UCSF MAGAZINE

Winter 2022

Shelter from the Storm

Helping asylum-seekers escape persecution

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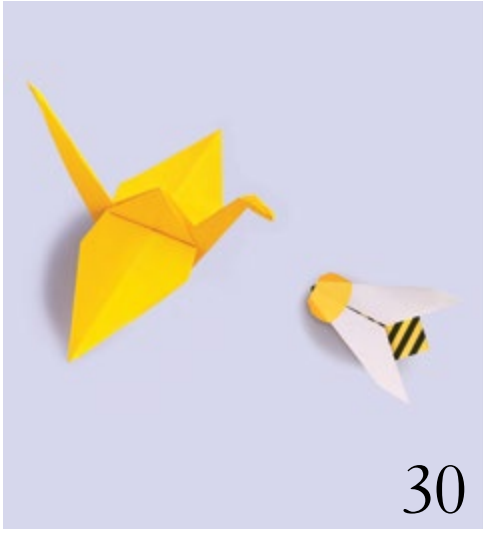
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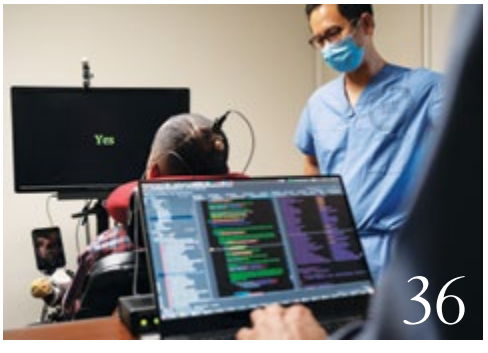

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The Very Best of UCSF

October 4 was a brilliant day for this university.

Before the sun had even risen, our own David Julius was awarded the 2021 Nobel Prize in Physiology or Medicine. What's more, his co-recipient, Ardem Patapoutian of Scripps Research, is a UCSF postdoc alumnus. These two remarkable scientists were recognized for independently discovering key mechanisms involved in how people sense heat, cold, and touch.

A biochemist and molecular biologist, David epitomizes the very best of UCSF science. Driven by the great need for effective pain medications without the side effects and addictive potential of opioids, he followed his curiosity to understand how we feel pain. His research lays the groundwork for new forms of painkillers and demonstrates the power of basic science. David, chair of Physiology and the Morris Herzstein Chair in Molecular Biology and Medicine, is an inspiration to everyone engaged in our mission to solve life's biological mysteries. You can look forward to a deep dive into his spectacular science in the next issue.

This issue spotlights another exceptional achievement at UCSF. In the first clinical trial of its kind, a team led by Eddie Chang, chair of Neurological Surgery and the Jeanne Robertson Distinguished Professor of Psychiatry in the Weill Institute for Neurosciences, restored the speech of a paralyzed man who had lost his ability to speak. The story explores their decade-long quest to unravel how the human brain gives rise to speech and to harness the power of artificial intelligence to translate neural signals into words. The technology they developed could eventually help others who have suffered speech loss and accelerate the evolution of brain-machine interfaces.

David Julius's research to decode how we sense pain earned him science's most prestigious prize. He is UCSF's sixth Nobel laureate.

Finally, our cover story showcases UCSF's public service mission in action. This feature introduces you to UCSF students and physicians who use forensic techniques to assess and document the trauma, violence, and persecution their asylum-seeking clients have endured. These evaluations can make the difference between deportation and a new life in the U.S. With all the tumult in our world today, this effort is more crucial than ever.

I hope you enjoy these stories and the others inside that reveal the best of UCSF's curiosity, creativity, and compassion.

Sam Hawgood

Sam Hawgood, MBBS
Chancellor
Arthur and Toni Rembe Rock Distinguished Professor

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PHOTO: NOAH BERGER

Five Questions for Monica Gandhi

Monica Gandhi, MD, MPH, an infectious disease expert and professor of medicine, has been an ardent voice for science during the coronavirus pandemic.

COVID thrust infectious disease specialists into the spotlight. What was that like?
I am glad to be able to disseminate information but don't like the attention it brought during such a politicized pandemic. For instance, I wrote about the importance of face masks early on, which earned me ire from the right. I have now been writing about off-ramps for restrictions like masks, which seems to make the left unhappy. I cannot wait to go back to my day job!

What's the biggest pandemic public health lesson?
You can develop a highly effective tool that could effectively end the pandemic – the vaccines – but that is not enough. The politicization of this pandemic worries me that the U.S. won't be prepared for the next one.

What's the most persistent misunderstanding about COVID?
I believe we set up a false expectation that immunity from the vaccine is impenetrable. The vaccines are actually doing what they were designed to do: prevent severe disease. Because antibodies wane with time, vaccines' ability to prevent disease transmission does decline. However, T-cell and B-cell immunity continues to prevent *severe* disease among most groups.

What's your biggest pandemic regret – and success?
My biggest regret is thinking India had more immunity than it did when it opened in February 2021. Like others, I was lulled into complacency before the delta variant became so formidable. Three of my relatives in India died during the terrible second wave. In terms of success, I wrote many op-eds on the importance of and strategies for school reopenings, the first one after vaccines for teachers were available. I hope I contributed to that dialogue in the U.S.

What are you most optimistic about for 2022?
That we'll be able to keep the virus under control in the U.S. once it becomes endemic. I am also optimistic about child vaccinations and the development of targeted oral antivirals.

Favorite book?
One is *The Great Gatsby*. I recently reread it, and it reminded me that the rich will always be okay in times of hardship, even a pandemic, but the poor and disenfranchised always suffer.

PHOTO: STEVE BABULJAK

Can This Controversial New Drug Curb Alzheimer's Disease?

By Ariel Bleicher

In June, when the U.S. Food and Drug Administration (FDA) approved the drug aducanumab (marketed as Aduhelm) for treating Alzheimer's disease, reactions were mixed. Some experts considered the decision a breakthrough moment for a field that hasn't offered a new therapy in more than 20 years. Others – including three members of the FDA's own advisory committee, who resigned in protest – called it a regulatory failure. UCSF neurologist Gil Rabinovici, MD, the Fein and Landrith Distinguished Professor of Memory and Aging, explains the controversy and shares why he thinks Alzheimer's care is entering a new era "regardless of whether aducanumab proves to be a blockbuster or a bust."

How does aducanumab treat Alzheimer's?
Alzheimer's disease is defined by two protein deposits that are found in the brain: amyloid plaques and tau tangles. Aducanumab targets the plaques. It's what's called a monoclonal antibody, which works like the antibodies made by the immune system: It attacks amyloid plaques as if they were a virus or other foreign entity. Aducanumab is the first Alzheimer's drug that is very effective at clearing these plaques.

How did the drug become controversial?
In February 2019, the manufacturer, Biogen, suddenly announced that they had stopped the phase III trials of aducanumab, which were designed to test whether the drug slowed cognitive decline for patients with amyloid plaques who were in the early stages of memory loss. Basically, Biogen's statisticians had determined that there was a very low likelihood that the drug would show a difference in clinical outcomes compared with a placebo.

Then, eight months later, the company made another sudden announcement: As more of the trial data had become available, they had found that one of the trials – in which more people received the highest dose of the drug –

ILLUSTRATION: DICKGRAFT/CHUHAIL

actually was successful. In the following months, Biogen worked closely with the FDA to try to understand these very complicated data. There are now allegations that this relationship was a little too close; at least two congressional committees and the Office of the Inspector General are investigating.

What happened next?

On June 7, 2021, the FDA introduced yet another twist in the story: It approved aducanumab, against the advice of its own advisory committee. The agency did this through an accelerated path designed to increase the availability of new drugs for severe diseases that have very limited therapeutic options. In accelerated approval, you can approve a drug based not on evidence that it has clinical benefits – which is the standard for most drugs – but rather based on evidence that it changes the biology of a disease in a way that is *likely* to have clinical benefits.

So in the case of aducanumab, the phase III trials consistently showed that the drug removes plaques effectively – a 55% to 60% reduction, on average. There is a lot of controversy about whether removing amyloid plaques really benefits patients. It's not a cure by any means. But based on the trial data for aducanumab and early results from two similar plaque-busting antibodies, my opinion is that these drugs do have a modest effect on slowing cognitive decline.

Other experts disagree with you, including some of your own UCSF colleagues who are not convinced there is enough evidence that aducanumab can help people.

I agree that this is not a home-run drug, I agree that the data could be clearer, and I can understand physicians who are worried and reluctant. I wish the FDA had required Biogen to complete a third phase III trial with the higher dose so that there wouldn't be any confusion about whether the drug does or doesn't work.

That being said, I'm not ready to throw this drug out entirely now that the FDA has approved it. Alzheimer's disease is a devastating illness. Given the choice between the certainty of decline and the chance that a drug like this might slow that process – even if the benefit is modest, and there is risk involved – many patients will choose to take that risk. I feel we have an obligation to discuss this drug as an option with our patients who might benefit.

Who might benefit?

Patients who are in an early stage of Alzheimer's – what's called mild cognitive impairment. Based on what we know about the disease, it is unlikely that people who are in more advanced stages of Alzheimer's are going to benefit. Physicians also should verify that patients have amyloid plaques before starting this treatment. It's not enough to have the clinical symptoms; you want to have evidence of the molecular changes in the brain that define Alzheimer's disease.

How are amyloid plaques detected?

The most accurate tests are amyloid PET scans, which can image the plaques in the brain. Unfortunately, these scans are very costly and not very accessible. But there are also spinal fluid tests that are more affordable and highly accurate. And soon, we may have reliable blood tests, which would greatly increase the cost effectiveness of and access to testing.

What are the drug's side effects?

Mainly swelling or bleeding in the brain. This sounds really scary, but the swelling is reversible, and the bleeds are tiny – what we call microbleeds. In the trials, fewer than 1% of people treated with aducanumab had what we would consider very severe symptoms, including seizures or stroke-like episodes. Most participants who experienced swelling or bleeding had no symptoms or only mild ones, like dizziness or a little more confusion.

These side effects are more serious than with other Alzheimer's drugs, but they can be managed. They resolve when patients stop taking aducanumab, and in most instances, patients can safely restart the drug later. However, people who are on blood thinners or who otherwise might be prone to bleeding should avoid taking aducanumab altogether.

Are you concerned about the cost?

Biogen has set the wholesale price for aducanumab at $56,000 a year. That's way too high. Even if the drug is covered by Medicare, patients might still be liable for up to 20% in copays. A lot of people won't be able to afford that. There is huge concern that this will exacerbate the racial and socioeconomic disparities that already exist in access to dementia care. I think the solution is for companies to price these drugs more reasonably and offer robust patient-assistance programs so no one is denied treatment because they can't afford it.

How will aducanumab impact the future of Alzheimer's care?

I think it's going to herald a new era in Alzheimer's therapy. There are now two other monoclonal antibodies for treating Alzheimer's – lecanemab and donanemab – that are showing similar promise in early studies. In the next two to three years, as more clinical-trial results are published, a lot of the controversy and smoke around these drugs should clear. We will have a clearer picture of what these drugs do, who they help, and who they don't help.

Consider the history of treatment for HIV and many cancers. The first drugs that were used to treat these diseases had serious toxicity and modest benefit – a lot like aducanumab. Yet we now have highly effective drug cocktails that allow people with HIV to live normal lives and keep the virus under control, and we have extremely sophisticated ways of understanding individual tumors and developing targeted therapies to treat them. With Alzheimer's, we have just reached the precipice of this precision approach to treatment, and aducanumab is the first drug, hopefully, of many.

I wish it were a better drug. I wish it were less controversial. But I do think it's a step in the right direction.

Disclosures: UCSF served as an enrollment site for the clinical trials of aducanumab. Gil Rabinovici was not involved in the trials. He has done consulting work unrelated to aducanumab for Eisai Co. Ltd., which has a partnership with Biogen Inc. to develop and commercialize aducanumab and other treatments for Alzheimer's disease.

ADUCANUMAB AT UCSF

Providers at UCSF have not started prescribing aducanumab. UCSF is determining how the drug might be considered for use in appropriate patients already receiving care at the Memory and Aging Center.

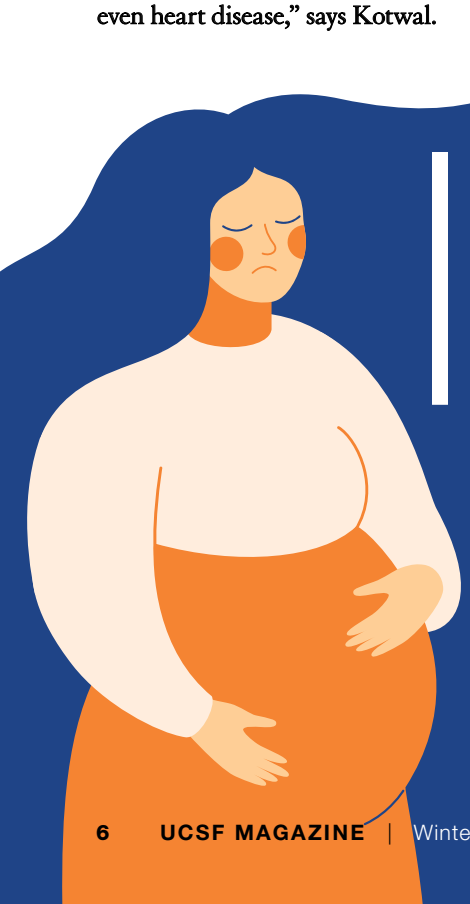
Over 65 and Lonely? Don't Talk to Your Doctor About Another Prescription

Lonely older adults are nearly twice as likely to use opioids to ease pain and two and a half times as likely to use sedatives and anti-anxiety medications, according to a UCSF study. This puts them at risk for drug dependency, impaired attention, falls and other accidents, and further cognitive impairment.

"There's a misconception that as we age, we become more withdrawn and less sociable," says first author Ashwin Kotwal, MD, an assistant professor of geriatrics. "In fact, older people are more socially active than other age groups and frequently play major roles in their communities. When older people are not socially active, we need to recognize that there's a problem."

Kotwal recommends fewer prescriptions of psychotropic drugs for older adults who are lonely, and in their place advocates "social prescribing" – connections with amenities such as senior centers, exercise classes, grief groups, or volunteer programs.

"We don't want to pathologize loneliness. Most people experience loneliness at some point in their lives, but when experiences of loneliness persist for many months or years, [they] can cause physiologic changes, such as a ramped-up stress response, sleep problems, and even heart disease," says Kotwal.



COVID-19 During Pregnancy Associated with Preterm Birth

Pregnant individuals with COVID-19 are 40% more likely to deliver their babies prematurely, according to a large UCSF study. And their risk of experiencing a very preterm birth, before 32 weeks of gestation, increased by 60%. The study also found that people of color face a disproportionate risk of being infected with coronavirus while they're pregnant.

"Preterm birth is associated with many challenging outcomes for pregnant people and babies, and very preterm births carry the highest risk of infant complications," says lead and corresponding author Deborah Karasek, PhD, MPH, an assistant professor of obstetrics, gynecology, and reproductive sciences and a researcher with UCSF's California Preterm Birth Initiative. "Our results," she adds, "point to the importance of preventative measures, including vaccination, to reduce COVID-19 infection among pregnant people to prevent preterm birth."

In July 2021, the American College of Obstetricians and Gynecologists issued updated guidance strongly recommending that all pregnant individuals get vaccinated against COVID-19. Pregnant people are considered a high-risk population for COVID-19 infection, yet less than a quarter have received at least one dose of vaccine, according to the U.S. Centers for Disease Control and Prevention.

ILLUSTRATIONS: MARISVECTOR (TOP); MARIA PONOMARIOVA (BOTTOM)

Generic Drugs: Are They on a Par with Pricier Brands?

Americans save billions of dollars using lower-cost generics instead of brand-name drugs. Are they as effective?

By Ann Brody Guy

More than three-quarters of prescriptions in the U.S. are for generic drugs – off-brand medications that can cost less than half of their brand-name counterparts. Generic drugs saved Americans and our health care system over $300 billion in 2019 alone.

The use of generics has more than doubled over the past decade, thanks to legislation promoting generic-drug production and to the expiration of patents on widely used medications. Despite this enormous growth, myths about generics' quality persist. UCSF drug safety experts help us understand what's the same and what's different, and whether brand should affect your choices.

MYTH #1: Generic drugs are second-rate knockoffs.

Off-brand products like spaghetti sauce or facial tissue have often earned their reputation for being less good – they may taste mediocre or be less durable than the products they're imitating. Consumers sometimes lump generic drugs in with second-rate knockoffs because of their cheaper price tags; there's even skepticism among some providers.

It's time to shake off this lingering myth once and for all. Generic drugs aren't like other off-brand products, says Candy Tsourounis, PharmD, a professor of clinical pharmacy. They are in their own highly controlled category.

The myth of shoddiness may be reinforced by the way generics look, feel, or taste compared to brand-name drugs consumers are familiar with. That's because inactive fillers, coatings, or liquids that help deliver the active ingredient – the actual drug – can vary.

"Many people view generics as somehow being inferior because of observable differences," Tsourounis says, because generic manufacturers tweak these inactive components. This also explains why branded over-the-counter treatments like headache or allergy medications look different from over-the-counter generics. "For example, the brand name might be a tablet with a shiny coating that tastes nice and goes down easy, whereas the generic might be a chalky white pill with a bitter aftertaste."

"Those differences exist, but the pharmacology – how the drug works in the body, the actual medicine it contains, and how long it takes to get to where it needs to be in the body – is the same," says Tsourounis, who oversees UCSF Health's medication formulary, the list of safe and effective medications approved for use within the institution. "Those are the most critical pieces," she says. "The rest is just aesthetics."

MYTH #2: Testing of generics is not as rigorous.

Generic drugs don't go through the same testing protocols as name-brand medications, but there's a good reason, Tsourounis explains.

"It's not that the testing is less rigorous, but that it's different," she says. It takes eight to 12 years of research and development, including clinical trials, to ensure that a new drug is safe and effective. All the steps to bring a drug to market add up to major costs for the company holding the patent.

By contrast, generics are not new drugs. When the patent becomes available on an existing approved drug, a generic manufacturer simply purchases or produces the already developed, tested, and approved active component and formulates it into a tablet, capsule, or other delivery vehicle. "That timeline is *months*, not years," Tsourounis says, so it costs far less to bring a generic drug to market. When multiple manufacturers produce the same generic drug, competition drives prices down further.

The FDA requires that generics contain the same active ingredient as the branded version, be the same strength and format (such as a ▶

ILLUSTRATION: FARAH HAMADE

tablet or capsule) and use the same delivery route (such as oral or injection). To prove that their formulations work like the original drug, generic manufacturers must meet strict requirements for bioequivalence, which means the medicine must be absorbed by the body and measurable in the blood at levels comparable, within a strict range, to those of the brand-name drug.

Tsourounis also points out that FDA regulations govern every detail of pharmaceutical manufacturing, from laboratory facilities to the training required for individuals who handle and package drugs.

Shalini Lynch, PharmD '92, an associate professor of clinical pharmacy, co-authored a study that found generic-drug skepticism is higher among ancillary providers like nurses and physician assistants, who receive limited pharmacology training, than among physicians. "Additional training on specific concepts such as bioequivalence," Lynch explains, "could … foster a better understanding of the generic approval process."

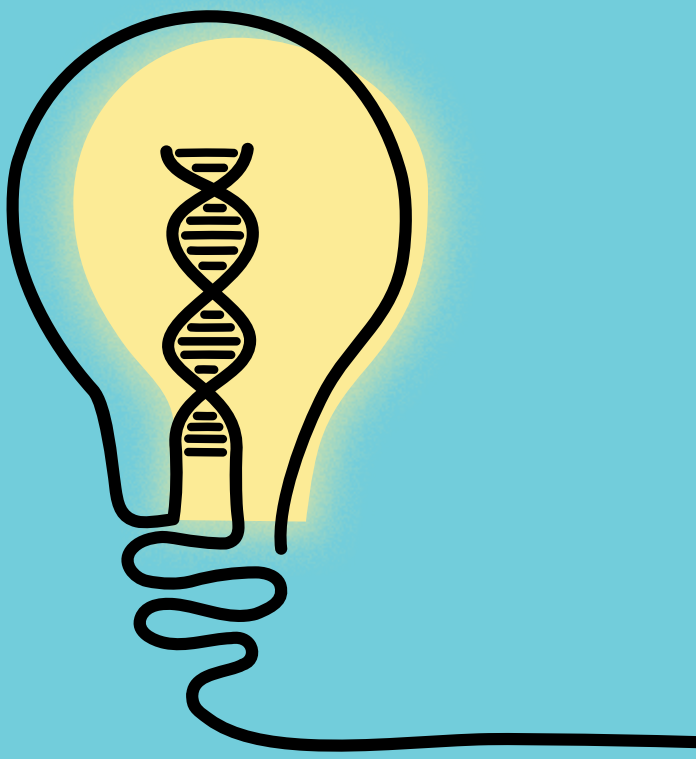
MYTH #3: Generics just don't work as well as brand-name drugs.

Especially when people switch from a name-brand drug to a generic, they may experience modest changes. Tsourounis says to avoid jumping to the conclusion that the generic isn't up to snuff.

"There's a lot to evaluate before concluding that the generic drug is not working as well as the brand," she says. Are there interactions with food or other medications that affect the way the drug is being absorbed? Is the person taking the medicine at the same time every day? When she hears complaints that a drug didn't work as quickly or caused a side effect, "there's generally no pharmacological reason for these impacts, so I look to other causes or possibly even a placebo effect based on these myths about generics not being as good," she says.

Pharmacies stock both AB-rated generics – drugs with the highest bioequivalence assessments – and B-rated drugs, which still meet rigid FDA requirements but have slightly lower bioequivalence. B-rated generics may be better suited for initial use of a drug rather than replacing a name-brand version. While Lynch cautions that additional monitoring may be required for patients with conditions where small changes in blood levels could pose "immediate and serious risks," she says that caveat is about individual situations and risk, not classes of drugs. Lynch and Tsourounis assert that it's beneficial for all patients to talk with their physicians about generic drug options.

"The bottom line is that generic drugs provide the same active ingredient as the brand for a lower cost, and they should be used whenever appropriate," Tsourounis says. "They're good medicine."



New, Safer Gene-Editing Tool

Researchers have developed a new way to alter gene activity without making any permanent changes to DNA. This fully reversible system – so far studied only in cell cultures – could open new pathways to study and treat a range of diseases and genetic disorders.

The new tool, called "CRISPRoff," extends CRISPR's basic DNA-editing ability beyond the genome and into what's known as the epigenome – proteins and small molecules that latch onto DNA and control when and where genes are switched on or off.

In a paper published in the journal *Cell*, scientists at UCSF and the Whitehead Institute showed how CRISPRoff could switch off almost any gene by using small chemical tags, in a process called DNA methylation. Although DNA methylation occurs naturally in all mammalian cells, CRISPRoff offers scientists unprecedented control over the process. Once a gene was switched off, it remained inert in the cell's descendants for hundreds of generations, unless it was switched back on with a complementary tool called CRISPRon, also described in the paper.

Because the epigenome plays a central role in many diseases, from viral infections to cancer, CRISPRoff technology may one day lead to powerful epigenetic therapies.

And since this approach doesn't involve any DNA edits, it's likely to be safer than conventional CRISPR therapeutics, which have been known to cause unwanted and potentially harmful changes to the genome.

"Though genetic and cellular therapies are the future of medicine, there are potential safety concerns around permanently changing the genome, which is why we're trying to come up with other ways to use CRISPR to treat disease," says Luke Gilbert, PhD, the study's co-senior author and UCSF's Goldberg-Benioff Professor.

ILLUSTRATION: CHANAKARN PHINAKAN

PHOTO: JASON DOIY

Wildfire Smoke Could Harm Your Skin

Wildfire smoke can trigger a host of respiratory and cardiovascular symptoms, ranging from runny noses and coughs to potentially life-threatening heart attacks or strokes. A new study suggests that the dangers posed by wildfire smoke may also extend to the human body's largest organ and our first line of defense against outside threats – our skin.

During the two weeks in November 2018 when wildfire smoke from the Camp Fire choked the San Francisco Bay Area, the study found that clinics in San Francisco saw an uptick in the number of patients with eczema (also known as atopic dermatitis) and general itchiness, compared to the same time of the year in 2015 and 2016.

The findings suggest that even short-term exposure to air polluted with wildfire smoke can be damaging to skin health. The study was conducted by researchers from UCSF and UC Berkeley, led by senior author Maria Wei, MD, PhD, a professor of dermatology and a melanoma specialist at UCSF.

"Existing research on air pollution and health outcomes has focused primarily on cardiac and respiratory health outcomes, and understandably so," says the study's lead author, Raj Fadadu, a student in the UC Berkeley-UCSF Joint Medical Program. "But there is a gap in the research connecting air pollution and skin health. Skin is the largest organ of the human body, and it's in constant interaction with the external environment. So it makes sense that changes in the external environment, such as increases or decreases in air pollution, could affect our skin health."

Tips for protecting your skin during wildfire season

- Stay indoors.
- If you do go outside, wear long sleeves, long pants, and a mask.
- Use emollients, which can strengthen the skin's barrier function.
- Watch for a new medication to treat eczema called Tapinarof; it is now in clinical trials and could be a useful tool during times of bad air.

Recommended:

Books, Videos, & Podcasts

READ

Wildhood: The Astounding Connections between Human and Animal Adolescents

Does your rambunctious teen seem like an animal? You may be on to something. Harvard evolutionary biologist Barbara Natterson-Horowitz, MD '87, and science writer Kathryn Bowers reveal startling similarities between humans and animals in young adulthood.

WATCH

UCSF Women's Sports Performance Center webinar

See the story behind the first and only women's sports medicine center on the West Coast. Learn how the center's physicians – all athletes – are helping women and girls, from weekend warriors to pros, optimize their performance and heal from injuries. See specialevents.ucsf.edu.

LISTEN

UCSF's Robin Carhart-Harris, PhD, on "The Psychedelic Therapy Podcast"

Explore the power of psychedelic therapy to treat the ailing human mind with international expert Carhart-Harris, who joined UCSF in 2021 as the Metzner Distinguished Professor and director of the new Neuroscape Psychedelics Division. Discover what his comparison of psilocybin with an antidepressant revealed on the Aug. 19 episode.

Breakthroughs and Other Buzz

No vaccine in breast milk:

Messenger RNA vaccines against COVID-19 were not detected in human milk, according to a small UCSF study, providing early evidence that mRNA from vaccines is not transferred to nursing infants.

COVID drug misses the mark:

Despite widespread prescription of azithromycin to treat COVID-19, a UCSF study found that the antibiotic was no more effective than a placebo in preventing symptoms of the disease among nonhospitalized patients – and that it may even have increased their chance of hospitalization.

Poison critters' secrets revealed:

Some poisonous birds and frogs may evade their own toxins through molecules that act as "toxin sponges," according to a team from UCSF, the California Academy of Sciences, and Stanford University. The finding may lead to a much-sought-after antidote to paralytic shellfish poisoning, which can cause severe illness and death in humans.

Altering brain pathways to alleviate addiction:

UCSF researchers have devised a two-drug treatment for alcohol use disorder, aimed at the neurological underpinnings of addiction. In mouse studies, the approach completely eliminated cravings and changed behavior, without the side effects or complications associated with current treatments.

AI is as good as your cardiologist:

Clinicians rely on electrocardiograms (ECGs) to detect common cardiovascular conditions, but accurate diagnoses require significant expertise. Now, UCSF and UC Berkeley researchers have developed an artificial intelligence algorithm that can outperform a common commercial ECG analysis algorithm – matching the accuracy of expert cardiologists.

Ranked #1 in neuro and among the top 10 hospitals:

UCSF Medical Center is ranked #1 in the nation for neurology & neurosurgery – specialties that are part of the UCSF Weill Institute for Neurosciences – and among the top 10 hospitals in the nation overall, according to U.S. News & World Report's 2021-22 Best Hospitals publication.

Good news for coffee drinkers:

In the largest study of its kind, UCSF researchers found no evidence that moderate coffee consumption can cause cardiac arrhythmia. In fact, each additional daily cup of coffee consumed was associated with a 3% lower risk of any arrhythmia for the several hundred thousand subjects in the study.

Where have all the nurses gone?

The pandemic has accelerated the retirement of older nurses in California and delayed the hiring of less experienced ones, according to a new report by UCSF researchers. To address the resulting shortage, employers need to retain older RNs, develop career paths for new graduates, and rapidly find ways to mitigate the trend, say the report authors.

Action urged for oral health:

Nearly half the world's population suffers from untreated oral diseases, but a new World Health Organization resolution offers an opportunity for bold action, says the *Lancet* Commission on Global Oral Health, which includes UCSF scientist Cristin Kearns, DDS, MBA. Tackling sugar as a major common risk factor and emphasizing equity and social justice are among their recommendations.

Microbiome and weight loss:

Scientists at UCSF have found that very-low-calorie liquid diets alter the gut microbiome in ways that could help with weight loss but might also result in an increased population of a pathogenic bacterium that can lead to severe diarrhea and colitis.

Young and skeptical:

In the U.S., about 1 in 4 unvaccinated adults aged 18 to 24 said they will "probably" or "definitely" decline COVID-19 shots, according to a UCSF study. More than half of the skeptics were concerned about side effects. Their hesitancy may stall efforts to achieve herd immunity.

Better care for millions with TB:

Since the 1980s, the treatment for tuberculosis – which still kills 1.5 million people worldwide each year – has been six months of daily antibiotics. Now, thanks to a clinical trial co-led by UCSF experts, a cure can be achieved in just four months. The new regimen has the blessing of the World Health Organization.

A record of pandemic citizen-science:

The Atlantic's COVID Tracking Project – a 15-month endeavor to catalog statistics from throughout the U.S. related to the pandemic – will become part of UCSF's permanent library collection. The pop-up volunteer effort will serve as an important record of grassroots science.

BACTERIUM: JENNIFER OOSTHUIZEN/CDC; WEBSITE: THE COVID TRACKING PROJECT; COFFEE: AMENIC181; FROG: GLOBALP; BADGE: U.S. NEWS & WORLD REPORT

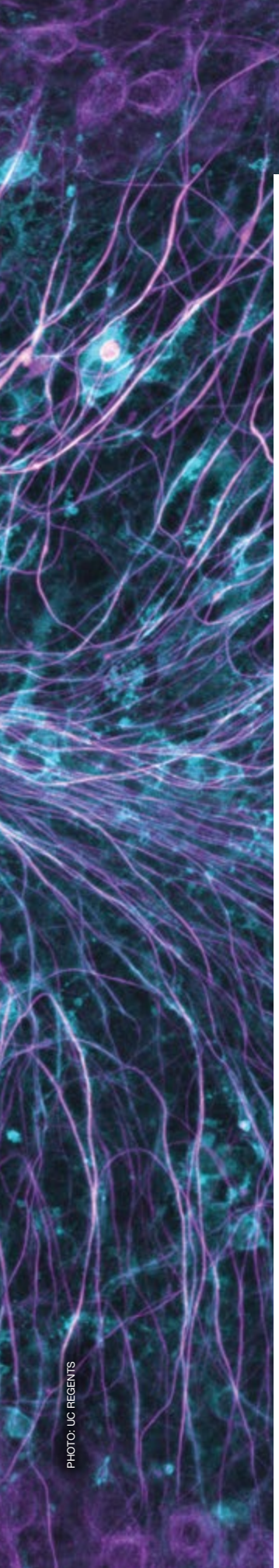


PHOTO: UC REGENTS

New Frontiers in Living Cell Therapies

By Laura Kurtzman

Human cells have abilities that go far beyond the fastest, smartest computer. They can, for example, generate mechanical forces to propel themselves around the body and sense their local surroundings through myriad channels, constantly recalibrating their actions.

The idea of using cells as medicine emerged first with bone marrow transplants, then with CAR T-cell therapy for blood cancers. Now, taking a page from computer engineers, biologists are trying their hands at programming cells – by building DNA circuits to guide their protein-making machinery and behavior. These engineered cell therapies would be a huge leap from traditional therapies like small molecules and biologics, which can only be controlled through dose, combinatory activity, or the passage of sufficient time for the body to clear them.

With philanthropic and institutional support of more than $250 million for UCSF's new Living Therapeutics Initiative, scientists across the institution are advancing these and other cell-based solutions.

Tiny depots

Tejal Desai, PhD '98, UCSF's Deborah Cowan Professor and the chair of the Department of Bioengineering and Therapeutic Sciences, is employing nanotechnology to create tiny depots where cells that have been engineered to treat type 1 diabetes or cancer can refuel with oxygen and nutrients.

"Having growth factors or other factors that keep them chugging along is very helpful," she says. "Certain cytokines help specific immune cells proliferate in the body. We can design synthetic particles that present cytokines and have a signal that says, 'Come over to me.' Basically, a homing signal."

Damage control

Ophir Klein, MD, PhD, a professor of orofacial sciences and of pediatrics, employs stem cell biology to research treatments for birth defects and conditions like inflammatory bowel disease. He is working with Wendell Lim, PhD, the Byers Distinguished Professor and director of UCSF's Cell Design Institute, and Zev Gartner, PhD, a professor of pharmaceutical chemistry, to create circuits that induce cells to grow in new ways – for example, to repair intestinal damage in individuals with Crohn's disease.

"Cells and tissues are able to do things that historically we thought they were incapable of doing," says Klein, who holds UCSF's Hillblom and Epstein Professorships. "We don't assume that the way things happen or don't happen is the best way that they can happen, and we're trying to figure out if there are even better ways."

Gut regeneration

Faranak Fattahi, PhD, a Sandler Faculty Fellow, is developing a cell replacement therapy for damaged or missing enteric neurons, which regulate the muscles that move food through the gastrointestinal tract. She generated these gut neurons using so-called iPS cell technology.

"What we want to do in the lab is see if we can figure out how these nerves are misbehaving and reverse it before transplanting them inside the tissue," she says. Now, she is working with Lim to refine the cells so they integrate into tissues more efficiently, without being killed off by the immune system, and work better at reversing disease.

Islet transplants

Matthias Hebrok, PhD, UCSF's Hurlbut-Johnson Professor of Diabetes Research, has created pancreatic islets, a complex cellular ecosystem containing insulin-producing beta cells, glucagon-producing alpha cells, and delta cells.

Now, he is working on how to make islet transplants that don't trigger the immune system, so diabetes patients can receive them without having to take immune-suppressing drugs. "We might be able to generate stem-cell derived organs that the recipient's immune system will either recognize as 'self,'" he says, "or not react to in a way that would disrupt their function."

In a healthy individual, the ecosystem of cells in these islets performs the everyday miracle of keeping your blood sugar on an even keel, regardless of what you ate or drank or how little or how much you exercised or slept. "To me, at least, that's the most remarkable thing about our cells," says Gartner, who is collaborating with Hebrok. "All of this stuff just happens on its own."

Building **the Brains** of Precision Medicine

Ten years ago, **Keith Yamamoto, PhD**, helped lay the foundation for the precision medicine revolution. Even back then, he knew this mode of medicine, sometimes dubbed "the right care for the right patient," could deploy a new tool – a knowledge network. Yamamoto, now UCSF's director of precision medicine, explains what this network entails and how it will transform health care.

By Ariel Bleicher

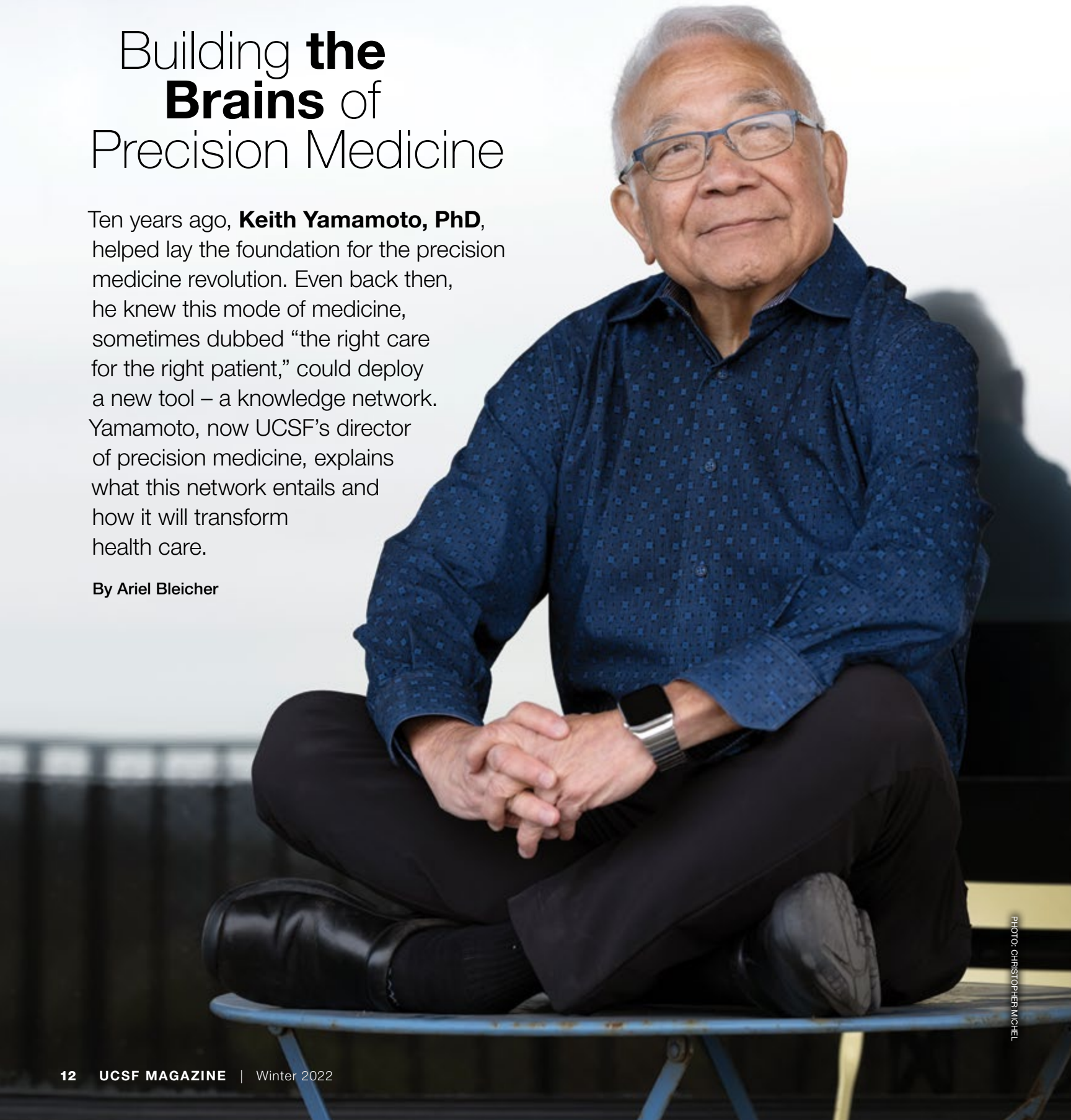


PHOTO: CHRISTOPHER MICHEL

What is a knowledge network?

It's the brains of precision medicine. It combines on a single computational platform all research findings about normal and abnormal biological processes. The information is derived from molecules, from experimental organisms, from well and ill people, and from social determinants of health. Machine learning algorithms sort through all this information and find patterns, producing a knowledge network that continuously expands and improves.

Then we link *your* information to the network – your genome, your blood sugar levels, the stresses you're under, the quality of the air you breathe, the food you eat – and we ask: What can we say about *you*? The network seeks to tell you what diseases you're at risk of; what you can do to prevent them; and, if you do get them, how to treat them in a way that's most effective for *you*, not for some statistical group similar to you.

UCSF is building a knowledge network called SPOKE. What kinds of data go into it?

SPOKE merges over 40 huge public databases onto a common platform. It includes information about all human genes, including those that predispose people to disease; proteins those genes encode, including their molecular structures and how they interact with each other; all microbial genes; chemical compounds that interact with proteins; drugs and drug candidates and their effects and side effects; and much more. SPOKE ties all that together and reveals correlations. We're now seeking to add databases on social determinants of health. Finally, we overlay patient data onto the knowledge network to produce rich individual patient profiles that reveal new insights. The databases are updated weekly, so the network is continuously growing and evolving.

How will SPOKE change patient care?

Profoundly. On the front end, it will enrich our understanding of each patient by connecting individual patient data with SPOKE's huge, dynamic repository of information, enabling more informed decisions about a patient's health and health care. Eventually, we should be able to predict someone's risk of chronic diseases years, even decades, before symptoms appear. My father died of Alzheimer's when he was 85. In retrospect, I think there were hints of problems 10 years earlier. I'm confident that knowledge networks will be able, early in life, to identify risk and causal factors that predict such diseases, propose optimal treatments for them, and even prevent them through behavioral or environmental interventions.

On the back end, SPOKE will continuously relate discoveries made by basic scientists to human physiology, health, and disease. That will sharpen the hypotheses scientists set out to test and will speed the clinical application of their discoveries. Today, the median time between a basic science discovery and its development into an FDA-approved drug is over three decades! Knowledge networks have the potential to reduce that period manyfold.

And for patients who are already sick? How could SPOKE help them?

There are many ways to answer that question. Here's one: UCSF data scientists showed recently that type 2 diabetes patients at UCSF are on over 1,600 different treatment plans. Across the five UC medical centers, 6,500 treatment plans were found for this one disease! Clinicians select an approved drug and dosage for each patient and typically adjust them every few months, looking for an optimal response. These choices are based on individual physicians' expertise, savvy, and experience. But in the future, they could be informed by knowledge network-derived profiles that predict an optimal treatment plan based on a patient's particular history and biology.

So a knowledge network will reduce trial and error?

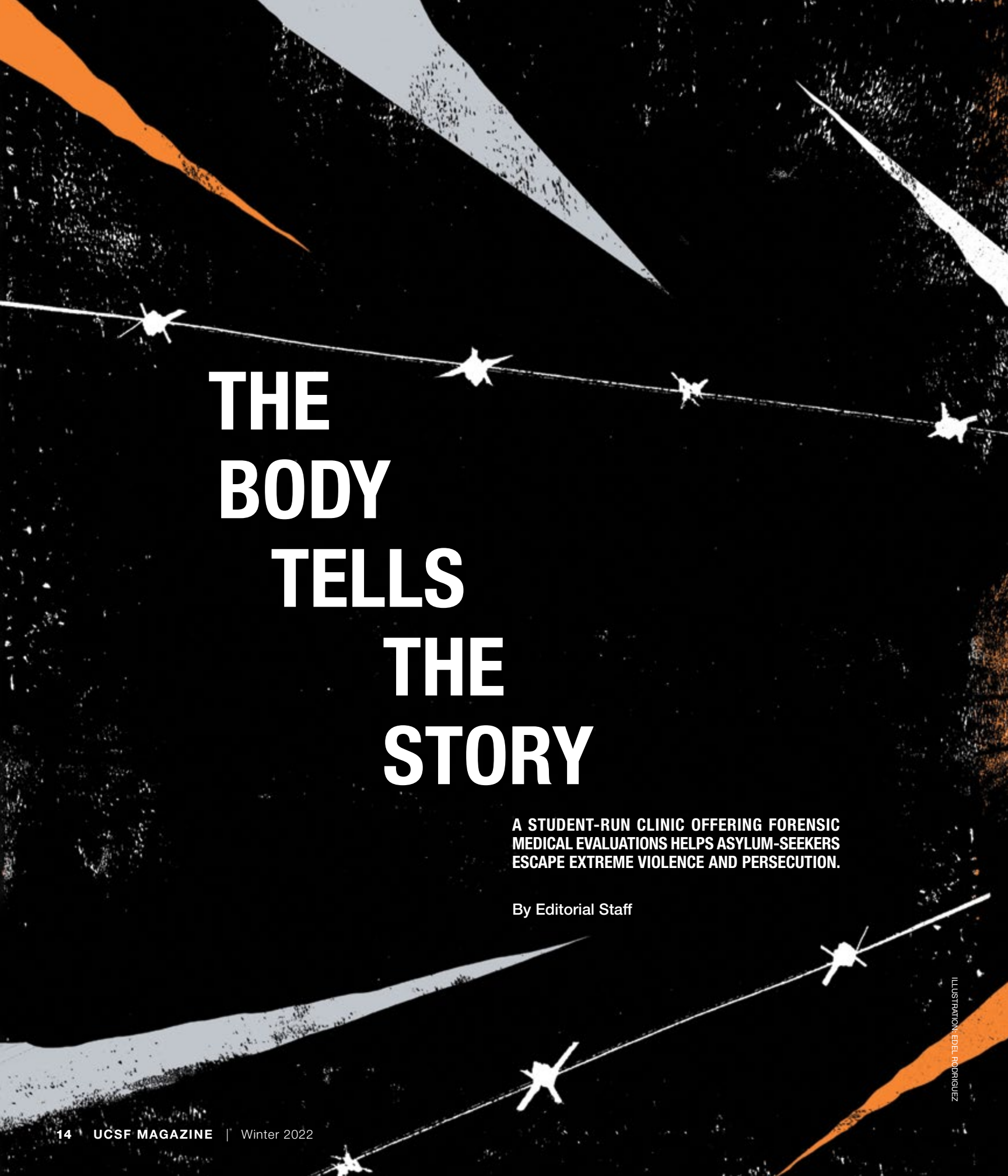
Exactly. Here's an example: Today, clinical trials can take years and cost a billion dollars. But if we better understand a disease's molecular mechanism, a trial cohort can be focused on patients who have defects in that mechanism and who thus are more likely to respond favorably to a drug specific to that mechanism. This will reduce the number of patients who need to be tested and the duration and cost of trials, and will increase the likelihood of trials' success. That would reduce trial and error.

Interestingly, SPOKE predicted that the drug dexamethasone would help COVID patients on ventilators, based on what was happening in patients' lungs at the molecular level. That study was published in May 2020. A couple of months later, a clinical trial confirmed dexamethasone's efficacy. So a knowledge network could elevate our preparedness for the next pandemic.

What does all this mean for the future of science?

Progress in understanding biological processes and disease mechanisms now comes not just from biologists and clinicians but also from physicists, chemists, engineers, computer scientists, and social scientists. If we integrate their findings into a knowledge network, we will expand the kinds of questions scientists can ask and speed up the pace of discovery. Knowledge networks have the potential to sustain a seamless continuum of science and technology, promoting transformative progress in addressing existential societal challenges – not only in health but also in the environmental, climate, energy, food, and water sectors.

Keith Yamamoto is also UCSF's vice chancellor for science policy and strategy and a professor of cellular and molecular pharmacology.



THE BODY TELLS THE STORY

A STUDENT-RUN CLINIC OFFERING FORENSIC MEDICAL EVALUATIONS HELPS ASYLUM-SEEKERS ESCAPE EXTREME VIOLENCE AND PERSECUTION.

By Editorial Staff

ILLUSTRATION: EDEL RODRIGUEZ

THE CIRCULAR MARKS – DARK RINGS AROUND LIGHTER CENTERS, WHERE EMBERS BURROWED INTO FLESH – ARE FROM CIGARETTE BURNS. The serpentine welts branching four ways – like tributaries of a river – are from lashings with an electrical cable, its four braided wires unraveling at the ends. The glossy patches of skin are from a dousing with caustic chemicals, the butterfly-shaped blotches from an electrocution, the shallow gouges from the blade of a machete.

The photographs go on and on. Each one shows a scar, a signature of torture correlating to the chosen weapon. The scars belong to clients of UC San Francisco's Human Rights Collaborative (HRC), a monthly student-run clinic that provides free forensic medical evaluations for people who have fled extreme violence or persecution in their home countries and are seeking asylum in the United States. Often, their scars are the only material evidence they have left of the agony they endured.

One chilly Saturday morning in August, medical students arrive at the clinic early to set up. They unpack boxes of snacks from Trader Joe's – apples, sandwich wraps, potato chips, string cheese, granola bars, and cupcakes. On a table in the staff room, they lay out reference guides ("Electrical Injury and Torture," "Sexual Dysfunction Following Torture," "Sleep Deprivation," "LGBTQI Patterns of Injuries," and so forth) detailing the look, feel, and dimensions of scars and other vestiges of trauma. Next to the guides, they place soft rulers for measuring clients' scars so they can precisely identify their cause.

Today's clients are three women from Central America who have come to the HRC on the advice of their pro bono lawyers. Like all the clinic's clients, they are among the 1.3 million immigrants who have applied for U.S. asylum and are waiting – often for years – for their cases to be heard in court. These women are lucky to have lawyers at all. Only one-third of asylum-seekers do. With a lawyer, the chance of being granted asylum averages around 30% – up from 10% without one. And a good lawyer knows that a forensic evaluation raises the odds even more.

The students greet each woman at the clinic entrance, offer her tea and snacks, and usher her into an exam room. Each evaluation – performed by a UCSF clinician with help from a student apprentice and, when necessary, a medical interpreter – takes up to four hours. The evaluators listen to the client's story and record in objective detail any physical or psychological signs of abuse. They then summarize their findings in an affidavit to support the client's case in court.

"The people we see have left their homes without photos, documents, or family, so there's nothing and no one to verify their stories," says Coleen Kivlahan, MD, MSPH, an international expert in torture evaluations and chair of the UCSF Health and Human Rights Initiative, which oversees the HRC. "The voice of the clinician can bear witness," she says. "We look at every inch of their skin and interpret and reconstruct what happened. The body tells the story." For many asylum-seekers, obtaining a medical affidavit "is a matter of life or death," she points out. Even with legal representation, asylum-seekers are three times more likely to win their cases with such a document than without one; those who lose are often deported immediately. "They might literally be taken from the courtroom in handcuffs and put on a plane," Kivlahan says.

Every year, more than 1 million migrants attempt to enter the U.S. in search of safety, and their numbers continue to increase due to shifting immigration policies, climate change, and humanitarian crises like those playing out in Afghanistan, Haiti, and elsewhere. The HRC is one of dozens of student-run clinics that have popped up at medical schools across the country over the past decade to help secure refuge for immigrants who fear returning home due to the threat of injury or death. To date, these clinics have together supplied thousands of pro bono medical affidavits to asylum-seekers, filling a gap left by private doctors, who aren't typically trained to provide this service or who may charge high fees, Kivlahan says.

U.S. ASYLUM SUCCESS RATE

10%
WITHOUT A LAWYER

30%
WITH A LAWYER

90%
WITH A LAWYER AND A FORENSIC MEDICAL AFFIDAVIT

"THE PEOPLE WE SEE HAVE LEFT THEIR HOMES WITHOUT PHOTOS, DOCUMENTS, OR FAMILY, SO THERE'S NOTHING AND NO ONE TO VERIFY THEIR STORIES."
– COLEEN KIVLAHAN, MD, MSPH

DATA SOURCE: TRAC IMMIGRATION; J IMMIGRANT MINORITY HEALTH (2008) 10:7–15

It's no surprise that students are leading the way, she adds. Like the U.S. itself, medical schools are becoming increasingly diverse. More students than ever before come from immigrant families and communities of color, and they are demanding the skills and knowledge to care for these populations. "So many of our students have migration stories of their own," Kivlahan says, "and their commitment to health justice and social justice is changing American medicine."

MIGRATION STORIES

The HRC was founded in 2019 by three medical students: Francesco Sergi, Katrin Jaradeh, and Aaron Gallagher. Sergi's mother and grandmother fled El Salvador during its bloody civil war in the 1980s and remade their lives in the U.S. Knowing their struggles, he says, "I have always been interested in trying to make the process of immigration easier." Jaradeh emigrated from Syria with her family when she was 8 years old. "We feared being tortured because of our religion, so we did not feel it was safe for us to live there," says Jaradeh, who was granted asylum just months before getting into medical school. Gallagher, who hails from Alaska, developed a passion for working with immigrants while teaching English to Somali refugees living in Anchorage. "They've endured incredible hardship, and yet they have a ton of positivity and resilience," he says. "All they want is a better life."

The three students decided to start the clinic after attending a lunchtime talk in which Kivlahan presented her work with asylum-seekers and other victims of torture. Kivlahan grew up "on the wrong side of the tracks," as she puts it, in a small steel town in Ohio. Her father, whose family had immigrated from Ireland, worked as a roofer; her mother was a secretary. With six kids to feed, they couldn't afford health coverage. To supplement the family's meager diet, the children hunted frogs, and Kivlahan passed the time by dissecting the remains, which is how she fell in love with science. By second grade, she had made up her mind to become a doctor even though she had never seen one. After medical school, she did her residency and earned a master's degree in public health at the University of Missouri and then took a job at a Missouri county clinic. It was there that her obsession with forensics began.

One day, a man arrived at the clinic carrying a bundle of old towels. Wrapped inside was the burned body of his 6-year-old stepson, barely alive. Kivlahan called 911, and while she waited for an ambulance, she noticed that the boy's front teeth were broken and his forehead was dappled in yellow bruises. After he died, in a nearby hospital some hours later, she couldn't get those marks out of her mind. "What struck me was how incredibly useless I was in being able to diagnose what turned out to be an extreme case of child abuse and homicide," she says. "As physicians, we have very little training in those kinds of intentional injuries."

Kivlahan devoted herself to learning everything she could about how to identify and give testimony about child abuse, sexual assault, and other forms of criminal violence. She observed hundreds of autopsies, studied forensic photography, shadowed detectives at crime scenes, and cajoled the county prosecutor into preparing her to be an expert witness. Soon, she was teaching the techniques of forensic evaluation to other care providers across the state. In the mid 2000s, she started volunteering with Physicians for Human Rights – offering evaluations to asylum-seekers and helping train doctors, nurses, lawyers, judges, and police officers in conflict zones how to document medical evidence of war crimes, including rape and the use of chemical weapons, and how to use that evidence to prosecute offenders. She has done this work in Guatemala, Sierra Leone, the Democratic Republic of the Congo, and most recently Syria, where people risk their lives collecting proof of the government's atrocities that can be brought before international criminal courts.

Meanwhile, back in Missouri, Kivlahan continued to build a career in public health, eventually working her way up to director of the state's Department of Health during the height of the AIDS crisis. After that, she bounced around the country – to Chicago, then Phoenix, then Washington, D.C., practicing family medicine and taking on various medical leadership roles – until, in 2016, she landed at UCSF as the executive medical director of primary care and a professor of family and community medicine. At that lunchtime talk in 2019, she recalls, she explained to a roomful of UCSF students how "a simple document from a doctor describing what happened" could save the life of an asylee. Soon afterward, Sergi, Jaradeh, and Gallagher got in touch with her. "We've heard there are clinics in other places that do this work," they said. "Can we start one here?"

The three students spent the following months working with Kivlahan and Triveni DeFries, MD '13, MPH, an assistant professor of medicine, to get the HRC up and running. The two professors promised to match however many hours the students invested. "We were putting in 25 to 30 hours a week, and they were right there with us," Jaradeh says. To prepare medical students to work in the clinic, the team designed an elective course. "We thought we'd be lucky if we got five or 10 people who wanted to do it," Kivlahan says. Instead, over the past three years, more than 100 students have taken the class. ("Compared with other electives, this is massive," Gallagher notes.)

WHO COMES TO THE UCSF CLINIC?

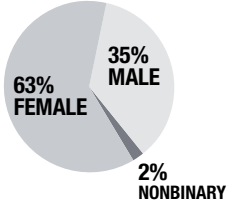
AGE:

9%
<18 YEARS

47%
18–29 YEARS

44%
>29 YEARS

GENDER:



EDUCATION LEVEL:

44%	<8TH GRADE
41%	8–12TH GRADE
15%	>12TH GRADE

COUNTRY OF ORGIN:

31%
GUATEMALA

25%
EL SALVADOR

19%
HONDURAS

6%
MEXICO

5%
ERITREA

14%
OTHER

DATA SOURCE: UCSF HUMAN RIGHTS COLLABORATIVE; CURRENT AS OF JUNE 2021

HOW WERE CLIENTS TORTURED?

17%
WITNESSED THE TORTURE OF OTHERS

79%
TRAUMATIZED DURING CHILDHOOD

11%
FORCED INTO STRESS POSITIONS

16%
HARASSED FOR SEXUALITY OR RELIGION

62%
SEXUALLY VIOLATED

21%
WITNESSED THE DEATH OF OTHERS

TRAUMA STORIES

Mar C. was the HRC's first client. Mar, who uses the gender pronouns they/them, was raised in Brazil as a boy. Because they wore pink and liked boys and science (rather than soccer), they were bullied by classmates. Starting at age 6, their parents tried to "cure" their homosexuality with bouts of electroshock therapy. They were harassed by gangs and beaten by police. Mar went to college hoping to find peace in studying chemistry, but the abuse continued; they decided their only chance at survival was to flee the country. They crossed into the U.S. over the Mexican border and eventually made their way to San Francisco. By the time Mar arrived at the HRC, at the age of 35, they were sick with AIDS and living in their car. After receiving asylum a year later, in 2020, they went back to school to train as a medical assistant and got an apartment and a job with the city health department, helping HIV patients navigate the health system. "My life changed entirely," Mar says.

The clinicians and students who volunteer with the HRC have documented dozens of stories like Mar's. Like the story of the drama professor from sub-Saharan Africa who was kidnapped by paramilitary forces and whipped, beaten, electrocuted, and sexually violated. Or the story of the young indigenous woman from Guatemala who had been trafficked for labor and sex since the age of 6, whose hands were marred by cigarette burns, and whose face was deformed from repeated blows. Or the story of the teenager from Eritrea who was conscripted into the military and disciplined cruelly and, when he protested, was shot and thrown into a cell with 35 other prisoners and no toilet. He escaped, ran barefoot through the desert to a refugee camp in Sudan, and then trekked to Kenya, where he met someone willing to smuggle him into the U.S. He was caught by border police and detained. "Our country put him in another prison after that journey," Kivlahan says despairingly.

"These aren't people who are coming here because they are trying to scam the system or get away with a crime," Gallagher says. "These are people who have undergone very traumatic experiences with serious repercussions to their physical and mental health." Entrusting their stories to strangers – immigration agents, lawyers, judges, even doctors – takes tremendous courage. "Having grown up undocumented here, I know our clients' fear of deportation," Jaradeh says. "The fear of going to the hospital, of asking for help – we were always scared that we would be sent back."

75%
BEATEN

23%
CUT OR STABBED

62%
THREATENED

13%
BURNED

15%
ASPHYXIATED

To help clients feel safe, evaluators at the HRC practice trauma-informed care. They set clear expectations and let the client's mental state guide the pace of the evaluation. As they listen and make notes, they look for signs of retraumatization. "I was with a client once who was sharing what life was like in their country," Sergi says, "and they started wrapping their arms around their body, trying to make themselves smaller, closing in on themselves. They started crying and shaking their leg. I could tell they were dissociating. They were no longer in the room; they were somewhere else, reexperiencing something in their life."

Such dissociative behaviors are the "scars" of psychological trauma. Nearly all the HRC's clients show symptoms of major depression and post-traumatic stress disorder. "They tell us they can't sleep well, that they feel isolated or scared of being in public, that they can't relate to friends or family anymore," says DeFries, who co-directs the HRC with Kivlahan. These are important data points for an affidavit, but evaluators are careful not to overwhelm clients with questions. If they see that a client is dissociating, for example, they pause the evaluation. They might guide the client through a mindfulness exercise. "You ask them to become aware of the chair they are sitting in, their feet on the ground, their hands in their lap," Sergi says. "You remind them that they are safe." Another tactic is to hand the client a piece of paper and invite them to imagine their trauma playing out across the page, outside of themselves.

"These interviews require so much awareness and consciousness to be able to ground a patient who is going through a difficult moment," says Zoë Onion, a third-year medical student who co-ran the HRC until 2020. She plans to bring the skills she developed at the clinic to her home

DATA SOURCE: UCSF HUMAN RIGHTS COLLABORATIVE; CURRENT AS OF JUNE 2021

state of Maine, where there is a large population of Somali refugees. "This experience has broadened my perspective on what I can do as a doctor," she says, "and the impact I can have on the world."

But the work of forensic medical evaluation can take a psychological toll itself. "You are exposed to the clients' pain," says Cristina Biasetto, MSW, the HRC's mental health director and the clinical coordinator of the UCSF Trauma Recovery Center. "There is no way to escape being touched profoundly by their stories," she says. "They become part of you." Over the past year, Biasetto has run a support group for HRC volunteers. "We support one another in processing the experience," she says. Part of that processing, she notes, is acknowledging that doing the job well requires deep empathy. "Being touched by this work is a sign that we are fully present for it."

"EVEN IN THAT ONE SESSION, WE CAN PROVIDE OUR CLIENTS WITH A SENSE THAT WE SEE *ALL* OF THEM – THEIR HUMANNESS, TRAUMA, RESILIENCE, AND HOPE."
– SUZANNE BARAKAT, MD

HUMAN STORIES

The end of an evaluation is always emotional. "Our patients say to me, 'Dr. K, something broke inside of me,'" Kivlahan says. "What they mean is that something broke apart, broke open. Watching them leave the clinic with that feeling of freedom and peace is an extraordinary gift."

"Even in that one session, we can provide our clients with a sense that we see *all* of them – their humanness, trauma, resilience, and hope," says Suzanne Barakat, MD, a UCSF assistant professor of family and community medicine who joined the Health and Human Rights Initiative as its executive director in 2020. Born and raised as a Muslim in North Carolina, she has lost five family members to callous deaths: A brother and two in-laws in the U.S. were murdered by an Islamophobic neighbor, and an aunt and a cousin were assassinated in Turkey. "Because I have lived my entire life fighting just to be seen as human, I can understand why our clients feel like third-class citizens," she says. "We want to empower them to achieve what they are capable of achieving, despite having to work through a broken system."

In a recent episode of the podcast *Hippie Docs 2.0*, host Paul Linde, MD, asks Kivlahan if she feels she has been able to "make a dent" in the problem of human depravity. "You know, Paul," she replies, "I've given up on that. Not that I've given up on a personal level, but I've given up on whatever 'making a dent' means. What I realize is that hatred and ignorance are everywhere. I think about the pyramid of hate, in which we begin with racial biases and ethnic biases and stereotypes; and we then move into a phase of speaking those things and acting on them; and then we move into policies around them; and then we move into things like genocide, which I've clearly seen."

And yet, she continues, "I'm a perpetual optimist. I believe in human beings and I believe in our hearts, and when we're touched and when we see [the pain and suffering of others], it changes us. The most hardened Congolese military guys, whom I've spent time with alone, have been completely impacted when they imagine their own daughters being sexually violated."

The people who come to the HRC are our neighbors, Kivlahan notes. They are our housecleaners, our cooks, our dishwashers, our rideshare drivers, our students, our future doctors. Do we imagine them being sexually violated, stabbed, strangled, beaten, and burned? Do we imagine them fleeing their homes with only the clothes on their backs and the scars on their bodies? Do we imagine them learning English, finding new work, and raising their kids while being haunted by their past and the terror of being deported?

The work of the HRC, Kivlahan concludes, is to tell the stories many of us never could have imagined. "And we're going to tell them in details that most of you don't ever want to hear, and we're going to show you photos that you don't want to see," she says. "But *this is what happens*."

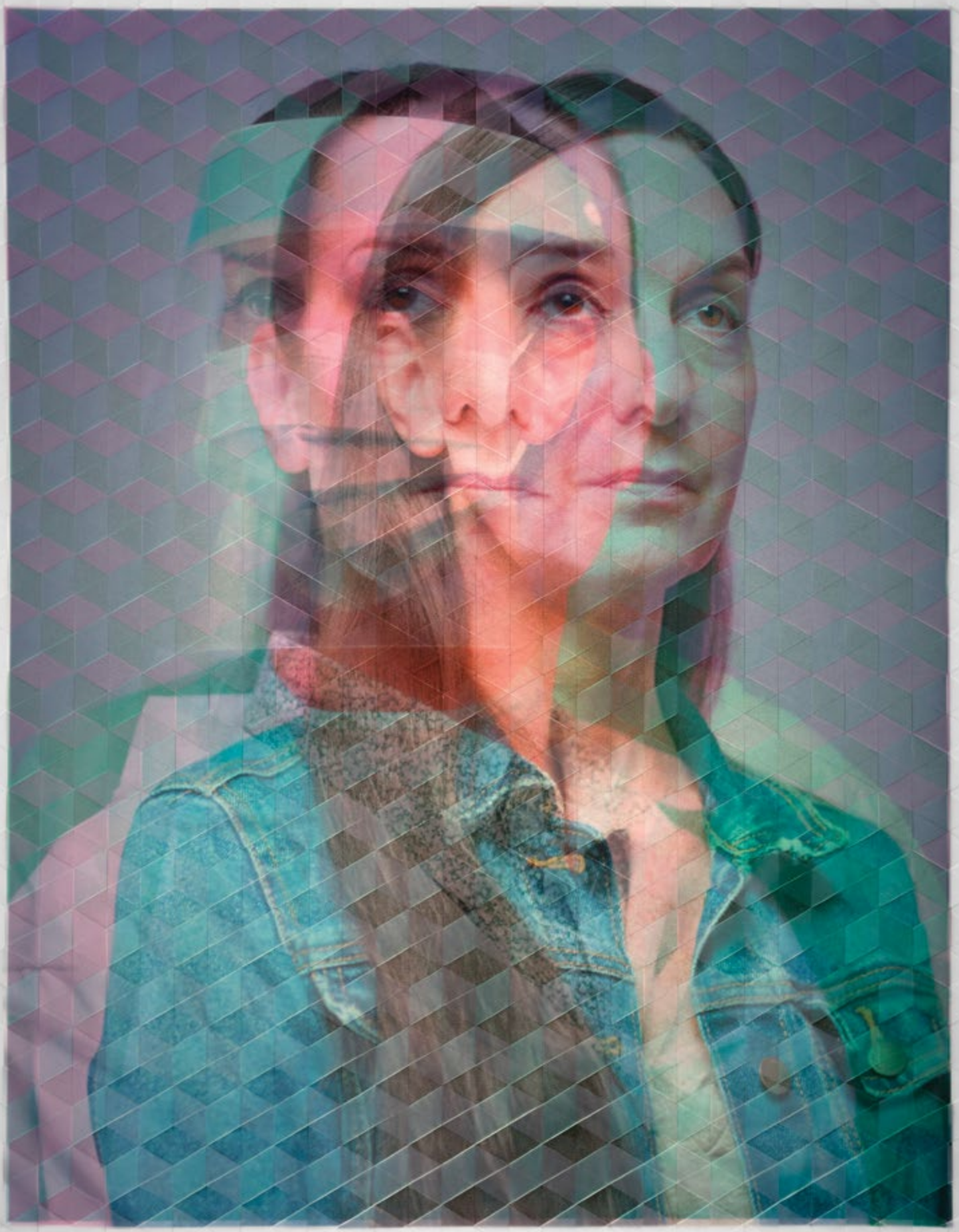


PHOTO: DAVID STERN

THE LONG HAUL

An all-hands-on-deck research effort gave UCSF scientists early insight into long COVID. It also showed patients that they weren't in the fight alone.

By Mara Grunbaum

In early April 2020, a few weeks after San Francisco officials issued their first stay-at-home order of the COVID-19 pandemic, Cliff Morrison, MSM, MSN, showed up for work at one of the behavioral health facilities he administers. He had barely begun his day when he suddenly spiked a temperature of 101°F. He started packing his things to go home but quickly felt so exhausted he had to lie down in his office. His primary care doctor at Zuckerberg San Francisco General Hospital (ZSFG) diagnosed him with COVID-19 that same afternoon.

When it came to pandemics, Morrison thought he'd seen the worst already. In the early 1980s, as a psychiatric nurse at ZSFG, he was on the wards as the first patients fell ill and died of what came to be known as HIV/AIDS. So much fear and uncertainty accompanied the disease that doctors treated AIDS patients largely in isolation, which upset Morrison. In 1983, he helped ZSFG open the first dedicated inpatient AIDS unit in the country, and it went on to become a global model for compassionate treatment of patients hospitalized with AIDS.

After his COVID-19 diagnosis, Morrison, who is 70, isolated at home with his two cats. He expected to return to work after two or three weeks. But a month later, he still had severe headaches, digestive troubles, extreme fatigue, and memory lapses. "Everybody kept saying to me, 'This is a 14- to 19-day deal,'" Morrison remembers. "I was starting to wonder if I had lost my mind."

That's when Morrison's doctor told him about a study that UC San Francisco researchers had launched at ZSFG to look into the long-term effects of COVID infection. Morrison, who knew many of the research staff from his days as an HIV nurse, called and signed himself up immediately. He wanted to contribute to science, certainly – but he also wanted answers about what exactly was happening to him. "It was extremely reassuring and made me feel so much better, that at least someone was interested in what was going on," he says.

Though it wasn't widely known at the time, Morrison wasn't the only person still struggling with COVID long after most experts expected them to get better. Consensus had it that mild to moderate infections cleared the body within a few weeks, so many clinicians and scientists were skeptical of claims like Morrison's of ongoing symptoms. Some people spoke publicly about their problems only to find themselves dismissed as having anxiety, or maybe lockdown-induced hysteria. It wasn't until December 2020 that federal health officials declared "long COVID" real and worthy of being taken seriously.

According to the National Institutes of Health (NIH), anywhere from 10% to 30% of people infected with SARS-CoV-2, the virus that causes COVID, experience persistent and potentially incapacitating complications that last far longer than their original illness. With nearly 50 million known COVID cases in the U.S. alone, that may already amount to as many as 14 million people experiencing long-term effects. And the ranks of those with long COVID are still growing, particularly among the unvaccinated, who are thought to be at higher risk for developing long-term symptoms. The result may be its own public health crisis – compounding the original one – with at least some patients unable to live normally for weeks or months after their original illness.

But in the early weeks of the U.S. outbreak of COVID-19, long COVID was practically unheard of. The researchers who started the UCSF study, which they named Long-term Impact of Infection with Novel Coronavirus (LIINC), did so without entirely knowing what they were even looking for. While most of the medical community was still focused – as it should have been – on preventing and treating the most severe cases of COVID-19, "we were really the only group that was focused on what happens after the acute phase," says Michael Peluso, MD, one of the study's leaders. For many patients with lingering COVID symptoms, LIINC was also the first place they found validation that they weren't imagining things.

Morrison was one of the earliest of the more than 400 participants to enroll in LIINC, which includes a diverse assortment of patients. Some of them survived knock-down, drag-out cases of COVID, while many barely noticed that they were ill in the first place. LIINC gave UCSF researchers a uniquely broad and early window into how people in different circumstances experienced infection and recovery. And the data from those patients will help illuminate how SARS-CoV-2 infiltrates the heart, lungs, brain, and other critical organs – and hopefully start to explain how it continues to wreak havoc on the body months after the original infection is gone.

About a month before Morrison first came down with COVID-19, Peluso was seeing patients at ZSFG's infectious disease clinic. At the time, he was a research fellow working with people with HIV. For months, Peluso had been aware of the looming threat that COVID-19 represented, but it didn't truly hit him until March 5, when he heard that San Francisco authorities had detected community spread of the disease. Peluso called his mentor, Steven Deeks, MD '90, who had just flown back to San Francisco after the second leg of a business trip had been abruptly canceled. "Something is happening, and I want to be ready to work on this from a scientific perspective," Peluso remembers telling him.

Since 2017, Peluso and Deeks had been working together on the SCOPE study, a long-term research project that aims to reveal how HIV infection persists and affects the body despite treatment. Deeks – a professor of medicine at UCSF and a member of ZSFG's Division of HIV,

Cliff Morrison expected to recover from COVID in a few weeks. Instead, his extreme fatigue, headaches, and memory lapses persisted. Seeking answers, he was among the first to join UCSF's LIINC study.

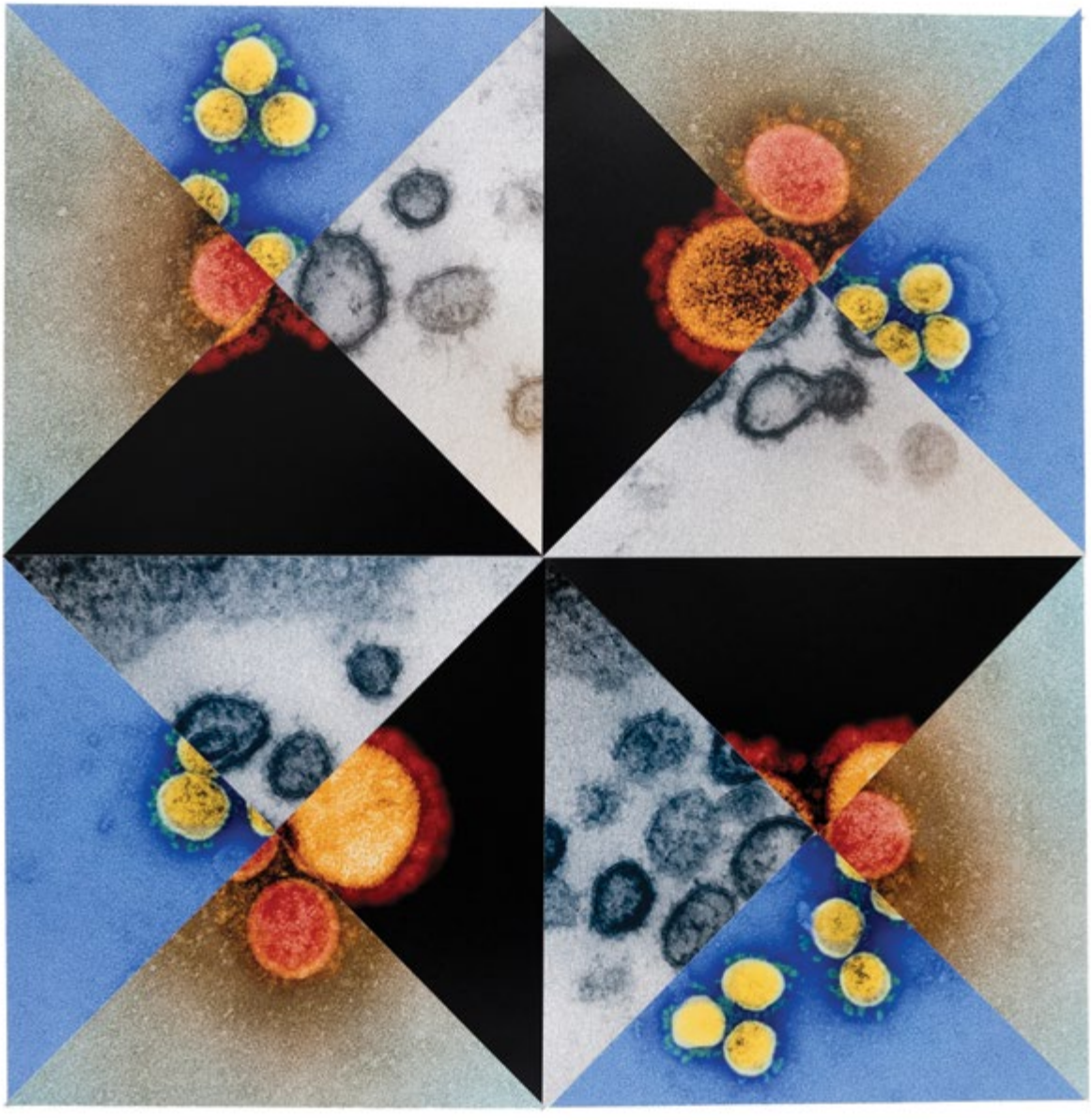
Infectious Diseases, and Global Medicine – had co-founded the SCOPE study back in 2000. For more than 20 years, the SCOPE team has regularly collected blood and tissue samples from a cadre of volunteers with and without HIV. This ongoing relationship with participants and an ever-growing library of their biological specimens have helped researchers worldwide investigate how to thwart the virus.

Peluso and Deeks knew they couldn't do much to stem the tide of acutely ill COVID patients who were about to flood intensive care units at hospitals all over San Francisco. Their expertise was not in *Hot Zone*-style virus hunting or emergency respiratory medicine, but in deep, careful investigations that unfold over the course of decades. So Peluso wondered if they could take the same systems they'd developed to follow patients with HIV over many years and use them to trace how the immune system responds in the months following a SARS-CoV-2 infection. "I thought it was brilliant," Deeks recalls of the idea. "It was the obvious thing to do."

Peluso spent the next two weeks, as the city locked down around him, scraping together a research proposal from his living room. He sought help over Zoom from colleagues, including UCSF epidemiologists Dan Kelly, MD, MPH, and Jeffrey Martin, MD, MPH. Peluso didn't know yet that he was designing one of the first research studies to address long COVID. He only knew he wanted to study the body's long-term response to the virus by measuring antibodies and other signs of immune activity. He decided to collect blood and saliva from recovering COVID patients beginning 28 days after their acute illness ended – the soonest, according to UCSF guidelines at the time, that he was allowed to see them in the research clinic. Some of the samples would be tested for levels of COVID-specific antibodies, and the rest would be stockpiled in the hope that they could eventually help answer questions researchers hadn't yet thought of.

On April 21, less than seven weeks after conceiving the study, Peluso enrolled the first participant. Over the next six weeks, the team recruited 70 recovering COVID patients who represented the ethnic diversity of the Bay Area and ranged in age from 18 to 85. Unlike many studies at the time, which focused on patients who had been hospitalized with COVID, LIINC primarily recruited recovering patients who never fell critically ill. That would make it more likely that any lasting symptoms they reported were caused by the novel coronavirus rather than by the many physical, mental, and emotional stresses that follow treatment in an ICU.

PHOTO: ANASTASIIA SAPON



Long COVID was practically unheard of when these now-iconic images of the novel coronavirus were published by the National Institute of Allergy and Infectious Diseases in early 2020. But by March, UCSF fellow Michael Peluso, MD, had already begun his quest to study how the immune system responds long-term to a SARS-CoV-2 infection.

Before the scientists could dig into the data, though, they had to scramble to find somewhere to store the hundreds of vials of biological material they were suddenly collecting. Though he normally focuses on curing HIV, Timothy Henrich, MD, offered to turn his research facilities into an ad-hoc sample processing lab. Henrich had to buy several new freezers to hold the samples that were quickly accumulating from LIINC participants. "I had staff members there for hours every day just processing and storing cells and plasma and serum and saliva," Henrich recalls.

Even though the LIINC team hadn't ironed out all of its research questions yet, banking these specimens beginning in April created a kind of scientific time capsule. As new questions emerged, they figured, having samples on hand from the weeks immediately following participants' acute COVID infection would prepare them to launch investigations at the drop of a hat. That's what had happened with SCOPE, as doctors treating patients with HIV encountered new symptoms and tested new treatment strategies. "Over 20 years, we've had maybe 10 new areas of investigation pop up, and SCOPE has changed on a dime to help answer those questions," Deeks says.

Still, putting so many eggs into the post-COVID basket was a bit of a gamble, admits Peluso. What if COVID had been like the common cold or flu after all, and any symptoms of a mild case invariably dissipated within a few weeks? That was the going wisdom at the time, which was why Peluso planned to focus on how the body built immunity after kicking a COVID infection. "We were expecting that people would feel totally fine, and *(continued on page 26)*

PHOTO COLLAGE: DAVID STERN; PHOTOS: NIAID

RAPID RESPONSE

Since the early months of the pandemic, physicians throughout UCSF have pitched in to help support hundreds of long COVID patients.

Coordinated Care

UCSF's OPTIMAL clinic is a one-stop outpatient center for patients recovering from COVID. After pulmonologists assess their patients' needs in the clinic, they can immediately refer them to colleagues in physical therapy, psychiatry, integrative medicine, and other specialties. By streamlining this process, clinic founder Lekshmi Santhosh, MD, MAEd, hoped to take some of the burden off post-COVID patients and their families to coordinate their own care. That's especially important for survivors who have already been through the wringer in the ICU.

Santhosh treated some of these same patients when they were intubated and unresponsive. "Seeing those folks in clinic afterward is so powerful that often both of us are crying," she says. "There were many times [in the ICU] when we thought they would not survive."

Sniff Test

An inability to smell is one of the best-known early indicators of a SARS-CoV-2 infection – and the symptom that seems to stick around the longest. In the clinic of ear, nose, and throat specialist Patricia Loftus, MD, patients who are struggling with smell loss take a 40-question scent identification test – basically a scientific scratch-and-sniff activity – to quantify their degree of impairment. She then prescribes a regimen of smelling essential oils and other aromatic substances to help them gradually retrain their damaged olfactory nerves.

The good news: About 75% of people who lose their sense of smell seem to recover it within about four weeks. By six months, the recovery rate improves to about 95%. Loftus hopes the pandemic will spotlight smell loss, which can also happen with age or as a result of other diseases. "If we can find better treatment," she says, "it can definitely be used across the board."

Investigating the Brain

Several weeks after the LIINC study got started, neurologist Joanna Hellmuth, MD, MHS, started seeing participants who were complaining of headaches and memory problems. Post-COVID patients as young as 17 were feeling confused and distracted and were unusually slow to retrieve names or find the right word on the tip of their tongue. In many cases, doctors had already dismissed the symptoms as the result of stress or sleep deprivation. But they sounded familiar to Hellmuth: "The cognitive syndrome we're seeing with COVID is almost exactly the same as what we see with HIV," she says.

Many physicians don't know that viral infections can be associated with cognitive disorders, explains Hellmuth. But the phenomenon is well documented, even if it remains poorly understood. To try to change that, Hellmuth is collecting spinal fluid and running neurological tests on post-COVID patients who report cognitive symptoms. She hopes to learn what's physiologically responsible – inflammation? blood vessel damage? – in the hope of finding ways to alleviate the issues.

If nothing else, Hellmuth hopes the data she's collecting will help validate her patients' experiences. Anxiety over not being believed only compounds their struggles, she says. "If patients tell us something's going on with their bodies, let's trust them," she says. "I'm hoping this pandemic will bring some humility to medicine and bring to light the fact that viruses can do this."

Group Therapy

As early as April 2020, Meghan Jobson, MD, PhD, started hearing from patients with long COVID symptoms. Their toes were numb, they were paralyzed by depression, their ears wouldn't stop ringing, they had no sense of taste. "I was like, I don't know what to do for these people. We didn't know anything," remembers Jobson. But she did know some tactics for coping with ongoing medical uncertainty.

Jobson, a UCSF attending physician, joined forces with neurologist Juliet Morgan, MD, chief resident for education in the UCSF adult psychiatry program. Together, they organized a virtual integrative medicine skills group to support patients recovering from COVID. They started meeting over video once a week with about a dozen patients. The physicians share nutrition guidance, mind-body exercises, and mindfulness practices that have been shown to reduce stress and inflammation. With no solid answers yet about long COVID, their goal is to guide patients toward these evidence-based general wellness strategies.

The groups have also allowed long COVID patients to share their struggles and successes with each other. "A lot of the pain of long COVID is feeling misunderstood, invalidated, tossed aside," says Morgan. "This gave patients a place to come together and hear that this is real and that they're not alone."

María Milián thought researchers might attribute her lingering post-COVID brain fog to her multiple sclerosis. But UCSF neurologists knew that viral infections can be associated with cognitive disorders and have been studying her and other long COVID patients in the hope of finding treatments.

we would just be measuring how their antibodies changed over time," he explains. But as his patients would soon help him discover, recovering from COVID wasn't going to be as straightforward as had been assumed.

María Milián, a 69-year-old retired cancer researcher, fell ill in late June 2020, after her brother visited from Arizona. Milián has multiple sclerosis (MS), a degenerative neurological disorder, but she could tell that this was different from anything she'd experienced with that disease. For three weeks she felt deathly tired, she hurt all over, she barely ate, and she couldn't smell or taste anything. Her vision blurred, and her arms and legs were tingly; she saw flashing lights and numbers behind her eyelids when she tried to sleep.

Milián was still having trouble concentrating and remembering things a couple of months after her positive COVID test. She enrolled in LIINC, but she wondered if scientists there would simply chalk up her brain fog to MS. Instead, she says, Peluso and the rest of the team listened with interest and told her they wanted to track whether her neurological symptoms got better or worse over time. "They took seriously that I had this brain thing that I didn't understand," she says.

And there were reports of other conditions from other patients: sleep problems, dizziness, anxiety, and depression. Some had shortness of breath and chest pain that stuck around for weeks – months, even – after the active viral infection was gone. Peluso and Deeks realized they could use the seat-of-the-pants nature of their study to good advantage if they started polling LIINC participants about symptoms the investigation hadn't originally accounted for. It was much like how SCOPE had shifted over the years to adapt to new information, but instead of happening over decades, LIINC was changing from week to week. "We had nightly meetings between our epidemiology team, our clinical research team, and an army of volunteer medical students," says Peluso. These meetings often lasted four or five hours; Peluso sometimes took part in them from his exercise bike.

PHOTO: ANASTASIIA SAPON

When brain fog emerged as one of the most common and frightening symptoms, the team turned to neurologist Joanna Hellmuth, MD, MHS. She'd spent years at the UCSF Memory and Aging Center studying how HIV could compromise cognition in a strikingly similar way. In November 2020, Hellmuth, who is also an assistant professor at the UCSF Weill Institute for Neurosciences, started recruiting LIINC patients struggling with brain fog into a specialized neurological substudy. She asked participants to help her understand their fogginess: Was it confusion? Attention problems? Memory lapses? Then she administered cognitive and other neurological tests to quantify the problems and try to ferret out their cause. Hellmuth also started running experiments on samples of blood and cerebrospinal fluid she collected from her set of volunteers. That allowed her to hunt for patterns in who experienced brain fog, when it happened, and for how long.

As the pandemic has continued, LIINC has spun off similar substudies in cardiology, pulmonology, hepatology, and even sleep medicine. That all of these specialties can draw from the same centralized group of post-COVID patients has allowed investigators to ramp up new studies relatively quickly. "If we didn't have that infrastructure, everyone would be working in their silos," trying to recruit volunteers from scratch, says Mandana Khalili, MD, MAS '05, a UCSF professor of medicine and chief of clinical hepatology at ZSFG who is studying COVID's effects on patients with liver disease. "But leveraging that existing infrastructure is leading to what we call a team science effect."

Overall, Peluso and others have found, most long COVID patients are gradually improving. While roughly half of previously infected LIINC participants still have some symptoms after four to eight months, those symptoms have been debilitating for fewer than 5%. For Milián, recovery has been bumpy and nonlinear, but she's getting there. Her fatigue and brain fog reared back up after she was vaccinated in February 2021, but these days she has enough energy and focus to attend virtual yoga classes and work in her garden again.

Morrison doesn't feel fully recovered yet, but he does think he's learning to cope better with his ups and downs. Meanwhile, the data collected through LIINC and its substudies are turning up clues that could prove valuable for helping long COVID patients like him. The team has realized, for example, that whether someone suffers aftereffects from an acute COVID infection doesn't necessarily depend on how severe the original illness was. While some people are slow to bounce back after their initial, excruciating illness – but eventually do – others are largely asymptomatic during the acute phase but have new and puzzling problems pop up some time after that.

The LIINC team has found some indications that people with long COVID have higher inflammation levels than people who were back to normal four months after their infection. That could mean that some of the more protracted symptoms are related to an aggressive immune response. The virus can damage bodily tissues while it's active, which could certainly cause health problems down the line – another potential culprit. Even once SARS-CoV-2 stops replicating, scientists have found, viral proteins continue to litter the body like shrapnel in a wound. Social and economic factors also seem to tip the scales, with early evidence indicating that people from underserved communities may be more likely to experience long-term problems. But as far as explaining what causes long COVID or how to treat it, says Peluso, "none of these are a slam dunk."

The search for answers will soon get a boost from the NIH's Researching COVID to Enhance Recovery (RECOVER) initiative. The four-year effort will enlist researchers at more than 30 institutions to amass data from tens of thousands of long COVID patients across the country. "The diversity of symptoms and presentations leads us to believe that long COVID is not just one condition," said retiring NIH Director Francis Collins, MD, PhD, in September, when he announced $470 million in funding to assemble the research consortium. "The only way, therefore, that we're going to sort this out is with very large studies that collect lots and lots of data about symptoms, physical findings, and laboratory measures."

If that sounds familiar, it's because Peluso and the rest of the LIINC team have been doing just that ever since March 2020. That's one reason RECOVER leaders sought their help in developing research protocols that will be applied across the country. It makes Peluso optimistic that he and other physicians will soon have better answers for long COVID patients and more ways to help them. The sudden scientific interest in viruses due to the pandemic could also shed light on other illnesses possibly triggered by viral infections, such as myalgic encephalomyelitis (formerly called chronic fatigue syndrome).

Peluso, now an assistant adjunct professor of medicine at UCSF, still spends at least a few minutes chatting with study participants every time they visit. "You get to know people really well, and you're invested in their well-being," he says. For Milián, who didn't know anyone else struggling with long COVID while she was under lockdown, that has been one of the biggest benefits of participating in the study. "What helped was that there was actual contact – seeing people and talking about what was ailing me," she says. She could ask whether other patients had experienced a particularly confusing symptom and hear that Peluso and his colleagues were already trying to get to the bottom of it.

"And then that kind of reassured me that I'll get better," Milián says. "It'll be okay."

PHOTO: NOAH BERGER

Surprise! It's a Nobel Prize

"It was really a shock – a blast out of nowhere and quite a thrill," says David Julius, PhD, about learning in October that he'd won the 2021 Nobel Prize in Physiology or Medicine. Julius, a professor and chair of Physiology and the Morris Herzstein Chair in Molecular Biology and Medicine at UCSF, received the prize jointly with Ardem Patapoutian, PhD, a professor at Scripps Research and a UCSF postdoc alum. The two were recognized for their independent discoveries of receptors for temperature and touch. Curious about how our bodies sense pain – and acutely aware of the need for new drugs that can treat pain without the side effects or addictive potential of opioids – Julius turned to the natural world for insights. He studied toxins from tarantulas and coral snakes; capsaicin, the molecule that produces the "heat" in chili peppers; and the chemicals underlying the pungency of horseradish and wasabi. His research homed in on a class of proteins called TRP ion channels as key players in the nervous system's pain signaling apparatus. These compounds could serve as potential targets for new painkillers. The secret to his success? "I think science is to some degree like real estate – location, location, location – and UCSF has been just such a fantastic place to work."

David Julius, PhD, and his wife – UCSF professor Holly Ingraham, PhD, the Herzstein Professor of Molecular Physiology – field congratulations in the early morning of October 4 from their home in Walnut Creek.


SCIENCE OF ATTRACTION
HORMONES
SEXUAL HEALTH
BIOLOGY

What You Didn't Learn in School about Sexual Health

UCSF experts share some tips. Do you need every single one of them? Maybe not. Will you read them anyway? Yeah, probably.

If you're looking for science-based, judgment-free intel, a lot of sexual health stories leave something to be desired. *Cosmopolitan* has decided on "10 Sex Things Every Woman Should Do." *Every* woman – got that? No exceptions! And if you *really* want to feel bad about yourself, *Maxim* claims to know "Exactly How Much Sex You Should Have, According to Your Age." Spoiler alert: It's more than some of us are having.

This is not that kind of story. Instead, we asked UCSF experts about the sexual health topics they find intriguing or surprising or just flat-out misunderstood by most people. What we discovered isn't always sexy, at least not in a headline-grabbing sense. But you might learn something new. That's hot, right?

By Elizabeth Daube

PHOTO: MARGEAUX WALTER

Adolescence

Not Quite What It Used to Be

Not so long ago, standard sexual health education didn't cover much: puberty, reproduction, pregnancy prevention, maybe some infections.

Today, sex ed has expanded. Many teenagers now learn about a host of related topics, such as gender identity, sexual orientation, consent, and the basics of healthy relationships. And they're having a lot less sex. In 1991, 54% of American high schoolers reported having intercourse; as of 2019, that proportion had dropped to just 38%.

Adolescents are getting more of the information they need to make decisions about their own lives and bodies. And when they do have sex, they're more likely to use contraception. The birth rate among teenagers in 2018 was less than half what it was in 2008.

But access to more data doesn't necessarily make sexual development easy for today's adolescents, according to Erica Anderson, PhD, a psychologist at UCSF's Child and Adolescent Gender Center. While gender identity is distinct from sexual orientation, Anderson thinks many teenagers struggle to peel these topics apart.

"There's much more chatter among young people about exploring identities," says Anderson, who is transgender herself. "There's also a lot of confusion in individual kids."

Most of her clients try on gender identity and sexual orientation labels well before they try flirting or dating or having sex. That's fine, Anderson says, but it also means many young people now explore their sexual identities almost exclusively online. She's encountered clients as young as 11 who declare they're asexual, a classification she considers premature.

"It's almost like sexuality, and even gender identity, is an abstraction for this generation," Anderson says. "But sexuality is a biopsychosocial experience. You can't just excise out any *physical* experience.

"I worry kids may be trying to compartmentalize themselves. Many girls do this. Before they know it, the gaze of older males comes upon them, and they're creeped out. They don't know what to do with that. Sometimes it's easier for them to not be sexual."

Many teenagers are also embracing gender terms that defy strict definition. A few UCSF experts have noticed a rise in youths identifying as gender-nonconforming, nonbinary, or gender queer. Annesa Flentje, PhD, the director of UCSF's Center for Sexual and Gender Minority Health, says that's a healthy shift.

> "My teenage son said to me in the car today, 'Did you know that all of my friends are LGBTQ? Everyone is now.' In a sense, that means people don't have to be subject to prescribed gender roles. It's pulling people out of boxes."

"My teenage son said to me in the car today, 'Did you know that all of my friends are LGBTQ?'" Flentje says. "He's like, 'Everyone is now.' In a sense, that means people don't have to be subject to prescribed gender roles. It's pulling people out of boxes."

In Anderson's view, young people sometimes conflate gender identity (your internal concept of yourself as male, female, a mix, or neither) with gender expression (your external look and behavior, which may or may not conform to traditional expectations).

"Can someone be female and be very aggressive, a trait we often associate with males? Yes, of course," Anderson says. "The categories are much more a continuum than mutually exclusive choices. And it's fine to change. Teenagers go through phases."

Still, Anderson underscores that identity development is idiosyncratic. She also works with transgender teenagers who know who they are and what they want. When teens are "insistent, consistent, and persistent," Anderson supports medical treatment for gender dysphoria.

Whether her clients are discussing their gender or their sexuality, Anderson says, "it's generally a good idea to be accepting of a young person. I never tell a kid who they are. But sometimes I say, 'Be kind to yourself. You may change your view. And when in doubt, doubt. It's okay. You've got time.'"

PHOTO: LIGHT FIELD STUDIOS

Shame
The Enemy of Sexual Health

"And it's always been a bit of a dance in terms of two people coming together and getting their libidos to mesh. The secret sauce is communication."

One theme popped up again and again in UCSF interviews about sexual health: shame.

Take, for example, sexual health education. Mara Decker, DrPH, MHS, an assistant professor at UCSF's Institute for Health Policy Studies, thinks sex ed has gotten a lot better in some places – like California, where she evaluates the state's program. But historically, sex ed has often been delivered with a finger-wagging tone that smacks of scared-straight campaigns against drugs.

"It's not 'You're doomed if you do this' anymore," says Decker. "Ironically, by not shaming, we're actually seeing some young people become less sexually active. They feel like they have a little bit more power over their own decisions."

Decker says most public health research has found shaming to be counterproductive, whether the goal is to reduce sexually transmitted infections or decrease drug use. That's likely because of how lousy shame can feel to those on the receiving end. Research links it to depression and anxiety, and people prone to shame often have low self-esteem.

"Shaming dialogue just completely turns people off," Decker says. "They stop listening. Instead of saying things like 'Gonorrhea is horrible, and it's a sign that you're a horrible person,' which it's not, we're expressing 'This is gonorrhea. These are the symptoms.'"

A lot of people feel shame for wanting or having sex. But what if you're *not* having sex? Or you have zero desire for it? Is that bad?

It's such a common concern that Tami Rowen, MD '09, MS '07, an associate professor of obstetrics, gynecology, and reproductive sciences, brought it up before dispensing any advice about ways to improve sexual function. Despite what other magazines might tell you, a low sex drive isn't a problem unless you're bothered by it. And if you are? That's okay, too! There is no wrong answer.

"Sexual desire is so variable," Rowen says. "And there's this stereotype that women's sexual desire is not innate and that it's only responsive, and that's just not true."

Meanwhile, men are often acutely ashamed of low sexual desire, according to Alan Shindel, MD, MAS, a professor of urology. Their partners' expectations – real or projected – can make matters worse.

"There's a cultural paradigm that men are supposed to want sex all the time," he says. "But it's not realistic.

"And it's always a bit of a dance in terms of two people coming together and getting their libidos to mesh. The secret sauce is communication. It's shocking how often couples don't talk about sex."

Shame can also have unique effects on the sex lives of LGBTQ people. Flentje studies "minority stress," which includes feelings of shame.

"People have faulty internalized beliefs about some supposed heterosexual 'ideal,'" Flentje says. "Those beliefs can get in the way of not just healthy sexual functioning but also healthy psychological functioning."

Harmful beliefs surface in different ways. Some LGBTQ people suppress their sexual desires; others use alcohol or drugs before sex to mute negative thoughts. To help, Flentje is testing whether cognitive-behavioral therapy can reduce minority stress.

"They may have developed an unhealthy habit as a 17-year-old of getting really intoxicated before sex," she says. "But that habit is just a habit. There may not be a place for it anymore.

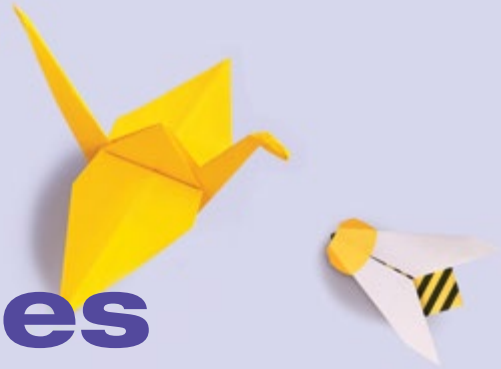
"What are the thoughts behind it? Maybe they're not valid. We can have automatic thoughts that stem from what was once a core belief, like 'Being queer is not okay.'"

These kinds of beliefs have deep roots in messages we receive during our formative years – whether from family, peers, religion, or American culture at large. But how do you challenge a stubborn belief?

Flentje recommends shifting perspective. For example, try applying the belief to someone you love. It's not a conversation, but a thought exercise: How would you feel if someone spoke to that person the way you're speaking to yourself? Most people are much kinder to others, Flentje says, than they are to themselves.

If you want guidance from a sex therapist, several UCSF experts recommend *Come as You Are: The Surprising New Science that Will Transform Your Sex Life*. Author Emily Nagoski covers a wide range of topics – from the science of pleasure to body shame to recovery from sexual trauma – with a voice that's anything but judgmental. (The title of the introduction: "Yes, You Are Normal.")

PHOTO: EASYBUY4U



Hormones

They Can Mess with Your Relationship

Sex hormones like estrogen and testosterone have a profound influence on our bodies. That influence extends to our brains and, to some extent, how we think, feel, and act. The result is the premise of pretty much every romantic comedy ever made: Sometimes men and women confound each other.

That's why Louann Brizendine, MD, UCSF's Benioff Professor of Psychiatry, writes about the neuroscience of hormones and how they shape our romantic and sexual relationships. She focuses on heteronormative partners – there aren't many studies of other identities and pairings yet – but Brizendine's books are immensely popular.

One of Brizendine's books, *The Female Brain*, became a *New York Times* bestseller. Comedian Whitney Cummings even adapted it into a movie.

"The male and female brain are much more alike than they are different," Brizendine says. "But our different hormones are specified by nature to make behavior differences. It's probably not politically correct to say this, but it is biologically correct.

"I'm making some generalizations here, but it's so you can step out of yourself and say, 'Okay, now I understand there might be biology behind this.' Otherwise, people start to blame themselves or others."

Biological differences can show up in sexual relationships in many ways. One example: If popular dating shows like *FBoy Island* are any indicator, a lot of straight women struggle to sort men who want a relationship from men who just want sex. Brizendine believes hormones are behind this dilemma. Women might be prone to rapid attachment to an attractive partner because of oxytocin, a feel-good bonding hormone. Intimacy, cuddling, and sex can unleash it in anyone, but the extra estrogen and progesterone in female bodies encourage their brains to ratchet up their oxytocin, especially when they ovulate. Compared to women, men may need two to three times more touch to maintain the same level of oxytocin.

Did someone ever hold your hand, and you instantly felt the gesture meant something *super meaningful*? You might be right. It could also be a surge of chemicals that feels fantastic but essentially means "your judgment is toast," according to Brizendine. For many women, it's biologically difficult to *not* crave commitment after sex with someone they really like.

"Biology is destiny unless you know what it's doing to you," Brizendine says. "We often don't know anything about who we're dating. Having ways to assess trustworthiness quickly is imperative. This is a situation in which you have to outsmart your own hormones."

Monogamy-minded women can do this in a few ways, Brizendine says. If you track your cycle, avoid scheduling hot dates on the days around ovulation. When you do meet up, consider what matters most to you in a partner. For example, does your date really listen to you – or wait for his turn to speak? Delaying sex can also help keep that oxytocin under control – and weed out dates who just want to hook up.

Meanwhile, Brizendine says testosterone *does* make sexual conquest a priority for many men, especially during adolescence. But research also suggests that social conditioning pressures men to evade emotion and hide it away – which might make close relationships difficult for some men to initiate or maintain.

"From childhood on, males learn that acting cool and hiding their fears are the unwritten laws of masculinity," Brizendine writes.

That said, Brizendine argues that some gender stereotypes – on average, women are more emotionally adept, men more rational – are backed by neuroscience.

"The differences are important to understand because they help reset your expectations," Brizendine says. "Women may be fast on the uptake of emotional nuance. What a woman would get in one conversation, it may take him three. It takes patience."

Likewise, Brizendine recommends that men practice patience with female experiences they don't instinctively understand. A common one: For many women, feeling physical pleasure requires turning off the fear and anxiety center of the brain. Stress can profoundly inhibit arousal and ability to orgasm for females – hence, the conventional advice for men to dial up the intimacy and take it easy. Make time to talk. Go out for dinner. Hold those hands! (Okay, not hands necessarily. Any welcome touch helps light the oxytocin fire.)

"Foreplay for a man is basically everything that happens 24 seconds before sex," Brizendine says. "For a woman, it's everything that happens 24 hours before."

"Foreplay for a man is basically everything that happens 24 seconds before sex. For a woman, it's everything that happens 24 hours before."

PHOTO: KSENIIA IVANOVA/MANDRIXYTA

Sexual Function
Troubleshooting the Genitals

"A lot of young women come to me and say, 'I may have orgasmic dysfunction' because their partners are like, 'My last three partners had orgasms from intercourse. There's something wrong with you.' No, there's not."

While much of sexual health is psychological, it's also very much about the body. Let's get into the physical stuff!

First up: female anatomy and orgasm. For a long time, scientists knew surprisingly little about the clitoris. This organ holds thousands of nerves that give women sexual pleasure. It's shaped kind of like a wishbone, and it's bigger than you might think.

"We don't see the majority of the clitoral tissue," Rowen says. "It's deep, and it wraps around the vagina."

Does that mean vaginal orgasms and clitoral orgasms – the latter once deemed inferior by some male physicians – are actually the same? Rowen says scientists aren't studying this enough to know for sure. She suspects female orgasms involving vaginal penetration engage more muscles and thus cause different sensations, even though the nerves involved are probably similar. What we know for sure is that most women need external clitoral stimulation to achieve any orgasm.

"People don't understand this," Rowen says. "A lot of young women come to me and say, 'I may have orgasmic dysfunction,' because their partners are like, 'My last three partners had orgasms from intercourse. There's something wrong with you.' No, there's not."

Unfortunately, a lot can throw off women's enjoyment of sex. Some women taking hormonal birth control find their sex drive plummets; Rowen blames that on the high dose of hormones required to stop ovulation. And as women age, menopause can cause a host of unpleasant symptoms, including vaginal dryness and lower libido. Luckily, Rowen says, the progesterone and estrogen used in hormone replacement therapy are far less potent than those in the pill, so they don't dampen desire.

Women looking to boost their libidos have some relatively new prescription options. One is Addyi, a drug originally investigated as an antidepressant. (Note to women already on an antidepressant: A lot of them actually curb sexual desire. That applies to men, too.) While there's been some controversy about how well Addyi works, Rowen says most of her patients who try the daily pill decide to keep taking it.

There's also Vyleesi, which indirectly affects dopamine, a neurotransmitter that stokes our pursuit of pleasure. You're supposed to inject it under your skin – yep, with a needle – about 45 minutes before sex. On the plus side, you find out whether it works quickly, whereas Addyi can take weeks to kick in.

And what about men? There are well-established options to help them get or keep an erection. You've probably heard of Viagra, one of the most popular prescriptions in the U.S. It boosts blood flow to the penis.

Tom Lue, MD, UCSF's Tanagho Professor of Clinical Urology, discovered how the body traps blood in the penis during an erection and advanced our understanding of nitric oxide, which is crucial to how Viagra and similar drugs work.

But Shindel notes that the ability to get an erection is not always the problem. Some men just have low libido, which might be more mental and emotional than physical. Still, the problem can get worse over time.

"The analogy is, 'Who wants to play baseball if you know you're going to strike out?'" says Shindel. "They don't want to fail. That becomes a vicious cycle.

"But the pills work in many cases to help boost erection response, regardless of arousal or libido. A lot of men get some confidence back. That is psychological, but real."

Among older men, surgery or radiation for prostate cancer can damage nerves and make erections especially difficult. If nothing else helps, surgeons like Benjamin Breyer, MD, MAS '11, a professor of urology, can implant a device in the penis. When the patient wants an erection, he just pumps a small bulb in his scrotum – ta-da, science! Other promising (but still experimental) solutions include shock wave and stem cell therapies.

"We see a lot of men in their 50s and 60s," Breyer says. "That's one of the more gratifying things in our work – helping restore men to how they had been before their cancer. For a lot of people, it helps them feel more normal."

Still, Breyer thinks everyone should know there are far less invasive ways to improve their sexual function.

"Whatever is good for you overall is also good for sexual health: exercise, eating well, getting rest, de-stressing," he says. "Mental health, hormonal health, vascular health ... all these things intersect and lead to sexual wellness."

PHOTO: FLOORTJE

Speaking_Again

A stroke left him paralyzed and unable to speak. Fifteen years later, neuroscientists harnessed the power of artificial intelligence to give him back his voice.

By Anil Ananthaswamy

Restoring Speech

Center: Pancho is the first person with vocal paralysis to communicate through a speech neuroprosthesis, a brain implant that converts neural signals into text. *Top:* Neurosurgeon Edward Chang, MD, connects Pancho's neuroprosthesis to a computer through a port in his skull. *Bottom:* Chang, left, and three members of his lab – Sean Metzger; David Moses, PhD; and Jessie Liu – work with Pancho at his nursing home in Sonoma County, California.

PHOTOS: MIKE KAI CHEN; GRAPHICS: AKRAIN

On a fateful day in 2003, about a month away from turning 21, Pancho woke up with a terrible headache. His body began stiffening, his speech was slurred, and he could barely stand upright. In the ambulance on the way to the hospital, the paramedics asked him questions, but Pancho – a name he uses to preserve his privacy – couldn't get any words out. He was admitted to the ER and given a battery of tests. And then everything went blank.

He came to about a week later. "I tried to move and speak, but I couldn't," Pancho recalls. "It was terrifying." He learned he had suffered a stroke, likely a consequence of injuries from a recent car crash. The stroke, his doctors explained, had occurred in his brainstem, severing communication between his brain and the muscles of his body, including those in his face. It dawned on him that he might never move or speak again.

But Pancho is "a man with a lot of faith," as he puts it. "I thought I would get better somehow, because God is always here with me." Before his stroke, his life had revolved around working in the vineyards of Sonoma County, California. Afterward, he was confined to hospitals and later to the nursing home where he resides today. "I was at the mercy of anyone in charge of my care," Pancho recalls. "The worst thing is I couldn't talk, and even though I tried to nod and signal someone passing by, I couldn't say what was wrong."

Eventually, he was given an electric wheelchair that he could operate with residual movements in his arms. He also learned to use residual movements in his head and neck to control a pointer fastened to a baseball cap, with which he painstakingly tapped out words on a virtual keyboard. "It was very slow, but it worked well, and I was able to communicate," he notes. (He recently upgraded to a typing system that uses a laser pointer mounted on his glasses, which is how he answered questions for this story.)

Then, in 2018, Pancho's neurologist alerted him to an intriguing clinical trial co-led by Edward Chang, MD '04, a neurosurgeon at UC San Francisco's Weill Institute for Neurosciences. For about a decade, Chang and his colleagues had been working to understand how the human brain gives rise to speech. They had even learned to transform electrical activity in the brain's speech center into intelligible sentences. The time had come to attempt the next step: restore speech to someone who had lost the ability to talk. Pancho was the first to volunteer. "I didn't think twice," he recalls. (Chang designed the trial with UCSF neurologist Karunesh Ganguly, MD, PhD, whose work focuses on restoring movement in paralyzed patients.)

Chang, who is also the chair of Neurological Surgery and the Jeanne Robertson Distinguished Professor of Psychiatry, began the trial by implanting an array of 128 electrodes embedded in a thin silicone sheet beneath Pancho's skull, on the surface of his brain. These tiny metal discs, which record signals from neurons firing in the brain, connect to a skull-mounted port that breaches Pancho's scalp, allowing the implant to be plugged into a computer. Chang's team then set about programming the system, called a neuroprosthesis, to translate Pancho's brain signals into words.

In July 2021, they announced the results: Pancho became the first person with vocal paralysis to successfully generate words by controlling a speech neuroprosthesis with his brain. Granted, his speech was expressed as text on a computer screen, and he was initially limited to a 50-word vocabulary. But this feat could be the beginning of a sea change for people like him who cannot speak on their own.

The communication tools available to such patients today all rely on typing using eye trackers or other non-brain-based technologies, which are far less efficient than natural speech. The late physicist Stephen Hawking, for example, whose iconic "voice" emanated from a synthesizer that turned text into computer-generated speech, could compose messages at a pace of only a word a minute toward the end of his life. With his laser pointer, Pancho can type about five words a minute. With the neuroprosthesis, however, he can already speak up to 15 words a minute, and, in theory, future generations of the system could enable conversational speeds of about 150 words a minute.

> "It's a precise spatial-temporal pattern of neural activity that occurs when we speak."
> —Edward Chang, MD

What makes this technology so powerful is that it combines new knowledge about the neuroscience of speech with a form of artificial intelligence called machine learning. Machine-learning algorithms enable researchers to teach computers to recognize complex and sometimes subtle patterns in data that humans are unable to see. These algorithms have proven hugely successful at tasks such as image classification, language translation, and speech recognition (think Siri on your iPhone). Now scientists like those on Chang's team are using machine learning to augment impaired brains, blurring the boundary between the natural and artificial.

But before Chang's team could train a machine to help someone like Pancho speak again, they first had to figure out how an unimpaired brain orchestrates the extraordinary array of sounds that make up human speech.

Sea Change
Pancho gets around in an electric wheelchair that he operates using residual arm movements. To communicate, he uses a laser pointer mounted on his glasses to type at five words a minute. In experiments with his neuroprosthesis, he can speak up to 15 words a minute; in theory, future generations of the system could enable conversational speeds of about 150 words a minute.

The_Shape_of_Speech

The human vocal tract is a marvel of musculature. When we speak, our brains engage a hundred or so muscles in our jaws, lips, tongues, throats, and lungs. “By themselves, these movements have no meaning,” Chang says, “but when they’re coordinated, like a symphony, they give rise to every consonant and vowel, and from that, every word and sentence. It’s an incredible generative system that allows us to convey an infinite number of messages and meanings.”

Chang’s lab specializes in mapping the patterns of neural activity that control many of the muscles in the vocal tract to produce the sounds of speech. To create these maps, his team has made use of another area of Chang’s expertise: epilepsy surgery. Chang treats patients with drug-resistant epilepsy by excising the brain tissue that causes seizures. To determine what tissue to remove, he temporarily implants an electrode array similar to Pancho’s on the surface of a patient’s brain. He uses the array to both record from and stimulate the brain while the patient is awake, which allows him and his colleagues in the UCSF Epilepsy Center to pinpoint where the seizures originate and steer clear of regions that carry out important functions like language.

Over the past 10 years, more than a hundred epilepsy patients have volunteered to participate in Chang’s speech research. For these studies, researchers record neural signals from the speech center of volunteers’ brains while they speak aloud. In some experiments, the researchers simultaneously monitor the movements of the volunteers’ vocal tract muscles using, for example, video and ultrasound tracking of their lip, tongue, and jaw movements. As a result, Chang’s lab has been able to determine which neural activation patterns correlate to which vocal-tract movements and how these movements form particular sounds.

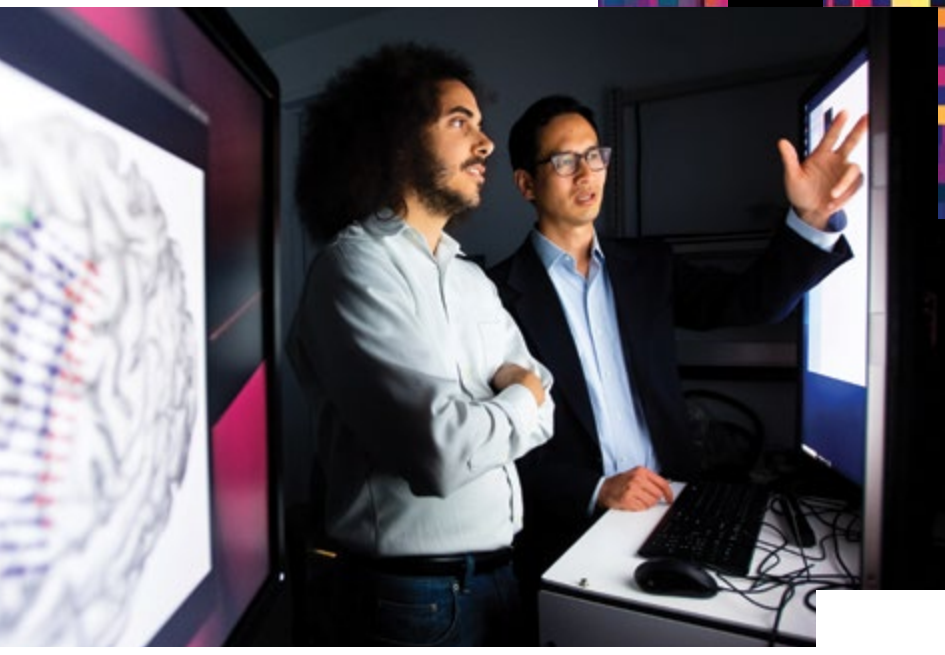
For example, the team has found that certain neurons fire when the lips close briefly to make the plosive “p” sound in “proof.” Meanwhile, mere millimeters away, different neurons fire when the tongue protrudes forward to make the “th” sound in “that.” Chang’s team has verified such correlations by electrically stimulating these neurons in patients’ brains and observing how the muscles of the vocal tract move in response.

The brain regions involved in speech have been known for over a century. Chang’s lab has not only delineated these regions in more detail but also deciphered the neural code behind every speech sound, or phoneme, in the English language — the DNA of speech, if you will. “It’s a precise spatial-temporal pattern of neural activity that occurs when we speak,” Chang says.

In a surprising twist, his team even discovered a second, previously unknown brain region representing the movements of the larynx, or voice box. This region is absent in nonhuman primates, suggesting that it has a unique role in human speech. Indeed, as Chang’s lab later figured out, the newly discovered region helps control the vocal folds in the larynx to change the pitch of a word, which humans often do when we stress a word to change the meaning of a sentence. (For example: “I *never* said she stole my money” versus “I never said *she* stole my money.”)

But Chang’s team wasn’t satisfied simply with cracking the neural code of speech movements and sounds. “We’ve always been interested in translating that knowledge to restore function to someone who’s been paralyzed and lost the ability to communicate,” Chang says. He knew, however, that making that leap wouldn’t be easy. For one thing, the precise neural signatures for speech must be reliably identified amid a

PHOTO: MIKE KAI CHEN; GRAPHICS: AKRAIN



Signals to Sentences
David Moses, PhD (left), and Edward Chang, MD (right) – together with their colleagues – have shown it's possible to decode a person's brain signals into every possible speech sound, or phoneme, in English. These sounds could then be assembled into any possible word. "You could theoretically decode words that a person is trying to say even if they never actually said those words before," Moses says – including newly minted words.

cacophony of brain signals. For another, speech codes, like genes, vary from person to person. Although they share some common features, no two codes are exactly the same. Accurately transcribing a person's unique neural signals into their intended phonemes or words, therefore, would require more sophisticated algorithms.

Enter machine learning. Overseeing the development of the algorithms that led to Pancho's breakthrough was David Moses, PhD '18. He joined Chang's lab as a doctoral student in 2013 and then continued on as a postdoctoral fellow. In 2019, Moses and his colleagues published a proof-of-concept study showing that a machine-learning system could be taught to decode phonemes from a person's brain activity in real time. Three of Chang's epilepsy patients volunteered for the study. Each volunteer listened to questions and responded aloud with answers that they selected from a multiple-choice list, while the researchers recorded their neural signals. Moses's team then used these data to train the system using a technique called supervised learning.

In supervised learning, researchers feed into machine-learning algorithms examples of inputs matched with their corresponding outputs. An algorithm tasked with learning to identify cats, for example, might be fed images labeled "cat" or "not cat." In this way, the algorithm learns to discern the distinguishing features of a cat. In part of Moses's study, the researchers fed their algorithm each volunteer's neural signals (inputs) matched with the corresponding audio clips of the volunteer's speech sounds (outputs). The algorithm thus learned how certain patterns in the signals corresponded to certain phonemes.

Once trained, the machine-learning algorithm could use these correlations to predict the likeliest phoneme a volunteer uttered based solely on their neural activity. Moses wrote another program that then converted those predictions into the likeliest response. His team found that their system could decode a volunteer's answer to a given question with an accuracy rate of 76% – a significant improvement over chance, at 20%.

Use It_or_Lose It?

Moses's demonstration and others like it convinced Chang's team they were on the right track. But the machine-learning systems they had built so far all worked with people whose ability to speak was fully intact. What would happen if they tried to train a system using neural signals from someone like Pancho, who hadn't spoken for years? Would the brain regions responsible for speech still generate meaningful signals after years of lying fallow?

The brain is plastic: When a region stops being tapped for its original use, the brain can co-opt it for other purposes. By the time Chang's team began working with Pancho, more than a decade had passed since his stroke. It was entirely possible that the neurons in his brain's speech center had already been repurposed, erasing their ability to encode the intricate muscle movements that beget intelligible speech.

Even if that weren't the case, however, Pancho's disability presented another challenge. "When he tries to say a word, it comes out like a grunt," Moses says, or like a moan. "It's much harder to tell exactly when each phoneme occurs," he adds, than it is with speaking volunteers. Training a machine-learning system to identify phonemes from Pancho's neural signals would therefore be difficult. So instead, the team – which by then included graduate students Jessie Liu and Sean Metzger – decided to try decoding entire words, since it's easier to tell when Pancho is trying to say a word than a phoneme.

For that, they turned to the most powerful form of machine learning: deep neural networks. Inspired by neural networks in the brain, deep neural networks, or deep nets for short, consist of layers of artificial neurons – simplified computational models of biological neurons. When a deep net is fed training data (pairs of inputs and outputs), it strengthens or weakens the connections between these copycat neurons, analogous to how the human brain tunes the synapses between biological neurons when we learn.

Typically, deep nets are data-hungry hogs: Give them enough training examples, and they'll learn patterns in just about anything. They're

PHOTO: NOAH BERGER; GRAPHICS: AKRAIN

superb at tasks like identifying images or voice commands, mainly because Internet companies have amassed decades of image and voice data, as well as the massive computing resources needed to store and process them. But Chang's team didn't have those luxuries. "When you are working with someone who is paralyzed, you're very data constrained," Chang says.

What the team *did* have, however, was more than a decade's worth of knowledge about the neural basis of speech. They could thus use that knowledge to enable a machine-learning system to decode Pancho's brain signals with fewer training data by first using filters to extract content in the relevant frequency range. The team then used the filtered signals to train a deep net to recognize when Pancho was attempting to speak and identify brief time segments of neural activity representing words.

Next, the researchers fed those time segments into another deep net, which learned to decipher the likeliest word being spoken. With Pancho's help, the team taught this algorithm to recognize 50 common words from his brain signals, including "hello" and "thirsty." For each time segment of neural activity, the algorithm spit out 50 numbers signifying the probabilities that Pancho was trying to say each of the 50 words.

Finally, the team trained a third machine-learning algorithm called a language model to convert a series of word probabilities into the most likely sentence. For example, if the second deep net predicts that a word Pancho is attempting to say is equally likely to be "hello" or "thirsty," but his previous words were most likely "I" and "am," then the language model would output the sentence "I am thirsty."

After months of training, the AI powering Pancho's neuroprosthesis was ready. All that remained was for Pancho to test it out.

A_Voice_of_His Own

"My family is outside."

Pancho remembers that this was the first sentence he spoke through his neuroprosthesis. The words appeared almost immediately on the computer screen before him. "I was so excited, I couldn't believe it," he recalls. "Whenever I get excited about something, I have a spontaneous laughter – a horrible laugh that comes out of nowhere and messes everything up." Nevertheless, he adds, "I was able to pull myself together and keep going."

Since completing the 50-word study, Chang and his team have continued to work with Pancho, visiting him at his nursing home in Sonoma two days a week. They are experimenting with ways to make the neuroprosthesis faster and more accurate. In the study, for instance, the team reported an average error rate of 26%. They have since found that they can reduce that rate if Pancho attempts to speak without grunting. Simply speaking through his mind, and stopping short of vocalizing, is both easier for him and more effective. "In his mind, he's more free," Chang says, echoing something Hawking wrote about his own travails: "Although I cannot move and I have to speak through a computer, in my mind I am free."

The team is also working to increase Pancho's vocabulary. But expanding to even 100 words isn't trivial. "You have to collect tons and tons more data each time a new word is added," Moses explains. With more than 150,000 words in the English language, it's unlikely that a neuroprosthesis based on decoding words directly could ever give someone like Pancho back a full English vocabulary, let alone a bilingual one. (Pancho is a native Spanish speaker.)

> "I was so excited, I couldn't believe it." —Pancho

A more scalable approach would be to build a phoneme-based system like the one Moses built in his 2019 study. That's a much tougher bioengineering task given Pancho's inability to clearly articulate sounds. But because English has only 44 distinct phonemes, a neuroprosthesis trained to decode all 44 would be able to piece together any word a person wants to say. "You could theoretically decode words that a person is trying to say even if they never actually said those words before," Moses says – including newly minted words.

Meanwhile, Chang's team is exploring a third approach that involves decoding intended movements of the vocal tract to create synthesized speech rather than text. "One of our bigger goals is to actually have audible words come out," Chang says. A recent study led by Gopala Anumanchipalli, PhD, an assistant professor, and Josh Chartier, PhD, a postdoc in Chang's lab, demonstrated such a system with epileptic volunteers. Remarkably, the system could synthesize speech from the volunteers' neural signals even when they silently mouthed the words.

Chang envisages still more futuristic enhancements. With advances in hardware, he believes, implantable electrode arrays will soon be able to communicate with computers wirelessly. He imagines restoring speech not just in one language but two or more, for multilingual patients. He thinks about children with cerebral palsy, who have never been able to speak, and wonders if a neuroprosthesis similar to Pancho's could help them, too. He speculates about implanting a second set of electrodes in a paralyzed person's vocal tract muscles to stimulate them using commands from electrodes in their brain, letting them speak again in their own voice.

Inevitably, people always ask Chang if his lab's technology will one day be able to read private thoughts. "In a theoretical sense, if the brain is truly the source of our thoughts, concepts, and knowledge, then it's absolutely possible," Chang says. Pancho's neuroprosthesis, however, doesn't even come close, he points out. "He can't just be thinking about a word or imagining it. It's got to be a volitional act." Still, Chang concedes, "it's worth talking through the potential implications now."

For his part, Pancho can't wait for the day when he can use his speech neuroprosthesis in everyday life. "I am very hopeful about that," he says. "It is going to be something so amazing, I can't even describe it. It blows my mind just to think about it."

ALUMNI HUB

The world needs UCSF-trained experts more than ever. Meet five who are improving lives from Alaska to Australia and beyond.

SCHOOL OF PHARMACY

Madalene Mandap, PharmD '12

Hand in Hand with Alaska Native People on the Journey Toward Health

The voice on the other end of the phone was urgent. A patient at Southcentral Foundation in Anchorage was starting transition treatment and needed lessons in hormone injections.

As the organization's pharmacy expert on gender-affirming care, Madalene Mandap, PharmD '12, was needed STAT. "We don't do it a lot," she explains, referring to transitioning treatment in the 49th state. "It's still fairly new here."

So Mandap raced to the clinic to explain injection protocol to a person about to embark on a new life. It's not unusual for the veteran pharmacist to guide patients taking significant steps. Another decided to begin treatment for hepatitis C, though still a heroin user. Mandap discussed options for addiction treatment and ensured the person left with naloxone nasal spray in case of overdose.

"My job is never boring," she says. "We're not just sitting there, plugging and chugging prescriptions. If there's a way to improve health, we can find it."

Southcentral Foundation, where Mandap has worked since 2013, after finishing her residency, is well known in the health care world. The recipient of two prestigious Malcolm Baldrige National Quality Awards, Southcentral is a sprawling system of clinics that serves 65,000 Alaska Native and American Indian people. Thanks to the Baldrige awards, the highest honor in U.S. health care, the foundation hosts experts

ILLUSTRATION: JOHN JAY CABUAY

from all over seeking to understand its success in treating Indigenous populations.

A chief reason is respect for those it serves. Since 1999, Southcentral has practiced a care model called Nuka – a relationship-based approach that aims to improve outcomes and reduce costs. The respect for patients – called "customer-owners" in Southcental's parlance – is what attracted Mandap to Anchorage.

Her recent gender-affirming interaction was a case in point. Already working with a therapist, the patient was ready to start the physical process and needed guidance. "It was a co-visit," Mandap recalls, "so the primary care provider was there, as well as the nurse case manager. It was awesome, all of us being in the room together, each with our own specialty." In one fell swoop, the team handled education, injection training, behavioral health support, and paperwork.

"We went from identifying a person who says, 'I want to start hormone therapy,' to my dispensing the medication within a week. We were able to get in and out and answer all questions. Whew!" she concludes.

The anecdote illustrates why Mandap, a Navy brat who grew up in Barstow, Calif., decided to serve her residency in a place she'd never visited, 3,500 miles from home and her close Filipino family. She explains that not only was she drawn to the organization's mission, but Alaska also wooed her from the start when she stopped in at a bar featuring live music.

"I found that you get pulled into a family, almost like it's a chosen family," she says. "You show up as a stranger and quickly get interconnected and taken care of. Then you want to take care of others around you because up here, the weather, the snow, the ice can strand people," she notes about the state that is now home for Mandap and her wife, Ariel Berg, whom she married in September. "It's all about safety, so people fall into this 'help each other' mindset."

Southcentral Foundation exemplifies that mindset. The federal Indian Health Service provided health care for Alaska Native people until the early 1980s, when the tribes took control. Now health care is tribally owned and operated – an arrangement Mandap describes as empowering to both participate in and witness.

"From my time at UCSF, what really spoke to me, what really lit my fire, was serving the underserved. Part of it is personal experience," she says. "I'm Filipino American. My parents immigrated here after my dad joined the Navy, so I've seen health disparities – like language barriers – that result in people getting inferior care."

That philosophy also explains her decision to join the Commissioned Corps of the U.S. Public Health Service (PHS). As the nation's front-line public health force, the PHS can send officers on a moment's notice to health emergencies. In 2019, Mandap was deployed to Texas to provide care for people who'd lined up the night before to obtain free dental care and eye exams and to have their glucose levels checked. The assignment was right up her alley.

"There's something to be said for wearing the uniform. We're serving our country. We're at the ready to be deployed," she says. "Now, I am in service of Alaska Native and American Indian people to improve their health care, with their help. It's a passion of mine to find those gaps and stand in them to do what I can to help."

Katherine Conrad

PHOTO: MUDDYMAPI

SCHOOL OF NURSING

Kimberly Baltzell, RN, PhD '05, MS '10

Supporting Nurses so Giving Birth is Safe for All Women

Kimberly Baltzell, RN, PhD '05, MS '10, calls the "nimbleness of nursing" health care's best-kept secret. "There are so many meaningful ways to be a nurse," she says.

Baltzell herself embodies that agility. She spent a decade working on Wall Street to save money for medical school. But she felt drawn to the bedside, pivoted to nursing, and has never looked back. Her career has taken her from UCSF's medical center, where she cared for kidney-transplant patients; to Zanzibar, where she studied malaria; to Tennessee, where she's promoting reproductive health for Black women. Along the way, she earned a doctorate in nursing and a master's in global health sciences.

She's now a professor of family health care nursing and director of UCSF's Global Action in Nursing (GAIN) program, which supports nurses and midwives in underserved parts of the world. "I'm never going to retire," Baltzell says, laughing. "I love it."

The seeds for GAIN were planted on research trips she took to sub-Saharan Africa, where almost every provider she interacted with was a nurse or midwife. "In many regions, they are not only the front-line provider, they are the only provider," she says. Nurses and midwives often bear huge responsibility but lack support, supplies, and adequate training. Later, in Malawi, which has a high maternal mortality rate, Baltzell and colleagues envisioned a way to help reduce that rate: offer intensive training and long-term mentorship to nurses and midwives.

She launched GAIN in 2017 in collaboration with the nonprofit Partners in Health. After its success in Malawi, the program expanded to Sierra Leone and Liberia. Baltzell then wondered if the same model could be used in the U.S. "We have the worst rates in maternal and neonatal outcomes in the developed world," she says, noting that outcomes "are poorest in southern states and are worse for women of color, particularly Black women."

Through Monica McLemore, RN, PhD '10 – a friend of Baltzell's and a fellow UCSF PhD grad and faculty colleague – GAIN recently partnered with CHOICES, a reproductive health center based in Memphis, Tennessee, to establish a 12-month fellowship for Black midwives. "I'm looking forward to deepening partnerships in places like Memphis, where hopefully we can help support not only nursing and midwifery but also women's reproductive rights," she says – another nimble move.

Terri Leker

GRADUATE DIVISION

Cecily Rose Miller, PhD '17, MPH

TB Sleuth: Finding Hidden Cases Worldwide

While not her official title, "tuberculosis detective" would be an apt one for Cecily Rose Miller, PhD '17, MPH. An epidemiologist, she helps lead a global effort to locate the "missing millions" – the estimated 4 million out of 10 million people with tuberculosis (TB) whose illness goes unreported or unnoticed every year.

Early discovery is key in treating TB: Many patients don't exhibit symptoms of the slow-moving disease for years, if at all. In the meantime, they can unknowingly spread the airborne TB bacterium to family members and in their communities. In 2020, for the first time in a decade, the number of TB deaths worldwide rose – to more than 1.5 million.

"The need to find those people with TB is more urgent than ever," says Miller, a technical officer with the World Health Organization (WHO) Global Tuberculosis Program and director of a recent update of WHO's TB screening guidelines. The new guidelines include improved X-ray technology and other tools new to the WHO-sanctioned detection arsenal.

"A chest X-ray can detect TB in people before they start developing symptoms," Miller says.

Modern chest X-ray equipment is safer (it emits negligible radiation) and far more portable (it's the size of a large Polaroid camera instead of a van), making screening feasible even in remote communities. Equally exciting is a new way of interpreting those X-rays, given the scarcity of trained radiologists in many resource-constrained settings.

Advancements in artificial intelligence have led to computer-aided detection (CAD) software capable of automatically detecting TB on chest X-rays with an accuracy equaling that of a human reader. Miller led the process of WHO's endorsement of CAD technology under the new screening guidelines, released in March 2021 – the first time the organization has approved artificial intelligence for health care.

Born and raised in the Bay Area, Miller landed at the UCSF Center for Tuberculosis as a data manager and research assistant after earning her MPH at UC Berkeley. Within a decade, she was conducting research in East Africa and Indonesia as part of the center's investigations into undiagnosed TB – and had earned her PhD in epidemiology and biostatistics.

"I'd had a long-term interest in global health but hadn't focused on TB. I really just loved it," she says. "It felt at the heart of both a social and a biomedical problem, a disease that tracks so much with poverty and vulnerability."

Janet Wells

ILLUSTRATIONS: JOHN JAY CABUAY

SCHOOL OF DENTISTRY

Carrie Tsai, DMD, MPH, Resident Alum

Tackling the 'Food Environment' to Improve Oral Health

Dentists are well known for "telling patients how to avoid dental decay: 'Don't eat that, do this,'" says Carrie Tsai, DMD, MPH.

A more effective, lasting approach – one that melds her education in dentistry, public health, and sociology – is "improving the food environment to improve oral health," says Tsai, who completed her pediatric dentistry residency at UCSF in 2013. Today, she is on the faculty at Sydney Dental School at the University of Sydney in Australia and a staff specialist at the Sydney Dental Hospital.

Her target is heavily-processed, sugar-laden food and drinks, which are often cheaper for consumers, hyperpalatable, highly-promoted – and associated with diabetes, obesity, and tooth decay. "Oftentimes, what's bad for the mouth is bad for the overall body," Tsai says.

A California native, Tsai has sought to combine research with advocacy near her new home in Sydney. She started by conducting food and beverage audits to assess the "four Ps" – product, placement, promotion, and pricing – at local hospitals, as well as at Australian Catholic University. Her findings and discussions with stakeholders led to a new policy – the replacement of sugar-sweetened beverages with healthier options in vending machines at the university's seven campuses.

"There was pushback," she concedes. "We needed to build community support and buy-in, and did so through a simultaneous health promotion campaign. It's not about simply taking things away, but also about making healthier options the easy choice."

During her residency, Tsai participated in the UCSF Global Health Sciences Clinical Scholars Program. For her immersion experience with the program, she investigated the role that nurses in Roatan, Honduras, could play in childhood oral health – delivering dental counseling and applying fluoride varnish during immunization visits by children less than 5 years old, "an age group that often hasn't had their first dental visit," Tsai says.

Her subsequent research, published in *Community Dentistry and Oral Epidemiology*, reviewed practices that lead to successful oral health outcomes for Indigenous populations. "Dental disease rates are often higher among socioeconomically disadvantaged groups," she explains, "including many Indigenous populations globally, which is why community-informed health promotion is particularly important for these communities."

Her findings suggest that programs are more successful when Indigenous stakeholders are involved in their development and when they are comprehensive. "Because health is intertwined with housing, the environment, poverty, food security," Tsai says, "we need to address these larger issues to improve oral health."

Janet Wells

SCHOOL OF MEDICINE

Terry O'Connor, MD '04

Climate Medicine: Rethinking 'No Harm' in a Changing World

Four years ago, in a sweltering slum in Kolkata, India, Terry O'Connor, MD '04, came face-to-face with the basic principle of his profession: First, do no harm.

In a shack's dark confines, O'Connor thanked a young Muslim woman for allowing him into her home to treat her sick brother. She wept in response: *This is not my home.* The family, along with their entire community, had been uprooted from the Sundarbans area of Bangladesh, their rice fields ruined by rising sea levels.

"I had come all the way across the world to help, but did my flight alone cause more [environmental] harm than I could possibly repair in a few weeks of volunteering?" wondered O'Connor, an emergency physician at St. Luke's Wood River Medical Center in Ketchum, Idaho.

"If we as a health care community are to be true stewards of global health, we must not only seek new solutions to fight disease in this changing world but also reconcile with our own contributions to these problems," O'Connor says.

An avid mountaineer and athlete, he had already established a nonprofit organization and podcast, both called *The Adventure Activist*, exploring the nexus between adventure-seeking and altruism. He was incorporating health and climate change when COVID-19 hit.

Within weeks, his region had one of the highest per capita concentrations of COVID-19 in the country. "A quarter of our hospital staff was ill or quarantined," says O'Connor, who is also the director of emergency services for the Blaine County-Sawtooth region.

Recently, thanks to high vaccination rates and abating case rates in Blaine County, O'Connor has been able to refocus. He enrolled in the MPH program at Johns Hopkins Bloomberg School of Public Health.

He also signed on in 2017 as the director of medical education programs for the Climate and Health Program at the University of Colorado Anschutz Medical Campus. Now, O'Connor is helping develop the nation's first diploma in climate medicine, to offer training in the health effects of climate change, the "greening" of health care systems, and more.

"It's about health providers putting a voice and a face to the impacts, whether it's from forced migration, raging wildfires, or extreme heat," O'Connor says. "It's not enough to be a clinician anymore. The stakes are too high. We must now effectively communicate what we see and change what we can."

Janet Wells

ILLUSTRATIONS: JOHN JAY CABUAY

Postcards from the Living

By Jenny Qi, PhD '17

I light incense on the stovetop, trail cinders
through an empty house. I've decided to believe

in the power of ashes: *Here I am*,
buying fruit, mending torn shirts, brushing teeth

in cramped bathrooms, living
someplace new. *Wish you were here.*

I sprinkle sandalwood dust on the ribbon
from my first 5k, the token from my first solo trip –

milestones so small and unremarkable
only you could understand and be proud.

Remember world history class, how I translated
lectures to you each night, partly to practice,

partly to keep you with me. Every day,
there's so much new I want to show you,

like the spongy tang of injera, pork belly
banh mi melting like butter on the tongue,

all these places I have traveled without you
so I can forget how without you I am.

Remember when I was ten and hateful, trying
too hard to be cool, how in a rare moment

you said all you wanted was for me to love
my life, my only life, this life you started.

Here, look how the clouds blush so fiercely;
the stark blue winter, so cold and bright.

Jenny Qi received her PhD in cancer biology from UCSF in 2017. This poem was first published in *The Atlantic* and appears in her first book, *Focal Point*.

Illustration by Eleanor Davis for *UCSF Magazine*.

UCSF Benioff Children's Hospitals

Spreading Cheer All Year

For a child, being hospitalized is hard. Being hospitalized during the holidays is heartbreaking.

Project Cheer Virtual Toy Drive, a crowdfunding opportunity that puts gifts and toys in the hands of hospitalized kids, adds a little magic that makes a big difference during a holiday season away from home.

Join us in bringing extra cheer to our patients this holiday season. You can make a gift or create your own fundraising page to mobilize your community around a great cause. And the cheer doesn't stop at the end of December. Donate or raise funds through Project Cheer any time, and help our patients feel the joy of toys all year.

together.ucsf.edu/cheer

Point your mobile device camera at the QR code to access the link.

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