S T A N F O R D

M E D I C I N E

Issue 2 / 2025

special report

RECLAIMING HEALTH:

Solving the chronic disease puzzle

STANFORD MEDICINE

Issue 2 / 2025

LAUGH, CRY, REPEAT

HOW THERAPY, HUMOR AND COMMUNITY CAN EASE THE PSYCHOLOGICAL TOLL OF CHRONIC ILLNESS

Mental health is an often-overlooked aspect of living with a chronic illness, especially for young people and their families. Diana Naranjo, PhD, a psychologist working with patients managing diabetes and cystic fibrosis, believes the emotional weight is just as significant as the physical one.

"I think people would be surprised at how much mental real estate is consumed by chronic illness," said Naranjo, a clinical professor of pediatrics in endocrinology and diabetes. "It's incredibly common to be managing anxiety and depression alongside the disease itself. And those conditions can make everyday tasks feel nearly impossible."

Psychologist Diana Naranjo, PhD, shares mental health advice for people living with chronic conditions.

Naranjo's passion for this work is deeply personal. Growing up in an immigrant Latino family and witnessing firsthand their difficulties obtaining mental and physical health care shaped her understanding of societal barriers. Her father's struggle with bipolar disorder and cancer revealed the profound challenges of navigating complex health systems without adequate support.

In this Q&A, Naranjo shared what she has learned from working with patients and studying ways to help families and individuals manage chronic disease.

What would you like people living with a chronic condition to know about mental health?

It's important to be kind to yourself. When you first learn about the illness, there's often a trauma response: shock and grief about the loss of a healthy self. You're also taking in a lot of information — a data download — about your condition. Learning and adjusting can create a lot of stress. Next comes maintenance. There will be moments when you feel good and there will be moments of burnout, when you feel really disengaged and overwhelmed. Burnout is normal, so don't get freaked out. The whole family — especially one with young children — can be affected.

Beyond general recommendations of getting enough sleep, exercising and practicing mindfulness, what are some mental health strategies that are especially helpful for people with chronic illness?

I suggest finding a group of people who have a similar condition. You can breathe a sigh of relief when you're with someone who knows what you're going through. You can also create new habits and routines that might sound silly but can make a chronic illness feel less onerous, more fresh. For instance, some teens with diabetes like to decorate their insulin pump case with stickers. And finding humor in silly, weird, gross things can go a long way, even for adults — whether it's making fun of yourself or something that went wrong.

How about therapy?

Therapy can make a big difference because a lot of specific treatments can help with your spirit. An example is a type of psychotherapy called acceptance and commitment therapy. It focuses not on "how do I fix this and make it go away?" but on how to live the best quality life with the symptoms you have and with the uncertainty of your condition. It asks, "What is meaningful to you? What is so important that you don't want to miss it?" If you are missing important things because the chronic condition is all consuming, how do we change that?

Living with a serious chronic disease is a marathon, not a sprint. It's a road with valleys and peaks, and it's expected that extra support will be needed along the way. Seek it out or ask for help if you need it.

— BY ROSANNE SPECTOR

PHOTOGRAPH BY MISHA GRAVENOR

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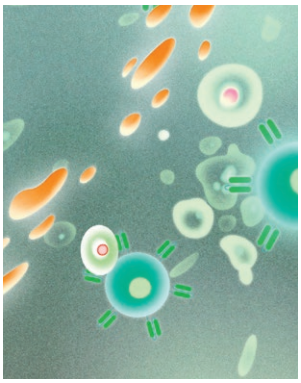
SPECIAL REPORT

Reclaiming health

Solving the chronic illness puzzle



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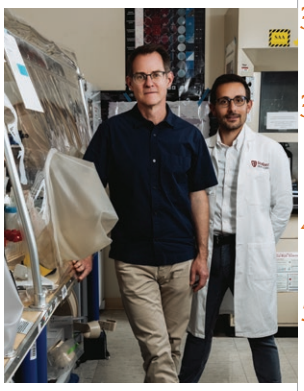

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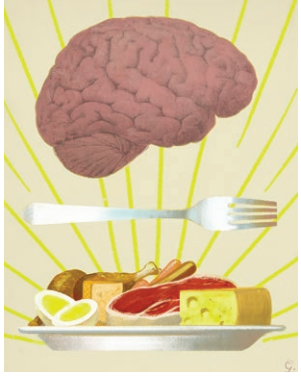


COVER: BRYCE WYMER

letter from the dean

The human body is one of the most complex — and astounding — systems in the natural world. From the microscopic cell to the sophisticated brain, the body, when healthy, performs a phenomenal variety of physical, intellectual and creative activities.

Unfortunately, for the 3 in 5 Americans living with at least one chronic disease, this system has malfunctioned in some fundamental way. And the resulting physical, emotional and economic burden can be devastating.

Chronic conditions and diseases, by definition, are persistent and require ongoing management. Finding better therapies and helping patients more easily manage their conditions — whether diabetes, autoimmune disorders, Alzheimer's disease or dozens of others — can make a dramatic difference in patients' quality of life. This issue of *Stanford Medicine* magazine highlights biomedical discoveries and technological advances that are pointing teams of scientists to exciting new avenues of research.

Key breakthroughs often come when researchers identify disease subtypes — as they have for depression and diabetes — allowing for better diagnosis and more precise treatment. Stanford Medicine faculty have developed an AI-powered algorithm to help identify 3 of the 4 most common Type 2 diabetes subtypes. Similarly, faculty have combined brain imaging with machine learning to identify six biotypes of depression.

Smarter and easier-to-use digital health tools enable patients to monitor and manage chronic diseases without impinging on their day-to-day activities. This provides multiple benefits, including preventing serious complications and improving quality of life by allowing patients to remain untethered from the clinic or hospital.

Researchers at Stanford Medicine and beyond have also deepened their understanding of the profound effects a healthy diet and plentiful exercise can have in preventing and managing so many chronic diseases. There is a veritable feast of new insights into how certain types of foods can be remarkable interventions for gastrointestinal issues, mental health, cardiovascular conditions and even aging.

It is important to note that many of these breakthroughs are possible because of decades of fundamental research that laid the groundwork for comprehending the complexities of human biology and disease progression. Thanks to those earlier efforts, scientists today can focus on translating these discoveries into therapies for a host of conditions, including autoimmune diseases, chronic fatigue syndrome, celiac disease and sickle cell disease.

The programs and research projects you'll read about in these pages also highlight the potency of team science. When dealing with a system as complex as the human body — in all its sophisticated elegance — it is imperative that we assemble multidisciplinary teams with the combined expertise to unravel the complexities of chronic disease and identify the most effective therapies and treatments for patients to lead a life well lived.

Sincerely,

Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of Stanford School of Medicine
Vice President for Medical Affairs at Stanford University
Professor of Otolaryngology-Head & Neck Surgery

PHOTOGRAPH BY CAROLYN FONG

upfront

Cyber-diagnostic

THE IMMUNE SYSTEM harbors a lifetime's worth of information about threats it has encountered.

Stanford Medicine researchers devised an artificial intelligence algorithm to identify diseases by investigating this immunological Rolodex. Specifically, the tool analyzed the receptors on B and T cells, two immune cell types.

The researchers believe the AI algorithm, abbreviated Mal-ID for "machine learning for immunological diagnosis," can help diagnose tricky diseases and guide treatments.

To develop this tool, the team assembled a dataset of over 16 million B cell receptor sequences and over 25 million T cell receptor sequences from 593 study participants. (B cell receptors recognize free-floating pathogens, whereas T cell receptors recognize infected cells.) Participants were healthy, representing the control group; diagnosed with COVID-19, HIV, lupus or Type 1 diabetes; or recently inoculated against the flu.

The algorithm was highly successful at identifying who had which disease or a recent flu vaccination.

The research, published Feb. 20, 2025, in *Science*, found that T cell receptor sequences provided the most relevant information about lupus and Type 1 diabetes. B cell receptor sequences were most informative in identifying HIV or SARS-CoV-2 infection or recent influenza vaccination. In every case, combining the T and B cell results increased the algorithm's ability to accurately categorize the disease state.

"Mal-ID could help us identify subcategories of particular conditions that could give us clues to what sort of treatment would be most helpful for someone's disease state," said Scott Boyd, MD, PhD, the Stanford Professor in Food Allergy and Immunology and co-director of the Sean N. Parker Center for Allergy and Asthma Research.

Boyd shares senior authorship with Anshul Kundaje, PhD, associate professor of genetics and of computer science. Postdoctoral scholar Maxim Zaslavsky, PhD, and graduate student Erin Craig are the lead authors.

The researchers believe the algorithm could quickly be adapted to identify immunological signatures specific to many other diseases and conditions. They are particularly interested in autoimmune diseases such as lupus, which can be difficult to diagnose and treat effectively.

RESEARCHERS BELIEVE THE AI ALGORITHM … CAN HELP DIAGNOSE TRICKY DISEASES AND GUIDE TREATMENTS.

ILLUSTRATIONS BY BRYCE WYMER

Ozempic alternative?

A NATURALLY occurring molecule identified by Stanford Medicine researchers appears similar to semaglutide, also known as Ozempic, in suppressing appetite and reducing body weight.

Notably, testing in mice and pigs also shows that it works without some of the drug's side effects, such as nausea, constipation and loss of muscle mass.

The newly discovered molecule, BRP, acts through a separate but similar metabolic pathway and activates different neurons in the brain. It promises a more targeted approach to body weight reduction.

"The receptors targeted by semaglutide are found in the brain but also in the gut, pancreas and other tissues," said Katrin Svensson, PhD, assistant professor of pathology. "That's why Ozempic has widespread effects including slowing the movement of food through the digestive tract and lowering blood sugar levels. In contrast, BRP appears to act specifically in the hypothalamus, which controls appetite and metabolism."

Svensson is the senior author of the study, published March 5, 2025, in *Nature*. Senior research scientist Laetitia Coassolo, PhD, is the lead author.

'NOW, WE HAVE THIS ADAPTIVE TECHNOLOGY THAT LISTENS TO BRAIN ACTIVITY AND ADJUSTS STIMULATION ACCORDINGLY.'

Jolt of progress

A NEW, SMARTER version of deep brain stimulation for treating Parkinson's disease has been approved by the Food and Drug Administration.

Helen Bronte-Stewart, MD, a professor of neurology and neurological sciences at Stanford Medicine, led final large-scale testing of the new approach, called adaptive deep-brain stimulation, or aDBS.

In DBS and aDBS, electrodes connected to thin wires are implanted into the brain. Like a cardiac pacemaker that responds to the rhythms of the heart, aDBS uses a person's individual brain signals to control the electric pulses it delivers, making it more personalized, precise and efficient than older DBS methods.

"Until recently, these stimulation devices delivered a one-size-fits-all train of electric pulses to the brain around the clock," said Bronte-Stewart, the John E. Cahill Family Professor. "They have helped some people but are a pretty blunt tool for trying to correct the brain arrhythmias associated with Parkinson's. Now, we have this adaptive technology that listens to brain activity and adjusts stimulation accordingly."

Her lab has conducted experiments on aDBS since 2015.

"The FDA approval is exciting because it means that everyone with Parkinson's who has a compatible DBS device in the U.S. could use aDBS," she said.

Jostling for distinction

STANFORD MEDICINE researchers have described a previously unknown type of cell movement they believe helps stem cells transform into different types of tissue.

The finding, reported Nov. 1, 2024, in *Nature Materials*, suggests that differentiation depends not only on chemical signals, which is how researchers typically induce stem cells to differentiate in the lab, but also physical signals.

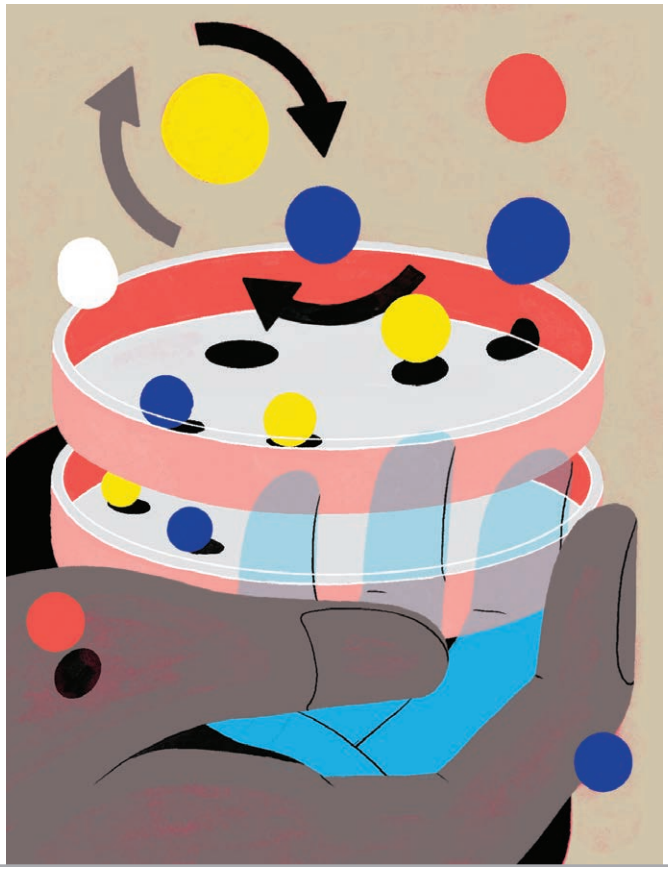
Manish Ayushman, a graduate student in bioengineering and the paper's lead author, watched more than 1,000 hours of microscopic footage of stem cells. At first, the cells seemed to be not doing much of anything. But when Ayushman looked more closely, he noticed they were turning and pulsing ever so slightly.

When he sped up the footage, the movements became clearer: Each stem cell appeared to be shimmying and shaking with purpose. The researchers call the movements cell tumbling.

They showed that cell tumbling enhances stem cell differentiation into other tissues in the lab, such as bone and fat, though they do not know whether it occurs naturally in the human body. After the researchers chemically induced stem cells to differentiate into cartilage, the cells that were allowed to tumble unimpeded over the initial four days formed the most cartilage.

The researchers hope to translate the discovery into more efficient ways to generate replacement cartilage and other tissues from a patient's own stem cells.

"Cartilage is one of the most commonly injured tissues in the human body, yet it has very limited capacity to regenerate," said the paper's senior author, Fan Yang, PhD, associate professor of orthopaedic surgery and of bioengineering.



Lower risk prostate cancer treatment

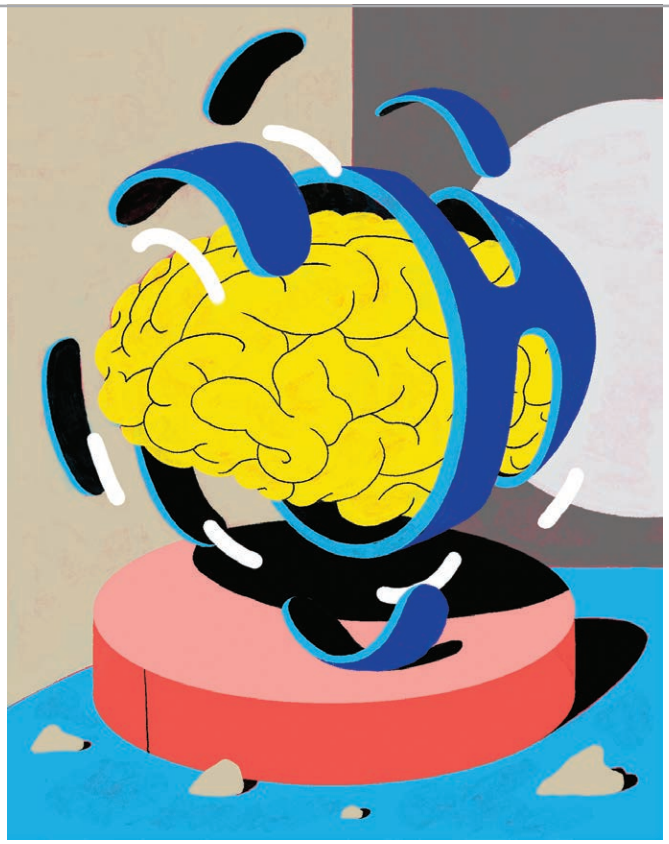
WHEN STANFORD UNIVERSITY alumnus Bill Faulkner, 73, discovered he had cancerous lesions on his prostate, he considered several standard treatment options.

But Faulkner and his wife worried about the side effects of surgery, such as incontinence and sexual dysfunction. Radiation therapy, while less invasive, was lengthy and carried its own risks. In consultation with Geoffrey Sonn, MD, associate professor of urology, and Pejman Ghanouni, MD, PhD, associate professor of radiology, Faulkner chose a newer, less common approach with less risk of side effects: MRI-guided ultrasound ablation, which harnesses ultrasound waves to obliterate cancerous tissue.

At Stanford Medicine's Minimally Invasive MR Interventional Center (MR for magnetic resonance), doctors developed a plan tailored to the locations of each of the two cancerous masses: magnetic resonance-guided transrectal focused ultrasound (MRgFUS) for one lesion and magnetic resonance-guided transurethral ultrasound ablation (TULSA) for the other.

Sonn and Ghanouni co-authored a recent study showing that MRgFUS is effective for intermediate-risk prostate cancer. They are now studying the effectiveness of TULSA compared with traditional surgery. Stanford Health Care is the only Northern California hospital offering both.

Faulkner had no significant side effects and is cancer-free more than 2 1/2 years later. "The team at MIMRIC was phenomenal," he said.



Sugar coating for brain health

CHANGES IN THE COMPLEX chains of sugars that cover certain cells could be key to understanding cognitive decline and diseases including Alzheimer's, Stanford Medicine researchers said.

Neuroscientists have long focused on proteins and DNA as the likely culprits in dementia — not on sugars.

"This is like landing on a new planet," said Nobel laureate Carolyn Bertozzi, PhD, professor of chemistry and the Baker Family Director of Sarafan ChEM-H. "We're stepping outside for the first time and trying to make sense of what's out there."

In a study in aging mice, graduate student Sophia Shi, PhD, a former Stanford Bio-X fellow, uncovered striking age-related changes in the sugary coating — called the glycocalyx — on cells that form the blood-brain barrier, a membrane that protects the brain by filtering out harmful substances while allowing in essential nutrients.

"This work lays the foundation for a new field of inquiry into how the aging brain loses its resilience," said Tony Wyss-Coray, PhD, the D.H. Chen Professor II, a professor of neurology and director of the Knight Initiative for Brain Resilience.

The study, published Feb. 26, 2025, in *Nature*, was jointly supervised by Bertozzi and Wyss-Coray. Shi is the lead author.

Wyss-Coray's lab has extensively studied how aging impacts the blood-brain barrier, But Shi's project was the first to investigate how age affects its sugary armor. The results were striking: In older mice, bottlebrush-shaped, sugar-coated proteins called mucins, a key component of the glycocalyx, were sharply reduced. This thinning of the glycocalyx correlated with increased blood-brain barrier permeability and heightened neuroinflammation.

When the team reintroduced the critical mucins in aged mice, restoring a more "youthful" glycocalyx, their blood-brain barrier integrity, neuroinflammation and cognitive function all improved.

Incredibly shrinking tumors

THE RESULTS of a recent clinical trial at Stanford Medicine offer hope for young people with rare but deadly cancers that grow in the brain or spinal cord, or both.

Eleven participants with the cancers, known as diffuse midline gliomas, received engineered immune cells known as CAR-T cells. Nine had functional improvement in the disabilities caused by their disease. Four had the volume of their tumors reduced by more than half. And one of those four participants had a complete response: His tumor disappeared from brain scans. Although it is too soon to say whether he is cured, he is healthy four years after diagnosis.

The findings were published online Nov. 13, 2024, in *Nature*.

Diffuse midline gliomas are diagnosed in a few hundred U.S. children and young adults each year. The median survival time is about a year. In October 2024, the CAR-T cell therapy received a regenerative medicine advanced therapy designation from the Food and Drug Administration, giving the researchers access to a fast-tracked version of the FDA approval process.

"While there is still a long way to go to figure out how to optimize this for every patient, it's very exciting that one patient had a complete response," said the study's lead author, Michelle Monje, MD, PhD, the Milan Gambhir Professor in Pediatric Neuro-Oncology at Stanford Medicine. "I'm hopeful he has been cured."

breaking the cycle

INNOVATIONS TO ALLEVIATE THE CHRONIC DISEASE CRISIS

Joie Goodkin first noticed something wasn't right more than 20 years ago when she started having shortness of breath while climbing stairs. She saw a cardiologist, who diagnosed her with cardiomyopathy, a disease where the heart muscle weakens and has difficulty pumping blood as it should. It may have been caused by a thyroid medication she was prescribed for an underactive thyroid, said Goodkin, who is 84 and lives in Carmel, California.

She armed herself with a team of doctors she trusts at Stanford Medicine and for a long while the cardiomyopathy didn't slow her down much. She loves getting outside and spends much of her retirement from a busy publishing job on long hikes. But at the end of 2023, she started regularly having shortness of breath. This time, she was diagnosed with heart failure — her heart wasn't pumping enough blood for her body. It turned out she has a leaking mitral valve, which caused blood to leak back-

By Rachel Tompa

ILLUSTRATIONS BY ARD SU

PHOTOGRAPHY BY MISHA GRAVENOR

ward between the chambers of her heart. She had surgery to repair it and, at the time, her doctor asked her what she wanted to do that her condition had prevented her from doing. Goodkin told him she wanted to climb mountains again.

While she's not quite climbing mountains, she does get out with her dog — who also has heart failure — for a few neighborhood walks a day. Goodkin has also been living with chronic lymphocytic leukemia for several years, a type of blood cancer that often grows very slowly. She doesn't need treatment for it, but it's regularly monitored. Together with her heart medications and cardiology appointments, there's a lot to manage, she said.

"You have to play a role in your own health, and you have to recognize you have power in your situation," Goodkin said. "Once you have a chronic disease, the best thing you can do is accept that you have it, do what you can and think about what you're grateful for."

Goodkin is one of the approximately 130 million Americans living with a chronic disease, defined as any disease that persists for a year or more and significantly impacts a person's life, whether by limiting activities, requiring ongoing medical care or both. According to RAND, around 60% of adults in the United States have at least one chronic disease, and 40% have two or more. We spend 90% of our $4.5 trillion health care expenditure on chronic conditions, according to the Centers for Disease Control and Prevention. Chronic diseases account for 5 of the top 10 causes of death in this country, the CDC says.

While those numbers sound grim, the reality of chronic disease is nuanced. Many are tightly linked with aging — like Goodkin, 85% of U.S. adults older than 65 have one or more chronic diseases — and Americans have been living longer. That's thanks to advances in medical treatments for acute diseases like cancer and heart disease. As the number of elderly people increases, so does the number of people with age-related chronic diseases.

Not all chronic diseases are tied to aging, though. Many — like mental health conditions, Type 1 diabetes and other autoimmune diseases, and addiction — can strike people of any age, including children. And chronic conditions are increasing in children: According to a study from researchers at the Children's Hospital of Philadelphia, the percentage of children aged 3-17 with a chronic condition as reported by a parent rose from 26% to 31% between 2011 and 2023. Mental health conditions such as depression and anxiety showed some of the largest increases, as did autism spectrum disorder, although recent improvements in autism screening and diagnosis are likely responsible for at least some of that increase.

While chronic conditions such as high blood pressure or cholesterol levels can return to normal levels with medication or lifestyle changes, others, such as depression or autoimmune diseases, are often lifelong. And experiencing a chronic disease is more complex than suffering an acute ailment, when friends and family tend to rally around to help.

"Besides the burden of the disease, there's the financial burden on the individual and the emotional burden on the patient, their caregivers and family," said Euan Ashley, MB ChB, DPhil, the Arthur L. Bloomfield Professor in Medicine and chair of the Department of Medicine. "There's a very significant opportunity here to improve people's mental, physical and financial health by treating and managing these diseases better, and that's one way that our research can be of huge value to society."

Policy makers are also grappling with the chronic disease crisis. One concerted area of focus for federal agencies is nutrition, including defining ultraprocessed foods, investigating additives and improving nutrient labels.

Building on a strong foundation of innovative chronic disease treatment at Stanford Medicine, researchers are developing new approaches to cure what were once lifelong ailments, advocate for preventive approaches to stop them before they start, and enable patients to thrive despite these illnesses.

BRINGING RESEARCH TO PATIENTS

One such project takes aim at hypertension, or high blood pressure, that without proper treatment can increase the risk of heart disease or stroke. Nearly half of adults in the U.S. have hypertension, making it one of the country's most common chronic diseases, and only one-quarter of those people successfully control their blood pressure.

So Paul Wang, MD, director of the Stanford Cardiac Arrhythmia Service and a professor of cardiovascular medicine, and colleagues including Vivek Bhalla, MD, an associate professor of nephrology, built a digital system to track blood pressure at home and update physicians when it's too high.

This technology, called HrtEx, can save patients and their care providers a huge amount of time and resources, Wang said. When someone is diagnosed with hypertension, finding the right treatment can take a lot of trial and error as medications are adjusted, often requiring weekly clinic visits that take up time for patients and primary care teams. In a small clinical trial, an early version of HrtEx substantially lowered participants' blood pressure. The researchers are now enrolling subjects for a larger trial of 600-800 participants.

"We just don't have the ability in this country to manage all chronic disease patients at the level they need," said Wang, the John R. and Ai Giak L. Singleton Director. "We believe that we

‘The health care system is set up primarily to treat people, and it falls mostly to primary care physicians to do prevention, and we don’t have enough of them.’

can leverage digital technology to serve a broader group of patients. This is a pretty unusual opportunity where we use fewer resources and actually get better outcomes.”

Stanford Medicine supports several programs that move research and inventions like HrtEx to market and the community. Wang and Bhalla are working within one of these, the Stanford Medicine Catalyst program, in hopes of commercializing HrtEx for broad use.

Another Catalyst project to improve access to care for chronic disease patients targets Parkinson’s disease. Helen Bronte-Stewart, MD, the John E. Cahill Family Professor and a professor of neurology and neurological sciences, is leading the effort to enable physicians to monitor patients’ Parkinson’s disease symptoms remotely and in real time through a brief finger-tapping test on a portable device. The technology, called the Quantitative Digitography platform, is undergoing expedited regulatory review through the U.S. Food and Drug Administration’s Breakthrough Devices Program.

Another innovation that will improve lives of chronic disease patients has made the trip from idea to reality, aided by Stanford Medicine’s SPARK program, which provides funding, education and mentorship to translate research discoveries into patient care. In 2012, Stanford Medicine researchers began working with SPARK to develop a medication for the chronic and life-threatening heart condition transthyretin amyloid cardiomyopathy, which lacked an effective treatment. The new drug, acoramidis, received approval from the FDA last year.

A QUESTION OF ACCESS AND RESOURCES

Stanford Medicine researchers are also trying to understand the factors that influence chronic disease and patients’ experiences with their illnesses. Epidemiologists, for example, are studying individual lifestyle factors and environmental and societal pressures that contribute to risk, said Melissa Bondy, PhD, chair of the Department of Epidemiology and Population Health. Wildfires and warmer climate in America are increasing allergies and lung disease. Social factors such as where people live, their financial status, and their race and ethnicity can also influence disease risk.

“One of the biggest chronic diseases we have is poverty,” said Bondy, the Stanford Medicine Discovery Professor.

Stanford University health economists and policy researchers are also focused on access and prevention. Trillions of dollars are spent every year in the United States on chronic disease, according to the CDC. Better screening guidelines and prevention efforts could lower costs and improve patients’ health, said Doug Owens, MD, the Henry J. Kaiser, Jr. Professor and chair of the Department of Health Policy.

“The health care system is set up primarily to treat people, and it falls mostly to primary care physicians to do prevention, and we don’t have enough of them,” he said. “From a prevention standpoint, we could do a much better job.”

Owens’ work centers on national guidelines and recommendations for disease prevention. He pointed to a recent study in which he and other Stanford Medicine researchers presented evidence that adults 55 and older should be routinely screened for chronic kidney disease. New medications have dramatically improved outcomes for chronic kidney disease, changing the treatment landscape such that screening more people for the disease, and catching it earlier, is now cost effective.

MANAGING COMMON PROBLEMS AMONG THOSE WITH CHRONIC ILLNESS

Kate Lorig, PhD, emerita professor of medicine, has focused her research career on helping people with chronic diseases live better lives. “We looked at how people live the 99% of the time that they’re not in direct medical care, and the concerns turned out to be very similar across diseases,” Lorig said. “We came up with this crazy idea of trying to put people with all kinds of long-term conditions together in one program at one time.”

That idea became the Chronic Disease Self-Management Program, launched in the early 1990s. It aims to build participants' self-confidence and help them manage symptoms by teaching them such lifestyle skills as healthy eating, physical activity, dealing with difficult emotions, and better communication with their caregivers and health care providers. Lorig's research has shown that the program, and others like it, can lower participants' rates of depression and visits to the emergency room and improve symptoms and well-being.

In 2015, Lorig and her team spun the concept into a company, the Self-Management Resource Center. Its programs, which include disease-specific education for diabetes, cancer and HIV, have been licensed by hundreds of health care systems, community organizations and other groups around the world. Lorig estimates they reach between 50,000 and 75,000 patients every year.

PIONEERS IN PREVENTION

The late John "Jack" Farquhar, MD, founder of the Stanford Heart Disease Prevention Program, was among the first to recognize the major impacts of lifestyle on heart disease and, with the late Nathan Maccoby, PhD, Stanford professor of communications, took prevention methods directly to local communities. Starting in the early 1970s, they and their team studied large populations in various Northern California communities, sharing research findings with residents through television and radio programs, billboards, newspaper columns, and other public announcements in English and Spanish. Study participants changed their diets, reduced smoking, and lowered their blood pressure and cholesterol levels.

"That was really quite innovative — to try to change the behavior of a community instead of doing a clinical trial on a person-by-person basis," said David Maron, MD, the C. F. Rehnborg Professor, a professor of medicine and division chief of the Stanford Prevention Research Center, which evolved out of the Stanford Heart Disease Prevention Program.

Maron and colleagues at the Stanford Prevention Research Center are hoping to prevent not only heart disease but also other diseases including Type 2 diabetes, cancer and osteoporosis. Maron has led the development of imaging techniques and AI methods to identify people at high risk of heart disease sooner.

"We need to start our interventions earlier to have a greater chance of keeping people free of disease through their lifespan," he said.

Read on for more stories describing solutions from Stanford Medicine for tackling the widespread impact of chronic disease. — *Contact Rachel Tompa at medmag@stanford.edu*

REWRITING THE RULES OF SICKLE CELL TREATMENT

STANFORD CHEMICAL BIOLOGIST LAURA DASSAMA IS ON A PERSONAL MISSION TO DESIGN A SIMPLER, MORE AFFORDABLE SICKLE CELL THERAPY

By Sarah C.P. Williams

BY THE TIME LAURA DASSAMA, PHD, was 5, she had already met the disease that would help define her future. The pain was unpredictable and searing, sometimes flaring in her limbs, sometimes in her chest. Sickle cell disease, a hereditary blood disorder, was something she and her sister would learn to navigate together while growing up in Liberia.

Today, as an assistant professor of microbiology and immunology and of chemistry at Stanford University, Dassama is confronting sickle cell disease from a new vantage point: the laboratory.

"I've seen it firsthand. I've lived with it," she said. "And I know that, for many people, the current treatments just aren't enough. We need more options, and we need therapies that are both effective and accessible."

Sickle cell disease stems from a single mutation in the gene responsible for helping make hemoglobin, the oxygen-carrying protein inside red blood cells. The resulting faulty version of hemoglobin tends to clump, distorting normally round red cells into stiff, crescent-shaped "sickles." These misshapen cells can clog blood vessels and break down easily, leading to chronic anemia, pain and organ damage.

Doctors have long known that one way to counteract sickle cell disease is to induce the body's production of a fetal version of hemoglobin, which binds more tightly than the adult form, ensuring that developing fetuses can claim some of the oxygen circulating through their mom's body.

Shortly after they're born, babies' bodies switch to making adult hemoglobin and, for most people, production of fetal hemoglobin stops altogether. But some people keep small amounts into adulthood — and studies have found that people with sickle cell disease who retain some fetal hemoglobin tend to fare far better. Red blood cells with higher levels of fetal hemoglobin are more resistant to clumping and sickling — even when the sickle cell mutation is still present. "If we could reliably boost fetal

LAURA DASSAMA

hemoglobin levels, we could dramatically reduce symptoms for many people," Dassama explained.

For decades, researchers have dreamed of turning the production of fetal hemoglobin back on in adults with sickle cell disease. One drug, hydroxyurea, does so in some patients, though no one's sure why it works — and it doesn't work for everyone. More recently, gene-editing therapies have been shown to disable the genetic switch that normally shuts fetal hemoglobin production down, allowing it to turn back on. But these therapies are complex, expensive procedures that require harvesting, editing and re-implanting a patient's own bone marrow cells. "It can take over a year," Dassama said. "And the cells don't always survive the process."

REAWAKENING HEALTHY HEMOGLOBIN

DASSAMA'S LAB IS exploring a simpler, cheaper and faster way to switch on fetal hemoglobin production. Her team is targeting a protein called BCL11A, which acts as the genetic off switch to prevent most adults' bodies from making the fetal hemoglobin. Her lab has designed a molecule that tags BCL11A for destruction by the cell's own waste-disposal system. Her new molecule acts like a "get rid of me" flag for BCL11A, and once BCL11A is cleared away, fetal hemoglobin can reemerge.

"It's a different kind of precision medicine," Dassama said. "We're not rewriting the genome — we're guiding the cell to do something it already knows how to do."

While still in early stages, the approach reflects a growing interest in finding druglike molecules that can eliminate disease-driving proteins, especially those long considered "undruggable." BCL11A is one of them — its structure doesn't have the usual nooks and crannies that drugs can recognize. But Dassama's background in chemical biology gives her a unique tool kit.

Her lab has already identified a molecule that binds BCL11A, and they've added the flag that sends it to the cellular trash bin. The next step: ensuring the drug can effectively get into blood cells to do its job. Dassama said she hopes the strategies developed in this project will apply to other so-called undruggable targets.

But Dassama's motivation goes beyond the science. She's acutely aware of the need for treatments that are not only effective but also accessible — especially in parts of the world where sickle cell is most common, including sub-Saharan Africa.

"This disease affects millions of people, but too often they don't have access to cutting-edge therapies," she said. "My goal is a treatment that you don't need a specialty clinic or a million-dollar lab to receive. Something people could access." — *Contact Sarah C.P. Williams at medmag@stanford.edu*

ENGINEERING A COMEBACK

HOW T CELLS ARE TAKING ON AUTOIMMUNE DISEASE

By Rachel Tompa

SOMETHING STRANGE AND PROMISING happened to the autoimmune disease patients enrolled in the first studies of an experimental, immune cell-based treatment: They went into complete or near-complete remission after a single infusion of the therapy.

Autoimmune diseases like lupus, Type 1 diabetes and multiple sclerosis are chronic diseases where a patient's immune system mistakenly attacks healthy tissues in the body. In these early-stage trials, the patients' immune systems appear to reset themselves after being knocked down by the therapies, roaring back to a healthy immune state without the self-attacking cells and molecules that characterize autoimmunity.

The treatment, called cell therapy, involves removing a patient's own immune cells from their blood, modifying them in the lab to recognize and attack disease targets, and then reinfusing the cells into the bloodstream to go after the patient's disease-causing cells. Over the past decade, cell therapies have successfully treated many patients with blood cancers, and now Stanford Medicine researchers are translating that success to autoimmune disease, including through a first-of-its-kind cell therapy trial for multiple sclerosis. Using cell therapy to treat autoimmune disease was named a runner-up in *Science* magazine's 2024 Breakthrough of the Year competition.

The "immune reset" had been observed in patients with both autoimmune disease and blood cancer who underwent bone marrow transplants, one of the first developed cell therapies, for their cancer, said Everett Meyer, MD, PhD, director of Stanford Medicine's center of operations for trials of cell therapy in autoimmune disease, the Cellular Immune Tolerance Program.

Because bone marrow transplants have historically been hard on the body, they were typically used only to treat people whose cancer was not responding to other treatments or had relapsed. Now that bone marrow transplants are much safer, they are being tested as an autoimmune disease treatment.

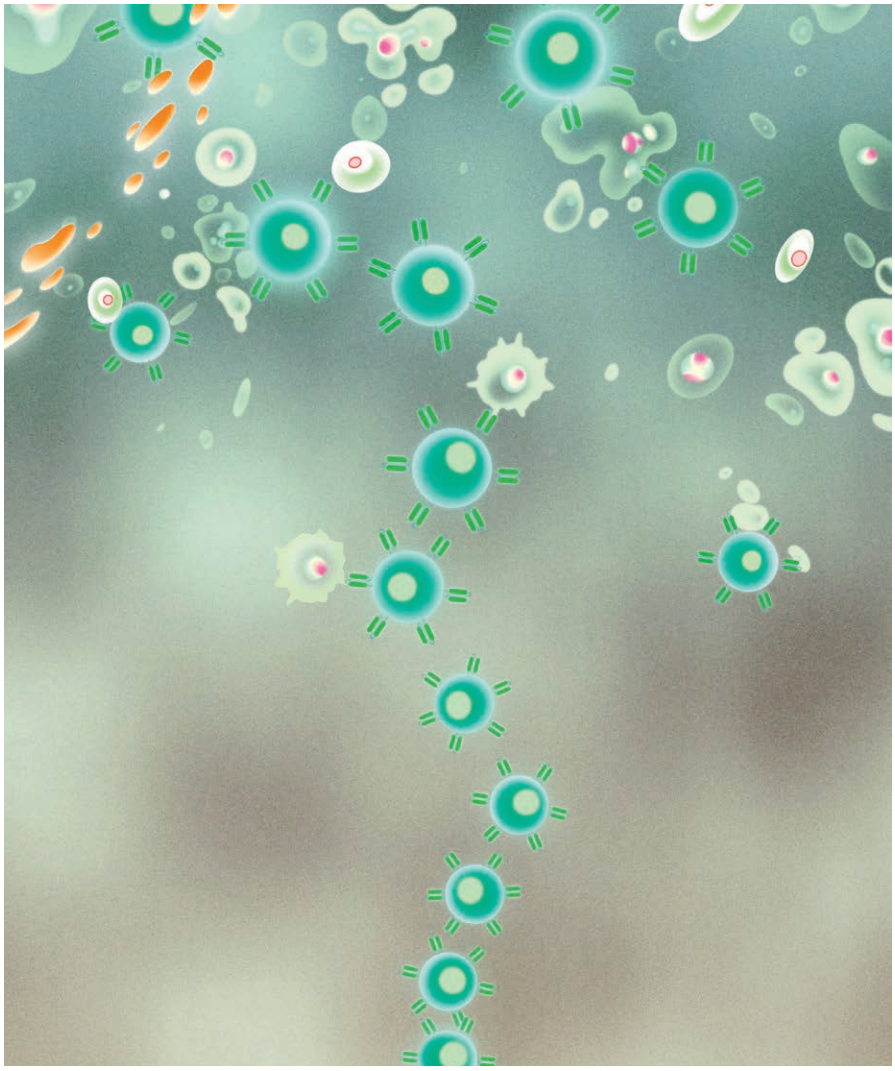
"Safety is a big part of the revolution that's happening in cancer treatment," said Meyer, a professor of blood and marrow transplantation and cellular therapy and of pediatrics. "Within the realm of cell therapy is the potential for much more sophisticated engineering of the immune system. That's the future we're trying to push for."

Instead of reversing the underlying cause of autoimmunity, most treatments for autoimmune disease suppress the immune system, which can lead to side effects such as increased risk of infection. Meyer and his colleagues are exploring a treatment that could address the root cause of an autoimmune disease: cell therapy for Type 1 diabetes. Their approach, which they hope to test in a clinical trial, combines the boosting of immune cells known as regulatory T cells with an islet cell transplant, which replaces nonfunctional insulin-producing cells with functional versions from a deceased donor. Animal studies have shown that regulatory T cells can help ease the transplant without the need for harsh immunosuppressing drugs; the cells may also retrain the immune system to stop attacking the pancreas.

SUPPRESSING MULTIPLE SCLEROSIS

ONE CLINICAL TRIAL RUN through the immune tolerance program is testing cell therapy in patients with progressive multiple sclerosis. In this chronic disease, the immune system mistakenly attacks the protective covering of nerve fibers, leading to nerve damage, muscle weakness and fatigue. Many multiple sclerosis patients have periods of remission and relapse, but for those with progressive disease, their symptoms worsen relentlessly.

The Stanford Medicine trial, led by Jeffrey Dunn, MD, a clinical professor of neurology, and Robert Lowsky, MD, a professor of blood and marrow transplantation and cellular therapy, is testing a cell therapy similar to those developed for certain blood cancers. In this approach, T cells, a kind of immune cell, are extracted from a patient's body, engineered in the lab with a special protein (called a chimeric antigen receptor, or CAR) that recognizes other immune cells known as B cells, and then reinfused into the patient. The souped-up T cells, armed with the special protein attached to their surface, home to B cells and direct the immune system to kill them. In the case of blood cancer, the therapy eliminates cancerous and healthy B cells alike, and, if the therapy works, the B cells grow back without cancer. Researchers hope the same sort of purge and renewal could happen in multiple sclerosis, which also involves bad behavior by B cells: Among a subset of people who've been infected by the Epstein-Barr virus, the B cells make an antibody against the virus that damages the protective sheath of nerve fibers. Encouragingly, Dunn and his colleagues have found that the CAR-T cells can enter the central nervous system, where multiple sclerosis does the most damage.



In the early-phase trial, which is the first trial testing a cell therapy in multiple sclerosis patients, researchers have treated four patients of a planned 12. The first patient in the trial is six months past the treatment, and spinal taps have shown a complete absence of inflammation-associated antibodies in the central nervous system. The team is now determining whether antibodies against Epstein-Barr virus are specifically depleted. All four patients report decreased fatigue.

"These are very early numbers, but the data are really exciting and certainly demand that we continue forward," Dunn said. — *Contact Rachel Tompa at medmag@stanford.edu*

TRACKING PAIN'S PATHWAYS

RESEARCH ON CLUSTERS OF NERVE CELLS IN A DISH REFINES OUR KNOWLEDGE ABOUT PAIN AND HOW TO TREAT IT

By Bruce Goldman

STANFORD MEDICINE INVESTIGATORS HAVE replicated, in a lab dish, one of humans' most prominent nervous pathways for sensing pain. This nerve circuit transmits sensations from the body's skin to the brain. Once further processed there, these signals will translate into our subjective experience, including the uncomfortable feeling of pain. The advance promises to accelerate progress in understanding how pain signals are processed in humans and how best to alleviate pain.

A study published in *Nature* led by Sergiu Pasca, MD, the Kenneth T. Norris, Jr. Professor II of Psychiatry and Behavioral Sciences, describes the successful assembly of four miniaturized parts of the human nervous system to reconstitute what's known as the ascending sensory pathway. The sensation of pain travels from skin to the brain in a relay involving nerve cells, or neurons, centered in four different regions of this pathway: the dorsal root ganglion, dorsal spinal cord, thalamus and somatosensory cortex.

Human pain has often proven tough to study in laboratory animals, Pasca said. "Their pain pathways are in some respects different from ours. In addition, these animals experience pain. Our dish-based construct doesn't," he said.

"Pain is a huge health problem," said Vivianne Tawfik, MD, PhD, associate professor of anesthesiology, perioperative and pain medicine, who wasn't involved in the study. "Some 116 million Americans — more than 1 in 3 people in the United States — are dealing with chronic pain of one kind or another." This pain often persists even when observable damage is no longer evident, possibly the result of lasting changes in the ascending sensory pathway.

Yet treatments for chronic pain are few and far from ideal. "I can't even tell you how sad it is to sit in front of a patient who's suffering from chronic pain after we've tried everything, and there's nothing left in our arsenal," Tawfik said.

The most effective painkillers today are opioid drugs, which have the severe drawback of being habit-forming, leaving chronic-pain sufferers susceptible to addiction.

Tawfik said she thinks the team's new construct is highly relevant to the study of chronic pain. "The pathway they've reconstructed is the most important one for conveying pain-related information," she said.

The regions that compose the ascending sensory pathway are linked by three sets of neuronal connections: The first set relays sensory information from the skin through the dorsal root ganglion to the spinal cord; a second set of neurons passes the signals from the spinal cord to a brain structure called the thalamus; and the third relays this information from the thalamus to the somatosensory cortex for further processing of the signal originating from the periphery.

Until now, nobody has been able to watch information being transmitted through this entire pathway. But Pasca and his colleagues witnessed never-before-seen waves of electrical activity travel from the first component of their construct to the last. They were able to enhance or disrupt the wavelike patterns by gene alterations or chemical stimulation of elements of the circuit.

Pasca, the Bonnie Uytengsu and Family Director of the Stanford Brain Organogenesis Program, has pioneered the creation of what he calls regionalized neural organoids, grown in a lab dish from stem cells and representing various brain regions. In recent years, Pasca has pushed this technology forward, pairing organoids of one type with organoids of another type in a dish so they fuse into what he's named assembloids. Neurons from one organoid can penetrate the other organoid to form working circuits similar or even identical to those they're meant to mimic.

STIMULATING NEURONAL ACTIVITY

IN THE NEW STUDY, Pasca and his colleagues developed human organoids recapitulating the ascending sensory pathway's

Stimulating the sensory organoid with capsaicin — the ingredient in chili peppers that produces a burning sensation in our mouths — triggered immediate waves of neuronal activity.

four key regions, then fused them together in a series to form an assembloid mimicking the pathway. Starting with cells from skin samples from volunteers, the team first transformed them into induced pluripotent stem cells, which are essentially de-differentiated cells that can be guided to become virtually any cell type in the human body. The researchers used chemical signals to coax these cells into aggregating into neural organoids — tiny balls less than a tenth of an inch in diameter — representing each of the four regions of the pathway.

Pasca and his colleagues lined up the organoids of those four different types side by side and waited. By 100 days later, they had fused into an assembloid consisting of nearly 4 million cells — less than 1/42,000 of the number in an adult human brain.

Yet, the construct regenerated the pathway's circuitry, and its four constituent organoids were anatomically connected: Neurons from the first had formed working connections with neurons from the second, the second with the third and so on. Plus, the circuit worked as a unit. Neuronal activity in the sensory organoid tripped off similar action in the spinal organoid, then in the thalamic organoid and finally in the cortical organoid.

Stimulating the sensory organoid with capsaicin — the ingredient in chili peppers that produces a burning sensation in our mouths — triggered immediate waves of neuronal activity.

Mutations in a protein called Nav1.7, which abounds on the surfaces of peripheral sensory neurons but is scarce elsewhere, can lead to debilitating hypersensitivity to pain or, conversely, a life-threatening inability to experience pain — radically increasing the physical dangers that life serves up.

The scientists made an assembloid with its initial sensory component's normal version of Nav1.7 replaced by the mutant pain-hypersensitivity version. The resulting assembloids displayed more-frequent waves of neuronal transmission from the sensory organoid all the way to the cerebral-cortex organoid.

When Pasca's team instead rendered Nav1.7 non-functional, firing from that organoid in response to a pain-inducing chemical continued — but the synchronized wavelike transmission of pain information through the circuit mysteriously vanished.

The assembloids represent an early phase of fetal development. Pasca's lab is working on ways to accelerate development of the assembloids to better understand how the pathway they represent works — or doesn't — in adults.

"We think screening for drugs that tame sensory organoids' ability to trigger excessive or inappropriate waves of neuronal transmission through our assembloid, without affecting the brain's reward circuitry as opioid drugs do — which is why they're addictive — could lead to better-targeted therapies for pain," Pasca said. — *Contact Bruce Goldman at goldmanb@stanford.edu.*

LIGHTING UP THE GUT TO DETECT CELIAC DISEASE

A CLINICIAN AND SCIENTIST COLLABORATE ON NEW METHODS TO DIAGNOSE, TREAT AND TRACK CELIAC DISEASE

By Sarah C.P. Williams

FOR NIELSEN FERNANDEZ-BECKER, MD, diagnosing celiac disease at times feels like working in the dark.

When a patient complains of abdominal pain, nausea and diarrhea, Fernandez-Becker typically orders a blood test and an intestinal biopsy to screen for celiac disease — a gut-inflaming autoimmune reaction triggered by gluten, a type of protein found in some grains.

But neither test is completely accurate, especially if someone is already avoiding gluten, minimizing the telltale signs of damage caused by the disease.

"It's frustrating," said the gastroenterologist, who leads Stanford Health Care's celiac disease program. "We don't have a perfect test that can always tell someone with complete certainty whether they have celiac."

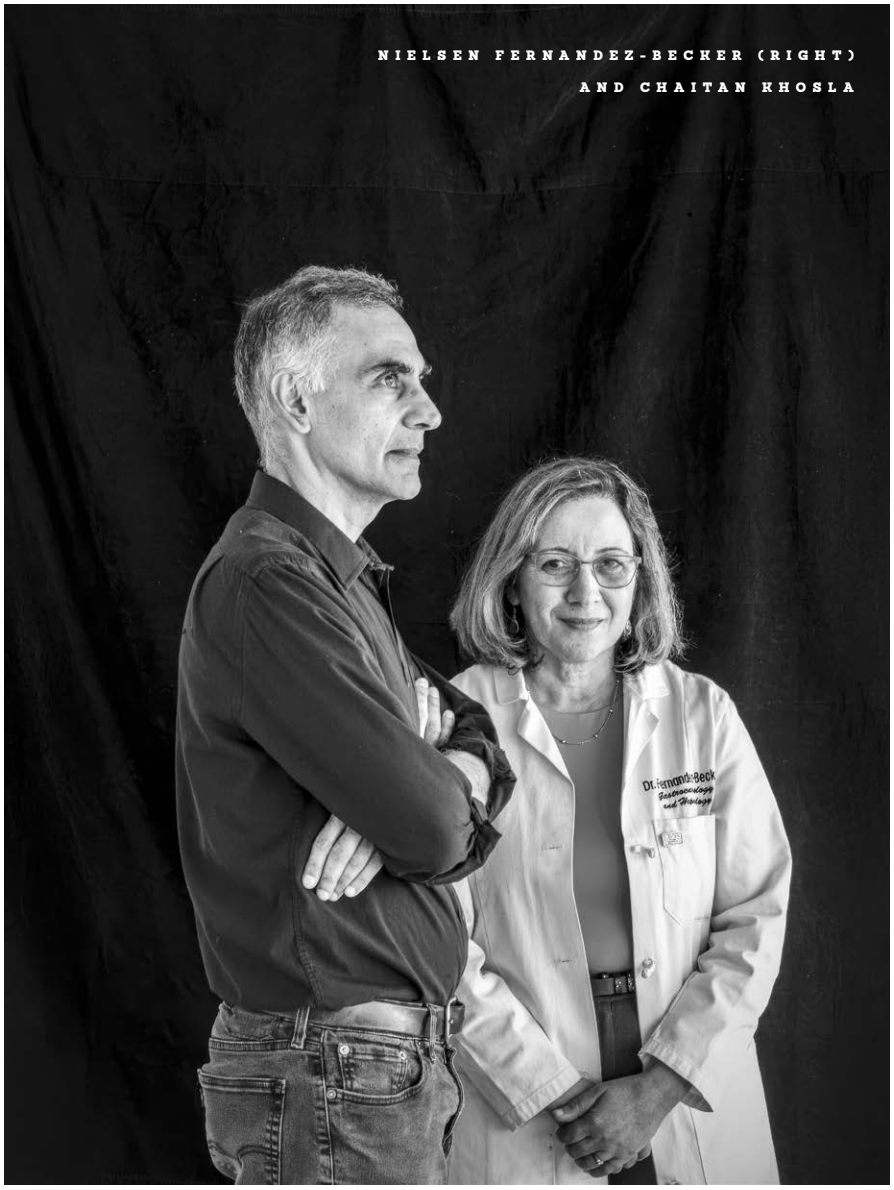
Now, Fernandez-Becker and longtime collaborator Chaitan Khosla, PhD, are testing a more reliable way to detect the disease with the help of Stanford University's Innovative Medicines Accelerator. The two are launching a clinical trial of a fluorescent compound that literally lights up a celiac disease-triggering molecule. When a doctor peers at intestinal cells under a microscope, the presence or absence of celiac disease will be clearly illuminated. The team's initial goal is to improve the diagnosis and monitoring of the disease — but their findings could also lay the groundwork for new treatment strategies.

Celiac disease is one of the world's most common autoimmune conditions, affecting an estimated 1 in 100 people. In people with celiac disease, the body's immune system overreacts to gluten. But it's not gluten that sets off the response — it's gluten that has been chemically altered by an enzyme called tissue transglutaminase 2, or TG2.

"I got interested in TG2 about 25 years ago when I first started looking at celiac disease. This protein seems to play a very important role in causing celiac disease in patients," said Khosla, the Wells H. Rauser and Harold M. Petiprin Professor and a professor of chemistry. "It seemed like this might be

a good target to make a medicine for celiac disease."

Khosla was inspired to shift his research to celiac disease after his young son was diagnosed with the condition. He reasoned that there must be a way to stop the immune reaction that causes symptoms. Blocking TG2, for instance, would stop the conversion of gluten to its modified form and prevent the inflammatory immune reaction from taking place.



NIELSEN FERNANDEZ-BECKER (RIGHT) AND CHAITAN KHOSLA

TIMOTHY ARCHIBALD

ROADBLOCKS TO CELIAC SOLUTIONS

BUT THE ENZYME IS a tricky target. It doesn't just hang out in an "on" state, ready to wreak havoc at the first bite of bread. In healthy people, the enzyme is usually off — it's quiet, inactive, just sitting there. In people with celiac disease, however, TG2 becomes persistently active, modifying gluten and triggering gut inflammation.

Over several decades, Khosla's laboratory studied how TG2 is activated. His team's work led to the launching of a company, Sitari Pharma, that exploited their findings to develop a drug that inhibits the active form of the enzyme.

Following the acquisition of Sitari by GlaxoSmithKline, the drug entered early clinical trials as a potential treatment for celiac disease. But after a successful Phase 1 clinical trial, the company repurposed the drug for further studies in a different disease. So, Khosla felt he had no choice but to go back to the drawing board in search of a solution for celiac patients.

The same challenges that Fernandez-Becker faces in initially diagnosing celiac disease also plague clinical trials for drugs designed to treat this condition. Other than asking a patient about their symptoms, how can doctors — without a definitive test for celiac — track whether a drug is working?

"This represented a huge problem for the pharmaceutical industry in developing a celiac medicine," explained Khosla.

'This represented a huge problem for the pharmaceutical industry in developing a celiac medicine. There were no benchmarks to show whether the disease was improving.'

"There were no benchmarks to show whether the disease was improving," he said.

This roadblock led to a new idea for Khosla: One could convert a medicinal TG2 blocker into a kind of tracker. So, Khosla and his students made a new variation of the drug bearing a fluorescent tag that would light up only in the presence of active TG2.

"This could have a profound impact on how we diagnose and treat celiac disease," said Fernandez-Becker, a clinical professor of gastroenterology and hepatology. "We can give patients a much more definitive answer that, yes, this immune reaction against gluten is causing your symptoms."

In the new clinical trial, enabled by the Innovative Medicines Accelerator and slated to start once the team receives approval from the Food and Drug Administration, patients will drink a solution containing the TG2-binding molecule a few hours before a scheduled endoscopy, during which doctors collect an intestinal biopsy. If TG2 is switched on, the probe will light it up in the biopsy.

Fernandez-Becker and her colleagues will first study the safety of the probe and then begin asking questions about how well it detects celiac disease and monitors disease progression.

For patients, the potential benefits go well beyond diagnosis. The researchers hope the probe will also show whether a gluten-free diet is working — or if lingering symptoms point to ongoing disease or another condition. That's a particularly important distinction, Fernandez-Becker said, because some patients continue to struggle even after eliminating gluten — and it's not always clear why. The presence or absence of TG2 activity could help clarify.

"Right now, we don't have a way to measure mucosal healing in real time," Fernandez-Becker said. "But if we could use this to see whether the gut is still inflamed, we'd have a powerful new way to guide treatment."

PROBING FOR ANSWERS

IT MIGHT ALSO CLEAR a path for future therapies. A definitive test for active TG2 could finally give researchers the biomarker they've been missing to study how well TG2-blocking drugs work — it would provide a way to track whether a drug is making a meaningful difference inside the gut, not just easing symptoms on the surface.

"Often times, people begin to heal from celiac disease enough that it's hard for a pathologist to tell whether their intestines are normal just from a biopsy. With a molecular marker for active TG2, we may be able to give them a much better idea," Khosla said. — *Contact Sarah C.P. Williams at medmag@stanford.edu*

TRAINING DOCTORS TO TREAT ADDICTION

A PIONEERING PROGRAM PREPARES PHYSICIANS TO TACKLE ADDICTION — WITH HEART AND SCIENCE

By Nina Bai

IF SOMEONE IN A DIABETIC CRISIS walks into an emergency room, the doctors know what to do. They recall their training and have well-established protocols to follow.

But if a person struggling with addiction and desperate to stop using walks into an emergency room, the reception is less predictable. Many emergency rooms — and health care settings in general — still lack the resources and trained staff to help patients with substance use disorders.

"Early in my career, if someone came in withdrawing from alcohol, you would just keep them in the emergency room long enough to sober them up and then discharge them — with few resources to help them make connections to addiction treatment," said Anna Lembke, MD, professor of psychiatry and behavioral sciences.

Lembke completed her medical training in psychiatry in the early 2000s, during which she recalls receiving limited dedicated teaching on addiction. Later, as a young psychiatrist at Stanford Health Care, she was at first reluctant to take on patients with addictions, in part because she was unaware that effective treatments — including medications and behavioral therapies — were available. But there was no avoiding the growing number of patients with concurrent mental health disorders and substance use disorders.

By 2010, she had founded a clinic to focus on these patients — the Stanford Addiction Medicine Dual Diagnosis Clinic. The opioid crisis brought addiction into view for many Americans, and doctors were grappling with their role in overprescribing opioids.

"It was very evident that we were seeing more and more people struggling with all different forms of addiction," she said. "But we had too few doctors trained in addiction medicine to be able to meet the need, and we had limited infrastructure inside the house of medicine to treat patients with addiction."

In 2012, with the support of the then new chair of the Department of Psychiatry and Behavioral Sciences, Laura Roberts, MD, Lembke started Stanford Medicine's addiction medicine fellowship.

Three years later, it became one of the first addiction medicine fellowships to be authorized by the accreditation organization for U.S. graduate medical training programs. For the first few years, there was enough funding for only one fellow a year.

Chinyere Ogbonna, MD, was the fellow in the third year of the program. Trained in family medicine and psychiatry, her work with veterans and underserved populations motivated her to learn more about addiction medicine. The fellowship showed her that addiction touches everyone. "One of the biggest lessons I learned was to be aware of my biases about who's affected by addiction," she said. "You really can't look at someone and say that person has addiction or that person would never have addiction."

Though the fellowship is part of the psychiatry department, Lembke wanted the program to welcome doctors from all fields. "Most people with addiction are not showing up in psychiatric settings," Lembke said. "They're showing up in emergency rooms, hospitals and trauma centers. They're showing up in primary care doctors' offices." Now in its 13th year, the addiction medicine fellowship has trained doctors from a wide variety of specialties — including family medicine, pediatrics, emergency medicine, anesthesiology and psychiatry.


ANNA LEMBKE

Bobby Singh, MD, had worked for eight years as a hospitalist in Santa Cruz, California, where he'd become well-versed in treating withdrawals and overdoses. Yet he knew little about options for patients outside the hospital. He'd seen friends and family struggle in treatment programs that took a punitive approach, lacked evidence-based treatments and offered no support afterward. "I thought things could be done differently, but I just didn't know how to do it back then," he said. He took a midcareer leap of faith to attend the fellowship in 2021, while still working part time.

Unlike most fellowships, which have fellows rotating through a different site each month, the Stanford Medicine program is structured longitudinally, with fellows working at multiple sites

Often the whole-person perspective reveals the angle from which to best tackle their addiction — whether it's their love for their children or a need to find stable housing.

in parallel over six months or a year. For example, on Mondays they might work at Stanford Hospital, on Tuesdays they might work at Stanford's dual diagnosis clinic for people who have both mental health and substance use disorders, and on Wednesdays they might work at the VA Palo Alto Health Care System.

The continuity is key, Lembke said, because addiction is a chronic relapsing and remitting disease. "We wanted our fellows to be with patients long enough to see the natural ebbs and flows of the disease process, to see people get better, but also to see what relapse looks like."

Sara Marie Cohen-Fournier, MD, who trained in psychiatry in Montreal, Canada, attended the fellowship in 2021. She was drawn to its humanist approach, which allowed doctors to connect with patients, many of whom have faced rejection by their peers, family or community. "The idea of putting the story of the person at the forefront, instead of the problems of the person, is a big shift in psychiatry, where a lot of times our interviews are focused on 'What's your problem? Why did you come here?'" she said. Often the whole-person perspective reveals the angle from which to best tackle their addiction — whether it's their love for their children or a need to find stable housing.

SEEDING CHANGE

THE FELLOWSHIP NOW ACCEPTS six fellows a year. Its 56 graduates have dispersed to varied careers in addiction medicine, seeding change wherever they practice.

Less than two years after finishing the fellowship, Ogbonna became the medical director of addiction medicine and recovery services at the Kaiser Permanente San Jose Medical Center, where addiction treatment is very much a part of the ecosystem. "All the doctors know about our department and know they can refer patients to us," she said.

Shortly after graduating in 2022, Singh co-founded an addiction treatment clinic in Santa Cruz with residential and outpatient programs. It offers science-based medication management and emphasizes long-term planning and the patient's dignity. It's what he wishes had been available for his family and friends.

Cohen-Fournier works as an addiction medicine specialist in remote areas of northern Quebec, Canada, helping indigenous populations and other local communities. Many of her patients contend with addiction and trauma. In addition to providing screening, psychotherapy and medications, a major part of her job is advocating for her patients — to receive the right care in a system that often dismisses them.

Lembke can see the tide shifting with a new generation. "People are much more aware of addiction. They want to learn about it," she said. "Some people even want to specialize in it."
— *Contact Nina Bai at nina.bai@stanford.edu*

AI GETS SPECIFIC ON TYPE 2 DIABETES

DATA FROM CONTINUOUS GLUCOSE MONITORS CAN PREDICT PREDIABETES SUBTYPES

By Rachel Tompa

WHEN STANFORD MEDICINE geneticist Michael Snyder, PhD, was diagnosed with prediabetes, he decided to hit the gym.

In prediabetes, blood sugar is elevated past normal levels but not yet to the levels that indicate Type 2 diabetes. An estimated one-third of American adults have prediabetes; more than 1 in 10 have Type 2 diabetes, which makes up around 95% of all diabetes cases.

Snyder, the Stanford W. Ascherman, MD, FACS Professor in Genetics, lifted weights, knowing that exercise and increasing muscle mass can lower blood sugar levels. He put on 10 pounds of muscle, he said, but his blood glucose stayed stubbornly high and he eventually developed Type 2 diabetes.

While many with prediabetes and diabetes have what's known as insulin resistance, where certain cells respond abnormally to insulin, Snyder's condition had a different underlying cause: beta cell dysfunction. This kind of diabetes doesn't respond to exercise the way insulin resistance does. It took Snyder a few years to identify his diabetes subtype and develop a working treatment plan.

"We're still lumping all Type 2 diabetes patients together, but they're not all the same. It's like telling someone they have autoimmune disease or mental health problems without getting more specific — it's too big a bucket," said Snyder, who is also director of the Stanford Center for Genomics and Personalized Medicine. "We can get a lot more precise in our diagnostics, and I'm a great example of how tailoring the right treatment can be beneficial or not."

Recently, Snyder paired up with Tracey McLaughlin, MD, a Stanford Medicine professor of endocrinology, to make prediabetes and Type 2 diabetes diagnoses more precise and help patients more quickly find lifestyle management practices or medications that work for their specific disease.

The team used a machine learning algorithm to analyze data from continuous glucose monitors, which use tiny sensors placed under the skin of the upper arm to assess the body's glucose levels every few minutes. Their approach identified several known subtypes among the 29 participants who had normal-range or prediabetes-range glucose values.

"Over the years, we've noticed a lot of people who have glucose abnormalities who aren't insulin resistant, which is unexpected because the dogma says that insulin resistance is the first step toward diabetes," McLaughlin said. "We'd been doing continuous glucose monitoring studies and we noticed that the shapes of the curves differ a lot between people."

In a paper published in the journal *Nature Biomedical Engineering* in late 2024, the researchers studied participants' responses to an oral glucose tolerance test, in which the volunteers drank a syrupy liquid containing 75 grams of sugar. The scientists applied their algorithm to continuous glucose monitoring data for three hours after participants took the drink, following participants' blood sugar levels as they rose and fell. Higher blood sugar spikes and slower returns to baseline are both hallmarks of prediabetes and diabetes, but with their AI approach, the scientists found more subtle differences among the data.

The algorithm accurately predicted several prediabetes subtypes about 90% of the time. These subtypes represent distinct metabolic processes that all lead to elevated blood sugar. Insulin resistance is perhaps the most well-known; others include beta cell dysfunction, where the pancreas can't produce insulin efficiently, and incretin deficiency, characterized by defects in a hormone that also regulates insulin. Most participants in the study had one dominant subtype; some had two co-dominant subtypes contributing to their prediabetes.

AT-HOME TESTING FOR WIDER ACCESS

THE TEAM ALSO applied their approach to specific foods. In another study, published June 4, 2025, in the journal *Nature Medicine*, they showed that people varied in their responses to different carbohydrates and that some prediabetes subtypes affect food-specific responses. For example, people with insulin resistance were more likely to be "potato spikers," (people whose blood sugar spiked highest to potatoes versus other same-carbohydrate foods) while "grape spikers" (people whose blood sugar spiked highest to grapes versus other same-carbohydrate foods) tended not to have insulin resistance.

With more than 30 million Americans living with Type 2 diabetes, the health advantages and cost reductions that would stem from less reliance on trial-and-error approaches to treatment could be huge. Insulin resistance also carries health risks besides increasing the risk of Type 2 diabetes, such as stroke and cardiovascular disease. So patients who have this subtype of prediabetes might choose to more aggressively pursue lifestyle changes like exercising more and losing weight. The team also showed the glucose tolerance test can be performed at home, and many people already use continuous glucose monitors.

"What's exciting is this approach can be scaled to reach a large number of people," McLaughlin said. "We think it's going to be really helpful to identify patients at highest risk of worse outcomes and tailor interventions to help more people get their blood sugar under control and prevent progression to Type 2 diabetes." — *Contact Rachel Tompa at medmag@stanford.edu*

CHIPPING AWAY AT THE MYSTERIES OF ME/CFS

RENOWNED GENETICIST HAS SPENT THE PAST 12 YEARS FOCUSED ON THE DISEASE THAT HAS TAKEN SO MUCH FROM HIS SON

By Rachel Tompa

LAST YEAR, WHITNEY DAFOE DID something extraordinary: He started eating regular food.

Dafoe, 41, has severe chronic fatigue syndrome, also known as myalgic encephalomyelitis or ME/CFS, and had relied on a feeding tube for all his nutrition for years.

Dafoe is also the son of Stanford Medicine's Ron Davis, PhD, a pioneer in the field of genetics who has devoted the past decade-plus of his life and career to studying and understanding the disease that has robbed Dafoe of so much.

For people with very severe forms of ME/CFS, life is often curtailed by the same symptoms Dafoe experiences: unexplained pain, exhaustion, and sensitivity to noise and light. Also, as with Dafoe, their symptoms can become so severe that they are unable to talk, read, eat, drink or get out of bed.

Davis said his son has seen some improvement in his symptoms recently by taking an off-label medication, but he's not cured. A photographer who, before his illness, traveled the world for his work, Dafoe now makes self-portraits and short videos that capture the realities of life with ME/CFS and is active on ME/CFS forums and his blog.

Much of ME/CFS treatment is built on trial-and-error solutions for each patient — the Food and Drug Administration has not approved any drugs to treat the disease. The treatments that do exist focus on managing symptoms rather than addressing the root cause of the disease, which is still unknown.

Though at least 3.3 million people live with ME/CFS in the United States, federal funding for researching the disease has been minimal, and many medical professionals still dismiss the illness as psychological or due to other conditions.

Since 2013, when Davis pivoted from researching genetics to studying ME/CFS, his work has largely been supported by private donations that have helped him make strides in cracking the mysteries of the disease. In 2015, he and his colleagues launched a "big data" approach to understanding the disease, deeply profiling several different types of molecular systems in 20 patients with severe ME/CFS who were bed-bound and 10 healthy control volunteers. The resulting dataset, the largest ever generated in ME/CFS, was completed in 2018.

And it uncovered a lot. Maybe too much. "Oh my god, there's an unbelievable number of things wrong," Davis said. "Then it's a matter of trying to take this apart and figure out what could be going on."

Davis and his colleagues published a study in the journal *Healthcare* in 2021 describing clinical symptoms of the 20 pa-

RON DAVIS

The resulting dataset, the largest ever generated in ME/CFS, was completed in 2018. And it uncovered a lot. Maybe too much. 'Oh my god, there's an unbelievable number of things wrong,' Davis said.

tients, including the similarity between their symptoms and those of long COVID, and another in the journal *Frontiers in Human Neuroscience* early in 2025 that investigated the genes and networks that go awry in the disease.

ZEROING IN ON METABOLISM

MANY OF THE MOLECULAR differences between the people in the study with ME/CFS and the healthy volunteers were related to their metabolism. Davis has developed a theory that infection permanently changes a specific aspect of metabolism in people with ME/CFS, many of whom see their conditions develop after a severe viral infection. In fact, ME/CFS and long COVID — caused by infection with the virus SARS-CoV-2 — have many parallels, and some scientists, Davis included, think the two might be the same disease.

In this hypothesis of the root cause of ME/CFS, immune cells make a certain product of metabolism in response to infection. This metabolite, known as itaconate, ramps up other parts of the immune system's virus-fighting abilities, but it also shuts down the normal energy production pathway in favor of one that's less effective, which is part of the reason we feel tired when we have a cold or flu. Normally, this switch is short-lived, but in ME/CFS it could become permanently stuck in the lower energy mode. Several molecules are involved in this process and Davis believes different parts of the process might go wrong in different patients.

Another hypothesis from the big data study centers on the body's production of nitric oxide, a small molecule with many important roles in biology, including regulating the brain-signaling molecules dopamine and serotonin, levels of which are often out of whack in ME/CFS. Davis and his colleagues have also found mutations in several genes related to the metabolic and nitric oxide pathways in people with ME/CFS.

FINDING HOPE IN THE RESEARCH

ALTHOUGH THESE HYPOTHESES need further testing, Davis is buoyed by the fact that several drugs exist that target the pathways involved. A few patients taking a JAK-STAT inhibitor, a drug that affects the metabolic pathway, have seen a reversal of their symptoms, but it doesn't work for other people and side effects can be severe, Davis said. Still, the successful cases give him hope that research will find a better way forward.

"I've talked to quite a few doctors who say, 'We don't cure chronic diseases.' And my comment back to them is, 'Because you think you can't cure them, you never try,'" he said. "With ME/CFS, we're left in that mode of no, it's not curable. Well, I'm not quite sure I believe that." — *Contact Rachel Tompa at medmag@stanford.edu.*

FROM DATA OVERLOAD TO DIABETES CARE OPTIMIZATION

HOW A COLLABORATION BETWEEN MEDICINE AND ENGINEERING IS RESHAPING PEDIATRIC DIABETES MANAGEMENT

By Erin Digitale

THANKS TO CONTINUOUS glucose monitors, diabetes has morphed into a disease of data management.

People develop diabetes when their bodies stop making or lose sensitivity to the sugar-regulating hormone insulin. In the past, to guide their decisions about diet and insulin doses, patients measured their blood sugar levels manually, pricking their fingers five or six times per day and squeezing a drop of blood into a handheld glucometer each time.

With continuous glucose monitors, patients wear a sensor wire that's inserted under their skin. It measures blood sugar every five to 15 minutes around the clock — meaning they get more detail about their disease without sore fingers. In theory, the data that is automatically transmitted to patients' phones can unlock insights to better diabetes management.

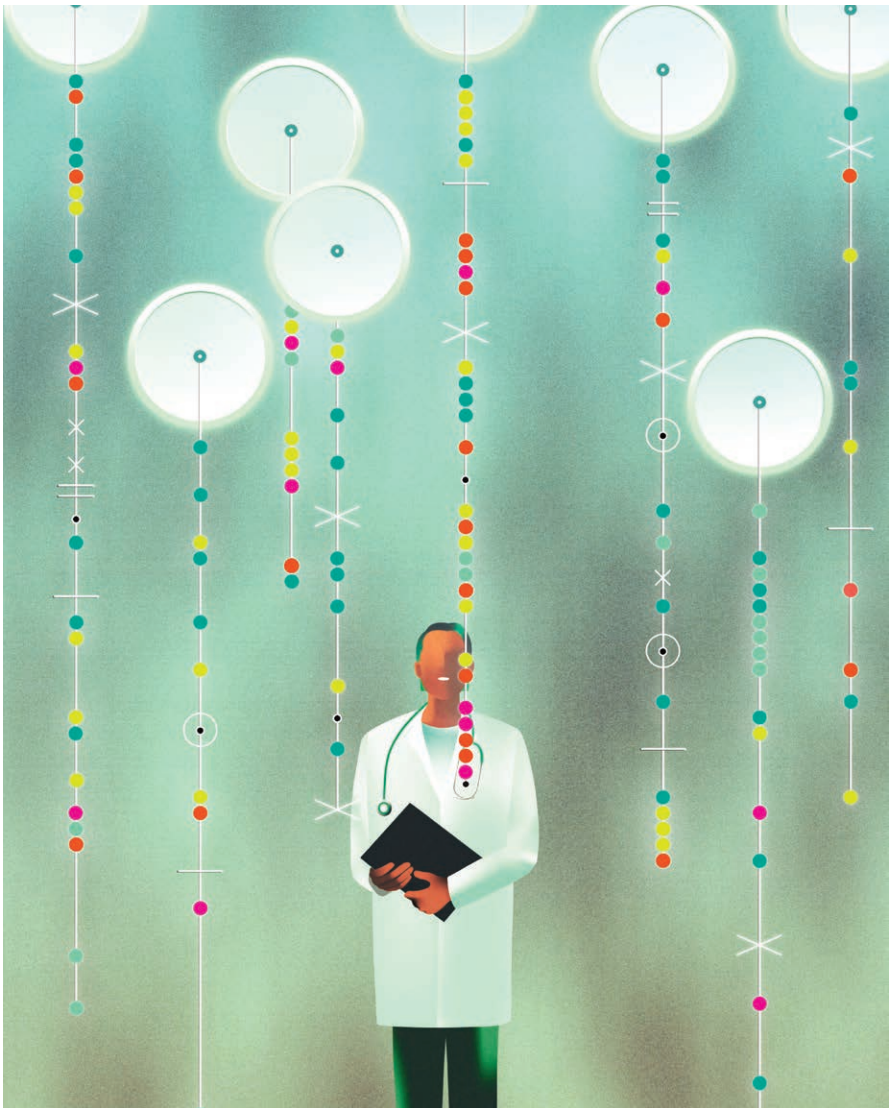
But in practice, many children and teens need help from an expert to translate their blood sugar measurements into action.

In the past five years, the pediatric endocrinology team at Stanford Medicine Children's Health has collaborated with experts from Stanford's School of Engineering to build a digital dashboard that filters blood sugar data — up to 288 measurements per patient per day — so endocrinologists and certified diabetes educators can easily identify struggling patients.

The project has required a just-right balance between artificial intelligence and human knowledge. Commercial products were inadequate; one app the team tried made unhelpful recommendations for diabetes care.

"It didn't know the patients like I do," said diabetes educator Jeannine Leverenz, RN, who played a big role in developing Stanford's diabetes dashboard. "It wouldn't know, 'This is a 2-year-old, and he's not meeting his blood sugar targets because he's snacking all day' versus 'This is a teen who is really into sports and is not meeting targets because of her practices and games.'"

To check on these kids in the past, Leverenz was at a computer manually switching between her list of patients and an



app that gave access to two weeks of blood sugar data for one person at a time. It was cumbersome to spot patterns: For instance, who was having a lot of dangerously low blood sugars?

To redesign and improve a simple early version of the dashboard, Johannes Ferstad, PhD, then a graduate student in management science engineering, observed Leverenz at work and asked what she and her colleagues needed. David Scheinker, PhD, clinical professor of pediatrics and of medicine, brought Ferstad to the project when he took Scheinker's classes on health care systems design. Scheinker also runs a program called Systems Utilization Research that connects physicians, engineers and mathematicians to build data-filtering tools for medicine. The diabetes dashboard, which became Ferstad's dissertation project, has been one of the program's most successful initiatives.

"First, we put the list of patients and the most important summaries of weekly glucose data into a single view, so Jeannine could see the summary statistics without having to click around a bunch," Ferstad said. "We also came up with a way of ordering the patients so those who needed the most attention were shown at the top and didn't fall through the cracks."

FLAGGING STRUGGLES TO REDUCE RISK

THE IDEA SOUNDS simple but it required a lot of behind-the-scenes engineering to obtain data from different sources, matching the clinic's internally stored list of patients with their individual data from the glucose monitors, which was stored in the cloud, then processing it with the algorithm Ferstad developed, and running it all on the health system's computer servers.

The endocrinologists and engineers refined the dashboard to detect key flags, including if patients were not wearing the continuous glucose monitor at all, spent too little time in the target blood sugar range, or had too much time with hazardously low blood sugar levels.

'Automating some of the process, in a way that is based on the real needs of our clinical team, helps us target their attention to where it's really needed.'

People with diabetes try to keep their blood sugar levels in a range that would be normal for a person without the disease. Very low blood sugar can make a person lose consciousness or even result in death. High sugar levels increase the risk for long-term complications, including blindness, kidney failure and nerve damage in the feet.

The flags now help the care team prioritize who needs to receive messages about adjusting their insulin doses.

The team published a scientific study in 2021 in *Pediatric Diabetes* showing that the dashboard sped up review of patients' glucose data, increasing by 56% the estimated clinic capacity — how many patients the clinic could accommodate.

Patients who were struggling could get messages from their caregivers as often as every week, while those doing well received the usual checkups every three months.

"It helps our team shift their focus to the kids who need it most," said David Maahs, MD, the Lucile Salter Packard Professor in Pediatrics and chief of pediatric endocrinology.

EYEING MORE AUTOMATION OPTIONS

THE DASHBOARD IS PART OF a larger research project, published in *Nature Medicine* in 2024, which showed that the right automated tools and management — initiated soon after a diabetes diagnosis — can result in long-term improvements in kids' blood sugar levels, which are linked to lower risk for diabetes complications later in life. Patients in the study also used insulin pumps, which are worn all the time and deliver insulin automatically, avoiding the need for injections.

Maahs and Scheinker are leading an effort to make the dashboard available to other hospitals. The team also wants to integrate other kinds of information, such as data from patients' insulin pumps, in the dashboard — though pump data is often locked in proprietary manufacturers' software.

"There's a challenge with who owns that data — the manufacturer, the health system or the patient," said Priya Prahalad, MD, PhD, clinical associate professor of pediatrics.

The researchers hope to bring all this data into an integrated platform that makes it more efficient for diabetes clinicians to care for their patients.

After all, we've known for three decades — since the landmark Diabetes Control and Complications Trial was published in the 1990s — that patients do better when they have timely input from their diabetes team.

"That can be really hard to do given the resources of real clinics," Maahs said. "Automating some of the process, in a way that is based on the real needs of our clinical team, helps us target their attention to where it's really needed." — *Contact Erin Digitale at digitale@stanford.edu*

SCALING UP WEIGHT LOSS

A WEIGHT MANAGEMENT PROGRAM FOR YOUNG PEOPLE EXPANDS ACCESS

By Erin Digitale

FOR MORE THAN TWO DECADES, experts at the Stanford Medicine Children's Health Pediatric Weight Control Program have helped families who live near Stanford learn how their kids with obesity can reach and maintain healthy weights. The program, which guides children and families on eating better and increasing their activity levels, was in the vanguard of behavior-based pediatric weight management programs when it was developed in the late 1990s. It has enabled more than 80% of participants to achieve healthier weights.

Now, the program's leaders are taking a Silicon Valley-inspired approach to sharing that success across the country: They are using design thinking and technology to package the weight control program, available only at Stanford Medicine, into a format that can be delivered by health professionals and community leaders anywhere.

"It's important to provide pediatric weight management programs that are accessible, acceptable and affordable for the populations with the greatest need," said Thomas Robinson, MD, MPH, professor of pediatrics and of medicine at the Stanford School of Medicine.

Fewer than two dozen well-regarded behavioral pediatric weight control programs exist around the country, mostly at academic medical centers, Robinson said, but most children and teens don't live near centers that offer this care. The U.S. Preventive Services Task Force, which makes evidence-based recommendations for primary care, endorses such programs as the mainstay of pediatric obesity treatment. Some physicians are beginning to prescribe weight loss drugs such as semaglutide (the active ingredient in Ozempic) for certain adolescents with obesity; these newer drugs mimic glucagon-like peptide-1 hormone and suppress appetite signals in the brain. But because there are few studies in adolescents and the medications' long-term effects on youth who are still growing is uncertain, the task force has not recommended their use in teens. That leaves behavioral programs that focus on healthy eating and exercise as the main method for addressing obesity in young people.

Unlike drugs or medical devices, widespread rollout of public health interventions is unusual, said Robinson, who holds

THOMAS ROBINSON

the Irving Schulman, MD, Professorship in Child Health. "We have an efficacious program. The challenge is: How do we get it out there?"

CHILDHOOD OBESITY ROOTED IN SOCIAL INEQUALITY

SINCE THE 1970S, pediatric obesity rates have nearly quadrupled, according to the CDC, putting millions of young people at risk for medical problems such as high blood pressure and Type 2 diabetes. Disadvantaged children and teens, including those who are racial or ethnic minorities or from low-income families, are the most likely to be affected.

"That's the group at greatest need, and it also tends to be the group that has the least access to effective weight management programs," Robinson said.

The expansion his team is planning was funded through a five-year grant from the CDC's Childhood Obesity Research Demonstration Project 3.0, intended to give low-income families access to safe, evidence-based weight management programs. The Stanford Children's Pediatric Weight Control Program fit that bill. Robinson's team is now gearing up to offer the program nationwide and is starting the final phase of testing whether their rollout will work as planned.

Children and teenagers in the program attend six months of weekly group meetings with one or more parents or guardians, learning how to incorporate healthy eating habits and physical activity into their lifestyles while receiving support from other families facing similar challenges. They learn to classify foods with a traffic-light system — red designates calorie-dense foods to eat much less of, yellow is for foods to eat in moderate portions and green indicates the healthiest foods. They are encouraged to get more physical activity and reduce sedentary behaviors, especially screen time. To make all these changes, they tap into well-tested behavioral tactics, such as using journals to track everything they eat, all their physical activity and their screen time. They practice setting goals and solving problems regarding food, activity and screen use. They also learn how to establish a healthy balance of decision-making between parents and kids.

"Children live in the context of families, and their parents have so much control over resources like nutritious foods, physical activity opportunities and screen time," Robinson said. Parents also set the tone in their families — for instance, by modeling and supporting diet and activity changes for the sake

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a school is born

ALICE WALTON AND LLOYD MINOR ON LAUNCHING A NEW MEDICAL SCHOOL AND THE BENEFITS OF COLLABORATION

This summer, a new medical school with bold ambitions to reimagine medical education welcomed its inaugural class. The new institution is the Alice L. Walton School of Medicine, and at its heart is a strategic collaboration with Stanford Medicine. Several Stanford faculty are contributing to AWSOM's academic foundation — teaching students, mentoring faculty and supporting curriculum design. The collaboration also includes Stanford-led research mentorship programs, leadership development, clinical skills training and more. Alice Walton, founder of AWSOM, and Lloyd Minor, MD, dean of the Stanford School of Medicine, vice president for medical affairs of Stanford University and chair of AWSOM's board, reflect on the journey that led to this moment and discuss the promise it holds in this conversation with Priya Singh, the executive vice president, chief strategy officer and senior associate dean of Stanford Medicine.

PRIYA SINGH: *What does opening AWSOM mean for you both personally, and what do you hope it represents for the future of medical education?*

ALICE WALTON: This is a watershed moment in our organizations' efforts to transform health care to treat the whole person. It began with founding Heartland Whole Health Institute in 2019, expanded with the founding of AWSOM in 2021, and today we have a new school of medicine in a building designed to foster wellness on the campus of Crystal Bridges Museum of American Art.

Over the past several years we've hired faculty and staff, developed an innovative curriculum, secured preliminary accreditation status by the

Liaison Committee on Medical Education and taken many other steps that led to us welcoming 48 students to our campus in July. About half of those students are from our state or region, providing them with the opportunity to learn closer to home and potentially serve our region in the future. It's a dream come true to me, and I hope that we create a ripple effect, influencing how medical education is taught across our country.

LLOYD MINOR: Reaching this milestone is deeply important to me. I grew up in Arkansas and know how health and health care can feel very different depending on where you live. AWSOM welcoming its first class marks a historic moment not just for Arkansas, but for all of us who believe that medical education should serve the full breadth of our nation. For me, it also represents an important step toward the kind of medical training we are all striving toward: preparing physicians who are grounded in the human experience of their patients while also equipped with the best tools science can offer. I'm proud to share in this moment and to partner with Alice in realizing her bold vision.

SINGH: *How do you envision this collaboration advancing the way we prepare future physicians, particularly in tackling the major problem of chronic disease?*

WALTON: Dean Minor and the Stanford Medicine team have been fantastic partners to our new school, and we envision this collaboration as an example of how institutions can work together in meaningful ways.

Tackling chronic disease in rural areas is a critical issue for our country, and our partnership with Stanford includes exploring the use of AI with a goal of providing better access to care in rural America. AWSOM graduates will demonstrate competency in AI through a structured progression of milestones and assessments within the curriculum. To ensure AWSOM faculty are equipped to meet this demand, we're facilitating opportunities such as our Stanford Seminar Series, where educators and researchers from Stanford are sharing their knowledge and experiences with our faculty.

MINOR: What excites me most is how this collaboration allows us to learn from one another. At Stanford Medicine, we've been advancing precision health — applying data, technology and new biomedical discoveries to predict and prevent disease before it takes hold. AWSOM is a school that is rooted in the lived realities of heartland communities. And Alice's vision for whole-person health, which integrates the arts and humanities into medical training, adds another essential dimension.

Through this blending of strengths and focus, we can prepare physicians who not only deliver excellent care but also gain skills to address the complex underlying factors that contribute to our nation's chronic disease crisis. That includes training future leaders who can develop and deploy AI solutions to meet this challenge.

SINGH: *Addressing chronic disease is a central health challenge nationwide. Lloyd, how do you see Stanford Medicine's collaboration with AWSOM advancing this goal, especially for communities far from academic medical centers?*

MINOR: The burden of chronic disease is felt most in communities farthest from specialty care. Today, nearly half of all U.S. counties lack a practicing cardiologist — yet these same areas often experience higher rates of heart disease, diabetes and other chronic illnesses.

While innovation and system-level change are essential, education is one of our most powerful levers. Through this collaboration, we aim to train a new generation of physicians who will be better prepared to meet the realities of chronic disease — not only with clinical expertise but also with a deeper understanding of the factors that drive it.

That means equipping them with tools to navigate complex care environments, coordinate across disciplines and use data to guide timely decisions. It also means instilling the skills — and the mindset — to build trust; engage patients holistically; and understand the role that food access, transportation and community conditions play in shaping health outcomes.

It's an exciting vision — one that I'm looking forward to seeing unfold in the years to come.

SINGH: *AWSOM's mission is deeply rooted in serving the heartland and rural communities — places that often face the steepest barriers to care. Alice, how does this mission shape your vision for medical training and community impact?*

WALTON: It's essential for the future of our country that we train physicians who are equipped to care for underserved and rural populations. Community-centered care is a part of AWSOM's curriculum, including early clinical experiences, virtual care and an understanding of the barriers to health that rural communities face. Students will be empowered to use AI and digital health tools to provide rural communities with greater access to health care through

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MEREDITH MASHBURN

too small to fail

ARIANNA HUFFINGTON ON THE POWER OF TINY BEHAVIOR CHANGES TO BOOST HEALTH

Chronic conditions like diabetes, obesity and cardiovascular disease are enormous modern-day hurdles, but the behaviors that help prevent them don't have to be. Around the world, noncommunicable diseases underlie roughly three-quarters of all deaths. Yet, small changes in our daily behaviors can reduce our risk of developing chronic diseases, especially when they lead to better sleep, more movement, improved stress management and healthier eating.

Arianna Huffington, founder and CEO of behavior change technology company Thrive Global, introduced the concept of "microsteps" to help people improve their health and move from merely surviving to thriving. The strategy, based on insights from behavioral scientists at Stanford Medicine and elsewhere, relies on tiny, science-backed actions

designed to fit into real lives and to compound over time: Think about charging your phone outside the bedroom, taking a 60-second pause between meetings or writing down a priority task before bed rather than losing sleep trying to remember it. Instead of grand gestures, these low-friction actions build momentum and resilience.

In the following conversation, Maya Adam, MD, PhD, Director of Health Media Innovation at Stanford Medicine and host of the Health Compass podcast, spoke with Huffington about what it takes to make healthy choices the easy default.

MAYA ADAM: *You've championed the idea that small, science-backed changes can have a profound impact on our well-being. How did your focus on "microsteps" come about?*

ARIANNA HUFFINGTON: Behavior change is difficult, but there's a lot of solid science on what makes it more likely.

We've worked with a great group of behavior change scientists, including behavioral economists Dr. Kevin Volpp and Dr. David Asch at the University of Pennsylvania School of Medicine.

And what the science shows is that the best way to start a new habit is to start small — in fact, as small as possible. So, all the five foundational health behaviors we work on — food, movement, sleep, stress management and connection — are broken down into microsteps that are designed to be too small to fail.

ADAM: *In public health, we often struggle with bridging the gap between knowing what's healthy and actually doing it. How can we help people move from awareness to sustainable action when it comes to lifestyle habits?*

HUFFINGTON: That's a great way of putting it — and a core part of Thrive's mission is just that: helping people move from awareness to action. It's like the doctor telling us to eat a Mediterranean diet or become a gym person. Of course, eating healthier and getting some exercise are things most of us know we should do, but simply being told to do them doesn't set us up for success. People don't know where to start, so they give up.

Microsteps are the way to move from awareness to action. It's about lowering the friction as much as possible to make the healthier choice the easier choice. By taking just one small step — and celebrating small wins when we do and not judging ourselves on those days when for whatever reasons we don't — we slowly gain momentum and begin to create healthier habits.

ADAM: *Sleep is a signature theme in your work. What simple things can people in high-demand jobs do to improve sleep, and how do you persuade leaders to dedicate time to rest?*

HUFFINGTON: Persuading leaders has gotten a lot easier as more have come to recognize that prioritizing key daily behaviors doesn't take away from high performance but, rather, is an essential element of high performance. Sleep isn't indulgent — it's simply part of the job of being an effective leader.

My favorite sleep microstep is to pick a time at night when you turn off your devices — and gently escort them out of your bedroom. Our phones are repositories of everything we need to put away to allow us to sleep — our to-do lists, our inboxes, the demands of the day. Charging our devices in another room allows us to wake up as recharged as our phones. And if that's hard for seven nights a week, start with one!

ADAM: *What are options for people who are time-crunched, carry caregiving burdens or lack control over their schedule?*

HUFFINGTON: By making microsteps too small to fail, we also make them more accessible and equitable. For example, instead of telling you to get more exercise or sign up for a gym membership, we suggest creative ways to add more movement to your day — such as adding a moment of movement onto something you already do, like doing a few calf raises while you wait in line or a few squats after you brush your teeth.

And this is important: A judgment-free zone is key. If a specific microstep doesn't resonate with you or feels beyond your reach right now — for any reason — that's OK. It's all about finding options that are relevant and feasible for you.

ADAM: *If you could rewrite one workplace norm tomorrow to reduce burnout, what would it be?*

HUFFINGTON: Small breaks would be built into the workday. That's why at Thrive we created a 60-second tool called Reset that is embedded in the workflow. Focusing on conscious breathing — along with images and music that give us joy and gratitude for just 60 seconds — has a dramatic effect on the brain, moving us from the sympathetic to the parasympathetic nervous system and getting us out of the fight-or-flight response.

Of course, stress in life and at work is inevitable, but cumulative stress — which leads to burnout — is avoidable. And it would be great if more workplaces created a norm of building short breaks into the workday and into the workflow. **SM**

COURTESY OF THRIVE GLOBAL

DID YOU KNOW?

HOW RESEARCH IS IMPROVING THE LIVES OF PEOPLE WITH CHRONIC DISEASE

It's never a good time to live with a chronic illness — but it's getting better.

Medical research has transformed chronic disease management for many conditions, reducing suffering and enhancing well-being. And ongoing research promises further advancements. How has treatment for chronic illness changed, and what might the future bring? Stanford Medicine doctors who care for people with lung disease, diabetes and the aftermath of a stroke provide their perspectives.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE — COPD

Living with lung disease can make carrying out even simple tasks feel monumental.

The good news is that research has recently led to better treatments for COPD, a group of lung diseases that cause breathing difficulties. The conditions, which include emphysema and chronic bronchitis, are often due to long-term exposure to harmful substances including cigarette smoke.

COPD is a major source of disability and a leading cause of death worldwide. In the U.S., 6.4% of adults have been diagnosed with the disease, according to a 2021 Centers for Disease Control and Prevention survey.

One of the main symptoms of COPD is dyspnea, or shortness of breath, which can have a profoundly negative impact on a person's life. "Dyspnea can cause anxiety, limit daily activities and often leave patients feeling helpless," said Jennifer Williams, MD,

By Rosanne Spector

ILLUSTRATION BY MATT CHASE

co-director of the Stanford Health Care Chest Clinic and a clinical assistant professor of pulmonary, allergy and critical care medicine. "My interest in pulmonary medicine stems from a deeply personal experience: witnessing a family member struggle with long-term breathing issues. Being by their side through moments of breathlessness left a lasting impression on me."

For many years, the main medical treatments for COPD have been corticosteroid drugs, which reduce inflammation in the airways, and bronchodilators, which relax the muscles surrounding the airways, opening them up and easing breathing. However, corticosteroids don't work for everyone and can have side effects that prevent their use.

Though there's no cure for COPD, basic research and clinical trials have led to therapies that not only tamp down flare-ups but also, in some cases, eliminate symptoms entirely.

"Two things that have happened during my career that have really amazed me are T2 biologics — targeted treatments for people who have both asthma and COPD — and virtual pulmonary rehab," said Lauren Eggert, MD, director of the airways disease program and a clinical assistant professor of pulmonary, allergy and critical care medicine. "Both of these tools are really transforming patient care and allowing patients to live longer, healthier lives."

Other advances include enhanced methods to identify specific types of COPD, which helps identify the best treatments; new drugs that are safer than corticosteroids; and better strategies to bypass the diseased parts of the lungs.

To help patients with severe emphysema who don't get relief through other treatments, for example, doctors can turn to procedures like a bronchoscopic lung volume reduction (BLVR) to reroute respiration. The method typically involves inserting one-way valves into the airways to block airflow to diseased parts of the lung. The minimally invasive procedure addresses the problem of air trapping, which occurs when air gets stuck in the lungs during exhalation. Air trapping leads lungs to expand beyond their normal size, making it harder to breathe.

"BLVR has the potential to improve shortness of breath and quality of life," said Harmeet Bedi, MD, medical director of interventional pulmonology and a clinical associate professor of pulmonary, allergy and critical care medicine.

However, lung volume reduction isn't always a good option, especially for people whose lungs exhibit widespread disease or have extensive collateral ventilation — breathing routes that bypass the lung's usual airways.

"Unfortunately, a large proportion of COPD patients fit into this category," Bedi said. "R&D for bronchoscopic lung volume reduction is really focusing on therapies that can provide less air trapping regardless of collateral ventilation status. Numerous companies are working on different devices that could be implanted and achieve success in such patients."

DIABETES

Just a few years ago, GLP-1 receptor agonists burst into the public consciousness as weight-loss wonder drugs.

But the advent was no surprise to diabetes researchers. Seung Kim, MD, PhD, has watched the discoveries underlying the drugs accrue over many years. In 2021, Wegovy became the first GLP-1 drug the Food and Drug Administration approved to treat obesity, but initial applications for GLP-1 drugs were for diabetes, not weight loss. Kim, the director of the Stanford Diabetes Research Center, believes these drugs have the potential to greatly lessen the impact of the condition.

Diabetes affects 1 in 9 people globally, according to the International Diabetes Federation. It leads to a high level of blood sugar, or glucose, which over time can cause damage throughout the body, including to the blood vessels, eyes, heart, kidneys and nervous system. At the root of the disease is a problem with insulin, a hormone that helps regulate the blood sugar by letting glucose into the body's cells to be used for energy. If you have diabetes, your body either produces too little or no insulin (Type 1 diabetes) or it fails to make good use of the insulin it does produce (Type 2 and gestational diabetes).

GLP-1 receptor agonists work by mimicking GLP-1, a hormone produced in the small intestine and likely the pancreas. GLP-1 and its copycat molecules stimulate the release of insulin; suppress a hormone, glucagon, that raises blood sugar; and slow the movement of food through the gastrointestinal tract, thereby reducing hunger. They flip the switch to launch these events by latching onto the GLP-1 receptor, a protein embedded in the surface of cells throughout the body.

"The targeting of satiety is a major step in diabetes care and prevention. The finding that drugs targeting the GLP-1 receptor can be used for weight reduction and glucose control has the potential to be transformative for many with Type 2 diabetes — the most common form of this disease — or with conditions like obesity that increase diabetes risk," said Kim, the KM Mulberry Professor and a professor of developmental biology and of medicine.

"Only time will tell how durable and useful these agents will be. But a principle for complex diseases like diabetes is that multiple agents working through distinct mechanisms can be very powerful, especially if safely combined."

Researchers and clinicians are now exploring combining the GLP-1 drugs with other medications for diabetes, such as met-

formin and SGLT2 inhibitors, as well as exercise and behavior modification.

And some researchers, including Kim, are hunting for ways to cure the disease by providing functional versions of the faulty insulin-producing cells. These cells, known as beta cells, develop in structures within the pancreas known as the islets of Langerhans. Kim's laboratory is investigating the mechanisms that control islet formation, growth and survival, and asking how this knowledge can be harnessed to generate replacements, including beta cells from human stem cell lines.

People with Type 1 diabetes and some with Type 2 diabetes need insulin from an external source to survive, so they must monitor their blood sugar levels and administer insulin, usually through an injection, often multiple times per day. Technological solutions such as insulin pumps that automatically monitor glucose and continually supply the insulin make managing insulin easier, but they have drawbacks — among them high cost, potential for malfunction and infection at the infusion site.

"We think the best devices for delivering insulin, ultimately, are the cells that actually know how to do that. The beta cell is exquisitely tuned to controlling a very tight range of glucose and other important metabolites," Kim said. "Devices can approximate this, but when it comes to controlling glucose, beta cells along with other islet cells are the professionals.

'THE BETA CELL IS EXQUISITELY TUNED TO CONTROLLING **A VERY TIGHT RANGE** OF GLUCOSE AND OTHER IMPORTANT METABOLITES.'

STROKE RECOVERY

Recovering from a stroke can take weeks, months or even years — with some people experiencing lifelong disabilities. Challenges survivors face can include paralysis, spastic movements, balance problems, difficulties with speaking and swallowing, memory troubles, and emotional changes including depression. The leaders of the Stanford Stroke Recovery Program are out to eliminate these challenges. Their program runs clinical studies to understand stroke recovery and develop new treatments, and they're optimistic that new treatments and technologies will transform stroke rehabilitation.

"There are some emerging therapies that I am very excited about but that are still in early phases of development," said Maarten Lansberg, MD, PhD, co-leader of the stroke recovery program and a professor of neurology and neurological sciences. Among these is the injection of stem cells into the brain post-stroke, a treatment being explored by Stanford Medicine's Gary Steinberg, MD, PhD, the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences. A small, early stage study of 18 patients found that patients experienced improvements in walking, hand and arm use, and coordination. Some patients in wheelchairs even regained the ability to walk. A larger study is underway.

Another exciting development lies in the integration of technology into rehabilitation. "New technologies such as artificial intelligence and virtual reality will make it possible to deliver personalized intensive rehabilitation therapy to patients in the comfort of their homes," Lansberg said. This shift could revolutionize how patients engage with their recovery, making therapy more accessible and tailored to individual needs.

"The first thing that comes to people's minds when thinking about stroke is lack of movement, speech and sensation, and these are indeed large problems that stroke recovery research is addressing," said Marion Buckwalter, MD, PhD, who co-leads the program with Lansberg. However, less well-researched issues such as memory problems, fatigue and depression affect many stroke survivors.

"New therapies aimed at treating these problems will dramatically increase quality of life for people who've had a stroke," said Buckwalter, a professor of neurology and neurological sciences and of neurosurgery.

Bringing the various advances together can be expected to have an even greater impact, the experts said. "We know that children and young adults recover much better after stroke than older patients," Lansberg said. "Hopefully, we will be able to create the conditions — by combining new medical therapies with more intensive rehabilitation — in which a patient recovers as well as or better than someone who is 10 years younger."

"I think in the next five years we will see the first early stage trials for promoting recovery of movement after stroke and the first trials to prevent dementia after stroke," Buckwalter predicted.

"I hope in 10 years we will be testing our first therapies for post-stroke fatigue and will have established treatments to promote rewiring and plasticity for movement and to promote healthy brain blood vessels that sustain normal thinking and memory." **SM**

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gut feelings

UNTANGLING THE COMPLEX CONNECTIONS BETWEEN THE GUT, BRAIN AND MICROBIOME TO HEAL CHRONIC GI CONDITIONS

On Halloween 2021, Brittney Doutt
was at her dad's house, preparing for an evening of fun,
when she had a sudden wave of nausea.
"Out of nowhere, I was like 'Oh, I'm going to throw up!'" said
Doutt, who is now 30. As her stomach churned, she panicked;
she has always had a phobia of vomiting. Doutt drank
some ginger ale and went outside for fresh air.
Her nausea slowly subsided.
"This ... is ... strange," she recalled thinking.
If that had been the only episode, she might have dismissed it.
Instead, over the next few weeks, more unexplained
bouts of queasiness resulted in Doutt feeling ill all the time.
"It was just nausea 24/7," she said. "I couldn't sit comfortably.
The moment I would lie down, it was 10 times worse.
At that point I stopped eating because
I just could not deal with adding anything new."

By Erin Digitale

ILLUSTRATION BY GÉRARD DUBOIS

PHOTOGRAPHY BY MISHA GRAVENOR

As she struggled to find an explanation, Doutt became part of a group nobody wants to join: patients whose gastrointestinal symptoms resist diagnosis. Doctors might tell these patients something hand-wavy — maybe they have anxiety, or perhaps it's irritable bowel syndrome — and advise cutting various foods from their diets. Patients can become mired in vicious cycles: Dietary restrictions drive abnormal shifts in the populations of microbes living in their gastrointestinal tract (their gut) and, thanks to strong neurological links between the gut and the brain, their stress and GI symptoms compound each other.

An interdisciplinary Stanford Medicine team aims to provide people stuck in these cycles with off-ramps. These experts are helping patients reset the connections between their guts and brains while advancing the science of how the gut microbiome influences our health.

"Instead of just the gut-brain interface, what I talk to my patients about is the food-microbiome-immune-gut-brain interface, that ecosystem and how it can become disordered," said gastroenterologist Sean Spencer, MD, PhD, who sees patients at Stanford Medicine's Digestive Health Center.

Soon after arriving at Stanford Medicine as a fellow in 2017, Spencer recognized that his interests in these overlapping areas could be especially helpful for patients with what are termed "disorders of the gut-brain interface," often those whose GI symptoms remain unexplained after excluding such diagnoses as celiac disease or lactose intolerance. Patients suffer combinations of nausea, gas, cramping, diarrhea and/or constipation without an obvious cause.

"Their guts and brains are not speaking well together," Spencer said. "Unless you put a really careful lens onto why they're having symptoms, they end up afraid of food, with trauma and stress around food and restrictive eating disorders."

Untangling the many threads of what has gone wrong for these patients requires several kinds of experts to work in concert, he added, with attention to patients' physical and mental health.

"A lot of this has a root cause of some physiologic process that becomes cognitively amplified times a million, but there's still an underlying physiology that is perturbed," Spencer said. "We have to attack it from all angles so we can fix the physiology and address the food-related traumatic stress."

Finally being heard

DOUTT'S INITIAL visits to her primary care doctor didn't explain what was wrong. A prescription for Zofran, a powerful anti-nausea drug given to cancer patients to help manage side effects of chemo, didn't solve the problem either. Over a two-month period, she lost a lot of weight and barely slept. Finally, her very worried partner, Kyle Vanden Brand Horninge, helped her connect with Stanford Medicine gastroenterologist Irene Sonu, MD, a clinical associate professor of medicine, who, like Spencer, sees patients at the digestive health center.

The first thing that stood out for Doutt was that Sonu didn't make assumptions.

"Other doctors didn't really give me the time of day; they saw that I was crying and distraught and, I think, jumped to, 'Oh, you have anxiety,'" Doutt said. "Dr. Sonu has been my savior. It was like, somebody who is actually listening to me! This is so comforting!"

After Sonu asked Doutt to describe her symptoms, Sonu ordered a smart pill test. This involves swallowing a capsule of electronics that, as it travels through the digestive tract, collects key information about the patient's gut, such as the speed of different parts of the journey, as well as pressure, pH and temperature.

Doutt's test showed that gastroparesis — slow stomach emptying — was the likely cause of her nausea. To help with the condition's symptoms, Sonu prescribed the drug mirtazapine — not for its typical use as an antidepressant but for its ability to suppress nausea and increase appetite.

The next step was to help Doutt start eating again, a complex task because she had become so wary of food. At first, her list of "safe foods" was tiny: sautéed spinach, mushrooms and egg whites, Hawaiian rolls — a soft, sweetened dinner roll — and coconut water. "I just ate the same thing every single day," Doutt said. "It stayed that way for over a year."

Some things can be explained

AS CHALLENGING AS Doutt's situation was, her gastroparesis could be diagnosed with the right test. Many patients have debilitating GI symptoms that no standard medical test can explain.

They might have visceral hypersensitivity, meaning normal gut physiology and hyperactive nerves. "We don't know why this hypersensitivity occurs," Spencer said, adding that scientists suspect a combination of genetic vulnerability and environmental insult. A patient might, for example, take antibiotics for an infection and have lasting symptoms.

Before coming to Stanford Medicine, such patients have often been told they have irritable bowel syndrome. Standard treatment for the syndrome leans heavily on cutting out foods.

"Patients have gone to five GI doctors and every doctor has told them to eliminate something from their diet," Spencer said. Some have been advised to start the low-FODMAP diet, discontinuing foods that contain fermentable oligosac-

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charides, disaccharides, monosaccharides and polyols, which may cause GI symptoms in some people.

In practical terms, this means patients stop eating wheat, dairy, legumes, and many fruits and vegetables. After a few weeks, they're advised to work with a dietitian to resume eating foods one at a time so they can pinpoint a few troublemakers to avoid, then return everything else to their diets. But some patients try the first phase of the diet, feel better and never expand what they eat, or have trouble getting access to a dietitian.

In extreme cases, "They say, 'I'm eating chicken and white rice, and that's all I can eat. I eat anything else and I get diarrhea, I get abdominal pain,'" Spencer said.

Severe dietary restrictions feed long-term problems — both psychological struggles and biological issues that Stanford Medicine researchers are investigating. The biggest biological problem is that a low-fiber diet banishes key gut microbes, which are difficult to get back.

Spencer is an early adopter of a diagnostic test that helps provide direct evidence of which foods are irritating an individual patient's intestines. Pioneered in Europe and marketed under the trade name Cellvizio, the test directly images the gut's response to specific foods. In an endoscopy procedure, the clinician adds a small amount of suspect food to the interior of the intestine, then uses confocal laser endomicroscopy to monitor for inappropriate migration of immune cells and leaking of blood vessels into the intestine.

"It's a pathophysiologic explanation for a food-induced leaky gut," Spencer said. The test can give patients a much faster path to a targeted list of foods they should avoid. Spencer hopes this will allow patients to bypass the risks to the gut microbiome that come with very restrictive diets, including low-FODMAP diets.

The mysterious gut-bug landscape

"IT'S HARD TO COMPREHEND the number of bacterial cells in our guts," said Justin Sonnenburg, PhD, the Alex and Susie Algard Endowed Professor and a professor of microbiology and immunology. His research on gastrointestinal microbiota helped attract Spencer to Stanford. We have more microbes in our guts than human cells in our entire bodies, a fact that prompted Sonnenburg to say, only half-joking, "We are a fancy culturing flask, here to acquire food to feed these microbes."

In healthy people, gut microbes break down plant fiber that we can't digest. The bugs' metabolic byproducts, such as short-chain fatty acids, are absorbed into our blood.

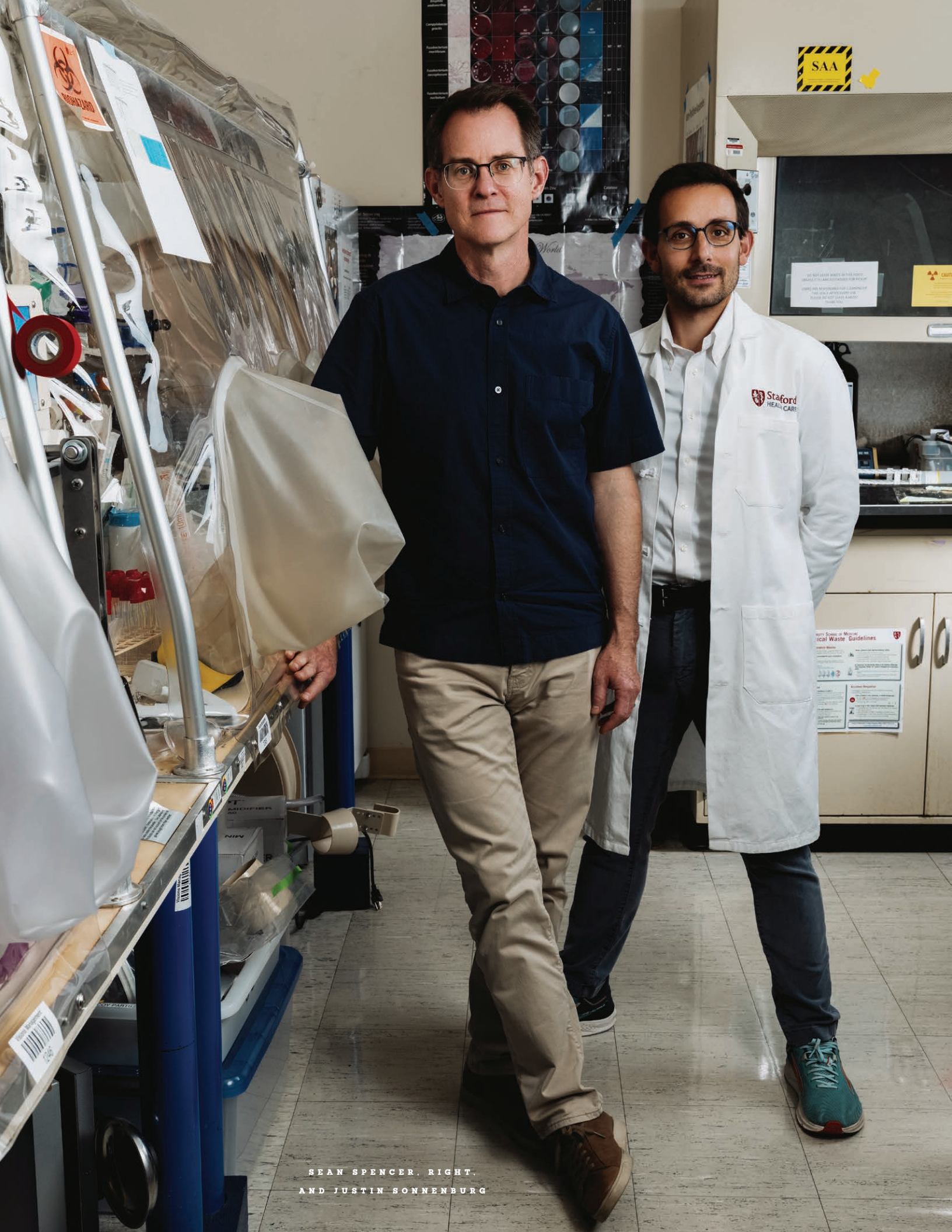
"They look like pharmaceuticals, little drugs, and they behave like drugs. We don't understand everything they are doing to influence our health, but they end up everywhere," Sonnenburg said. Studies hint at a variety of benefits from these bacterial byproducts, everything from keeping the immune system in check and lowering obesity and cardiovascular risks to improving bone and brain health. In short, we want these bugs on the job.

Sonnenburg's team has shown that gut microbes look quite different in people eating typical Western diets than among hunter-gatherer populations, who consume much more fiber. As we've industrialized and moved away from fiber-heavy ancestral diets, our gut microbes have shifted to use more oxygen and promote inflammatory host responses such as the generation of reactive oxygen species, aka "free radicals," that could contribute to inappropriate immune responses and chronic disease.

Worse, people with severe GI symptoms might eat so little fiber that their gut microbes starve. Not only are these patients deprived of beneficial bacterial metabolites, but the microbes also damage the mucus lining that normally keeps gut bugs away from the walls of our intestines.

"If you're not feeding the microbiome fiber, it starts eating you, consuming the mucus layer and causing inflammation," Sonnenburg said. "The adage 'Good fences make good neighbors' is true in the gut microbiome."

Spencer has another way to describe how we get along with our gut microbes: "In health, we feed our bugs and we have this close relationship; it's like a hug between us, our diet and our bugs," he said, knitting his fingers together to show what he means.



SEAN SPENCER, RIGHT, AND JUSTIN SONNENBURG

"Sometimes our bugs change, and then our diet changes, and rather than hugging, they're fighting. We want to reharmonize the gut."

He aims to practice restoration ecology for his patients. "I grew up in Wisconsin, where naturalist Aldo Leopold is a big figure because he pioneered the field of restoration ecology by working with nature to restore complex prairie ecosystems," he said. "It's kind of like that. The ecosystem is dysfunctional, and we're trying to reharmonize it. We need to understand which parts we can change. Do we manipulate the immune system? The microbiome? The diet? Ideally, we do it all in combination."

The gut-brain connection

As Stanford Medicine experts seek to understand the intestinal ecosystem, they are also putting knowledge about the gut-brain connection to work helping patients.

Not long after diagnosing Doutt with gastroparesis, Sonu referred her to other members of the Stanford team, including clinical psychologist Meredith Craven, PhD, who specializes in GI psychology. Craven teaches a class in hypnotherapy techniques that address gut-brain miscommunication, which Doutt took to help her cope with GI symptoms.

They also had individual appointments. In one of them, Craven asked Doutt to describe her relationship with food, a question she poses to every new patient.

"I remember what I said to her: 'I have always been a foodie. I love food!'" Doutt said. "And I was hating food."

Before she got sick, Doutt eagerly explored restaurants, flavors and tastes: "Spicy, seafood, raw, I'd try it." She could be particular — she'd order sauces on the side so she could decide how much she wanted — but approached food with an adventurous spirit. Now that was replaced with fear and frustration.

"I couldn't stand how every social interaction revolves around food," she said. "I felt very excluded."

Doutt's struggles are common among Craven's patients, so she recognized that Doutt met diagnostic criteria for avoidant/restrictive food intake disorder, which causes low food intake but isn't motivated by a desire to lose weight. Instead, patients fear food or the consequences of eating. It's not unusual for ARFID to develop in the wake of a disorder of the gut-brain interface; one study of more than 900 irritable bowel syndrome patients found that 13% had the eating disorder.

Craven uses cognitive behavioral therapy to help ARFID patients, starting with education about gut-brain communication. Stress — including worry about GI symptoms — arouses the autonomic nervous system, putting a person into a "fight or flight" state.

This, alone, makes the gut churn.

"Patients will say, 'Oh, see? I'm experiencing GI symptoms; I must not be able to eat this,'" Craven said. "It can become a self-fulfilling prophecy. The more you're avoiding food, the scarier it's going to become."

When she explains these connections to patients, they often have an Aha! moment. "They're like, 'That's me!'" Craven said. "They get a lot of hope. The whole idea is that if we can change one part of this cycle, we can change the rest."

With that motivation, Craven and her colleagues can guide patients through the next steps, such as the hypnotherapy class Doutt took, as well as exposure planning to help them reintroduce foods. In exposure planning, therapists ask patients to list every food and food-related situation they avoid and rank each one according to how much anxiety it provokes. Then patients pick some foods from the middle of the list — not too intimidating — to try.

At first, Doutt thought, "I don't want to risk anything! I'm OK, I'm eating the foods on my safe list and that's how I'm gonna live my life." But a Stanford dietitian pointed out that her safe list was so small it wasn't providing adequate nutrition. So Doutt joined an exposure therapy class at Stanford Medicine for a group of people in similar situations, which helped her expand what she was willing to eat.

"One of the days, I picked an avocado, and it was, OK, let's try one bite, and you talk through what worked for you and what your plan is." Another day it was three bites, then five. Participants talked about what they were feeling — "I had a little

'ONE OF THE DAYS, I PICKED AN AVOCADO, AND IT WAS, OK, LET'S TRY ONE BITE, AND YOU TALK THROUGH WHAT WORKED FOR YOU…' ANOTHER DAY IT WAS THREE BITES, THEN FIVE. WITH REPEATED EXPOSURES, DOUTT COULD TOLERATE ALL OF THE EMOTIONS AROUND EATING SOMETHING NEW.

discomfort but it wasn't extreme," for example. With repeated exposures, Doutt could tolerate all of the emotions around eating something new.

Foods to heal the microbiome

For patients like Doutt, who are making a journey back to a more varied diet, Spencer and his colleagues encourage gradual reintroduction of fiber-rich foods to provide a foundation for the right bugs to return to their intestines and set up housekeeping. "When people increase their fiber intake, we always say, 'Go slow and steady; your microbiome will adjust,'" Spencer said. He often suggests oats and sweet potatoes as the best starting points.

Fermented foods, such as yogurt, kimchi, miso paste and sauerkraut could also play important roles in restoring gut health. A Stanford Medicine team led by Sonnenburg; his wife and research partner, Erica Sonnenburg, PhD, a senior scientist; and Christopher Gardner, PhD, the Rehnborg Farquhar Professor and professor of medicine at the Stanford Prevention Research Center, conducted a study published in *Cell* in 2021 in which healthy people were randomly assigned to eat diets high in fiber or high in fermented foods for 17 weeks.

On the high-fiber diet, improvements in immune profiles were observed mostly in people whose microbiomes were diverse to begin with. But in the group eating fermented foods, more dramatic benefits accrued, including a gain in microbial diversity for all participants and decreased levels of immune markers of inflammation. The research team is now exploring which components of the fermented foods cause these changes, and how they work.

These findings feed into Spencer's research on more efficient, evidence-based ways to remodel the microbiome. Some patients have microbiomes so out of whack that a diet-only approach might never help, he said: "What I'm envisioning in the future is to identify the dysfunction in a patient's microbiome and fix it."

He'd like to be able to offer his patients better probiotics, for one thing. Currently, probiotics for sale at health food stores generally contain mixtures of bacteria similar to those found in yogurt; they don't match what lives in a healthy person's intestines. They are not designed to degrade fiber or integrate into the intestinal ecosystem.

To bridge the gap, a Stanford Medicine project, the Microbiome Therapies Initiative, led by Michael Fischbach, PhD, the Liu (Liao) Family Professor and professor of bioengineering, is identifying the right microbes and testing how to give them to people. Working with Spencer, the initiative's members are developing a combination of bacteria to give to patients with IBS based on previous work published in *Cell* in 2022.

During his time at Stanford, Spencer, with a diverse set of collaborators, has catalogued gut microbes at different locations along the 20-foot length of the small intestine. (Traditionally, assessments have been done only on the microbes present in poop, which offers a limited window to the digestive ecosystem.) They have collected microbes from locations along the intestines of deceased organ donors, as described in a study published in *Science* in 2022.

In addition, the scientists devised a method to sample what grows in different locations along the intestine in living people. In one study, researchers gave healthy volunteers sets of four capsules to swallow. Each capsule had a coating that dissolved at a different pH or time, corresponding to a different region of the intestine.

When the coating dissolved, a one-way valve was exposed, allowing the capsule to capture intestinal fluid. After the capsules were excreted, the researchers analyzed the contents to catalog which types of bacteria, phages (which are viruses that attack bacteria), human proteins and bacterial metabolites predominated in each intestinal region. They also measured bile acids — digestive acids produced by the liver and secreted into the intestine during digestion — and assessed how bacteria in different intestinal locations had modified the bile acids there.

The study found that, while fecal bacteria were fairly similar in everyone, small intestinal ecosystems had more variation between different healthy individuals. The findings, published in 2023 in *Nature*, laid groundwork for studies to understand how the microbiome changes in disease. The research was led by David Relman, MD, the Thomas C. and Joan M. Merigan Pro-

SPENCER AND HIS COLLEAGUES ENCOURAGE GRADUAL REINTRODUCTION OF FIBER-RICH FOODS TO PROVIDE A FOUNDATION FOR THE RIGHT BUGS TO RETURN TO THEIR INTESTINES AND SET UP HOUSEKEEPING. '...WE ALWAYS SAY, "GO SLOW AND STEADY; YOUR MICROBIOME WILL ADJUST."'

fessor and a professor of microbiology and immunology, and KC Huang, PhD, a professor of bioengineering and of microbiology and immunology.

Researchers also have early data showing that a few bad players might have taken over the microbiome of some people with digestive problems, so instead of fiber breaking down normally, the bacteria cause symptoms such as bloating or diarrhea.

The next steps are to figure out which bacteria from each gut locale are most important to restore, and whether it's possible to do that with a "next generation" of probiotic supplements designed to improve microbiome health. "It's a dream right now, but all the pieces are present," Spencer said.

A foodie again

TODAY, DOUTT IS PAST her miserable months of nausea. She's eating well, is still adding foods to her diet, and her ARFID is in remission. She has a toolbox of strategies to use when her symptoms flare, including the techniques she learned in the hypnosis class and occasional doses of Zofran. She has returned to social activities like dining in restaurants and enjoying holiday meals with her family.

She also has a deeper sense of gratitude for her partner, who has been steadily supportive. One Stanford psychologist long ago told Doutt that people who are struggling don't always want answers and directives; sometimes they just want someone to "sit in the puddle with them."

"I'm very lucky to have my partner, because he sat in the puddle with me for a very long time," Doutt said. She and Vanden Brand Horninge recently took a two-week trip to Ireland, London and the Netherlands, something she could not have imagined a few years ago. Although Doutt felt trepidation about eating away from home, she loved the "cozy weather food" in Ireland — mashed potatoes, gravy, comforting desserts. In the Netherlands, her partner, who is Dutch-Indonesian, wanted them to try some of the country's Indonesian food.

"It was really good, but definitely a little spicy, and that upset my stomach," Doutt said. "I was like, OK, I'm going to take a Zofran, I haven't taken one in a while, and I'm going to walk it off. I have things to distract me. It'll be fine."

It's a good example of how her strategies for handling symptoms have helped move food to a healthier position in her life. She once again considers herself a foodie, with caveats.

"I love food, but sometimes food doesn't love me. That's how I see it," she said. "And I don't know if I want to say that I'm thankful for it, but I think I have a better understanding of my body and truly who I am, mentally and physically.

That has been really nice." **SM**

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About ARFID

WHEN FOOD BECOMES THE ENEMY

Gut conditions tend to cause anxiety about eating — and that anxiety can be extreme, leading sufferers to develop a condition known as avoidant/restrictive food intake disorder, or ARFID. Though ARFID was designated as a new eating disorder in 2013, it's not yet widely recognized or understood. Fortunately, effective treatments are available. Here are some other facts about the condition:

- In avoidant/restrictive food intake disorder, patients don't eat enough. They can experience malnutrition.
- Patients are not trying to lose weight, nor are they worried about body image.
- ARFID patients experience sensory aversions to food or are afraid of possible consequences of eating, such as choking or nausea. They may have little or no appetite.
- The condition is most common in kids, including children with autism or attention deficit hyperactivity disorder, but it can develop in anyone, at any age. It affects more than 10% of people with disorders of the gut-brain interface.
- ARFID isn't the same as picky eating, which does not interfere with getting enough nutrients and often resolves on its own. ARFID needs treatment.
- Treatment includes cognitive behavioral therapy, starting with helping patients identify motivations for change. Treatment also helps them understand how their thoughts and behaviors concerning eating may harm their health.
- As part of treatment, patients may list foods they avoid, then slowly reintroduce them during planned exposures. They practice building tolerance to sensory and emotional challenges as they eat, with guidance from a therapist or doctor.

a taste of health

UNCOVERING THE ROLE OF DIET IN PREVENTING AND TREATING DISEASE

We've all heard the adage, "An apple a day keeps the doctor away." But despite the common-sense connection between diet and health, until recently, nutrition hasn't been a core focus of modern medicine. Today, that's quickly changing as researchers discover new links between what we eat and our physical and mental health. Increasingly, scientists are recognizing that food can be a potent preventive and therapeutic tool, affecting everything from heart health to psychiatric symptoms.

By Katia Savchuk

ILLUSTRATIONS BY GÉRARD DUBOIS


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"Despite all our drugs and devices and spending more on health care, Americans' health is not as good as that in most developed countries," said Christopher Gardner, PhD, the Rehnborg Farquhar Professor and a professor of medicine. "The power of food, which is so basic and less expensive, is becoming clearer and clearer."

Gardner is one of the Stanford Medicine researchers who are at the forefront of unearthing how diet affects well-being, paving the way for nutrition to become an integral component of medical education and patient care.

The link between diet and mental health

WHEN SHEBANI SETHI, MD, was a resident training at an obesity clinic, she encountered a 31-year-old patient who needed help losing weight for medical reasons. The woman also had schizophrenia that had not responded to multiple medications or to electroconvulsive therapy. The physician overseeing her care prescribed a ketogenic diet — one high in fat, moderate in protein and low in carbohydrates.

The patient lost weight, as intended. But Sethi observed another outcome: Her psychiatric symptoms also improved. "She saw major reductions in her hallucinations and delusions, and that really intrigued me," said Sethi, a Stanford Medicine clinical associate professor of psychiatry and behavioral sciences.

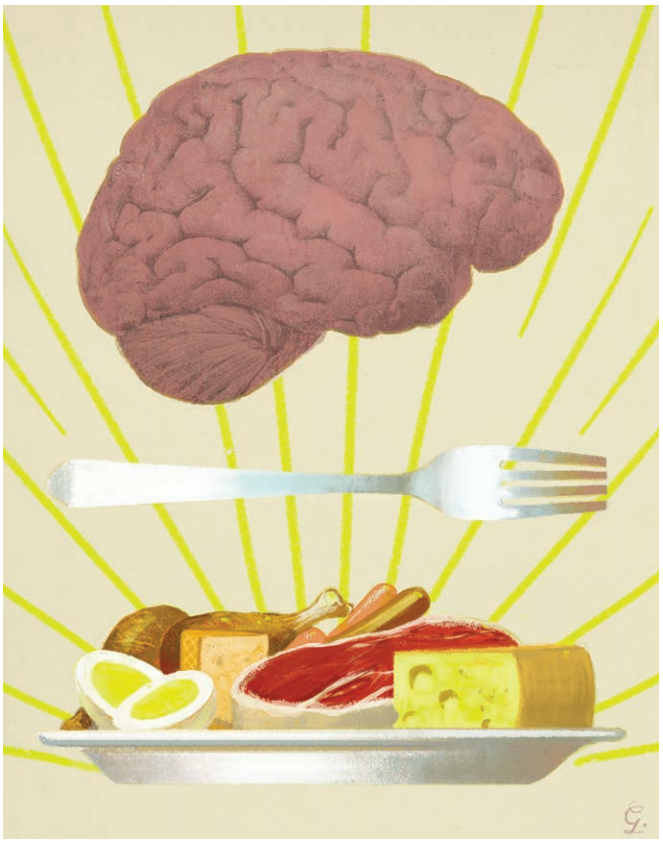
As a medical student and resident training in psychiatry and obesity medicine, she often saw patients struggling with physical ailments such as diabetes and hypertension, along with mental health problems, such as treatment-resistant depression or schizophrenia. Sethi observed that the issues were treated largely in isolation. "To me, it made sense to address both simultaneously and collaboratively so patients have better outcomes," she said.

In 2015, while still a resident, Sethi coined the term "metabolic psychiatry" and founded the nation's first clinical research program in metabolic psychiatry at Stanford Medicine. The discipline focuses on exploring how disruptions in the body's process of converting food into energy, known as metabolism, contribute to mental illness. Research has linked psychiatric conditions including depression, bipolar disorder and schizophrenia to metabolic dysfunction, such as insulin resistance and mitochondrial abnormalities. Metabolic psychiatry offers a way to shift how these disorders are understood and new avenues for treatment, such as diet and medications that address metabolic issues.

Sethi's most recent research, published in *Psychiatric Research* in March 2024, provided preliminary evidence that the effect she observed in her patient with schizophrenia was not an anomaly. Sethi and her team recruited 21 participants, including five with schizophrenia and 16 with bipolar disorder, who were either overweight or had a metabolic condition, such as insulin resistance or high cholesterol. Each followed a keto diet that prioritized high-fat foods including nuts, cream and oils and avoided high-carb options including starchy fruits, bread, pasta and sugar.

After four months, participants who stuck to the diet experienced significant weight loss, a 27% drop in a measure of insulin resistance and a 36% drop in fat located deep in the abdomen. Their mental health improved, too: Patients with schizophrenia showed a 32% reduction in the intensity of their psychiatric symptoms. Among all participants, the severity of mental illnesses improved by an average of 31%, as measured by the Clinical Global Impression scale, a tool clinicians use to track patients' psychiatric conditions. Life satisfaction also jumped by 17%, and sleep quality improved by 19%.

"This was the first clinical trial done since 1965 with a ketogenic diet in both bipolar illness and schizophrenia, and the outcomes are quite encouraging and worthy of further exploration," Sethi said. The reason the diet may help, she noted, is likely that it leads the body to use fat instead of sugar as fuel,



producing chemicals known as ketones. Many patients with psychiatric conditions show signs of struggling to efficiently process sugar in the brain, according to Sethi. Ketones can serve as a more efficient energy source that "circumvents the pathway where we're seeing metabolic deficits," she said, improving cognitive function.

The field is expanding quickly. In another pilot study, published in February 2025 and led by researchers at the University of Edinburgh, scientists asked people with bipolar disorder — regardless of whether they had a metabolic condition — to follow a keto diet for six to eight weeks. Participants saw their weight and blood pressure fall. The researchers also noted that higher levels of ketones were linked to higher mood and energy levels and to lower impulsivity and anxiety. Sethi is aware of more than 10 other studies around the world exploring the effects of a keto diet on various mental health conditions.

In March 2025, Sethi and her team launched a randomized clinical trial to evaluate the effects of a keto diet on around 120 people with bipolar disorder, schizophrenia and major depressive disorder, some but not all of whom are diagnosed with metabolic dysfunction. The study, which is expected to be completed in 2028, will assess changes in well-being, quality of life, cognitive function and severity of symptoms, along with detailed measures of metabolic function.

Despite promising findings to date, Sethi doesn't recommend that patients switch to a keto diet independently. "It's not safe to do it on your own, especially when you're taking medications or have health conditions such as psychiatric illness or diabetes," Sethi said. "You need to be followed by someone who has expertise."

Still, Sethi said everyone's mental health would benefit from a more nutritious diet, including eating fewer refined carbohydrates and ultra-processed foods. "It may not move the needle on psychiatric symptoms, but these things are going to be helpful — there's no question," she said.

The benefits of a vegan diet

IN THE FALL OF 2021, Gardner received a call from Louie Psihoyos, the director of a Netflix documentary series called *You Are What You Eat*. He asked if Gardner wanted to oversee a research study that would be featured on the show. Funding was available, and the filmmaker promised his team would recruit participants. But Gardner had to agree to two criteria: evaluate a vegan diet and study identical twins.

"Wow, this is cool!" Gardner thought at the time. He had spent decades researching the effects of specific foods and supplements, as well as popular diets, such as Atkins, vegetarianism and the Mediterranean diet. So he jumped at the opportunity to evaluate a strictly plant-based diet, especially in identical twins. For the director, this approach was mainly a tactic to attract viewers; for Gardner, it added scientific rigor.

First, he decided to explore whether eating a vegan diet would improve heart health. To find out, Gardner and his team conducted a randomized controlled trial with 22 pairs of identical twins without cardiovascular disease who'd been eating standard American fare. All participants were asked to follow a healthy diet for eight weeks that prioritized vegetables, legumes, fruits and whole grains and avoided sugars and refined starches. One twin in each pair, however, avoided meat, dairy and other animal products.

The study, published in *JAMA Network Open* in 2023, found that the twins who ate a vegan diet had larger drops in low-density lipoprotein cholesterol (sometimes called "bad" cholesterol), fasting insulin level and weight, on average, than their siblings. These improvements are linked to a lower risk of heart attacks and cardiovascular disease.

Next, Gardner and his team wanted to know whether eating a plant-based diet slows down physical aging. In a parallel analysis published in *BMC Medicine* in 2024, they observed that the twins who followed a vegan diet showed differences in DNA methylation, a chemical process that affects how genes are expressed, and the length of telomeres, protective caps at the ends of chromosomes. This suggested that the twins who ate a plant-based diet were aging significantly more slowly on a

cellular level than the omnivorous twins.

"In just eight weeks, vegans improved their biological age," Gardner said, "They were metabolically healthier."

Gardner's approach reflects a shift in nutrition research, from a focus on individual nutrients to specific foods and now to dietary patterns. Plant-based diets have such a positive effect, he said, because they're higher in fiber, antioxidants, certain vitamins and minerals, and unsaturated fat, and they're lower in saturated fat and cholesterol, as well as the hormones and antibiotics often found in animal products. But going vegan alone isn't enough: "This was a healthy vegan diet — not French fries, Oreos and Coke," Gardner said.

You don't have to avoid meat entirely to benefit from eating more vegetables, fruits, legumes, nuts and seeds. Americans, who eat more meat than residents of almost every other country, could cut back considerably, and Gardner pointed out that any increase in plant-based foods is likely to have some positive effect.

"The conclusion wasn't that the world should go vegan — I don't think that's practical for a lot of people," he said. "But when clinicians are advising patients, they can feel a little more confident that this diet has multiple benefits."

Gardner became a vegetarian in 1983 and has been vegan for 15 years. "Every once in a while, if there's a cookie, I don't ask if there's dairy in it," he said. "I'm a pretty healthy 65-year-old."

Cooking for health

AROUND A DECADE AGO, when Michelle Hauser, MD, was a postdoctoral research fellow at Stanford Medicine, she joined a task force to improve how medical students learn about nutrition. As was the norm at medical schools, the required curriculum included sparse lectures on the topic, largely focused on biochemistry, and student feedback was negative. "They had trouble seeing the connection to medicine," said Hauser, a clinical associate professor of surgery and of medicine.

This wasn't the first time she encountered skepticism about the role of nutrition in medicine. Throughout her medical education, she observed a defeatist sentiment among doctors about patients considering nutrition in their care: "People won't eat healthy. Don't waste your time. Just prescribe medicines."

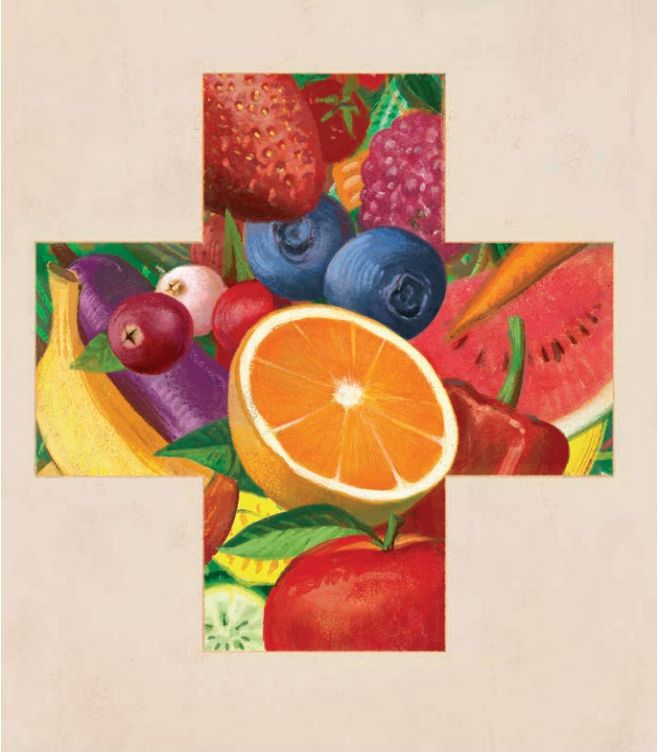
Hauser wasn't buying it. She had trained as a chef at Le Cordon Blue and spent time in the kitchen of Chez Panisse, a Bay Area restaurant known for its focus on farm-to-table cuisine, then taught sold-out classes in healthy cooking. She knew that diet and other lifestyle changes were critical for promoting well-being. The only way to get people to eat nutritious meals, she believed, was to make them delicious. "It's not that people don't want to eat healthy food," she said. "People don't want to eat food that doesn't taste good."

In January 2017, while still a postdoc, Hauser launched an elective course in culinary medicine, which combines evidence-based nutrition and culinary skills to help providers guide patients toward healthier diets.

She secured a small grant and donated her time to develop the curriculum, which includes eight sessions on topics including sautéing, roasting and healthy breakfasts. Medical and physician assistant students cook and share a wholesome meal, then absorb a lesson on nutritional topics such as healthy proteins, fiber and techniques for counseling patients. They also participate in a discussion board where they practice advising a hypothetical patient on dietary changes.

Hauser said the course, which remains popular, transforms students' own diets, as well as their ability to offer clinical guidance. Surveys comparing students who took the class to those wait-listed have shown a significant difference in knowledge, attitudes and behaviors about cooking and nutrition, she said.

"Students get the importance of nutrition when they're do-



ing it hands-on instead of just learning about it in lectures," Hauser said. "It's much more effective."

In December 2019, Hauser collaborated with the American College of Lifestyle Medicine, where she later became president-elect, to publish a culinary medicine curriculum based on her course. It's free online at stan.md/CulinaryMedEd and has been downloaded more than 12,000 times by people in more than 100 countries.

Hauser is publishing a second edition in October 2025 that includes videos of knife skills and recipe preparation and shares nutrition information. She said she hopes the curriculum makes it easier for medical schools and health professional education programs to teach culinary medicine, even if they lack specialized instructors or kitchen facilities.

With the American College of Lifestyle Medicine, Hauser has also launched a free website, stan.md/CulinaryMed, that translates course materials for the general public and includes educational handouts. In addition, she's developing a training course for health professionals that will be the basis of a board certification exam in culinary medicine.

Hauser is heartened to see that interest in culinary medicine is growing but, for her, change can't come fast enough. "Our patients come to us thinking we know about nutrition, but so much of our medical training isn't focused on that," she said. "We need to understand the mechanics of how things work, but we're missing an important tool if we're not trying to translate that into material we can talk to patients about."

Prescriptions for food

JANICE OWENS took pride in cooking recipes passed down through generations — fried chicken, corn bread, mac and cheese, potato salad. But after years of too much fried food and not enough fruits and vegetables, her health was suffering. Owens, 62, lives in Castro Valley, California, and was struggling with high blood pressure and depression. Severe arthritis made movement painful, and she could make it only a short distance with her walker before taking a break.

Then, in December 2024, Owens' doctor at Hayward Wellness, a primary care center in the Alameda Health System, referred her to Recipe4Health, a three-month program that sent her weekly deliveries of fresh produce through what was dubbed a "Food Farmacy." She also participated in a "Behavioral Pharmacy," weekly group health coaching meetings led by a community organization called Open Source Wellness. Sessions covered topics such as deciphering food labels, healthy recipes, movement and stress reduction.

Owens learned to switch from white rice to brown, to sauté instead of deep fry, and to cut back on salt and instead use seasoning blends. She picked up stretches that helped with her arthritis, and her daily walks grew longer and less painful; sometimes, she even traded her walker for a cane. She started taking her blood pressure medication regularly, quit smoking and took up meditation. As a result, her blood pressure dropped, and her mood improved.

"It really kind of changed my life," said Owens, who extended her participation in Recipe4Health for three months.

"Produce prescriptions," which subsidize access to healthy foods and nutrition education, are one pillar of Food as Medicine, a growing movement that promotes access to nutritious foods as a tool for improving health and treating disease.

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'STUDENTS GET THE IMPORTANCE OF NUTRITION WHEN THEY'RE DOING IT HANDS-ON INSTEAD OF JUST LEARNING ABOUT IT IN LECTURES. IT'S MUCH MORE EFFECTIVE.'

MAKING IT EASIER TO REAP THE MOLECULAR BENEFITS OF EXERCISE

farewell to the couch

By Amy Adams

ILLUSTRATION BY BRYCE WYMER

EXERCISE: a panacea for what ails you, but also kind of sweaty. And time-consuming. And tiring. It's not for everyone, even if the benefits are without question. Regular exercise has been linked to lower risk of cardiovascular disease, forms of cancer, diabetes, stroke, mental health conditions, low bone density, arthritis and much more. The relationship between exercise and health is so strong Stanford Medicine's Euan Ashley, MB ChB, DPhil, chair of the Department of Medicine, has called it, "the most powerful drug we've ever known." He said, "Every single system in the body, every single organ of the body, every single disease we've ever looked at — there's a benefit to exercise."

The question is how to deliver the undeniable health benefits of exercise to more people. Could it be packaged into a less sweaty, less time-consuming pill? Barring that, could exercise be made easier to swallow? Research underway suggests a pill isn't likely, but there are several approaches being tested for sneaking exercise into busy lives.

IMPACT OF A WORKOUT

ANSWERING THE QUESTION OF whether a drug could mimic exercise requires knowing what exercise does for and in the body. That's the subject of a 23-center research effort funded by the National Institutes of Health called Molecular Transducers of Physical Activity Consortium (MoTrPAC), which is intended to identify how, at the molecular level, exercise improves and maintains healthy organs and tissues.

Ashley is an investigator on MoTrPAC (pronounced "motor pack") along with Michael Snyder, PhD, the Stanford W. Ascherman, MD, FACS Professor in Genetics; Stephen Montgomery, PhD, the Stanford Medicine Professor in Pathology and a professor of genetics and of biomedical data science; and Matthew Wheeler, MD, associate professor of cardiovascular medicine.

For the initial portion of the MoTrPAC project, the group studied 344 rats running on miniature treadmills, taking samples from 19 tissues and measuring differences in every available molecule: DNA changes, differences in proteins or types of lipids present, increases or decreases in which genes are active, changes in immune cells present in the tissue. If the scientists could measure it, the molecules were in the study.

The group published six consecutive papers in spring 2024 with the initial rat data and are now turning their attention to humans at a range of life stages, sampling only easily accessible blood, fat and muscle. The results from the human studies are not yet in.

The initial papers showed that, at least in rats on treadmills, what's happening through exercise at the molecular level is sweeping.

"There was a whole-body response to exercise," said Ashley, the Roger and Joelle Burnell Professor in Genomics and Precision Health and the Arthur L. Bloomfield Professor in Medicine, who is a devotee of all ball sports. His lab has a regular Friday soccer game that brings together data analysts, research fellows, software developers, graduate students and Ashley in a fast-paced yet friendly game. "I was sport mad," Ashley said of his childhood in Scotland. "There were days as a kid I would play a rugby game in the morning for my school, then play soccer in the afternoon for my local boys' club, and then I'd go to a sports club in the evening. I played sport all day."

"Basically, all tissues respond in some way, not just the obvious tissues, like muscles, heart and lungs," Ashley said of the rats in the study "Every single organ had changed with training and changed quite dramatically."

Looking at the molecular data, Ashley said the rats looked like completely different animals when sedentary versus after eight weeks of rodent boot camp. The changes are so systemic that both Ashley and Montgomery said it's unlikely there can ever be a pill to replace the effects of exercise.

"I think what we learn from these studies looking at rats is that it would be very hard to mimic the benefits of exercise synthetically," Montgomery said. "It's not likely that we could create a synthetic exercise pill so you could be sitting in the office not doing anything and you're going to get all of these benefits of exercise." Montgomery is a self-proclaimed weekend warrior focusing on running and gym workouts. "Every day, I wake up and I'm like, how do I fit exercise in?" he said, "And many days I can't."

The rat data (and eventually human data) is publicly available to other groups of researchers who want to dig into their own disease, organ or molecular pathways of interest.

Those studies could help re-create the benefits of exercise at least in particular organs, tissues or diseases. For example, a more detailed understanding of how exercise influences molecules associated with a type of cancer could lead to drugs or other therapeutics that further reduce the risk in people with a family history, or it could reveal new treatments or recommendations. Or these studies could one day provide personalized exercise advice based on disease risk and life stage, Montgomery said.

Supported in part by the NIH and the Wu Tsai Human Performance Alliance, Montgomery and Ashley are exploring ways their discoveries about exercise can be used to benefit humans.

A PRESCRIPTION FOR EXERCISE

IF EXERCISE ACTS LIKE A DRUG IN THE BODY, scientists from the American College of Sports Medicine want physicians to treat it as such. They have launched a program called Exercise is Medicine, which encourages health care providers to consider physical activity as standard of care. They recommend recording a person's physical activity levels as a vital sign and concluding appointments with exercise prescriptions. Their website offers printable prescription pads for exercise.

Shuchi Anand, MD, Stanford Medicine associate professor of nephrology, ran a pilot study with collaborators at Emory University testing the Exercise is Medicine model in people with chronic kidney disease. Doctors involved in the study

wrote participants a prescription for a group exercise class they'd organized with a local provider. Anand said people in the study were enthusiastic about the opportunity, but many still struggled to follow through on attending class. She's now conducting a similar study called Sit Less, Interact and Move More in collaboration with researchers at the University of Utah, also in people with kidney disease. This study provides resistance training coaching to people with kidney disease, with the goal of helping people continue exercising beyond the study period.

"We know that exercise is beneficial for everyone with kidney disease," Anand said. Past studies have shown that people with kidney disease who are more physically active have slower disease progression and live longer.

Anand called exercise "a whole-body intervention" and said, "The magnitude of its effect is the same as some of the most expensive medicines we have for kidney disease."

The challenge, she found, is getting people to stick with it.

"When we first approach people about these studies they are excited," Anand said. "But as time moves on, people do lose motivation."

Anand jogs 20 minutes a day on a treadmill and has started trying to incorporate yoga and weights. "I'm a work in progress just like everyone else," she said. She also looks to her step counter for motivation.

BUT THE SWEAT …

THIS QUESTION OF MOTIVATION REMAINS the biggest challenge in helping more people gain the health benefits of exercise.

Marily Oppezzo, PhD, is looking at ways to overcome one barrier: the time commitment. Oppezzo, whose background is as a behavioral scientist, advocates exercise in 30-second to five-minute doses, which she and others call "exercise snacks." These can include doing jumping jacks while lunch heats in the microwave, or a particularly adorable "pet the puppy" exercise that involves bending to pet an imaginary puppy then stepping over the imaginary puppy, on repeat. (Left out of the description is the potential mental health benefit of interacting with imaginary puppies.)

Oppezzo is an instructor of medicine at the Stanford Prevention Research Center, a personal trainer and an extremely tough power yoga teacher. "I mostly love strength training," she said of her own exercise regimen. "I'll do intervals because I have to, but I love strength." She is running several studies, each looking at ways to help people incorporate exercise snacks into their daily routines. One technique that has been shown to work is to give people something visible such as wristbands to indicate the number of times they are supposed to move.

"It takes the reminder out of your brain and onto the world," she said. Other people use Post-it notes on their computers, or bands on their water bottles.

To make it easier for study participants, she is producing short exercise videos people can follow at work — she even has recommendations for exercises that can be done in a bathroom stall.

Even with the short duration and multiple options, Oppezzo said follow-through remains the biggest challenge. That's where the work of Abby King, PhD, comes in.

'BASICALLY, ALL TISSUES RESPOND IN SOME WAY… . EVERY SINGLE ORGAN HAD CHANGED WITH TRAINING AND CHANGED QUITE DRAMATICALLY.'

King, the David and Susan Heckerman Professor and a professor of epidemiology and population health and of medicine, has focused primarily on turning exercise into a habit. Her lab runs a program called Active Choices, which provides materials to train professional health educators and peer mentors to offer phone-based motivation to help people be active. She has also been working with colleagues at the Stanford Institute for Human-Centered Artificial Intelligence, including doctoral student Matthew Jörke, to develop an AI model designed to mimic the role of a live Active Choices adviser. In an additional series of "human versus computer" physical activity intervention studies that King and her team have conducted over the past several decades, they have demonstrated that the Active Choices counseling method can also be effectively delivered through interactive voice menu systems, text messaging and an artificial intelligence-enabled virtual agent. The virtual agent, named Carmen, used interactive facial expressions and, like the texting program, could communicate in both English and Spanish. Carmen provided personalized feedback and assistance with goal setting via on-screen prompts.

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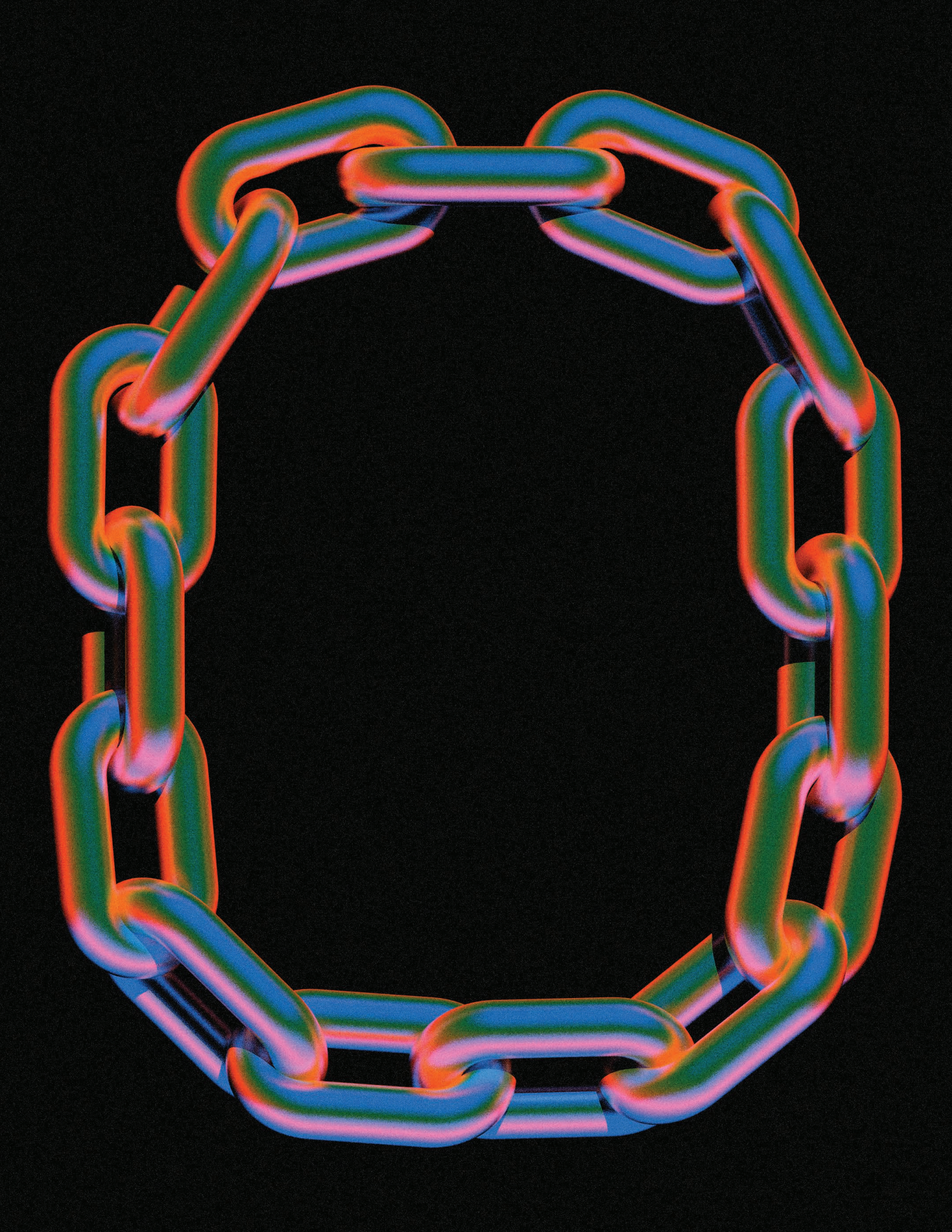

How past microbial incursions can lead to neurodegenerative diseases

INFECTION CONNECTIONS

For most of human existence, getting sick has meant getting infected by a microbe. A viral, bacterial, fungal or parasitic infection was the chief reason many — if not most — kids didn't survive childhood, much less grow up to have kids of their own. Evolution has shaped our immune system accordingly, priming it to fight off infectious disease and keep us alive into adulthood and not worrying too much about things that happened after we succeeded in warding off the acute effects of microscopic pests and pestilences.

By Bruce Goldman

ILLUSTRATION BY KARAN SINGH

Yes. We still catch colds, flus, COVID-19 and other diseases caused by infectious microbes. But by and large, the torch of health problems has been passed to chronic diseases — neurodegenerative disorders, autoimmune diseases, cardiovascular troubles, cancer and more — that crop up as we reach childbearing age and beyond.

Gathering evidence indicates that some of these conditions may owe their existence to earlier acute microbial infections. The causal connections aren't always obvious, because the acute infectious episode and the chronic sequel may be separated by decades.

If we knew which infectious microbes cause, or contribute to, which chronic diseases (still mostly a big if), we might know when and how to intervene before the one gives rise to the other. After all, it's got to be a heck of a lot easier to cure or prevent an infection than to undo, decades later, the damage to our organs and tissues that infection set in motion. It would be like handing Humpty Dumpty a seat belt before the fall.

Here are some stories of how Stanford Medicine investigators, among others, have pieced together disparate clumps of evidence to tie acute infections to chronic conditions.

INFLUENZA AND PARKINSON'S DISEASE

Say what you like about the COVID-19 pandemic of recent years, the influenza pandemic that swept the world in and around 1918 was arguably far worse.

That virus infected one-third of the globe's population, killing 50 million people. In a single year in the United States, the pandemic knocked 12 years off people's life expectancy.

Strangely, said Victor Henderson, MD, a professor of epidemiology and population health and of neurology and neurological sciences, "a number of recovered pandemic-flu patients developed a movement disorder that looked a lot like Parkinson's disease."

The experience of the 1918 pandemic made flu infection a prime suspect.

So, Henderson and colleagues at Stanford Medicine, Harvard Medical School and Aarhus University Hospital in Denmark looked into it. Denmark's national health service maintains scrupulous records of that country's population, including data on patients' doctor visits, physicians' diagnoses and hospital stays. The investigators probed 61,626 patients' records for any links between an influenza infection and a later diagnosis of Parkinson's. They knew that 10,271 of the patients they selected had eventually received Parkinson's diagnoses.

Henderson and his associates found, in a study published in 2021 in *JAMA Neurology*, that an influenza diagnosis equated with a 70% increase in risk for Parkinson's disease 10 or more years down the road. By 14 years after a flu diagnosis, that risk increase had risen to 90%.

"The risk was specific for influenza, not any other infectious disease, and this increased risk showed up only a decade or more after the viral infection," Henderson noted. "That makes sense, because Parkinson's disease takes a long time to manifest. You wouldn't expect it to be caused by an illness that occurred just a few months or a couple of years ago."

Why the connection? That's far from clear, although Henderson said that the flu typically triggers systemic inflammation (that's what makes you feel rotten), which has been implicated in numerous chronic diseases.

Flu is no fun. Parkinson's disease is worse. Might getting vaccinated for seasonal influenza help stave off Parkinson's? That's an open question, difficult to answer definitively, Henderson said, because to set up a credible observational study, "you'd need a country with a large group of unvaccinated people and with great health records." That combination doesn't come along often. But sometimes, it does.

SHINGLES AND DEMENTIA

A quirky decision by another national public-health authority, this time Welsh, enabled Pascal Geldsetzer, MD, PhD, an assistant professor of primary care and population health, to show that getting vaccinated against shingles protects people against dementia.

In 2022, Geldsetzer began to take a hard look at the results of a 2013 national shingles-vaccination rollout in Wales. He got hold of a detailed database kept by the Welsh government, which had decided to make the then-dominant shingles vaccine, Zostavax, available for free to all citizens age 70 and older who hadn't turned 80 by Sept. 1 of that year. Anyone born more than 80 years before that date, even by one day, was out of luck — they'd have to spend their own money to get the vaccine.

"They were ineligible for life for a free shot," Geldsetzer said. "It was a raw deal for them. They could still go out and pay for one, but very few did."

Geldsetzer zeroed in on the many hundreds of people born just before, or just after, the cutoff date. These 80-year-olds were virtually indistinguishable in every way except for being a week or two apart in age — and, obviously, in their probability of being vaccinated against shingles.

"They were all alike, except for that," Geldsetzer said. "They had everything in common but their birth dates. Here we had this beautiful natural experiment — a scenario in which we have randomization just as would happen in a clinical trial, but done by nature, not by the investigator."

The scientists followed those two groups for up to eight years and showed that the vaccine clearly reduced shingles incidence — no surprise, given that clinical trials of Zostavax had shown reductions of around 60% over five years.

More interesting was another result: Vaccination had a pronounced protective effect on the incidence of dementia.

"Our findings strongly implied that 1 in 5 new dementia diagnoses among unvaccinated people could have been averted by vaccination," Geldsetzer said. "If these are truly causal effects, then getting vaccinated for shingles is far more effective, far less risky and much less expensive than anything else out there now for dementia."

Geldsetzer's findings were published in *Nature* in 2025. He and his colleagues have since seen similar results in studies conducted in several other countries where arbitrary age cutoffs were imposed on shingles-vaccine eligibility.

What does getting vaccinated for shingles have to do with preventing dementia in the first place? That's not certain, but there are hints.

The virus responsible for causing shingles, varicella zoster virus or VZV, is the same one that causes chickenpox. It used to be that everyone got chickenpox, an immensely contagious disease, in childhood. Since the advent of a vaccine, routinely administered to kids in the United States since the 1990s, not many do.

VZV is a member of the herpesvirus family, some of whose members are neurotropic: They preferentially target the nervous system. After causing a bout of chickenpox, VZV hibernates in our sensory nerves for the rest of our lives.

"The virus plays hide-and-seek with the immune system," Geldsetzer said. As we age and our immune surveillance weakens, the dormant virus can reactivate and make its way down our sensory tracts to the nerve endings at the surface of the skin, where it pops out and brings on the painful patchy rash we call shingles.

A link between neurotropic viruses and dementia diagnoses has been known for a while, Geldsetzer said. But it took a massive natural experiment to convincingly nail down VZV, in particular, as a culprit.

It's smart to get vaccinated for shingles, Geldsetzer said.

But how about younger people who've been vaccinated for chickenpox? "They could still be infected," Geldsetzer said, "About 15% of vaccinated people still do get chickenpox, although it's typically only a mild case. Besides, if the protection is due to some still-unknown broader mechanism — say, a vaccination-induced boost to the immune system that's independent of viral infection, then it doesn't matter whether you carry VZV or not."

'IF THESE ARE TRULY CAUSAL EFFECTS, THEN GETTING VACCINATED FOR SHINGLES IS FAR MORE EFFECTIVE, FAR LESS RISKY AND MUCH LESS EXPENSIVE THAN ANYTHING ELSE OUT THERE NOW FOR DEMENTIA.'

Another question: Was it prevention of herpes or the generation of an immune response to Zostavax that was performing the protective trick?

"We don't know," Geldsetzer said. That matters, because there's a new kid on the block: Shingrix, a shingles vaccine introduced in 2017. Shingrix, whose composition is substantially different from Zostavax's, might prove even more protective against dementia than Zostavax was, Geldsetzer said, because it's more effective than Zostavax was in reducing viral reactivation — by upward of 90%, in clinical trials leading to its approval.

Or it might not.

Geldsetzer is seeking funding from private foundations and philanthropy to start a clinical trial to find out. He also intends to extend his previous studies' findings by incorporating cognitive-performance tests rather than simply settling for dementia diagnoses. And he wants to unravel the precise mechanism by which shingles vaccination protects people from dementia.

EPSTEIN-BARR VIRUS AND MULTIPLE SCLEROSIS

Another herpesvirus, Epstein-Barr virus, or EBV, has been tied to a different neurological condition: multiple sclerosis.

About 1 million people in the United States and 3 million globally (nearly three-fourths of them women) have this autoimmune disease.

Our immune system attacks cells and proteins it deems suspicious: belonging, perhaps, to a bacterial or viral pest. Blessedly, the immune system has been trained in early fetal and childhood development to recognize our own proteins as perfectly normal and to be nice to them.

But that peace treaty isn't perfect. Now and then, the immune system becomes sensitized to a "self" protein toward which it should show forbearance and becomes angry instead. That's what's called autoimmunity.

Multiple sclerosis is but one of more than 100 identified autoimmune disorders. In this disorder, the immune system attacks brain cells called oligodendrocytes, whose job is to wrap our neurons in fatty coatings that insulate neurons electrically and vastly speed up signal transmission in the brain.

The attacks leave patches of "bare wire" on random neurons, resulting in a grab bag of defective circuits. And while their exact location in the brain varies from patient to patient, these patches are uniformly the hallmarks of multiple sclerosis. Symptoms depend on where the destruction has occurred.

Some 20 or more studies have provided epidemiological evidence suggesting a link between EBV and multiple sclerosis, said Tobias Lanz, MD, an assistant professor of medicine at Stanford's Institute for Immunity, Transplantation and Infection and in immunology and rheumatology. Virtually 100% of multiple sclerosis patients were infected with EBV before they were diagnosed with MS.

But that's not definitive proof, Lanz said. Understanding the evidence he and his colleagues unearthed requires an excursion into the land where virology meets immunology.

EBV, one of nature's most successful viruses, is living the dream. No vaccine is yet available, and the vast majority of us humans are infected by EBV by the time we reach age 25. While typically asymptomatic, the infection can trigger an acute condition called mononucleosis (also known as "the kissing disease" because it's most commonly transferred through saliva). Symptoms — including fever, sore throat, severe fatigue, swollen lymph nodes and feeling rotten — can last for weeks before fading away.

The Epstein-Barr infection itself, though, is a life sentence because the virus uses our cells as safety-deposit boxes for its genes, which are the recipes for its proteins. More than 95% of the human population, however otherwise healthy, is carrying EBV's dormant genetic material inside their B cells (the antibody-producing cells of the immune system) and salivary glands — without ever becoming too sick to continue transmitting the virus to others.

Lanz was the lead author of a 2022 paper in *Nature* that pieced together an explanation of why an Epstein-Barr infection is a necessary prelude to multiple sclerosis. He worked with colleagues including Stanford Medicine faculty members William Robinson, MD, PhD, the James W. Raitt, MD, Professor and a professor of immunology and rheumatology; Law-

THE IMMUNE SYSTEM HAS BEEN TRAINED IN EARLY FETAL AND CHILDHOOD DEVELOPMENT TO RECOGNIZE OUR OWN PROTEINS AS PERFECTLY NORMAL AND TO BE NICE TO THEM. BUT THAT PEACE TREATY ISN'T PERFECT.

THE TEAM WAS WONDERING WHICH PROTEINS IN THE BODY HAD FEATURES THAT COULD CONFUSE THE IMMUNE SYSTEM INTO REVVING UP AND CAUSING MULTIPLE SCLEROSIS.

rence Steinman, MD, the George A. Zimmermann Professor and a professor of pediatrics and of neurology and neurological sciences; and Chris Garcia, PhD, the Younger Family Professor and a professor of molecular and cellular physiology.

In 2015, Lanz was a postdoc in Robinson's lab. The team was wondering which proteins in the body had features that could confuse the immune system into revving up and causing multiple sclerosis. If they could find the culprit, they reasoned, it might be possible to find some way to prevent this confusion and treat or prevent the autoimmune disorder.

"We knew that myelin — the fatty material oligodendrocytes lay down on nerve cells to insulate them — is the immune system's target," Lanz said. "But we didn't know which protein constituents of myelin get mistakenly targeted by our immune system."

He and his teammates had a hunch, though. As EBV hides out forever in people's immune cells over the decades, just one of its 80 or so proteins, called EBNA1, continues to be produced by the cells harboring that sleeping virus. The virus persists in infected people's cells for a lifetime, leaking EBNA1 into their bloodstreams all the way.

That made EBNA1 a prime suspect. And it turned out that a narrow stretch of EBNA1 was very similar to a piece of a protein called GlialCAM that sits on the outermost membrane of oligodendrocytes, the myelin-producing cells.

Similar, but not identical. "There's still enough of a difference between the two that our immune systems generally don't get confused into mistaking one for the other," Lanz said. Otherwise, an Epstein-Barr infection would always trigger MS.

But it's known that from time to time, our cells' enzymes snap tiny chemical caps onto specific spots on proteins that have already been made. The scientists showed that this can happen to GlialCAM, sometimes making it look all the more like EBNA1.

Meanwhile, when B cells (the antibody-producing immune cells) are continually stimulated by an ever-present immunogenic substance (like EBNA1), they keep on dividing. As they do, they mutate. The resulting mutant antibodies gradually diverge, some becoming more strongly targeted to the protein stretch they were originally generated to attack and others aimed at similar but not identical targets.

The researchers looked closely at B cells from MS patients to see how their antibodies differed from those of healthy people. They found that many patients' B cells produced at least one antibody that grabbed firmly onto not only the telltale region of EBNA1 but also its look-alike stretch on some versions of post-production-modified GlialCAM.

That's called molecular mimicry: similarity between a pathogenic and a human protein that confuses the immune system, which conflates the two. "This may explain how we could develop a strong immune response to EBNA1, and eventually to GlialCAM, over the decades," Lanz said. It takes two to tango.

It may take a long time before Epstein Barr-infected people's antibodies reach the stage where they're pumping out antibodies directly targeting GlialCAM.

But, Lanz said, "Time is what EBV's got."

The 2022 study's results were fleshed out and extended in a 2024 study in *Proceedings of the National Academy of Sciences*, conducted in collaboration with Karolinska Institute researchers. The new study, in addition to confirming all of the above, pointed to some genetic factors that may play a major role in determining which EBV-infected people develop multiple sclerosis.

THERE'S MORE WHERE THOSE CAME FROM

Numerous other examples of an "infection connection" link a pathogen to a chronic condition.

Cervical cancer is attributed to infection by the human papilloma virus. Ulcers, we now know, are mainly caused by a stomach-inhabiting bacterium, Helicobacter pylori. Lanz coauthored a 2023 study led by Robinson that linked periodontal infection by bacteria to rheumatoid arthritis. Other Stanford Medicine researchers have identified infection-triggered autoimmune disorders. And more links will be found. Each such discovery is a concrete step toward finding a way to relieve humanity of the burden of chronic disease that weighs ever more heavily upon us. **SM**

— Contact Bruce Goldman at goldmanb@stanford.edu

A second chance

Mysteries of life and cancer treatments

BY JEANIE KORTUM

PHOTOGRAPHY BY MISHA GRAVENOR

It was a year of waiting, a devil's bargain with the weekly poison of chemo that was keeping my husband alive yet destroying him. Jabbing us with its sharp elbows, this brutal cancer had come to live with us nearly 10 years ago. Mike had already cycled through five different chemo medicines. This was the last one.

"What's going to happen when the chemo no longer works?" I wondered every day. It was a question I never spoke aloud. It is hard to live without a horizon — without an idea of a future.

And Mike, he looked like a giant question mark. Bones eaten by the cancer, his head falling forward from the weak, rounded curve of his spine. So skinny he was almost two-dimensional.

Each day I asked myself if it would be the last time I hear him speak my name, the last time we hold hands. Would I ever hear him say again, "I love you"?

Time was sanding us down in its relentless, impersonal caress. Days never punctuated by hope. Stillness rippled only by the sound of my breathing, the slap of my footsteps across our wooden floor, my occasional whispers of Mike's name.

Though quiet, I was manic. I was supposed to be finishing my third novel, but like Jack Nicholson in *The Shining*, I ended up writing the same chapter over and over again.

Hoping to kindle joy, surprise, I looked through old books, read poems I once loved, but all those words I used to love just wilted in my hands like a bouquet of wildflowers clutched too long.

Weeks stretched into a month, another month and then a whole summer. Finally came the word we had been dreading.

"Hospice," his doctor said one day in a video call.

Here it was. No deal with God, no political strategy, no wily campaign: We could not outthink this one.

Except maybe, just maybe, we would.

The bald-headed alien

"WHAT IS THE LATEST APPROACH TO multiple myeloma?" I typed into Safari search late one night. A strange new phrase floated out of the digital hemisphere. CAR-T, approved by the FDA only the previous summer. I clicked on the link.

It looked like a drawing done by a third grader, a picture of what looked like a bald alien, surrounded by blue bubbles of information. Bubble one: Remove blood from patient to get T cells. Bubble two: Make CAR-T cells in lab. Bubble three: Grow millions of CAR-T cells. Bubble four: Infuse CAR-T cells back into patient. Finally, bubble five: CAR-T cells bind to the cancer cells and kill them.

Wow. Could a bald-headed alien be our savior? It sounded like an Old Western shoot 'em up.

Even its name, CAR-T, seemed whimsical. Though I now know its pronunciation is "car" followed by "tee," I first read the term as "cart" and it reminded me of a scene in *The Wind in the Willows*, my favorite children's book. In that tale, Mr. Toad builds a rolling Roma home, a swaying cart pulled by an old horse, wheels painted bright red and blue, shelves ingeniously folding out to become a table and bed, even a canary cage with a live canary. At the end of the chapter, however, a car comes down the road, the horse rears up and the cart overturns. No one is hurt — and the toad, now completely enraptured with automobiles, sits in the middle of

JEANIE KORTUM (RIGHT) AND HER HUSBAND, MICHAEL O'MAHONY, AT THEIR HOME NEAR THE SEA IN RURAL MARIN COUNTY, CALIFORNIA. O'MAHONY IS A CANCER SURVIVOR WHO RECEIVED CAR-T CELL THERAPY.

the road and watches the car disappear.

We asked Mike's oncologist to transfer his case to Stanford because they were on the cutting edge of this new approach. Again we waited, this time to be approved for this innovative procedure.

911, and suddenly Mike was in the hospital fighting for his life. His spine, grown weak from multiple myeloma, was laced with holes. Then a problem with a twisted bowel. After his release he was so weak he could not even sit up in bed, so we decided he should stay with a caregiver friend, Tenzin, who is a devout Buddhist. For months, Tenzin worked with Mike; his daily administration of care was his own particular form of prayer. Exhaling great clouds of warmth and comfort, every day Tenzin brought Mike plates of delicious food. But he refused to eat. New hollows in his cheeks, he had lost nearly 50 pounds and, as his spine collapsed, nearly 6 inches of height.

But Tenzin kept at it. First, he persuaded Mike to sit up in bed and later to walk with a walker, then a cane. Eventually, Mike walked by himself.

And then Mike is back home, but still we are waiting for approval. Winter 2023 turns into spring 2024. Time seems malicious, immutable. New daffodils push their golden heads up through the dirt, but each bloom reminds me only that Mike's cancer cells are multiplying.

Where ghosts still speak

MIKE IS FROM A spit of land in southern Ireland, a thin peninsula sticking out into the Atlantic. If the beauty of Leonard Cohen's "Hallelujah" could be translated into geography, Sheeps Head would be it.

In Mike's early years there was no electricity. His mother cooked the family's meals on a peat fire, people worked the fields with horses.

While walking the spine of Seefin Mountain, one can read the temperaments of Mike's parents in the terrain. His mother is from the wild and beautiful north, as impassioned as that landscape. Deep crevices, pounding surf, the north is a place puckered with loss, fermented secrets, wild urges. The wind, harsh with history's breath, reminds anyone who ventures forth that they are superfluous. The north's Priest Rock is where people went to pray in secret during the British occupation.

Mike's father came from the south side. The land, a fastidious log of used days, seasons, used lives, is arithmetic perfect, quilted with geometric squares, stone houses, long rock walls that run down to Dunmanus Bay. A little stern, Mike's father did not speak much. He worked hard his whole life and was re-

CANCER SPECIALIST HITOMI HOSOYA (LEFT) AND NURSE COORDINATOR JENNIFER ROCHA WERE PART OF THE STANFORD MEDICINE TEAM THAT CARED FOR KORTUM'S HUSBAND DURING HIS TREATMENT FOR MULTIPLE MYELOMA.

nowned for his judicious fairness, legislating neighbors' quarrels.

Present-day Sheeps Head is a place of origins where the past and its history are always close by. On Sundays, the descendants of Mike's paternal grandparents, now dispersed like seeds on the wind to Australia and the United States, join a Zoom call to hear from Mike's brother James, a local historian, about the distant relatives who began them.

Time folded so many times, it's almost as if ghosts have joined their conversation — they rock in rocking chairs, light their pipes, extract an old watch from a vest pocket. A joke first spoken 50 years ago can be resurrected at any moment, evoking fresh laughter.

There's another meaning of CAR-T — not as whimsical as *The Wind in the Willows* yet a similar but heartbreaking storyline. Before Mike was born, his 12-year-old sister Mary was steering a horse and cart down a road with a few of her little brothers in the back when the first car to drive through Sheeps Head approached. The horse reared; the cart fell over; and Freddie, Mike's older brother, hit his head on a rock and died. Mary carried his body across the pasture to her mother. A year later, her mother, then 46, gave birth to Mike. A miracle child, incubated in loss and a mother's grief, Mike was adored by his family, eventually growing up to become a thoughtful man, exquisitely attuned to sorrow and comfort.

Though Mike arrived in America with only a few shillings, using both his father's business acumen and his mother's generous capacity for friendship, he created a prosperous business. He sired three biological kids, adopted another, became a stepfather. As though loving itself is a conscious, tender act, Mike consistently remained a kind, unselfish man even through the rigors of fighting cancer.

Meeting Mike's doctor

ONCE MIKE IS approved for the procedure, we travel to Palo Alto to meet his doctor, Hitomi Hosoya, and her nurse coordinator, Jennifer Rocha.

Dr. Hosoya, who comes from a family of doctors, has both a medical degree and a PhD in cancer work and seems comfortable, even excited, to be living with the mystery at the outer stratosphere of medical knowledge. Meeting Ms. Rocha and Dr. Hosoya, I am reminded that certain people can quickly become a kind of home, though not in a sense of four walls, a foundation and a roof, of course. It's more that these rare people give you an inside place to rest; for the moment you feel safe.

In the months during and after the procedure, Dr. Hosoya quickly becomes Hitomi and Ms. Rocha becomes Jennifer, eventually morphing into the deeply affectionate "Jenn."

Like those bubbles surrounding the bald-headed alien, Hitomi describes how Mike's cells will be extracted in a blood draw and sent to a lab where they will be militarized to attack his cancer. Three days of intensive chemo will kill everything off and make more room for the new cells, and then those upgraded replacements will be deployed into Mike's body.

Hitomi warns us of the potential for severe medical responses. About a week after infusion, she tells us, when the cells hit full strength, Mike will need to stay in the hospital for at least a week — or more if he has a bad response. After his release he must remain near the hospital for about 30 days of constant monitoring.

The charts and graphs Hitomi shows us are like sacred portals into the articulation of what makes life. CAR-T cell therapy is called *living medicine*, she tells us. We carry our history in our cells, and that often determines how we respond to disease. She tells us that by the time Mike is treated, she will have performed only 40 of these procedures and, because it is so new, not a lot of information is available about how people will respond beyond three years. Though we understand the science behind CAR-T, she states, we still do not know exactly how it works.

Getting ready

AFTER OUR MEETING WITH Hitomi and Jenn, we return home to prepare for at least six weeks in Palo Alto. Because we live in Point Reyes, hours away from Stanford, we rent an Airbnb and get a house sitter and a dog walker. Mike updates his will.

Though he is a semi-lapsed Catholic, to fortify Mike for the fight ahead, I ask his sister Dympna in Ireland to look for their mother's rosary. She hunts for weeks, eventually finding it in an old purse, wedged behind a wardrobe. I imagine the moment she opens it, uncoupling the antique clasp, the rusty sigh as the purse unhinges its jaws for the first time in 40 years.

Within the purse, Dympna found some medals for Saint Teresa, tied with a turquoise thread. The rosary was inside a modest pouch, and "My Rosary" was inscribed on it in formal, slanted type. The purse also held a frayed letter from Mike from when he lived in Alaska and an old photograph, washed in the brown sepia of time. Her head raised, Mike's mother looks as if she has just spoken. His father stands next to her wearing a hat, his face in the shadow. Mike, a teenager wearing a lumpy homemade sweater, is obviously laughing, his elf ears turned outward as though listening for the next joke.

Dympna mails these items to us, and I give them to Mike the night before we go to Stanford for the treatment. He opens the package, spreads everything on the bed, then extracts the rosary's plastic beads and small silver cross from the pouch.

As I watch him run his hands across the beads, I find myself wondering if a collection of long-lost items now clustered on a bed in California could still whisper a living prayer of hope and love into a son's ear, 40 years after it was last spoken.

Mike doesn't say anything, but as I watch his eyes well with tears, I know it has happened: His mother's last supplication for her beloved son has joined him in the fight for his life, each bead of the rosary charged with the edict, "survive."

Cells going in

NOW THE DAY IS HERE. We crowd into a small room with doctors and nurses, all wearing blue latex gloves, white gowns and masks. Mike lies prone in a recliner, a blanket over his knees. "We're defrosting his cells," a doctor tells us, pointing to a Styrofoam box.

"Kind of like defrosting a TV dinner," I joke nervously. A few polite chuckles.

Fierce protocol is observed. They check Mike's electrolytes, kidney functions, everything checked twice. One of those blue-gloved hands points to his name. "Is this you?" Mike raises his glasses and squints. "Yes," he replies. "What is your date of birth?" He tells them. Someone else types his reply into the computer.

Fierce protocol is observed. They check Mike's electrolytes, kidney functions, everything checked twice. One of those blue-gloved hands points to his name. 'Is this you?'

Mike asks a pretty nurse how her day is going, and I text the kids, "I think he's flirting!"

It's like a sci-fi movie. The lid of the Styrofoam box is lifted, a hiss of smoke-like vapor released. Mike's bag of cells is extracted and hung on an apparatus near his chair. Filled with the ruby-red harvested cells, it looks for all the world like a beaded evening purse. The familiar thump by one of those blue hands trying to find a vein and I wonder if the nurse notices the mementos of a life that are doodled on Mike's body — a bite mark from a donkey, one index finger marred with rings from when he dropped a herring net too soon and it squeezed his fingers as the boat sped away.

A jab of a needle and the IV line is connected into Mike's left arm. At first I try to pay attention to everything; watching blood carrying his reprogrammed DNA travel down the long tube and enter his body. It is eerie and ordinary and

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Paging Dr. Algorithm

At Stanford Medicine, AI is becoming part of the curriculum, clinical training and patient care

BY KIMBERLEE D'ARDENNE

Artificial intelligence, which is already changing medicine and patient care, will soon be in all Stanford Medicine classrooms.

AI technologies are expected to improve patients' and doctors' lives by speeding up breakthroughs in medical science and assisting with health care administrative tasks, giving doctors more time to care for patients. For these reasons, Stanford Medicine is revamping its curriculum to incorporate all that AI has to offer medicine as a teaching aid and practitioner's tool, according to Reena Thomas, MD, PhD, senior associate dean of medical education and a clinical professor of neuro-oncology.

"Imagine if a student could have access to a teaching tool that they can use any time they want to practice asking the questions that give the information they need to make an accurate diagnosis, and it is just like having a conversation with a patient," Thomas said.

Starting this fall 2025 quarter, all students pursuing degrees in medicine and physician assistant studies will learn about and from AI technologies. The curriculum will cover how different types of AI work so students learn to evaluate the information provided by them — which can sometimes be inaccurate or biased — and to determine how to best use the technologies when caring for patients.

Teaching the future now

AS STANFORD MEDICINE'S **AI faculty champion**, bioinformatics researcher Jonathan Chen, MD, PhD, is responsible for leading the integration of the AI curriculum into existing instruction and ensuring that the material being taught aligns with best practices for bringing new technology into clinical use.

Chen recalled that, as a medical student, he imagined just this future: While memorizing "100 bugs and 100 drugs," he knew there had to be a way for humans to use computers to improve health care, he said. Yet, even Chen, an assistant professor of medicine and of biomedical data science who has studied the application of computers and intelligent systems to medicine for over 20 years, was taken aback by the implications of AI for medicine.

"In 2022 when ChatGPT came out and blew up as the fastest-growing internet application in history, I thought, 'Whoa, this is like when the internet was invented. This is going to change the entire nature of clinical practice, and we cannot ignore it,'" Chen said.

"Everything about education, especially with training and evaluating people based on what they read and write, just got turned upside down, and we have to rethink how to train new students and how to retrain an entire generation of the health care workforce."

The curriculum is being created by a steering committee and a working group made up of AI researchers and programmers, clinician faculty and students. They have settled on four learning objectives that form the basis of what students will be taught: how different types of AI work, how AI-based tools can be used in clinical practice, ethical and legal implications of using AI in medicine, and how to critically evaluate the information AI provides.

"Unlike how there is a curriculum for teaching how the kidney works, we cannot pin down a fixed curriculum for AI in health care because the technology is a moving target," Chen said. "We need to have an adaptable framework. Luckily, many of the concepts needed for AI education are foundational, and we are already talking about them."

Some concepts will be new, while others will build on the existing curriculum. For example, the students will learn to assess AI results using the same statistical methods taught for interpreting diagnostic tests and clinical trial results. Though diagnostic tests are very accurate, incorrect results are always a possibility, and

ILLUSTRATION BY ARD SU

doctors are taught how to interpret results and how to use them in patient care. The same thinking applies to AI in health care because the algorithms can provide information that sounds correct but is actually wrong. The concepts of sensitivity (how well a test correctly identifies people with a condition) and specificity (how well a test identifies people without a condition) can help students evaluate AI, Chen said.

Earlier learning opportunities

ADITYA NARAYAN, a student in Stanford University's MD/MBA program and member at-large of the Association of American Medical Colleges Board of Directors, started medical school years before generative AI took off. He said he truly started to learn medicine during his clinical clerkships — hands-on learning experiences with patients after two years of predominantly classroom learning.

"A great deal of my basic preclinical training did not directly translate to the wards," he said.

"With AI, we can instantly generate patient cases that ground classroom concepts in real-world context and test students' understanding in real time."

Getting AI into the classroom could give students opportunities to use what they are learning as they are learning it.

Narayan explained that instead of memorizing possible causes of an abnormally high level of potassium in the blood, students could learn about the condition by interacting with an AI chatbot that immediately produces scenarios that might lead to high potassium. These could include a dialysis patient who missed a treatment, a trauma patient whose muscle tissue breaks down and enters the bloodstream or a child whose adrenal glands don't make enough hormones.

Such AI-based tools could be a game-changer in the early years of medical school because there would be no limits on how much students could practice, Narayan said.

Traditionally, students have practiced on actors trained to play a patient, called standardized patients. Faculty members supervise and evaluate the encounters.

"Standardized patient scenarios are useful but rarely have the complexity and emotional texture of real patients," Narayan said. "Having access to tools that simulate clinical encounters with patients would let students get instant feedback and opportunities to justify their reasoning in a low-stakes way. This can also open opportunities to gather more longitudinal data on student outcomes even before they reach higher-stakes hospital environments."

The Stanford University-developed Clinical Mind AI platform does this, letting students start practicing patient-interviewing skills much earlier.

The app was developed under the direction of Thomas Caruso, MD, PhD, a clinical professor of anesthesiology, perioperative and pain medicine, and Shima Salehi, PhD, an assistant professor in the Graduate School of Education. Marcos Rojas Pino, MD, a doctoral student in education, leads the project.

The platform uses a chatbot, similar to ChatGPT, but rather than requiring students to type their questions, they can communicate by talking, just as they would in a conversation with a patient.

Students can take medical histories from simulated patients, and the app gives them real-time feedback so they can learn which questions they should have asked. The purpose of the app is to teach students the clinical reasoning skills they will need when interacting with and treating patients.

"Asking relevant questions to get the information you need to arrive at a correct diagnosis is a skill that is developed and honed throughout your time in the early years of practicing clinically," Thomas said.

The app, like the AI curriculum, is designed to be flexible given the fast pace at which AI is changing.

"Clinical Mind AI is built like a Lego set, so that when AI changes and comes out with a new type of 'piece,' we can take a brick off and add in a new one as needed, without changing the user interface," Caruso explained.

A small group of students in the Pathophysiology Capstone class, the final part of the two-year Practice of Medicine course that all medical students take, recently tried Clinical Mind AI, and Caruso and Rojas Pino have fielded licensing requests for the app from medical schools spanning the globe.

The updated curriculum also includes the use of AI Clinical Coach, an app that listens in as a student presents a patient case to a faculty instructor. It then summarizes the patient's medical history, symptoms, tests and treatment plan and creates a report that a faculty instructor can use to guide instruction and give feedback to the student.

Led by Sharon Chen, MD, a clinical professor of pediatrics, infectious diseases, researchers developed the tool within Stanford Medicine's electronic health record system so students can practice evaluating actual patient cases.

"AI Clinical Coach facilitates the learning experience by providing real-time feedback to students and faculty educators about strategies the student is using. It also identifies whether students made the correct diagnosis and used all the relevant information to reach that diagnosis," Thomas said.

Embracing change

THE INTRODUCTION of any new technology changes what people need to learn, and AI is no different, said Natalie Pageler, MD, Stanford Children's Health's chief medical information officer and clinical professor of medicine and of pediatrics and clinical informatics. Pageler co-founded the Stanford Clinical Informatics Fellowship, which trains doctors how to apply new information technologies to health care.

For example, before electronic medical record systems became widespread at hospitals, every medical resident needed to know how to write treatment instructions for a newly admitted patient — admission orders — from scratch. "This used to be a core skill that all residents did over and over," Pageler said.

Now, electronic medical records systems have pre-written sets of orders that can be selected and edited as needed. Instead of learning how to write admission orders in their entirety, residents learn about the individual components that make up orders, which gives them a foundation upon which they can evaluate admission orders and revise them when necessary.

Even when technology picks up tasks formerly performed by doctors, it's still important for students to understand the underlying logic, Pageler said, much as how K-12 students master math concepts such as multiplication tables before using a calculator. For example, using Clinical Mind AI and AI Clinical Coach to learn how to interview patients, arrive at a diagnosis and propose a treatment plan will set up Stanford Medicine students to effectively use AI-based applications like Microsoft's DAX Copilot that record entire patient-doctor interactions and draft visit notes.

AI joins other past advances that drastically and immediately improved patient care — vaccines, anesthesia, antibiotics, imaging technologies and even the humble stethoscope, to name a few. And right now, though the impact AI will have on medicine is inevitable, the nature of that impact is uncertain.

"When the stethoscope was invented two centuries ago, it essentially shifted how clinicians conceptualized themselves — from anatomists to diagnosticians who had privileged access to the hidden language of the body. Now we are at another one of those inflection points," Narayan said. "AI will change the way we learn to practice human-centered medicine, and we need to be prepared to shape that future or be shaped by it." SM

— Contact Kimberlee D'Ardenne at medmag@stanford.edu

How to talk to a chatbot

No computer science background required

DONG YAO, MD, AND SHIVAM VEDAK, MD, both clinical informatics fellows at Stanford Medicine, have created a workshop for health care professionals on how to prompt, or talk to, generative AI models like ChatGPT or Stanford Medicine's secure GPT, a HIPAA-compliant chatbot that can answer questions and summarize text and files. They also get into the nitty-gritty of how generative AI works, using language non-computer scientists can understand.

Part one of the workshop is available free of charge at **stan.md/Workshop**

FEATURE

Breaking the cycle

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of the whole family's health, rather than singling out one child.

"But children need to be motivated to set their own goals and make changes themselves," Robinson said. "Otherwise it's them versus the parents, and that rarely works."

As Robinson's team expands access to the program, they are also always looking for ways to make it more effective for participants who struggle to succeed. They are collaborating with Stanford University psychologists to explore whether two brief social psychological interventions will help families overcome barriers to success. They will test the benefits of helping participants adopt a growth mindset, a state of mind in which one believes in one's own ability to gain new skills through effort. They are also studying activities that help people escape stereotypes about groups they belong to, such as those about children and families with obesity. The researchers want to know whether adding these elements to the existing program helps participants reach their goals.

This research project was recently funded by the National Institutes of Health, and collaborators include Carol Dweck, PhD, the Lewis and Virginia Eaton Professor, a professor of psychology and a pioneer of the growth mindset concept; Geoffrey Cohen, the James G. March Professor of Organizational Studies in Education and Business; and Gregory Walton, a professor of psychology.

Empowering community leaders

One key aspect of the program — face-to-face interaction — will be preserved in the new rollout. "I believe it's part of the secret sauce of why these family-based, group programs have worked," Robinson said.

The newly packaged curriculum, which will be available through an online platform known as Stanford HEALTHY, will help pediatricians, hospitals, community organizations, public health departments and employers deliver effective weight management programs to groups of families in their own communities across the country.

"Many primary care providers, after-school programs and other community organizations want to be able to do this," Robinson said. "But it's not something they have much training in." The Stanford researchers have developed an array of online materials — including videos and animations; assessment, monitoring and feedback tools; and group-management resources — to help people lead the weight loss program. Training for group leaders will be incorporated online as well and is designed to be accessible to leaders with minimal experience.

"We want to make it easy for anyone, whether they're a health care provider, a high school teacher or a youth leader at the Y, to be able to deliver the program in a way that maintains fidelity to what we do here at Stanford," Robinson said. Providers will pay an annual subscription fee based on the size of their organization and their ability to pay.

To create a road map for scaling his team's work, Robinson drew on insights he gained in an eight-month Stanford Mussallem Center for Biodesign faculty fellowship, which provided advanced training in health technology innovation and prepared fellows to bring those solutions to market.

"We are exploring business models to create a sustainable program for many different provider types," he said, noting that the team hopes the program can ultimately be delivered not only by health care professionals but also, for example, by community leaders at public health agencies or after-school programs. Another hurdle is that insurance reimbursement for behavioral pediatric obesity treatments is poor. "We're thinking about how to make it both affordable and sustainable over time."

Components of his team's plan have been influenced by Silicon Valley concepts, such as business-to-business and software-as-a-service models, he said.

"It's really a huge step for us, being able to share a program we strongly believe in, that has great evidence supporting it," Robinson said. "Now we can make it available, hopefully, to everyone." SM — *Contact Erin Digitale at digitale@stanford.edu*

FEATURE

A school is born

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programs that can play a role in addressing chronic disease.

We also need to reduce the barriers to medical education for those coming from rural or underserved communities, which is part of the reason AWSOM is located in Northwest Arkansas. Additionally, to ensure that this transformative educational experience is accessible to a wide range of applicants, we've waived tuition for the first five cohorts of students.

SINGH: *Alice, you've made integrating the arts and humanities into medical education a hallmark of your approach to training. How do you believe this can transform the way physicians understand and care for their patients, especially those living with chronic illness?*

WALTON: It's proven that the arts enhance our health and well-being, and for someone with a chronic condition — and I speak from experience here — it can provide a respite and help foster whole health. I went through a decade of hospital visits and surgeries to address a chronic condition, and as one of the tools in my toolkit to support my health, I brought watercolors with me and painted where I wanted to be instead of where I was. Even now, walking into an art gallery and viewing art helps lower my blood pressure.

Our curriculum at AWSOM includes a focus on the arts as a way to further develop empathy, critical thinking and a host of other skills. Students take drawing classes to sharpen observational and empathetic skills and practice close-looking at art to enhance their attention to details. Through a range of interactions with the arts, we hope to develop doctors who are not only clinically competent but are also skilled in fostering human connections and caring for the whole person. SM

FEATURE

A taste of health

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Research from Lisa Goldman Rosas, PhD, a Stanford Medicine associate professor of medicine and of epidemiology and population health, offers evidence that the strategy works. Collaborating with Alameda County Health and the University of California, San Francisco, Rosas and her team studied more than 2,600 people who participated in Recipe4Health between 2020 to 2022. They published their findings in the *American Journal of Preventive Medicine* in November 2024.

Participants, who were referred to the program by providers at community health centers in Alameda County, California, all faced chronic nutrition-related conditions, and many were food insecure.

Participation in the Food Farmacy and Behavioral Pharmacy increased their intake of fruits and vegetables by about half a serving a day, the researchers found. "You might say, 'That's not much,' but Recipe4Health was giving 16 servings a week, which is really not a lot," Rosas said. "The fact that you saw participants increasing their produce consumption on a daily basis is quite encouraging."

Food prescriptions boosted both physical and mental well-being, the researchers found. Whether participants enrolled in only the Food Farmacy or both the Food Farmacy and Behavioral Pharmacy, all reported marked improvements in loneliness, quality of life, and the number of days they felt physically or mentally unwell, on average. In addition, electronic health records showed that participants had lower levels on average of non-HDL cholesterol, which is linked to higher risk of heart disease, than a control group a year after the intervention.

Participants who took part only in the Food Farmacy program also saw a significant drop in their HbA1c levels — a key indicator of diabetes risk — a year later, compared with a control group. Researchers didn't see this effect in patients who also attended the Behavioral Pharmacy, which Rosas said might have been because that group had lower HbA1c levels before the program.

"The fact that we saw benefits compared with a control group suggests that Food as Medicine really is contributing to improvements in health outcomes, which is quite promising," Rosas said.

The program also improved patients'

mental health, Rosas and her team concluded in a complementary article published in *Health Services Research* in January 2025. Based on surveys and interviews, they found that people who received produce deliveries and group health coaching saw improvements in symptoms of depression and anxiety. (Patients who didn't have coaching improved only if they didn't have clinical depression or anxiety before the program.)

Patients who joined the Behavioral Pharmacy generally had better physical and mental health outcomes. "Nutritional education or health coaching is a fundamental component to help participants take that produce the last mile," Rosas said. "Otherwise, it can be kind of overwhelming."

Rosas recently launched a broader evaluation of Recipe4Health, collecting more detailed data on participants' diets and health outcomes. She and her team are also examining Food as Medicine initiatives targeting Latinas, patients with diabetes and cancer survivors. Her hope is that hard data will encourage providers to adopt the approach and insurers and lawmakers to offer coverage. SM — *Contact Katia Savchuk at medmag@stanford.edu*

FEATURE

Farewell to the couch

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"We're still not totally clear on what kinds of factors would drive someone to do better with a texting program versus a human phone program or AI program," King said. "But we are starting to learn about that."

King called this the "whiches" conundrum. "At the end of the day, we want to know which program for which people under which circumstances, to get which types of outcomes," she said. King admitted that she struggles to exercise at times, especially during a busy week, but she finds it easier when she combines it with something she enjoys such as dancing. "It's important to find something in physical activity that you enjoy, where it doesn't feel like a chore."

She has conducted studies with a variety of midlife and older populations in which she has compared different approaches to motivating people to move. King said that, regardless of the population or the way people receive prompts, basic behavioral principles are at play. These include regular physical activity monitoring, goal setting, looking for role models and thinking about the benefits of following through. She added that tying the goal to a person's values also helps.

"If your value is your family, then finding ways to be active with your family is going to satisfy that," she said. "For many people, I don't think that understanding health consequences alone is nearly as motivating as recognizing how being physically active can improve life in ways that truly matter to them."

Wearable devices and fitness trackers also serve as motivational tools. Whether it's tracking steps or watching your resting heart rate go down over time, Anand said the data can motivate people. "You look at all this information and you get all excited," she said. "We're very responsive to whether we get a positive or a negative effect, and that might make someone decide to walk their dog farther."

If the advice to exercise rather than wait for a pill brings heartache to those opposed to sweat — whether by preference or by physical limitations such as age, injury or disability — the researchers have some good news. Studies suggest that more exercise produces more molecular benefits, and "more" can mean relatively small increases in exercise levels.

The goal isn't to make people feel bad if they don't complete long bouts of hard exercise. "The problem in our society is not whether people do 70 minutes of high intensity exercise instead of 60, our problem is that people sit on the sofa and eat pizza," Ashley said.

Even small changes can add up. "If you can just stand, if you can take a meeting walking, if you can take a walk after dinner, or if you could do any kind of exercise, that is better than sitting," he said. "You don't need to go to the gym, and you don't need to sweat, you don't need to jump in a pool in the morning if you don't want to. Those are great things to do, and the more you can do, the better. But getting up and standing is worth something."

King agreed that small steps matter. "Move more, sit less, is really the mantra," she said. "For inactive people and older adults, along with people with chronic conditions, lighter types of walking intermixed with some more moderate activities work very well to help get some of those important benefits."

Taken in small doses and linked to things you value and enjoy, exercise doesn't have to be a hard pill to swallow. SM — *Contact Amy Adams at medmag@stanford.edu*

FEATURE

A second chance

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wondrous all at the same time. Would his newly militarized army of cells march in and annihilate the enemy?

Trying to honor the sacred in my own maudlin way, I begin to hum "Amazing Grace," one of my favorite songs.

Is it because I am so off key? Mike asks me to look for something to listen to on YouTube. Thinking it might comfort him, I look for a Gaelic lullaby, eventually arriving on a singer dressed in a black cape, thick red hair tumbling down her back. Rough and sweet, her voice moves up through the cold mechanics of the iPad speaker, seeming to lift and spread into the sky, each round vowel filled with hope and beauty.

I place the iPad before Mike on a tray. His eyes close, and I wonder if he is sailing back home on the breath of the woman's song.

Maybe this is a song his mother used to sing. Maybe he is once again a 9-year-old boy on a man's errand, walking up Seefin Mountain with his dog Shep looking for his family's cattle. Or maybe the song has him traveling even further back into Ireland's ancient bog, the peat that holds all that has ever lived, all pursuits, all time, along with the carcasses of animals, the roots of old trees, stones, shells and long-ago germination.

Watching Mike's face soften, the song seems like an aerial explanation of the principle behind CAR-T cell therapy. Living medicine. Like the ancient Gaelic lullaby filling the sterile hospital room, our cells float through eternity like messages in a bottle, carrying both our past and our future.

When the song ends, Mike opens his eyes and speaks quietly, almost to himself. "This is big," he says, closing his eyes again and falling asleep. His mother's rosary slips from his hands.

Six minutes. That's how long the infusion takes. The question is, after nearly 10 years of pain, would all of these new cells, deputized by Gaelic song, be his cure?

The Airbnb

NOW COMES A PERIOD of watching. We are staying near the hospital with our friend Dora. After the procedure, we were given long lists of instructions and told to return immediately if Mike gets a fever or any bad neurological reactions. The symptoms could start after only four days. He could lose his voice, begin shaking, become confused, even start to hallucinate. Dora and I test his cognitive clarity every morning and night. "What is your name?" we ask. "Who is the president?" We keep charts on the refrigerator of everything he eats and drinks and monitor his temperature around the clock. We give him a pot to bang on if he needs us in the middle of the night.

It is as if Mike is a pioneer homesteading the land of hope for us all. Recognizing that this treatment is both dangerous and innovative, family and friends cheer him on. "Go T cells," they text day after day.

As his cells multiply and rage, Mike grows restless. His body churns with ceaseless movement. When he is awake, he never seems comfortable, an unending chorus of throat clearing, body spasming. He seems to be speaking more slowly as well, no longer releasing words longer than a couple of syllables. A hard look comes into his face; he is slow to respond to questions, stares at me as though he doesn't know me.

Where is he? It is as though someone else has stepped into his skin. This new emotionless person still answering to the name of Mike is at once someone I know and a stranger. "Mike," I say, covering his legs with a blanket. "Come back to me." Maybe, just maybe, the lab had forgotten to program our love.

He has never looked so old, never been this new. I like it best when he is asleep. I sneak into his bed, try to rhyme my breath with his. In a photo I have from that time, we

are holding hands, the cuff of his flannel shirt, my hippie jewelry, a pirate's haul of silver.

We have to return to the hospital every day for blood work. I ask a doctor about this new Mike. "In all my years I've rarely seen him so shut down," I tell her. She tells me he's adjusting to his new cells, reminds me that they don't understand everything that happens with CAR-T cell therapy.

Not exactly comforting. The wonder and humility that charmed me at the beginning of the process now frightens me. I want guarantees, want to cheat and jump to the end of the book, read the conclusion.

I begin to hate suburbia's vapid uniformity, the ranch houses, chemical-fed lawns, kitchen decor from Target, ugly paintings of gold and black circles in our rental, chosen just because they matched the upholstery. The unfaltering blandness masks the violence we are living, the war rippling under Mike's skin. No drones, no guns, but beneath the surface his body is exploding with interior land mines, a paradigm both political and medical I still have trouble with: that waging war can make peace.

It is a strange kind of hypervigilance, staying attuned to danger but trying to turn off thought, every day a circular rhythm, packing Mike into the car, plugging in the GPS, dropping him off at the hospital, driving to the parking lot and taking a photograph of the number slot so I won't forget where I parked. Kindness begins to matter, conversations in the shuttle driving to the hospital, the big woven blooms on the wall hangings, even the sentimental piano music becomes a coded language for hope.

Hospital

THE 2024 SOLAR ECLIPSE is happening the day Mike is scheduled to check into the hospital. His room is bright, filled with clucking, beeping instruments. Teams of doctors and nurses pass through. After weeks of an invisible miracle, I want to see an exterior miracle, want to watch the moon eat the sun the way Mike's new cells are eating his cancer. Hoping to record the eclipse, I place my iPhone on a small ledge and push the button. Maybe I have the time wrong; the sky above the hospital remains its singular blue.

Mike is prodded awake every four hours. A board is posted outside with the names of about 20 patients undergoing CAR-T cell therapy, a rash of red circles indicating the patients in the intensive care unit, about four or five calm green spots of patients who are not acute.

We are lucky. Mike remains a calm, green spot on that board and is released after only seven days in the hospital. A few more weeks at the rental, visiting the hospital every day for blood work, and then, finally, we are authorized to go home. We head back north where the air smells like the sea; the dark, almost breathing night is filled with silence and old stars; and our beloved dog waits for us. I text the dozens and dozens of people who have regularly checked on Mike's progress. "Mike's doing great! Bone biopsy in a month will tell us if this worked."

Home again

Mike is so loved. Though he is too immunocompromised to meet face to face with people, all the people who have been with us every step of the way — our five kids, relatives in Ireland, friends and business colleagues — call to congratulate him. With bated breath we all wait for the biopsy results.

When Hitomi calls, her professional doctor's voice is spun with all the colors of the aurora borealis. "We got the results," she reports. "It's good. No multiple myeloma showed up. The procedure has worked."

We have been given a second chance.

How do you resume life when the world is new, everything formerly prosaic, suddenly enhanced. How do you say "thank you" with the rest of your life? I think of poet Mary Oliver's quote, "What is it you plan to do with your one wild and precious life," and ask myself every day, "What do I plan to do with my second wild and precious life?"

As if newly appreciating life's different stanzas, Mike is different these days, more quiet, easily relaxing into spaces filled just with his own thoughts, his own memories … just being. Maybe this shiny sliver of time is what mystics live. Eternal gratefulness.

I know I will feel that fear again. Our time here is only a brief fleeting now, a slight comma punctuating history's long sentence. Bones, cells and blood stitched together with the fine, gossamer thread of DNA, we are all mortal, traveling toward endings.

As I stumble through my days, I try to understand the lessons learned in the past few months. Are there any accidents, I wonder? All those cells, those thousands of tiny vessels pushed up through time by the ghost hands of the dead … do they dictate the recipe of us? Are even these words programmed into the genome of me?

It's a truth too elusive, too large to hold onto for long and, anyway, all I want to do is resume the ordinary. Birds, the night sky, family and friends, love, the taste of food, the grit of sand beneath my feet.

And Mike. Always Mike. SM

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Stanford MEDICINE

A KILLER IN THE FIELDS

A MYSTERIOUS KIDNEY DISEASE AFFECTING THOSE WHO LABOR UNDER A HOT SUN

So many men in Chichigalpa, Nicaragua, have died from kidney failure, the town is known as the Island of the Widows.

The condition that afflicts them — called chronic kidney disease of unknown origin, or CKDu — is, as its name implies, a mystery. It is a tubulointerstitial kidney disease that affects people everywhere. But researchers don't know why rates are much higher in low-lying, hot agricultural areas like Chichigalpa, which is surrounded by sugarcane fields.

Shuchi Anand, MD, a Stanford Medicine associate professor of nephrology, has been interested in the disease since it was first described in the 1990s.

"Two-thirds of the people with this disease are men, many in their 30s and 40s," said Anand, who is the director of the Center for Tubulointerstitial Kidney Disease. "This is the prime age of work and income generation. They are the breadwinners. This disease can devastate families."

Nephrologist Shuchi Anand and a team of other scientists are trying to pinpoint causes of a stealthy kidney disease.

MISHA GRAVENOR

Nephrologists have identified hot spots for the condition in Central America and South Asia, where up to 30% of households include someone with it. Anand has found that California's agricultural regions also show higher-than-typical rates of kidney disease, though she hasn't been able to confirm them as hot spots for CKDu. Because most farmworkers are migrants and are often transient, they're difficult to study.

The disease is stealthy. Most of its victims experience no symptoms until they reach end-stage renal disease, when their bodies swell, they lose their appetites and they experience brain fog. Without dialysis or transplantation, treatments not readily available in communities where the disease is common, it is fatal.

While most patients work in agriculture, Anand said researchers are finding high rates of the disease among brickmakers and construction workers who also labor under a hot sun. "Our primary premise is that heat is amplifying the disease," she said.

Contaminated water is a suspect. Shuchi's research suggests that communities with poorer water quality are seeing more cases. One hot spot is in a mining area, indicating that metal exposure could also be a factor.

"These deaths of young workers didn't occur in the 1960s and 1970s," Anand said. "And that gives some hints as to the cause. We're looking at changes in the environment, whether that's temperature, agricultural practices, water quality or a combination of factors."

To help pinpoint a cause, Anand and a team of epidemiologists, biostatisticians and body temperature experts plan to study devices such as cooling gloves or headbands to see if they result in fewer cases of the condition.

She is also studying the outliers — women. Because men are more likely to contract the disease, finding what sets apart the women who have it may offer clues. She also hopes to sniff out differences by comparing communities that are severely affected with those that are less affected.

There is some good news. In parts of South Asia where the disease cluster was first detected, Anand said, clinicians feel that rates of the disease are leveling off, perhaps because agricultural workers are being provided more shade and more work breaks or because drinking water is cleaner.

Since she began her quest to find the culprit behind the condition, Anand said, "We have better data now, but we still don't have a smoking gun. We all hope to find it so we can eliminate the cause and eliminate the disease."

BY MANDY ERICKSON

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What's so special about ginger cats?

SCIENTISTS TRACK DOWN THE SURPRISING MUTATION THAT MAKES DOMESTIC FELINES ORANGE

In a new study, Stanford Medicine researchers discovered the long-posited but elusive genetic mutation that makes orange cats orange — and it appears to occur in no other mammal.

Many mammals come in shades of orange — think tigers, golden retrievers, orangutans and red-headed humans — but only in domestic cats is orange coloration linked to sex, appearing much more often in males.

"In a number of species that have yellow or orange pigment, the causal mutations almost exclusively occur in one of two genes, and neither of those genes are sex-linked," said Christopher Kaelin, PhD, senior scientist in genetics and lead author of the study published in May 2025 in *Current Biology*. Greg Barsh, MD, PhD, emeritus professor of genetics and of pediatrics, is the study's senior author.

While scientists have pinpointed the typical mutations in other mammals that induce pigment cells to produce yellow or orange pigment instead of the default black or brown, they had only a rough idea of the location in cats: They knew from the preponderance of male orange cats that the mutation — dubbed sex-linked orange — was somewhere on the X chromosome. (As in most mammals, females have XX while males have XY sex chromosomes.) Any male cat with sex-linked orange is entirely orange, but a female cat needs to inherit sex-linked orange on both X chromosomes to be entirely orange — a less likely occurrence.

In the new study, researchers looked for variants on the X chromosome found in orange cats but not in non-orange cats. The most likely candidate was a variant that increased the activity of the Arhgap36 gene.

Arhgap36 is normally expressed in neuroendocrine tissues, where increased activity is associated with tumors. "The mutation in orange cats turns on Arhgap36 expression in pigment cells, where it's not normally expressed," Kaelin said.

This rogue activity inhibits a step in the same molecular pathway that controls coat color in other orange mammals.

Besides a marmalade coat, could sex-linked orange be responsible for orange cats' reputation as friendly agents of chaos? "The expectation, based on our current observations, is the mutation specifically affects color," Kaelin said, adding that orange cat behavior remains a tantalizing mystery ripe for rigorous investigation. — BY NINA BAI

ALEXANDR_DG/ADOBE STOCK IMAGES

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