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AI

For humanity in medicine



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**Geroscience:
Then and now**

Thank you for your recent article on geroscience at Yale as part of your Science of Aging special report.

Yale was one of the first academic medical centers to train resident physicians and medical students in the care of older patients, when I, along with the help of my colleagues, established a geriatrics medical resident rotation in 1976, which continues to this day.

Yale faculty members in geriatrics have made major contributions to the medical literature in such areas as falls, delirium, functional decline, driving problems, sleep disorders, and goals of care for older individuals.

A number of leaders have been key supporters of Yale Geriatrics, including Robert Gifford, MD, one-time chief of General Internal Medicine and later deputy dean for education; former chairs of Medicine Samuel O. Thier, MD, and Ralph

Horwitz, MD; former Dean of Yale School of Medicine (YSM) Leon Rosenberg, MD; former YSM Deputy Dean Robert Donaldson, MD; and Marna Borgstrom, MPH, one-time CEO of the Yale New Haven Health System. In addition, Mary Tinetti, MD, Gladys Phillips Crofoot Professor of Medicine (Geriatrics), who established the Yale Program on Aging, has been instrumental in the success of Yale Geriatrics.

Our mission in the Geriatrics section is to ensure that all Yale students and resident physicians are well trained in the care of the older person. We are pleased that four of the 2025 graduating Yale internal medicine residents will pursue geriatrics fellowships—three at Yale. Yale's impact on the field of geriatrics will thus continue for decades to come.

*Leo M. Cooney Jr., MD
Humana Foundation Professor
Emeritus of Medicine (Geriatrics),
Yale School of Medicine*



Leo M. Cooney Jr., MD, with Mary Tinetti, MD, assessing a patient for fall prevention. Together, they review gait, arm swing, and balance.

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Abbreviations used in Yale Medicine Magazine include HS to denote the final year of residency for house staff, FW for the final year of a fellowship, and YNH for Yale New Haven Hospital.

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A CONVERSATION WITH DEAN NANCY J. BROWN

YSM's brave new AI world

AS AMERICAN SOCIETY CONTINUES its rapid adoption of artificial intelligence (AI), physician-scientists and students at Yale School of Medicine (YSM) are leveraging the use of this technology across multiple disciplines. For insights into AI's role in advancing discovery and innovation at YSM, we spoke with Nancy J. Brown, MD, the Jean and David W. Wallace Dean of Yale School of Medicine and C.N.H. Long Professor of Internal Medicine.

How is Yale School of Medicine uniquely positioned to maximize the benefits of AI? Yale School of Medicine has a long history in informatics that was distributed throughout the school, and we've now brought that together in a single academic home—the Department of Biomedical Informatics and Data Science. Because our informatics was distributed, there's a wonderful hub-and-spoke model and grass-roots effort that's been taking place in AI, involving both the basic sciences and the clinical departments.

What are some of the most impactful ways that the school is currently using AI? We are using AI to do computational biology to develop new ways to analyze very complex data coming from single-cell expression, for example, which is allowing us to make fundamental discoveries about how molecules work, how cells work, and potentially then to identify druggable targets. At the other end of the spectrum, we're using AI in the clinical arena to detect disease, often before we can identify it clinically. It's very exciting stuff!

Is there a particular moment that allowed you as a physician-scientist/dean to fully grasp the potential of AI? In the fall of 2023, the Provost's Office organized a field trip to the Bay Area for members of the university cabinet. We spent several days talking with experts engaged in this work—focusing on what is the role for academia in AI versus industry, and how could we complement each other? When we got back, the Provost's Office organized a series of faculty panels, which then presented to the Yale Task Force on AI. All the deans attended other schools' faculty panels, which identified cross-cutting themes. That whole process really energized the university about AI.

What foundational principles are being applied in the school's use of AI? FAIR [Findability, Accessibility, Interoperability, and Reusability] principles. For example, when large language models use patient data, often those models are trained on very homogeneous populations, resulting in findings that may not be applicable to other groups. Because of our diverse patient population in New Haven and across Connecticut, our faculty has the ability to test and validate models and develop new models in populations that are reflective of the population of the United States.

How is multidisciplinary collaboration advancing Yale School of Medicine's adoption of AI? When you think about AI in medicine or in science, you need teams that are trained in biology and have domain expertise as well as those that are trained in AI or know how to think about AI. One of the outcomes of the task force meetings was the appreciation that our graduate students in the biological sciences need to be educated in AI, and our graduate students in computational science need to be educated in biology.

What excites you most about the school's use of AI? What excites me the most, [speaking] personally, is that this work is being driven by our young, smart faculty.



Murat Günel, MD, is chair and chief of neurosurgery at Yale Medicine and Yale New Haven Hospital, and director of the Yale Program in Brain Tumor Research.

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Unlocking the brain’s secrets

Murat Günel looks toward the next era of neurosurgery

BY MARY ANN LITTELL

IN NEUROSURGERY, THERE IS NO SUCH THING AS A ROUTINE PROCEDURE. Whether repairing an arteriovenous malformation, attacking an aneurysm, or removing a deadly brain tumor, a single millimeter in either direction may mean the difference between recovery or significant impairment.

With this high risk in mind, neurosurgeon Murat Günel, MD, calls upon every piece of knowledge at his disposal. He sees the operating room as an extension of his research and laboratory—a place in which discoveries and innovations can improve patients’ lives.

“Everything we do in the lab and the OR is toward one goal: providing the best care for our patients,” says Günel, chair and chief of neurosurgery at Yale Medicine and Yale New Haven Hospital; Sterling Professor of Neurosurgery; professor of genetics and of neuroscience; director of the Yale Program in Brain Tumor Research; and co-director of the Yale Program on Neurogenetics.

At Yale, Günel wears many hats—surgeon, scientist, administrator, and mentor. A highly respected researcher and collaborator, he focuses his work on the genetic causes of brain disorders, including brain development, vascular disease, and tumors. His discoveries have led to the identification of genetic defects in several brain disorders, including intracranial aneurysms. Günel’s lab also studies the molecular genetics and biology of cerebral cavernous malformations (CCMs)—abnormal tangles of vessels in the brain—as well as brain and central nervous system tumors, all with the goal of identifying effective treatments.

On the clinical side, Günel’s expertise is in treating brain aneurysms, complex vascular malformations, and brain and

central nervous system tumors. “We offer every type of subspecialty care at Yale neurosurgery,” he says. “I’m extremely proud of the work we do.”

This focus on excellence has propelled Günel’s career, all of it spent at Yale. In recognition of his talent and commitment, he was elected chair of the Yale Medicine Board in September 2024, succeeding Nita Ahuja, MD, MBA, outgoing chair of the Department of Surgery. He will serve a renewable two-year term. “I’m excited to have this opportunity during a pivotal period of growth,” he says.

As a youngster living in Istanbul, Turkey, Günel was a voracious reader who loved to learn. “I was particularly interested in human intellect and the mysteries of the brain,” he says. He and his best friend talked about studying computer science together, but Günel decided he would rather become a physician.

After high school, he entered Istanbul University’s special undergraduate/MD program. His role model was his molecular biophysics professor, who was also the head of the TÜBİTAK branch in Istanbul—an agency akin to the U.S. National Institutes of Health. Günel worked with his professor on a small-budget project funded by NATO, learning to optimize different ways to transfer DNA into cells. It was his first exploration into genetics research.

Approaching graduation, Günel considered his options for residency. At the time, Turkish medical education was a crowded arena.

In medical school, he shared space and resources with 400 students in his class. A former classmate was traveling to the United States to do her residency. “She highly recommended it—said her training was outstanding, very structured and merit-based,” says Günel. “I decided to pursue that.”

Günel wrote to more than 50 U.S. residency programs and heard back from three: YSM and two academic health centers on the West Coast. “Knowing of Yale’s excellence, that’s what I wanted,” he says. He studied a map, confirming the school’s location on the East Coast, “much closer to Turkey—that clinched it.”

Günel’s letter of acceptance specified a three-month rotation with no financial support. If he did well, he could apply for a residency. There was, however, no guarantee he’d be selected. “Being a foreign graduate, it was a long shot,” he says.

Arriving in New Haven in March 1990, Günel moved into a small room in Harkness Hall and got to work. His efforts paid off. Impressed with this Turkish émigré, the then-chair of neurosurgery, Dennis Spencer, MD, asked him to do an additional two-month medical rotation. “When I completed it, Dr. Spencer said, ‘Congratulations, you got the job,’” Günel says.

Günel’s residency included two years of research. The renowned geneticist Richard Lifton, MD, PhD, now president of The Rockefeller University, became his mentor. Lifton had

Murat Günel, MD //

“I tell students and residents: You’re in a place that is the best humanity can create. Take advantage of that. Surround yourself with smart people and learn from them.”

recently published a paper in *Nature* identifying the first gene that harbored mutations causing high blood pressure in glucocorticoid remediable aldosteronism (GRA), the most common monogenic cause of hypertension. “Rick Lifton asked me what I wanted to work on,” recounts Günel. “I wanted to do vascular neurosurgery—aneurysm clip-pings, resecting arteriovenous malformations—and had a keen interest in identifying genes that cause aneurysms.” Lifton pointed out that such an area of study would be challenging, given the complex inheritance pattern of aneurysms. He suggested that Günel take a different, more Mendelian approach, by

identifying and studying a disease with clear hereditary patterns.

After hours poring through medical journals, the 26-year-old Günel located three families that had several members with cavernous malformations. He completed a genetic study under Lifton’s guidance that was published in *The New England Journal of Medicine*, with Günel as first author.

His residency completed, Günel joined the Yale faculty in 1999, putting his clinical skills to work at Yale New Haven Hospital and other facilities while continuing his research. “Rick Lifton was right about the difficulty of finding the first intracranial aneurysm gene,” notes Günel. “Still, we pursued it and finally accomplished it. It only took us 25 years! We’ve gone on to publish many impactful studies on cavernous malformations and aneurysms. This work has been incredibly rewarding.”

Günel rapidly rose through the ranks, becoming a professor of neurosurgery, neurobiology, and genetics in 2008. Three years later, he received an inquiry that altered the direction of his research. A Turkish businessman named Mehmet Kutman posed an intriguing question: Would Günel be interested in studying brain tumor genetics? Günel’s answer was an emphatic yes.

Kutman’s interest in brain tumors had been fueled when his friend and colleague, Gregory M. Kiez, was diagnosed with glioblastoma multiforme, one of the most complex, deadly, and treatment-resistant cancers. To address the great need for effective treatments, the Gregory M. Kiez and Mehmet Kutman Foundation provided a gift of \$4 million to launch the Yale

Program in Brain Tumor Research. Under Günel’s direction, these efforts are unlocking the secrets of how brain tumors form—and how to treat them.

Named chair of neurosurgery in 2014, Günel set his sights on expanding the department’s surgical and research talent. A decade later, he has tripled the number of procedures performed. The department now has 34 ladder faculty; of these, 21 are neurosurgeons. “All of our surgeons are incredibly skilled,” he says. “No matter what neurological disease or problem arises, we have the expertise to treat it.” He’s also built an outstanding basic science program within the Department of Neurosurgery with eight PhDs or MD/PhDs who are ladder faculty. “For training, we accept two MDs or MD/PhDs every year,” he notes.

Another effort addresses issues of global public health. In 2022, Günel recruited Steven Schiff, MD, PhD, as vice chair for global health in neurosurgery. With a goal of treating and preventing deadly infant infections in the developing world, Schiff is launching the Center for Global Neurosurgery at YSM.

“There are so many exciting things happening here,” Günel sums up. “I tell students and residents: You’re in a place that is the best humanity can create.

Take advantage of that. Surround yourself with smart people and learn from them.”

As Yale Medicine Board chair, Günel speaks enthusiastically about current initiatives, including making strong progress on aligning with Yale New Haven Health System to strengthen the position of both Yale Medicine, YSM’s faculty practice, and the Northeast Medical Group (NEMG), the health system’s affiliated network of community-based physicians. The “new and improved” faculty practice is expanding health care and building referrals throughout the state and beyond.

“Synergy between medical schools and hospitals is vitally important—it’s the ultimate driver of patient care,” explains Günel. “The alignment of our school and hospital has never been better, thanks to outstanding leadership at the hospital, medical school, and health system. This alignment enabled us to make exciting clinical and research programs a reality, even though we have more work to do to translate this to our front lines.”

During the COVID-19 pandemic, YSM Dean Nancy J. Brown, MD, was inspired to create a multidisciplinary disaster response coordination team that included faculty from the medical school, Yale School of Engineering & Applied Science,

the humanities, and many other disciplines. “Bringing these individuals together opened the door to communication, allowing us to build relationships with faculty members across the university, including our tech colleagues,” says Günel. “We continued to build on those relationships and now have collaborations with engineering and other departments.”

“Medicine is increasingly technology-dependent,” he adds. “We will all find greater success working together as a team.” To that end, the Department of Neurosurgery recently recruited its first engineer: Jiangbing Zhou, PhD, Nixdorff-German Professor of Neurosurgery and Biomedical Engineering. Zhou’s lab focuses on developing translational nanomedicine and gene and stem cell therapy, including investigation into a new gene editing therapy for Angelman syndrome, a rare, disabling genetic disorder that primarily affects the nervous system.

There are also exciting infrastructure projects on the horizon. Construction is underway on the 500,000-square-foot Adams Neurosciences Center on Yale New Haven Hospital’s Saint Raphael Campus. The facility comprises two towers and will focus on innovations in neuroscience from movement disorders to neuroregeneration, the regrowth or repair of nervous tissue, cells, or cell products. Günel believes this is the next era for neurosurgery.

“When brain function is lost due to Parkinson’s, stroke, brain tumors, or trauma, how are we going to bring this function back?” he asks. “That is what we are now focusing on. With the

combined strengths of our basic neuroscience, neurology, neurosurgery, and psychiatry departments, Yale consistently ranks among the top medical schools in the country for NIH funding in neurosciences. We have an ambitious idea about an initiative to treat neuropsychiatric and neurodevelopmental disorders, including autism: ‘From Molecules to Mind.’ It begins with the molecules, going all the way to clinical care in neurology, neurosurgery, and psychiatry.”

He adds: “We’re here to train the next generation—but as educators and clinicians, we cannot exist without the science to build on. That’s why we are so focused on scientific discovery. Exceptional medical and surgical outcomes depend on it, as well as the expertise of our surgeons. These elements must work together, and no place does this better than Yale.”

Murat Günel, MD //

“Yale consistently ranks among the top medical schools in the country for NIH funding in neurosciences.”



NEW INSIGHT INTO CELL MIGRATION

It's normal for cells to move around the body to do their jobs—but when cell migration goes awry, it can lead to chronic inflammation, cancer metastasis, and other disease processes. Stefania Nicoli, PhD, associate professor of internal medicine and genetics, and Liana Boraas, PhD, an associate research scientist in the Nicoli lab, study bundles of molecules known as “cellular feet,” which allow for cellular migration. One molecule associated with cellular feet is messenger RNA (mRNA)—previously believed to play a role only in cellular protein production. In research recently published in *Cell Reports* (February 2025), Nicoli and Boraas found that this mRNA does not make protein but instead is part of the cellular footwear itself. This newly discovered role for the molecule may lead to new avenues of research into cellular mechanisms that are fundamental to health and disease.



RISKS OF ‘MIRROR BACTERIA’

In a report published in *Science* (December 2024), Ruslan Medzhitov, PhD, Sterling Professor of Immunobiology, and colleagues worldwide warned of the risks posed by so-called “mirror bacteria.” Background: Many asymmetrical molecules within cells can exist in two mirror-image forms. DNA, for example, is built from “right-handed” nucleotides, while proteins consist of “left-handed” amino acids. Some synthetic biologists are now considering creating bacteria in which molecules like these are reversed. The report warns that populations of mirror bacteria could grow out of control, and human immune systems would likely be unable to fight off infections by the reversed bugs. According to the researchers, their report demonstrates the need for careful consideration of future mirror bacteria research.



A TARGET FOR TREATING AUTOIMMUNE DISEASES?

In such autoimmune diseases as lupus, the immune system attacks the body's own cells. Previous research by Noah Palm, PhD, professor of immunobiology, and Martin Kriegel, MD, PhD, associate professor adjunct of immunobiology and of medicine (rheumatology), indicated that in a mouse model of lupus, the bacterium *Enterococcus gallinarum* travels outside the gut, where it spurs the development of inflammatory T cells and an autoimmune response. In a recent study published in *Science Translational Medicine* (February 2025), the researchers reported that the bacterium also drives the development of inflammatory T cells in human cellular models—a finding that suggests *E. gallinarum* could be a future target for treatment of autoimmune diseases.



PRETERM INFANT IMMUNITY

Studying preterm infants is key to improving their care, but it's also difficult: They have too-little blood to provide a standard-sized blood sample safely. Liza Konnikova, MD, PhD, associate professor of pediatrics, immunobiology, and reproductive sciences, and Bunmi Olaloye, MD, assistant professor in pediatrics, have identified a way to study the immune systems of extremely preterm infants by taking just two drops of blood. Using this method, the researchers recently reported in *Science Translational Medicine* (March 2025) that preterm infants have all the immune cells found in adults and full-term infants, but greater signs of inflammation than their full-term counterparts. In future trials, Konnikova plans to explore the implications of these findings for the long-term health of individuals who were born preterm.

PERSONALIZED KIDNEY CANCER VACCINE

High-risk kidney cancer is typically treated with surgery followed by immunotherapy drugs, which ramp up the body's immune system with the hope that it attacks cancer cells. But the body's activated immune cells cannot always find their cancerous targets. To address this problem, David Braun, MD, PhD, assistant professor of medicine (medical oncology) and Louis Goodman and Alfred Gilman Yale Scholar, led a phase 1 trial in which nine advanced kidney cancer patients received personalized cancer vaccines, which train the immune system to attack cells with mutations specific to each patient's cancer. Braun and colleagues reported in *Nature* (February 2025) that all trial participants mounted an immune response to the vaccine. Three years after vaccination, all patients remained cancer-free.

MODULATING NEURAL SIGNALS

When neurons fire to transmit messages that control everything from our sense of smell to that of hearing, the release of neurotransmitters can vary in both intensity and speed. Previous research by Shyam Krishnakumar, PhD, assistant professor of neurology, and colleagues identified a protein—Synaptotagmin-1—as a key driver of rapid neurotransmitter release, but the researchers suspected that another protein fine-tuned this process. Using a stripped-down in vitro model of the synapse, the team recently confirmed that the Synaptotagmin-7 protein is responsible for dynamically adjusting neurotransmitter release. The findings, reported in *Nature Communications* (December 2024), could pave the way to develop new therapies for epilepsy and other neurological disorders.

from the journals

a collection of recent scientific findings

INTRODUCTION

A SPECIAL REPORT ON AI FOR HUMANITY IN MEDICINE

SUPERCHARGED DATA

Generative AI and the future of medicine.

BY STEVE HAMM



FERNANDO VOLKEN TOGNI ILLUSTRATION

WHILE
DECADES
OF MAJOR ADVANCES

—from antibiotics and anesthesia to genome sequencing and immunotherapy—have transformed the practice of medicine, the field is now at the threshold of yet another seismic shift. Today, generative AI, a new approach to artificial intelligence, has the potential to reshape clinical practice, research, and education in ways that defy imagination.

It was 75 years ago that the computer scientist Alan Turing posed a profound and prescient question, “Can machines think?” in his seminal research paper Computing Machinery and Intelligence. A few years later, in 1956, a Dartmouth professor coined the term artificial intelligence to describe a burgeoning field of research.

Driven by algorithms, data, and computational power, AI technologies mimic processes of the human brain with breathtaking speed. Generative AI, which became widely adopted just over two years ago, differs from classical AI by creating new information or content based on large computing models trained by using machine learning techniques on text, images, videos, sounds, and software code often gathered from the internet. With such popular applications as ChatGPT, DALL-E, and Perplexity, generative AI has quickly become a driver of innovation and economic activity.

Generative AI harnesses clusters of high-performance computers in data centers; it uses new machine learning techniques to build vast models based on real-world scenarios to do everything from writing software code to forecasting the effects of climate change. Observers have said that society is experiencing a new industrial revolution—this one powered not by coal or oil but by data. Generative AI has the potential to supercharge data for human progress at an unprecedented rate.

Within the medical domain, generative AI shows great promise in relieving a highly stressed health care system. The technologies can help health care providers become more effective and efficient at a time when high-quality health care is expensive and inaccessible to many, and where there aren’t enough physicians to go around.

“I’m very optimistic that AI—including generative AI—will help address the big challenges faster and propose solutions,” says Lucila Ohno-Machado, MD, PhD, MBA, Waldemar von Zedtwitz Professor of Medicine and Biomedical Informatics and Data Science. She chairs the Department of Biomedical Informatics and Data Science (BIDS), which is spearheading the use of AI in research and clinical practice.

EMBRACING INFORMATION TECHNOLOGIES

Yale School of Medicine (YSM) is known for being an early adopter of information technologies, and the creation of BIDS as a department in May 2024 signals the importance of AI to the school’s future. The department has already worked with the university to establish a computing environment that’s compliant with federal privacy and security standards, so that faculty members can develop AI models using real patient data while adhering to the highest ethical standards to protect confidentiality and trust.

On an even broader scale, Yale University has committed to spending \$150 million over the next five years to support its AI ambitions. It is hiring faculty, adopting new AI applications, and, in a sustainability move, has joined other universities including Harvard and the Massachusetts Institute of Technology at the Massachusetts Green High Performance Computing Center (MGHPCC) in Holyoke, Mass. Yale’s project leaders expect to transition at least one megawatt of on-campus power to green hydroelectric sources, and eventually to operate dozens of racks of computing hardware there—many of which will be dedicated to YSM, says Wies Rafi, PhD, associate chief information officer of Yale’s Health Sciences Division.

Meanwhile, more than a dozen YSM faculty members assisted the Yale Task Force on Artificial Intelligence in publishing a 119-page report in June 2024 laying out a strategy to leverage the new technologies. In the report, YSM faculty members wrote that AI “is already driving a revolution in health care and is poised for mass adoption,” further predicting that “it is only a matter of time before nearly all health care workers engage with AI solutions on a daily basis.”



“

I’m very optimistic that AI—including generative AI—will help address the big challenges faster and propose solutions.

—LUCILA OHNO-MACHADO, MD, PHD, MBA



We need these tools
to help us stay afloat.
They can rapidly
scour information
across multiple records
and help us
make sounder
clinical decisions.

—ARJUN VENKATESH, MD, MBA, MHS

For decades, YSM has fostered the development and adoption of AI technologies. For example, Perry Miller, MD, PhD, professor emeritus of biomedical informatics and data science, developed PUFF, an AI program that interpreted lung function data and was used at Yale New Haven Hospital beginning in the 1980s.

Fast-forwarding to 2023, Rohan Khera, MD, MS, assistant professor of medicine (cardiovascular medicine) and of biostatistics (health informatics), has used novel deep learning techniques to develop a smartphone app that analyzes electrocardiogram images. The app enables cardiologists to screen patients for left ventricular systolic dysfunction and other conditions that, if undiscovered, can result in hospitalizations and premature deaths.

Within health care, AI has so far had its most significant impact on diagnostic radiology. Pattern recognition technology is used widely to prescreen medical images and spot diseased tissues, bone breaks, and other conditions. Now, researchers across the country experimenting with generative AI are creating highly detailed 3D models of organs and tissues that can be trained to simulate the effects of radiation therapy on a particular patient, allowing physicians to customize treatment plans.

AI IN ACTION

Innovation is accelerating across the medical school with the emergence of generative AI. One project that could impact researchers and clinicians in practically every department is the Me-LLaMA chatbot. Working with associates, Hua Xu, PhD, Robert T. McCluskey Professor of Biomedical Informatics and Data Science, built a medicine-specific chatbot on top of Meta’s LLaMA large-language model, training and fine-tuning it on biomedical literature and clinical notes from electronic health records. One of the first applications of Me-LLaMA is to suggest diagnoses in complex clinical cases.

Yale New Haven Health System, which is staffed with YSM faculty members, is among those already using generative AI technologies to ease administrative burdens on clinicians. With the use of a new generative AI application called Abridge, AI agents can “listen in” on

office visits and create summaries, enabling doctors and nurses to focus on human interactions. Other technologies suggest responses to emails from patients, thus saving human time and effort.

In an environment in which delays can be devastating, clinicians at Yale New Haven Health’s three emergency departments are utilizing Abridge to capture conversations with patients and automatically integrate that information into their existing electronic medical records—enabling a physician to better evaluate the patient’s condition. The next version of the application is expected to provide rapid diagnostic help. “We need these tools to help us stay afloat. They can rapidly scour information across multiple records and help us make sounder clinical decisions,” says Arjun Venkatesh, MD, MBA, MHS, professor and chair of Emergency Medicine.

For example, Venkatesh points to the complete blood count (CBC), a blood test that is frequently used in emergency departments. Today, physicians typically evaluate just a handful of perhaps 20 lab values produced by the test. Venkatesh anticipates that new generative AI applications will be able to quickly review all the lab values obtained, and identify relationships and implications that a harried ED physician simply does not have time or the mental bandwidth to evaluate.

On the research front, YSM faculty members expect generative AI to accelerate the development of new therapies, and to deepen our understanding of how diseases work and what it takes to cure or control them—delivering on the promise of truly personalized medicine. For instance, María Rodríguez Martínez, PhD, associate professor of biomedical informatics and data science, has been using AI models to understand immune system function in such complex diseases as cancer and autoimmune diseases.

Steven Reilly, PhD, assistant professor of genetics, is working with scientists from other research organizations to use generative AI to design synthetic DNA elements that switch on genes in certain cell types but not in others. The technology could help develop the next generation of genetic therapies, specifically targeting gene replacements or CRISPR sequences to affect only diseased tissues.

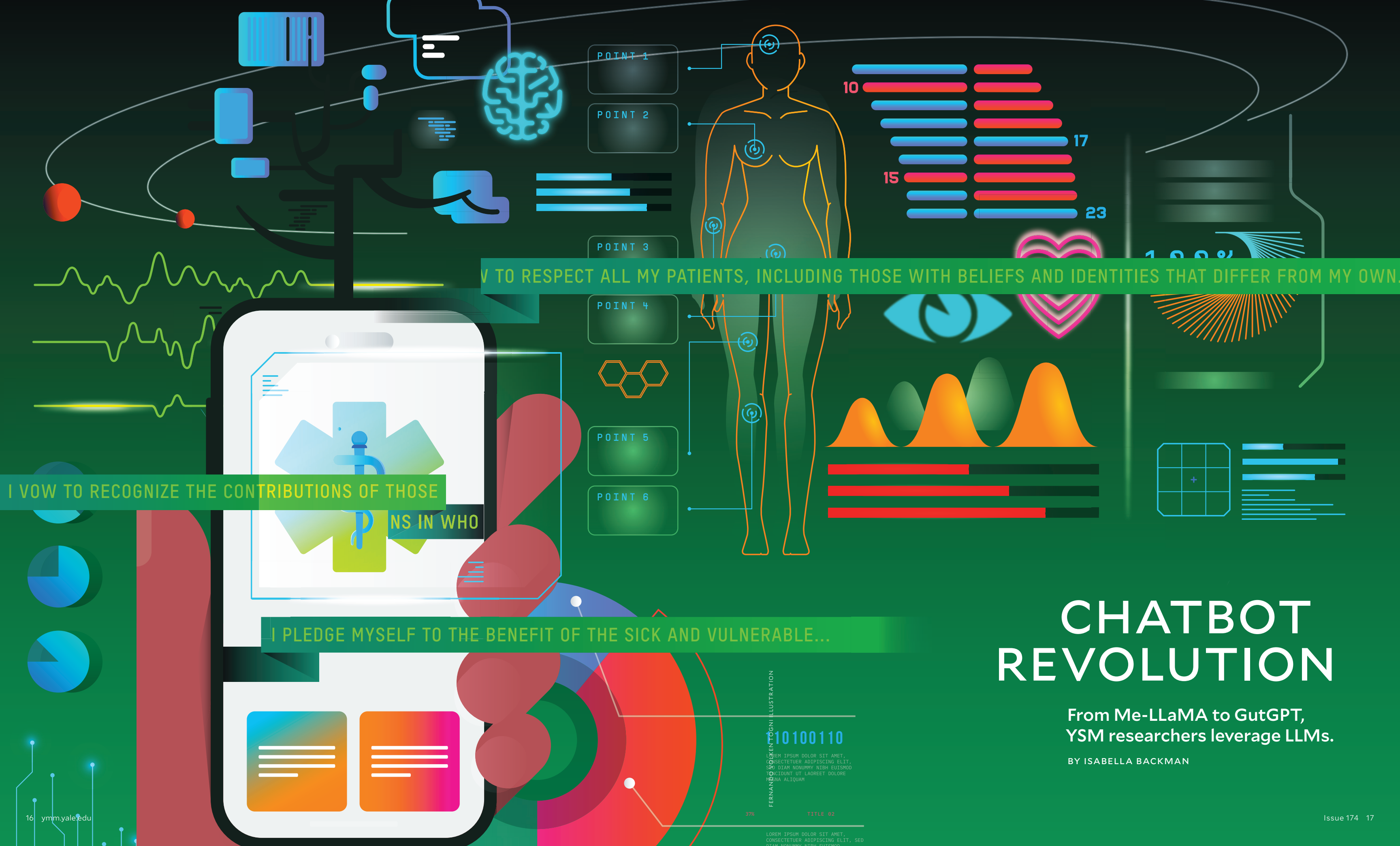
For many YSM students, generative AI is already part of their lexicon. In the first-year Professional Responsibility course last fall, about one-third of the students indicated that they already had experience with AI, according to David Rosenthal, MD, assistant professor of medicine (general medicine) and co-director of the course. The course now includes lectures on AI concepts and medical applications in addition to discussions of ethical issues.

Technology leaders expect advances in AI to pick up speed in the coming years, eventually producing machines that are sentient and autonomous. At that point, Rosenthal believes medical schools will need to rethink medical education. “We will have tools that outperform the best humans on knowledge tasks,” he says. “We need to prepare so physicians will be able to use these tools to help patients heal, to promote healthy behaviors, and to help patients live well.”

While AI’s potential has not yet been fully realized, YSM leaders say the future is bright. Yale is well positioned to conduct groundbreaking research at the intersections of biology, medicine, and AI, and to train the next generation of clinicians and biomedical researchers to use the technology responsibly and enhance it to promote better health for all.

[/yale medicine magazine](#)

Editor’s note: Because OpenAI is rapidly evolving ChatGPT, various models reflecting a particular time frame are referenced in the special report articles.



I VOW TO RESPECT ALL MY PATIENTS, INCLUDING THOSE WITH BELIEFS AND IDENTITIES THAT DIFFER FROM MY OWN.

I VOW TO RECOGNIZE THE CONTRIBUTIONS OF THOSE WHO HAVE SHAPED THE FIELD AND INSPIRE US IN WHO WE ARE BECOMING.

I PLEDGE MYSELF TO THE BENEFIT OF THE SICK AND VULNERABLE...

CHATBOT REVOLUTION

From Me-LLaMA to GutGPT,
YSM researchers leverage LLMs.

BY ISABELLA BACKMAN

YOU’VE
HEARD
OF CHATGPT.

Since its launch in 2022, it quickly became one of the fastest-growing applications (better known as “apps”) in history, amassing 100 million active users within its first two months. For many, the enormously popular chatbot from OpenAI was an eye-opener to the massive potential of large language models (LLMs)—a type of artificial intelligence (AI) designed to understand and generate human language.

Now, LLMs have become a major subject of interest in medical research. Scientists at Yale School of Medicine (YSM) are exploring ways to train specialized chatbots to act like a clinician’s personal AI assistant. As the thinking goes, LLMs could one day assist doctors with answering clinical questions quickly, diagnosing diseases, interpreting test results, selecting appropriate therapies, and more. By reducing physicians’ heavy workload, these chatbots could revolutionize the ways in which doctors deliver care and improve patients’ experiences.

“One of the biggest breakthroughs of AI in the past three years has been these large language models,” says Lucila Ohno-Machado, MD, PhD, MBA, Waldemar von Zedtwitz Professor of Medicine and Biomedical Informatics and Data Science (BIDS), deputy dean for biomedical informatics, and chair of BIDS. “With ChatGPT and other LLMs, everyone now has had a chance to see how these generative AI models work in practice.”

NEW LLMs RECEIVE SPECIALIZED
BIOMEDICAL TRAINING

ChatGPT made headlines in 2023 after it identified the cause of a young boy’s mysterious chronic pain. His mother had taken him to 17 doctors over three years, but none could figure out the cause of her son’s suffering. Out of frustration, she then turned to ChatGPT. After entering as much information as she could on his condition, she finally received the long-awaited answer—tethered spinal cord syndrome. She made an appointment with a neurosurgeon who confirmed the chatbot’s diagnosis. The boy finally received surgery to treat his chronic pain.

Indeed, chatbots show potential in assisting doctors in diagnosing complex medical cases. One 2023 study

in *JAMA* found that OpenAI’s chatbot GPT-4 accurately identified the final diagnoses of challenging medical cases 39% of the time, and it included the correct diagnosis in its list of possible conditions 64% of the time. While promising, the chatbot’s lack of specialized training, however, still leaves much room for improvement.

Me-LLaMA is a novel family of LLMs introduced by YSM researchers. This chatbot is similar to its cousins ChatGPT and GPT-4, but these LLMs are closed-source—meaning they aren’t easily accessible to or customizable by researchers.

To address this issue, Hua Xu, PhD, Robert T. McCluskey Professor of Biomedical Informatics and Data Science and assistant dean for Biomedical Informatics, and his team are developing this new family of LLMs collectively known as Me-LLaMA, which is one of the first and largest open-source models to be trained on extensive biomedical and clinical data. “Me-LLaMA is an open-source medical foundation model that we are continuously training on large amounts of biomedical text and releasing to the community,” Xu says. His team used over 129 billion tokens—small pieces of text, like words or parts of words, that the model processes—to train Me-LLaMA. “We are doing both pre-training and fine-tuning to improve its performance on many biomedical applications.”

Xu’s team is training these models on massive amounts of data, including millions of biomedical articles from the PubMed database, clinical notes from anonymized databases, clinical guidelines, and more. The researchers are also studying how well the models perform various tasks. For example, users can ask the chatbot questions about specific publications or ask it to extract relevant information about a clinical trial.

The researchers are also comparing the performance of Me-LLaMA and other LLMs using publicly available datasets that test these models in different areas, such as answering medical questions. So far, they are finding that Me-LLaMA outperforms such other existing open medical LLMs as Meditron-70B and such commercial models as ChatGPT and GPT-4 across these kinds of tasks.

“We are showing that large language models have great potential as an AI assistant that helps with

clinical diagnostic reasoning, accelerating clinical documentation, and making clinical work more efficient while improving patient care,” says Qianqian Xie, PhD, associate research scientist in Xu’s lab. Xie is currently exploring Me-LLaMA’s ability not only to come up with potential diagnoses when given a summary of a particular case but also to explain its reasoning for each one.

Updating Me-LLaMA requires significant computational resources. Fortunately, says Xu, Yale is dedicated to supporting the development of robust graphics processing units (GPUs) infrastructure. Recently, the Office of the Provost announced it will invest over \$150 million in AI development.

FROM CHATGPT TO GUTGPT

Other chatbots are undergoing an even greater degree of specialization. At the Yale Center for Healthcare Simulation, which allows members of YSM and the Yale New Haven Health System to practice using various clinical methodologies, researchers are evaluating the usefulness of an LLM designed to support clinicians treating patients with gastrointestinal (GI) bleeding.

Meet GutGPT, an LLM trained on the latest clinical practice guidelines on GI bleeding—the most common GI condition that leads to hospitalization in the United States. The chatbot is designed to help clinicians predict the severity of a patient’s bleed and offer evidence-based treatment recommendations.

GutGPT’s development is being led by Dennis L. Shung, MD, PhD, MHS, assistant professor of medicine (digestive diseases). The first thing a gastroenterologist needs to do when a patient enters the emergency department with acute gastrointestinal bleeding is to assess whether the individual needs inpatient treatment. For about half of these patients, he says, hospitalization is not necessary. “They just need to go home and make an appointment for an outpatient endoscopy.”

Shung wondered whether AI could help clinicians distinguish low-risk patients who could safely go home from high-risk patients who need hospitalization. Using electronic health records from patients seen in the Yale New Haven Health System for GI bleeding, his team created a machine learning model that produces

a clinical risk score to identify very-low-risk patients who do not require a hospital-based intervention for gastrointestinal bleeding. The model allows providers to obtain a real-time risk assessment quickly while the patients are in the emergency department, saving valuable time.

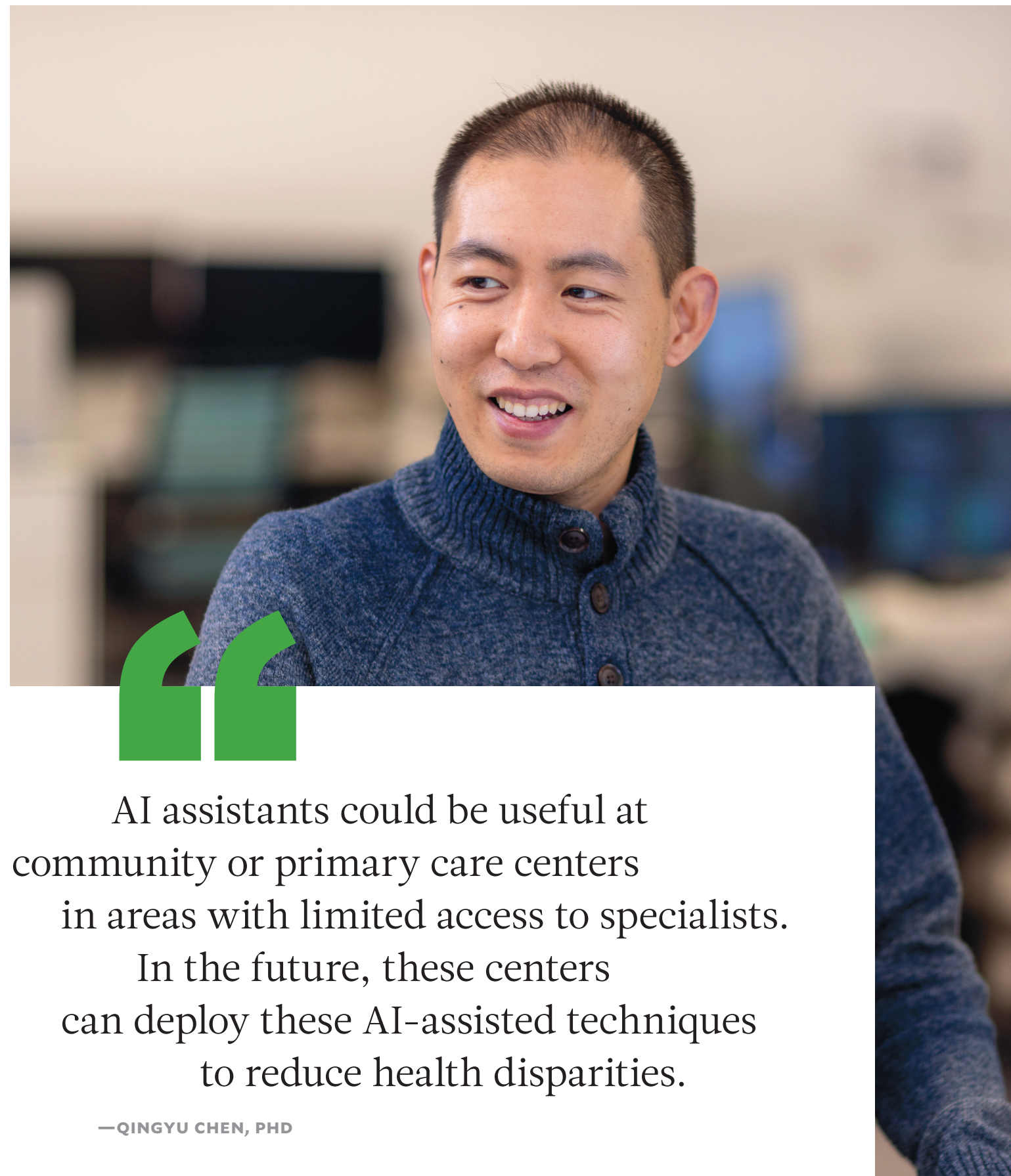
Shung’s team then integrated the risk model into GutGPT. “Now, providers can not only ask, ‘What is the risk?’ but also things like ‘Why is the risk so high?’ or ‘What are the factors driving it?’” Shung says. Beyond risk assessment, users can also ask the chatbot a range of questions about how best to treat patients with gastrointestinal bleeding with evidence-based responses drawn from national clinical guidelines.

To better understand how physicians, residents, and medical students use these tools, Shung’s team conducted a randomized controlled trial at the Yale Center for Healthcare Simulation measuring the efficacy of GutGPT versus the risk model alone. By observing how users engage with GutGPT, the researchers are learning how to fine-tune the chatbot and optimize its usefulness. Shung’s team has published results of its work on the machine learning model in *Gastroenterology*, and the preliminary qualitative results of GutGPT in the *Proceedings of the 2024 CHI Conference on Human Factors in Computing Systems*.

Because risk changes over time—a bleed may worsen after a patient enters the hospital—Shung’s team has also explored novel generative AI algorithms to better understand an individual’s risk trajectory. “We’re really excited about not only identifying the risk initially, but being able to track a patient over time so we can identify those who need more attention versus those who are stable and should go home.” In conjunction with a group led by Yoshua Bengio, PhD, at Mila-Quebec Artificial Intelligence Institute, they have published their work in *Proceedings of the Advances in Neural Information Processing Systems*.

BEYOND TEXT: RESEARCHERS TEACH LLMs
TO PROCESS MEDICAL IMAGERY

LLMs have grown tremendously in their ability to understand, process, and generate text. But other



AI assistants could be useful at community or primary care centers in areas with limited access to specialists. In the future, these centers can deploy these AI-assisted techniques to reduce health disparities.

—QINGYU CHEN, PHD

LLMs that have the ability to “see” or “hear” are also in the works. In other words, researchers are training LLMs to interface with input beyond text, including images and audio.

Over 3 million adults in the United States aged 40 and older suffer from severe visual impairment—and experts predict that this number will double by 2030. Early detection of such eye diseases as diabetic retinopathy, cataracts, and glaucoma can help prevent vision loss or blindness.

In the lab of Qingyu Chen, PhD, assistant professor of biomedical informatics and data science, his team is developing and studying the potential of multimodal LLMs that process both text and medical images to help doctors analyze eye images, diagnose ophthalmic diseases, and formulate treatment plans. The current version includes an ophthalmology-specific foundational language model called Language Enhanced Model for Eye (LEME). It has been evaluated on 10 downstream tasks in ophthalmology, including real-world validation on patient records for disease diagnosis and management. It has outperformed eight baseline LLMs in commercial, general, and medical domains.

“A clinician can, for example, directly input medical images from the patients, and then the AI system will make predictions [about the patient’s condition]. It can also highlight features of the image to aid the decision-making,” says Chen. “Based on these insights, the doctor can make the final decision [on disease management].”

Chen’s team has also created a large set of data specifically for testing these LLMs known as LMOD. LMOD is the first multimodal ophthalmology benchmark consisting of 21,993 instances across several ophthalmic imaging modalities: free-text, demographic, and disease biomarker information; and such primary ophthalmology-specific applications as anatomical information understanding, disease diagnosis, and subgroup analysis. This dataset contains different types of ophthalmic images as well as texts on patient demographics and disease biomarkers. The team’s research has identified the shortcomings of models in interpreting clinical imagery and offered insights into ways to improve the reliability of these models.

As scientists continue to troubleshoot these models, Chen is excited about their potential to boost accessibility to eye care. “AI assistants could be useful at community or primary care centers in areas with limited access to specialists,” he says. “In the future, these centers can deploy these AI-assisted techniques to reduce health disparities.”

Meanwhile, at the Cardiovascular Data Science (CarDS) Lab, researchers are training LLMs to interpret diagnostic cardiac imaging. ECG-GPT, for example, is a novel model that analyzes images from electrocardiograms and generates full text reports. The tool is currently available for use on the CarDS Lab website.

“These projects are meant to enhance the scalability of diagnostic services by making workflows easier at our very overloaded health systems and diagnostic environments,” says Rohan Khera, MD, MS, assistant professor of medicine (cardiovascular medicine) and of biostatistics (health informatics). “Often, the bottleneck is the expertise in interpreting [cardiac diagnostic tests]. This might just change how we deliver care.”

Khera is similarly optimistic about the potential of these LLMs to bring diagnostic testing to areas that lack adequate medical resources. In parts of the world where there are very few experts, waiting lists to see a cardiologist who can interpret cardiac tests can be extensive and greatly prolong the time it takes to receive necessary treatment. ECG-GPT, for instance, could more rapidly produce test reports that a specialist would confirm and then initiate treatment.

Khera’s team is launching multiple studies that evaluate the performance of their models in underserved clinical settings around the world. “We have the opportunity to democratize high-quality care,” says Khera. “You wouldn’t have to be near the best doctors—we can create algorithms that can transform care for the majority of the population.” [/yale medicine magazine](#)



A MILESTONE IN MEDICINE

How AI is advancing
clinical care.

BY ISABELLA BACKMAN

TODAY,
WHEN YOU
GET A RASH,

you might call a dermatologist, only to find that the next available appointment is weeks away. When you finally get in, the doctor relies on their own eyes and brain to look for patterns and arrive at a diagnosis. They write you a prescription and send you on your way.

The evolution of artificial intelligence (AI) is about to transform this process—providing patients better care faster. Soon, when you get a rash, you might be able to simply upload a picture onto your computer. From there, AI-assisted technology will use pattern recognition that is more likely to provide an accurate diagnosis than human senses alone. You are immediately prescribed the appropriate treatment that previously would have taken weeks to receive.

As AI continues to evolve at a rapid rate, doctors at Yale School of Medicine (YSM) are already implementing some of these clinical applications, while others are just over the horizon. Both in the clinic and behind the scenes, AI is about to permanently transform the way medicine operates, YSM experts say.

“We’re on the cusp of a moment that will shift everything forever,” says Harlan Krumholz, MD, SM, Harold H. Hines, Jr. Professor of Medicine (Cardiology). “It’s as if we’re just discovering microbes and the underlying cause of disease for the first time. AI is just as much a transformative milestone in medicine, and maybe more so.”

AI BEHIND THE SCENES

Many of the clinical AI applications both in use today and soon to be introduced are ones that patients will never see. Radiologists were among the earliest adopters of AI. The technology helps biomedical imaging technology become smarter and faster in acquiring, reconstructing, and interpreting images. “The images interpreted by radiologists make a really nice dataset for AI to leverage,” says Lee H. Schwamm, MD, associate dean for digital strategy and transformation and chief digital health officer, Yale New Haven Health System. “This is an opportunity for the machine to recognize patterns or signatures that the human eye can’t recognize.”

Radiologists have actually been using AI for decades—as far back as the 1990s and 2000s, says Melissa Davis, MD, MBA, associate professor of

radiology and biomedical imaging. Back then, they used computer-aided detection (CAD) to help detect such abnormal features as lesions. “This was basically the early stages of AI,” she says.

Over the last five years, there has been a push within radiology for even greater incorporation of AI technologies. This is especially true for technology that assists with triaging—or prioritizing radiology cases on the basis of urgency. A patient may come into the emergency room, for example, in need of a CT scan after hitting their head. Before a doctor even looks at the scan, AI can detect and flag the odds of such risks as internal bleeding. “It’s not always right, but it allows us to have some sort of triage capacity for patients on our list who have acute issues, so we know to prioritize your scan,” Davis says.

Pathology is another field undergoing an exciting transformation. The specialty has traditionally relied on manual (human) analysis of tissue samples. Now, AI can analyze a digital slide of abnormal tissue and search for patterns, potentially generating earlier and more accurate diagnoses. For example, one study at Stanford Medicine published in *Nature Communications* found that AI is capable of predicting the presence of genetic mutations that are likely fueling a cancer based on the appearance of the tumor biopsy.

Chen Liu, MD, PhD, Anthony N. Brady Professor of Pathology, is leading the effort to bring YSM into a digital pathology revolution. He is especially focused on using AI to identify digital biomarkers—in other words, using AI to find markers of disease. “Human tissue contains a lot of information,” he says. “AI has the potential to mine huge amounts of data from human tissue to look for different diseases.”

Researchers at YSM are also learning how to use AI to help identify patients who might be eligible for clinical trials—a task that is currently complicated and labor intensive. Pamela Kunz, MD, professor of internal medicine (medical oncology), is part of a team that is developing a tool to help identify patients for clinical trials accurately and efficiently. “This is going to revolutionize how we find patients,” says Kunz. “The work of doing clinical trials can be very time-consuming, and if



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—CHEN LIU, MD, PHD

there’s any way we can speed up that work, that’s going to help us get important drugs to patients sooner.”

Kunz also hopes this work will help ensure that clinical trials are more representative of the populations her team studies by flagging patients who may have been missed by conventional methods. “The more diverse our study population is and the more it matches our communities, the more we’ll know about how the drug will perform in the real world,” Kunz says.

Hospitals across the country are deploying AI models that identify which patients are at high risk of clinical deterioration—in which they experience a sudden or serious decline in their condition. For instance, a patient admitted to the hospital for gallstone surgery could later suffer a cardiac arrest or develop a severe infection. “For most patients, there are markers of that impending deterioration that can be very subtle at first,” Schwamm says. “So by the time you recognize that there’s a problem, it’s too late for drugs and interventions to be helpful.”

Last year, Yale New Haven Health System introduced eCART, an AI deterioration index developed by researchers at the University of Chicago. While these models are still new, and it will take time to

demonstrate whether they will improve clinical outcomes, such AI capabilities will become more readily available as the technology continues to advance.

AI IN THE CLINIC

AI is radically improving patient experiences in the clinic. Abridge, for example, is an AI-powered ambient clinical documentation tool that Yale Medicine and Yale New Haven Health rolled out in April. It works as an AI scribe that records the interaction between doctor and patient, analyzes the key components of that conversation and physical examination, and reconstructs it into the format required for a clinical note—which once reviewed, edited, and approved by the clinician, goes into the patient’s medical record. Abridge allows providers to be more present with their patients and have more meaningful encounters because they don’t need to take extensive notes during the appointment.

“It’s less critical for me to type into the computer every last detail while I’m seeing the patient,” says Michael Karellas, MD, assistant professor of urology. “I don’t have to spend as much time facing the computer and am able to face the person I’m treating.” Patient



It’s like a
nanny cam
on steroids.

—LEE SCHWAMM, MD

data collected by Abridge are kept safe and confidential, and Karellas says all patients have the opportunity to opt out of being recorded.

Furthermore, Yale New Haven Hospital is one of a handful of health systems investing in a pilot initiative in which they will be wiring 450 beds with ambient AI video technology. This platform will “allow our nursing leaders to reimagine the nursing care model,” says Schwamm. The “smart beds” will also bring the right care to the right patient in the right amount of time by removing geographic constraints. It allows nurses, physicians, pharmacists, interpreters, or anyone else whom the patient needs to be right at their bedside through telehealth.

The beds also will help protect patients. For example, high-risk patients—such as individuals prone to falling—often require a patient observer to sit in their room to ensure safety. Using advanced AI algorithms, the beds can detect various risks and promptly alert staff. This feature allows one observer to keep an eye on multiple patients at a time.

Over time, Schwamm says, the ambient video technology has the potential to recognize visual patterns that are precursors of concerning behavior. Delirium, for example, is a significant problem for hospitalized patients

that can also increase their length of stay and risk of death. “If you could train an algorithm to recognize the signs of delirium before they happen, we have the opportunity to intervene and prevent harm,” Schwamm says.

These ambient vision algorithms could also be trained to recognize and document various activities—like emptying the urine catheter container or turning the patient in bed—into the medical record for a nurse or provider to edit and sign off on. “Think about it as sort of a virtual assistant who is always there and always processing,” Schwamm says. “It’s like a nanny cam on steroids.”

OUT IN THE REAL WORLD

Over the last decade, the use of such wearable biosensors as smartwatches has risen in popularity. These devices have become increasingly sophisticated, with some having the ability to track motion, heart rate, sleep, and more. Researchers are interested in accessing the massive amounts of data these devices collect, and using AI to recognize patterns associated with various conditions, including strokes, mood disorders, and more.

Among them is Mark Gerstein, PhD, Albert L. Williams Professor of Biomedical Informatics and professor of molecular biophysics and biochemistry, of computer science, and of statistics and data science. In one recent study, his team used smartwatch data from over 2,000 adolescents to train AI models to predict whether an individual has such psychiatric conditions as attention deficit hyperactivity disorder (ADHD) and anxiety. The measurements taken by the watches included heart rate, calorie expenditure, activity intensity, number of steps taken, and sleep quality.

The team found that heart rate was the most useful measure for predicting ADHD. Youth with the disorder often experience episodes of heightened arousal—in other words, they may experience more intense emotional responses like excitement or anger compared to those of their neurotypical peers. These episodes could be reflected in the individuals’ heart rates. Meanwhile, quality of sleep was the most significant predictor of anxiety—individuals with anxiety disorder tend to suffer from disrupted sleep patterns. The study points to

how wearable sensors could help reshape psychiatry by providing new diagnostic tools.

Brain disorders such as ADHD and anxiety are heritable—in other words, a person’s genetic makeup is predictive of whether they will develop a particular disease. So, Gerstein’s team also studied whether smartwatch data could help identify genetic factors linked to psychiatric illness. Using smartwatch and genetic data from a subset of individuals with ADHD and healthy controls, they identified 26 genes associated with the ADHD cohort. For example, they found an association between heart rate patterns in the ADHD group and a variant of the MYH6 gene, which encodes an important protein in cardiac muscle.

This finding highlights how wearable sensors could help clinicians better understand the underlying mechanisms of neurological conditions. “Brain diseases like Alzheimer’s disease, Parkinson’s disease, schizophrenia, and so on are major issues,” Gerstein says. “This research is a promising direction to help us manage brain and behavioral disorders.”

As AI is becoming increasingly prevalent in both the clinic and at large, concerns are also rising about patient privacy and compliance. “Keeping patient data safe and private should be everyone’s concern, and health system leaders and providers need to take extra steps to ensure that data is either fully de-identified or that it never leaves the health system data ecosystem,” Schwamm says. These tools should always have human oversight, and providers should be careful about the ways that data are accessed, stored, and moved. Through taking such proper precautions as using anonymized datasets, clinicians can engage with AI in ways that keep patients safe. At YSM, Schwamm says, “We have very rigorous processes to review and establish the security, the privacy, and the appropriateness of use of AI.”

THE FUTURE OF AI

Further advances in AI could have exciting applications for the future, YSM experts say. The ability to talk to a machine that can understand a question and quickly respond by summarizing information it gathered from thousands or millions of documents is unprecedented,

says Lucila Ohno-Machado, MD, PhD, MBA, Waldemar von Zedtwitz Professor of Medicine and Biomedical Informatics and Data Science (BIDS), and chair of BIDS. When asked about what excites her the most regarding AI research, she says that it is the long-term potential to create robotic caretakers that can assist vulnerable patients when human help is not available. “The ability of an elderly patient to stay at home and tell a robot what they need or to have a robot to sense that they need help—this type of AI is what we are all working toward,” she says.

The future of wearables is also ripe for innovation, says Krumholz. Scientists could potentially combine wearable biosensors with ambient listening technology to create AI assistants that work alongside a doctor in real time as they see patients. “You may have a plug-in in your ear that can give you guidance and clinical decision support,” he says. “Or maybe something similar to Meta’s smart glasses that helps you more easily spot an indicator of a disease that you wouldn’t normally be able to with a patient.” All of these technologies can help further augment clinicians’ abilities to diagnose and treat various conditions.

The evolution of these tools could also help health care workers provide care that would ordinarily require higher levels of training. This development could help bring medicine to remote areas that currently lack access to adequate specialized clinical care. Many village doctors in rural areas of China, for example, have only a high school level of education. With AI assistance, “these individuals will likely be able to work at the levels of nurse practitioners and PAs,” Krumholz says. “These assists are going to be like an expert on your shoulder that elevates your performance beyond what might have been expected if you were just working by yourself.”

He is looking forward to the transformation AI will bring to health care. “It’s my hope that AI will usher in a time where we will be able to meet people where they live, to be able to provide care that’s precise for their needs, and to be able to ensure that all we know in medicine is available to them,” he says. “And I think that’s what this new era is going to be about.”

/yale medicine magazine



CAN AI PREDICT OUR FUTURE?

Yale scientists are using sophisticated AI models to forecast disease risk, improve diagnoses, and develop better treatments.

BY RACHEL TOMPA, PHD

FERNANDO VOLKEN TOGNI ILLUSTRATION

IMAGINE VISITING A DOCTOR'S OFFICE FOR NEW SYMPTOMS

and getting tested with thousands of different drugs in the blink of an eye—only it's not your physical body receiving the medications, it's a faithful replica of you stored inside the doctor's computer.

This concept is known as a digital twin, and it could one day help physicians make diagnoses and predict the best treatment for each patient. While these virtual models of ourselves are still far from clinical use, such researchers as Jun Deng, PhD, professor of therapeutic radiology and biomedical informatics and data science at Yale School of Medicine (YSM), see a future in which our computational doppelgangers could help physicians make personalized medicine a reality.

"The beauty and the power of the digital twin is that it's individualized," says Deng, who is working on digital twins for cancer patients. "Each person has their own digital twin, and their data becomes the basis of that twin."

If the idea of a collection of ones and zeros (that is, binary code) making diagnoses or prescribing treatments gives you pause, not to worry—computers aren't going to replace human doctors anytime soon. In medicine, AI is a tool, not a stand-in. Human doctors are still very much needed to catch errors and make final decisions.

"Ultimately, all these tools are evaluated as human versus human plus AI," says Xenophon Papademetris, PhD, professor of biomedical informatics and data science, and radiology and biomedical imaging at YSM. "It's not AI versus human. We haven't reached that point. That might happen, but not anytime soon."

But we also don't need to wait for scientists to program full human replicas to harness the power of AI in predictive medicine: Scientists at YSM are building powerful computational models to forecast our disease risk, speed accurate diagnoses, and build more precise treatments. AI is helping researchers delve deeper into many aspects of human biology and disease, from predicting the detailed molecular structure of an immune protein when it encounters a diseased cell to modeling the human brain and how it changes in psychiatric disorders.

AI BEFORE IT WAS COOL

Although AI is the au courant buzzword, its applications in predictive medicine far predate the 2022 launch of the chatbot ChatGPT. AI has been used in medical imaging for decades, aiding diagnostics and flagging potentially abnormal results. The first FDA-approved AI-based tool, authorized in 1998, was a computational method to assist radiologists in detecting breast cancer on mammography images. Now, of the more than 1,000 AI-based technologies that have been approved by the FDA, around 75% of them are related to imaging. But other areas of medical AI are catching up quickly.

In research too, AI has been helping scientists make important discoveries about human biology for many years. Generative AI, the type of AI that underlies such popular tools as ChatGPT, has its place in research, but there are many other computational research methods that have been developed outside the limelight.

"Scientists have been doing AI since before it was cool to do AI," explains Mark Gerstein, PhD, Albert L. Williams Professor of Biomedical Informatics and professor of molecular biophysics and biochemistry, of computer science, and of statistics and data science at YSM. "In the past few years, there's been somewhat of a revolution, but for us, it's more of an evolution in terms of what we're doing with AI."

Gerstein's expertise is in using machine learning, a subset of AI, to mine large amounts of molecular data for biological meaning. Recently, he led an analysis of nearly 400 human brains that offered new insights into the genetic variants that underlie such neurological and psychiatric diseases as schizophrenia, bipolar disorder, and Alzheimer's disease. A better understanding of the genetic bases of these diseases is critical, because while most brain diseases and disorders are highly heritable, the specific biological factors that cause these diseases remain a mystery.

"Genetics for mental disease is extremely predictive, but people have no clue how these diseases work," Gerstein says. "That's a big problem when it comes to developing drugs."

In that study, Gerstein and other researchers from the large nationwide collaboration known as PsychENCODE



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In the past few years, there’s been somewhat of a revolution but more of an evolution, in terms of what we’re doing with AI.

—MARK GERSTEIN, PHD

built a computational model that encapsulates key aspects of the human brain, using molecular information from millions of brain cells from 388 different people who’d donated their brains to science for use after death. Some of the donors had been healthy; some had had brain diseases and disorders.

The team’s model was built to replicate how cells in the brain connect to each other and the complicated networks of proteins and gene expression in individual cells. The brain model can predict whether a certain genetic variant leads to a psychiatric disease, such as schizophrenia, and suggest the kinds of brain cells in which that variant plays the biggest role. The computational approach also shows how dialing up or down individual genes can tune the brain model toward a healthy or diseased state, offering insight as to how new drugs might tackle these disorders.

Gerstein’s work is also helping to make sense of cancer’s complexity. He’s led studies seeking to understand the full repertoire of mutations that drive cancer’s growth. Although tumors often contain thousands of genetic mutations, the belief widely held in the field states that a few or even just one of those mutations is responsible for each cancer’s formation—so-called driver genes. Gerstein and his colleagues used computational modeling to show that all the other cancer mutations—the passenger genes—also impact tumor development and growth, so they shouldn’t be ignored when it comes to drug development.

FROM HEALTH RECORDS TO DIGITAL TWINS

Deng is also using AI to make headway into preventing cancer. He’s developed models to predict cancer risk earlier and more accurately, potentially intervening before the disease begins. “Instead of waiting for the patient to come to us with symptoms, we want to move the battlefield earlier—detect and diagnose the cancer earlier,” Deng says.

Unlike Gerstein’s models, which rely on molecular analyses of individual cells, Deng’s prediction models use patients’ electronic health records. He and his colleagues built a model they dubbed a “statistical biopsy,” which predicts the risk of 15 different cancer types for men and 16 for women. The model uses such data as

age, body mass index (BMI), family history, blood test results, and patient-reported symptoms. Deng and his colleagues trained the model on a public dataset from cancer patients in the United States and then tested the model’s accuracy on a different database from the United Kingdom. In that test, the statistical biopsy was able to predict cancer likelihood with 80 to 90% accuracy for 10 different cancer types, including female breast cancer, colorectal cancer, lung cancer, and melanoma.

Such prediction models are early steps toward Deng’s ultimate goal: building digital twins for cancer patients. These sophisticated models would incorporate not only patients’ health records and history, but also detailed virtual representations of individual organs and body systems, including the immune system or gut microbiome.

Some aspects of the digital twin will be based on nonindividualized but highly detailed models of parts of the human body—patients won’t have to undergo invasive biopsies to precisely replicate all their organs in the model, for example. But a cancer patient may have their tumor biopsied and its complete genetic profile sequenced, providing valuable personalized data that can be added to the model. Digital twins are also dynamic, Deng adds, incorporating new information such as how a tumor responds to a given treatment to update themselves and provide accurate real-time predictions.

Looking ahead, digital twins might one day even be used to speed clinical trials, Deng says. If new drugs can be tested virtually before they’re given to patients in the physical world, that would save resources and precious time for patients who are waiting for new treatments for their cancers. Right now, Deng and his collaborators at Yale and at other institutions are working on models of organs and body systems. The next challenge will be integrating those individual models into a larger, multiscale model of the entire body. Optimistically, Deng predicts it will be at least five years before a true digital twin becomes available for clinical use.

“We don’t want to underestimate the complexity of the human body,” Deng says. “There is so much data generated every day, and so many phenomena where we still don’t completely understand the biology.”

PROTEIN BINDING PREDICTION

On a smaller physical scale, YSM Associate Professor of Biomedical Informatics and Data Science María Rodríguez Martínez, PhD, is using AI to make predictions that could lead to better cancer immunotherapies—a type of cancer treatment that harnesses the natural power of the immune system to attack tumors.

Rodríguez Martínez is building models to understand how certain kinds of immune cells known as T cells interact with their targets. T cells patrol our bodies, searching out and identifying cells or molecules that shouldn't be there, such as cancerous cells or foreign invaders including bacteria and viruses. T cells' surfaces are studded with proteins known as T-cell receptors that allow the immune cells to sample their environment by binding to other cells or molecules. T-cell receptors are amazingly flexible—both literally and figuratively. These proteins can bind to a wide repertoire of other molecules, and they rapidly change their 3D shapes to do so.

But not every T-cell receptor can recognize every disease protein. We all have many different types of T-cell receptors, and not everyone's T-cell receptors are the same. Understanding whether a given T-cell receptor will bind to a given disease molecule would be a huge leap in the field of cell therapy—a form of immunotherapy in which a patient's own T cells are engineered to better recognize and destroy cancer. Rodríguez Martínez is working on models to predict T-cell receptor binding, the first step toward designing new T-cell receptors that are tailored to certain kinds of cancer cells.

To date, many researchers have used AI to attempt to predict T-cell receptor binding, but there's room for improvement, Rodríguez Martínez says. Current models use the genetic sequence of T-cell receptors and disease proteins to predict binding, but the sequences don't capture the full picture.

"It's like trying to define Mount Everest without a three-dimensional map; it's akin to just giving someone the mountain's total height and telling them to go ahead and climb it," Rodríguez Martínez says. "The whole community has been doing it this way because until very recently we didn't know how to do better."

Rodríguez Martínez is now working on models that incorporate T-cell receptors' 3D structures. The models are made possible by advances such as the recent Nobel Prize-winning AlphaFold, an AI technology that predicts protein structures from their amino acid sequences. However, because T-cell receptors are such good shape-shifters, it's not as simple as just plugging their information into AlphaFold, Rodríguez Martínez explains, but this and related technologies give researchers a good starting point to predict T-cell receptor binding more accurately.

DOCTOR, MEET AI

Deng and Papademetris are also working to bridge the gap between humans and computers. Deng is working on models that could better personalize radiation treatments in real time, incorporating patient preferences into the model's input in the clinic. The AI is designed to help the radiation oncologists and their patients in shared decision-making, Deng says.

Papademetris is increasingly focused on training current and future physicians, software engineers, and others in medicine and industry on how to interact with medical AI. Like any sophisticated new tool, education is a key part of AI's rollout to the clinic. Papademetris has launched a new online nondegree program at YSM, Medical Software and Medical Artificial Intelligence, and an accompanying series of video interviews with experts in the field of medical AI aimed at anyone interested in or currently working in this area.

"How do we train the people who are going to be working in this space to create these products, to use these products, to manage their integration into hospitals?" Papademetris asks. "It's not just about building better software, because the software also needs to talk to humans. If the humans are part of the system, we can improve things by training the human as well, not just by improving the AI." */yale medicine magazine*

THE AI BALANCING ACT

Keeping pace while prioritizing ethics.

BY STEVE HAMM



ARTIFICIAL INTELLIGENCE (AI) TECHNOLOGIES ARE INCREDIBLY COMPLEX,

but the ethics of implementing AI may be even more challenging. At Yale, these issues are being addressed from many different angles.

Before diagnostic radiologists at Yale New Haven Health adopt a new AI technology, for example, a committee of faculty members spends months evaluating it. Their reviews include careful analyses of the ethical implications of using the technology. “We’re very excited about what generative AI can do, but it’s important for us to assess it before it’s implemented,” says Melissa Davis, MD, MBA, associate professor and vice chair of medical informatics in the Department of Radiology and Biomedical Imaging.

Generative AI shows great promise in boosting the effectiveness of diagnostic radiology, enabling radiologists to identify and triage medical anomalies more efficiently, resulting in improved diagnosis and treatment planning. Bias, however, is the group’s particular concern. When Davis and her associates conducted a study of the popular ChatGPT chatbot to see how it performed in translating radiologists’ reports into language that a layperson can understand, the findings raised questions. The group found that the translations produced for Black patients were written at a lower reading grade level than those produced for Caucasian and Asian patients. “The question is what other kinds of biases will surface in the future?” says Davis.

This study exemplifies the kind of unsettling ethical issues that clinicians, researchers, and administrators across the Yale School of Medicine (YSM) and the Yale New Haven Health System are confronting as AI technologies proliferate. They welcome the new capabilities but insist on safeguards that will prevent the technologies from violating ethical standards.

“There are enormous potential benefits, along with some known risks and some unknown risks, that are only going to become apparent as we gain further experience,” says Benjamin Tolchin, MD, associate professor of neurology at YSM and director of the Center for Clinical Ethics at Yale New Haven Health.

Ethical issues were top of mind last year when the Yale Task Force on Artificial Intelligence developed a university-wide strategy to consider the myriad questions arising from the emergence of generative AI. The group’s

report contains no fewer than 22 references to ethics. “We have started down the road of trying to get our arms around AI. Things are moving incredibly quickly. AI tools are just coming out of the woodwork,” says Yale University Chief Privacy Officer Susan Bouregy, PhD.

BIOMEDICAL ETHICS: PAST AND FUTURE

YSM has long been committed to ethics and corresponding codes of conduct. The school has published detailed standards of professional behavior—aligning them with those established by Yale University, federal funding agencies, and medical professional associations.

Lucila Ohno-Machado, MD, PhD, MBA, Waldemar von Zedtwitz Professor of Medicine and of Biomedical Informatics and Data Science (BIDS), and chair of BIDS, plans to convene faculty members from across the medical school to develop a strategy for applying medical ethics to all the uses of AI in a uniform way. “We need to establish guidelines for what we should touch, what we should not touch, what it can be used for, and what it cannot be used for,” she says.

Biomedical ethics have evolved over time to keep pace with advances in modern medicine. Today, the four basic principles are:

- Autonomy: respecting the patient’s wishes.
- Nonmaleficence: doing no harm.
- Beneficence: balancing benefits against risks or costs.
- Justice: fairly distributing benefits, risks, and costs.

However, generative AI poses new ethical concerns, says Jessica Morley, PhD, who researches the governance, ethical, legal, and social implications of digital health technologies as a postdoctoral research associate at Yale’s new Digital Ethics Center. The stakes are higher, in part, because generative AI comes closer than previous AI technologies to mimicking human general intelligence.

The computing models underlying generative AI applications are general-purpose systems, including OpenAI’s GPT-4.1 and Google’s Gemini 2.5, rather than tightly controlled domain-specific tools, such as traditional machine learning-based models of disease diagnosis. “This is a systemic change,” says Morley. “How do you put bounds on something that can be easily used for many different things?”

The new technologies give rise to a host of ethical concerns in the realms of clinical care and research. Data are sometimes used and shared indiscriminately by AI technology providers, so safeguarding the privacy of patient data is even more critical now. Because of concerns about AI “hallucinations,” or gross errors, it’s also important for the users of these systems to be able to understand how the answers are formulated and to review them for accuracy.

TACKLING SUSTAINABILITY CHALLENGES

At a time when humanity is threatened by the impact of climate change, there is growing awareness of the massive electricity and computing resources AI systems use. That’s because generative AI is much more energy-intensive than most other data-focused technologies. A study published in the peer-reviewed scientific journal *Joule* forecast that by 2027, AI computing worldwide will consume at least 85.4 terawatt-hours of electricity annually—more than many countries use in a year.

For socially conscious institutions such as Yale, intensive use of AI could make it more difficult to meet climate and sustainability goals. That’s one reason why Yale has joined Boston University, Harvard, the Massachusetts Institute of Technology, Northeastern University, and the University of Massachusetts along with other schools as equal partners in the Massachusetts Green High Performance Computing Center (MGHPCC) consortium in Holyoke, Mass. MGHPCC is a not-for-profit, state-of-the-art data center dedicated to supporting computationally intensive research. Yale’s inclusion in this consortium marks a milestone in its research infrastructure development, says Kiran Keshav, Yale director of the MGHPCC Transition. Members collaborate on research, pool knowledge, reduce redundancies in research computing operations, and benefit from a more sustainable source of energy for research computing infrastructure. This partnership provides a gateway to addressing challenges in computing on a scale too great for one academic institution to tackle alone. MGHPCC is the first university research data center to achieve LEED Platinum Certification, the top award from the U.S. Green Building Council.

Over time, Yale—including the medical school—will perform most of its research computing at the MGHPCC. “It’s a really good move on Yale’s part to recognize our increasing need and to look for a facility that can address that in a sustainable way,” says Amber Garrard, director of Yale’s Office of Sustainability, which manages all greenhouse gas emissions reporting for the university.

A MULTIDISCIPLINARY APPROACH TO PROBLEM SOLVING

YSM and Yale New Haven Health already have numerous jointly administered bodies governing their data technology activities—including oversight of ethical matters. These include the Joint Health Data Governance Council, the Health Sciences Technology Advisory Committee, and the institutional review boards that govern human subjects research. All three bodies are currently reviewing AI technologies. Ohno-Machado plans to offer her department’s expertise to help them assess the far-reaching impacts of generative AI.

Medical ethics experts urge such review bodies to include many points of view when they consider the ethical implications of these new technologies. “Assessment criteria require expertise and insights from multiple disciplines both within and outside health care, ranging from medicine to computer science to social science to ethics and law,” says Bonnie Kaplan, PhD, a lecturer in the Yale School of Public Health’s Department of Biostatistics, Division of Health Informatics, and an associate of YSM’s Program for Biomedical Ethics. “Criteria also need to incorporate patient and community views.”

That kind of multidisciplinary collaboration is already fundamental for the Center for Clinical Ethics at Yale New Haven Health—a grassroots problem-solving organization whose primary role is to advise patients, family members, and hospital staff concerning difficult health care decisions. The center also has a policy-making role in the health system, and it uses multidisciplinary ethics committees in each of the system’s delivery networks to get that work done.

Tolchin, the neurologist who heads the center, says the group is evaluating generative AI technologies and developing policies concerning their use. Clinicians,

INTERVIEW WITH AN ETHICS CHATBOT

Yale’s Digital Ethics Center developed a chatbot known as LuFlot, trained on the writings of its director and founder, Luciano Floridi, PhD, MPhil, professor in the practice in the Cognitive Science Program. We interviewed the chatbot. Here’s one of its responses. Floridi says he wouldn’t change a word.

PROMPT

What new guidelines should medical schools develop in response to the emergence of large language models and generative AI applications?

OUTPUT

Luciano Floridi’s work can provide foundational insight into the type of guidelines medical schools might consider in response to the emergence of large language models and generative AI applications. Given the potential of these technologies to significantly impact medical education, research, and practice, guidelines should be developed with several key considerations in mind:

1. TRANSPARENCY AND EXPLAINABILITY

Medical schools should ensure that AI applications are transparent in their operations and outcomes. It’s crucial that users understand how AI-generated information or decisions are derived. This could involve ensuring that AI systems can provide explanations for their outputs that are understandable to both professionals and patients.

2. PRIVACY AND DATA PROTECTION

AI systems often require massive datasets, including sensitive personal health information. Guidelines should enforce strict adherence to data protection laws and ethical standards, ensuring that all AI applications safeguard patient confidentiality and data integrity.

3. BIAS AND FAIRNESS

AI technologies are susceptible to biases present in their training data. Medical guidelines should mandate regular audits and updates to AI systems to mitigate biases and ensure equitable health care outcomes across diverse patient demographics.

4. CLINICAL ACCOUNTABILITY

There must be clear protocols about who is responsible when AI systems are integrated into clinical settings—whether in diagnostic processes, patient management, or treatment recommendations. The guidelines should delineate the responsibilities of human professionals versus AI systems.

5. CONTINUED EDUCATION

As AI technologies evolve rapidly, ongoing education should be mandatory for medical practitioners to stay informed about new AI tools, ethical considerations, and regulatory requirements. This includes understanding the limitations and appropriate usage contexts of AI applications in medicine.

6. PATIENT CONSENT AND ENGAGEMENT

Patients should be informed when AI tools are part of their health care process, including what data is used, how it is processed, and the implications of AI involvement in their treatment options.

ethicists, technologists, community members, and others participate in the deliberations. “This will be essential to protect patients and clinicians, and to allow us to benefit from these technologies while mitigating the risks,” he explains.

Among Tolchin’s concerns are potential biases in the systems, improper use of patient data, and AI hallucinations that provide erroneous, though often convincing, information. For starters, he believes, patients should be notified when AI systems are being used by their clinicians, and they should be informed—and asked to give consent—if their personal information is going to be used to train AI models.

The privacy and consent issues are of particular concern to biomedical researchers, who often perform longitudinal studies that involve following groups of patients over long periods of time. Generative AI offers the potential for researchers to capture information on treatments and outcomes from thousands or even tens of thousands of patients, and then to use that data to train computing models and provide clinicians with better guidance on treatment plans for particular patients. There’s a conundrum, though: How do you mine all that vital information without violating privacy rules?

One solution that is being explored by some medical researchers is creating so-called synthetic data. In this approach, researchers train generative models to understand the statistical patterns and relationships in existing real-world training data. Then the models use that knowledge to create synthetic data. This type of data mirrors the real-world data that was used to create it, but is completely artificial and isn’t related to any real patients, so it is not covered by privacy laws. The resulting models can be used by researchers to analyze a broad array of cases and treatment outcomes.

INNOVATION WITH CAREFUL EXPERIMENTATION

According to Tolchin, YSM leaders recognize that changes are coming so fast in generative AI, and the technologies are so complex that it can be difficult to apply ethical principles quickly to new applications. If an organization is too slow, it might delay the arrival of important new capabilities for research and clinical

practice. If an organization is not cautious enough, it risks running afoul of the principles of biomedical ethics. That’s why technologists, researchers, and clinicians typically experiment with new applications in limited ways in pilot programs before using them more broadly.

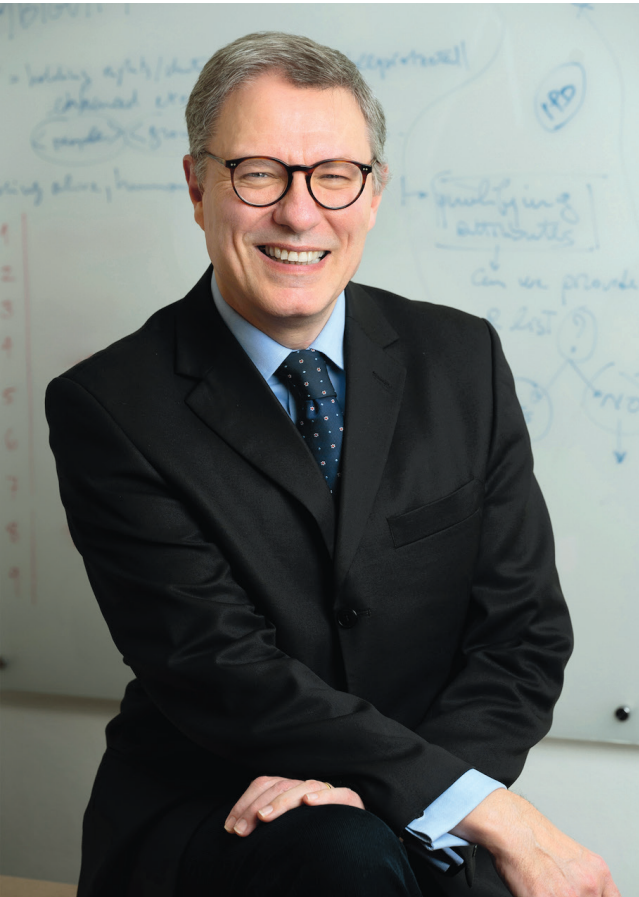
The spirit of experimentation will be critical to fostering innovation at the university and identifying emergent ethical issues, according to Nicolas Gertler, an undergraduate studying cognitive science and a fellow at Yale’s Digital Ethics Center. He is the university’s first-ever AI Ambassador—a role within the Yale Poorvu Center for Teaching and Learning that involves explaining the technology to faculty and students. Gertler urges university students to take the initiative and experiment with AI technologies rather than waiting to see what new capabilities technology vendors will provide. “We should think about what we want the future to look like and help create it,” he says, and “we should implement an ethics-first approach.”

In the coming years, it will be important for YSM and other medical schools to consider the ethical implications of machines that will likely be able to out-think humans in most areas of cognition, will be capable of autonomous action, and may even possess sentience, according to David Rosenthal, MD, assistant professor of medicine (general medicine) and co-course director of the medical school’s Professional Responsibility course for first-year students. “We need to start thinking about what that means in health care,” he says.

Advances in AI raise many questions requiring answers. If machines are so smart, what tasks and responsibilities will humans reserve for themselves? What limits will we place on the machines, and how can that be done? Might it even be possible to encode biomedical ethics in the computing models and applications?

There are many more questions than answers in the space where AI crosses paths with ethics. The bottom line, says Kaplan, the informatics bioethicist, is this: “These technologies should be employed to support clinicians and patients in ways that keep human values and compassionate, quality care at the forefront.”

/yale medicine magazine



Luciano Floridi, PhD, MPhil



‘Talk to Me, Not My Mom’

Teaching students
how to care for patients
with intellectual disabilities

By Jeanna Lucci-Canapari

Jaideep Talwalkar, MD, (left) includes training on the care of individuals with intellectual disabilities within a course he leads for YSM medical students.

It’s a basic humanitarian principle that everyone deserves excellent health care, but such care isn’t always easy to obtain—especially for those with disabilities that can significantly impact their overall health and quality of life.

For people with such intellectual disabilities as trisomy 21 (Down syndrome) or autism spectrum disorder, health care needs can be complex and wide ranging, necessitating a greater breadth and intensity of services

than the general population requires. Meanwhile, people with intellectual disabilities, in particular, may experience inferior health care or find themselves in situations that leave them distrustful of their providers.

Perhaps surprisingly, research shows that only about half of U.S. medical schools have specific curricular content dealing with the care of people with disabilities. Yale School of Medicine (YSM), in a collaboration among faculty, students, and community members, is addressing this need by putting curriculum enhancements in place to help ensure that graduates are prepared to meet the specific health

care needs of individuals with intellectual disabilities.

“We know that patients with disabilities face excessive barriers to care, and they often state that their health care providers don’t really understand how to provide the care that they need,” explains Beverley Sheares, MD, MS, associate professor of pediatrics (pulmonology) and leader of YSM’s Health Equity Thread—one of nine longitudinal threads that weave teaching on essential issues throughout the curriculum. “Patients with disabilities should not have to ask for everything they need in order to navigate the health care system. A health system that seeks to actively engage and respond to the needs of people with disabilities is one that is accessible, accommodating, and recognizes that the needs extend beyond the walls of the clinical space.”

A focus on clinical excellence

In previous decades, shortened lifespans for people with intellectual disabilities meant they received most of their care early in life from pediatric specialists. Now, medical advances are extending their lifespans.

Since the early 1960s, for example, lifespan for people with intellectual disabilities has significantly improved, according to research published in the *Journal of Intellectual Disability Research*. While the severity of an intellectual disability plays a role in longevity, average lifespan continues to

move closer to that of the general population.

“People with intellectual disabilities are living long, productive lives, and it’s important to have a workforce of physicians who know how to care for them,” says Jaideep Talwalkar, MD, associate professor of medicine (general medicine) and pediatrics, and associate dean for education technology and innovation, medical education. Talwalkar has incorporated training on the care for individuals with intellectual disabilities within the curriculum of Clinical Skills, a hands-on course that he leads, covering such topics as physical examinations and communication strategies.

Longer life expectancy leaves many people with intellectual disabilities at a loss for finding sensitive and appropriate medical care beyond the pediatrician’s office, and they need guidance and support throughout that transition. “Anyone who has an adult problem rooted in childhood, such as an intellectual disability, might well have difficulty finding the right type of provider as an adult,” says Talwalkar.

This disconnect is even evident in how or whether patients are directly addressed by clinicians. “There is a tendency for clinicians to talk to the third party in the room, rather than to the patient themselves,” Talwalkar says. This conversational pattern can occur for a variety of reasons: the doctor may believe the third

party (often a caregiver or family member) can provide more reliable information; they may think that it might be faster or more efficient; or they may worry that the patient may not understand. “That may be true in some cases, but our role as clinicians is to make the patient feel that they are the most important person in the room—which they are—with a direct line of communication with them tailored to their ability to understand.”

As pediatricians, Talwalkar and Sheares rely on a strengths-based approach to care for all their patients. “No matter what they are going through, people have strengths and talents,” explains Talwalkar. “We try to find what those are and emphasize them. That is no different for adults with intellectual disabilities.” This approach provides guidance that medical students can use effectively to address the needs of people with intellectual disabilities.

Lessons learned in the community

As part of the enhanced Clinical Skills course, YSM students now visit residents of Chapel Haven Schleifer Center, a residential community in New Haven in which people with intellectual disabilities learn skills to help them navigate social and work settings.

“All of our medical students now spend an afternoon as a guest of one of the people living at Chapel Haven,” says Talwalkar.

“Students are surprised at the strengths of the people they meet there. They see the residents of Chapel Haven bringing a lot to their community. They are able to hold the ear of a group of medical students all afternoon, teaching them how they live and who they are.”

The impetus for the Chapel Haven initiative came from medical student Harry Doernberg, now in his fourth year, who had prior experience working with people with intellectual disabilities. Early in his time at YSM, Doernberg noticed that many of his fellow students had questions about delivering care to people with intellectual disabilities: What kind of accommodations do you need to make in physical access to clinical settings, and in communication? What are the patients’ living situations? Who coordinates care inside and outside the clinic?

“There was space in the curriculum to expand the teaching on the diverse types of patients we care for,” says Doernberg. “At the start of medical school, you are taught to ask very open-ended questions and perform the physical exam in a standard way. For people with intellectual disabilities, it’s important to recognize when adjustments to that approach might be necessary—using closed-ended, yes-or-no, plain-language questions; seeking shorter answers; allowing for extra processing time; and collecting corroborating information from third parties

only when required—or even letting patients direct portions of the interview and physical exam themselves.”

YSM students have had classroom learning on these issues for several years, says Talwalkar. “But it took the students to push us to create more experiential learning on this,” he adds. “They didn’t just ask for it. Students like Harry created it, and it will last beyond their time at Yale.”

Observing patients with intellectual disabilities in their homes, as is done at Chapel Haven, can give students a more complete picture of the health care barriers these individuals may face. This holistic approach is the heart of the social model of disability, which has become a guiding force in the medical school curriculum. While medical models of care center on treating disorders, the social model considers a patient’s life outside the clinic.

“The social model does not mean that the medical problems that are associated with a disability won’t be addressed,” says Sheares. “It says that this person with some defined disability needs care beyond what happens in the office. The social model takes all of that into account; it focuses on the whole person, not just the disability.”

This approach often involves partnering with other care team members such as the patient’s family or home nursing caregivers. The key is recognizing the importance of an interdisciplinary

team that breaks down barriers for patients not only within the clinic, but also outside the clinic walls.

An expanded curriculum takes shape

These new skills and perspectives are being reinforced throughout the YSM curriculum. A group of medical students, including Doernberg, Alexandra Kimmel, and MD/PhD student Nora O’Neill, worked with Erin Nozetz, MD, associate professor of pediatrics (general pediatrics), to add a lecture on caring for patients with intellectual disabilities to the second-year course titled Across the Lifespan. Doernberg, O’Neill, and Nozetz also co-authored an editorial advocating for more medical education to support patients with intellectual and physical disabilities, which was published in the *Journal of General Internal Medicine* in May 2024.

“It really all started with the students,” says Nozetz. “Then very quickly, within 18 months, we were able to integrate these items into the curriculum.” During the lecture, students learn how to communicate with patients and explore strategies for taking histories, modifying physical exams, and engaging caregivers who attend appointments. “We are drilling home that this is a structural problem, but also something that you as a future provider can change,” says Nozetz, who serves as the

disability domain representative on the Health Equity Thread Advisory Committee.

Virtual visits have recently been shown to ease difficult transitions for many patients. “Telehealth is a silver lining of COVID-19,” says Nozetz. YSM students now train in this increasingly common medium for provider visits to patients of all kinds.

Other classes have also adjusted their curriculum to meet the particular needs of different populations. In the Professional Responsibility course, students are taught about the Americans with Disabilities Act and the protections it provides to patients with disabilities. In Population and Methods, students participate in case-based learning as well as training in methodology and statistics centered around disability and public health. Before YSM students enter their clerkships, they meet with patients with disabilities who share what they wish their doctors would do and ask about during office visits.

“When the Health Equity Thread first started in 2020, disabilities were covered in disparate pockets in the curriculum. Now I see the thread pulling those pieces together so that students get broad-based medical education focused on caring for people with disabilities,” says Sheares.

“We are grateful both to be given space in the curriculum and that the enthusiasm by people in the YSM administration has matched ours,” says Talwalkar.



Anesthesiology is at an inflection point

BY RACHEL TOMPA, PHD

The chair of Yale’s Department of Anesthesiology shares insights on obstetric pain management, the opioid crisis, and career development for anesthesiologists.

LISA LEFFERT, MD, SEES PATIENTS at a pivotal time in their lives—when they are delivering babies. As a specialist in obstetric anesthesiology, she is privy to some of the most vulnerable and intimate moments in medicine. As chair of Yale’s Department of Anesthesiology, physician-in-chief of anesthesiology at Yale New Haven Hospital and Bridgeport Hospital, and Nicholas Greene Professor of Anesthesiology at Yale School of Medicine, Leffert is also responsible for anesthesiology and pain management across the entire Yale New Haven Health System.

In addition, she is an editor or editorial advisor for several anesthesiology journals and recently completed a term as the president of the Society for Obstetric Anesthesia and Perinatology.

We sat down with Leffert to learn more about her approach to medicine, what she’s most proud of since joining Yale in 2021, and what makes the Yale Department of Anesthesiology stand out.

ROBERT A. LISAK PHOTO

Pain relief is so fundamental to how a patient experiences delivery. What is it like to be part of this major life event for your patients? I’ve had someone holding a baby literally run up to me at a rest stop on the turnpike and say, “Oh, you did my anesthesia!” It’s incredible to witness a birth. As anesthesiologists, we see more of the actual births in cesarean deliveries than in vaginal deliveries, but it’s so remarkable. It’s no less remarkable now than it was when I first began to practice. It’s a time of joy, but there’s also a lot of anxiety and a sense of lack of control for many people. A huge part of obstetric anesthesia is offering not only physical pain relief, but also emotional support and partnership. When people think of anesthesia, they often think, “Oh, all your patients are asleep.” Well, it’s rare for my patients to be asleep, as it turns out!

You also work with high-risk obstetric patients. What is that like? And what are the unique challenges in caring for pregnant patients? We see all kinds of patients: people with neurologic diseases, lung disease, genetic disorders, cancer, and many other comorbidities. The commonality is that they’re all coming to have a baby. In obstetric care, you typically cannot choose the optimal moment of delivery. If someone in labor has COVID or they’re in heart failure, we can’t say we’re going to treat that condition and then have you come back later for your delivery, the way we might delay some other procedures with similar complications. It’s pretty much a situation of you get what you see, and that’s challenging but also very rewarding.

You’re known nationally and internationally not only for your clinical expertise in obstetric anesthesiology, but also for your specialization in patients with neurologic disorders. Can you talk about that? There are two sides to this. Patients with neurologic conditions and their physicians often worry that they cannot have the same options (such as labor epidural pain management) as patients without such disorders as scoliosis, back surgery, and even brain tumors or other brain abnormalities. In fact, many of these patients can safely have the same anesthetic choices as other patients, as long as they are properly evaluated by their neurologic and anesthesia doctors. Also, some patients are denied these anesthetics because of concern for complications—specifically bleeding in the area of an epidural that causes compression on the nerves and possibly nerve injury. People who are on blood thinners at the time of the procedure or have clotting issues could fall into this category.

In my research, I have led national expert task forces focusing on such situations, where there may be data about patient outcomes but a lack of consensus in the field. I worked to bring together experts from various fields to look at these data and find the best available evidence to reach a consensus recommendation for how to best treat these patients. These recommendations also address how to present this information to patients so they can be part of the decision, which is hugely important. I’ve also had the honor of being the anesthesia representative on other organizations’ pregnancy-related task forces, such as the American Heart Association and the Canadian Stroke Consortium.

How has the opioid crisis impacted the field of anesthesiology? These medications really came to the forefront when the medical field shifted toward always treating pain—which is very valid—but that led to an extreme reliance on prescribing opioids, which clearly had a negative fallout. Later, it shifted to the other extreme; many practitioners are now wary of using opioids at all. Like most things in life, it’s not all or nothing; it’s important to find that moderation. As anesthesiologists, we’re lucky to have multiple modalities of treating patients in pain. Pain relief is our business, and opioids are only one of many options in our armamentarium. We treated pain before the current crisis; we’ll continue to treat pain during and after it as well.

You were on the faculty at Harvard Medical School and chief of the division of obstetric anesthesia at Massachusetts General Hospital for many years before joining Yale. What were you aiming to accomplish in this new position? I had been in Boston for 50 years and I didn’t think I would leave that area, but this opportunity at Yale was really something special. It was an opportunity to build the department with the support of the dean and the chief of surgery, and everyone I met in the department shared this feeling that we needed to transform and do the work together.

One particular challenge we face is that we’re a health system—an academic health center that has joined with community hospitals. And it’s pretty common for that kind of system to be a system in name only, and for the hospitals to function fairly independently. But at Yale, we want true integration

across the system, collaborating and figuring out how to meet the needs of the academic center and the community hospitals while providing the best quality of care at all of them.

What are you most proud of in the time you’ve been here? I’m most proud that people want to come to our department and stay. There’s a huge deficit of anesthesia providers nationally, so the fact that we have all these people who want to be here means we can care for a large number of patients. We’re not turning patients away because we don’t have enough anesthesiologists—which is, unfortunately, the case in some places.

What makes the Yale Department of Anesthesiology stand out? The faculty here can really do anything. You can be anyone you want—an executive, a master clinician, a basic scientist. We realize that for career satisfaction, people need purpose and autonomy, and we can offer those things here. On the patient side, they experience having the best people caring for them. Patients are putting their lives in our hands, quite literally. When you do that, you want to trust that person and know that they have your best interest at heart. They know that we have their backs. That’s what our department embodies.

How does the department approach research? Collaboration is the lynchpin to our research, and that’s not the norm for all institutions. Science at Yale is so strong, and it’s extremely important for our department to be able to collaborate with other departments. We have a neuroscience research program, a clinical outcomes research informatics



team, and a clinical trials program, among others. It’s a quite diversified group of folks.

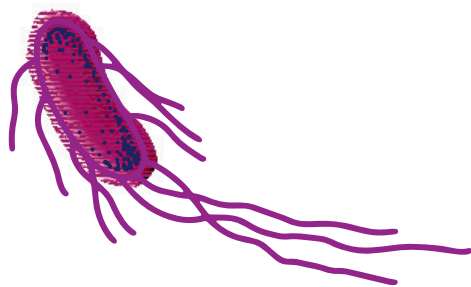
What advances do you see coming in the field of anesthesiology in the next few years? Anesthesiology was an early adopter of AI and large language models, in particular, because we generate a tremendous amount of physiologic data in our work that can be harnessed for predictive models. Rather than waiting to see whose blood pressure or oxygen levels will drop, we can use past data to predict these outcomes and decide who may need to be treated preventatively.

These models are going to become much more pervasive in the next few years; they will help us personalize what we do for patients. Because there’s a nationwide shortage of anesthesiologists, I think the

anesthesiologists themselves will focus more and more on the complex patients, and use the models to help with more standard care. It’s not like AI is going to take off and have a life of its own; we’ll still be involved with all our patients’ care.

On the surgery side, more procedures are taking place outside of the operating room, and more laparoscopic and robotic approaches are being used. As surgery changes, anesthesiology changes as well in partnership with surgery. There is a growing list of regional blocks available to patients, and the goal is increasingly focused on rapid recovery from surgery and anesthesia. Anesthesiologists also play an important role beyond the operating room and labor and delivery floors. We’re intensivists in the ICU. We’re also expert pain management physicians in and outside of the operating room, and that area is expanding as well. Things are very much at an inflection point in the field, and it’s very exciting.

Lisa Leffert, MD, center, reviews patient information with colleagues.



Antibiotic resistance: Fighting a global threat with phage hunting and infection control

BY EVA CORNMAN

WHEN ANTIBIOTICS WERE DISCOVERED almost 100 years ago, they changed the practice of medicine. What followed brought us into a burgeoning antibiotic era in which such infections as pneumonia and syphilis—ones that once would have been highly debilitating or even fatal—became treatable.

But there is also a dark side to antibiotics. The adaptability of bacteria and other microorganisms has driven evolution that enables them to thwart these powerful drugs via a phenomenon known as antimicrobial resistance (AMR). Antimicrobial resistance is a naturally occurring process that happens when bacteria encounter what evolutionary biologists call selective pressure

(a force that affects an organism’s ability to survive)—in this case, pressure from an antibiotic. Through random DNA mutations or by sharing resistance genes that lead to adaptive mechanisms, bacteria will evolve in order to survive this selective pressure. Unfortunately, when antibiotics are overused and misused, as has been the case across the world in health care settings, agriculture, animal husbandry, and beyond, evolutionary pressure on bacteria intensifies. By generating defenses against the antibiotics that were designed to

kill them, these microorganisms can multiply and spread antibiotic resistance genes.

AMR is now one of the top global public health threats. It was estimated to have contributed to 4.71 million deaths worldwide in 2021 (with a significant increase in resistant organisms after the COVID-19 pandemic) and is projected to cause 40 million deaths by 2050, according to a paper published in *The Lancet* last year. Because of a lag in the development of new antibiotics—due in large part to reduced financial incentives for pharmaceutical companies to develop these drugs—this crisis has ushered in what some experts call the post-antibiotic era, marked by a lack of sufficient antibiotic options to treat a wide range of infections.

“Now that we’re in a post-antibiotic era, it puts all those medical advances under a threat,” says Richard Martinello, MD, professor of medicine (infectious diseases) and pediatrics at Yale School of Medicine (YSM), and chief medical officer of Yale Medicine. “Many years ago, we may have been able to easily treat [patients] and cure their infections, but it may not be so easy anymore.”

Certain infections have become almost impossible to treat. Last May, the World Health Organization released its updated Bacterial Priority Pathogens List, which includes four critical priority bacteria (*Acinetobacter baumannii*, *Mycobacterium*

tuberculosis, and two groups of Enterobacterales) that are resistant to last-line antibiotics. For instance, a class of broad-spectrum antibiotics called carbapenems is highly effective, but physicians can use them only as a last resort when an infection fails to respond to any other antibiotic. And they must be used sparingly to avoid the development of resistance. Thus, the rise of carbapenem-resistant bacteria is especially concerning.

“Every week we have new patients we’re finding in the hospital with bacteria that are resistant to carbapenems, and we have few good options for how we can treat these patients,” Martinello says. In these cases, he says, physicians may seek a newer antibiotic or an antibiotic alternative.

Because AMR is a significant problem on a global scale, an urgent search for solutions is underway. At YSM, researchers are investigating longer-term answers while health professionals at Yale New Haven Health are taking immediate steps to combat this issue on the clinical side.

Yale’s Antimicrobial Resistance Faculty Network
Founded in the fall of 2022, the Yale Antimicrobial Resistance Network connects researchers from across multiple disciplines and departments for monthly meetings to discuss their AMR-related work.

Members’ research interests span a wide variety of topics.

For example, Reza Yaesoubi, PhD, associate professor of public health (health policy) at Yale School of Public Health (YSPH), uses simulation and mathematical modeling to predict trends in antimicrobial resistance patterns and determine the best combinations of antibiotics to use.

“The main advantage of simulation mathematical models is that they allow you to project the long-term impact of different policies, strategies, and interventions,” he says. “The work that we try to do is to have a principled way to make decisions, given that there’s always a battle between these conflicting objectives of wanting to treat as many patients as we can with the newest antibiotic but also protecting the newest antibiotic against the emergence of resistance.”

Another member of the network, Sunil Parikh, MD, MPH, professor of epidemiology (microbial diseases) at YSPH and of infectious diseases at YSM, focuses on malaria in highly vulnerable groups in sub-Saharan Africa. He studies everything from the combinations of malaria drugs that are least likely to lead to resistance at the individual and population levels to continent-wide policy recommendations for surveillance of drug-resistant malaria.

“It’s going to be years before novel drugs are available on the marketplace [for malaria],” Parikh says. “We need to urgently determine how to combat the current emergence of

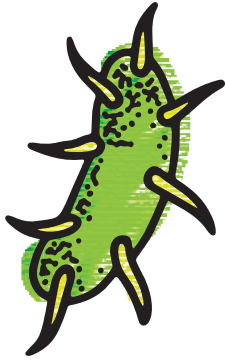
resistance to malaria drugs in Africa, as it could have devastating public health consequences.”

Other members of the network research a variety of topics both locally and worldwide, including drug-resistant tuberculosis, hookworm infections, skin conditions like acne, pneumococcal disease, and AMR in hospitals. One group is even looking at potential alternatives to antibiotics in the form of microscopic viruses called bacteriophages.

Fighting AMR with phages

Led by Paul E. Turner, PhD, Rachel Carson Professor of Ecology and Evolutionary Biology, the Center for Phage Biology and Therapy at Yale has been using bacteriophages (phages for short) to treat infections caused by multidrug-resistant bacteria since 2013. This usage was made possible through the Food and Drug Administration (FDA)’s expanded access pathway, which allows for the use of experimental treatments in life-threatening conditions when no other comparable treatments exist.

Phages are naturally occurring viruses that infect and kill specific bacteria. Just as a human cell can be infected with an influenza virus or a cold virus, bacterial cells are infected with phages. Turner’s group, along with those of other researchers worldwide, has capitalized on phages’ specialized ability to kill bacteria for clinical benefit.





Through a process called “phage hunting,” the research team looks for clinically relevant phages both locally and around the world. The researchers categorize and store these phages to create a library of potential candidates for phage therapy. To treat human infections, team members obtain bacterial samples from patients and test them by the phage library to identify which phages are best suited to kill the bacterium in question. Once the team has the right phage or series of phages and obtains FDA approval, the team uses the phage, which can be delivered to the patient through inhalation, injection, or ingestion.

Jon Koff, MD, associate professor of medicine (pulmonary, critical care & sleep medicine) at YSM, is director of the Adult Cystic Fibrosis (CF) Program and the medical director of the Center for Phage Biology and Therapy. Koff has been collaborating with Turner and Benjamin Chan, PhD, scientific director of the Center for Phage Biology and Therapy, to treat both cystic fibrosis patients and those without CF since 2018.

“There are some unique attributes of phages in terms of treating some infections that allow for them to be potentially synergistic with and also potentially independent of antibiotics,” says Koff.

Turner, Chan, and Koff have received requests from their colleagues to use phages to treat infections of the bone, prosthetic joints, the urinary tract, sinuses,

and other parts of the body. The center recently completed several clinical trials focusing on phage therapy for cystic fibrosis; found a novel phage to treat methicillin-resistant *Staphylococcus aureus* (MRSA) that can actually resensitize the infection to antibiotics; and received a number of large National Institutes of Health (NIH) and foundation grants to continue its research.

Despite the success that Turner’s group and others around the world have had, phage therapy has still not been approved by the FDA for use beyond expanded access and clinical trials. Researchers are hopeful that this will change in the next five to 10 years.

“We maintain a unique position at Yale in the center because we can find phages and design their use; we can study them, and we can treat patients and study the bacterial pathogen(s) before and after phage therapy—that’s a unique combination,” says Koff.

Reducing the spread of AMR in hospitals

While phages might be a promising new treatment, other researchers and clinicians at Yale are working to impede antimicrobial-resistant organisms from infecting patients in the first place. This precaution is especially important in hospital settings, where there is a greater risk of negative health consequences for immunocompromised or otherwise susceptible individuals.

“Most people who are healthy and have functioning immune

systems are really not at risk for a lot of these multidrug-resistant bacteria and fungi,” says Scott Roberts, MD, assistant professor of medicine (infectious diseases) at YSM and assistant medical director of infection prevention at Yale New Haven Health (YNHH). “It really impacts the most vulnerable patients.”

In the hospital setting, Roberts sees two different situations in which patients experience multidrug-resistant infections. On the one hand, a patient may come in with a preexisting resistant infection that was contracted outside the hospital. But there are also patients who pick up a bug or become resistant to antibiotics during the course of their hospital stay—a problem that occurs in hospitals everywhere.

This second situation can develop for a number of reasons. For patients who are admitted for extended stays, repeated exposure to antibiotics during the course of their treatment may reduce the drugs’ efficacy over time. But there’s also a problem with the transmission of multidrug-resistant pathogens through such routes as contaminated surfaces, equipment, and human hands.

Handwashing, Roberts and Martinello stress, is one of the most effective measures to reduce the spread of resistant pathogens in the hospital setting—but bacteria can also spread through such medical equipment as thermometers, probes, stethoscopes, catheters, and such

nonmedical items as furniture and other surfaces in a patient’s room. Martinello and Roberts have implemented procedures to reduce the spread of pathogens through these routes.

“We focus on handwashing; we focus on disinfection of the environment, disinfection of reusable equipment that gets shared between patients, and ensuring that it’s a safe space,” Roberts says.

In addition to strategically placing hand sanitizer dispensers in locations that allow for maximal and convenient hand hygiene for hospital workers, Roberts and Martinello have also begun piloting UV light disinfection technology to sanitize entire patient rooms. The efforts have paid off, as YNHH is currently experiencing better than national average rates for such health care-associated infections as catheter-associated urinary tract infections and MRSA infections.

Pathogens in the pipes

While hand hygiene is one of the most important measures a hospital worker can take to reduce the spread of multidrug-resistant bacteria, there’s a good chance that the very sink where they wash their hands could splash resistant bacteria right back into the patient’s room.

“Pathogens in sink drains have been increasingly tied to nosocomial [originating in a hospital] infections, and a lot of antibiotic-resistant nosocomial infections,” says Hannah Greenwald Healy, PhD, assistant professor of environmental health and exposure science at Harvard T.H. Chan School of Public Health, and previously a postdoctoral associate

at Yale in the lab of Jordan Peccia, PhD, Thomas E. Golden Jr. Professor of Environmental Engineering. “I think we’re just beginning to recognize the importance of plumbing systems and how big a problem they are.”

Healy’s research focuses on the ways in which bacteria from hospital drains can cause these infections, as well as how to stop contamination routes. Bacteria thrive in wet environments, which makes the liquid stuck in the P-trap (a bend in the sink pipe that prevents sewer gases from coming up through the drain), the perfect place for them to grow. Once in the P-trap, bacteria can grow along the sides of the pipe in sticky sheets called biofilms, sometimes even extending as far as the drain cover. Thus, when someone uses the sink, water can strike these biofilms, causing bacteria to disperse and enter the patient’s room through droplets of water or even through the air, Healy says.

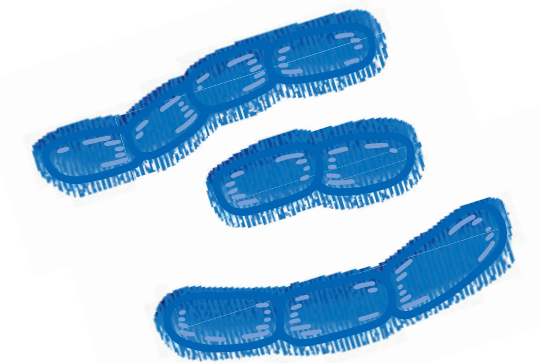
Hospital sink basins are disinfected on a daily basis, but disinfecting inside the drains and pipes is a bit more challenging. While at Yale, Healy tested a foam-based disinfectant that expands inside the pipes, contacting more of the surface inside the pipe than a traditional liquid disinfectant. Healy and her team found, however, that

while the foam reduced bacterial counts immediately, microorganisms returned at higher than initial levels after about a week, and with higher proportions of antibiotic resistance—especially bacteria that are carbapenem-resistant. “This emphasizes how challenging control of these resistant microbes can be,” Healy says. Beyond these measures to reduce the spread of resistant pathogens in the hospital, Yale physicians and researchers are also working to combat the AMR problem in general through responsible use and stewardship of antibiotics.

Pathways for antibiotics

One of the main contributors to the antibiotic resistance crisis is the overuse and misuse of antibiotics. The Yale New Haven Health System has more than 600 clinical pathways, called Care Signature Pathways, built into the electronic health record system to guide clinical decision-making, including decisions involving antibiotics.

“In the busy moment of caring for a patient in the hospital or in the ambulatory space, one often doesn’t have time to look up the optimal choice and duration of treatment or to access the antibiogram, which is the pattern of antimicrobial resistance specific to our institution that may influence the choice of an antibiotic agent,”





says Deborah Rhodes, MD, professor of internal medicine (general medicine), and enterprise chief quality officer of Yale Medicine, who launched the Care Signature Pathway program in the health system and oversees the Care Signature team. “The pathways integrate up-to-date evidence, the consensus of our clinician and research experts, and access to precise orders and resources at the point of care, and the pathway is suggested to the care provider within the electronic health record when relevant to a patient they are evaluating.”

Rather than prescribing a commonly used antibiotic that

might be too broad for a particular patient, a clinician can use these pathways to quickly and easily prescribe what might be a less well-known antibiotic, but ultimately one that would be more appropriate for their patient and less likely to lead to the development of antibiotic resistance.

“Somebody who may not have that degree of expertise can use [the algorithms] to help guide them to make sure that not only are they picking the best antibiotic for a patient, but also that they are minimizing any risk that patient may incur,” Martinello says.

The pathways are regularly updated with the expert knowledge of Yale pharmacists and physicians who review antimicrobial resistance trends. The

team also recently convened an expert group to create new pathways for recognizing, isolating, and treating patients for measles—a disease that many providers in Connecticut have never seen before.

“These pathways are built by faculty representing all different specialties literally volunteering their time to come to meeting after meeting, and to refine these pathways so that they are concise, accurate, and up-to-date,” says Rhodes. “I think it’s an extraordinary tribute to the collective commitment that this school and system have to excellence in patient care.”

The journey to drug discovery and development

Physician-scientist William Pao ’97 PhD, ’98 MD, was 13 years old when his father died during a difficult surgery for colon cancer. The loss had a profound impact on Pao, inspiring a lifelong commitment to making a difference for patients like his father. Two decades later, he became a medical oncologist and translational science researcher, dedicating his career to advancing cancer treatment.

Now, after working as a researcher at Memorial Sloan Kettering Cancer Center, a professor and head of the personalized cancer medicine unit at

Vanderbilt University, and an executive at Pfizer and Roche Pharmaceuticals, Pao has written a book titled *Breakthrough: The Quest for Life-Changing Medicines*. With a foreword by Nobel Prize winner Harold Varmus, MD, the book follows the journeys of scientists, physicians, and patients whose ingenuity and persistence led to the discovery and development of eight modern lifesaving drugs.

Among the eight stories, Pao explores how

paracetamol (marketed in the United States under brand names including Tylenol®), now among the most widely used painkillers, remained overlooked for decades; how a mother’s relentless advocacy spurred a medical breakthrough for spinal muscular atrophy (one of the world’s most common rare diseases); and how countless hours of painstaking experiments with a reengineered immune molecule (antibody) transformed hemophilia treatment. Pao also reflects on his own experience in lung cancer

research as a postdoc in Varmus’ lab, bringing a personal perspective that enriches each of the drug-discovery stories with insights into the world of academic science.

Pao offers readers a compelling, up-close look at the science, creativity, and innovation that has led to some of the most significant medical advances of recent decades. It is a fitting tribute to the power of team science to enhance human health.

—Kenny Cheng

YSM scientists receive NIH support for bold research ideas

The National Institutes of Health (NIH) has honored a group of Yale School of Medicine (YSM) scientists with High-Risk, High-Reward Research (HRHR) grants. These esteemed awards support innovative and high-impact ideas that may be deemed too risky or premature for conventional peer-reviewed funding mechanisms.

Of the 72 U.S. investigators receiving 67 grants in 2024, six are from YSM—more than from any other institution. The NIH awarded a total of approximately \$207 million in HRHR grants, with Yale-led research receiving \$17.1 million.

“The HRHR program champions exceptionally bold and innovative science that pushes the boundaries of biomedical and behavioral research,” said Tara A. Schwetz, PhD, NIH deputy director for program coordination, planning, and strategic initiatives. “The groundbreaking science pursued by these researchers is poised to have a broad impact on human health.”

New Innovator Awards, which support unusually innovative research from early-career investigators, were granted to Salil Garg, MD, PhD, assistant professor of laboratory medicine; Diyendo Massilani, PhD, assistant professor of genetics; and Wan-Ling Tseng, PhD, assistant professor in the Child Study Center.

Garg’s project, Genomic Encoding of Heterogeneity, investigates how different cell states emerge and are maintained—processes crucial in development and in such diseases as cancer. The findings could provide insights into cell state regulation, potentially leading to new strategies for targeting tumor heterogeneity and treatment failures in cancer.

Massilani, in Tracing the Evolutionary History of Human Adaptive Traits Through Ancient DNA, will use a novel method to retrieve ancient human DNA from sediments, enabling genomic analysis without skeletal remains. The study focuses on several archaeological sites in Mongolia, examining 500,000 years of human occupation to understand

past population dynamics in the region and the traits that shaped the groups’ survival.

Tseng’s project, Multi-Level Mechanisms and Predictors of Irritability: An Innovative Approach Bridging Laboratory and Real-world Measures, will identify neural, social, and environmental factors contributing to chronic irritability in children, which affects 10% of U.S. youth and leads to severe mental health issues. The goal is to develop effective interventions for this common issue in child psychiatry.

Julien Berro, PhD, associate professor of molecular biophysics and biochemistry, and of cell biology; Xiaolei Su, PhD, associate professor of cell biology; and Boston University collaborator Alexander A. Green, PhD, received Transformative Research Awards, which fund interdisciplinary research that could create or challenge existing paradigms. In their project, Programming Cellular Behavior by Mechanical Forces, the team will develop programmable systems that can trigger specific cellular actions in response to mechanical signals, laying the foundation for new therapeutic strategies to target these signals in diseased cells.

Sedona Murphy, PhD, associate research scientist in cell biology and YSM science fellow, received an Early Independence Award to study Spatial Regulation of Epigenetic Memory, a process crucial for development but often disrupted in diseases like cancer. The study seeks to uncover how chromatin regulates gene repression and epigenetic stability, ultimately influencing cell behavior and plasticity.

—Jennifer Torrance



William Pao, MD