UCSF MAGAZINE

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Scroll, Swipe, Rot

UCSF scientists are researching how the digital environment affects our minds — and what to do about it.

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UCSF research is upending long-held assumptions about what causes sudden death.

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LOOKING AGAIN



Cardiologist Zian Tseng (left), with pathologist Andrew Connolly and clinical research coordinator Brielle Kinkead, asked a question few had thought to ask: How do we actually know certain deaths are cardiac?

Sudden cardiac death was long believed to claim millions of lives each year. Then a UCSF cardiologist partnered with the San Francisco medical examiner's office to autopsy nearly every out-of-hospital sudden death in the city and discovered that many weren't cardiac-related at all.

Weight-loss drugs were developed to treat obesity, but now patients are reporting that the same medications seem to quiet the urge to drink.

And the costs of our digital lives were framed as a distraction problem, until researchers began documenting something broader: that the constant pull of screens may be reshaping how we pay attention, think intently, and distinguish what's true.

The stories in this issue arrive at a common realization: Accepted wisdom often turns out to be incomplete. New understanding begins with someone willing to question an assumption and ask whether the prevailing explanation still holds.

That habit runs deep at UCSF. Researchers here are clarifying causes of death, questioning what drives addiction, and documenting what screens are doing to our minds. And, in perhaps the most audacious example, they're designing entirely new proteins from scratch — molecules that have never existed in nature, built to do what 4 billion years of evolution never did.

The discoveries that change medicine rarely begin with certainty. They begin with someone willing to look again.

COVER TO COVER



"Our collective lack of attention and the erosion of our ability to focus because of the digital environment are such major issues right now. I think humans will look back at this moment in a hundred years and marvel that we created a technology we ultimately couldn't control.

"I think it's so timely because I have an 18-year-old daughter who spends the majority of her waking hours glued to her phone. That's what drew me to this story and to finding a cover image that would get to the visceral, emotional heart of it in a startling, unforgettable way. I recommended photo-illustrator Justin Metz for the job, and I think he delivered exactly that."

— DJ Stout, Cover design adviser

PHOTO: NOAH BERGER

The Right Drug, the First Time

Akinyemi Oni-Orisan, PharmD, PhD, is using genetics to end the guesswork in prescribing and helping ensure that no one gets left behind.

By Paula Hermann

Why do drugs work differently from person to person?
Many factors shape how our bodies process medications. Genetics is one piece of that picture, but age, diet, and other medications matter too. That's why two people can take the same dose of the same medication and have very different results. Even identical twins can respond differently. The goal is to understand those variations well enough to prescribe the right drug at the right dose for each patient.

What is pharmacogenetics?
It's the study of specific genes — primarily those that govern how the liver breaks down and moves drugs through the body. Certain gene variants can change how much of a medication reaches its target and how a person responds to it. Prescribing has long been based on averages from clinical trials, which works for many people but not everyone. Pharmacogenetics moves us toward a more individualized approach.

Can you give an example of how genetics change a drug's effectiveness?
My favorite example is statins. They help lower cholesterol and prevent heart attacks, but they can cause severe muscle pain in people who have a genetic variant that makes it harder for their bodies to clear the medication, so higher levels stay in their bloodstream and leak into their muscle tissue.

How does pharmacogenetic testing work?
Patients at UCSF can have a panel of genes tested, often as part of their routine care, and the results stay in their medical record for future use. Clinicians can then use that information to guide drug and dosage decisions, reducing costly and potentially serious complications, hospitalizations, or ineffective treatments.

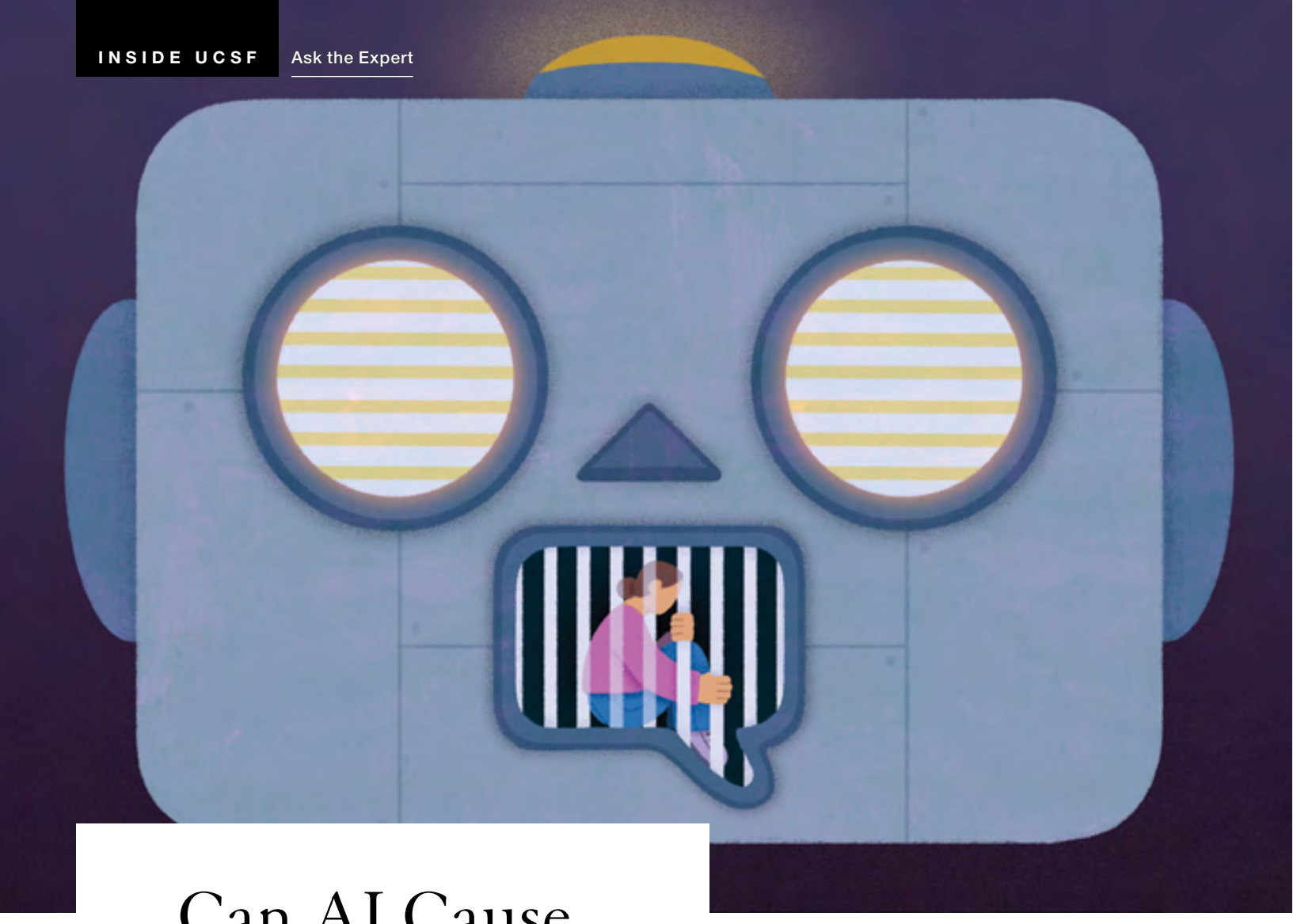
How do you ensure equitable access to testing?
One lesson we've learned repeatedly is that when new medical advances are introduced, they often reach some people sooner than others. At UCSF, we're tracking who gets pharmacogenetic testing and whose medications or dosages change as a result — across race, ethnicity, income, and insurance cohorts — to ensure no group is left out.

Beyond UCSF: I volunteer at Folsom State Prison, playing soccer, basketball, and board games with incarcerated individuals. On the surface, it's recreation, but on a deeper level, it's helping people maintain dignity through human connection.



Oni-Orisan, a professor of clinical pharmacy and postdoc alum, leads an award-winning research lab focused on pharmacogenetics.

PHOTO: ANASTASIIA SAPON



Can AI Cause Psychosis?

Probably not, says a UCSF psychiatrist — but chatbots might compromise mental health in other ways.

"AI psychosis" has become the popular term for situations when people lose touch with reality during extended conversations with chatbots. These reports are disturbing, but what's really going on? Karthik Sarma, MD, PhD, a resident in psychiatry and a computational health scientist, founded UCSF's AI in Mental Health Research Group to help answer such questions. He explains the mystery around the phenomenon and what he and his colleagues are doing to better understand the link between chatbots and mental health.

You don't like the term "AI psychosis." Why?
The implication is that AI is causing the psychosis directly, which may not be true. I prefer the term "AI-associated psychosis."

What else could explain it?
One possibility is that excessive chatbot use is a *symptom* of the psychosis. I have a patient with bipolar disorder who takes a lot of showers when they're experiencing a manic episode. The showers aren't *causing* the mania; they're an early sign of it. So it may be that when some people start having a psychotic episode, they tend to use chatbots more and are more likely to talk about delusions while doing so.

Another possibility is exacerbation. Perhaps these people would have had an episode regardless, but using a chatbot somehow made the episode worse or happen earlier. It's unlikely that someone without any risk factors or underlying vulnerability to psychosis or mania would have it triggered by a chatbot, but we don't know for sure.

By Ariel Bleicher | Illustration by Paige Stampatori

Chatbot conversations have also been linked to suicides. Are there links to other symptoms of mental illness?
I've heard of cases related to anxiety and obsessive-compulsive disorder. My colleague has a patient who worries a lot about her health. She'll go to ChatGPT and describe an ache or pain, and the chatbot will say something like, "That sounds pretty normal, but if you experience these more serious things, you should call a doctor." As an individual response, it's appropriately reassuring. But unfortunately, this patient is giving ChatGPT the same prompt 20 times a day and getting the same answer. And because there's no person on the other side to recognize the pattern, it becomes reinforcing and could make the anxiety worse.

You're leading a study of the relationship between chatbots and mental health. What do you hope to learn?
We're inviting patients at UCSF's psychiatry and behavioral health clinics to send us the logs of their chatbot conversations, and then we'll compare those logs with what we know about their mental health. For example, if someone is depressed, do they use different kinds of words? Do they talk more or less? Similarly for mania, psychosis, and other mental illnesses, we're interested to see if we can find markers of those illnesses in the chatbot logs, which could help us understand these conditions better and improve our treatments. And if people are having conversations that seem out of the ordinary or unsafe, we want to dig into those to learn what's happening and how it relates to their illness.

You're also creating a screening tool for problematic chatbot use. How does it work?
It's a questionnaire, like the ones you've probably filled out at your doctor's office for depression or alcohol use. Psychiatrists have a set of warning signs we use to screen for problematic use disorders that don't involve substances, like gambling disorder or internet gaming disorder (which is not officially a diagnosis but may soon become one). We ask questions like "Are you being honest with other people about what you're doing?" or "Is it affecting your performance at work or school?" or "Have you ever tried to stop but can't?"

All those factors apply to chatbot use, and we identified three potential new ones. The first we're calling functional dependence: Are you no longer able to complete tasks without using a chatbot? The second is relational dependence: Do you prefer to spend time chatting with a chatbot rather than with your family or friends? Do you feel the chatbot understands you better than anyone else? And then the third factor is related to AI literacy: How often do you believe AI over a human expert? Do you believe the chatbot has genuine feelings or its own consciousness? None of these factors are necessarily problematic on their own; it's the combination that may be concerning.

What can doctors do to help?
There aren't yet any evidence-based interventions specifically developed for problematic chatbot use. But generally speaking, if a clinician is worried about a patient, they should ask them how they use chatbots and why it's important to them. Then, depending on the nature of the problem, there may be psychotherapeutic techniques or therapies that could be adapted to address it.

Do you use chatbots yourself?
I use AI systems routinely to write and analyze computer code and to flesh out research ideas. I don't use them for my emotional life, but I have close colleagues who do. They'll talk through conversations they've had with a partner or share their thoughts and feelings.

Do you worry about the impact of chatbots on your or their mental health?
I can't say that I do. I don't think there's a lot of danger in using these tools as long as you understand what they can and can't do, and you're able to reason and think clearly.

That said, there may be something unique about the way chatbots appear to have real conversations. I suspect these systems tap into parts of our brain that are attuned to interacting with other people, which no other technology in human history has been able to do. What that means, we don't know yet, but it's important that we find out.

PHOTO: ERIN LUBIN

How Exercise Shields the Brain

Exercise does more than strengthen muscles. It also helps protect the brain. UCSF researchers have identified a key player in that effect, a protein called clusterin that rises in the bloodstream after physical activity.

In studies in mice, higher levels of clusterin reduced inflammation and helped preserve connections between brain cells. When researchers blocked the protein, those benefits disappeared — suggesting it plays a central role in the brain's response to exercise. The team also found that clusterin appears to act on the brain's blood vessels, helping dial down inflammation that can damage tissues over time, a process linked to diseases like Alzheimer's. The findings help explain how physical activity helps keep the brain resilient over time.



Rethinking Breast Cancer Screening

A pioneering study suggests that adjusting mammogram frequency based on a patient's risk, rather than automatically recommending annual mammograms, can avoid unnecessary screenings while still limiting the incidence of advanced breast cancers. The finding could transform screening guidelines and alter clinical practice.

The Skin: Visible Clues to Disease

Here are nearly a dozen ways UCSF researchers are using the skin to detect cancer earlier, decode immune diseases, and reveal how conditions throughout the body show up on its surface.

AGING CELLS MAY HELP HEAL

Some senescent cells — long associated with aging — are actually present in young, healthy skin, where they can help repair damaged tissue.

GUT TROUBLE, SKIN TROUBLE

Researchers have found that gut inflammation can drive skin disease even without changes to the skin microbiome, revealing a direct immune link between our innards and our skin.



WHEN WILDFIRE SMOKE HITS THE SKIN

In a first-of-its-kind study, researchers found that heavy wildfire smoke is linked to increased clinic visits for eczema and itchy skin, suggesting that pollution can trigger flares outside the lungs.

CANCER RISK BEYOND SUNLIGHT

In a UCSF study, women with higher exposure to PFAS "forever chemicals" had greater odds of being diagnosed with melanoma, suggesting there are environmental risks beyond ultraviolet (UV) exposure.



AN ITCH THAT CONTROLS INFLAMMATION

Itch-sensing neurons, it turns out, don't just trigger scratching — they also help regulate inflammation, revealing that they play an unexpected role in immune control.

A smarter way to read a rash

Developed at UCSF, RashX is a molecular profiling tool that matches a patient's genetic data to a database of known skin diagnoses, helping clinicians differentiate between similar conditions like psoriasis and eczema with greater precision.



Seeing what others miss

Dermatologists are working to ensure that conditions like melanoma and inflammatory rashes are caught just as early in people with darker skin tones, who have historically been diagnosed later, delaying treatment.

CLOSING IN ON A LONG-OVERLOOKED DISEASE

UCSF's HS PROGRESS registry is tracking patients with a condition called hidradenitis suppurativa to better understand this painful, inflammatory skin disease, which often goes undiagnosed for years.

ECZEMA & ASTHMA, LINKED

New work is uncovering shared immune pathways in eczema and asthma, raising the prospect of treatments that could address inflammation across organs.

A RESEARCH TROVE

UCSF holds one of the world's largest and most diverse collections of melanoma tissue samples, giving researchers a rich resource to study how such tumors grow, spread, and often evade treatment.



The hidden cost of a tan

In tanning bed users as young as their 30s, researchers found more cancer-linked genetic mutations than in nontanners twice their age — evidence that artificial UV radiation ages skin far faster than the passage of years.

ICONS: FLATICON.COM; TANNING BED: BSD STUDIO



PHOTO: NOAH BERGER

Andy Josephson Named Dean of the School of Medicine

S. Andrew Josephson, MD, has been named the next dean of the UCSF School of Medicine, as well as vice chancellor for clinical affairs of the university. A neurologist who has led the top-ranked Department of Neurology since 2017, Josephson joined UCSF in 2001 for his internship and residency and has spent his entire career here.

Under his leadership, the Neurology department became the nation's top recipient of National Institutes of Health neurology funding, receiving nearly $120 million in 2025. He helped launch the neurohospitalist model of care, now a national standard, and has championed cross-disciplinary collaborations that have led to advances in the treatment of depression, dementia, and other neurological conditions. He also serves as editor-in-chief of *JAMA Neurology* and is UCSF's Castro Franceschi and Mitchell Neurohospitalist Distinguished Professor.

Colleagues describe him as a gifted teacher and connector. "He has incredible energy and optimism, and a deep knowledge of the university in all of its missions, including research," says Chancellor Sam Hawgood.

Josephson's appointment comes as Talmadge King, Jr., MD, concludes an 11-year tenure leading the School of Medicine.

Early Clues to Pregnancy Complications

Many pregnancy complications are difficult to detect early, and conditions like preeclampsia often emerge only after damage is underway. Now, UCSF researchers have found early warning signals in the placenta — the vital link between mother and baby.

The team analyzed cells at the maternal-fetal interface and identified patterns in how they communicate that were linked to a higher likelihood of complications, including preeclampsia. These cellular interactions help regulate how the placenta develops and functions. When that communication is disrupted, it may set the stage for problems later in pregnancy.

The finding suggests that such early shifts could eventually help identify at-risk pregnancies, making earlier intervention possible.

Recommended:

Books, Videos, & Podcasts

READ

The End of Violence: Eliminating the World's Most Dangerous Epidemic

In this provocative book, UCSF resident alum and epidemiologist Gary Slutkin, MD, draws on his decades of work combating tuberculosis, cholera, and HIV at the World Health Organization to reframe violence as a contagious disease. He offers a blueprint for prevention grounded in interruption, community intervention, and shifting social norms.

WATCH

UCSF's Last Lecture

Jennifer Cocohoba, PharmD '01, MAS '08, a professor of clinical pharmacy, reflects on time, connection, and the meaning of care. Shaped by her years providing HIV care and her long-term relationships with patients, she shows how trust is built slowly — and why the moments that matter most are when someone finally lets you in. Watch it on UCSF's YouTube channel.

LISTEN

GeriPal Podcast

Hosted by UCSF physicians Alex Smith, MD '02, MS, MPH, and Eric Widera, MD '02, GeriPal explores aging and serious illness through frank conversations with clinicians, researchers, and patients. It's thoughtful, occasionally funny, and focused on helping people live well, even in life's hardest circumstances.

Is Testosterone a Miracle Hormone?

Politicians, influencers, and telehealth startups want you to think so.

By Cyril Manning | Illustration by Farah Hamade



Testosterone is having a moment. Politicians tout it as a pillar of vitality. Telehealth startups sell it like a subscription service. But much of what the public hears about testosterone is incomplete, oversimplified, or flat-out wrong.

We asked two sexual health specialists — urologist Alan Shindel, MD, MAS, and ob-gyn Tami Rowen, MD '09, MS '07 — to bust the most persistent myths about testosterone therapy.

MYTH #1: Men's testosterone levels are in crisis.

Scroll through enough health news, and you'll come away believing that modern men are in the grip of a testosterone emergency — that environmental toxins, processed foods, and sedentary lifestyles have sent male hormone levels plummeting at an alarming rate.

Shindel isn't buying it.

True, rising rates of obesity and sedentary behavior aren't doing testosterone any favors. As people become heavier and less active, there's reason to believe these changes could be dragging down average hormone levels. However, that's a broad health problem, not a testosterone-specific crisis. "The ramifications of obesity and sedentary lifestyles go well beyond testosterone," says Shindel, a professor of urology.

In other words, the trend is real but overhyped. A long-running study found average testosterone levels have dropped roughly 1% per year over the past two decades. The decline shows up even in young men with healthy weight, so obesity and inactivity explain part of the downturn, but not all of it. Environmental pollutants, changes in sleep patterns, and shifts in diet are all under investigation as additional explanations. It appears to be a generational drift with no single villain.

MYTH #2: Men hit a testosterone "cliff" at middle age.

In women, estradiol levels really do drop off sharply at midlife. But men experience hormone changes differently. For them, it's a slow, steady downhill slope that begins well before middle age and continues for the rest of their lives. Sudden drops can happen due to an injury to the testicles or certain medical treatments, but these are exceptions, not the rule.

What muddies the picture is that many men start feeling the cumulative effects of aging in midlife: sleep worsens, stress accumulates, and waistlines expand. "It's tempting to think that maybe if we hormone ourselves up, we'll be eternally young," Shindel says. "But that's not the case. The public is being fed information about testosterone that is incomplete."

MYTH #3: Testosterone therapy causes heart attacks and prostate cancer.

For years, these two fears dominated conversations about testosterone therapy. But neither is supported by recent evidence.

The decade-old studies behind the cardiac scare had serious methodological flaws. In 2023, the *New England Journal of Medicine* published a rigorous, large-scale study of 5,200 men with low testosterone who were at elevated cardiovascular risk. It found no significant difference in the rate of heart attacks, strokes, or other major cardiovascular events between patients receiving testosterone and those receiving a placebo.

The prostate cancer fear has an even older pedigree. Doctors have long known that castrating a man with prostate cancer causes the cancer to regress. However, the logical assumption — that testosterone must cause cancer — has not held up to a quarter-century of evidence: In men who are properly screened and monitored, testosterone therapy does not appear to meaningfully increase prostate cancer risk.

That doesn't mean testosterone is risk-free. It can cause modest increases in blood pressure and raise hematocrit — the proportion of red blood cells in the blood. If hematocrit climbs too high, it can increase the risk of blood clots.

But perhaps the most common adverse outcome, Shindel says, is underwhelming results. "Plenty of people get on testosterone, give it a good try for three to six months, their numbers come up, things look pretty good on paper — but nothing feels different."

MYTH #4: Testosterone is a male hormone.

"Women actually have more circulating testosterone than estradiol," says Rowen, an associate professor of obstetrics, gynecology, and reproductive sciences. She recalls pushing back on her children's elementary school for teaching the testosterone-equals-male shorthand — a misconception she also encounters when training medical students. "That's just not true," she says.

Yet research on testosterone in women lags decades behind work done in men. Studies examining whether supplementation improves cognition, mood, or muscle recovery in women have mostly come up short, with one exception: Testosterone has been shown to improve libido, particularly in postmenopausal women.

Despite that evidence, there's no FDA-approved testosterone product for women. Not because it doesn't show a beneficial effect but because the FDA determined there wasn't enough long-term safety data, particularly around breast cancer risk. "Viagra was fast-tracked," Rowen says. "Other medications for men are fast-tracked long before there's long-term safety data — including testosterone for men."

And without a product approved for women, it's hard to run the studies needed to generate the data the FDA wants — a catch-22 that has stalled progress for years. Rowen will consider testosterone therapy for peri- and postmenopausal patients, depending on their symptoms, but with clear caveats: The treatment is off-label, it comes with side effects, and the evidence for many of its purported benefits remains "very equivocal."

MYTH #5: If you have low energy and low libido, it must be a testosterone problem.

Fatigue, flagging sex drive, trouble concentrating, depressed mood — these can be symptoms of many things, including poor sleep, chronic stress, depression, cardiovascular disease, medication side effects, and relationship problems.

"It's a little chicken-and-egg," Shindel says. "Are you sleep-deprived and fatigued because you're low on testosterone? Or is your testosterone flagging because you're sleep-deprived and fatigued?"

He sees this confusion regularly in his clinic, particularly with erectile dysfunction. Patients arrive expecting a simple hormone explanation. "Well, a lot goes into erections," he says. "It's about your vascular health. It's about your neurology. It's about the medicines you're taking. It's about how you feel about your partner."

Testosterone affects many biological functions, and deficiency in it correlates with real quality-of-life problems. But correlation isn't prescription. "It's not a panacea," Shindel says. "Plenty of other things are going to cause that same set of symptoms."

MYTH #6: Testosterone boosts male fertility.

Even some doctors get this one wrong.

It sounds intuitive: Testosterone is the quintessential male reproductive hormone, so taking more of it should boost fertility, right? In fact, the opposite is true.

When testosterone enters the body from an external source, the pituitary gland detects the surplus and shuts off the signals that drive the production of both testosterone and sperm inside the testicles. The result: A man's testosterone levels look fine on a blood test, but his sperm count can plummet to zero. And the effects can persist well after he stops taking it.

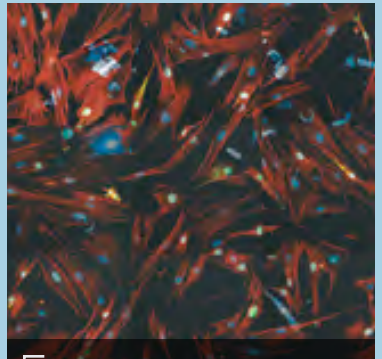
"It is a pretty potent inhibitor of sperm production," Shindel says. For any man who plans to have biological children — even in the distant future — this needs to be part of the conversation before starting testosterone therapy.

How widespread is the confusion? A striking survey found that a quarter of urologists, when asked how they would treat a man with fertility concerns, said they'd prescribe testosterone. "This is completely, flat-out wrong," Shindel says. If specialists can get it wrong, it's no surprise that patients and primary care doctors might, too.

Why Healing Slows with Age — and How to Speed It Up

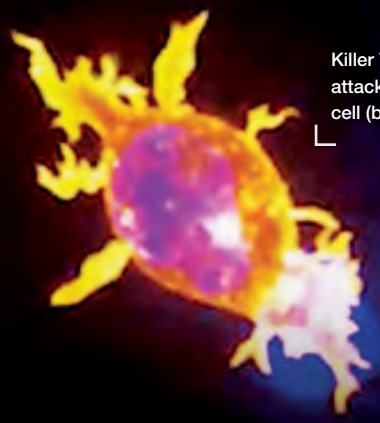
As we age, the body's ability to repair damaged tissue declines. Wounds heal more slowly, and recovery takes longer. UCSF researchers have identified a set of proteins that may help reverse that trend.

In studies in older mice, boosting these proteins helped restore the activity of fibroblasts, cells that are essential for rebuilding damaged tissue. The treatment sped up healing, bringing it closer to levels seen in younger animals. The researchers found that these proteins help reactivate gene programs involved in repair that become less active over time, limiting the body's ability to regenerate. The findings suggest new ways to restore the body's natural repair systems.



Fibroblasts (green) are the cells that prop up the 3D shapes of all of our organs. When we age, they slow down, leading to wrinkles in the skin and poor healing everywhere.

FIBROBLASTS: LI LAB



Killer T cell (orange) attacking a cancer cell (blue).

Turning the Body into a Cancer Fighter

For years, one of the most powerful weapons against certain blood cancers, CAR-T therapy, has required an elaborate process: Doctors extract a patient's immune cells, send them to a specialized lab to be genetically reprogrammed to fight cancer, then return them to the patient's bloodstream. The approach has transformed cancer care — but the time and expense of the process put it out of reach for many patients.

Now, UCSF researchers have found a way to do it inside the body. In studies in mice, they used targeted nanoparticles to deliver genetic instructions that reprogrammed T cells to recognize and attack cancer cells.

By turning the body into its own manufacturing site, this approach could make such therapies faster, simpler, and more accessible. While still early, the work points to a new generation of cancer treatments that could reach far more patients.

Sun Protection Doesn't Have to Be Pricey



Protecting your skin from sun damage doesn't require expensive products. In a recent UCSF study, researchers found that many lower-cost sunscreens provide protection from harmful ultraviolet (UV) rays comparable to that of higher-priced options.

The basics matter most: Use a broad-spectrum sunscreen that's SPF 30 or higher, apply it generously, and reapply it every two hours. But sunscreen is only part of the equation. Seeking shade, wearing protective clothing, and avoiding peak sun hours can further reduce your UV exposure.

The bottom line: Consistency, not cost, makes the biggest difference.

The Hidden Risks of Thirdhand Smoke

Even after a cigarette is extinguished, toxic residue from its smoke can linger on clothes, furniture, and other surfaces, posing risks long after the air clears. Researchers are increasingly concerned about this "thirdhand smoke."

Scientists at UCSF, who lead the California Thirdhand Smoke Research Consortium, have been studying these risks. Their findings helped inform a new California law that requires disclosure of thirdhand smoke in real estate transactions, the first of its kind.

Studies show that these chemicals can be absorbed through the skin, inhaled, or ingested, especially by young children, who spend more time on floors and put objects in their mouths. Exposure has been linked to respiratory problems and other health risks. Unlike secondhand smoke, which dissipates, thirdhand smoke can persist for months in indoor environments.

Eliminating indoor smoking remains the most effective way to combat thirdhand smoke.



T CELL: ALEX RITTER; CIGARETTE: ABSCENT04; PIG: ALEX SECRET

Breakthroughs and Other Buzz

Is your brain aging faster than you are?

Your "brain age" may matter more than your chronological age. Using AI to analyze the brain's electrical signals during sleep, UCSF researchers have linked accelerated brain aging to higher dementia risk, opening a window for earlier detection.

When medications spiral: Side effects from common drugs, including those used to treat pain and heart disease, can trigger a cascade of additional prescriptions. UCSF researchers found this pattern can lead to unnecessary treatment and hospitalizations, exposing patients to avoidable risks.

MS's most vulnerable victims:

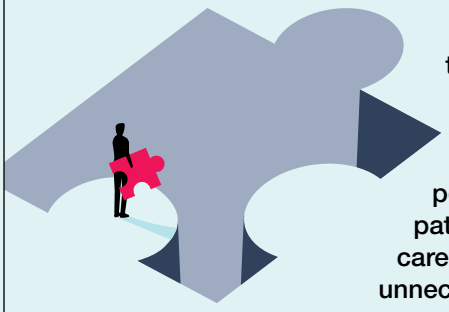
UCSF scientists have uncovered how multiple sclerosis kills neurons — and why some of the brain's most advanced cells are especially vulnerable. The work offers new clues to the disease's progression and potential treatment targets.

A new target on tumors: UCSF scientists discovered that a cancer-causing enzyme appears on the surface of many tumors, making them easier to target with drugs. The finding could lead to more precise cancer therapies.

A faster test for TB:

Diagnosing tuberculosis can take hours or even days. A new portable test developed by UCSF researchers delivers lab-level accuracy in just minutes. It could speed treatment, especially in low-resource settings where quick diagnosis is crucial.

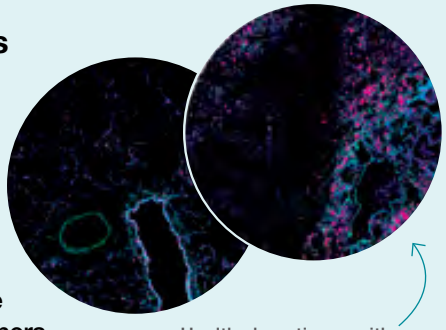
The missing piece in modern medicine: The right diagnosis is an essential precursor to effective treatment. A UCSF-led analysis found that diagnostic testing is often underfunded and underused, even though it guides most medical decisions. The researchers argue that strengthening diagnostics should be a priority for health systems and policymakers, to help patients get the right care sooner and avoid unnecessary treatment.



HIV control without daily drugs:

Could HIV be controlled without lifelong medication? In a small UCSF study, an experimental immunotherapy agent helped most participants keep the virus in check even after stopping treatment. By reprogramming the immune system, the approach points to a future when some patients may not need daily therapy.

How age fuels dangerous inflammation: Older adults are more likely to suffer severe illness from infections like COVID-19 and the flu. UCSF researchers found that aging lung cells can overreact, triggering damaging inflammation, meaning that calming this response could help reduce severe illness.



Healthy lung tissue with calm immune cells (left). Lung tissue from a patient with severe COVID-19 (right), showing overactive immune cells (pink) that contribute to excessive inflammation.

The opioid pullback's hidden cost:

Efforts to reduce opioid use and thus abuse may have had unintended consequences. UCSF researchers found that guidelines designed to limit opioid overprescribing have left some nursing home residents, especially people of color, with undertreated chronic pain. The findings highlight the challenge of balancing safety and care.

The body's defense against Alzheimer's:

A newly identified enzyme helps clear toxic tau proteins from the brain. UCSF researchers found that this cleanup process is associated with resilience against dementia, suggesting a potential new strategy for slowing Alzheimer's disease.

Bridging the digital divide in care: Telehealth is expanding — but not for everyone. UCSF researchers found that fewer than half of health systems assess whether patients can use digital tools. If the issue isn't addressed, the shift to online care could widen health disparities.

IDing schizophrenia early:

UCSF researchers are studying biomarkers that may identify people at risk for schizophrenia before symptoms appear. Earlier detection could allow intervention sooner, potentially delaying or reducing the severity of the disorder.

Transplant care: Kidney transplant recipients often must take multiple drugs daily. A UCSF study suggests that instead, a monthly infusion of two proteins could simplify care, reduce side effects, and better protect transplanted organs.

Stopping lung scarring:

Pulmonary fibrosis gradually replaces healthy lung tissue with scar tissue, robbing people of their ability to breathe. UCSF scientists identified a key cellular switch driving the disease and blocked it in early studies to halt scarring.

PUZZLE: YUTTHANA GAETGEAW; LUNG SAMPLES: PENG LAB

How Can We Fix the **Health Care Workforce** Shortage?

The health care worker shortage is one of the defining challenges facing medicine today, affecting everything from worker burnout to access to care. We spoke with **Joanne Spetz, PhD**, director of UCSF's Philip R. Lee Institute for Health Policy Studies, to find out what's causing the shortage — and how to solve it.

By Jaimie Seaton
Photography by Anastasiia Sapon





What factors are driving the shortage?
It's not a uniform issue, and the factors vary. In some health care professions and parts of the United States, there is no shortage, but rural regions worldwide consistently face shortages. A series of trends has converged over the past seven or eight years, including the aging of baby boomers. Their medical needs are rising at the same time as many boomers who work in health care are retiring.

The COVID pandemic also contributed, due to burnout and workplace stress, although those effects do seem to have calmed down. Additionally, some training programs took a hiatus from admitting cohorts, and some students took extra time to finish.

What are the biggest economic forces shaping the workforce right now?
The rising cost of health care is a concern, and efforts to control spending by federal and state governments are another driver. For example, HR1, the so-called Big Beautiful Bill, will enact significant cuts to Medicaid. For many health care organizations, this will substantially constrain their revenues and their ability to hire staff.

Inflation is also putting pressure on organizations and workers, especially those in jobs that don't require a license. If you're an unlicensed nursing assistant, for example, your pay is often not much above minimum wage, and you have little career trajectory unless you go back to school. That becomes a real challenge for recruiting and retaining people.

Is the situation throughout the industry or in specific practice areas?
Primary care often faces shortages. Primary care physicians typically earn less than specialists, and research has documented that the combination of lower salaries and high medical school debt can steer doctors toward specialty training. The United States has also long relied on international medical graduates to help fill primary care gaps, but recent immigration policies may make that harder.

Geriatrics also faces ongoing shortages, as do licensed and certified occupations, such as occupational therapy and clinical laboratory jobs. Entry-level jobs in the long-term care field are another trouble spot. Turnover rates are extremely high, while demand is rising because of the aging population.

How do patients experience shortages?
It can be difficult to get an appointment with a primary care provider, even in cities like Boston, which has one of the highest numbers of doctors per capita. It's often worse in rural communities. If you're on Medicaid or have really high copayments, finding affordable care gets more and more difficult.

People also see it as delays in the emergency department (ED) and boarding in the ED because there aren't enough beds in other units. And it can be hard to get appropriate assisted living or nursing home placements or to find a home care aide.

What is UCSF doing to better understand and address these challenges?
UCSF conducts research that informs health workforce policy and planning, looking at its supply, demand, and stresses as well as at barriers to growth and factors driving burnout. The Healthforce Center at UCSF, which I've been affiliated with since I joined the faculty 25 years ago, leads much of that work. We collaborate with the California Department of Health Care Access and Information, the state medical board, and other health professions boards to advance state and federal investments in the workforce.

Additionally, UCSF has programs to generate job opportunities for people in our local community. They provide training in clerical and administrative health system roles and health IT support, as well as accelerated pathways to becoming medical assistants, phlebotomists, or EKG techs.

What would a more stable, sustainable workforce look like, and how would it improve patient experiences?
Professionals in the field would feel well supported with reasonable workloads, adequate support staff, and enough colleagues to prevent burnout. Turnover rates would be low, and entry-level jobs would have viable career pathways.

Patients would get timely care that goes beyond emergency department diagnosis and treatment, including help navigating the broader range of services they need after discharge.

Patients would also have team-based care customized to the clinical setting and their individual needs. One model is the patient-centered medical home, pioneered by UCSF's Department of Family and Community Medicine, which brings together a physician, an advanced practice nurse, RNs, and medical assistants to provide coordinated, proactive care. Each team member offers specialized skills. For example, one medical assistant might use the electronic health records system to flag patients due for monitoring, while another might connect people to community nutrition programs.

What will it take to get us to where we should be?
We need two big changes. First, health care financing must shift to a value-based payment structure. The current fee-for-service model pays physicians per procedure, incentivizing doctors to do everything themselves rather than delegate to a broader team. Value-based payment rewards health outcomes over volume, creating both the room and the incentive for true team-based care. Second, we must eliminate the term "unskilled" for jobs without formal degrees, creating viable career pathways so these workers get the respect and reward they deserve.

Joanne Spetz is also the Brenda and Jeffrey L. Kang Presidential Chair in Health Care Financing and the Claire D. and Ralph G. Brindis Professor of Health Policy Studies.



How Digital Life Erodes Cognitive Health — and How You Can Get It Back

Screens keep us constantly connected and entertained. Scientists are beginning to understand the costs.

By Elizabeth Daube
Photo Illustration by Justin Metz
Interior Illustrations by Farah Hamade



For Jason Nagata, MD, the wake-up call came during the pandemic.

A specialist in adolescent eating disorders, he watched as the number of teenagers admitted to his unit tripled. Some weren't getting better. They were hooked up to heart monitors and facing life-threatening complications, still scrolling through pro-anorexia content on their social media feeds. A few girls even used the hospital's Wi-Fi to find each other online.

"They were sharing tips on how to continue to lose weight," says Nagata, an associate professor of pediatrics and 2013 UCSF alum. "We actually had to remove devices from several patients because social media was undermining their recovery."

He's not the only UC San Francisco researcher worried that the technology we tote around 24/7 might be hurting our health. For years, neuroscientist Adam Gazzaley, MD, PhD, has argued that we've entered a "cognition crisis" — that the information overload supplied by digital devices is degrading our ability to pay attention, make decisions, and regulate our emotions.

Evidence has stacked up. An analysis of 70-plus studies linked heavy consumption of short-form videos to poorer attention spans and impulse control, raising the question of whether "brain rot" is real. Researchers at UC Irvine found that people only stick to a single screen for about 47 seconds now — down from 2.5 minutes in 2004. Reading scores among high school seniors recently hit their lowest point since 1992. It's the kind of decline that inspired the *Financial Times* to ask, "Have humans passed peak brain power?"

No single study can answer that question. But scientists are trying to understand the risks of constantly checking our apps, and their work isn't limited to a particular diagnosis, like ADHD.

"The cognition crisis is not just a clinical problem," Gazzaley says. "It's a problem for our species."



Your Brain on Distraction 😵‍💫

When Gazzaley started seeing neurology patients in the early 2000s, they often described "senior moments," like finding themselves by the fridge, unable to recall what they wanted. They lost focus easily. Even then, some attributed it to new technology. Broadband internet, instant messaging, mobile phones — what had seemed impossible just a few years earlier was suddenly everywhere. Gazzaley, now the David Dolby Distinguished Professor, began studying distraction with those patients in mind.

Memory and attention are crucial to cognitive control, a brain system that enables humans to direct their mental resources. If you've ever attempted a complex task — say, writing a report — you know how fragile cognitive control can be. Your mind drifts, or your phone vibrates, or a calendar reminder pops up.

"Multitasking" wasn't even a word until the 1960s, when it was coined to capture a computer's ability to execute multiple processes,

The Pull of the Infinite Scroll

seemingly all at once. At some point, humans started using it to describe our productivity. The thing is, humans are not computers. Experiments in Gazzaley's lab have found that people aren't just *bad* at multitasking; we're not capable of it.

You can walk and talk because walking requires little effort from your frontal lobe. But when you combine two tasks that require attention — for example, scrolling the news while you're on a call with a friend — neither goes well. Gazzaley's research shows that the brain has to shift its resources to the alternative input, then switch back. Even ignoring a distraction takes a toll.

The result of rapid switching, on purpose or not? Poorer memory. More errors. And, if you're caught barely listening, relationship trouble.

"Our cognitive control is really quite limited," Gazzaley writes in *The Distracted Mind: Ancient Brains in a High-Tech World*, a book he co-authored with Larry D. Rosen. "The conflict is between our goal-setting abilities, which are so highly evolved ... and our goal-enactment abilities, which have not evolved much."

Of course, people's minds wandered long before the internet. Technology doesn't have some magical ability to break your cognition; it just gives you access to infinite information, plus frequent reminders to open your apps. And that might push your delicate cognitive control past its limits. We also seek out digital disruptions, Gazzaley theorizes, because human brains evolved to forage not just for food but also for useful information. Now that we have access to almost limitless input, some of us tap it constantly — even when info foraging pulls us away from our goals.

When I ask Gazzaley if he'd change anything about his book, which was published in 2016, he shakes his head. If anything, the challenges captured in *The Distracted Mind* have only gotten worse.

"The book has aged really well in terms of cognitive neuroscience," he says. "From a societal perspective, it's sad that it's aged so well."

The morning after our interview, I'm feeling sharp. Ambitious. I'm almost done reading Gazzaley's book — a once-ordinary feat of focus that even some college professors no longer expect of their students. As I pull out a mug to make coffee, my cat jumps on the counter, and her water fountain rushes to mind; *when did I last refill it?* I load the grounds, hit a button, and scurry to the fountain. As I turn away, I hear the reassuring hum of the espresso machine at work.

When I turn back, the evidence of my hubris is pouring onto the counter, puddling on the floor. My mug sits nearby, forgotten the moment I attempted to multitask.

Fragmented attention can have much higher stakes. During the pandemic, a lot of kids used their devices pretty much nonstop. When Nagata and other researchers examined data from young teenagers enrolled in the Adolescent Brain Cognitive Development (ABCD) study, they saw that the teens' recreational screen time doubled in 2020, from about four hours a day to eight.

"Everyone was glued to their phones," Nagata says. "Many of these kids were also on Zoom for school for eight hours. That's like 16 hours online. It's *all* day."

ABCD, the largest U.S. study of brain development, has tracked 12,000 children since 2016, helping scientists unpack the consequences of how kids spend time online. In 2024, Nagata's team found teenagers' recreational phone use had ticked up to about 8.5 hours a day — dashing hopes for a post-pandemic drop. The increased screen time was linked to more severe symptoms of inattention, anxiety, and aggression.

Nagata also examined pre-teens, from about age 10 to 13, over a few years. (The legal minimum age for using social media platforms is 13, but two-thirds of 11- and 12-year-olds have accounts.) As they used more social media, their depression symptoms went up 35%. In a study released last fall, Nagata tracked a similar group and found that young teens spending more time on social media tended to do slightly but consistently worse on reading, memory, and vocabulary tests. The more they used it, the more their scores dropped.

> "Parents used to come to me asking a lot of questions about how to help their kids. Now, a lot of the parents are going, ***'I need help, too.'***"
>
> ***— Jason Nagata, MD***

"The effects are kind of all-encompassing," Nagata says. "Social media is crowding out time for homework and sleep — which are important for cognitive development and learning — and for being with family or friends.

"Then there's the actual content. If they're getting cyberbullied or exposed to distressing content, whether it's violent or sexual or extreme in some other way, they're not in a mental space where they can think about schoolwork."

It's difficult to tease out precisely why cognitive and emotional declines happen. Another recent analysis of the ABCD data suggests that attention problems do not merely occur alongside anxiety and depression; diminished attention might harm emotional regulation and, in turn, worsen mental health. Still, proving that social media causes such harm is tricky. Skeptics argue that kids spend more time on social media because they are already depressed. That's not, however, the story that ABCD tells: Higher social media use among pre-teens predicted increases in depressive symptoms over time, but their baseline depression did not predict increased social media use. In other words, the social media came first, then the depression.

While there's no formal diagnosis for social media addiction yet, Nagata's team has started documenting addiction-like symptoms in young teens. The patterns are similar to what he saw in patients hospitalized with eating disorders: trying to cut back on social media but failing and continuing to use it even when it's obviously harming them. Social media deploys a variety of features — like the infinite scroll, autoplay of video, and incessant notifications — designed to keep users engaged as long as possible.

"The psychological theory is called variable reward, and it's similar to slot machines," Nagata says. "The features create a loop in which your attention is constantly pulled forward, and then your brain's reward system reinforces checking behavior, even when the payoff is not consistent."

Concern about smartphones has led many schools to ban them. Despite the bans, Nagata's group recently found that the average teenager still spends about 70 minutes a day on smartphones at school. Because the study tracked app usage, the team could see exactly where that time went.

"Social media was the top," Nagata says. "YouTube was second, and third was video games."

When Nagata talks to families, they're concerned about this data but struggling to act on it. The American Academy of Pediatrics once recommended a screen time limit for children: two hours a day. They dropped the guideline in 2016 because almost no one was following it.

"Parents used to come to me asking a lot of questions about how to help their kids," Nagata says. "Now, a lot of the parents are going, 'I need help, too.'"

The Misinformation Superhighway



Your social media feed says a lot about you. Mine has headlines like "Why some cats bond ... and others just coexist forever" and "The truth about people pleasing" and "Suburban consumer cannot wait to try private equity-backed bakery." You can infer my preoccupations: animals, psychology, satire, fresh bread. If I didn't pay for news — 83% of Americans don't — this feed might supply most of the information I use to understand the world.

That would include a video from a supposed attorney, offering advice on French tax law. Typically, his account indulges my fantasy of retiring in Europe. But this clip was alarming: a 6.5% annual tax on all assets for health care alone? If I hadn't dug deeper, I might never have learned that it wasn't true. It was just clickbait.

In an information economy driven chiefly by our attention, there's a cost to not exercising much control over where we place it. The fragmented attention that Gazzaley studies in the lab and Nagata analyzes in adolescents might also make us worse at discerning whether the information we encounter online is accurate. It's a real problem, given how quickly misinformation can spread: In a recent analysis of 35 million Facebook posts, researchers found that 3 of every 4 news links were shared without being clicked — suggesting most people endorsed articles they never actually read.

Joe Pierre, MD, a professor of psychiatry, has spent years trying to understand how people come to believe things that aren't true. In his recent book *False: How Mistrust, Disinformation, and Motivated Reasoning Make Us Believe Things That Aren't True*, Pierre details how factual errors and even outright lies flourish in a digital news environment.





> “Instead of the ***free market*** of opinion, we’ve got a ***flea market***. There may be some hidden gems, but mostly there’s **a lot of junk**.”
>
> ***— Joe Pierre, MD***

“We live in a click-based information economy,” Pierre says. “One way to get clicks is to be salacious, ridiculous, gossipy. Misinformation is also a really good way to get people’s attention. Instead of the free market of opinion, we’ve got a flea market. There may be some hidden gems, but mostly there’s a lot of junk.”

All humans use cognitive shortcuts that, left unchecked, make it difficult to sort fact from fiction. According to Pierre, the main culprit is confirmation bias: favoring information that affirms what we already believe, while reflexively dismissing whatever challenges our beliefs. Pierre says algorithmically curated content feeds — which serve more of whatever you’ve already viewed or liked — fuel “confirmation bias on steroids,” entrenching users’ beliefs and stoking their outrage. In 2025, a Pew survey found that 4 in 5 U.S. adults believe voters from opposing parties cannot agree on basic facts.

“People fundamentally trust very different sources of information now,” says Pierre. “There is no shared universal reality.”

Unfortunately, the alternative to passively consuming misinformation requires exactly the kind of deliberate, high-effort cognition that digital distraction is making more difficult. Pierre’s antidote, which he calls the “Holy Trinity of truth detection,” involves three habits: intellectual humility (accepting you might be wrong), cognitive flexibility (changing your mind with new evidence), and analytical thinking.

“Analytical thinking means that when I encounter information, I’m slowing down,” Pierre says. “I’m thinking twice. I’m keeping in mind that what I’m reading might not be true, especially if it’s something that validates what I want to believe.”

Pierre’s seen this approach play out. He points to his college roommate, Adam Riess, who was once puzzled by Hubble telescope data that contradicted a prevailing theory of how the universe expands. Riess could have dismissed the data as an anomaly. Instead, he played a key role in the discovery of dark energy and was awarded the 2011 Nobel Prize in Physics.

“He said, ‘Well, we really have to look at this,’ and his data radically changed our ideas about the universe,” Pierre says. “Some people think of that as a sort of flip-flopping. That is actually the strength of science: It’s not dogma.”

But most people don’t approach the internet like a scientist. They just scroll.

Routes to Remediation



A "vigilance task" measures your ability to sustain your attention. It is not fun. You stare at a blank screen. A square briefly blinks into view, and you tap a button to confirm you saw it. That's it, over and over, for 20 minutes.

"It's very boring," says David Ziegler, PhD, an associate professor of neurology and a collaborator of Gazzaley's at UCSF's Neuroscape Center. But that's the point: The Neuroscape team needs to measure how well a participant can focus on something tedious. Otherwise, they won't be able to tell if the tools they're developing to hone cognitive control are working.

Their research aims to make exercising your focus less frustrating — "a little gamified," Ziegler says. He oversees trials of MediTrain, a meditation app that adjusts session length based on your ability to pay attention to your breath. The approach is akin to strength training: Start with a light lift, then increase the load over time. In 2019, the Neuroscape team found that the app significantly improved attention and memory in young adults over six weeks. Ziegler says it's also benefiting older participants in an ongoing study that tracks changes in cognition, plus markers of stress and well-being.

You might expect someone worried about a tech-induced cognition crisis to be a Luddite. Gazzaley's not. He views technology as a tool; whether it helps or harms is up to those wielding it. Some of Neuroscape's most promising research has been used to launch therapeutic video games. In 2020, one became the first video game treatment for ADHD in children to receive approval from the U.S. Food and Drug Administration.

Gazzaley sees the games and apps his team studies as "experiential medicine." He says experiences can selectively activate specific brain networks, a potential upside compared to medications that flood the whole brain, sometimes causing side effects.

"The medicine is the experience," he says. "Most of the digital tools we're creating have real-world versions that benefit people, like exercise, music and dance, meditation. We use technology to deliver experience in a way that's really accessible."

If you want improved cognition but less tech in your life, Gazzaley gets it. He happens to enjoy video games. He also likes to walk in the woods; spending time in nature has been proven to restore focus and boost mood. And Ziegler is quick to point out that meditation doesn't require an app. You can do it whenever you want, just by focusing on your breath.

> “Are we off-loading things like our ***creativity*** and ***reasoning*** and ***thinking***? Are we giving up too much of what it ***means to be human***?” 🤖 ***— Adam Gazzaley, MD, PhD***

Whether you *will* is another question. Ideas for how to reduce your time online abound, but habits are tough to change. Nagata suggests making a concrete plan focused on activities you want to add, not take away.

“It’s not enough to just say, ‘I want to limit my screen time,’” Nagata says. “Especially with kids, you have to have a fun alternative, or they’re just going to feel like they’re missing out.”

A household screen-time plan — which the American Academy of Pediatrics urges every family to create — typically includes rules everyone sticks to, like no phones in bedrooms. Nagata says this is the hardest part for parents: modeling the kind of self-control they want for their kids.

“I’m not perfect,” Nagata admits. His children are very young, but there’s a no-phone rule at the dinner table. “If I’m on call at the hospital, I’ll just explain, ‘Daddy has to help a sick kid, so that’s why I’m going to take this call.’ Eventually, they will have to learn to navigate these things, too.”

Broader changes to digital life — changes beyond our individual control — might be on the way. Gazzaley, Nagata, and Pierre all agree that government regulation of social media is needed, especially for young people. And recent landmark lawsuits against social media companies have persuaded juries that the design of the digital platforms is responsible for real-world harm.

“People ask what these companies *should* be doing, but that’s an ethical question,” Pierre says. “If you look historically at industries like Big Tobacco, when they make changes to make their product safer, that is typically motivated by regulation or class-action lawsuits.”

It will take time for researchers to explore how the latest tech innovation, artificial intelligence, is impacting our brains. Already, concerns are brewing about “cognitive off-loading” and “de-skilling.” Even Gazzaley is wrestling with whether AI can be deployed in ways that won’t eventually hurt us.

“We have always built technologies to help us,” Gazzaley says. If he’s got to do long division, for example, he’s using a calculator. “Then it gets more complicated. Do we over-rely on GPS? To-do lists? Reminders? With AI, are we off-loading things like our creativity and reasoning and thinking? And that, I really worry a lot about. Are we giving up too much of what it means to be human?”

Pierre tells me AI is part of why he struggled not to end his book on “a downer note.” When I ask whether he finds any hope in stories about young people buying “dumb” phones and rejecting AI, he’s honest: “I’m very, very skeptical that’s a movement gaining any traction.”

Personally, I’m not sure what to do. A “digital detox” sounds trendy in a way that piques my skepticism, too. But a randomized trial — during which internet access on participants’ phones was blocked for two weeks — boosted their sustained attention so much that the difference was comparable to reversing a decade of cognitive aging. They also showed an improvement in depression symptoms larger than what’s reported in many studies of antidepressants.

Still, it’s hard to voluntarily brick a device I use to control everything from my thermostat to my bank account. On vacation a few years ago, when my phone was stolen out of my bag, I found myself running through foreign streets — my route back to our rental barely pieced together by memory and the advice of strangers, who tolerated my breathless, rudimentary French. I was desperate to get to my laptop and change my passwords before someone else did.

For the rest of that trip, I had no phone. I was restless, mindlessly searching for it: waking up in the morning, sitting down to lunch, stepping out of the shower. I borrowed a friend’s phone to use the map, but mostly I was forced to shift my attention elsewhere. French radio. A book. Eventually, I could just sit on a beach or at a cafe, instead of reaching for my phone to take a photo.

I’ve gone back to that part of the world a few times now, trying to find that feeling. I want it back.



SUDDEN DEATH, MISUNDERSTOOD

BY ARIEL BLEICHER

Millions of deaths per year are attributed to sudden cardiac arrest, when the heart stops without warning. What if many of these diagnoses are wrong?

PHOTOGRAPHY Noah Berger

ILLUSTRATION Enigmatriz

CELINA SCHOUTEN is no stranger to death. She grew up in California's San Joaquin Valley, in a large, close-knit family descended from Portuguese immigrants. By middle age, she had lost her grandfather, her parents, and several uncles — all before the age of 75. She had watched many of them grow sicker as their hearts gradually gave out.

Her cousin Karen's death was different. The two women, born just weeks apart, were bonded like twins. In 2012, on the cusp of their 60th birthdays, Karen took a trip to San Francisco to visit friends. She was spirited and active, Schouten remembers, "just full of life." After a Giants game and a night on the town, the friends retired to their hotel. By morning, Karen was dead.

Because she died suddenly outside a hospital, the San Francisco County medical examiner's office investigated. There were no apparent injuries or illness. No drugs or poisons at the scene. No evidence of foul play. It was clear she had died naturally, from an invisible, interior foe. In most jurisdictions, an autopsy would have been foregone and the tragedy put down to sudden cardiac death — an unexpected and fatal stoppage of the heart, usually due to an electrical malfunction. But San Francisco is not like most jurisdictions.

For the past 15 years, cardiac electrophysiologist Zian Tseng, MD '98, MAS '08, the Murray Davis Professor at UC San Francisco, has been working with the county medical examiner's office to uncover the root causes of sudden cardiac death. This includes performing autopsies in many presumed cases that occur outside a hospital, a circumstance that accounts for about 90% of sudden deaths. Around the time Karen died, "sudden cardiac death" was being listed as the cause of death on hundreds of death certificates per year in San Francisco County. It was and is still considered a major global killer, credited with claiming the lives of an estimated 4 million to 7 million people annually, most of whom had no previous signs of heart trouble.

But as Tseng's research would reveal, many of those deaths weren't what they seemed.

A "CRAZY" IDEA

Tseng is what locals call a Bay Area lifer. "I've never left a 40-mile radius of San Francisco," he jokes. Born in the city, he was raised in Fremont, where his father, an earthquake engineer, and mother made their home after emigrating from Taiwan. When he was 6, he checked out a library

book about the heart and was hooked. "I'm one of those clichés," he says. "I knew in first grade that I wanted to be a cardiologist."

After medical school, residency, and a fellowship at UCSF, he joined the faculty in 2004. "I was really excited about clinical practice, just the thrill of curing people who had life-threatening rhythm disorders," he says. One of his specialties was implanting cardioverter-defibrillators, which detect dangerous irregular heartbeats and shock the heart back into a normal rhythm. Since the 1980s, cardiologists had been treating more and more patients known to be at risk of sudden cardiac death with these devices. Yet the death rate remained frustratingly high. "We were implanting a lot of defibrillators," Tseng says, "but a lot of people were still dying suddenly."

In many cases, their hearts seemed to be working just fine, so there was no indication that they needed a defibrillator. "Clearly we were missing something," Tseng says. Suspecting genetic factors, he set out to find them. In a small study of heart attack survivors, he identified a genetic marker that lowered the risk of cardiac arrest — a significant finding, because if a cardiac arrest isn't reversed, it results in sudden cardiac death. He was thrilled by the discovery, which he saw as the beginning of a fruitful research career. But just as the paper describing it was about to be published, he learned that a team at the University of Washington had shown the opposite effect: that the marker *raised* risk.

At first, he assumed his own result must be wrong. "I was a very junior faculty member, and these were very smart, senior scientists," he says. Their study was also much larger and hence, inherently more reliable. Whereas he had enrolled hundreds of subjects, the Washington team had cleverly recruited thousands by collaborating with local paramedics. "I *have* to figure out how to do a study like that," Tseng concluded. He began calling up emergency responders in San Francisco, asking them to send him blood from people who'd died of cardiac arrest. Which got him wondering: How did the paramedics know the patients' hearts were to blame?

"They said, 'It's paramedic primary impression,'" Tseng recalls. "That means the paramedic comes on the scene, and their impression is it's cardiac arrest. So I went to the medical examiner. I said, 'So your autopsies confirm these cases?' They said, 'We don't do autopsies unless it's a suspicious death.'"

The situation, he learned, was the same around the world: In the U.S., only 10% of sudden cardiac deaths outside hospitals are verified by autopsy; Europe has the highest rate, at 25%. "Wow!" Tseng thought. "How are we going to save victims of cardiac arrest if we don't know which ones are really cardiac? How are we going to study risk factors? How are we going to study mechanisms?"

Then he had a "crazy" idea: What if the autopsy rate for sudden deaths in San Francisco County was 100%?



TRUE CARDIAC ARRESTS: Just 56% of presumed cases.

> "How are we going to save victims of cardiac arrest if we don't know which ones are really cardiac? How are we going to study risk factors? How are we going to study mechanisms?"
>
> Zian Tseng **ZIAN TSENG, MD, MAS**

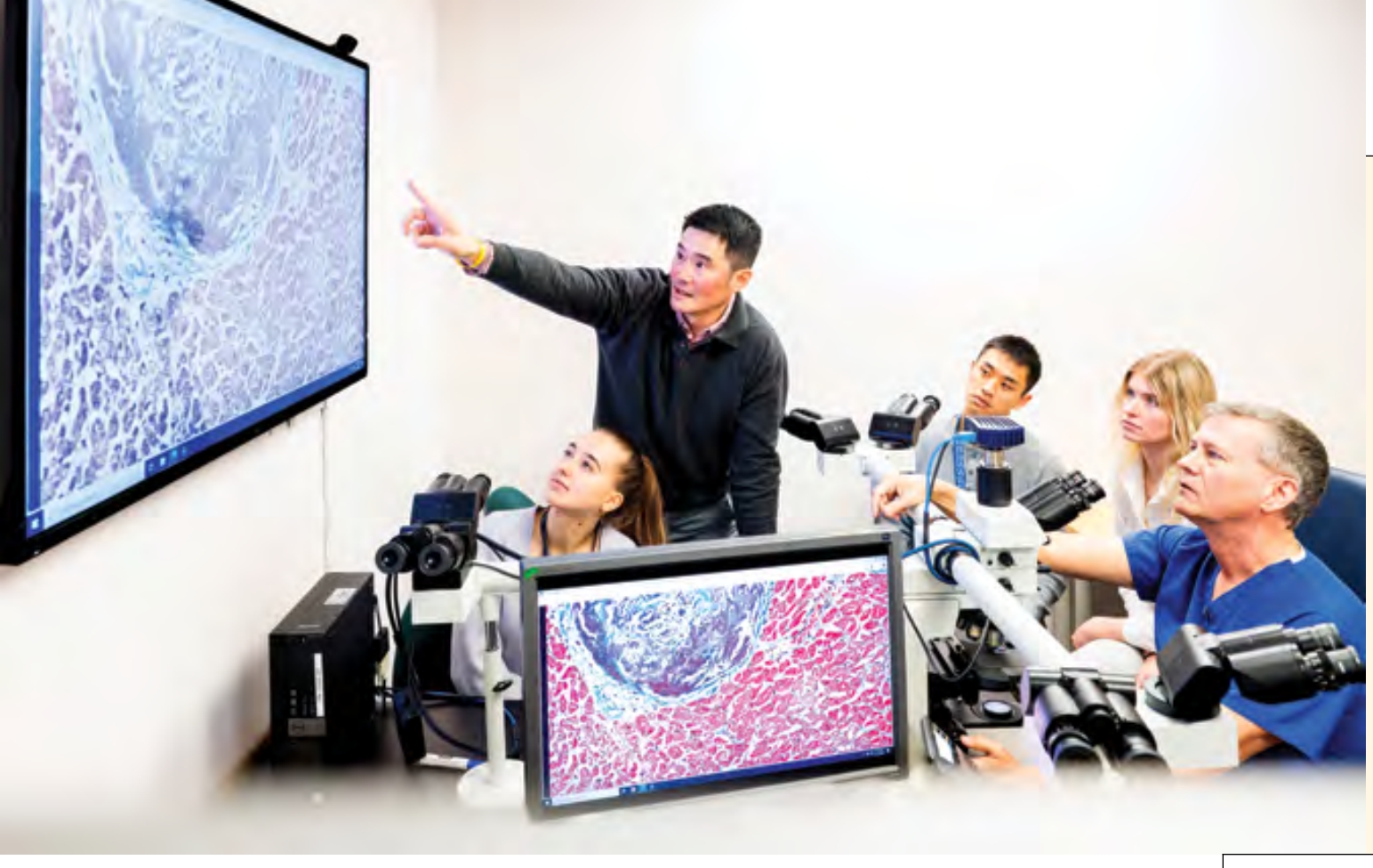
MYSTERIOUS FATHOMS

Sudden cardiac death is often described as an iceberg. The tip, scantly visible above the sea's surface, represents the cases doctors can predict and thus have a chance of preventing — people who survived a cardiac arrest, for example, or who have diagnosed heart-rhythm disorders or poorly pumping hearts. The rest of the iceberg, its hulking, submerged underbelly, represents the silent sick — people who will die, without warning, from a concealed cause.

Experts have long believed that hidden coronary artery disease, a narrowing or blockage of the heart's blood vessels, causes 80% of those unforeseen deaths by provoking heart attacks. Even when they don't stop the heart outright, these attacks, which may go unnoticed, leave scars that can disrupt the organ's electrical rhythm. But this oft-cited paradigm, Tseng argues, stems largely from older autopsy studies that he says were "hugely biased." Because autopsies are done sparingly, they tend to be done on young victims, after unusual deaths, or when a clinician requests one. As a result, studies based on these samples are not truly representative of all sudden deaths in a community, a phenomenon known as referral bias. "They're missing a lot of the pie," Tseng says.

Hoping to do better, in 2011, he pitched his "crazy" idea to Ellen Moffatt, MD, a forensic pathologist in the medical examiner's office and a UCSF associate clinical professor. She was eager to help. In the first three years of their collaboration, funded by a federal research grant, Moffatt performed autopsies on almost 900 out-of-hospital deaths — nearly all those in San Francisco County that responding paramedics had assumed were casualties of cardiac arrest. (Only 3% of families declined an autopsy. "The majority of families want to know what killed their loved one," Tseng says.)

In the meantime, Tseng's team of research coordinators and trainees collected medical records, paramedics' reports, family interviews — anything to help determine a definitive cause of death. Every week, the team met with Moffatt and a panel of medical specialists, including experts in pathology, cardiology, neurology, genetics, and



SUDDEN DEATH INVESTIGATORS

Tseng (standing) and pathologist Andrew Connolly, MD, PhD '97 (far right), work with their team to determine the true causes of sudden deaths initially attributed to cardiac events. Pictured with them (from the left) are Brielle Kinkead, Jelix Tsan, and Anna Fruehwirth.

infectious diseases, to review the latest cases. Jeffrey Olgin, MD, who today is UCSF's chief of cardiology and the Ernest Gallo-Kanu Chatterjee Professor, sat on the panel during the project's early days. He was surprised how often the group felt confident they knew what had killed a person — until they saw the autopsy report. "It was like, 'Oh! We're really bad at guessing the cause of death,'" Olgin says.

One of the earliest cases was a 74-year-old man who had been a patient of Tseng's. In the weeks before he died, he was admitted to the hospital with bronchitis and a high fever. The attending physician also noted that his heart was fluttering sporadically, a symptom of a previously diagnosed condition and a harbinger of sudden cardiac death. Rightly concerned, he consulted Tseng: Could he implant a defibrillator immediately? But Tseng was worried the patient was still too ill from the bronchitis to handle the procedure, so recommended scheduling it after the man was discharged.

"Two weeks later, he went home, and his wife found him dead the next morning," Tseng recalls. "I felt terrible. I thought I had missed the opportunity to save him." But when Moffatt conducted an autopsy on him, she found half a gallon of fresh blood in the man's digestive tract. What had killed him was something no one could have surmised: a rupture of his bowel.

COVERT KILLERS

That case was one of many that would challenge medical understanding of sudden death. When Tseng's team published their three-year findings in 2018, the results were stunning. A few hundred cases, it turned out, did not qualify as sudden deaths; upon closer inspection, the victims had been symptomatic for hours or days before they died. Of the more than 500 cases that remained, just over half — 56% — were true cardiac arrests. Another 4%, although they concerned the heart, resulted not from an electrical failure but from catastrophic structural damage, such as a tear in the heart's wall. That left 40% for which the heart was not culpable at all.

Of those noncardiac cases, drug overdoses made up the largest portion — 14% of sudden deaths overall. They had been easily overlooked, as no drug paraphernalia or other signs of substance abuse were observed. "You would never have known without doing the toxicology," Tseng says. He describes a representative case involving a 71-year-old man. His wife found him unconscious and called 911, but he could not be resuscitated. Because the man had a history of heart problems, for which he took a suite of medications, cardiac arrest seemed the most probable cause. "Well, in fact, his fentanyl level was double the lethal threshold," Tseng recounts.

"Overdoses are happening to people in their 60s, 70s, 80s," he says. "And not just with illicit drugs but also prescribed drugs. Nobody ever thinks of that." Extrapolating from the San Francisco data, he estimates that about 60,000 overdose deaths are missed yearly in the U.S. According to the Centers for Disease Control and Prevention, the number of annual overdose deaths in the country has climbed from around

BEYOND THE HEART: 40% of sudden deaths had noncardiac causes.

> "Our knowledge of death is far more limited than physicians like to admit."
>
> **ORRIN DEVINSKY, MD**

40,000 in the early 2010s, when Tseng's study began, to over 100,000 in recent years, a rise driven largely by the opioid crisis. If his projections are correct, its fallout may be even worse than experts have recognized.

Tseng suspects that mortality statistics also underestimate deaths from neurological causes, by as many as 25,000 per year in the U.S. In San Francisco County, these deaths comprised the second biggest category of sudden noncardiac deaths, accounting for 5% of all sudden death cases. The causes, determined through autopsy or by ruling out other possibilities, included strokes, brain aneurysms, and epilepsy. "All those deaths, which had been masquerading as cardiac, were actually neurologic," Tseng says. The finding was so striking that he coined a new term to describe the category: sudden neurologic death.

Next were infections, at 4% of sudden deaths in San Francisco County, followed by pulmonary embolisms, gastrointestinal hemorrhages, aortic tears, endocrine crises, kidney failures, and other motley causes. On a national scale, they added up to tens of thousands of annual deaths, all misattributed to cardiac arrest. "If you look under the hood at what really kills people, it changes the epidemiology of everything," Tseng says. The sudden death iceberg didn't just hide coronary disease; it harbored a whole host of uncharted threats.

"Our knowledge of death is far more limited than physicians like to admit," says Orrin Devinsky, MD, a neurologist at New York University who has collaborated with Tseng to better understand sudden death in patients with epilepsy. Devinsky has found that condition to be frequently overlooked as a cause of death because it's not detectable in an autopsy. "It's an issue of resource allocation," he says. "If we believe most sudden deaths in America are due to heart disease, we're going to continue to mainly fund heart disease research, and other causes of death will get underfunded because they don't get counted."

ARRIVING FULL CIRCLE

The chance of surviving an actual cardiac arrest remains abysmally low — less than 1 in 10 by most estimates. For noncardiac causes of sudden death, Tseng's research suggests the chance is even lower: in San Francisco, 1 in 50 overall and zero for neurological causes in particular. This makes sense, he says, because if paramedics assume you are in cardiac arrest, they will try to resuscitate you with a defibrillator and CPR and, if you are still alive, whisk you to a hospital specializing in heart emergencies — none of which helps if you actually are having a stroke.

So, what to do? Tseng maintains that risk factors identified in his autopsy study could help emergency responders give more accurate diagnoses and care during noncardiac crises. For example, "if you are a woman, if you had a prior stroke, and if you are on an anticoagulant, there is a much higher likelihood of a neurologic cause," he says. "So, if all three apply, then you should get triaged to a neurology center." Tseng's studies have similarly informed guidelines for treating drug overdoses that may be confused with cardiac arrest. "If we make a dent in some of these cases, it could make a big impact on the overall survival rate," he says.

Some cardiologists and sudden-death researchers note that additional studies in other communities will help determine how broadly the San Francisco findings apply. Still, Tseng's autopsy study, which remains ongoing, has brought necessary attention to the complexities of sudden death. "I think Zian is right that we are overestimating the number of cases related to the heart," says Eloi Marijon, MD, PhD, MSc, a cardiologist at the University of Paris who leads an international commission on sudden cardiac death of which Tseng is a member. "If our goal is to prevent sudden cardiac deaths, we need to understand the underlying factors because otherwise, our efforts will be misplaced."

Earlier this year, Tseng's team published in the *Journal of the American College of Cardiology* (*JACC*) a pair of papers, based on 12 years of autopsy data, that upheld the 2018 findings and delved deeper into confirmed cases of sudden cardiac death. Strikingly, one of the papers revealed that only 37% were attributable to heart attacks from clogged arteries — less than half of what has long been believed. The remaining 63% of causes included heart attacks despite clear arteries, chronically high blood pressure, problems with the heart muscle or valves, and electrical disorders.

"You and your colleagues have revisited one of the most enduring assumptions in cardiovascular medicine and shown clearly that it no longer reflects reality," wrote Harlan Krumholz, MD, a cardiologist at Yale University and the *JACC*'s editor-in-chief, in an email to Tseng accepting the manuscripts.

In the other paper, Tseng's team reported that evidence of disease had been missed in two-thirds of fatal cardiac arrest cases — including known risk factors like prior heart attacks, as well as more subtle pathology like increased heart weight or size. ("The dirty truth is that many people just don't have medical care," Tseng says.)

"Collectively, these studies redefine both the mechanisms of sudden death and the limitations of current prevention paradigms," Krumholz concluded, praising the work as "exceptional" and "field-shaping."

More revelations have emerged over the past decade. When Tseng's team analyzed cardiac deaths in people with pacemakers or implanted defibrillators, they discovered that half were caused by a technology malfunction, such as a broken wire or faulty sensor algorithm.



ALL IN THE FAMILY

Sisters (clockwise from top) Barbara Bourchier, Susie Borges, Celina Schouten, and Jane Hrusovszky learned more about their family's health risks after their cousin Karen's autopsy revealed a hidden heart condition.

"The failure rate for these devices is much higher than what the companies say," Tseng points out. Other studies showed that sudden cardiac death was more prevalent in people who are HIV-positive (which is thought to induce chronic inflammation that scars the heart and other organs) or who are homeless. "We need to expand the lens through which we're looking at sudden cardiac death, from a narrow focus on coronary blockages to all these other conditions," Tseng says.

Recently, he began exploring genetics again. "So, my work has come full circle," he says. Having separated actual cardiac deaths from spurious cases, he can finally do what he had intended to all along: investigate the biological drivers of cardiac arrest. "One of the most vexing problems in our field is, why do you die suddenly *today*?" he says. "Why not yesterday? Why not next year?" Cardiologists know that scarring, whether from a virus or heart disease, can provoke arrythmias. But what turns them deadly?

In a 2024 paper, Tseng's team offered a tantalizing clue. Examining autopsied heart tissue from more than 1,200 sudden deaths, they identified aberrant gene processes that appear to trigger cardiac death by laying down new scars over old ones. If this discovery leads to imaging or blood tests that can predict cardiac arrest, Tseng says, it would be a medical breakthrough.

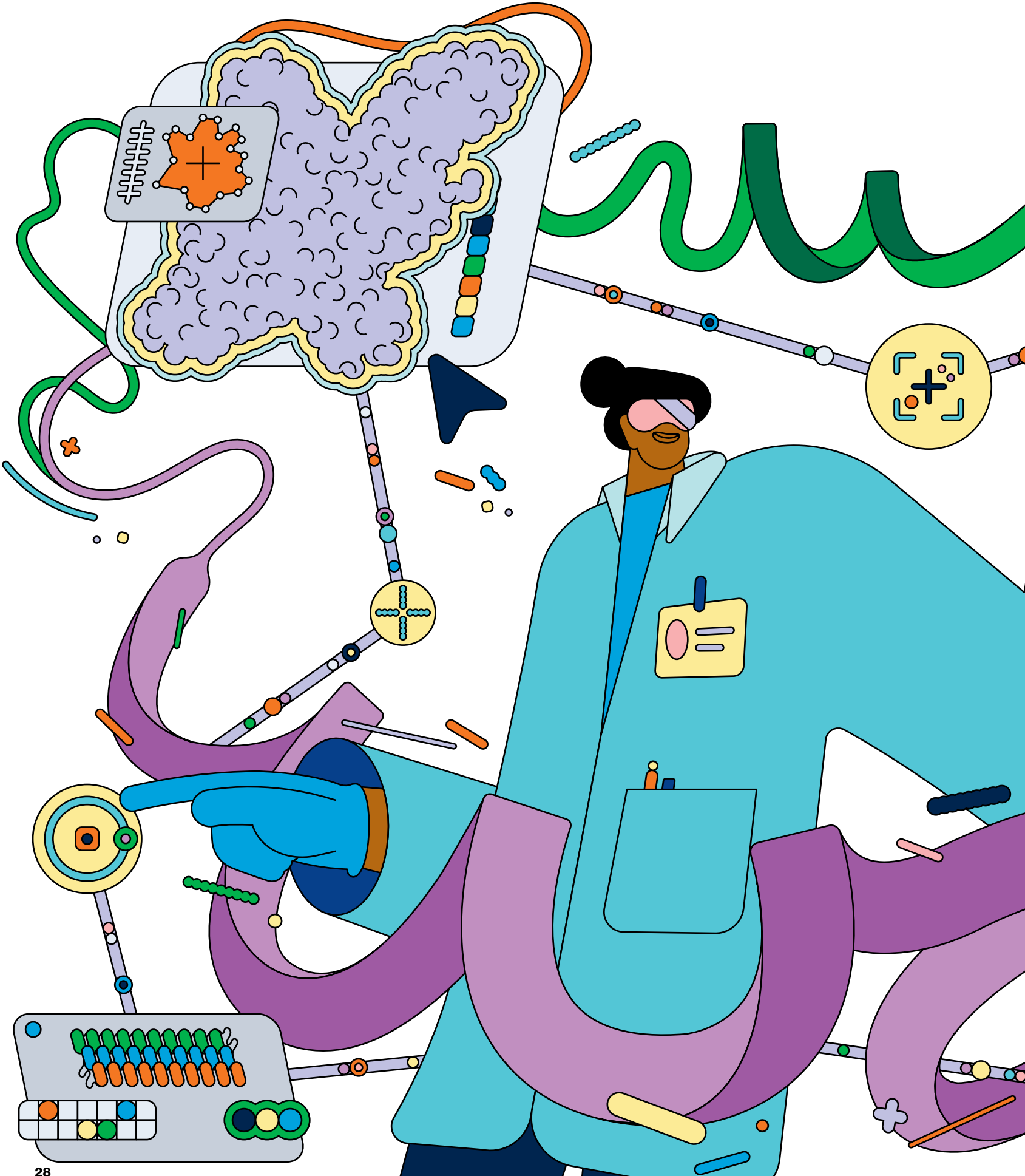
LIFE AFTER DEATH

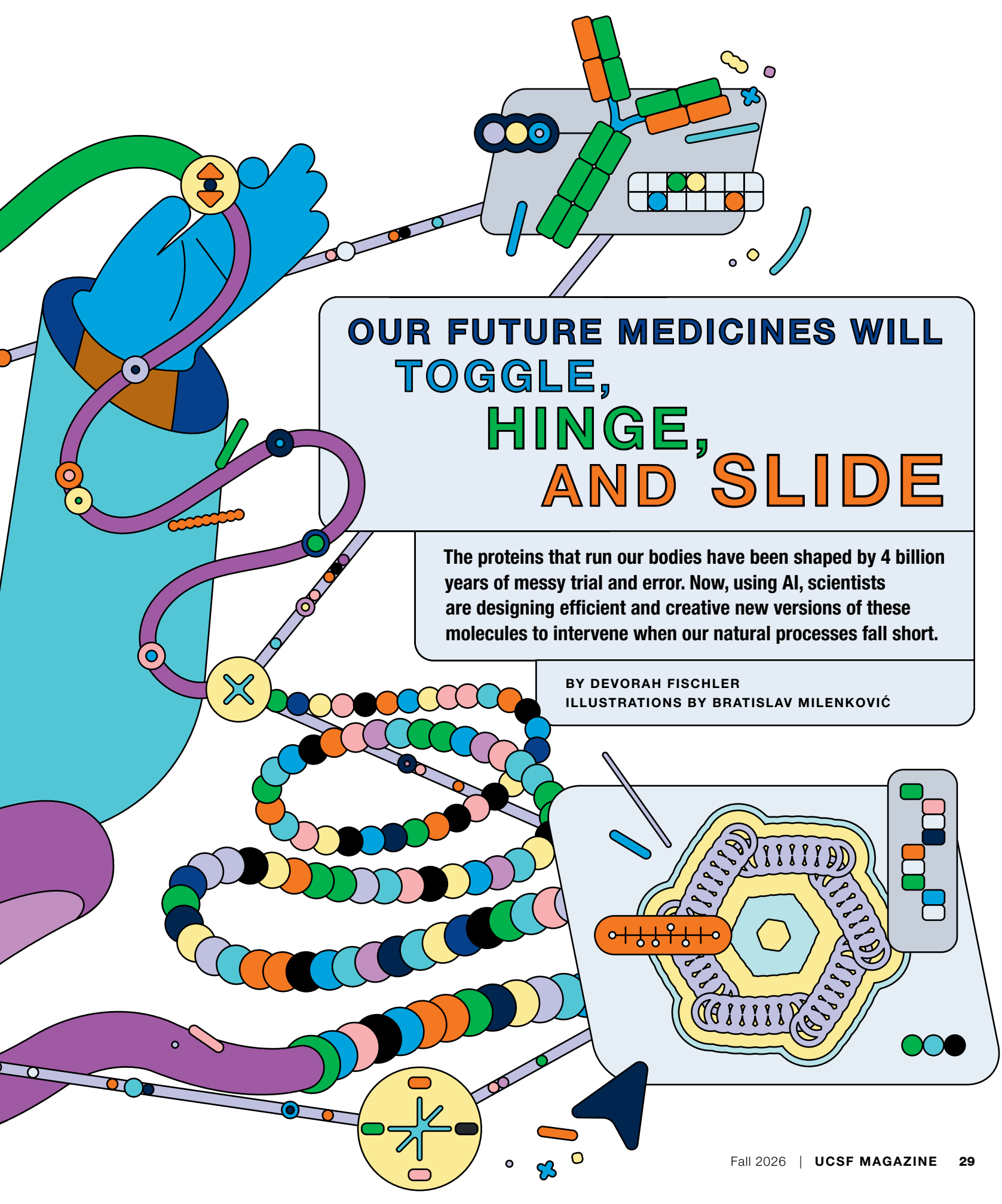
Science could not save Celina Schouten's cousin, but it may yet save the lives of some of those she left behind. A few weeks after Karen died, her family received her autopsy report. The paramedics had been right in her case: It *was* cardiac arrest. Subtle scarring, disorganized heart cells, and a thickening of her cardiac muscle all pointed to a heart-weakening condition called cardiomyopathy, although Karen had never been diagnosed with it.

"That was quite a shock," recalls Schouten, now 72. Many of her relatives had died from the disease, so she knew it ran in the family. But she had never realized it could kill so swiftly and unpredictably. Afraid she might also be at risk, Schouten had her genes tested and, after learning she carried a cardiomyopathy variant and developing other symptoms, decided to have a defibrillator implanted.

"I believe God knows when we're going to die," she says. "But I also believe that, through medicine, He gave me this chance to hopefully gain a few extra years." At her urging, many of her siblings and cousins and their kids and grandkids also took genetic tests, joining the thousands of grieving family members who, in knowing for certain what caused their loved ones' deaths, have acquired new insight into their own health.

Then, two years ago, Schouten's brother collapsed and died in his art studio in Merced County. He was 61 years old — the victim of another sudden death that looked like cardiac arrest. But, perplexingly, he didn't carry the cardiomyopathy gene. Was it a different heart condition? Something else entirely? No one ever found out because an autopsy was never performed.

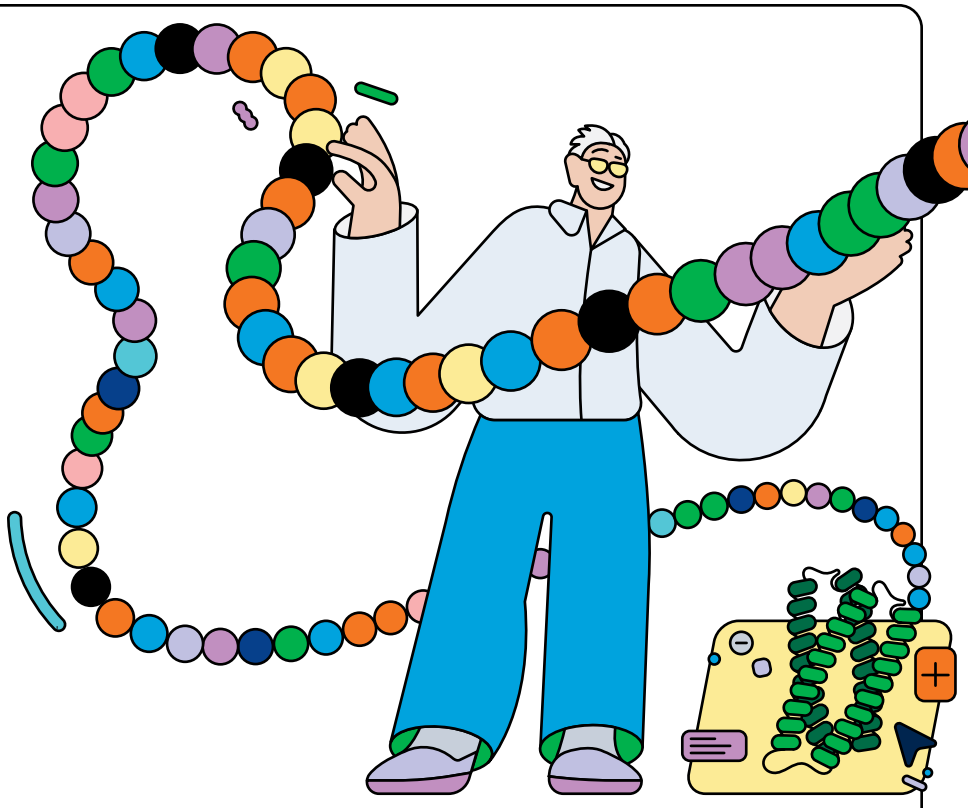




OUR FUTURE MEDICINES WILL TOGGLE, HINGE, AND SLIDE

The proteins that run our bodies have been shaped by 4 billion years of messy trial and error. Now, using AI, scientists are designing efficient and creative new versions of these molecules to intervene when our natural processes fall short.

BY DEVORAH FISCHLER
ILLUSTRATIONS BY BRATISLAV MILENKOVIĆ



Textbook illustrations don't do the human cell any justice. Maps and diagrams can give you a sense of what a cell is and how it works. But to truly understand the basic unit of life, you need to grasp how wildly *alive* it is.

A cell is hot and never still. Sloshing layers of external fat are anchored to a stiff scaffold of filaments that extend and retract as they renew themselves, a network of twinkling spikes. Inside, vibrating water excites a thick traffic of molecular machines — millions of them, in dizzying variety. Some spin like rotors, some squeeze like fists, and some move around on assemblages that look like running feet. A chaos of raw materials circulates, pelting larger structures in a constant hailstorm of energy. There's barely any room to move. Everything bumps into everything.

The body is a crowded scene, and within it, no molecular machine makes a greater impression than proteins, those folded chains of amino acids that evolved to bump into things in remarkably useful ways.

The usefulness of proteins far exceeds the muscle building for which they are best known. Cells manufacture proteins in highly specific three-dimensional structures to accomplish the tens of thousands of biological tasks programmed into our DNA. Think: Y-shaped disease hunters, tightly packed spirals of oxygen transporters, horseshoe communication systems, and hollow iron-storing spheres.

These jellylike microscopic tools bounce around the body's teeming landscapes — inside and outside the cell, depending on type — where their distinctive shapes provoke varied reactions. Crash into another molecule that doesn't match their shape? No reaction. Knock against a partial match? Small reaction. Encounter a series of complementary pockets? Something happens.

Immunoglobulins claw onto viruses to stop them from invading. Insulin binds to cell receptor slots to regulate blood sugar. Amylase, protease, and lipase break down chemical bonds in food with atomic precision. With ornate formulas and shapes, all these proteins rely on both chemistry and physics to execute our DNA's meticulous instructions.

For tens of thousands of distinctive functions, we have a mere 20 amino acids to thank. Alone, an amino acid can't do much. But when these clusters of atoms combine, they form molecules that spontaneously recoil from their watery environment and fold up into tools honed by eons of evolutionary selection.

Evolution hasn't come close to exhausting every possible amino acid combination, a number so large it likely exceeds the total number of atoms in the universe. But could science explore these untapped potentials? Is it possible to create new proteins to do new things?

In medicine, protein design would mean treatments with capabilities we've only ever dreamed of — drugs able to match the chaotic movements of biology and control them with sensitivity, rationality, and precision.

Artificial intelligence has vaulted this once far-fetched idea into near horizons of possibility. At UC San Francisco, a cluster of labs is focused on this opportunity, and together, they're building the systems needed to enrich newly powerful AI predictions with real-world proof.

DEGRADO LAB

THE FIRST PROTEIN DESIGNER

In the late 1980s, William DeGrado, PhD, was an industry chemist with time on his hands. His work in drug development had always been productive, and management was supportive of scientists ambitious enough to pursue their own open-ended projects on the side.

DeGrado, now UCSF's Toby Herfindal Presidential Chair for Entrepreneurship and Innovation, came of age as plastics were becoming ubiquitous in everyday life. His research focused on small-molecule medicines, but his fascination with chemistry was intertwined as much with lifesaving drugs as with the way the quiet science of constructing huge polymer molecules — plastics among them — had changed the world.

It was pure scientific curiosity that led him to design proteins and to coin the Latin prefix — *de novo*, meaning "from the beginning" — that has become the definitive scientific name for proteins built from scratch.

DeGrado envisioned de novo protein design as a chance to rethink the relationship between protein structure and function. Our bodies' native proteins achieved their precise forms and roles over billions of years of trial and error. Evolution is unmotivated and impersonal, a glacial process of response to biological and environmental pressures.

As a result, protein structures are florid and overcomplicated things full of hasty fixes, long ways around, and layers of historical baggage. Instead of modifying or imitating these Rube-Goldberg-like designs, DeGrado wanted to create completely different and radically simple amino acid structures. De novo proteins would be tailored to their goals with scientific intention.

Theoretically, these streamlined proteins would be easier to build and control. And, even more significantly, creating proteins from scratch could allow for benefits that evolution hadn't had time or reason to give us. We could imagine the way we wanted to influence molecular behavior — control immune responses, identify diseases, destroy tumors, preserve brain tissue — and then design a protein to make it happen.

When DeGrado brought an early design to a senior scientist at his pharmaceutical company, the reception was less than enthusiastic.

DeGrado laughs, recalling it. "He said to me, 'Bill, I don't know what you've designed, but it's not a protein. Humans can't design proteins.'"

The exchange lit a fire under him. "It was just so motivating to think that he was wrong," DeGrado says.

Very wrong, it turns out. Today, DeGrado's notion has developed into one of the most innovative and rapidly growing research fields, supercharged in recent years by the speed at which AI can now explore and test biological variables. Biotechnology and, yes, pharmaceutical companies are hard at work refining de novo protein capabilities into medicines that could soon vastly improve upon our current generation of modified natural ones — eliminating side effects, increasing effectiveness, and expanding the range of diseases they can treat.

While DeGrado's breakthroughs have contributed to these near-term wins, his sights are set much higher. Enzymes — the holy grail of de novo protein design — are the latest focus of his lab. Unlike other types of proteins, which accomplish their functions by binding to things, enzymes also do chemistry: They catalyze their target molecules, transforming them into different chemicals.

This type of dynamic molecular machine is hellishly difficult to create. It requires a population of atoms to move in *just* the right way and at *just* the right speed to recognize and modify only the *most* precisely defined targets.

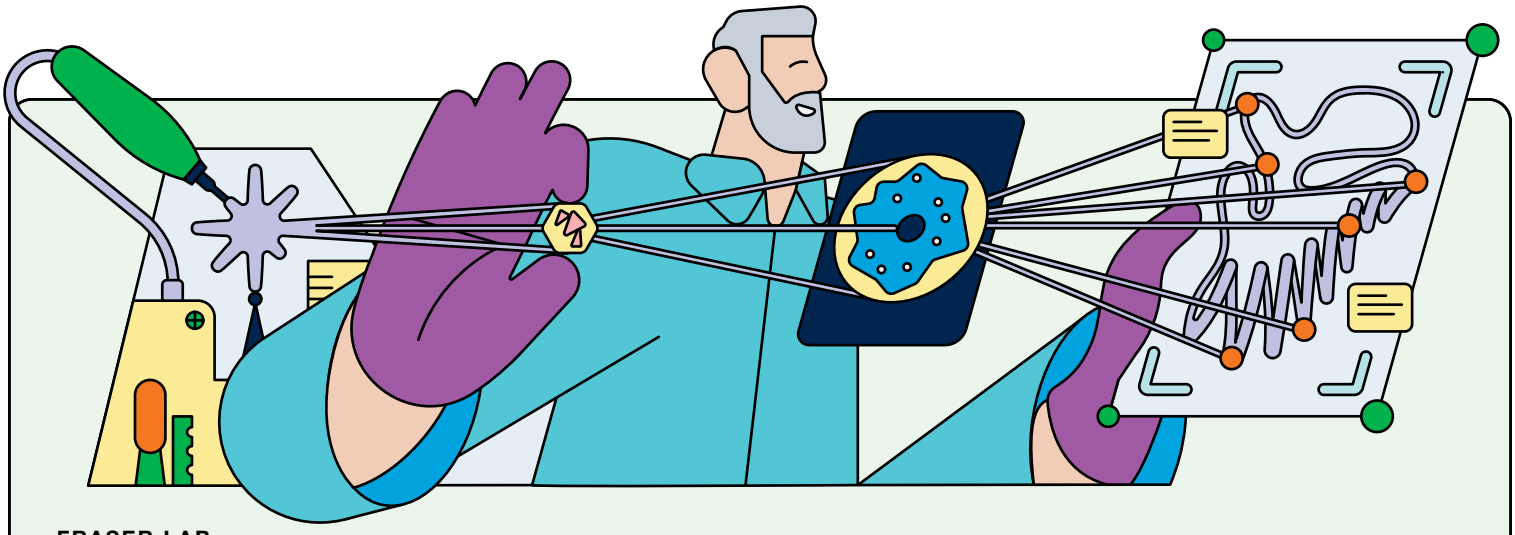
DeGrado's lab is getting there. His team of scientists recently collaborated with James Fraser, PhD, to create one of the most efficient and successful de novo enzymes on record.

Scientists in the DeGrado Lab are paving the way to an entirely new pharmaceutical era. The ability to build de novo enzymes — ones that can do what no natural enzyme can — has the potential to transform not only clinical care but also drug manufacturing, eliminating the need for the expensive and toxic materials required to make every medicine you can imagine.

> **"He said to me, 'Bill, I don't know what you've designed, but it's not a protein. Humans can't design proteins.' It was just so motivating to think that he was wrong."**
>
> **WILLIAM DEGRADO, PHD**

Those same advances could also help address environmental pollutants and their impacts on health. It's funny, the way that medicines and the rise of affordable synthetic materials inspired all this. In the end, de novo proteins could be just as lifesaving and world-changing. Maybe even more so.

"They'd be perfect for cleaning up plastics," DeGrado says.



FRASER LAB

THE CINEMATOGRAPHER OF LIFE

James Fraser is famous for shooting things with lasers. A single pulse, a flash of energy, and the molecule on the receiving end responds — often in unanticipated and informative ways.

An imaginative empiricist, Fraser, UCSF's Ernest L. Prien Professor, is known for this and other creative methods he's devised to capture the slipperier truths of life. For proteins, this means discovering how and why they like to move.

Natural proteins evolved over billions of years in an environment that rewarded flexibility. A protein that could shape-shift made it more adaptable, and cells put this flexibility to work.

And yet, for most of the time that biologists have been investigating protein structures, they have ignored this essential dynamic nature. Standard practice valued structural clarity: Freeze a protein into a stable crystal form and take an X-ray image.

As the science matured, it became clear that a static image provided as many obstacles as insights. Excited by water and heat, proteins are in a constant state of chaotic motion. They don't hold a single fixed shape. Rather, proteins exist in several possible shapes at once, some likelier than others.

Scientists represent this strange molecular state of affairs with what they call "energy landscapes" — mathematical representations of every possible form and gesture a protein can express. In these landscapes, "valleys" represent shapes that the protein can take, while "hills" show the amount of energy required to travel between them. The deepest valleys show the shapes a protein is statistically most likely to be in, while the tallest hills index unlikely or rare forms.

In their native environment, proteins are always sampling these different formations, responding to shifts in energy that, from our human-scale point of view, are absurdly small and imperceptibly fast. Over time, their random movements have evolved to become useful responses to cellular cues: Get a signal, change shape, do something new.

This animated reality is exactly what Fraser's experimental techniques are designed to capture. Where we once had only photographic stills of detailed protein structures, he gave us feature films.

It turns out, the malfunctioning proteins involved in our most difficult-to-treat diseases — cancer, Alzheimer's, and Parkinson's, for example — have very intricate energy landscapes. They don't present obvious chemistries and binding sites for drugs. Instead, these potential targets seem to be hiding in rare dynamic states. But how is it possible to find and understand these rare states? And how can we interact with molecular structures that flicker in and out of presence, there one moment and gone the next?

To answer these questions, Fraser stopped freezing molecules, instead creating ways to perform X-ray crystallography at room temperature so the proteins could remain active. He learned to treat proteins like probabilities, layering data about their many possible forms rather than smoothing out the math with averages. Using lasers, he blasted proteins with tiny jolts of energy to reveal hidden shapes. And, in his collaboration with DeGrado, he invented a way to expose different iterations of their de novo enzyme to a range of drug molecules, learning from their interactions.

Scientists in the Fraser Lab explore natural protein dynamics, providing insights into the fundamental mechanics of disease. Their work is crucial to de novo protein designers, who build new kinds of drugs that can take on these moving targets.

Importantly, the Fraser Lab also provides real-life verification for AI-designed molecules. These experiments test whether de novo proteins behave as predicted and identify how to improve them when they don't.

Before AI, the failure rate for de novo proteins was "something like 99.99999 percent," Fraser says. Not heartening to most, but normal and interesting for science. "Failure is exciting. When things fail, we get to figure out why."

Now, with AI, the failure rate is low enough that researchers are pivoting to learning from the flood of new ways that designs can succeed. "Things have never been more exciting," Fraser says.

KORTEMME LAB

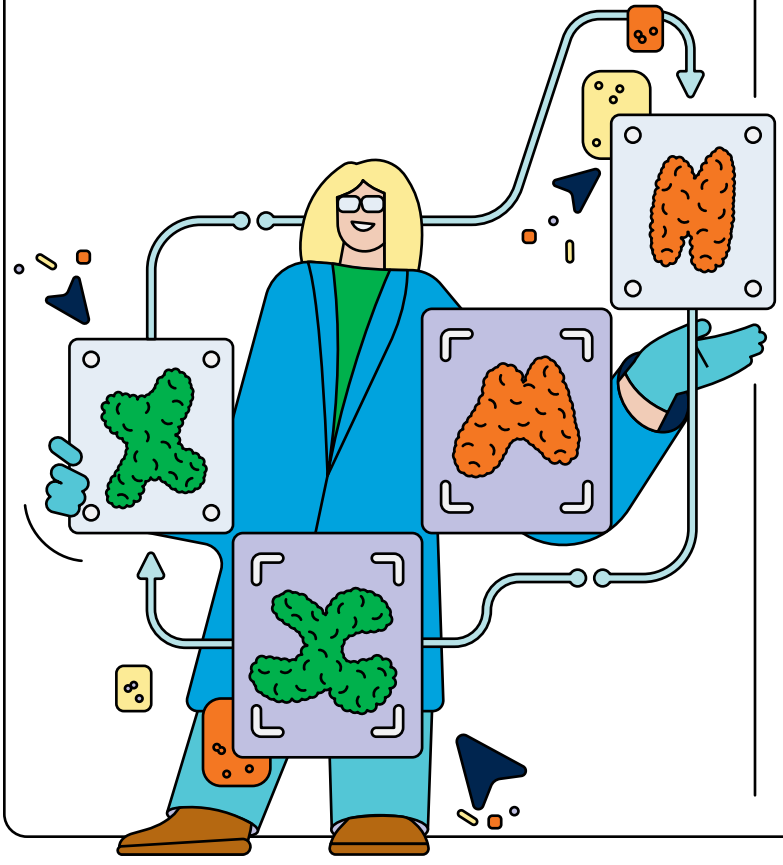
THE LOGICIAN OF NATURE

Tanja Kortemme, PhD, is, at heart, two very different kinds of researcher. She's a biochemist who has spent decades happily immersed in the chaotic molecular life of the cell, delighting in discovery. And she's also an engineer, someone who looks at nature's infinite capacity for surprise and sees a design opportunity.

It's the perfect combination for a scientist who creates de novo proteins that interact with mutable biological environments. Like natural proteins, Kortemme's molecules change shape. But unlike natural proteins, their energy landscapes are orderly and disciplined, devised for control.

"I've always cared about how proteins move," says Kortemme, a professor of bioengineering. "At first, it was because protein designs kept failing; they were either too flexible or not flexible enough."

Current protein therapeutics, made with modified natural proteins, have shortcomings that arise from their single active state. Like keys drifting around the body and smashing into locks, these proteins achieve their goals bluntly and without much discernment.



"I've always cared about how proteins move. At first, it was because protein designs kept failing; they were either too flexible or not flexible enough."

TANJA KORTEMME, PHD

These are drugs and therapies that have changed lives and cured diseases, but they can also cause side effects that can be painful, life-altering, or fatal. The single active state means that the proteins can enter a range of similarly shaped locks and wreak havoc where they aren't needed. They have no way of sparing healthy cells, adjusting potency, sensing location, or shutting down when their work is done — all things a natural protein would do by shifting shape.

"Plus, the only molecular targets these drugs can typically reach are ones that happen to be stable enough to be treated as static," Kortemme says. "This kind of target is very uncommon. Most druggable targets are dynamic. We need smarter medicines to interact with them."

Today, the Kortemme Lab is using AI to design these smarter medicines, creating molecules flexible enough to switch between two distinct forms but stable enough not to waver into other shapes. These new machines will speak the language of biology, but their grammar and syntax will be noticeably different.

The de novo proteins created in Kortemme's lab will be able to toggle into active and inactive states, only deploying where and how they're needed. They could hinge, sporting an open, lid-like structure that wouldn't snap shut and assemble the active protein until it was certain it was in the presence of a tumor. Or they might slide along a natural protein's surface, exposing hidden binding sites or amplifying a distress signal that's so faint, the immune system is unable to properly respond to it.

To help us graduate from rigid molecular fixes to intelligent therapeutics, Kortemme is working to engineer a suite of modular de novo protein components — defined movements and structures that can be assembled into predictable machines capable of correcting the damaging cell behaviors that make us sick.

For Kortemme, what began as an interest in understanding how proteins move has unfurled into an entire scientific vision: to program logic into life.



VIDEO: Watch at *tiny.ucsf.edu/PatientActors*

DRESS REHEARSAL: Before the curtain rises on another round of student exams, a handful of trained performers huddle over their scripts — fine-tuning symptoms, backstories, and the occasional curveball question designed to test a student's bedside manner. These standardized patients — part actor, part educator — help students at UCSF's Kanbar Center for Simulation and Clinical Skills practice the delicate art of listening, assessing, and delivering hard news with empathy. Scan the QR code to watch the prep and the learning sessions it leads to.

Video by Walter Zarnowitz | Photography by Noah Berger



Researchers are exploring a surprising possibility: whether GLP-1s might treat alcohol use disorder and other addictions.

Can the Latest Weight-Loss Drugs Curb Other Cravings Too?

By Roberta Kwok
Illustration by Jessie Lin



As a physician who treats diabetes and obesity, Suneil Koliwad, MD, PhD, often prescribes GLP-1 drugs — popular weight-loss treatments that reduce cravings for food. When his patients start taking them, some report another change: They drink less alcohol.

One such patient, a retired executive, had long enjoyed a few drinks a week. After he started Ozempic, he found alcoholic beverages so off-putting that he began avoiding social activities involving drinks, such as cocktail hours or Super Bowl gatherings. "He really isn't interested in drinking anything with alcohol anymore," says Koliwad, UC San Francisco's chief of endocrinology and metabolism.

While Koliwad's patient didn't need to cut back on his drinking, stories like his have raised an important question about GLP-1s: Could the drugs also dampen cravings for alcohol and other addictive substances, such as tobacco, opioids, cocaine, or methamphetamines? Early studies have sparked avid interest among researchers who study substance use disorders, and anecdotes from patients enrolled in clinical trials are striking. Khaled Moussawi, MD, PhD, UCSF's Fields Professor of Pharmacology of Addiction in Neurology, says some people prescribed GLP-1s have reported a sudden shift in their compulsion to drink. One patient described the change as "a light switch." Another told him, "One moment I'm not in control, and another moment I'm in full control."

The field still faces many unanswered questions — including *how* the drugs influence craving or consumption — and the patients in ongoing trials don't yet know if they're receiving actual GLP-1s or a placebo. In the meantime, physicians in addiction medicine are cautiously hopeful.

"We are in dire need of more options," says Triveni DeFries, MD, MPH, an associate professor of medicine who specializes in primary care and addiction medicine. "We're all anxiously awaiting more data."

A Desperate Need

Substance use takes a tremendous toll. Alcohol use disorder alone affects about 10% of people in the U.S. and causes 178,000 deaths per year. While the number of overdose deaths from opioids declined in 2024, the drugs still kill roughly 50,000 to 60,000 people per year. Addiction can tear families apart and render patients unable to function in their daily lives.

"The social and economic impact of this disorder is catastrophic," Moussawi says.



FDA-approved treatments exist for some substance use disorders, and "they're very powerful and they're very effective," says DeFries, who practices at Zuckerberg San Francisco General Hospital and Trauma Center. But the medications aren't widely used, in part because many people hesitate to seek treatment. Moussawi also notes that the drugs don't work for everyone and sometimes have undesirable side effects. For example, he often prescribes a medication called naltrexone for alcohol use. But in his clinical practice, it helps only about a quarter of patients.

For people with opioid addictions, buprenorphine and methadone can be lifesaving. These medications suppress cravings by targeting opioid receptors in a more stable way — avoiding the sharp peak-and-withdrawal cycle of drugs like fentanyl and heroin. They also reduce the risk of overdose.

"Many people take them, and they work miracles," Moussawi says. But some of his patients continue using other opioids while in treatment, or they stop the medication after about six months. At that point, he says, "they're back to where they were."

When treatments don't work, "many patients are desperate," Moussawi says. "They want their lives to be better." For instance, one patient knew that her drinking was damaging her relationship with her husband and kids. Another patient had developed an opioid use disorder after she was prescribed oxycodone for pain, but she wasn't able to break the dependency with buprenorphine treatment.

"You see a huge need," Moussawi says. "It's palpable. You feel it in these people's stories."

And for some substance use disorders, there are no approved medications at all. "We truly have nothing for cocaine or stimulant use disorder," says Andrew Kayser, MD, PhD, UCSF's Weinberger Professor of Addiction Research. "We're not in a place, in my opinion, to be picky."

> "You see a huge need. It's palpable. You feel it in these people's stories."
>
> — Khaled Moussawi, MD, PhD

Exploring an Unexpected Side Effect

The idea that GLP-1 drugs might treat addictions emerged as patients began reporting that they were drinking less. Observational studies also hinted that people on GLP-1s were less likely to develop a substance use disorder; if they had already been diagnosed with one, they experienced fewer incidents like overdoses or emergency room visits.

Much of the focus so far has been on alcohol use, but the evidence from clinical trials has been mixed. In one study of an older GLP-1 drug called exenatide, researchers reported no decrease in heavy drinking days overall; they saw reduced alcohol intake only among patients with obesity. However, the trial had a high dropout rate, which might have biased the results.

"It's an interesting study, but not nearly definitive," Kayser says.

In a more recent trial led by researchers at the University of North Carolina at Chapel Hill, scientists invited people with a history of heavy drinking to a hospital room resembling a dorm; some participants had received weekly injections of Ozempic. Each person was offered their favorite alcoholic beverage as they sat in a comfortable chair and watched a video.

The people on Ozempic drank less alcohol than those not taking the medication, the researchers found. Outside the lab, those participants didn't report fewer drinking days, but they had fewer drinks on the days they did partake. And they were much more likely to report zero heavy drinking days by the end of the study.

Earlier this year, another team of researchers in Denmark studying people with obesity and alcohol use disorder reached a similar conclusion: The participants using Wegovy drank less.

Even if GLP-1s merely reduce heavy drinking, Kayser believes that shift would still be valuable because it lowers the risk of serious incidents, such as car accidents. In the past, the mentality for treating alcohol use disorder was "abstinence or bust." Now, many providers focus more on curbing negative consequences. "Just reducing the harms of these substances would be a benefit," Kayser says.

Dampening Dopamine vs. Feeling Full

These tantalizing early results raise an unresolved question: How, exactly, might GLP-1 drugs reduce intake of alcohol and other substances? Some researchers believe that the medications work primarily by increasing satiety, while others suggest that effects on the brain's reward system play a more important role. The mechanism matters: The first points toward GLP-1s as a limited tool that's useful mostly for reducing drinking, while the second opens the possibility of a multipurpose drug that could treat many forms of addiction.

GLP-1 drugs mimic the natural GLP-1 hormone that our bodies produce when we eat. In the intestines, the hormone slows stomach emptying so nutrients can be absorbed. In the pancreas, GLP-1 boosts insulin release, which helps control blood sugar levels. And cells in the brainstem release the natural version of the hormone throughout the forebrain to inhibit food intake.

The drugs' weight loss effect occurs mainly through the brain, but they work differently from natural GLP-1, according to Zachary Knight, PhD '05, a professor of physiology who studies the regulation of hunger. The drugs seem to have trouble reaching deeper areas of the brain, but they could still act on regions where the blood-brain barrier is weaker and influence eating or substance use.

Some scientists hypothesize that GLP-1s diminish cravings by reducing reward signals in those parts of the brain. Whether someone's scarfing a pint of ice cream or reaching for another cigarette, "there's a lot of overlap in those two behaviors," says Ashley Mason, PhD, an associate professor of psychiatry at the UCSF Osher Center for Integrative Health who studies food cravings. Ultra-processed foods and drugs



like cocaine both trigger huge reward signals. "They're super-stimuli we did not neurologically evolve to contend with," Mason says. Neurons release dopamine molecules to various brain regions, essentially sending the message, "Let's do that again."

When mice are given a GLP-1 drug in a lab, they release less dopamine in response to food. One key brain region that receives dopamine signals is the nucleus accumbens, which controls the hedonic drive to eat — leading us to eat even after we're full because of the pleasure, comfort, stress reduction, or childhood memories associated with food. So weaker dopamine signals may tamp down the tendency to overeat.

And the nucleus accumbens "doesn't just create reward around food," says Koliwad, who holds UCSF's Grodsky/JAB and Woeber-Mount Zion Distinguished Professorships."It creates rewarding feelings around a whole host of addictive behaviors." If GLP-1s reduce signaling there, many kinds of reward-seeking and cravings — as well as addictive behaviors like gambling — might subside with it.

Some clinicians worry that if GLP-1s curb appetite in this way, the medications could also weaken people's motivation in general. Some of Koliwad's patients have told him that they're less enthusiastic about activities they used to enjoy, and their emotions have flattened out. But large-scale studies don't suggest an increased risk of depression due to GLP-1 drugs. "If anything, it's the opposite," Knight says.

Debate about how the medications function in the human brain is far from finished. Knight is skeptical that reward signals are the most important pathway that GLP-1s influence. "Most of what these drugs are doing has nothing to do with dopamine," he says; instead, the medications likely cause weight loss by making people feel satiated. GLP-1s bind to receptors in a small brain region called the area postrema, prompting signals that control appetite. As a result, people feel full faster when they eat, and they don't think about food as much between meals.

Kayser recalls a patient who took a GLP-1 for obesity and diabetes. "It made him feel like it was 45 minutes after Thanksgiving dinner every day," he says.

Ultimately, if GLP-1 drugs primarily reduce reward signals, they could perhaps treat many types of addictions. But if they mostly affect satiety, it's not clear whether they would work for addictions to substances beyond alcohol, Kayser says.

"Alcohol has calories," Knight explains. "Alcohol is a food." If you feel sated, the thought of downing a beer or cocktail won't seem as appetizing. But if you have a cocaine addiction, for example, feeling full might not factor much into your decision to use more.

Still, Kayser speculates that a feeling of being "done" could extend beyond food and drink to other substances. "Maybe you've had enough of everything," he says.

> “I feel like a huge weight has been lifted off of me.”
>
> — Patient in an alcohol use clinical trial

Waiting for Data

Many clinical trials are now underway to test the effects of GLP-1s on everything from smoking to cocaine use. One set of studies involves a new drug called brenipatide, which mimics GLP-1 as well as another hormone called GIP. Moussawi is overseeing patients taking brenipatide in trials for alcohol and opioid use, sponsored by the drug’s manufacturer, Eli Lilly.

The demand is tremendous. When Moussawi’s team opened enrollment for two alcohol use trials at the UCSF site, several hundred people expressed interest. “The need far outpaces our ability to screen those participants,” he says.

The alcohol trials will each enroll an estimated 1,100 people diagnosed with alcohol use disorder across more than 100 sites, and researchers are tracking outcomes like drinks per day and severity of cravings. For the opioid trial, which is targeting 465 patients, participants must already be on buprenorphine. Researchers will assess whether the GLP-1 drug is safe for these patients, monitor their opioid use, and determine if they are less likely to drop out of treatment.

The alcohol trials have already yielded some dramatic anecdotal reports. Before starting the trial, one patient had been drinking one and one-half to two bottles of wine a day, usually rosé or Sauvignon blanc. She had sunk into “doom and gloom” last year when a beloved pet suddenly died; she mostly drank alone at home. The day after receiving her first injection, she had a strange feeling that she didn’t need to stop at a liquor store after work, as she usually did. That weekend, she felt “zero desire” to drink.

The patient doesn’t know for sure whether she’s receiving a placebo or the drug. But she hasn’t had more than an occasional glass of wine or nonalcoholic beer at social outings, and she’s going out more: to the ballet, to a bread-baking class. “I feel like a huge weight has been lifted off of me,” she says. Whether these changes can be attributed to brenipatide “is not going to be revealed until the study is over,” Moussawi says.

But even if GLP-1 drugs prove effective for reducing substance use, caveats abound. Laura Schmidt, PhD, MSW, MPH, a professor of health policy, points to known side effects, including gastric upset, nausea, muscle wasting, and pancreatitis. Long-term side effects could become an issue if GLP-1s end up being lifelong treatments. Among patients who have taken them for weight loss, those who stop tend to regain the weight. “Do you have to take the medicine once a week for life, lest you start drinking heavily again?” Koliwad wonders. “Is there an off-ramp?”

And Schmidt — who spent the first couple of decades of her career studying alcohol use, particularly in women and people in poverty — cautions that medication alone will not solve heavy drinking that stems from trauma. Some patients will likely need other interventions to support their recovery, such as psychotherapy or movement therapy. Drugs like naltrexone are “a wonderful adjunct for treating alcohol use disorder, but they are not the be-all and end-all,” she says. Some patients are also dealing with the consequences of decades of heavy alcohol or drug use: lost jobs, estranged families, stints in jail.

“Taking away the drinking is one thing,” Schmidt says, “but that doesn’t guarantee a person’s going to be able to patch back together a life.”

For now, Moussawi is not prescribing GLP-1 drugs for patients with substance use disorders because “the evidence is not there yet,” he says. The brenipatide trials for alcohol and opioid use are scheduled to release results around spring 2028. But some people hoping to reduce their consumption of alcohol or other substances aren’t waiting for clinical trial data or FDA approval; they’re seeking off-label prescriptions from online medical providers and experimenting. That raises an equity issue for DeFries, whose patients generally can’t afford to pay out-of-pocket. For example, a patient with alcohol use disorder who also has diabetes might get a GLP-1 drug covered by insurance for the latter. But what about patients who don’t have another qualifying condition?

“We don’t want our patients to be left behind,” she says.

For people struggling with addiction, new treatment options are long overdue. And until new data arrive, many patients who desperately want to stop their substance use likely will continue to relapse.

“We see them again and again,” Moussawi says. “We really ought to do better.”

ALUMNI HUB

Alumni Humanitarian Service Award

Meet some of this year's UCSF Alumni Achievement Award winners — five leaders expanding what's possible in science, health care, and community.

By Paula Hermann
Illustrations by John Jay Cabuay

SCHOOL OF NURSING | Jane Norbeck Distinguished Service Award

Jessica Zègre-Hemsey, PhD '11, MSN '06, RN

Saving Minutes in Cardiac Emergencies

THE AMBULANCE STARTS THE CLOCK

Before a patient experiencing a heart attack even reaches the emergency room, the clock is already running — and critical data are already en route to experts. A monitor can now transmit an electrocardiogram (ECG) from a speeding ambulance, giving clinicians an earlier view of the heart in distress. Those minutes — when time can make a life-or-death difference — are the focus of Jessica Zègre-Hemsey's work. "Cardiovascular systems of care start the moment someone calls 911," she says. "We can't wait until they're through the ER doors to start treatment."

As an Emergency Department nurse at UCSF, Zègre-Hemsey began asking urgent questions: "Why weren't warning signs recognized earlier? Why did some patients delay calling 911? What could be done before irreversible damage occurred?" She didn't know nurses could earn PhDs until she met Barbara Drew, PhD '80, RN, a professor emeritus in the Department of Physiological Nursing and a nurse-scientist whose pioneering research in ECG monitoring reshaped Zègre-Hemsey's career. In Drew's lab, her clinical questions became research questions. A master's degree led to a PhD, which has led to a life devoted to detecting cardiac emergencies sooner.

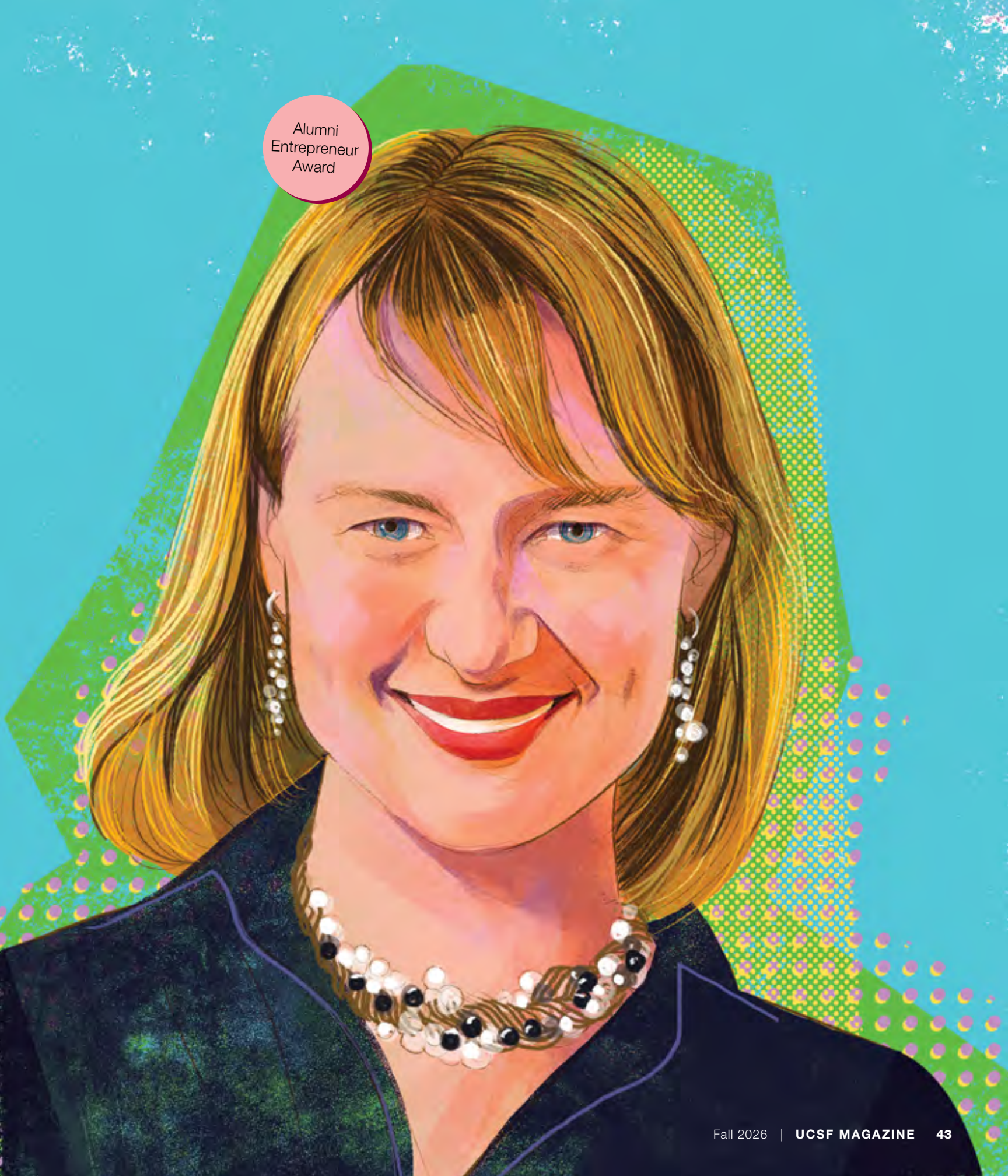
USING MACHINE LEARNING TO RECOGNIZE THE UNSEEN

Now an associate professor at the University of North Carolina at Chapel Hill, Zègre-Hemsey leads an interdisciplinary research program focused on emergency cardiac care. In work funded by the National Institutes of Health, she uses machine learning to analyze data collected before patients reach the hospital, helping clinicians spot warning signs they might otherwise miss. By studying ECGs, symptoms, and other physiological data gathered in ambulances, her team identifies patterns linked to worse outcomes — and opportunities to intervene sooner. She is also developing algorithms that analyze audio from 911 calls to detect vocal changes that may signal a heart attack in progress.

DRONES FOR FASTER DEFIBRILLATION

Zègre-Hemsey is also tackling cardiac arrest's most stubborn obstacle: access to lifesaving equipment. Every minute without CPR or defibrillation decreases a patient's survival chances by about 10%. In research sponsored by the National Science Foundation, she studies how drones equipped with automated external defibrillators (AEDs) could augment emergency response, with simulations showing dramatically faster response times. Collaborating with researchers in Sweden and Canada, she is determined to bring drone-deployed AEDs into U.S. emergency systems.

From ambulance-based diagnostics to AEDs in the sky, Zègre-Hemsey's work pushes lifesaving care into the community — closer to where emergencies begin and to the moments when rapid action matters most. "The ultimate goal is better outcomes," she says. "Earlier detection. Faster intervention. Preserving quality of life."


Alumni
Entrepreneur
Award

Jan Norbeck Distinguished Service Award

GRADUATE PROGRA CAL THERAPY | Alum of the Year

Lisa Oei, DPT '05, MSPT, PT

Movement Is Medicine

KEEPING PEOPLE WITH PARKINSON'S LIVING FULLY

When someone is diagnosed with Parkinson's disease, they often fear they'll have to give up activities they enjoy. Lisa Oei built her nonprofit to help people keep doing the things they love, often far longer than they expected. Oei is the founder and CEO of PD-Connect, a Bay Area nonprofit that offers exercise, education, and community programs for people living with Parkinson's.

FROM LOSS TO A CALLING

Oei was living in Hong Kong, working in sports marketing, when her father suddenly passed away. The loss reshaped her sense of purpose. "I decided that I didn't want to just make a living," she says. "I wanted to make a life." She returned to the Bay Area, enrolled at UCSF, and discovered her path through an unexpected phone call. Nancy Byl, BS '63, PhD, MPH, then chair of the Department of Physical Therapy, asked if she'd help with a research project on Parkinson's. "At the time, I didn't know a lot about the disease," Oei recalls, "but I said yes, got trained, and have never looked back." That same year, she began working one-on-one with Parkinson's patients and launched her first PD-Connect group class, expanding her reach to serve more people than she could through individual sessions.

MAKING LIFE BIGGER AGAIN

With Parkinson's, Oei explains, the default is small. "The patients' world becomes small — their voice, their posture, their movements. At PD-Connect, we focus on doing everything big — big movements, big voice, big community." That philosophy shows up vividly in programs like rock climbing, where participants who struggle to walk find something shifts when they get on the wall. "Something lights up in them," Oei says, "and they walk away without the walker they used when they came in." In community classes, held online and in person, participants newly diagnosed and those who've lived with Parkinson's for a decade come together to move, laugh, and encourage each other. "While science pursues a cure for tomorrow," Oei says, "we're helping people live fully today."



SCHOOL OF MEDICINE | Philanthropic Impact Awar

Alum of the Year Award

Edward Sickles, MD, Resident Alum

The Architect of Modern Mammography

SEEING WHAT OTHERS CAN'T

One of the things Edward Sickles loves about radiology is the ability to see through the body. "It's like I have X-ray eyes," he says. For nearly half a century at UCSF, Sickles has used that vision to help define modern breast imaging — seeing what others could not and teaching generations of radiologists to do the same. When he completed his radiology residency at UCSF, he was hired specifically to do mammography. There was just one problem: He had no formal training in the field. So he taught himself. At the time, UCSF was performing just five mammograms a day, giving him time to study, research, and refine his skills. From that quiet beginning, one of the most consequential careers in breast imaging took shape.

SHAPING MODERN MAMMOGRAPHY

Early in his career, Sickles developed magnification mammography, a technique that enlarges X-rays to reveal microscopic structures invisible with standard imaging. The advance helped radiologists detect cancers earlier and determine which findings required a biopsy. Today, millions of women benefit from this approach. Sickles has also played a dominant role in the American College of Radiology for decades, including serving on the committee that created BI-RADS, the standardized system radiologists worldwide now use to describe findings and track outcomes. He also led landmark research validating short-interval follow-up for "probably benign" findings, sparing patients unnecessary biopsies. Throughout his nearly 30 years as chief of breast imaging at UCSF, he helped establish performance benchmarks that define high-quality mammography practice.

A LASTING LEGACY

His commitment to excellence and passion for teaching are what keep Sickles, now a professor emeritus, still working one day a week well into his 80s. So when he and his wife, Dale, chose to give back to UCSF, a distinguished professorship in breast imaging felt like the natural extension of a lifetime of academic rigor and mentorship. "UCSF has basically shaped my life. It trained me, supported my research, and enabled a career that allowed us to give back. Someone will always hold this position. Knowing that you've done something long-lasting is very fulfilling."



Alumni Practitioner Award

GRADUATE EDUCATION ... DOCTORAL AFFAIRS | Discovery Award

Susan Acton, PhD '91

Connecting Discoveries Across Biology

FOLLOWING CLUES

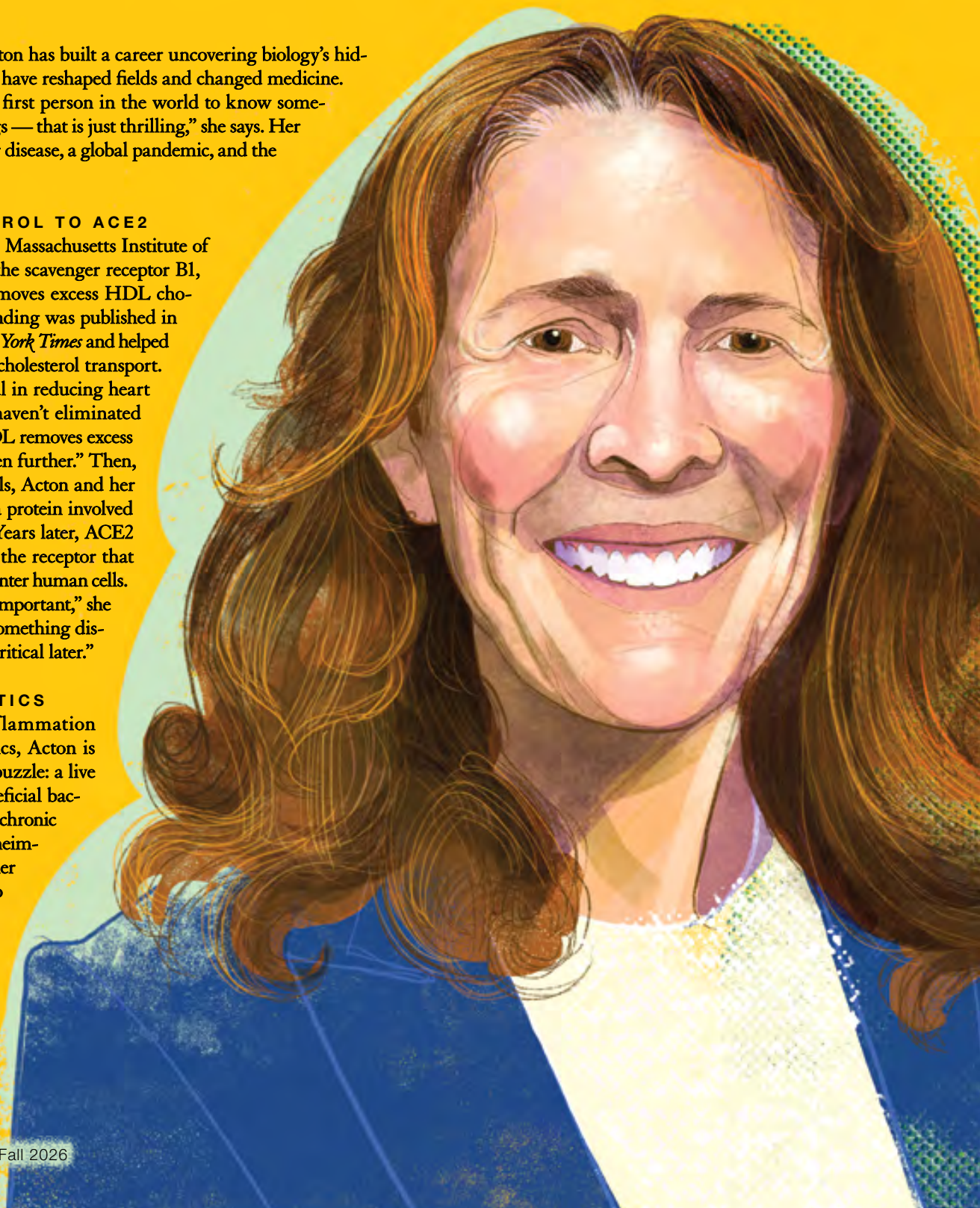
Over three decades, Susan Acton has built a career uncovering biology's hidden signals — discoveries that have reshaped fields and changed medicine. "The idea that I might be the first person in the world to know something about us as human beings — that is just thrilling," she says. Her discoveries span cardiovascular disease, a global pandemic, and the frontier of brain health.

FROM HDL CHOLESTEROL TO ACE2

As a postdoctoral fellow at the Massachusetts Institute of Technology, Acton identified the scavenger receptor B1, a long-sought protein that removes excess HDL cholesterol from the body. The finding was published in *Science* and covered in *The New York Times* and helped rejuvenate the field of reverse cholesterol transport. "Statins have been phenomenal in reducing heart attacks," she says, "but they haven't eliminated them. Understanding how HDL removes excess cholesterol could help us go even further." Then, at Millennium Pharmaceuticals, Acton and her colleagues discovered ACE2, a protein involved in blood pressure regulation. Years later, ACE2 became known worldwide as the receptor that the SARS-CoV-2 virus uses to enter human cells. "This is why basic science is so important," she says. "You never know when something discovered early on will become critical later."

BRAIN BIOTHERAPEUTICS

Today, as head of neuroinflammation research at Adiso Therapeutics, Acton is chasing the next piece of the puzzle: a live biotherapeutic agent — a beneficial bacterium — that turns down the chronic inflammation underlying Alzheimer's, Parkinson's, ALS, and other neurodegenerative diseases. Two principles in research, she says, are nonnegotiable: curiosity and perseverance. "Curiosity in science is key. If you don't have it, you will not be a good scientist. And perseverance. Experiments fail. If you give up, you will never succeed."



SCHOOL OF MEDICIN Alum of the Year Award e Year

Susan Buchbinder, MD ’84, Resident Alum

Turning HIV Into a Preventable Disease

INSIDE THE AIDS WARD

When Susan Buchbinder arrived at San Francisco General Hospital for her medical school clinical clerkships in the early 1980s, she walked into an escalating epidemic. Young men were coming in with mysterious cancers and opportunistic infections, and there was almost nothing medicine could offer them. “We could only provide care in its most fundamental way,” she recalls, “for both patients and their partners, who were often ostracized in other settings.” That early crucible of compassion would define everything that followed for Buchbinder. Over the ensuing decades, she would help turn HIV from a death sentence into a preventable disease.

MAKING TESTING POSSIBLE

After her residency, Buchbinder joined a landmark natural history study that drew on blood specimens collected from thousands of gay and bisexual men in San Francisco, originally gathered for hepatitis B research. That biobank helped develop the antibody test for HIV. “On the clinical side, I was helping patients, but when I started working in research, the community was helping me answer questions,” she says.

THE PrEP DRUG REVOLUTION

Buchbinder led the San Francisco site of the international iPrEx trial, which showed that preexposure prophylaxis (PrEP) — antiretroviral medication taken before potential exposure to HIV — could prevent infection. Named a groundbreaking achievement of 2010 by *Science*, PrEP became the standard prevention strategy. It paved the way for broader guidelines, community programs, and treatment options that have sent the rate of new infections plummeting globally. She’s continually innovating to ensure that patients adhere to the PrEP protocols. “If we have these drugs, but people aren’t able to use them or aren’t using them as directed,” she says, “then what was it all for?” As director of Bridge HIV, a clinical research unit within the San Francisco Department of Public Health, she and her team developed the SmartPrEP app to help patients determine their next dose and set reminders. A devoted champion for the community she’s served, she has also never given up on her decades-long pursuit of an HIV vaccine. “I do have great hope that we’ll have a vaccine in my lifetime,” she says.



Scanxiety

By Wei-Pei Cherng
Acrylic & permanent marker on canvas paper
9” x 12”

I grew up suppressing negative emotions. During my breast cancer treatment, that silence hindered my healing. After a recurrence, I found Art for Recovery and began painting my feelings. As an architect, I connect emotion to color, line, and space — releasing tension from my body when words are out of reach.



For patients facing life-threatening illnesses, art can be a lifeline. UCSF’s Art for Recovery program gives adults a safe space to express the intense feelings illness can bring. Last year, work by 30 patients — including this piece — was featured at the San Francisco Museum of Modern Art, in what is believed to be the first time a major museum has showcased art by patients from a medical center.

UCSF



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"I want today's learners to have the same amazing opportunities I had."

— Shelly Nakaishi, MSN '06, NP, UCSF School of Nursing alum and Dean's Associate since 2021

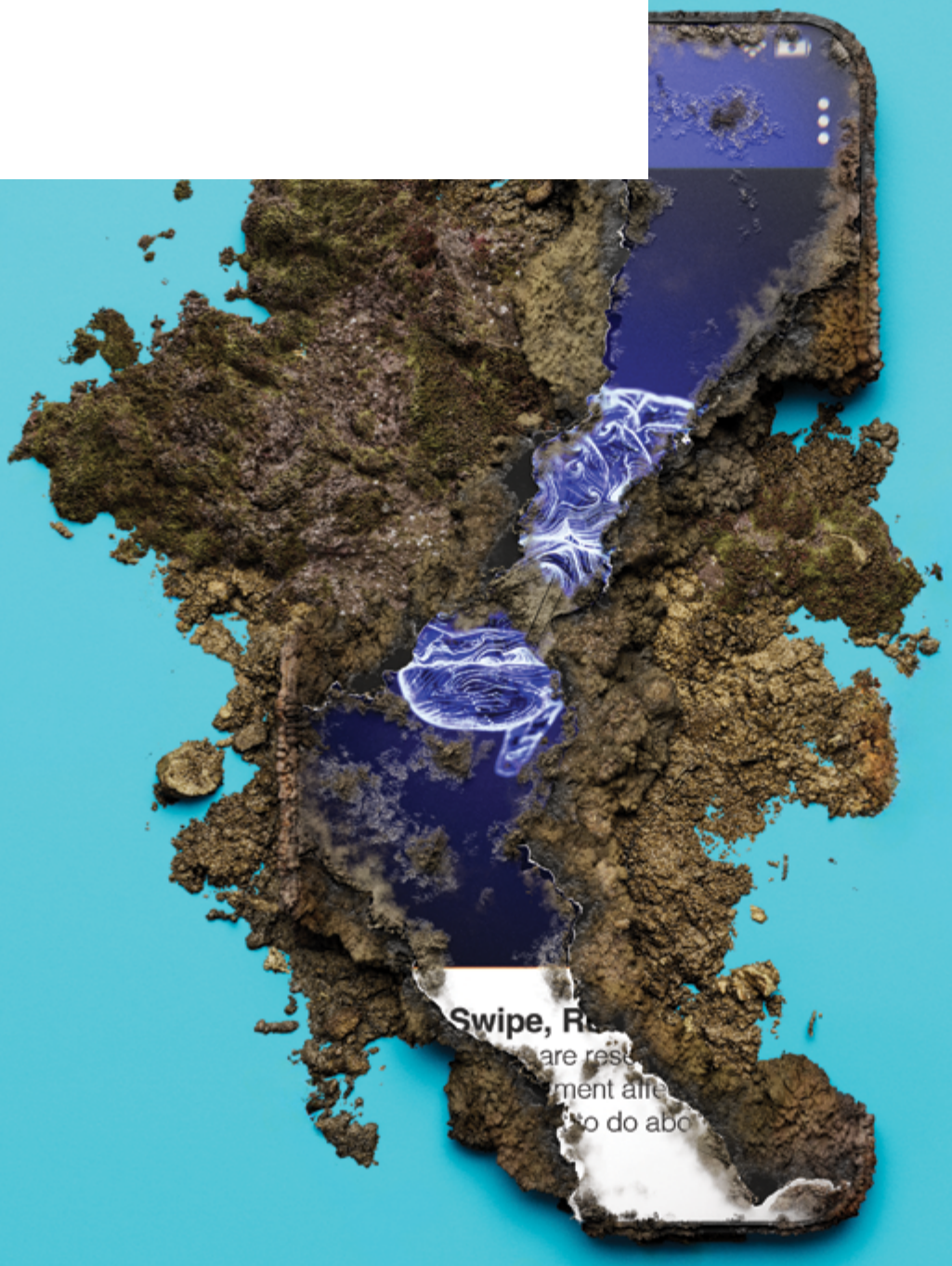
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"THE COGNITION CRISIS IS NOT JUST A CLINICAL PROBLEM. IT'S A PROBLEM FOR OUR SPECIES."
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