years. At least as far back as Plato's Ring of Gyges myth, thinkers were experimenting with hypothetical scenarios, testing out likely human responses should some device change the terms on which one navigates society's mores.

YMM's "Letters to the Editor" page has become a disused venue for alumni, faculty, and students to share perspectives on past issues and articles at the same time that society has been wrestling with how to evaluate and process information. Few fields have felt the impact of that crisis of confidence in authority more acutely than science, which has been subjected to fallacious questions about the efficacy of vaccinations, climate change, and even the significance of correlations between gun use and violence produced by guns.

As technology advances, it's important to consider its ramifications, something at which doctors and scientists are adept. The medical profession is one of the few that abide by an ethical oath—to "do no harm." It's also important to communicate those changes, once weighed, to the lay audience. I'm proud to play a small ancillary role in facilitating that communication, both in print and online, via social media.

Adrian Bonenberger
Editor, Yale Medicine Magazine

NOTE
As we transition to new mailing list software, we welcome any changes of name, address, or status at ymm@yale.edu.

SECOND OPINION
BY SIDNEY HARRIS

Send letters and news items to
Yale Medicine Magazine, 1 Church Street, Suite 300, New Haven, CT 06510 or email ymm@yale.edu.
Please limit letters to 350 words and include a telephone number. Submissions may be edited for length.

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Yale SCHOOL OF MEDICINE

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Using technology to drive scientific advances

FACULTY AT YALE SCHOOL OF MEDICINE have a long tradition of innovation in the technology sphere. Robert J. Alpern, MD, dean and Ensign Professor of Medicine, discusses the school's current technological strengths and initiatives he believes will help continue carrying the school forward into the 21st century.

How is Yale School of Medicine taking advantage of advances in technology? Increasingly, advances in science are limited by advances in technology. In some fields, without certain devices, it's impossible to conduct clinical research. Top schools, including Yale, have to identify which cutting-edge technologies will give science and researchers the best opportunities, and invest in them. Advanced technologies are often very expensive in terms of money and expertise, so we've stepped forward to fund facilities that have the potential to be widely used by researchers. Cryo-electron microscopy is one recent example of this; no individual investigator could afford it, so the medical school and the provost's office made a major investment in cryo-electron microscopy. Not just purchasing the equipment and finding a space for it, but also creating a core with technical expertise so that investigators who need it for research but lack the mechanical know-how are able to use it.

How has that changed over your tenure? We're able to do extraordinary things that just weren't possible 20 years ago. A great example of this is DNA sequencing. When the instrumentation became available so that any university could perform state-of-the-art DNA or RNA sequencing, Yale made major investments so investigators could have access to this technology. Those who have made use of this resource say it's been a game-changer.

What has spurred those changes here at Yale? From the moment I stepped on campus, it became clear to me that one of the people really driving investment in technology to support research was Carolyn Slayman. Carolyn always believed in supporting this cause, and as the medical school's finances have improved, it's been easier to support more and different technological investments for faculty and students. This type of thinking is now common in the top schools, but Carolyn was ahead of her time.

What does the school do if a device is difficult to use or to maintain? It depends. In some cases, it's just a question of giving researchers access and training and they'll be able to use the device themselves. In the case of the cryo-electron microscope, the machine is so complex that many investigators just don't know how to operate it correctly, and if they make an error, they'll break it. Some investigators can use it properly and do, in their research. For those who need it, we make certain technical assistance is available. The point is to facilitate research, not bog scientists down with tasks outside their realm of expertise.

How does YSM differ from competitor institutions? I tend to think about how we're similar to other top institutions—which strengths are common to leading innovators. First of all, we want to develop technology that's useful to science and medicine. Second, if we can't develop it ourselves, we want to be early adopters when others develop an exciting new device. DNA sequencing, again, was a place where we couldn't develop or adopt at first—if you weren't part of the Human Genome Project you couldn't build the DNA sequencers they were using. As soon as the DNA sequencers were developed commercially, we invested in resourcing our faculty with that capability. And it's really offered our scientists an advantage.

Prolific publication: One lab's secret to success

THE GRAUER LAB meets every Friday in an office suite of the orthopaedics department. Medical students, several residents, and a few attending physicians sit around the table, eyes fixed on a monitor at the front of the small conference room. They're examining graphs and tables designed to explain the significance of medical data from thousands of patients across the country.

Lab members comb through national (sometimes Yale-specific) medical databases looking at outcomes of interest in the field of orthopaedics. By analyzing data from thousands of patients, they can gauge how well a treatment works; determine which conditions lead to surgical complications; and propose ways to optimize outcomes.

To come up with research ideas, the group reads through published studies and asks how the so-called big data approach might find better answers to existing questions. "We define questions raised from the literature or from local discussions and see what we have the tools to answer well. Often, we can resolve questions that have not been answered in the past, or use larger or more defined patient populations to address questions in novel ways," said Jonathan N. Grauer, MD, interim chair and professor of orthopaedics and rehabilitation, and co-director of the Spine Center at Yale New Haven Hospital.

When Grauer joined the Yale faculty in 2003, he worked in a lab conducting preclinical animal studies focused on bone formation and spinal fusion. Over time his work evolved, and his research now relies on software and big data.

Grauer's conversion to this type of research came in 2012 when a student approached him with an idea for a study. Rafael Buerba-Siller, MD '14, MHS '14, then a Yale medical student, asked Grauer whether he would be willing to help him apply big data research techniques to orthopaedics. Previously, Buerba-Siller had used such tools for studies in endocrine surgery. Grauer agreed to help: "And sure enough the study went great," he said, opening "doors to novel approaches in orthopaedics and spine research."

The focus of Grauer's research shifted from gathering data to posing questions, assessing data, and deriving clinically useful conclusions. By applying contemporary clinical questions to big data sets, Grauer's Lab performed more and more studies on varying topics in spine surgery and orthopaedics.

"I think [the lab] ranks pretty high in terms of productivity," said Lee E. Rubin, MD, HS '09, associate professor of orthopaedics and rehabilitation, who works with Grauer and helps guide the student members of the lab. He estimates that among the medical students who spend a full year of research in the Grauer Lab, "each will typically achieve 10 to 15 completed projects that are presented or published."

Pat Bovonratwet, MD '19, joined the Grauer lab in 2016 after his first year at Yale. "The upperclassmen had always told me, 'Dr. Grauer's the man to go to if you're interested in orthopaedic research,' " he said. At the end of that summer, Bovonratwet published his first first-author paper. Since then, he has published a total of 33 peer-reviewed papers from the Grauer Lab. Bovonratwet is listed as first author on 14 of those papers.

This level of achievement is not unusual among the students in the Grauer Lab. "He's very inclusive of medical students," said Bovonratwet. "When I first joined, he told me, 'I will always support you and your co-students in leading the studies.' " Grauer gives the medical students autonomy when it comes to research, guiding them at each step of the research process, and "helping them to develop their researcher skills," Grauer said.

The lab is focused on making a clinical difference. "We review these projects at every stage," said Rubin. "Almost all of these publications find a way in [to journals] because it's high-quality research."

Part of the reason the lab can boast this high quality is that its members scrutinize the limitations of their methods. "We've written many papers that call out the limitations of the type of research we do," said Grauer. "In doing so, we become credible in the conclusions that we draw."

According to Bovonratwet, aside from the research experience, lab members also benefit from a dedicated mentor and a network of lab alumni. Bovonratwet noted that many of Grauer's previous lab members still remain involved, giving current members guidance, resources, or project ideas. This network is derived from Grauer's dedication to research and his group. "He is a great mentor and supports his students through medical school and beyond," said Bovonratwet.

—*Jackie Rocheleau*

Jonathan Grauer's lab has an impressive record of publications. The secret is using big data to identify likely problem areas with orthopaedic surgery, as well as potential solutions. After his patients, Grauer's students have been among the greatest beneficiaries of this efficient and effective process.

MakeHaven includes those interested in or connected to medicine

Gina Siddiqui, MD, had scarcely handled a screwdriver when she set foot last August in MakeHaven, the makerspace in downtown New Haven. "I didn't know the difference between a screw and a bolt," said Siddiqui, who's in her third year of an emergency medicine residency at Yale New Haven Hospital. Over the course of the next 30 days, with training from MakeHaven staff, she mastered everything from a hammer and chisel to a laser cutter as she built her husband a present for his birthday in early September—a large format view camera.

Working with maple and balsa wood, she crafted a camera with a holder for 5x7-inch film negatives, a tripod mount, and railings to support the bellows and lens she bought from a photo supply house. "I found it incredibly invigorating," Siddiqui said.

MakeHaven is one of about 100 community-based makerspaces around the country—part of a growing movement that emerged in the early 2000s as inventors, tinkerers, hobbyists, and artisans banded together to ply their crafts and indulge their passion for creativity. The fruits of those labors ranged from inventions that would obtain patents and spawn companies to toys that glow in the dark.

"There is some fundamental need and satisfaction in making something," said MakeHaven board member Joel Greenwood, PhD, director of neurotechnology in the Department of Neuroscience at the School of Medicine. "We are getting further and further away from making things," he lamented.

His passion for building comes from his childhood on a farm an hour south of Seattle, where his parents lived off the land, growing vegetables,

ROBERT LISAK PHOTO

ONLINE EXCLUSIVE

In 1965, a land mine landed Yale graduate George Cadwalader in a steamy tent of the 3rd Surgical Mobile Hospital (MASH) in Vietnam. Little did he suspect that his surgeon, Captain Kristaps Keggi of the 173rd Airborne, was another son of Eli. Keggi, a YSM graduate, would save Cadwalder's legs, and the two formed an unlikely friendship.

For more on their experience in Vietnam and after, visit ymm.yale.edu/battlebuddies

and raising sheep and chickens. Greenwood's father was a home builder who had a two-story woodshop on the property. "I grew up building stuff," Greenwood said. At Yale, he helps neuroscientists solve problems by teaching them to build the tools they'll need, or directing them to people who can make equipment for them.

Like its peer spaces around the country, MakeHaven offers its 300 members a place to work, access to tools, and a like-minded community that provides feedback and shares ideas and techniques. While New Haven has other makerspaces, like Yale's Center for Engineering Innovation and Design, MakeHaven is the only one that's open to the community at large.

The seeds for MakeHaven sprouted at a meetup in 2012. When critical mass grew to about 50 people, the participants chipped in to rent space on State Street and rummaged through their homes for tools. "Not all the tools were of the best quality," said J.R. Logan, one of the founders and now executive director. "They were hand-me-downs." In March 2018, MakeHaven moved to a larger space—5,000 square feet in the basement of 770 Chapel Street, a building that also houses SeeClickFix. Tools are no longer basement relics: they include woodworking and metalworking equipment, an electronics workbench, 3D printers, sewing

ROBERT LISAK PHOTO

machines, printing presses, and a home brewing machine. In addition to space, tools, and training, MakeHaven offers talks, classes, and workshops.

As MakeHaven grew, members realized they could no longer rely on volunteers to run the place day to day. Logan, whose father was an inventor, was the first full-time employee. Kate Cebik works full time as operations manager. Lior Treshman is MakeHaven's part-time "maker guru."

The space sustains itself with dues ($50 per month, $35 for students) and grants, including one from CTNext, which supports companies and entrepreneurs with funding and mentorship programs. Members come with a variety of ambitions. Some have patented their inventions, and some have given up their day jobs to pursue their projects. Others are hobbyists and tinkerers. "They find joy in whatever is their area of technology," said Logan. "They wanted a platform and to be able to share it. It has broadened and gotten bigger."

On a recent weekday, Nick McGhee was editing a presentation he and colleagues are making for a NASA design competition—a prototype of a human habitat for Mars. Upon their arrival on Mars, pioneers will need tools to turn Martian raw materials into a permanent home. "The project we worked on is to develop the necessary technology," said McGhee, who recently left his job as an aerospace engineer to devote himself to the project. His project took third place and won $32,000.

Another member has used MakeHaven's 3D printer to make prosthetic hands for children in the developing world. One member is working on a quadcopter, which is a helicopter lifted and propelled by four rotors. Still another is using DIY instructions available online to make a book scanner.

Like others involved in MakeHaven, founding member Ben Berkowitz, the CEO of SeeClickFix, grew up making things—his father was a carpenter. The past chair of MakeHaven's board, he still makes toys for his children and decorations for his office. "MakeHaven," he said, "is a place to learn new skills and share ideas, to build businesses, and for anyone to achieve their dreams of making something with their hands."

—*John Curtis*

Treating childhood autism one robot at a time

Parents can be resistant to hearing that their child faces a challenging health diagnosis. But when Thomas Leaf and Emanuela Palmares learned that their son Caio has autism spectrum disorder (ASD), the diagnosis answered many questions with which they'd been grappling as parents and as individuals.

It wasn't clear to them that Caio might be on the autism spectrum. Only after their insurance stopped covering hearing tests nearing Caio's third birthday, did the two bring him into Yale's Child Study Center to undergo evaluation for a study. It turned out to be a wise decision.

"When they described Caio's behavior in terms of autism, a lot of things clicked into place," said Leaf. "His focus on a tree on the horizon and tuning the rest of the world out. His fixating on a soccer line during a soccer game and ignoring the game around him. His difficulty discriminating foreground from background noise."

"I had some trouble as a kid—acting out, throwing tantrums—feeling misunderstood and apart. That's an awful thing to go through when you're young, and autism is the kind of disorder that, without therapy, can make alienation worse," said Leaf. "Hearing Caio's diagnosis, we wanted to give him the best treatment as soon as possible."

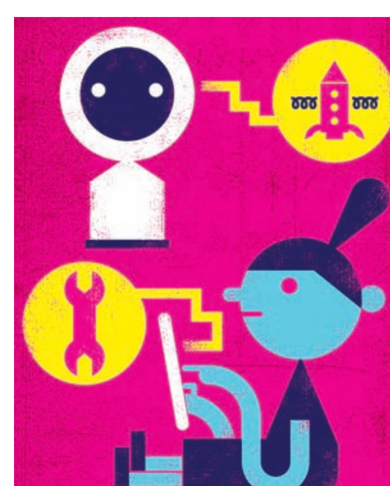
"For the first 18 months, we'd been raising an infant, basically," said Palmares. "Once we embraced what was happening, though, we started seeing improvements in Caio almost immediately."

ASD affects approximately 1 in 59 children, and is nearly four times more likely to be diagnosed in boys than girls, according to the Centers for Disease Control and Prevention. While many children are diagnosed after age 4, there are reliable mechanisms for diagnosing children earlier. The earlier children are diagnosed, of course, the more effective treatment can be. Caio's diagnosis at the age of 3 put him in a good position to lead the kind of life available to most children, fully integrated into society.

Fred Volkmar, MD, the Irving B. Harris Professor in the Child Study Center and professor of psychology, is one of the people driving efforts to expand early diagnosis and treatment of children with ASD. He said that just in his lifetime he's watched autism go from a once little-understood diagnosis considered by many a kind of lifetime prison sentence (think Dustin Hoffman's character in *Rain Man*) to a fully treatable condition, driven by a wealth of research.

"I've served as an editor for the *Journal of ASD*, and the number of submissions we get to publish papers has really taken off over the last 10 years," said Volkmar.

Even so, Volkmar said that there were gaps in research and treatment—specifically, studying two very promising fields, robotics and smartphone applications. Children on the autism spectrum have trouble with what psychologists call executive functions: monitoring multiple stimuli and completing complex tasks. Social interactions are among the most complicated tasks humans perform many times over on a daily basis. Navigating those interactions can quickly overwhelm children with ASD, which explains why they have difficulties interacting with others as well as with the specific



OPPOSITE New Haven's MakeHaven is one of a network of makers communities across the country where innovation-minded citizens pool resources to buy and use machines few could afford on their own. Yale School of Medicine faculty and students have been known to use the facilities.

MATTHEW DALEY ILLUSTRATON

ONLINE EXCLUSIVE

YSM's clinical research arm has benefited from two substantial behind-the-scenes technological advances. Sometimes software and integration of systems can produce outsize operational results.

For more on YSM's clinical research arm, visit ymm.yale.edu/electronicrecords

challenges they face in professional environments.

"Children on the autism spectrum get only about 10% of the social affective information in a scene, in large part because they're looking at mouths, not eyes," said Volkmar. "The top half of the face is where the action is, socially speaking, in terms of nonverbal communication."

Robots are interactive partners with which children on the autism spectrum can feel comfortable because there is little or no nonverbal communication. This simplicity can help children learn to express themselves without anxiety, which in turn can lead to better interactions with humans in the child's life (adults, siblings, and friends).

Brian Scassellati, PhD, the A. Bartlett Giamatti Professor of Computer Science and Mechanical Engineering and Materials Science, is developing robots designed specifically to help children on the autism spectrum improve social skills. He has worked with the Child Study Center and Volkmar to ensure that the robots are ideally designed for children with ASD, down to a narrative for their arrival in the house and their imminent departure. This narrative has been tested in a recent study that was published in *Science Robotics* in August 2018.

"From the first moment in the house, the robot tells a story about how it is a space explorer whose spaceship has broken down. The child, in interacting with the robot, is helping it to perform tasks to get its spaceship working again. At the end of the study, the robot has fixed its ship and can return to space, leaving the child's home," said Scassellati. "This story helps the children build empathy at the same time that they're building social skills, and makes the departure of the robot less disruptive."

Thus far, feedback has been extraordinarily and overwhelmingly positive, according to Scassellati. "All of the children in the study made significant gains in their social skills, and the robots were very well received. The parents don't want the robots to leave; even more so than the children, even." He said that after the robots left, some of the children lost the gains they had made, but that in and of itself isn't exceptional. "We didn't expect the robots to create permanent changes after just a month. Our best therapies don't work that quickly," he said.

Apps are another way to help children with ASD. David Grodberg, MD, FW '99, assistant professor of psychiatry and medical director of the Child Study Center's Outpatient Clinic, has been developing an application to help parents learn to use the same behavioral interventions with their children that are used by experts. "Much of the important work that's done by professionals in a clinical setting can—must, really—be augmented by engaging the parents and other caregivers," he said. Giving them tools to guide their treatment plans along carefully prescribed lines and with feedback from clinicians is key, he said, to maximizing the benefit to affected children.

Palmares, who has since remarried, noted that having a child with ASD requires great efforts as a parent, but also that the process has been personally rewarding. "Caio has made me a better mother and a better wife," she said. She and Leaf divorced not long after Caio's diagnosis, for reasons unrelated to his condition, and "co-parenting him has allowed both of us to forgive each other and have a healthy, respectful relationship. We have to, for Caio's sake."

Leaf agreed. "I think Emanuela and I both see raising Caio as a call to make ourselves better people. I remember my childhood, growing up as an outsider, not really feeling at home until I went to Hopkins [a private school in New Haven]. Caio's never going to feel like he's a bad kid, like he's weird or unaccepted. He is who he is."

Caio has become adept at using educational apps, and has his own programmable robot that he loves playing with. He's even mastered a form of programming to get the robot to perform different tasks. Increasingly, what could have been a debilitating condition is for Caio and children like him, just another one of life's manageable challenges.

—*Adrian Bonenberger*

round up

a collection of recent scientific findings

COUNSELING PARENTS TO HELP TREAT KIDS' ANXIETY

One in three American children will experience a clinically significant anxiety disorder before adulthood. Eli Lebowitz, PhD, associate professor in the Child Study Center, recently conducted a study that concluded that counseling the parents of anxious children can be as effective in treating common anxiety disorders as cognitive behavioral therapy for the children. Lebowitz's program is called SPACE (Supportive Parenting for Anxious Childhood Emotions). Parents in the SPACE program are counseled to be less accommodating; that is, to reduce the number of changes they make in their own behavior to lower the child's distress.

MEMORY LOSS IN OPIOID USE

Clusters of people with a history of opioid use who present without the ability to form new memories—a kind of brain damage—may offer a clue to amnesia, inflammation, and the process of memory loss. Adam Jasne, MD, assistant professor of neurology, observed swelling in the cerebellum and hippocampus (a part of the brain involved in memory formation) in six drug-overdose patients suffering from amnesia. Sometimes the brain swelling is fatal, and even when it isn't, the patient can have permanent memory impairment along with such physical problems as movement abnormalities and seizures.

TEXTING FOR A HEALTHY HEART

A project involving researchers at Yale and in China gauges the potential for smartphones to improve heart health in a country with high rates of heart disease. Patients in different regions across China diagnosed with chronic heart conditions received supportive text messages as well as texts offering guidance on daily activities to support specific health goals. While the messages did not result in significant changes to the participants' blood pressure, most of the subjects liked them and wanted to continue to receive informational and motivational support after the study ended.

UNDERSTANDING WOUND CLOSURE

Together with researchers at University College London, scientists at Yale looked closely at how cells behave when repairing skin tissue. By using traction force microscopy, the researchers identified two mechanisms by which muscle proteins are brought to the edge of a wound to close it: using protein actin projections called lamellipodia at the leading edge of a cell to move the entire cell, or by forming a "purse string" bundle of cells across the leading edge of the wound. Understanding these coordinated cellular behaviors will help researchers develop new methods of healing physical trauma.

RACIAL DISPARITIES IN KIDNEY TRANSPLANT

The kidney, according to the Centers for Disease Control and Prevention, is among the six most commonly transplanted organs in the United States. Recent research indicates, however, that Black patients encounter significantly more difficulty in receiving a kidney for transplantation. The reasons for the disparity are not completely clear, but one major factor is that Black patients are less likely to be moved from inactive to active status on the transplant waiting list after initial listing. Researchers suggest that better coordination between kidney dialysis units and transplant centers would help solve the problem.

GETTY IMAGES

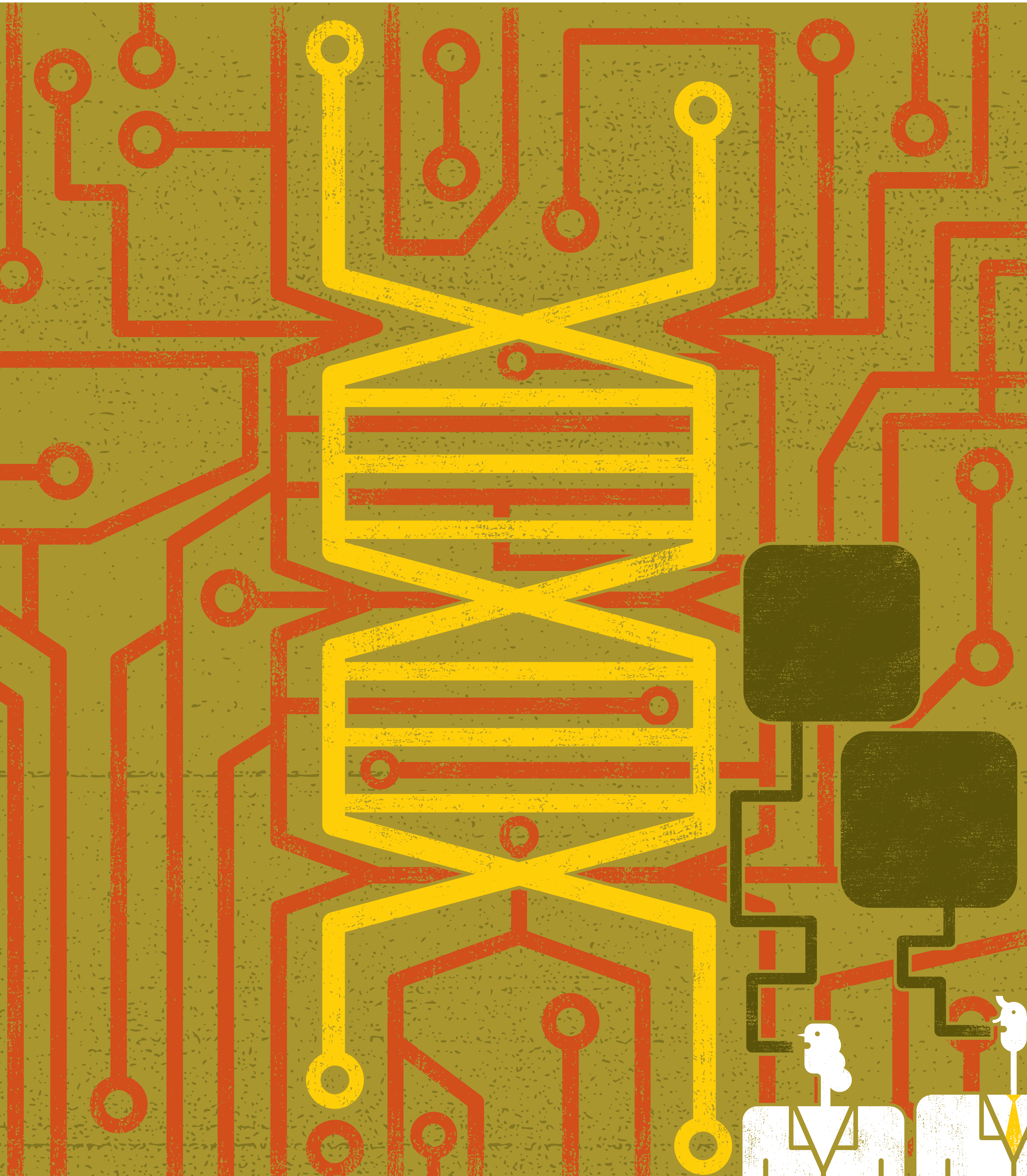
TECHNOLOGY: A TOOL FOR TREATMENT

AS DOCTORS AND RESEARCHERS become increasingly specialized in their fields, so too do the tools and technology they use to diagnose and treat patients as well as conduct research. These tools are themselves the product of expertise, and one of the strengths of Yale School of Medicine (YSM) is the wealth of informal and formal collaborations between clinicians and inventors.

This issue looks at some of those technological collaborations among doctors, scientists, and engineers that have led to breakthroughs, as well as innovations that are ongoing or imminent. Abby Roth's "Honing clinical skills with ultrasound" considers how advances in machines, as well as such pedagogical tools as smart tablets, can help students hone their skills before setting foot in the clinic. Ken Byron writes about an undergraduate class in biomedical engineering co-taught by assistant professor of surgery Daniel Wiznia, MD, and Steven Tommasini, PhD, which focuses on engineering solutions to real-world orthopaedics problems. And former *Yale Medicine Magazine* editor John Curtis has compiled a timeline of medical innovation that sets some of Yale's and YSM's more notable achievements in historical context.

There's a lot more—the synthesis between imaging and 3D printing could take up a whole issue by itself, and there are several stories in these pages that dive into advances in that field.

It's an exciting time to be working on technological solutions to medical problems, and YSM is proud to offer workshops, laboratories, and funding to people who contribute to that work.



THE NEW MACHINERY OF MEDICINE

BY STEVE HAMM | ROBERT LISAK PHOTO

For patients suffering from genetic disorders or diseases that may be cured by a combination of three new technologies, the clinical applications can't come quickly enough.

Just four months after Elsa Violante was born, she began to have seizures. The spasms lasted from 30 seconds to four minutes, and they came every 15 minutes to half an hour. Her parents, Alexis and Christiane Violante, rushed her to her pediatrician near their home in suburban Toronto. He sent them to the emergency department of a downtown hospital.

The diagnosis was early infantile epileptic encephalopathy, a rare and serious condition that can have debilitating lifelong effects. "After they told us what it really was, it became terrifying," says Alexis.

Physicians at the Hospital for Sick Children (SickKids) in Toronto tried one treatment after another to address Elsa's seizures, but they couldn't identify the underlying cause. So they sent the family's blood tests to Yale Medicine's Pediatric Genomics Discovery Program (PGDP). Using gene sequencing machines, high-performance computers, and CRISPR-Cas9 genome editing technologies, the PGDP team discovered that a rare variant of the gene *NEUROD2* on chromosome 17 is responsible for Elsa's condition.

Ultimately, a high-fat low-carbohydrate diet addressed Elsa's seizures, but physicians can't repair her damaged nervous system. At age 5, she is unable to walk or even sit up, and she has limited control of her arms and hands. Yet her parents hope that medical science will produce advances that will make Elsa's life better—and that the discovery of the *NEUROD2* variant will help other kids and families.

Elsa's story illustrates a powerful melding of technologies that's helping to solve the mysteries of life and to usher in the era of precision medicine. Gene sequencing, computer data analysis, and the simulation of scenarios using experimental genome editing techniques enable researchers to identify and understand the differences among people on the genetic level. As a result, we can better diagnose diseases and choose—or design—treatments tailored to help individual patients. "From the standpoint of medicine and health, this can be transformative—and in ways that we can't even appreciate now," says Saquib Lakhani, MD, assistant professor of pediatrics and clinical director of the PGDP program.

Yet this combination of tools is just one of many applications of technology to medicine that are changing the ways medical researchers do their work and physicians treat patients. For decades, technology has played a critical role in medicine. From the iron lung in 1929 through the cardiac pacemaker, the artificial heart, and robotic surgery in more recent times, engineers and medical scientists have long collaborated to produce innovations at the intersections of their fields.

Yale faculty members have been in the vanguard. Scientists and clinicians here were pioneers in the use of magnetic resonance imaging (MRI) machines. William V. Tamborlane, MD, FW '77, professor of pediatrics, and Robert S. Sherwin, MD, FW '74, the C.N.H. Long Professor Emeritus of Internal Medicine (Endocrinology), developed the insulin infusion pump for people with diabetes. Stuart Weinzimer, MD, professor of pediatrics, led a team that produced an artificial pancreas. And Jonathan Rothberg, PhD '91, professor (adjunct) of genetics, developed high-speed "Next-Gen" DNA sequencing.

Perhaps the most important advance in computer-related genetics research at Yale came in 2009, when a research team led by Richard Lifton, MD, PhD, who was then chair of the Department of Genetics and is now president of Rockefeller University, used new technologies to discover the genes and biochemical mechanisms that cause hypertension. Lifton's team developed a technique for performing whole-exome sequencing, enabling researchers to examine the protein-coding region of the human genome (about 1% of the whole) at much lower cost than sequencing the full genome.

Medical technology innovation accelerated after the Institute of Medicine in 1999 released a report titled *To Err is Human: Building a Safer Health System*, according to Peter Schulam, MD, PhD, chair of the Department of Urology and chief innovation and transformation officer for the Yale New Haven Health System. The report called for technology-based advances aimed at improving the quality of health care. Since then, a host of new devices and computer-based tools have been introduced that enable physicians to do their jobs better. "Technology has the potential to minimize human variability and improve patient outcomes," Schulam says.

Yale is newly committed to playing an even more prominent role in bringing technology to bear on humanity's most critical problems—with medicine as a top priority. The University Science Strategy Committee (USSC) last year unveiled a plan to accelerate discoveries, often through multidisciplinary collaborations. Focus areas in medicine include neuroscience, inflammation science, conquering cancer, regenerative medicine, and precision medicine. "A large fraction of the modern frontiers of scientific and medicine research is interdisciplinary," says Peter Schiffer, PhD, vice provost for research. "You've got data people working with fundamental scientists, with clinicians, and with the engineers designing devices."

Because data analysis plays an important role in most of these cross-disciplinary endeavors, Schiffer is working with leaders of schools and departments to provide researchers and students with the computational resources they need. Until recently, most faculty members and programs at Yale purchased and operated their own research computers. But in 2015, the university opened Yale Center for Research Computing (YCRC), which has five clusters of computers made available to researchers as shared resources.

Saquib Lakhani, Clinical Director of the Pediatric Genomics Discovery Program, is optimistic that increased diagnostic capabilities may help offer treatment to infants.

The YCRC's computers are housed in a nondescript former manufacturing building on Yale West Campus. One of the clusters is dedicated to genetic research. Named Ruddle (for Francis Ruddle, PhD, a Yale pioneer in genetic engineering), the cluster is made up of two parallel rows of metal racks containing computers, storage devices, and the networking equipment to allow them to communicate. Between the racks, it's hot and noisy.

Ruddle has roughly the same computational power as you would get by stringing together 2,000 or so high-end laptop computers. In addition, it possesses three petabytes (three quadrillion bytes) of digital storage. That's a lot. If you were to fill Ruddle's storage devices with MP3-encoded songs, you could play music for 6,000 years.

The reason Ruddle needs so much computing power sits directly across the street from the data center—Yale Center for Genome Analysis (YCGA). There, scientists and technicians use million-dollar gene-sequencing machines and other tools to help faculty members and students perform their research. The gene sequencing takes place at YCGA, while the analysis of the results is done with Ruddle. In some cases, diseases are caused by variants in multiple genes, so analysis of the interplay among the genes requires a large amount of computing power.

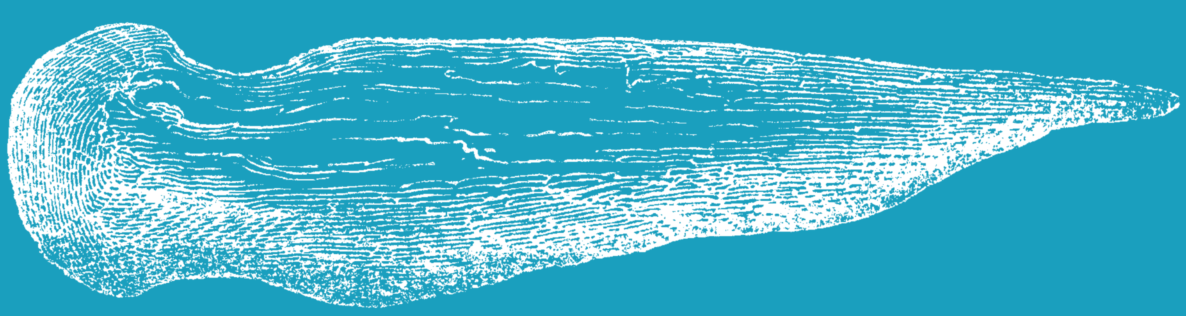
The scale of this type of computation is tremendous. Each individual human genome contains about 3 billion DNA base pairs. It took more than a decade and about $2.7 billion to sequence the first human genome—a feat completed in 2003. Now, because of advances in gene-sequencing techniques and high-performance computing, technicians can sequence and analyze an entire genome in a couple of days for about $1,000. Sequencing of the whole exome, which is the protein coding subset of the genome in which most disease-causing variants occur, costs about $200 and can be completed in a few hours.

The PGDP research team uses whole-exome sequencing to make discoveries in such cases as Elsa Violante's. Using techniques initially developed by Lifton, a family's blood samples are submitted to the YCGA or another facility like it for sequencing. Next, the computers are used to identify potential variants of interest. The research team looks at these results, as well as the specific problems a child has, to find the very best candidates for testing. In the case of Elsa and another child with similar seizures, variants in the *NEUROD2* gene became the focus.

The PGDP scientists used CRISPR-Cas9 genome editing in frog eggs to explore further. They introduced CRISPR-Cas9 molecules into the eggs through a tiny needle. The molecules worked together to target and eliminate the *NEUROD2* sequence. These eggs were then incubated and tadpoles emerged over the next few days. Researchers observed the tadpoles' behavior as they developed, and they noticed convulsions. Bolstered with other evidence, they concluded that *NEUROD2* variants were the cause of the seizures in both children.

"We hope this discovery helps other children with infant-onset epilepsy caused by *NEUROD2* variants to be identified sooner, to hopefully have appropriate seizure treatments sooner," says Lauren Jeffries, DO, the clinical genetics coordinator for PGDP. "Having a specific genetic diagnosis can help doctors and families have better understanding of treatments, outcomes, and predictions."

While giving a tour of the YCGA lab, its director, Shrikant Mane, PhD, professor of genetics, proudly shows off the latest gene sequencing machines, which are the size of small refrigerators. Then, with a twinkle in his eye, he removes a device the size of a smartphone from a box and waves it in the air like a magic



Medical devices and technology across the years

As long as humans have had the ability to craft tools, they've been using them to solve medical problems. Over time, the tools have become increasingly complex and sophisticated.

By John Curtis

wand. "The latest technology that's on the market—this is a sequencing machine," he says.

The device he's holding is a portable DNA sequencer developed by Oxford Nanopore Technologies, which is designed to enable physicians and researchers to sequence small fragments of DNA or RNA. In one scenario, health workers in Africa could use the device to test patients in remote villages for Ebola fever. The sequencer costs just $1,000. "You can carry this in your backpack. All you need is the human samples and a laptop. This is the future," Mane says.

While miniaturization in electronics will make such devices ever smaller and cheaper, the data sets that scientists and clinicians work with are getting ever larger. But that's a good thing. By combining detailed genetic information from hundreds of thousands (and soon millions) of people with data from electronic medical records and information from research databases, researchers and clinicians can take into account a wealth of information when they make decisions that guide research or patient care.

A new initiative at Yale is aimed at rapidly collecting genetic data that can be used for research and care. The Generations Project, launched earlier this year by Yale Medicine, Yale New Haven Health, and other partners, aims to create a DNA biobank with genetic data from more than 100,000 people over the next three to five years. Their genetic data will be linked to their electronic health records. Participants will have their genes sequenced and screened for early detection of diseases and for variants that pose risks. In addition, the data will be available to researchers performing broad-based studies.

Electronic health records are essential. Without the ability to examine an individual patient's biology closely and compare what's happening with that person to what has happened to many others, it's difficult to truly understand diseases, to treat patients optimally, and to measure treatment outcomes.

For Harlan Krumholz, MD, the Harold H. Hines, Jr. Professor of Medicine (Cardiology) and director of Yale's Center for Outcomes Research and Evaluation, all of this new data and computing power is a bonanza. "In the past, we looked at large averages and said the results applied to everybody," he says. "Now, with the combination of all that data and remarkable computing

6000 BCE
During the Upper Paleolithic and Mesolithic times, knives, saws, and drills made of stones such as flint are used for surgery, amputation, and trepanation.

950 BCE
The world's oldest prosthetic devices are toes for amputees, made in ancient Egypt of wood and leather.

300-500 CE
The Greeks and Romans set the patterns of modern surgical instruments with new tools, often made of bronze.

1268
It is hard to credit any single scientist with the invention of spectacles, but Roger Bacon's studies of optics lead to development of this visual breakthrough. Scholars and monks had used an early prototype held before the eyes or balanced on the nose.

1590
Zacharias Janssen, a Dutch spectaclemaker, is credited with the invention of the compound microscope, although controversy remains regarding this claim. In 1734, Yale becomes the first college in America to obtain one. More than 50 years later, Yale lists a microscope as one of the "machines for a course in experimental philosophy."

1714
Daniel Gabriel Fahrenheit, a Dutch-German-Polish inventor and instrument maker, invents the mercury-in-glass thermometer. The basic principles of the thermometer had been known to Greek philosophers 2,000 years earlier, while Galileo had invented a device to measure temperature called a thermoscope in the late 1603.

1816
A French physician René Laennec, MD, invents the stethoscope—originally a trumpet-shaped tube—to cover the embarrassment of pressing his ear to the chest of a female patient.

1851
Hermann von Helmholtz, a German physicist, invents the ophthalmoscope to examine the retina and other parts of the interior of the eye.

1853
Independently of each other, Charles Gabriel Pravaz, MD, a French surgeon, and Alexander Wood, MD, a Scottish physician, develop the hypodermic syringe. The general principle of injection had been known for at least 1800 years—Greek and Roman physicians had used thin, hollow tools known as piston syringes to inject fluids into the body.

1895
Wilhelm Conrad Roentgen, PhD, a German engineer and physicist, discovers X-rays. The first X-ray images in the United States were published a month later by Yale professor Arthur W. Wright, PhD and the first clinical X-ray was taken at Dartmouth College that same week.

power at our fingertips, we can make inferences that are much more focused on individuals."

Yale New Haven Health is in the process of building a computer system designed to fulfill the promise of precision medicine. It's bringing data from many of its existing computing systems into a centralized "data lake" where information can be readily accessed and analyzed. This huge collection of data includes not just basic electronic health records but also genetic data; test results from imaging systems and the pathology department; and real-time data collected from monitoring devices in the intensive care unit.

Krumholz predicts that medicine will be transformed by data within a decade. "We will move from a place where research and clinical care are separate domains to one where we learn from every interaction with a patient—it's built into the system," he says. "With every click, the system gets smarter and more customized. We leverage everything that everyone has done and is doing."

It's not just the *amount* of data that matters; it's also how *quickly* you can analyze them. High-performance computers are essential here. Krumholz can imagine a time in the not-too-distant future when a clinician who is meeting with a patient with complex health issues will be able to query a computer and get advice from an artificial intelligence program about a diagnosis or a personalized treatment plan on the spot—before the patient leaves the office.

In research settings, this kind of real-time response is already possible. Nicholas Turk-Browne, PhD '09, a professor of psychology and neuroscience, uses high-performance computing along with functional magnetic resonance imaging (fMRI) to better understand how the brain works. Measuring brain activity by detecting changes in blood flow, it correlates activities in various segments of a person's brain with different kinds of thinking and emotions. Today, with a collaborative research team, Turk-Browne is using the system to train people diagnosed with major depressive disorder to avoid negative thoughts and feelings. "If we can get people to change what they're focusing on, we can avoid some of the negative symptoms," he says.

With all of this mingling of medicine and computers, medical researchers and even clinicians are being asked to develop computer science expertise. Yale's

1903
Willem Einthoven, MD, a Dutch physician, refines the electrocardiogram developed by a British physiologist and devises an instrument to record the heart's electrical impulses.

1924
Hans Berger, MD, a German physiologist and psychiatrist, expands on Einthoven's work and develops a method for recording human brain waves through the skull known as electroencephalography or EEG.

1929
An American engineer, Philip Drinker, creates the iron lung, a device that breathes for polio patients who can no longer breathe on their own.

1931
German electrical engineers Max Knoll and Ernst Ruska design the first electron microscope, which magnifies tiny intracellular structures far beyond the capacity of light microscopes. George E. Palade and colleagues found the Section of Cell Biology at Yale in the 1970s, where they merge electron microscopy with biochemistry to lay the foundation of modern cell biology. Palade wins the Nobel Prize in Medicine or Physiology in 1964, a year after his arrival at Yale.

1937
The Soviet scientist Vladimir Demikhov makes the first artificial heart. It is transplanted into a dog, which survives for two hours after the surgery.

1943
Willem J. Kolff, MD, PhD, a Dutch physician invents the artificial kidney, which evolved into modern dialysis machines.

1947
John Bardeen, Walter Brattain, and William Shockley invent a semiconductor device called the transistor at Bell Labs. It becomes a key piece of virtually every electronic device, leading to the development of medical devices like cardiac pacemakers.

1949
With dime-store valves, glass tubing, and a pump from an Erector Set, a Yale surgeon, William W.L. Glenn, MD, and a medical student, William Sewell, create an external heart pump for $24.80. Yale used the pump to study the patterns of coronary blood flow and devise methods for its safe removal from the open heart.

1950
John Hopps, an electrical engineer, invents the first cardiac pacemaker. A year later, Paul Zoll, MD, a cardiologist in Boston, is credited with building on Hopps' work and developing an external tabletop pacemaker for treatment of heart block. In 1959, the first use of a cardiac radiofrequency pacemaker in the Western Hemisphere takes place at Yale under the direction of William W.L. Glenn, MD, chief of cardiovascular surgery.

1957
Edward H. Hon, MD, and Orvan W. Hess, MD, publish in *Science* a description of an electronic device to gauge fetal heart rate. Created by Hess, with Hon's assistance, the device is first used at Yale New Haven Hospital in 1960.

Center for Research Computing provides tutorials and training sessions in software coding for faculty researchers, and graduate programs have been created to teach data science and bioinformatics.

In the Yale Computational Biology and Bioinformatics program, doctoral candidates use high-performance computing to investigate such biomedical questions as how genes work together at the molecular level to mediate complex biological processes. William Meyerson, an MD/PhD candidate in the program, is studying non-disease-causing mutations—which will contribute to the understanding of disease-causing mutations. In his planned career as a physician-bioinformatician, Meyerson wants to facilitate the adoption of new computer-aided decision-making tools. "There are language and culture differences between doctors and computing experts," he says. "My role will be to bridge the gap between my computational colleagues and my clinical colleagues."

While many of the innovations that drive progress in medicine take place within the walls of medical schools, much of the discovery in the realm of medical technology happens in the wilds of the business world. That's why we increasingly see faculty members who have one foot planted in academia and the other in commerce.

Jonathan Rothberg, the gene sequencing innovator, shows how this two-step is done. While he remains on the adjunct faculty at Yale, his day job is running a startup incubator based in nearby Guilford, where seven companies so far are targeting health care. In all cases, they're developing medical devices that use deep learning, a form of artificial intelligence, to continually improve their performance. One of his companies, Butterfly Network, developed a handheld ultrasound device that costs less than $2,000.

Rothberg predicts that the combination of technology and medicine will have profound effects on the future of the human race—for instance, he believes that people will someday live to be 200 years old. "We have sequencing, we have medical records, we have high-performance computing, and we have AI," he says. "We'll understand the complex diseases, and we'll be able to intervene and extend life." ***/yale medicine magazine***

Steve Hamm is a frequent contributor to Yale Medicine Magazine.

1960
Theodore H. Maiman, PhD, operates the first optical laser at Hughes Research Laboratories in California. Lasers have many uses in medicine, including surgery, kidney stone treatment, ophthalmoscopy, and cosmetic skin treatments.

1970s
Computer technology begins to merge with medical technology; it is now used to store medical records, control instruments, and perform robotic surgery.

1971
Paul Lauterbur, PhD, applies magnetic field gradients to create nuclear magnetic resonance (NMR) images. Along with physicist Peter Mansfield, PhD, he develops MRI techniques like echo-planar imaging. In 1979, with the arrival of Robert G. Shulman, PhD, Yale becomes a leader in magnetic resonance research, and Yale faculty are the first to use MRI to measure the brain's performance of cognitive tasks.

1974
Raymond Damadian, MD, is granted the world's first patent in the field of MRI, after he discovers how to use magnetic resonance imaging for medical diagnosis. By 1977, Damadian completes construction of the first whole-body MRI scanner.

1975
Robert S. Ledley, MS, DDS, a physiologist, radiologist, and biophysicist, invents whole-body computed tomography (CT) scans. His device builds on early designs by Sir Godfrey N. Hounsfield, a British electrical engineer, who developed the computerized axial tomography (CAT) scanner, which combines cross-sectional X-rays taken at different angles around the body.

1978
Yale researchers William V. Tamborlane, MD, professor of pediatrics, and Robert S. Sherwin, MD, professor of medicine, develop the insulin infusion pump for people with diabetes. The pump provides a means of maintaining better control over insulin levels in children who would otherwise need multiple daily injections.

1982
The first permanent artificial heart is implanted at the University of Utah. Until then artificial hearts had served as a bridge to transplantation. The heart was developed by Robert K. Jarvik, MD, who modified earlier models and on December 2, implants an artificial heart into retired dentist Barney Clark, who survives for 112 days.

2015
Stuart Weinzimer, MD, and colleagues at Yale are at the forefront of efforts around the country to develop an artificial pancreas. The closed loop system of devices and software transmits blood glucose level readings to a device that controls insulin delivery.

BUILDING LUNG CAPACITY, LUNG-FIRST

JENNY BLAIR, MD ’04 | ROBERT LISAK PHOTO

The disembodied living lungs in one Yale researcher’s lab show that a standalone bioengineered lung is well along the road to reality.

Pneumonia, aspiration, fluid in the lungs, and injuries from mechanical ventilators can severely damage the lungs of people who are critically ill. Transplanted lungs are tragically scarce and beyond the reach of most such patients, including those burdened by such chronic lung diseases as cystic fibrosis or emphysema.

What if custom-grown new lungs were an option? The idea sounds like science fiction. But the disembodied living lungs in one Yale researcher’s lab show that a bioengineered organ is well along the road to reality.

“It’s an exciting time to be working in lung regeneration,” says Laura Niklason, MD, PhD, the Nicholas M. Greene Professor of Anesthesiology and professor of biomedical engineering.

“Our understanding of how the lung is put together is growing very rapidly right now.”

Trained as an anesthesiologist as well as a bench scientist, Niklason spent years in the ICU witnessing the devastating results of lung infection and damage. “Many organs heal, but after severe injury, lungs tend not to,” she says. When she arrived at Yale in 2006, she began working on lung regeneration; the possibility seemed even more far-fetched then than it does now.

Four years later, her team transplanted a regenerated lung into a rat; it performed effective gas exchange, albeit briefly. The achievement made it into the pages of *Science* in June 2010.

There are not nearly enough transplantable lungs available for the people who need them. Only about 15% of cadaveric donors provide useable lungs, in part because many patients linger on ventilators and accumulate lung damage, including infections, prior to death. (Contrast that with the 88% harvest rate for cadaveric kidneys.) Lungs also don’t take kindly to transport and typically have to be transplanted within a few hours of harvest.

In addition to the tight supply problem, lung transplant recipients face a lifetime of immunosuppressive drugs to prevent their bodies from rejecting the donor lungs. A lung engineered from the patient’s own cells could circumvent the immune system and spare patients the risks of long-term immunosuppression.

Fortunately, the lung makes for a more feasible bioengineering challenge than does a solid organ like a kidney or heart. The lung is mostly empty space, comprising a protein skeleton coated with thin cell layers that exchange oxygen and carbon dioxide.

The first step to building a new lung is to partially dismantle an existing one. Niklason’s team has developed a reliable method using detergents, salts, and enzyme solutions to remove the cells from an adult lung. Leaving that skeleton and its dozens of attached protein types intact is crucial. These proteins vary from one part of the lung to another, and they send signals that direct what kind of cells a progenitor cell landing on them will become.

The second lung-regeneration step is to wash the protein skeleton with hundreds of millions of new cells that lay down fresh airways and blood vessel linings.

Medically viable lungs are difficult to come by, and eagerly awaited by many suffering from conditions like cystic fibrosis. Bioengineered organs like this mouse lung represent a hopeful promise for patients.

If step one has left the proteins intact, the cells should in theory find their way to the right place.

"There are zip codes that are built into the matrix of the lung," says Micha Sam Raredon, an MD/PhD candidate in Niklason's lab. "If you seed a homogenous set of cells … depending on where they fall on the scaffold, they're going to get site-specific cues that can push them toward a certain phenotype."

"Getting the cells there, physically getting them there, is much easier. Getting them to behave and to do what you want them to do—that's the tricky part," Niklason says.

The new lung grows in a glass jar that bristles with tubes and connectors. Custom-made by the university's in-house glassblowing team, these so-called bioreactors suspend the growing lungs amid fluid that flows rhythmically around them. One set of tubes pumps the fluid through the lung vasculature as the heart would; another carries fluid away to be oxygenated as it would be by a placenta.

"Proper breathing motion is certainly critical for actually getting our lungs to form and getting the cells to differentiate the way they should," Niklason says. "We're mimicking the embryonic state of lung development."

"It looks exactly like what you're picturing," Raredon adds. "They're these pulsing organs in a glass jar that we're keeping alive."

When might patients with devastating lung diseases have access to brand-new lungs of their own? A first-in-humans implant could happen within 15 to 20 years, Niklason estimates. "It's a hard problem and it's a several-decade problem, and you need a lot of people and a lot of resources to try to tackle it," she says. "I tell everybody, 'I hope to do this before I die.'" ***/yale medicine magazine***

Jenny Blair is a frequent contributor to Yale Medicine Magazine.

A PERFECT DAY FOR A ZEBRAFISH

BY AMANDA M. DETTMER, PHD | ROBERT LISAK PHOTO

Ellen Hoffman has designed experiments that may provide insights about autism and epilepsy in humans. Using an advanced microscope built by Joel Greenwood, director of the neurotechnology core in the Kavli Institute for Neuroscience, she will be able to study zebrafish brain activity at a previously unattainable resolution.

Ellen Hoffman is developing a microscope that will enable her to look into zebrafishes' brains.

On a warm sunny morning last September, eight 4- and 5-year-olds in Phyllis Bodel Childcare Center's kindergarten class on the campus of Yale School of Medicine (YSM) sat outside at picnic tables with their eyes glued skyward. In the middle of the courtyard in front of them a large crane was slowly lifting enormous crates from a giant delivery pallet to a doorway in the Sterling Hall of Medicine. For over an hour, these youngsters sat nearly still with razor-like focus on the large machinery, discussing what was happening—and what was inside those crates.

The enormous crane was unloading parts of a microscope into YSM, one that would be built by Joel Greenwood, PhD, associate research scientist in neuroscience and director of the Neurotechnology Core in YSM's Kavli Institute for Neuroscience. Greenwood established the core in 2017, a design and fabrication facility that is free for other researchers to use. At the same time, Greenwood had just started to construct another microscope, one that also required special delivery of multiple component parts, a two-photon laser, and rigging for a large optical table. This microscope was being built from scratch, and is the only one of its kind in New England.

The gargantuan microscope that's being built? One dedicated to the study of tiny organisms—zebrafish. Ellen Hoffman, MD, PhD '14, assistant professor in the Child Study Center and of neuroscience at YSM, will use this microscope to perform whole-brain functional imaging in zebrafish to better understand the function of genes that increase the risk of autism. This microscope will enable her to look into the fishes' brains throughout development—their embryos are transparent—to examine brain structure in zebrafish lacking functional autism risk genes. Using this specialized microscope, Hoffman will be able to collect live images of the fish while watching neural signaling before, during, and after drug treatment. In this way, she will be able to glean information that wasn't possible before she acquired this microscope.

"This microscope will enable us to visualize how loss of function of autism risk genes leads to differences in neural signaling in the developing vertebrate brain in real time at the single-cell level," says Hoffman.

As with other colleagues at YSM, Greenwood is teaching members of Hoffman's lab to build and use components of the microscope while providing crucial oversight in the process. In this way, scientists will have an intricate understanding of this specialized piece of technology. This understanding also helps scientists think critically about their work and the specifics of how experiments can and should be conducted, Greenwood says.

This microscope had to overcome a primary challenge of working with zebrafish—how to record the animal quickly and without its knowing. Hoffman's microscope is a two-photon light sheet microscope, meaning that sheets of light rapidly "scan" through the entire fish brain to record whole-brain activity in less than one second. Traditional two-photon microscopes are slow, scanning the brain point by point. With a small zebrafish, the animal must be held still in a natural position and scanned quickly enough that it can't detect the light. Otherwise, its natural behaviors would be compromised.

To solve this problem, Hoffman and Greenwood relied on existing research publications to build the novel instrument that will precisely answer Hoffman's questions. They modified attributes of existing models to make her microscope a "double whammy"—one that increases the speed of the light sheet and is also invisible to the fish. The two-photon

David Jin, graduate student in the Interdepartmental Neuroscience Program, and Tianying Chen, MS, research assistant, work in the laboratory of Ellen Hoffman, MD, PhD, which is part of the Neurogenetics Program at the Yale Child Study Center, and is involved in translational research on the genetics of autism spectrum disorders.

light sheets are outside the visual spectrum of the fish, making the light undetectable to the animal, and the light can penetrate deeper, giving better resolution. The microscope will enable Hoffman and her team to see more neurons simultaneously in a live, functioning animal. This clarity will give her studies both ethological and ecological relevance.

Hoffman already knows the first experiments she will conduct with this microscope, which was funded by the National Genetics Foundation, the SPECTOR Fund, the Kavli Foundation, and the National Institute of Mental Health. She plans to study baseline brain activity in fish that have mutant forms of the *CNTNAP2* gene, which is strongly associated with autism and epilepsy in humans. Using transgenic fish expressing a form of green fluorescent protein that turns on when brain cells become active, Hoffman will learn what is happening at the cellular level. She then hopes to determine how compounds identified in related drug screening experiments affect brain signaling. For these studies, she will be able to use her new microscope to understand how changes occurring at the circuit level in the zebrafishes' brains might relate to behavioral differences resulting from loss of autism risk gene function.

With this new technology, Hoffman aims to answer fundamental questions about the mechanisms underlying brain and behavioral development so she can lay the groundwork for developing improved treatments for children with developmental disabilities. In so doing, she may also lay the groundwork for a future scientist—perhaps even one of the children admiring how carefully the crane's long arm moved microscope parts into YSM—to develop the next generation of technologies to make life-altering discoveries. ***/yale medicine magazine***

Amanda Dettmer, is an associate research scientist in the Yale Child Study Center and a contributor to Yale Medicine Magazine.

WHERE SCIENTISTS AND ENTREPRENEURS MINGLE

BY JEANNA LUCCI-CANAPARI | MATTHEW DALEY ILLUSTRATION

The Center for Biomedical Innovation and Technology provides a home for those who want to develop medical devices to meet unmet needs in health care, and bring them to patients.

Have an idea to develop a novel biomedical device, diagnostic, or health IT app that could have big patient impact? There's a place where scientists, clinicians, and entrepreneurs can connect at Yale's Center for Biomedical Innovation and Technology (CBIT).

During the past five years, CBIT has developed into a one-stop shop for would-be biomedical innovators and entrepreneurs. To date, CBIT has supported more than 3,000 members of the Yale community and over 200 projects that have attracted more than $24 million in outside funding.

"Yale is about getting good ideas out into the world," says CBIT co-founder Mark Saltzman, PhD, Goizueta Foundation Professor of Biomedical and Chemical Engineering. "Entrepreneurship is another way to do that, and to make an impact." He and Peter Schulam, MD, PhD, professor and chair of the Department of Urology, founded CBIT in 2014 in response to a cultural shift they saw happening in higher education. "Starting your own company directly out of school has become a more common career pathway," says Saltzman. "There is a lot of interest, but how do you get there?"

"When Mark and I co-founded CBIT, the idea was to more comprehensively support not only medical device development in this community, but also health IT, diagnostics, and processes," says Schulam. CBIT collaborates with the Office of Cooperative Research, which supports faculty and researchers in developing technology of all types. Saltzman and Schulam wanted to expand the support and expertise offered for biomedical innovation. "CBIT team members have multiple roles," Schulam says. "We educate and build culture. We provide mentorship, and help innovators successfully obtain seed funding."

To help innovators, CBIT centers its services around four fundamental domains of biomedical design, according to Schulam. These include the technical, clinical, regulatory, and business aspects of innovation. Setting milestones that address all four of these needs isn't always intuitive to science professionals who are unfamiliar with venture creation.

"Often our innovators have a technical or clinical background, so they are inclined to move their innovation all the way to the end from a technical perspective. CBIT works with them to make sure they are addressing the appropriate clinical, market, and regulatory issues as they evolve the technology," says CBIT's Innovation Director Margaret Cartiera, PhD '07.

"You have to understand the process if you are in the device or health IT world and you have an idea," adds Schulam. "At each step, you have to ask yourself whether you are meeting those four areas. If you are not, you have to pivot or you will end up with something that is not marketable."

Through formal coursework, informal mentoring, and campus activities like hackathons, students and faculty can explore innovation in the health care space "with guardrails or without," says Cartiera. A variety of partnerships within the university and beyond keeps innovators on the path to success.

For one-on-one mentoring, CBIT looks to industry to match innovators with experienced entrepreneurs. Co-Executive Director Michael Dempsey, having built three medical device companies, brings that perspective to CBIT.

"We work with the investigator on market analysis, while we simultaneously teach the investigator how to do it," Dempsey says. "CBIT's whole notion of mentoring is pretty intimate. You have to find the right combination of people who will spend a lot of time together to make the project successful."

Before he became co-executive director of CBIT, Chris Loose, who has a PhD in chemical engineering from MIT, had launched a successful biomedical venture of his own. At Yale, "I was eager to help students and faculty do the same," he says. "One of the real powers of CBIT is that we put MDs with business students with undergrads and others to create highly diverse collaborations that are critical for innovation." This collaboration extends to formal coursework offered by CBIT. Loose teaches a course called Creating Health Care Ventures, in which students from across Yale work on building business and product plans.

Another well-attended course, Medical Device Design and Innovation, is co-sponsored by one of CBIT's crucial partners, the Center for Engineering Innovation and Design, which also works with CBIT to build prototypes of the medical devices created.

CBIT also holds an annual hackathon, in which teams examine unmet medical needs and connect with experienced entrepreneurs, care providers, administrators, and others capable of coaching them toward generating new solutions. "We bring hundreds of people together across dozens of institutions, including internationally," says Loose. To date, CBIT has organized six hackathons around campus.

CBIT also develops funding sources for biomedical innovations. The group worked with the state of Connecticut to create Bio Pipeline CT, a collaboration with Yale, the University of Connecticut, Quinnipiac University, and the Connecticut Innovations agency which administers the Connecticut Bioscience Innovation Fund. CBIT founded a $1 million, two-year initiative that provides groups of faculty and students, or small start-up companies affiliated with any Connecticut university, with up to $30,000 per project of gap funding. For every dollar given, says Loose, "$14 in follow-on funding was raised by these companies supported by the Bio Pipeline to continue to advance their ideas, and four have gone to human trials." The program has just been renewed for another $1 million, two-year round of funding.

Saltzman's own project was one of the first to be funded by the Bio Pipeline. For guidance, Saltzman and his colleague, Michael Girardi, MD '92, professor of dermatology, turned to fellow experts at CBIT. They developed a biodegradable bioadhesive sunscreen using nanoparticle technology that does not absorb into the skin, unlike most commercially available sunscreens that may cause potentially harmful side effects. "We have a start-up company now that is going to put it into production, and hopefully into bottles and onto shelves," Saltzman says.

Now that the appetite for entrepreneurship has taken hold, the next step for CBIT is to continue building collaborations with campus organizations. "CBIT is docking into Tsai CITY," says Schulam. Tsai CITY (Center for Innovative Thinking at Yale), where Schulam acts as faculty director, operates as a portal and connector for organizations such as CBIT across the university. "CBIT is one component within a larger ecosystem of innovation," he says. "Through Tsai CITY, we are creating interconnectivity, collaboration, and a multidisciplinary approach to innovation."

Because of CBIT's success on campus and in the world beyond Yale, the idea and process remain at the heart of its mission. "We want our community to know that if you see an unmet clinical need and you have an idea, you should run with that idea. The exploration itself is useful, even if it doesn't end in a company," says Schulam. ***/yale medicine magazine***

Jeanna Lucci-Canapari is a frequent contributor to Yale Medicine Magazine.

The new ultrasound devices in Yale School of Medicine's clinical training rooms will give students an advantage when it comes to developing the diagnostic skills necessary to be effective physicians.

HONING CLINICAL SKILLS WITH ULTRASOUND

BY ABBY ROTH | HAROLD SHAPIRO PHOTO

Ultrasound augments learning opportunities for medical students.

In January 2019, Yale School of Medicine (YSM) completed a renovation project that included 14 new clinical training rooms equipped with ultrasound tablet devices. This technology did not exist in the former practice space and its addition has already had positive results for medical education.

These changes are particularly evident in the Clinical Skills Course, which spans the first 18 months for all medical students. In it, students learn how to communicate with and examine patients and develop their clinical reasoning skills.

Jaideep Talwalkar, MD, associate professor of medicine and of pediatrics and director of clinical skills explains, "The Clinical Skills Course has always been hands-on, but what is novel about using ultrasound is the added layer of visualization in real time that ultrasound provides, simultaneous with other learning modalities that we've already been using."

Rachel Liu, MBBCh, assistant professor of emergency medicine and director of point-of-care ultrasound education, is excited about the educational opportunities the renovation makes possible. Liu introduced point-of-care ultrasound into the longitudinal preclerkship curriculum six years ago with a pilot program converted into a preclerkship elective. She believes point-of-care ultrasound's central mission is to aid students in understanding how to integrate anatomy, physiology, and pathology while learning physical examination skills. This approach is different from ultrasound as a diagnostic tool that may be introduced in fourth-year electives, residency, and fellowship training. "Point-of-care ultrasound holds distinct roles in both education and patient care, but it is not a replacement for imaging performed by radiologists or other medical specialists," Liu says.

When Liu developed the preclerkship pilot, she combed the YSM curriculum to pair it with ultrasound uses. She then worked with Talwalkar and Joseph Donroe, MD, MPH, assistant professor of medicine and director of physical examination education, to bring ultrasound into the Clinical Skills Course. Donroe, who teaches small groups in Liu's curriculum, provides examples of how ultrasound is enabling him and his colleagues to better instruct students in the art of physical examination.

In the past, faculty would have students practice palpating the abdomen to look for the liver, but it was often difficult for students to understand exactly what they were touching. Now, by coupling the physical exam with ultrasound, students can literally see the liver, making the experience more concrete and memorable. A similar effect is achieved when students can see heart valves opening and closing in real time using ultrasound as they listen to a heartbeat with a stethoscope.

Elizabeth Woo, a third-year MD/PhD student, is grateful to have been in the ultrasound longitudinal course. She describes how during her preclerkship years, ultrasound "allowed me to better contextualize human anatomy as well as seeing the 'why' to different clinical maneuvers."

Second-year medical student Pablo Delis, who is taking the ultrasound elective, echoes Woo's praise for the course. "Being able to see a heart beating, bowel peristalsing, and lung pleura sliding in real time has been invaluable in solidifying my understanding of these organs. Knowing I am competent in performing essential ultrasound studies and interpreting the images taken by other medical team members has granted me a level of confidence I believe is rare among first-year medical students."

With the new space and equipment, students can now practice ultrasound in small groups. This opportunity will make it easier for students to develop their skills and take advantage of peer-to-peer teaching. Such shared learning had not been possible previously when students used vendor-loaned equipment at various locations.

Sixteen first-year students and seven second-year students who participated in the longitudinal ultrasound elective have been certified to help train peers. Michael Schwartz, PhD, associate professor of neuroscience and associate dean for curriculum, believes this peer-to-peer training aids students' development.

Students and faculty are enthusiastic about integrating ultrasound into the medical education curriculum, does it actually improve learning? Liu, Donroe, and Chris Moore, MD, associate professor of emergency medicine and section chief of emergency ultrasound, are conducting research to find out. Most studies involve tests specific to ultrasound teaching. However, Liu says, "nothing has really looked at the effect of ultrasound teaching to the more general curriculum, and this is the part that is important."

In her research to date, Liu looked at students' qualifying examinations and the examinations that all students in every medical school must pass (objective structured clinical examinations or OSCEs, and United States Medical Licensing Examinations or USMLEs). "Overall we found that the area where ultrasound teaching seemed to have a beneficial statistical significance was in the physical examination performance of their OSCE." These findings are limited by a small sample size. The YSM curriculum changed in 2015, and Liu was able to obtain only two years of data from the old curriculum. She plans to repeat the study, as she will soon have access to up to four years of data from the new YSM curriculum.

Evidence that the ultrasound device is enhancing education is critical. As Schwartz says, "If two years later we are talking about the technology of ultrasound, we have missed the boat. The key is not a technological tour de force; it is how the technology enhances education."

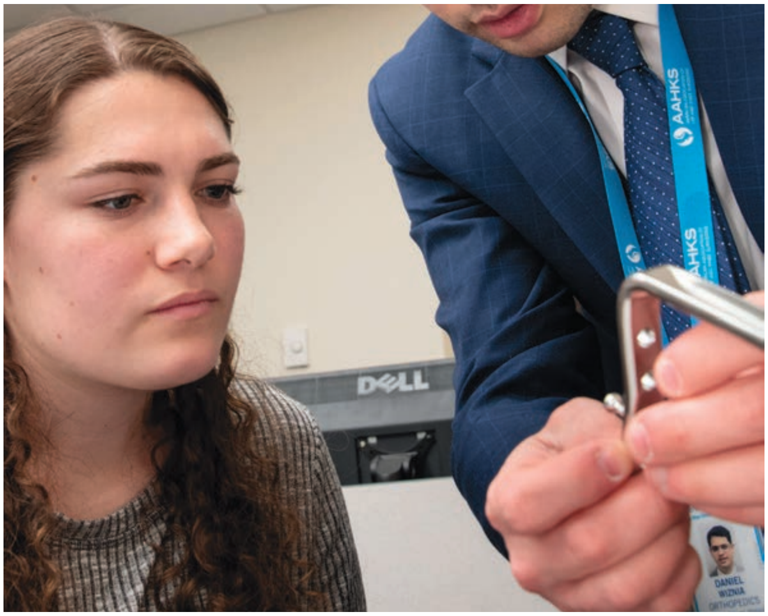
Liu says that when the Department of Emergency Medicine offers point-of-care ultrasound training courses to faculty, "we routinely have attendees from many different specialties." Both Talwalkar and Donroe attended these courses. Before his initial training, Talwalkar spent a month-long sabbatical in late 2018 in Santiago, Chile, with Liu's colleague, Pablo Aguilera, MD, Chief of Emergency Medicine, Pontificia Universidad Católica de Chile. Talwalkar's main goal was to learn the basics of ultrasound because, as he explains, he has been helping "to build ultrasound into the YSM clinical skills curriculum, but had absolutely no ability to help out with the teaching. I was more novice than the students."

Like Talwalkar, many YSM doctors and residents are new to point-of-care ultrasound and eager for training because the technology's widespread use is a fairly recent development. Since returning from Chile, Talwalkar has used ultrasound in clinic and on hospital rounds to highlight its uses with residents and students. He says, "Learners are extremely enthusiastic about using it. They recognize the potential applications, but many residents have had little exposure."

Ultrasound training is standard in such residencies as emergency medicine, obstetrics, and radiology, but other specialties are just starting to incorporate it into their training. Liu plans to collaborate with YSM's Teaching and Learning Center to create more faculty development opportunities to train future educators.

Gail D'Onofrio, MD, MS, chair and professor of emergency medicine, reflects on the critical role of ultrasound in emergency medicine and as an educational tool. "Ultrasound has become an essential tool in the ED as we evaluate patients with acute life-threatening illnesses and injuries. Dr. Liu is a remarkable trailblazer in educating students, residents, and faculty in the skill of ultrasound. Her passion, expertise, and creativity are apparent in her teaching. She is world-renowned for helping to create the innovative SonoGames® and SonoSlam™ as pedagogical exercises. We are incredibly fortunate to have her here at Yale." ***/yale medicine magazine***

Abby Roth is a communications officer in the Office of Education and a contributor to Yale Medicine Magazine.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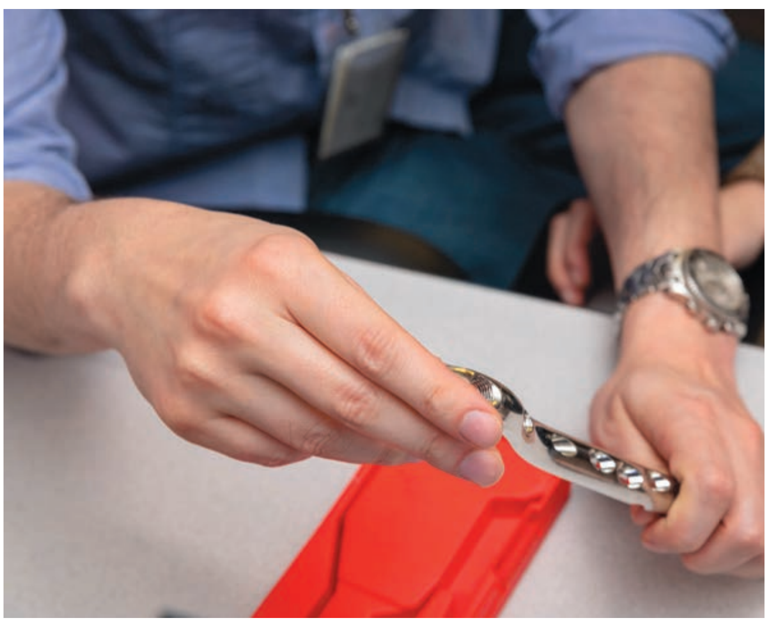


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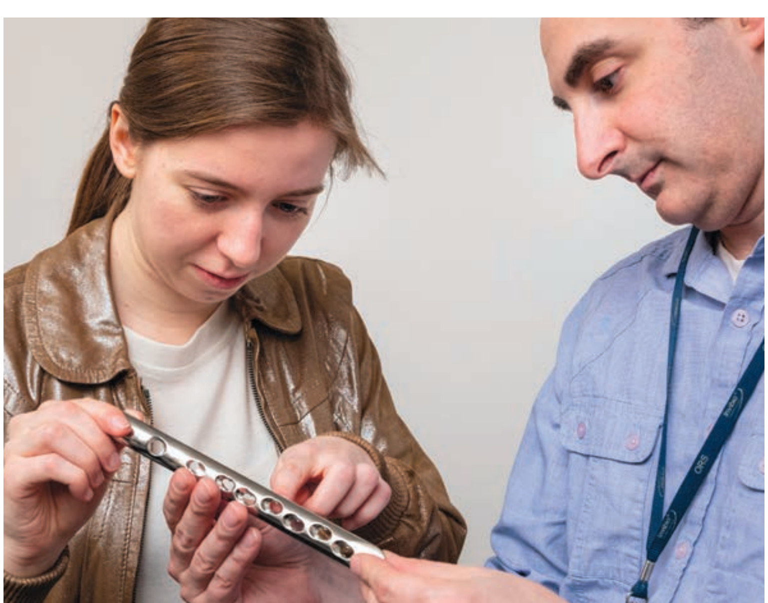


ENGINEERING INNOVATION

BY KEN BYRON | HAROLD SHAPIRO PHOTOS

Yale School of Engineering and Applied Science combines medicine, engineering, and problem-solving to increase the reliability of orthopaedic devices.

Maddy O'Neal held a shiny titanium screw in her hand while studying a computer model of the device on the screen in front of her, looking for potential weaknesses once the screw is put in someone's body to repair a broken hip. "There are lots of ways these can fail," says O'Neal, a senior majoring in biomedical engineering. "The screws can come out and float around in someone's body. There are a lot of moving parts, which is a good thing and a bad thing."

The device O'Neal is evaluating is one of several types designed to help mend broken hips that have one feature in common—a history of breaking. Improving those flawed devices is a challenge that O'Neal and her classmates have attempted to resolve this semester. O'Neal is among 20 undergraduate students in the medical device design class, which is offered by Yale School of Engineering and Applied Science. The course combines medicine, engineering, and problem-solving with the goal of improving unreliable devices.

Broken screws are a problem. In the case of one model, the shaft that runs along the femur can fail where the bone is broken. The bone is not supporting the patient's weight at that point—the metal shaft must do it. Sometimes the shaft is not up to the task, says Alexander Crich, a senior majoring in biomedical engineering and mechanical engineering, as he held the implant in front of him.

Students do much of their work with computer modeling software, but real-world experiences are an important part of the class. Accompanying one of the course directors, Daniel Wiznia, MD, in the operating room, students get a sense of the surgery in which the implants and screws are installed.

Another lecture features a presentation from Kristaps J. Keggi, MD '59. A professor emeritus and senior research scientist of orthopaedics and rehabilitation in the medical school, Keggi has performed over ten thousand hip-replacement surgeries and consulted for companies that produce the implants. He told students the work they are doing has been going on since the 19th century, when early implants were made of ivory or wood. Keggi told students that physicians have played a key role in improving implants. While the students are using sophisticated computer software for their projects, Keggi says he once sketched the preliminary design for an implant on a napkin in a restaurant while on a business trip in Cleveland.

"We learned as we were using them," Keggi says of the implants.

This is the fifth year the engineering school has offered the medical device design class. In previous years, students were asked to come up with an idea for a new device. Proposals included a lab coat sanitizer and technology aimed at helping people recover from concussions.

Steven Tommasini, PhD, a research scientist of orthopaedic rehabilitation at Yale School of Medicine who is co-teaching this semester's class, says that this year students are focused on improving existing devices. Hip implants were chosen because procedures for that part of the body are common, Tommasini says.

"Compared to other implants they are relatively simple. Also, they are in a spot that is the most heavily loaded spot in the body, so failure is not uncommon," he says.

Students are divided into teams charged with studying one of five different implants used to treat hip fractures. Each of these devices is on the market, but they have unique strengths and weaknesses for treating different fracture patterns, Tommasini says. The students use computer modeling to simulate the stresses on each implant to figure out where and how it fails. With that information, they can turn their attention to designing a better implant.

After studying the hip screws, the students model different kinds of artificial hip joints used for total replacement procedures. After that, they can choose their own idea for the final part of the class, Tommasini says. He teaches the class with Wiznia, who is an assistant professor of orthopaedics at the medical school as well as an assistant professor of mechanical engineering and materials science at Yale School of Engineering.

Wiznia says students are studying how well these hip implants treat an uncommon injury called a subtrochanteric fracture. This kind of fracture can result from an accident but is also seen in patients taking bisphosphonate therapy for osteoporosis. Although the implants are customarily used to fix this kind of fracture, Wiznia says that the implants were not designed for it. "They do an okay job, but they have a failure rate."

The class was not going to be held in the spring semester because of a scheduling conflict but was put on the schedule anyway after widespread student demand. "I was excited to take a class where you design something, get your hands dirty, and solve a problem," says Matan Cutler, a sophomore.

"They needed someone to take over this class and we're hoping we can keep doing it because we're having fun," Tommasini says. "This is one of the few classes where you get to build something and be creative. Engineering students don't get to do that a lot."

Wiznia says the class is a good way of bringing together two disciplines that can help each other. "As an engineer, you are a problem solver," he says. "As a surgeon, you are constantly trying to improve medical outcomes. This is a terrific fit for an engineer."

Most of the students who take the class are in the engineering department. Lauren Ribordy, a senior majoring in biomedical engineering, says she was excited to use the computer modeling technology but also found it sobering to find out more about bone fractures. "There is a lot of potential to help people," Ribordy says. "It should not be a case of 'We hope it will work.' Can we model it to see if it will fail before we give it to a patient?"

O'Neal says she wants to go into the medical field and work with implants. Initially she was interested in prosthetics but shifted her interest to hip devices, in part because of the experience of her grandmother who, she says, had both knees and a hip replaced. She also sees a growing need for better technology to repair joints.

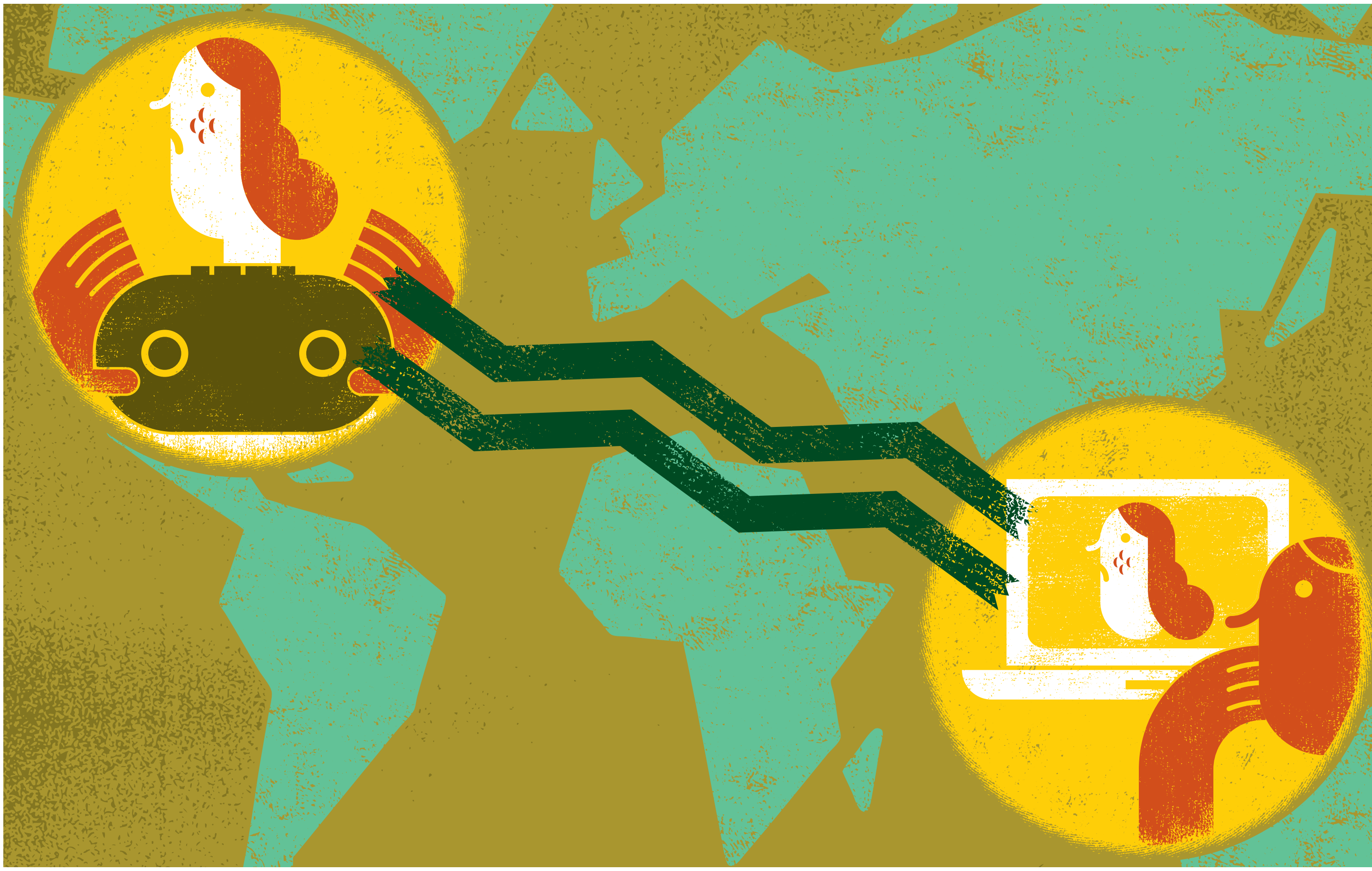
"This is really what I want to do, implants or something like that. They are so cool," O'Neal says. "As people get older our bodies are more likely to fracture; and now athletes are getting knee replacements that need to stay in place for 30 or 40 years. With people living longer, implants won't be going anywhere." ***/yale medicine magazine***

Ken Byron is a contributor to Yale Medicine Magazine.

PREVIOUS SPREAD, LEFT Students from the engineering school's medical device design class examine an implant designed to treat hip fractures. The curriculum emphasizes out-of-the box problem solving for rare injuries for which there is no financial incentive to develop new products. Clockwise from top left: Sofia Griff; Sofia Griff (L) and Matan Cutler (R); Maddy O'Neal (L) and Fadzai Mataru (R); Sofia Griff (L), Dan Wiznia (M), and Matan Cutler (R); Lauren Ribordy (L) and Steven Tommasini (R); Steven Tommasini.

PREVIOUS SPREAD, RIGHT Daniel Wiznia, one of the class's two instructors and faculty at Yale School of Medicine (YSM), discusses one of the challenges facing designers when it comes to improving medical devices with student Alex Critch. Wiznia graduated Yale with a degree in Mechanical Engineering in 2006, and it remains an important component of how he views medicine at YSM.

ABOVE The last hundred years or so saw huge jumps with innovation as materials research made durable equipment more accessible and easily produced. Since that time, advances in ceramics and 3D printing technologies have made it possible to improve devices. This hip screw, or "sliding" hip screw, originated in the 1960s and still has excellent outcomes in most cases.



WHEN SKIN-DEEP IS ALL YOU NEED

BY CHRISTOPHER HOFFMAN | MATTHEW DALEY ILLUSTRATION

Working with faculty at Yale School of Medicine's Department of Dermatology, two Yale undergrads built a device that's helping doctors diagnose skin conditions from afar.

Elizabeth Asai, Yale College ’13, never dreamed she would one day co-found and run her own company. To her, entrepreneurship seemed too chaotic a way to make a living. “I thought I’d go to medical school or work for a larger tech company,” Asai says.

Fate intervened in 2011 when Asai and fellow Yale undergrad Elliot Swart entered a Boston-based student contest to build a primary-care medical device. The contest offered large cash prizes so winners could turn their prototypes into marketable products.

Before the contest, the pair—Asai was a biomedical engineering student, Swart was studying electrical engineering and computer science—had been working on what they now acknowledge was an overly ambitious project. They were trying to develop a probe that used 3D imaging technology to assess the texture and elasticity of such internal tissues as tumors.

Realizing their product would not fit the primary-care focus of the contest, Swart and Asai shifted gears. They decided to use knowledge they’d acquired in their first project to create a new, simpler device that took 3D pictures of skin to assist dermatology diagnoses.

Asai and Swart’s instincts proved spot on—their new device won second prize and $100,000. Key to the pair’s second-place finish was assistance from Yale School of Medicine’s Department of Dermatology. Doctors there fast-tracked a clinical study of the product involving 50 patients, producing results in just four months, Asai says. The 30-page writeup documented that their product works—a vital piece of their contest submission, Asai says.

Swart and Asai used the money to further develop their idea. The next year they founded a company they dubbed 3Derm Systems, evoking the firm’s combination of 3D imaging and dermatology.

Seven years later, 3Derm is thriving. The Boston-based company has a network of over 250 primary-care physicians using its 3D imaging and telemedicine products, Asai says. She is the company’s CEO, while Swart is its chief technology officer. The pair, now both 27, express deep satisfaction with the company’s success.

“I can definitely say it’s been a rewarding experience taking a product all the way through its life cycle, from its inception and experimentation, to commercialization and getting to see patients use it,” says Swart, who got so involved in the firm that he left Yale shortly before finishing his degree. “I think it was more rewarding to me than I would have anticipated.”

Yale was “very important” to their success, Asai says. In addition to early encouragement and assistance from the engineering department and Yale School of Medicine, the school also helped with the business side. “We knew the engineering and clinical needs,” Asai says. “But we really didn’t know how to pair that with a business model.”

Yale Entrepreneurial Institute paired them with an experienced serial entrepreneur who provided a crash course in business. He also introduced them to Blue Cross Blue Shield, which became and remains their biggest investor.

Over time, 3Derm’s product has evolved from straight 3D imaging of skin into a cloud-based dermatology platform, Swart says. Doctors who sign up receive one of the firm’s proprietary 3D cameras. When they see a problematic lesion or skin condition, they take a photo that is uploaded into the cloud, Asai says. Dermatologists chosen by the primary-care offices then examine the cases remotely to determine whether the patient needs to be seen in person.

“This is not dermatology in a box, where we have a room full of dermatologists reading cases all day,” Asai says. “All of the dermatologists we work with are out seeing patients in person.”

The company guarantees an answer within 72 hours, but typically provides one in 12 hours, she says. That’s much faster than scheduling appointments with dermatologists, who have wait times as long as 100 days. It also saves money because dermatologists conclude in 54% of cases that the patient can be treated in primary care, eliminating the need for an office visit. And when a skin issue is flagged, diagnosis and treatment can arrive faster, saving money and lives.

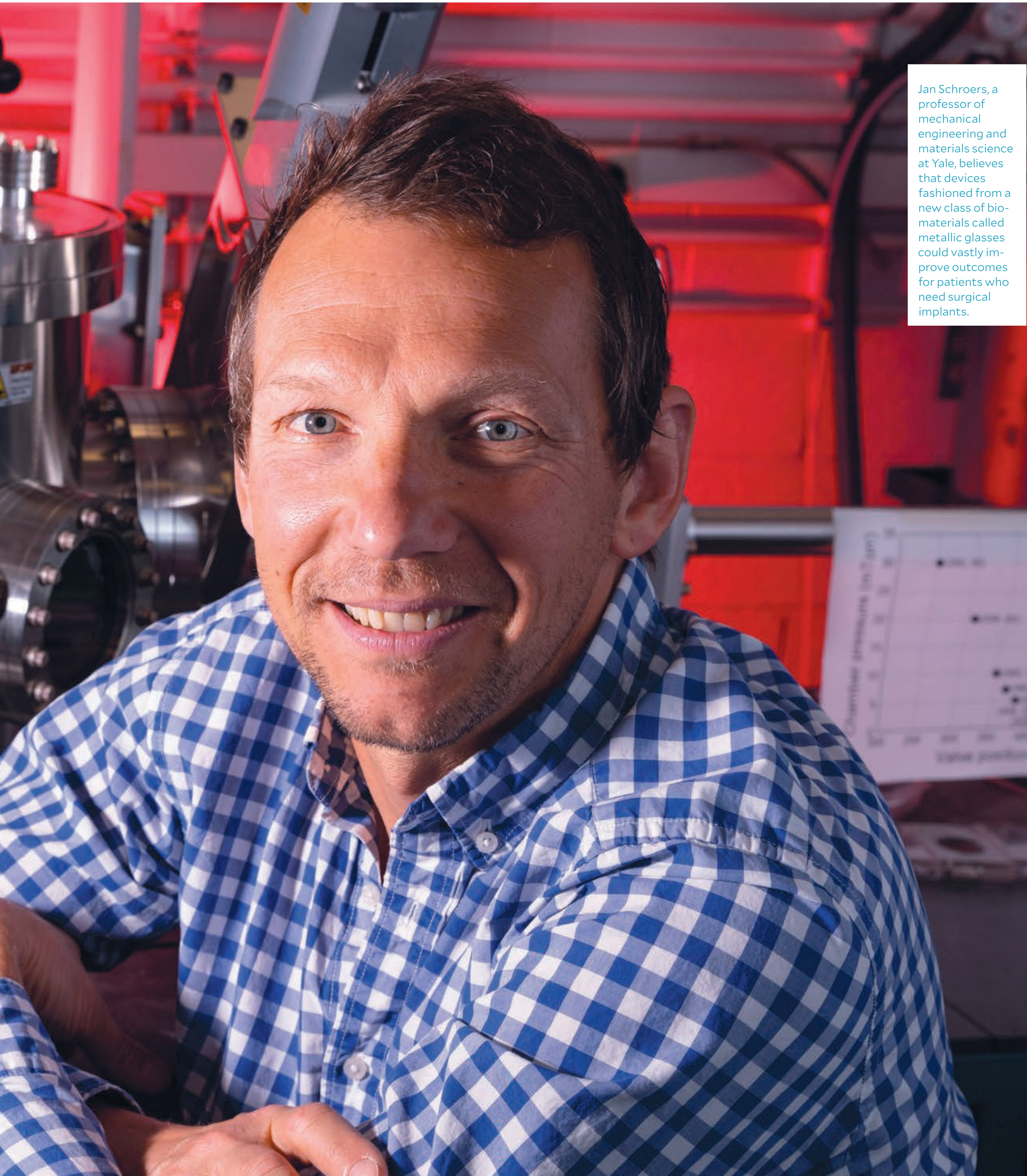
3Derm may have come a long way, but it is just getting started, Asai says. The firm is hard at work developing algorithms with diagnostic and triage functions, avoiding the need for referrals. One algorithm would help manage psoriasis, while the other will do the same for skin lesions. The firm expects to deploy one of the systems in the near future, Asai says.

3Derm remains privately held with no near-term plans to go public. Even discussing such a development is premature. “I think it is far enough in the future that we laugh when we hear that question,” she says. ***/yale medicine magazine***

Christopher Hoffman is a frequent contributor to Yale Medicine Magazine.

SCRATCHING THE SURFACE: METALLIC GLASS IMPLANTS

JENNY BLAIR, MD ’04 | HAROLD SHAPIRO PHOTO



Jan Schroers, a professor of mechanical engineering and materials science at Yale, believes that devices fashioned from a new class of biomaterials called metallic glasses could vastly improve outcomes for patients who need surgical implants.

A class of biomaterials called bulk metallic glasses could transform future implanted medical devices and other engineered objects.

Artificial joints, blood-vessel stents, bone screws, and other implanted objects—crucial tools to help patients—carry risks related to the materials they're made of. Valves and stents, for example, can provoke an inflammatory reaction that leads to deadly clotting. Joint replacements may gradually loosen and require replacement. And any implant can cause infection.

Such devices entail engineering tradeoffs: utility versus the strengths and weaknesses of their component materials. But a class of biomaterials called bulk metallic glasses could transform that calculus for future implanted medical devices, as well as for a host of other engineered objects. Found nowhere else in nature, these novel alloys may overcome many stubborn problems associated with today's implants.

Shiny, gray, and pliable, bulk metallic glasses resemble ordinary metals but are stronger and harder than steel. They are nontoxic and resist corrosion and wear, making them well suited to dwell inside the body. They are elastic enough to change form and spring back with ease. And they are easily shaped.

"Usually, metals processing is a big pain. It's kind of shocking—even 3D printing of metals is a big pain," says materials scientist Jan Schroers, PhD, professor of mechanical engineering and materials science. "Metallic glasses have this ability to be formed like plastics."

For example, when heated to temperatures achievable in a kitchen oven, a platinum-based bulk metallic glass softens to what Schroers describes as the consistency of refrigerated honey. "It doesn't really deform by itself under its own weight, but it's soft enough [that with modest] force you can deform it," Schroers says.

In a cross-campus collaboration that has their lab personnel learning both metallurgic and wet-lab techniques, Schroers and Themis Kyriakides, PhD, associate professor of pathology and biomedical engineering at Yale School of Engineering and Applied Science, are exploring how bulk metallic glasses perform as biomaterials.

For one thing, the materials are largely harmless to mammalian cells yet hostile to bacteria. This property might make them useful as an antibacterial coating on artificial joints, surgical instruments, or hospital doorknobs.

Metallic glasses can also exert a druglike effect. When cells interact with the surfaces of implanted foreign bodies, they may go down the path of inflammation and rejection, or alternatively, toward a more desirable repair-like response. Which path the cells choose depends in part on the object's tiniest surface features—its nanotopography. These surface irregularities attract nearby proteins, which in turn influence passing cells in various ways. Kyriakides and Schroers can manipulate these cell behaviors by molding specific patterns onto the surface of a metallic glass.

"We can dial in whatever we want to create in terms of the surface—they could be nanopatterned, they could be porous," Kyriakides says. "These are [abilities] that are usually restricted to polymers, and we can do it with metals."

That alone makes bulk metallic glasses "a fantastic toolbox," Schroers says. "You can design cellular responses that are desirable for a specific application."

One such application could be a coronary artery stent. Many stents on the market today are impregnated with a drug that diffuses into the body over time to prevent clotting and formation of fibrous deposits. But a bulk metallic glass stent with the right nanotopography could exert a similar effect, eliminating the need for a drug.

In orthopaedics, alloys made from calcium, magnesium, and phosphorus may gradually disintegrate in the body, a useful property for some types of bone hardware. Bulk metallic glasses can also be formed as strong, light foams—picture a solidified sponge—the density of which matches that of bone. That similarity is important because conventional joint implants tend to be stiffer than bone and absorb too much impact, allowing the surrounding bone to atrophy from disuse and resulting in a loosened, malfunctioning joint. An implant made from a metallic glass foam could avert those complications.

The term glass refers to a material whose atoms are arranged in an irregular non-crystalline pattern, and which reacts to heating by becoming viscous. To the eye and hand, metallic glasses look identical to ordinary metal. But familiar metal objects' atomic structure is crystalline, comprising rows of atoms bonded in a lattice. Metallic glasses are more like a liquid in which chaotically moving homogeneous atoms have been frozen in time.

That homogeneity brings major advantages. Ordinary metal alloys' crystals meet one another along countless microscopic edges called grain boundaries, which are vulnerable to slippage and corrosion. By contrast, metallic glasses are amorphous, homogeneous, and uniform in all directions throughout, making it harder for corrosive processes to gain a foothold.

Bulk metallic glasses are a brand-new material, according to Schroers. On our planet, at least, the co-occurrence of different metallic elements in a heated material that is abruptly cooled to form a glass has little or no precedent. (The closest analogue is volcanic glass, which consists mostly of silicon and oxygen, not metals.)

Oddly enough, cells survive and thrive on the new exotic materials. They seem especially at home on alloys based on the pricy element platinum, according to Kyriakides: "Our cells have pretty expensive taste," he quips.

In 2014, Schroers founded a company, Supercool Metals, based on his patented Yale-owned technique for shaping bulk metallic glasses that can be used in modified manufacturing operations typically used in plastics processing.

"[We have] commercialized the ability to make very complicated shapes you can't make with any other process, in this material that's very attractive for a large range of applications," he says. The company is working with NASA to develop parts for robots and satellites, and has developed a cellphone case with built-in flexible buttons that may allow the development of waterproof phones. Supercool Metals also manufactures tiny components for high-end watches.

Bulk metallic glasses are not ready for biomedical use just yet, but it might not take long before they are. In 2017, Kyriakides and Schroers built a glucose sensor from a platinum-based bulk metallic glass that is much more accurate than conventional sensors. Kyriakides estimates that such a sensor could be developed for clinical use within five years.

"We're hoping that when people see our results, they can get excited about using these materials," Kyriakides says. "We've barely scratched the surface." */yale medicine magazine*

Jenny Blair is a frequent contributor to Yale Medicine Magazine.

Themis Kyriakides

"We're hoping that when people see our results, they can get excited about using these materials."

Merle Waxman (foreground), Yale School of Medicine's associate dean of women in medicine, and the school ombudsperson, and Chenee Gallaher (background) of the school's office of Diversity, Inclusion, and Community Engagement, examine portraits from the school's "Aperture: Portraits of Women Faculty in Medicine" exhibit. Open to the public, the portraits highlight some previously overlooked faculty and administrators.

Art in Public Spaces: A mirror on the community

A new exhibit aims to show the school as it is, not as it was.

By John Curtis

In mid-March, the hallway that leads down the L-wing of the Sterling Hall of Medicine through the Rotunda to the historic Beaumont Room saw the opening of an exhibit of portraits. The bulletin boards and historic paintings usually on those walls gave way to about 30 archival-quality photographs of women faculty members, on display as part of an exhibit sponsored by the recently formed Committee on Art in Public Spaces (CAPS) at Yale School of Medicine (YSM). Over the course of the next year, images from the exhibit will rotate in order to include more women faculty, including those at different points in their academic career. Among the portraits hang empty frames that ask questions, including: "Who is missing? How do we celebrate all women at YSM?" and "If you could offer advice to your younger self, what would you say? What would you say to inspire the next generation of women in any profession?"

For most of its 200-plus years, the medical school has mirrored the patriarchal society in which it existed. The school's first women, Louise Farnam, Helen May Scoville, and Lillian Nye, matriculated just over 100 years ago. The first Black woman, Beatrix Ann Hamburg, was admitted in the late 1940s. The first Black man, Cortlandt Van Rensselaer Creed, graduated from the medical school in 1857, but over the next 100 years few followed him. Since the mid-1990s, women have made up half of each medical school class. Women and minorities have also increased their presence as faculty members. Faculty, students, and staff—and such groups as the Committee on Diversity, Inclusivity, and Social Justice; Minority Organization for Retention and Expansion; and Status of Women in Medicine, have called for public-facing art that reflects those changes.

As an example of the lack of diversity, they point to the only art collection on permanent display in the Sterling Hall of Medicine—paintings of past deans, all of them white men. "Those portraits are definitely central to the conversation," said Darin Latimore, MD, deputy dean and chief diversity officer. "Not just faculty, but students, staff, and our patients, are clear on what our walls should represent and who they should represent."

"Everyone is thinking about these issues," said Anna Reisman, MD, associate professor of medicine and director of the Program for the Humanities in Medicine. Reconsideration of historic images—such as a statue of Robert E. Lee or a portrait of John Calhoun—has roiled communities around the country, including Yale.

Latimore and Reisman are co-chairs of CAPS, which was formed last year. The interest was such that more than 100 people responded to the committee's call for volunteers last year. Two subcommittees were formed—one will identify spaces and develop themes for rotating exhibits, and the other will articulate the values the permanent or long-term art should embody.

The core executive team also includes Melissa Grafe, PhD, the John R. Bumstead Librarian for Medical History; Jill Max, MS, senior communications officer at YSM; and Jennifer Reynolds-Kaye, PhD, curator of education and academic outreach at the Yale Center for British Art. "Each of us brings some kind of unique expertise that has driven this project forward," Latimore said.

The committee is still considering ideas for future exhibits, as well as alternate spaces. "I'm pushing for Café Med," said Reisman, "and there are many, many hallways here."

As to their goals for this inaugural display, Latimore said, "I am hoping that it really will cause a conversation about Yale's past, present, and future."

"What is especially great about this hallway is that it leads to the Beaumont Room, which is a gathering place for so many groups, including medical school and residency applicants—people who are not yet part of this institution but may be considering becoming part of it," said Reisman. "The exhibits will say that this is a place where people are open to change."

Laura Ment, at left; Valentina Greco, below; and Yetsa Tuakli-Wosornu, at bottom, are three of the women featured in the first round of portraits in the photography exhibit, "Aperture."

TERRY DAGRADI PHOTOS

A champion for human rights gives back

David R. Kessler, MD '55, is directing $5 million from his estate to Yale School of Public Health to create an endowed professorship to support teaching and research on improving LGBTQ mental health.

As a psychiatrist, Yale School of Medicine alumnus David R. Kessler, MD '55, understands the swirling mix of anxiety and fear that can consume individuals who identify as part of the LGBTQ community during their struggle to come out about their sexual orientation.

Kessler is not only trained in such knowledge, he lived it. From the intense anxiety attacks he suffered as a closeted gay student in the 1950s to the fears of persecution he and other closeted gay doctors shared in the 1970s, Kessler lived through a turbulent time for LGBTQ people in American history.

Now retired and living on the West Coast, Kessler, who publicly affirmed his sexuality in 1978, wants to help others who may be struggling to come out or who are dealing with stigma, oppression, and other issues that affect their mental health.

"Coming out was a fantastic experience for me and that's why I'm so interested in helping others, because I realized from my own experience what a meaningful, life-changing event it is," said Kessler (no relation to former Yale School of Medicine Dean David Aaron Kessler).

Kessler recently made a gift of $200,000 to support the work of Yale School of Public Health Associate Professor John Pachankis, PhD, and his Esteem Research Group, which is dedicated to addressing the depression, anxiety, and substance use that disproportionately affect the LGBTQ community and can erode healthy relationships and behaviors. A clinical psychologist, Pachankis is internationally known for his development of novel psychosocial interventions to improve mental health in LGBTQ communities.

"John is just so energetic and productive on the issue of coming out," said Kessler. "I'm very supportive of his work not only in this country but internationally, which is really unbelievable. People around the world are dealing with issues related to coming out and John is studying how it affects them in a scientific and rigorous manner, which is very impressive."

Kessler also is directing $5 million from his estate to Yale School of Public Health (YSPH), part of which is intended for the creation of a David R. Kessler Endowed Professorship. The professorship and accompanying resource fund will support teaching and research associated with improving LGBTQ mental health.

The majority of the world still lives in homophobic and transphobic conditions, including many areas of the United States, said Pachankis. In some states and in some countries, so-called conversion therapy is common to try to turn gay people straight, he said.

"As a stigmatized minority in society, people who identify as LGBTQ are subject to continuous assaults on their self-esteem and sense of belonging in their families, schools, and workplaces," said Sten H. Vermund, MD, PhD, dean and Anna M.R. Lauder Professor of Public Health, who has made improving LGBTQ mental health a priority of his administration. "I cannot think of a higher-impact program in which Dr. Kessler could invest than Dr. Pachankis' Esteem Program. Kessler's generosity will ensure that LGBTQ mental health research geared toward preventive and therapeutic interventions will be part of YSPH under Pachankis' leadership and in perpetuity."

Pachankis' research is dedicated to delivering effective LGBTQ-affirming mental health treatments to vulnerable populations in the United States and around the world, such as those in rural Appalachia, China, and Eastern Europe. Some of the programs Pachankis has initiated since arriving at Yale in 2013 involve improving training for mental health providers, delivering mental health treatment via the internet and mobile applications, and finding ways to sustain such treatments in areas where LGBTQ stigma is present and strong.

"David's journey inspires all of us to be as courageous and creative as his generation has been in living proudly and meaningfully in the face of societal and emotional barriers," said Pachankis. "For a lot of LGBTQ people, that journey includes supporting the next generation of LGBTQ individuals. That's certainly one of David's major contributions and, in my own way as a researcher and teacher, I hope that it can be one of mine."

A recent designation by David R. Kessler ensures that the advocacy work he did on behalf of LGBTQ mental wellness continues long into the future.

After coming out in San Francisco, Kessler helped launch the country's first formal gay doctors' organization, Bay Area Physicians for Human Rights. He later served as president of the National Gay Caucus of Members of the American Psychiatric Association, which became the American Association of Gay and Lesbian Psychiatrists. *People* magazine highlighted his leadership and advocacy work in 1979. He gave one of the eulogies at the funeral of Harvey Milk, a key figure in the gay rights movement.

Kessler credits his friends in the gay community with providing the crucial support he needed to acknowledge his sexual orientation—and maintain his sanity—at a time when the leading psychiatric diagnosis manual, then the third edition of the *Diagnostics and Statistical Manual of Mental Disorders* or *DSM III*, classified homosexuality as a mental illness and perversion.

"I had been reading all this nonsense psychiatrists had written about how sick gay people are and I got so angry I couldn't stand it anymore," Kessler recalled. "I just said, 'That's it! We need to organize and put an end to this stuff and let people know who we are and that there are gay people everywhere and we're just like everyone else.' "

Despite San Francisco's burgeoning gay community, organizing wasn't easy, Kessler said. Other medical professionals were scared of losing patients if their homosexuality became

MICHAEL FITZSOUSA PHOTO

ONLINE EXCLUSIVE

Jeorg Bewersdorf didn't start out looking to become one of the foremost global experts in creating bespoke microscopes. A serendipitous class with future Nobel Prize winner Stefan Hell set Bewersdorf on his path to success.

For more on Bewersdorf's unorthodox career, visit ymm.yale.edu/microscopes

public. The early groups would meet after dark in the shelter of members' living rooms. There, discussion would drag on for hours about how members would be kept informed, whether there should be a printed membership list, who should possess the list, and what might happen if it fell into the wrong hands. Even the group's initial chosen name—Bay Area Physicians for Human Rights—made no mention of homosexuality.

After completing his psychiatric residency at Yale in 1961, Kessler went on to become a faculty member in the Department of Psychiatry at the University of California San Francisco Medical School and also a unit supervisor at the Langley Porter Institute. He retired as a clinical professor of psychiatry in 1986, just as his efforts were beginning to bear fruit.

The Lesbian and Gay Studies Center at Yale, established in 1986, was one of the first of its kind in the country. The Research Fund for Lesbian and Gay Studies (FLAGS), established in 1992, supports faculty and graduate student research, and the university is widely known for its national conferences. In 2001, Arthur Kramer '49, made a major donation in honor of his brother, the writer, AIDS activist, and ACT UP founder Larry Kramer '57. That led to the establishment of the Larry Kramer Initiative for Lesbian and Gay Studies. LKI, as it was known, was a highly successful five-year initiative to appoint visiting lecturers and dramatically expand Yale's archive of LGBTQ materials, including the papers of Kramer and fellow activists David Mixner and Harvey Fierstein.

Kessler said he has been interested in something at Yale for years, but it took two tries to get it done. The first time he approached the university, in the early 1990s, the people he met with weren't sure where the funds should be directed or how they might be used, and Kessler chose instead to create the David R. Kessler Lectures in Lesbian and Gay Studies at his other alma mater, the City University of New York.

A longtime supporter of Yale School of Medicine (YSM), Kessler decided to make an estate gift to Yale School of Public Health after speaking with Vermund and YSM Deputy Dean and Chief Diversity Officer Darin Latimore, MD, who introduced him to Pachankis last year. Kessler hopes his endowment encourages others to support YSPH's ongoing efforts to improve mental health outcomes for the LGBTQ community.

"Now Yale is ready, willing, and able, with a research program in full swing that is very close to my heart," Kessler said. "I am delighted to be able to come back and do it even bigger and better."

—*Colin Poitras*

Taking aim at sickle cell disease—an unfairly neglected malady

Global Blood Therapeutics (GBT) is a promising up-and-coming biotechnology company in South San Francisco. It is currently focused on bringing voxelotor, a potential treatment for sickle cell disease (SCD), to the public—the drug may be submitted for FDA approval this year. If successful, GBT stands to revolutionize health in a traditionally marginalized and overlooked community. Ted W. Love, MD '85, is its president and chief executive officer.

If you think there's a lot of stress on Love's shoulders, you wouldn't know it to talk with him. "It's a real honor, to be able to work with all the talented people here," said Love. "That's one of the perks of success: better access to bigger challenges, and the type of professionals who like to take on those challenges."

Even during his childhood in Alabama, Love was powerfully attracted to a career in medicine, though in interviews he's also expressed admiration for military pilots. The combination of excitement, potential to change the world for the better, and opportunity for ethical leadership appealed to him. Perhaps it isn't terribly surprising, then, that Love's interest in medicine led him to combine his passion for science with the excitement of entrepreneurialism.

His professional experiences prepared Love well for his responsibilities at GBT. Once he completed his residency and fellowship training in internal medicine and cardiology at Harvard Medical School (via Massachusetts General Hospital), he went on to serve in leadership roles at various companies and committees, including Genentech, Theravance Biopharma, Nuvelo, Onyx Pharmaceuticals, and California's Independent Citizens' Oversight Committee for stem-cell research, among others.

After his last job, Love could have easily retired to enjoy his wine collection in Sonoma, Calif., but GBT coaxed him back into action. The reason for his return was a lingering sense that he could do more for the African American community, which suffers disproportionately from SCD. Sickle cell was not viewed as an "urgent" disease like some other diseases that affect specific groups—evidence, perhaps, of systemic bias—and GBT's voxelotor offered a rare possibility to create a viable treatment in spite of the lack of traditional market incentives. Voxelotor, which is taken by mouth once daily, prevents red blood cells from becoming sickle-shaped and breaking down by increasing their affinity for oxygen and restoring normal hemoglobin function. The premature breakdown of red blood cells in people with SCD causes serious long-term consequences, including anemia, organ damage, stroke, and a shortened life span. "I wanted to make a difference, where in the past I didn't have the power to help," said Love.

The training and mentorship Ted Love received at Yale School of Medicine from teachers like Margaret "Peggy" Bia helped prepare him for the rigors of the business world. Now, the company of which he's CEO has a chance to bring an effective treatment for sickle cell disease to market.

CHUCK HALL PHOTO / CHALLPHOTOS.COM

With a résumé like Love's, it's hard to pick out specific moments on which to focus. Marriage and fatherhood (Love is married with three daughters and three granddaughters) have been sources of positivity and pride in his life, as has his educational path. Asked about his memories of New Haven, Love says that he learned important lessons about what it meant to be a doctor and practice medicine while at Yale. He emphasized one experience in particular.

"One day I was doing rounds, and Margaret 'Peggy' Bia, MD, FW '78, was my attending," said Love. "It was a night shift, and slow, and like most students I was perhaps slightly overconfident in my abilities … I let more patients in than usual, because I knew I could handle it."

Love said that the next thing he knew, unexpected patients flooded in, overwhelming him. "I called Dr. Bia, asking for help, hoping she could help me reduce my patient load," said Love. What she told him left an indelible mark on him as a young leader.

"She listened to me describe the situation, patiently. And when I was done, she said: 'When the going gets tough, the tough get going.' It was a long medical rotation, but I understood what she meant: being a doctor is a responsibility. You promise to help people, that's what you do. It's on you. I've never forgotten that lesson."

Mentors like Bia, professor emeritus of medicine (nephrology), who retired in 2018 after 40 years of service, are just part of the reason Love remembers Yale School of Medicine fondly. He described relationships with other students that have stood the test of time, and opportunities that the school opened up for him.

"The School of Medicine played a big role in who I am today," said Love. "Ultimately, I'm very grateful."

—*Adrian Bonenberger*

Minimizing blood vessel blockage

ALL CARDIAC PROCEDURES carry a risk of stroke because plaque or calcium buildup can break off in small pieces, float up into the brain, and block narrow blood vessels. A highly specialized tool called an embolic protection device is currently used to prevent some of the released debris from reaching the brain.

When Alexandra Lansky, MD, professor of medicine, finished her first fellowship in 1996, patients who needed swift intervention to clear plaque that threatened to block blood vessels supplying their hearts had limited options. Doctors used a catheter with an inflatable balloon to squeeze the plaque buildup against the vessel wall. Later came metallic stents that could be inserted over the plaque to widen the vessel. Open-heart surgery was the only option for correcting valve-related problems. "Interventional cardiology was in its infancy," Lansky said. The British-born, French-raised cardiologist felt drawn to the field by the opportunity to refine devices that could save lives and even permanently address heart disease.

Since she arrived at Yale eight years ago, Lansky has built a vast infrastructure of clinical studies—with countless moving parts, such as active patient recruitment, compliance, and research approval—within the section of cardiovascular medicine at Yale School of Medicine. Nearly 100 clinical trials are ongoing under her leadership as director of the Yale Heart and Vascular Clinical Research Program. She also directs the Yale Cardiovascular Research Group, which designs, plans, and executes multicenter studies that test medical devices in clinical trials.

Within these roles, Lansky started one of the earliest clinical research programs to offer transcatheter aortic valve implantation (TAVI also known as transcatheter aortic valve replacement, or TAVR). Performed in patients with a narrowed aortic valve, this procedure allows cardiologists to thread a catheter through a blood vessel in the leg up to the heart to implant a new aortic valve—thus avoiding open-heart surgery.

While cardiac interventional technologies have drastically improved over the past two decades, a stubborn risk remains: strokes. During any cardiac procedures, plaque or calcium buildup can break off in small pieces, float up into the brain, and block a narrow blood vessel there, causing a stroke. A highly specialized tool called an embolic protection device is currently used during TAVI to prevent some of the released debris from reaching the brain. However, the devices are not foolproof. After years of experience, Lansky decided she could do better.

Why did you see a need to invent another embolic protection device? During TAVI, when the new valve replaces the old valve, some debris can come loose. Stroke rates hover around 3% in patients who have this procedure. Stroke risk is lower with TAVI than with surgery. However, our studies with brain imaging show that virtually all patients have some degree of neurologic injury—they just may not show any symptoms. None of the current deflection technologies fully seals off the cerebral vessels. The device our team invented

To nominate a subject for Q&A, contact
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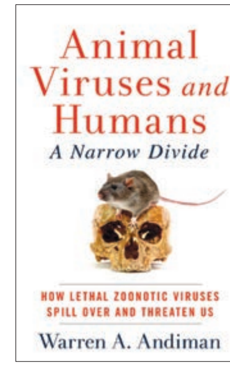
addresses this weak spot. It completely seals off blood flow to the brain using a mesh netting with pore sizes of less than 120 microns. We are in the early phases of development and hope to be able to bring this to our patients soon.

What else is your clinical research program looking at with TAVI? Our Yale research program has established a partnership with the Barts Heart Centre and Queen Mary University of London focused on cardiovascular-device innovation and evaluation. Minimally invasive and device-based approaches to ischemic and structural heart disease have taken center stage in our field. Procedures like TAVI are proving to be safe and effective, as well as reducing hospital-stay times. This has added up to lower health care costs, better outcomes, and happier patients. This has been a major initiative of the United Kingdom's National Health Service and is increasingly important in the United States as we try to contain health care costs. We've found that TAVI patients in the hospital stay two to three days compared to five to seven days following open-heart surgery. In general, TAVI patients do not need to go to a skilled nursing facility for recuperation. They just go home. It has completely changed the equation in terms of recovery and health care costs.

TAVI sounds like a revolutionary procedure in cardiology. TAVI has been a revolution for our patients, who generally want to avoid a visit to the surgical operating room if at all possible. After 15 years of rigorous clinical testing of patients with aortic stenosis, it has completely changed how these patients are being treated. At this year's American College of Cardiology (ACC) annual meeting, we heard Eugene Braunwald, MD, considered to be the father of modern cardiology, comment on the latest results of the use of TAVI in younger and low-risk patients with aortic stenosis. He said, "This is a historic moment. We will be telling our children and grandchildren about these remarkable results."

What will be the next medical innovation in heart disease? We are finding better ways to identify which patients need interventional treatment and how to evaluate them in less invasive ways. For coronary artery disease, the angiogram has been the gold standard. A wire-based assessment of the coronary blockage currently allows us to measure the pressure drop from before and after the blockage. If the pressure drop is below 80% of normal flow, then treatment with a stent is justified. This approach, though beneficial, is invasive and requires threading a wire through the blood vessel. Right now we are testing and validating a method that relies on the images produced by an angiogram to determine pressure changes. Using computational modeling based on the X-ray images, we can reliably simulate the pressure drop without having to rely on a wire or create potential complications and patient discomfort. This is expanding the diagnostic value of the angiogram and allows us to more broadly find out which patients should be treated. We are also working on integrating artificial intelligence into diagnostics and on better patient selection for treatment. I predict we will have much more to report on this area in the near future.

ROBERT LISAK PHOTOS



The narrow gap between animal and human viruses

By Cathy Shufro

When a pet prairie dog bit a 3-year-old in Wisconsin in 2003, the child contracted an infection endemic to central and western Africa. How had the monkeypox virus reached the American Midwest?

This is the kind of puzzle that Warren A. Andiman, MD, FW '76, explores in *Animal Viruses and Humans: A Narrow Divide*. The book teaches readers about mechanisms that allow zoonotic viruses to move from animals to humans and gives detailed accounts of viral outbreaks, including the severe acute respiratory syndrome (SARS), rabies, and Ebola. Andiman, professor emeritus of pediatrics and public health at Yale, also addresses the political, economic, and environmental forces that are escalating the threat of zoonoses worldwide.

In the case of the Wisconsin girl bitten by her pet, it turns out that an exotic-pet dealer in Illinois had housed prairie dogs with rodents imported from Africa, including a Gambian rat carrying monkeypox. Several other Midwesterners got sick, but nobody died, and no monkeypox has since been reported in the United States.

The prairie dog story illustrates Andiman's understanding of why viruses threaten us. Because they mutate "promiscuously," he explains, "viruses, unlike most living organisms, have found ways to populate every nook and cranny of the entire planet." Global travel, climate change, and refugees on the move have increased contact between animals and crowds of humans. Animal groups that carry five or more viruses that can infect us include birds, bats, pigs, primates, and rodents. To those carriers, add insects. "Imagine throwing billions of biting insects into the already swirling cauldron of animals and humans …" Andiman remarked.

When SARS appeared in southern China and began spreading in 2003, researchers around the world rallied to work on vaccines and antivirals, but the epidemic ended without the help of either. The same thing happened during the 2014-2015 Ebola outbreak in West Africa. Therefore, drug development doesn't appear in Andiman's "holy trinity" of zoonotic disease control; it requires too much time and money. Instead, local and national engagement come first in stemming transmission, including locating patients and tracing contacts; isolating the sick; minimizing stigma; alerting global health officials the minute an outbreak is discovered; and accepting outside help. Second, avoiding epidemics requires perpetual surveillance, perhaps even testing people working with pigs, such as the half-million Americans employed by the pork industry.

The third constituent of the trinity is foreign aid: building treatment centers, improving roads, and providing protective clothing for health workers and cold chains for medications. Foreign aid can support what Andiman described in an interview as "very basic public health practices we've known about for a hundred years: clean water, clean food, clean hands. When you give aid, you are helping yourself and your countrymen, because these viruses are borderless agents. There are no real borders anymore."

Andiman knows something about borderless viruses. He and nurse practitioner Leetha Fraulino established the first AIDS program in New Haven in 1982, at a time when health care workers risked their own lives. "We didn't even know it was a virus, and we knew nothing about the way it was transmitted. I was very worried." He directed the Pediatric AIDS Care Program at Yale New Haven Hospital for 32 years. When the program began, one in five mothers with HIV passed the virus on to their babies. By 1996, policies governing testing and patient care had brought the transmission rate to zero.

Andiman imagined an audience of educated but non-expert readers during the two years he spent writing *Animal Viruses and Humans*. His aim was to explain how the control of zoonotic diseases can benefit all of us in "the family of humankind."

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OPPOSITE: HAROLD SHAPIRO PHOTO

Fourth-year show returns with a blast

AFTER A THREE-YEAR HIATUS, an annual Yale School of Medicine tradition made its triumphant return to the stage on Saturday, March 30, to very positive reviews.

Written, directed, and performed by graduating medical students and MD-PhD candidates, *The Final Master Course* was a musical sendup of the Class of 2019's medical-school experience. Many of the parts were filled by enthusiastic students whose energy more than made up for their inexperience on stage, though some clearly had backgrounds in music and theater.

Formerly known as the "Second-Year Show" and held by second-year medical students, the reborn Fourth-Year Show gave students a chance to poke lighthearted fun at themselves, one another, beloved faculty, and administrators.

"We very much hope that this show will cement the newly revived tradition of the Fourth-Year Show for years to come," said Jack Zhao, fourth-year student and executive producer.

—*Adrian Bonenberger*