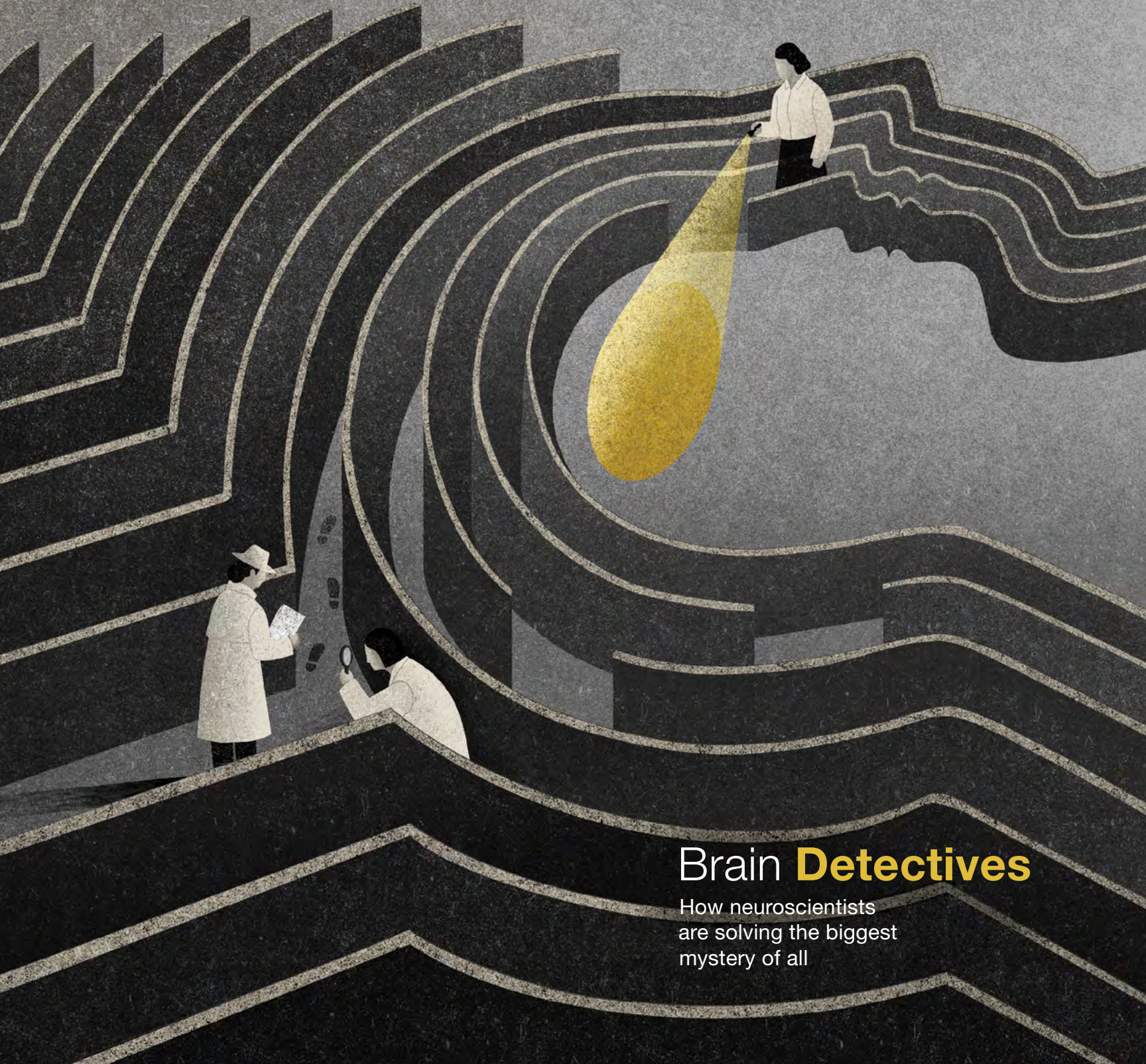


UCSF MAGAZINE

Summer 2024



Brain **Detectors**

How neuroscientists
are solving the biggest
mystery of all

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Mary is among the hundreds of patients with puzzling neurological symptoms who have come to UCSF hoping to end their diagnostic odysseys.



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Our genome may one day serve as a passport guiding our health care – from cradle to grave.

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The real answer isn't "yes" or "no." Here are six things you need to know.

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Perpetual stress runs us down. A truly restorative state counters its effects at the level of cells.



The new wave of weight loss drugs has inspired a lot of hope – and debate. Here's what UCSF experts have to say.

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A Pivotal Moment for UCSF



The 15-story UCSF Health Helen Diller Hospital will expand access to some of the nation's most complex care, in an iconic healing environment.



Chancellor Sam Hawgood (second from right), UCSF Health President and CEO Suresh Gunasekaran (right), and School of Medicine Dean Talmadge King, Jr. (left), celebrate with UCSF team members at a community event.

In April, UCSF broke ground on a beautiful new hospital with a bold vision for our historic Parnassus Heights campus.

When it opens in 2030, UCSF Health Helen Diller Hospital will be one of the most advanced hospitals in the country. It will integrate state-of-the-art medicine with a healing habitat incorporating natural light, plants, and human-centered design.

With 324 additional beds, a modernized emergency room, and 21 innovative operating suites, the new facility will expand our ability to care for patients with complex conditions and provide this care for generations. It underscores our dedication to the health of San Francisco, the Bay Area, and beyond and is perhaps the single most impactful investment in the history of UCSF Health. You can read more about its features on page 7.

Paired with the hospital will be a new research and academic building that is set to open in 2028. The proximity will foster

collaboration between scientists, health care professionals, staff members, and students from various disciplines throughout UCSF.

While these two projects will elevate our flagship campus in the years ahead, they mark the beginning of a decades-long transformation that will spur still more innovations in patient care, biomedical research, and health sciences education.

I am deeply grateful to everyone who has contributed to this milestone, from our faculty and staff to our donors and alumni to the broader San Francisco community. Your commitment to our shared mission is making this vision a reality.

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

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Five Questions for Sepideh Banava

Sepideh Banava, DDS, MSc, MPH, MBA, is a dental public health specialist. She has submitted a research grant to use artificial intelligence to develop a tool that will help dentists screen for intimate partner violence (IPV).

How is intimate partner violence related to dentistry?

An IPV survivor might visit a dentist with a bruised lip or fractured tooth but not tell their dentist how they got the injury. They may be afraid of their perpetrator or worried about stigma. Dentists should know IPV signs and symptoms, ask questions, and provide proper care. But they typically don't.

Why not?

They often don't have adequate training or time. They don't know what to ask or may be uncomfortable asking sensitive questions. Dentists may also be unsure how to guide patients or what resources to offer.

How will your tool help dentists?

It will be a clinical decision support tool, a computer program, that streamlines the IPV screening process. It will raise red flags and show alerts based on information dentists enter in the patient's chart – a fractured nose, for example. It will provide follow-up questions and a to-do list – call this organization, introduce the patient to a social worker, and so on – prompting dentists to provide better care.

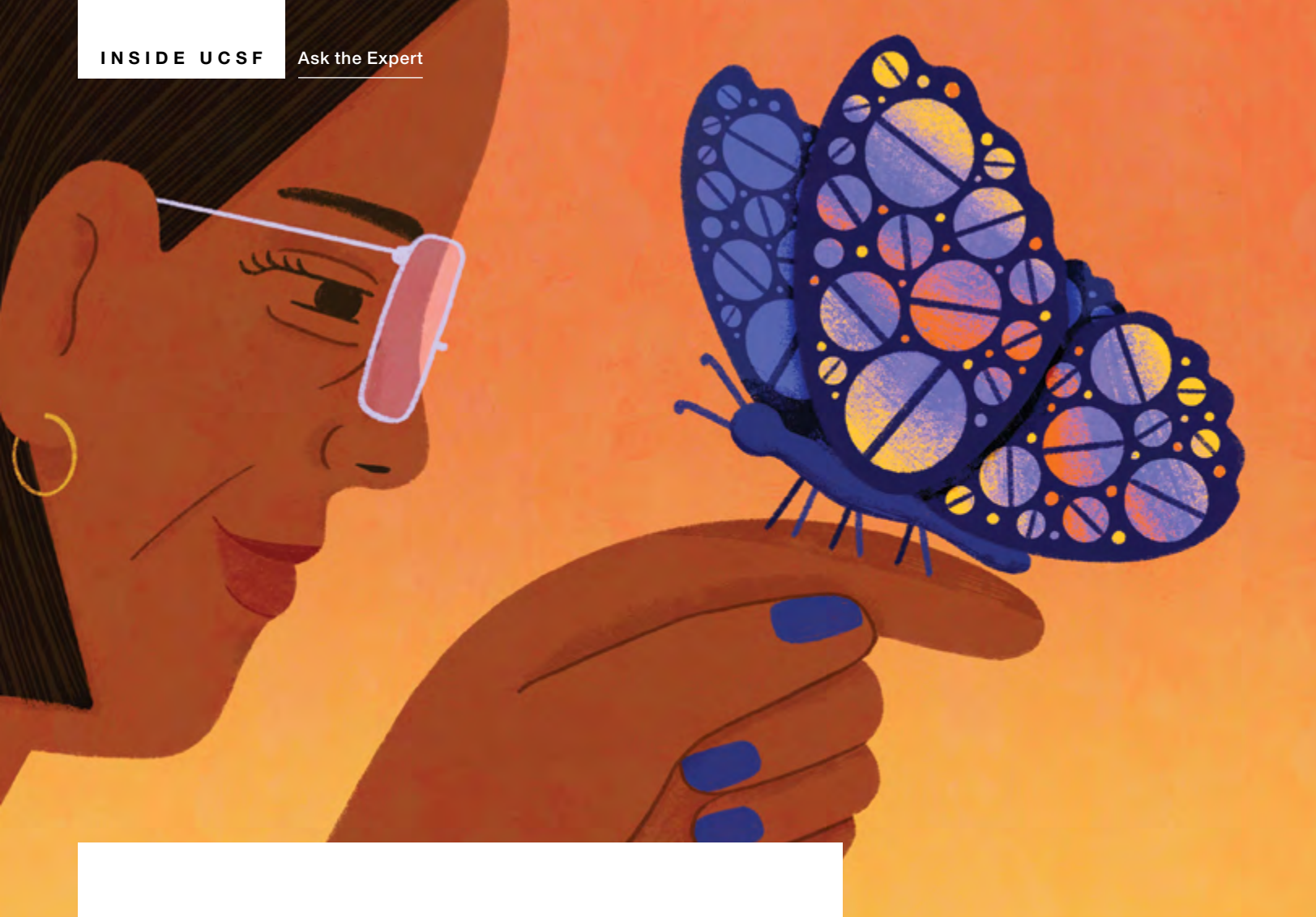
What role does AI play?

UCSF has immense data-science resources, including access for researchers to millions of de-identified patient records. I'll be trained to use AI tools like machine learning to develop the IPV screening tool. If a dentist enters patient symptoms like oral or facial injuries, the tool will help them detect or diagnose a possible IPV incident and provide support to prevent future IPV incidents. However, the dentist will make the final decision based on the system's suggestions.

What's your hope for patients?

I want to improve patient outcomes. If dentists don't diagnose IPV on the first visit, a cascade of problems could follow – another violent incident; fear of seeking further dental care; and neglected oral health, such as untreated cavities and periodontal diseases. I want patients to get the care they need early on.

←
Sepideh Banava is an assistant professor of preventive and restorative dental sciences at the UCSF School of Dentistry.



Should Women Take Hormones to Manage Menopause?

By Carin Moonin

The average woman will spend almost a third of her life in menopause. UCSF gynecologists Mindy Goldman, MD, and Tami Rowen, MD '09, MS, explain how hormone therapy may ease the transition.

Despite being a universal experience for women, menopause often seems shrouded in stigma or confusion. But menopause is having a moment: Women today can choose from a wealth of options to address their unique needs during this time in their lives, say UCSF experts.

What is menopause?

GOLDMAN: Menopause is defined as one year without a period. Perimenopause takes place in the years leading up to menopause. During this time, a woman may begin to have symptoms such as menstrual irregularities or hot flashes but still has periods.

ROWEN: These symptoms are caused by fluctuating and declining levels of the hormones estrogen and progesterone. Hormone therapy is medication that replaces the estrogen and progesterone the body stops making during the transition to menopause.

What are symptoms of perimenopause?

GOLDMAN: Well-known signs may include night sweats, mood swings, vaginal dryness, weight gain, and decreased sexual desire. Less common symptoms may include hair loss, joint pain, heart palpitations, dry mouth, and changes in gastrointestinal functioning.

ILLUSTRATION: PAGE STAMPATORI

ROWEN: Another symptom women may not recognize is cognitive changes, like word-finding ability. Women don't understand why they are struggling at work: Why is that word on the tip of their tongue, but they can't find it? It's not dementia; it's menopause.

How does hormone therapy work?

GOLDMAN: Hormone therapy includes estrogen and progesterone. Estrogen is typically the component of hormone therapy that alleviates most of the symptoms; progesterone is used if women have a uterus, as it prevents uterine cancer.

ROWEN: Also, hormone therapy isn't just pills to swallow. Oral estrogen can be associated with blood clots, so people who are at higher risk for blood clotting disorders should not be taking estrogen pills. But estrogen can also be given topically – via a skin patch, cream, gel, spray, or vaginal ring – which bypasses the liver and reduces the possibility of blood clots.

GOLDMAN: Perimenopausal women should also keep in mind that the dosage of hormones in hormone therapy is lower than in birth control; it's not an adequate form of contraception.

Does hormone therapy benefit the body in other ways?

GOLDMAN: Yes. Hormone therapy can have many other benefits: Progesterone can help with sleep, estrogen can help prevent bone loss, and if started around or soon after menopause, can prevent heart disease and possibly cognitive loss.

Why did hormone therapy fall out of favor?

ROWEN: After menopause, women's heart disease risk increases. More than 20 years ago, the Women's Health Initiative (WHI) study, a long-term national health study focusing on ways to avert heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women, aimed to assess hormone therapy's effectiveness in preventing heart conditions.

GOLDMAN: The intentions of the study were good: Researchers were evaluating whether the use of hormones prevented heart disease, the most common cause of death. But in 2002, the press published findings suggesting that the combination of estrogen and the specific type of progesterone the WHI study used increased the risk of breast cancer and didn't prevent heart disease.

Yet what *didn't* get publicized was that estrogen *decreased* the risk of breast cancer.

So, is there a link between hormone therapy and breast cancer?

ROWEN: Hormone therapy will not necessarily increase the risk of breast cancer – we know that specifically for estrogen alone, though the role of specific types of progesterone is more complicated, and there is likely a risk. However, it doesn't mean a woman won't get breast cancer on hormone therapy. I want to be very clear about that: One in eight women will get breast cancer – but not necessarily because of hormone therapy.

Women considering hormone therapy should speak with their health care provider to develop a plan specific to their personal health history.

Is there a good time for women to start and stop hormone therapy?

GOLDMAN: If a woman begins hormone therapy within 10 years of menopause or before age 60, the benefits usually outweigh the risks. And there's no reason to stop based on age. But as women get older, they may develop cardiovascular risk factors. For example, if you have plaques in your arteries or a history of blood clots, the use of estrogen is felt to be risky.

ROWEN: Yet if you take estrogen *before* artery plaque buildups are formed, research shows it can prevent cardiovascular disease.

GOLDMAN: I also don't want to imply that anyone who is over age 60 can't take hormones. Everyone's individual circumstances are different.

How reliable are blood tests to measure hormone levels?

ROWEN: Not at all reliable. During perimenopause, your ovaries are like a sputtering car; you've got your foot on the gas, but it comes out erratically. Tests for estrogen and follicle-stimulating hormone – the hormone that tells your ovaries to make estrogen – often show inconsistent results.

Does estrogen prevent bone loss?

ROWEN: Yes. Absolutely. Estrogen can help maintain bone density. There is no study that has *not* shown that estrogen is protective of bone health.

Who shouldn't take hormone therapy, and what are some alternatives?

ROWEN: I don't recommend it to anyone who has cardiovascular disease or a hormone-sensitive cancer that uses hormones to grow, such as some forms of breast, ovarian, uterine, or endometrial cancer.

GOLDMAN: If you can't take hormones, you may need to find other treatments for your individual symptoms.

In May 2023, the FDA approved Veozah, a new medication to decrease hot flashes. It works by blocking neurotransmitters in the brain that regulate heat and cold sensitivity. Other studies have shown symptom improvement from low doses of some antidepressants and neuropathic pain relievers, as well as anti-seizure, overactive bladder, and blood pressure medicines.

How can women maintain sexual health?

ROWEN: I encourage women to continue to maintain sexual activity as much as they feel like they're able to. I don't ever want anyone to have sex if they don't want to, but the truth is, the healthiest thing for your sexuality is to stay sexually active. It's incredibly good physically. It releases neurotransmitters associated with sexual desire. It's very good for the vagina. It bonds you with your partner by releasing a hormone called oxytocin.

But if sex hurts, you're not going to want to do it. Vaginal dryness can be treated with topical estrogen creams or inserts, or various lubricants. If it's truly a medically based lack of desire and not due to other medical or relationship factors, there are drugs that are approved for pre- and perimenopausal women, such as Addyi and Vyleesi.

What advice would you give women during this time in their lives?

ROWEN: Stay physically active. Cardiovascular disease, cancer risk, sleeplessness, sexual dysfunction, depression, and anxiety all improve if you move more. And not only cardio; women should build muscle mass, too, to protect their bones. You don't need to take up bodybuilding in your 60s, but resistance training is important.

GOLDMAN: Don't assume you have to suffer through symptoms or ignore how you feel and think, "This is just part of aging." Find a provider who understands perimenopause to help you figure out if your concerns are related to it.

14 Ways UCSF Is Exploring the Heart

In labs and clinics across UCSF, scientists are unraveling how to keep one of our hardest-working organs beating away.

Recently discovered dangers to heart health



Marijuana use (smoking weed) poses cardiac risks comparable to smoking tobacco. With more people across the U.S. using cannabis, more heart attacks and strokes could follow.

A single glass of wine can



quickly and significantly raise your risk for atrial fibrillation (A-fib), irregular heartbeats that can lead to blood clots, heart failure, stroke, and other heart-related problems.



A night of poor sleep might mean heart trouble in the morning. Bad sleep is tied to significantly higher odds of experiencing A-fib the following day.

Meth, opiates, and cocaine



can increase your risk of A-fib – meth by 86%, opiates by 74%, and cocaine by 61%.



E-cigarette use every day can nearly double your odds of having a heart attack.

Binge drinking



might land you in the emergency room. Booze-filled days like Super Bowl Sunday are associated with more ER visits for A-fib.



But drinking coffee is OK. It doesn't raise your risk for heart rhythm problems.



Coming soon: a fully automated, text-based AI chatbot to educate women about heart disease.



Long COVID leaves some people with a diminished capacity to exercise. The culprit? Their heart rate does not increase adequately during workouts.

Sharper detection of defects with AI

Doctors can double their accuracy in detecting most complex fetal heart defects in utero by combining routine ultrasound imaging with machine-learning computer tools.

UCSF BLOOD DISCOVERIES

Warm blood

Why can't our hearts regenerate after injury? Our earliest mammalian ancestors may have lost this ability in exchange for endothermy, or "warm-bloodedness."

Alzheimer's link

Genetics may predispose some people to both Alzheimer's disease and high levels of blood lipids such as cholesterol.

So long, salt

Cutting back on salt trumps other lifestyle changes in curbing stage 1 hypertension, the less severe of two tiers of high blood pressure.

Smart data, better hearts

The Health eHeart study – the first and biggest of its kind – is monitoring the heart health of participants online through smartphones and wearables like the Apple Watch and Fitbit devices. The data may eventually help physicians predict a heart disease diagnosis, when the disease will get worse, and what people can do to improve their heart health.



UCSF Health Celebrates Launch of the Hospital of the Future

More than 200 national, civic, business, and academic leaders gathered at Parnassus Heights on April 27 at a standing-room-only event to break ground for UCSF Health's new hospital of the future. The occasion launched construction of the \$4.3 billion UCSF Health Helen Diller Hospital, a 15-story, state-of-the-art facility that will aggregate some of the most complex care capacity in the country within one city block to serve San Francisco, the Bay Area, and beyond for coming generations.

The hospital will incorporate the latest technologies in diagnostics, robotics, and surgical procedures. Among its features will be innovative operating suites enabling more precise and personalized surgeries. Its inpatient rooms are designed to better accommodate patients and their families, and the new hospital will enable thousands more patients to access care at UCSF.

Scheduled to open in 2030 on Parnassus Avenue, UCSF Health Helen Diller Hospital is the eastern cornerstone of a comprehensive, 30-year plan to transform UCSF's flagship Parnassus Heights campus and drive innovations in care delivery, discovery, and health sciences education. The first decade of the plan will pair the new hospital with a research and academic building that is expected to open in 2028 on the western edge of the campus.

Pictured (left to right) are: UC Regent Janet Reilly; UCSF School of Medicine Dean Talmadge King, Jr.; California State Sen. Scott Wiener; UC Regent John Pérez; UC President Michael Drake; UCSF Health President and CEO Suresh Gunasekaran; UCSF Chancellor Sam Hawgood; U.S. Rep. and Speaker Emerita Nancy Pelosi; Lt. Gov. Eleni Kounalakis; San Francisco Mayor London Breed; UCSF Foundation Board Distinguished Director Jackie Safier; and UCSF Foundation Board Chair Philip Hammarskjöld.

PHOTO: SONYA YRUEL

Recommended: Books, Videos, & Podcasts



Tap Dancing on Everest: A Young Doctor's Unlikely Adventure

In this coming-of-age memoir, UCSF clinical fellow alum Mimi Zieman, MD, recounts her experience – while still in medical school – as the team doctor on a perilous climb. *New York Times* bestselling author Meg Wolitzer calls Zieman “brave, tough, and impressive when on Everest, and lively, engaging, and funny when on the page.”



How a Brain Implant and AI Gave a Woman with Paralysis Her Voice Back

UCSF scientists made international headlines when they developed a brain-computer interface that allowed a stroke survivor to speak for the first time in 18 years. Find this award-winning video, which has been viewed by millions, on UCSF's YouTube channel.



Mini Medical School for the Public

Curious about how magic mushrooms might treat depression? Or about new ways to manage back pain? Or the neuroscience of developing healthy habits? In this UCSF Osher Center podcast series, experts share the latest research on hot topics in health and science. Find it on Apple Podcasts.

Are Any Childhood Medical Myths Actually True?

Health advice doled out to children can blur the lines between reality and superstition.

By Carin Moonin

Whether it's a cautionary anecdote exchanged at the playground or advice murmured by a doting grandparent, children encounter a range of medical beliefs and misbeliefs. We asked our experts if any of this advice holds up.



MYTH # 1: Ginger ale helps a stomachache.

Got a bellyache? Think twice before reaching for a ginger ale, as you're likely opting for artificial flavor over real ginger.

"When it comes to nausea, ginger does have some benefits," says UCSF pediatrician Jason Nagata, MD '13. "But most commercial ginger ales don't contain ginger. And the ones that do are usually full of sugar, which can further upset your stomach," he adds.

"Unsweetened ginger tea might be a better option," adds Danica Cowan, MS, RD, an integrative dietitian at the UCSF Osher Center for Integrative Health.



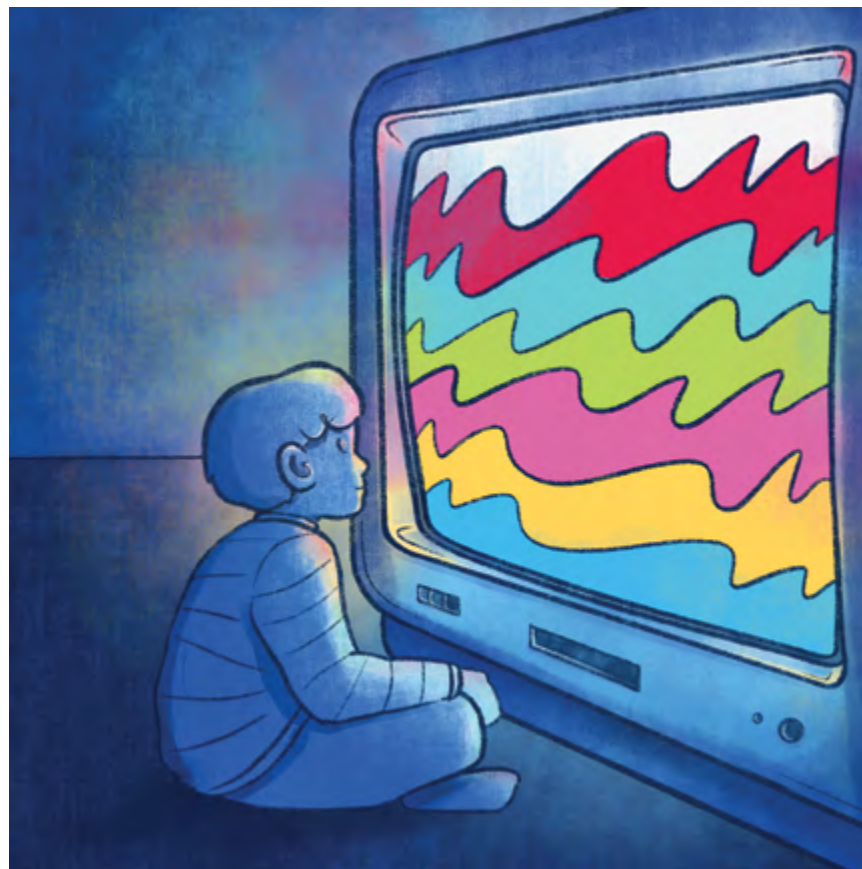
MYTH # 2: If you sit too close to the TV, you'll hurt your eyes.

Studies have shown mixed results, says Nagata. Most have concluded that watching a moderate amount of television, even at a close distance, doesn't affect vision (though if a child sits very near the TV, that might indicate an existing vision issue that should be addressed). However, too much television could lead to temporary eye strain.

The real red flag? The *indirect* effects of prolonged screen time.

"Unfortunately, during the pandemic, screen time skyrocketed. One study showed screen time doubled from about four hours a day to eight. That was just recreational screen time – not including schoolwork. If a child is in front of screens for eight hours, that's time they're not doing something else," says Nagata.

Although some screen time is unavoidable, it can offer benefits, he continues. "People can take part in online exercise classes or play video games that encourage exercise. You can use screens in a way that promotes health."



MYTH # 3: Carrots help your eyes – but if you eat too many of them, you'll turn orange.

"Carrots are a good source of vitamin A, which is a nutrient that's good for your vision," Nagata says. "And if you cut out foods in your diet that have vitamin A, that can lead to vision impairment. I remember taking care of one teenager who only ate Chicken McNuggets and wouldn't touch any fruits or vegetables. They actually did get vitamin A deficiency and had visual repercussions."

But, he adds, "although it's rare, eating too many carrots can turn your skin to an orange color, due to excess beta-carotene – a pigment found in fruits and vegetables like carrots and sweet potatoes. The condition is called carotenemia."



MYTH # 4: If you swallow gum, it stays in your stomach for seven years.

Chewed-up gum can stick to shoes, walls, or desks. Once it's stuck, it can seem immovable.

Fortunately, this doesn't apply to our insides, Nagata says.

"For most people, gum will pass easily through your stomach within 30 minutes to two hours. Gum generally does not stick to your stomach or adhere to intestinal walls. You'll excrete it out as you do other foods – about two to five days later," he explains.



MYTH # 5: Wait 30 minutes between eating and swimming.
The good news for those impatient to get back in the water: There's no medical foundation for this advice.

"I think the myth was, if you swim right after you eat, blood circulation gets diverted into your gut, and you can get tired and are more likely to drown," Nagata explains. But actually, he continues, "you're not at a higher risk of drowning or your other muscles becoming weak if your body focuses on digestion.

"That said, it may be uncomfortable to engage in exercise immediately after eating because of feeling full or bloated. But it's not dangerous," he emphasizes.



MYTH # 6: Oily food gives you acne.

This is mostly a myth – with caveats, says Nagata. "There is no strong evidence that consuming oily foods causes acne. Factors such as hormonal changes, inflammation, genetics, and bacteria are more important," he explains. "Acne tends to be an inflammatory condition. Foods high in carbohydrates or sugars could increase inflammation and subsequently exacerbate acne. However, studies linking diet to acne have reported mixed findings."

Nagata advises people concerned about acne to talk to their doctor. "There are many different treatment options available. The most effective way of getting rid of your acne is to take a medicine that's designed for it," he says.



MYTH # 7: Chicken soup cures a cold.

Your grandmother may not have picked up a carton of bone broth at the supermarket, but her suggestion of a steaming bowl of pho, ramen, or chicken soup is one age-old remedy that carries validity.

Cowan, the dietitian, says, "Soups are easy to eat and have protein and minerals – especially when you swap the noodles for extra vegetables – and the steam and warmth help congestion."

Food as medication is also among the principles of Ayurvedic medicine, one of the world's oldest whole-body healing systems. The precept stems from the belief that health and wellness are based on balancing the body and the environment, says Anand Dhruva, MD, a medical and integrative oncologist at the UCSF Osher Center.

If you have a cold with heavy mucus, you'd need the opposite qualities to promote healing – such as warming or spicy foods, he explains. "If I am starting to feel congested, I take those remedies right away. Sometimes, I find I can even avert developing a full-blown cold."

Turmeric is one of those warming spices and has been shown to have antioxidant and anti-inflammatory properties; it is an established go-to in Ayurvedic medicine. Radiation oncologist Kavita Mishra, MD '02, MPH, Osher's clinical director, recalls her mother handing her a glass of hot milk with turmeric whenever she was sick.

"Fast forward several decades, and now there is significant data around turmeric," she says. "Our ancestors knew that nature could help heal us. Our current language of medicine is helping us learn why."

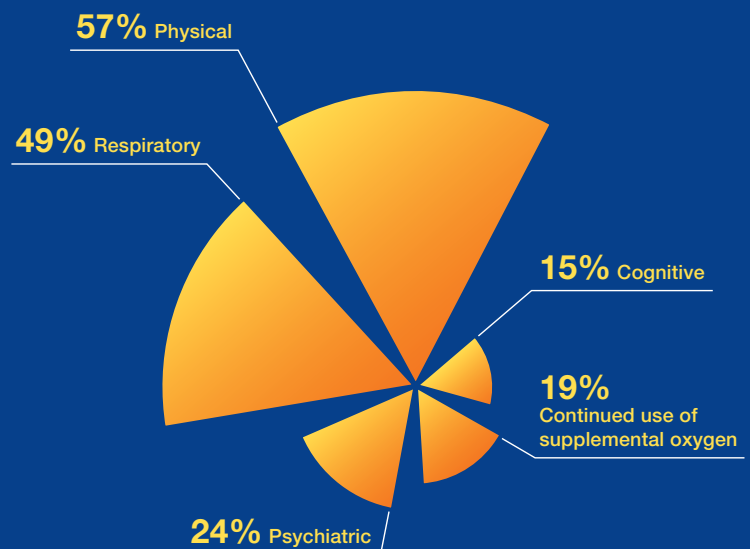
Ongoing Woes for Survivors of Severe COVID

UCSF researchers studied COVID-19 patients from across the U.S. who survived unusually long and harrowing battles with the illness and found that about two-thirds still had physical, psychiatric, or cognitive problems up to a year later.

Too sick to be discharged to a skilled nursing home or rehabilitation facility, these patients were transferred instead to special hospitals known as long-term acute care hospitals. These facilities specialize in weaning patients off ventilators and providing rehabilitation care, and they were a crucial part of the pandemic response.

"We have millions of survivors of the most severe and prolonged COVID illness globally," says the study's first author, Anil Makam, MD, MAS '13, an associate professor of medicine at UCSF. "Our study is important to understand their recovery and long-term impairments and to provide a nuanced understanding of their life-changing experience."

64% of study participants reported having a persistent impairment after one year, including:



47% had more than one type of problem

Harnessing Cancer's Strength to Combat It

Immunotherapies using engineered T cells have ushered in a new era of cancer treatment, but they have their limits. They may cause side effects or stop working, and for 90% of cancers, they don't work at all.

Now, scientists at UCSF and Northwestern Medicine may have found a way around these limitations by borrowing a few tricks from cancer itself.

By studying mutations in malignant T cells that cause lymphoma, the researchers zeroed in on a mutation that imparted exceptional potency to engineered T cells. The team inserted a gene for this unique variation into normal human T cells, which made them over 100 times more effective at killing cancer cells. This approach kept tumors in mice at bay for many months, and the cells showed no signs of becoming toxic.

While current immunotherapies work only against cancers of the blood and bone marrow, the new approach was able to kill solid tumors derived from mouse skin, lung, and stomach tissues. The team has already begun working toward testing this new approach in people.

T cells (green and yellow) in a skin carcinoma

Could a Drug Prevent Hearing Loss from Loud Music and Aging?



Human hearing can be damaged by loud noise, aging, and even certain medications, with little recourse beyond a hearing aid or a cochlear implant – until now. UCSF scientists have achieved a breakthrough in understanding what happens in the inner ear during hearing loss, laying the groundwork for preventing deafness.

The research links animal studies on hearing loss with a rare type of inherited deafness in humans. In both cases, mutations to the TMT4 gene trigger a molecular domino effect known as the unfolded protein response

(UPR), leading to the death of hair cells in the inner ear.

Intriguingly, hearing loss from loud noise exposure or drugs such as cisplatin, a common form of chemotherapy, also stems from activation of the UPR in hair cells, suggesting that the UPR may underlie various forms of deafness.

There are several drugs that block the UPR – and stop hearing loss – in laboratory animals. The new findings, according to the researchers, make a stronger case for testing these drugs in people at risk of losing their hearing.

AI Can Help Spot Early Risk Factors for Alzheimer's

UCSF scientists have found a way to predict Alzheimer's disease up to seven years before symptoms appear by analyzing patient records with machine learning.

The most influential predictors were high cholesterol and, for women, the bone-weakening disease osteoporosis. The work demonstrates the promise of using artificial intelligence (AI) to spot patterns in clinical data that can then be used to scour large genetic databases to determine what is driving risk.

"This is a first step toward using AI on routine clinical data, not only to identify risk as early as possible but also to understand the biology behind it," says the study's lead author, Alice Tang, an MD-PhD student at UCSF. "The power of this AI approach comes from identifying risk based on combinations of diseases."

Breakthroughs and Other Buzz

Tops in NIH funding:

UCSF received more funding in 2023 from the National Institutes of Health than any other public university. It's the 17th year in a row that UCSF has earned this distinction.

Sugar-gorger secrets:

Fruit bats survive, and even thrive, by eating up to twice their body weight in sugary fruit every day. UCSF scientists discovered that these critters have a genetic system that controls blood sugar without fail. They say learning from that system could lead to better insulin- or sugar-sensing therapies for human patients.

Staggering cost of vaping:

Electronic cigarette use among Americans 18 and older costs the U.S. \$15.1 billion in health care expenses each year, according to a UCSF School of Nursing report – the first of its kind to analyze the 18+ age range.

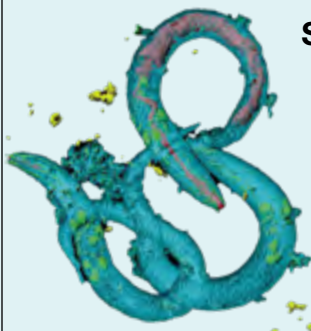
Depression's link to body temp:

People with depression have higher body temperatures, a UCSF-led study found. Stimulating self-cooling might be a novel way to treat the disorder.

Poor sleep and dementia:

Quality of sleep, not quantity, may play a part in the development of dementia decades before symptoms start. UCSF research found that adults in midlife who had fragmented sleep were more likely to show cognitive decline later in life.

Hammering prostate cancer: Combining testosterone-blocking drugs in patients whose prostate cancer has relapsed prevents the spread of the disease better than treatment with a single drug, a UCSF-led clinical trial showed.

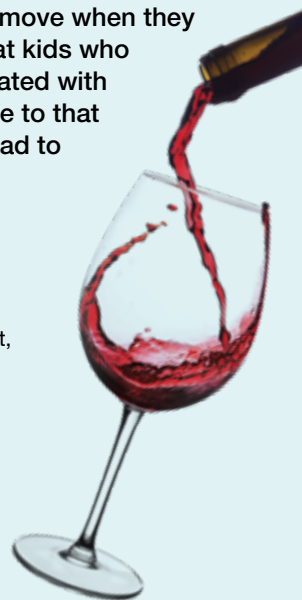


Steroid for brain health: A little-studied steroid called ADIOL, which serves as a building block for hormones like estrogen and testosterone, has been shown to enhance learning and memory. UCSF scientists made the discovery through research on *C. elegans*, a tiny worm that helps reveal fundamental biology. The finding could spur new treatments for neurodegeneration, schizophrenia, and depression.

Telehealth and abortion safety: Medication abortion, which now accounts for more than half of all abortions, can be delivered safely and effectively through telemedicine, according to a large, national UCSF study. The authors concluded that telehealth protects patients' privacy while making abortion more accessible.

Eye test for autism: UCSF scientists may have discovered a new way to test for autism by measuring how children's eyes move when they turn their heads. They found that kids who carry a variant of a gene associated with severe autism are hypersensitive to that movement. The finding could lead to earlier and faster diagnoses.

Red wine headache culprit? Ever get a head-throber after drinking red wine? A plant pigment, quercetin, might be responsible, suggests research from UCSF and UC Davis. Quercetin can block the metabolism of alcohol, resulting in the accumulation of a toxin called acetaldehyde. High levels of acetaldehyde can cause a headache, flushing, and nausea.



Future cure for pancreatic cancer?

UCSF researchers have designed a drug candidate that could help make pancreatic cancer, which is almost always fatal, a treatable, perhaps even curable, condition. The molecule modifies a wily mutation, K-Ras-G12D, that is responsible for nearly half of all pancreatic cancer cases.

Surge in liver disease:

For Latinx kids, food insecurity at age 4 almost quadruples the odds that they'll have fatty liver disease later in childhood, a UCSF-led study found. Marked by pain, fatigue, and jaundice, the disease can lead to cirrhosis, cancer, and organ failure. Latinx children and adults have a higher prevalence of fatty liver disease than white or Black people.

Ask, and flu shots flow:

Simply asking ER patients if they want a flu shot, plus providing helpful video and print messages, is enough to persuade many people to roll up their sleeves, according to UCSF-led research. This approach could lead to more underserved individuals receiving vaccines.

Long COVID clue:


SARS-CoV-2 can persist in the blood and tissue of patients for more than a year after the acute phase of the illness has ended. UCSF researchers found viral fragments in the connective tissue where immune cells are located, suggesting these pieces were causing the immune system to attack. The finding offers a clue to what might drive long COVID.



Digital Health: **Transformative Tech** or Unfulfilled Potential?

“Digital health” is an umbrella term that encompasses technologies ranging from electronic health records and telemedicine to fitness trackers and implantable medical devices. **Linda Park, PhD '13, NP**, studies how health care providers can best use such tools to boost patient outcomes. Can digital health really make individuals, and even populations, healthier?

By Christina Hernandez Sherwood



What are the biggest benefits of digital health?

Before, you were at the mercy of what your provider told you. You'd take a prescription and do your best. But digital health puts so much power in patients' hands. The benefit really happens when people want to implement healthy behaviors, whether physical activity, medication adherence, or something else.

From the provider's perspective, digital health is extremely efficient. There's health monitoring that happens on patients' cell phones and wearables, as well as more advanced technology like implantable sensors and devices. These give providers information that we wouldn't be able to get otherwise.

How are digital health tools being successfully used today?

Telemedicine now provides patients with fundamental access to health care providers. The telehealth boom is here to stay.

Here's a more complex scenario: I work in a cardiac catheterization lab at John Muir Health's Concord Medical Center. Managing patients with heart failure is very complicated. They have one of the highest hospital readmission rates. There are implantable devices for remotely measuring pressure and volume and fluid status in the heart for advanced heart failure management. These digital health tools offer different passive ways of diagnosing conditions. If the numbers are off, a nurse can call the patient and say, "Why don't you take an extra diuretic today?" We also have sensors that we implant into the chest wall to detect arrhythmias. Abnormal heart rhythms can otherwise be challenging to diagnose in real time when patients experience fleeting palpitations or pass out.

Digital devices can be as simple as blood pressure cuffs or weight scales. Those give us

important data points. Using the data, though, is the challenge. These are valuable tools, but we have to do better at integrating them into the clinical decision-making process.

What about the health data collected by our smartphones and smartwatches? Are these data points helpful to clinicians?

I've heard over and over again from patients in the clinical setting that they identified their atrial fibrillation through their smartwatch. In this context, an electrophysiologist would want to see the rhythm tracings. But it is unlikely a clinician would ask a patient for their entire record of step counts.

But providers don't yet have a way to merge all these insightful data points. Some health systems have tried to integrate data from wearables similarly to how glucometer and blood pressure data can be integrated: transmitting it directly to the electronic health record. But that's the gold standard for the future; there's no connection at this point.

Do digital health initiatives really make an impact on public health?

They can. One example that warms my heart is Text4baby, a free, national text-messaging program for people when they're pregnant. (Text4baby texts subscribers timely, reliable information and resources about maternal and child health. A randomized study found that program participants were three times as likely to believe they were prepared to be new mothers as those in a control group.) It's a positive model of what can happen with the simplest technologies. It's not this flashy mobile app. You don't even need a smartphone. Just a simple intervention has really improved things for moms and babies.

What worries you about digital health? What are the pitfalls?

Despite the investment, the potential to disseminate these technologies has not been realized. The secret sauce is being able to profit from them so health care systems will be incentivized to promote digital health.

A case in point is cardiac rehabilitation: Medicare never covered virtual home-based rehab – only facility-based rehab – until the COVID-19 public health emergency that ended in 2023. Too often, we realize the benefit of digital health but then backtrack because of reimbursement. It comes down to the payer and whether we figure out a pathway to profit. Analyzing the cost-effectiveness needs more focus. That's the only way we're going to get these products out there and get health care systems embracing them.

I also worry about access. There are millions of Americans without broadband internet, and many more in the rest of the world. That's very limiting for rural communities and minority and low-resource communities. I definitely worry about leaving people behind.

What will it take for digital health to fulfill its potential?

Providers need to be invested in the possibilities and take the time to look at the data patients bring them. It will also take smart and innovative engineering and computer modeling. Patients need to be invested in managing and engaging with the technologies we give them. And payers need to realize the benefits of digital health, like keeping people out of the hospital and achieving better communication between patients and providers. It will take a village, but I think the future is very bright.

Linda Park is an associate professor of community health systems at the UCSF School of Nursing.

THE BRAIN

How a team in a new neurology



DETECTIVES

clinic is cracking the hardest cases

By Ariel Bleicher

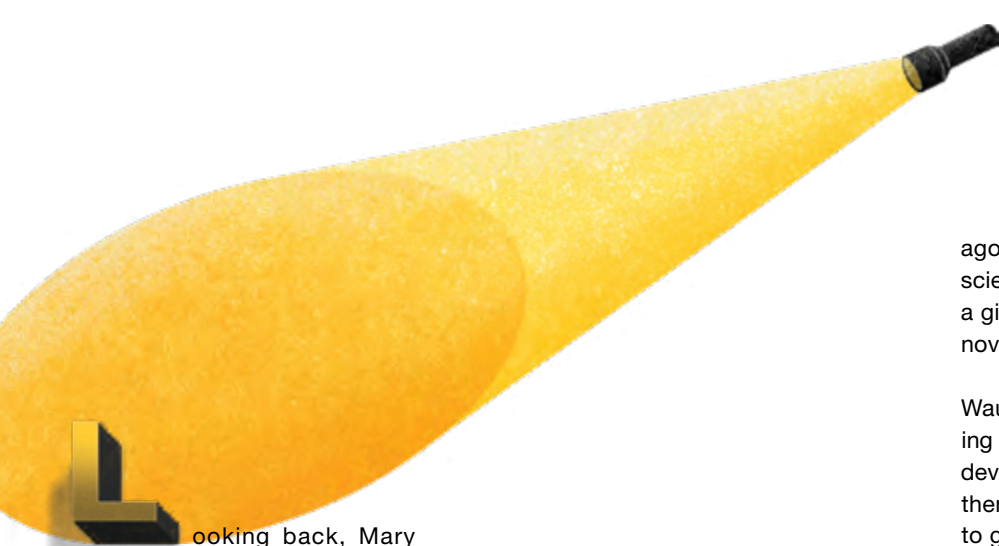
Photographs by
Elena Zhukova
and Sonya Yruel

Illustrations by
Sunnu Rebecca Choi



PHOTO: ELENA ZHUKOVA

Manetti Shrem Clinic founding director Maggie Waung (center) with nurse coordinator Jami Manning (third from left); neurologists Jessamyn Conell Price (left), Min Kang (second from left), and Alexandra Brown (right); and medical geneticist Joyce So (second from right).



Looking back, Mary suspects her symptoms started in childhood. An Air Force brat, she grew up in Oklahoma, France, Greece, and New York before settling in Northern California, where she still lives with her husband. “I was just a sick kid,” she recalls. Her muscles constantly ached and spasmed, and she had terrible allergies. “There was always something wrong with me,” she says.

Then, at 18, she injured her back in a car accident. Despite intensive therapy, the pain only worsened. It spread down to her pelvis and all the way up to her shoulders and neck. She’d get charley horses – one after another, like a bout of hiccups – that took her breath away. Meanwhile, she went on to build a career in the insurance industry and had children and grandchildren.

Decades passed, but her health troubles didn’t. Instead, they multiplied. Trouble breathing. Trouble swallowing. Trouble holding onto things. Her fingers would go numb and pinch together like lobster claws. She took painkillers. She went to a chiropractor. She got injections and had surgeries and started using an oxygen tank. “I saw every specialist you can think of,” says Mary, now 72. “Cardiologist, pulmonologist, nephrologist, neurologist... Nobody had an answer.”

Her resolve to find one would eventually lead her to UC San Francisco, which, in 2022, opened a new diagnostic clinic at the UCSF Weill Institute for Neurosciences for people with puzzling neurological symptoms. The Jan Shrem and Maria Manetti Shrem Neurology Clinic, named for the philanthropists, gets hundreds of calls a year from patients across the country hoping to finally end their diagnostic odysseys. Of the nearly 300 patients the clinic has seen so far, more than half have received a diagnosis – a remarkable rate, considering that many of them had been chasing one for years. “We see a lot of people on their second, third, or fourth opinions,” says Maggie Waung, MD, PhD, the clinic’s founding director.

Waung, who also holds one of four UCSF professorships endowed by Jan Shrem and Maria Manetti Shrem, understands such patients’

agonizing journeys better than most. She went into neuroscience because she’s always been drawn to mysteries – as a girl, she devoured Nancy Drew books and Agatha Christie novels – and the brain is one of the greatest mysteries of all.

After completing a neurology residency at UCSF in 2014, Waung joined the faculty and started a research lab studying headaches. In the years that followed, both of her parents developed rare neurological disorders. Waung didn’t know it then, but their struggles to figure out what was wrong and to get the right care – bouncing from one doctor to the next, undergoing test after test, fighting with insurers, not being believed – would mirror the experiences of dozens of patients who’d later come to her clinic.

Her parents’ illnesses and eventual deaths changed the course of Waung’s career. “With both my mom and dad, I remember just wanting someone smart to put it all together,” she says. She began feeling frustrated with the state of neurology, which, like other medical fields, was growing increasingly specialized and fast-paced; doctors were ordering more tests but spending less time with patients. “I felt like things were moving in the wrong direction,” Waung says. As a neurologist herself, she understood the urgency to accommodate the rising number of patients and knew that many cases could be resolved quickly. But she worried that the most complex cases, like her parents’, weren’t getting the scrutiny they deserved. “No one was stepping back and thinking about the big picture.”

Well then, she decided, I will.

A study in sensation

The Manetti Shrem Clinic is on the first floor of the Joan and Sanford I. Weill Neurosciences Building, a luminous glass mid-rise on UCSF’s Mission Bay campus. When I visited in January, the lobby was still dark and quiet. Patients weren’t expected to start arriving for another half hour.

I wandered down a hallway looking for Waung, who had invited me to sit in on some of that day’s appointments. Her office door was shut, but I could hear typing. I knocked softly. There was no answer, so I knocked again. After my third attempt, the door cracked open.

“Hi. Sorry,” Waung said, continuing to type, her eyes glued to the computer screen. “I just got a breakthrough on a case, so I was just messaging...” Her voice trailed off as she finished her note. I glanced around her small office. Above her desk hung a Chinese landscape painting that, she mentioned later, her father had given her. In the wintry mountain scene, bamboo trees bow under their burden of snow – a symbol of the resilient scholar who bends but does not break.

The case she was working on, it turned out, concerned a patient named Matthew. He’s 44 and teaches drama at an East Bay elementary school. He’d started accumulating “very odd symptoms” the previous April, he later told me. First, he lost some vision in one eye for about a week; not long after, he began having dizzy spells. “It usually started with

“No one was stepping back and thinking about the big picture.”

—Maggie Waung, MD, PhD

a massive headache,” he says. “The only thing that would make it better was to lie flat in the dark.” Acupuncture seemed to help, and by July he thought he was back to normal – but then he realized he couldn’t feel half his face.

He tried to get an appointment at UCSF’s regular neurology clinic but was told there wasn’t any availability for months. When I mentioned this to the chair of the neurology department, S. Andrew Josephson, MD, he was regretful but not surprised. Like most of medicine today, he says, neurology has a “huge shortage” of doctors. The situation is particularly dire in rural areas. UCSF has tried to fill the gap by expanding its clinical faculty so as to be able to help patients from well beyond the Bay Area who would otherwise “fall through the cracks,” says Josephson, the Castro Franceschi and Mitchell Distinguished Professor. But that hasn’t fixed the underlying problem, which is that demand for care is dramatically outpacing capacity everywhere.

Waung says she keeps an ear out for patients like Matthew, whose symptoms are rapidly progressing. “It’s not bad enough where they need to go to the ER, but they can’t wait three months for an appointment,” she explains. How to identify those patients, though, is a catch-22: The doctors most qualified to evaluate them and make a referral to her clinic are the same doctors who are booked up. Matthew (who, like Mary, prefers to go by his first name) ended up going to the emergency room just to get a neurology consultation quickly. “I was getting impatient,” he says.

Concerned he might have multiple sclerosis, the ER neurologist put Matthew in touch with Waung. When he met with her at the Manetti Shrem Clinic, what impressed him most was her attentiveness. “She was with me for *two hours*,” he says. “She never left the room. Every single human I’ve told that to is like, ‘What?!’”



Mary has been living with pain and other troubling symptoms for most of her life. She’s sought answers from a slew of specialists and tried all manner of treatments, to no avail. The team at the Manetti Shrem Clinic is now working to solve her case. “I really believe they’re going to figure it out,” she says.

Waung performed a lengthy physical exam – checking the fitness of Matthew’s muscles, nerves, and brain – and talked through his medical history. She then asked him a question that would crack open the case: “Has anything else ever happened to you that’s *not* in these records?” Matthew flashed back to when he was 13 and gravely sick with a “mystery case” of meningitis, a catchall for a swelling of the tissues surrounding the brain and spinal cord. The condition eventually subsided on its own, and no culprit was ever found.

Waung suspected that episode 30 years earlier was a flare-up of the same malady now rearing its head again. “It never would have crossed my mind to make that connection,” Matthew says. After a battery of tests ruled out multiple sclerosis and other more common conditions, Waung ordered an antibody screen that confirmed her hunch. The result had popped into her inbox on the morning of my visit: a positive hit for myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD),

a rare inflammatory disorder that can be managed with steroids or other immune-modulating therapies.

“It makes sense because MOGAD often presents in children,” Waung told me. Her voice, as always, was soft and measured, but she was clearly excited. “It’s one of those diseases that can be quiet for a long time.”

When Matthew learned of the diagnosis that evening, he felt mostly relief. “It had been almost nine months of not knowing what was wrong and feeling like I was crazy,” he says. “Just having reassurance that it’s something real and treatable – I didn’t know how valuable that was until I didn’t have it.”

In the genes

Soon, Waung hurried off to greet her first patient. I sat down at an empty workstation and waited for medical geneticist Joyce So, MD, PhD, a collaborator of Waung’s whom she’d arranged for me to shadow.

Once a month, So and her team of genetic specialists see Manetti Shrem patients who are suspected of having neurogenetic disorders. The service is an offshoot of UCSF’s Adult Genetics Clinic, which So was recruited from the University of Toronto to start up in 2019. Also UCSF’s Epstein Professor of Human Genetics, So believes that many neurological mysteries can be solved by genetics.

When I interviewed her later, she pointed to a 2023 study of more than 1,400 patients with unexplained neurological illnesses, which found that 10% had a genetic root. Because the study looked at only 725 genes, the real percentage is probably even higher, she argues.

I didn’t have to wait long before So swooped into a chair beside me, sweating and out of breath. “Of course today’s the day when public transit decides to go kaput,” she huffed, dumping her ID and phone, plus a stethoscope and reflex hammer, on her desk.

After she’d collected herself, I followed So and genetic counselor Sawona Biswas, MS, to back-to-back appointments. One patient, a former athlete sporting a North Face fleece, complained of burning pains in his legs and could barely walk. His condition had eluded a diagnosis for eight years.



“He’s a unicorn,” noted his sister, who had come with him.

“I’d rather not be unique in this way,” he said, despondently. He had hoped a genetic test would at least give his affliction a tangible shape. But he’d just been tested for several gene variants linked to neuromuscular diseases, and nothing had come of it.

So says that patients often think DNA testing will provide an easy “yes” or “no”: You either have a bad mutation or you don’t. In reality, genetic analysis is complex. Experts customarily test for between one and 1,000 or so mutations at a time, and the type of test they order



Neurologist Maggie Waung (right) launched the Manetti Shrem Clinic after seeing both her parents, who developed rare neurological disorders, struggle to get diagnosed. She often collaborates with medical geneticist Joyce So (left) to crack cases. So believes that many brain mysteries can be solved by genetics.



depends on the suspected diagnosis, she explains. For that reason, patients who have many seemingly unrelated symptoms or who develop new symptoms over time can be sent down testing rabbit holes. Zeroing in on the miscreant code – if it even exists – frequently takes years.

More comprehensive tests, like whole exome or genome sequencing, could shorten this

diagnostic quest by offering a “one-stop shop” for millions of gene variants, So says. But to her eternal frustration, most insurers refuse to pay for *any* neurogenetic testing for adults, and so most patients opt for cheaper one-offs, if they can afford them at all. “Coming from Canada, I was so naive,” she says. “I was telling patients, ‘I’m sure we can get you covered because we need it for a diagnosis.’ Boy, was I wrong.”

Medicare and Medi-Cal, she quickly learned, often cover genetic tests only for cancers or in kids, “which is ridiculous,” she says. “As for the commercial policies, they’re all over the map. Some of them explicitly state that the reason for denial is that there’s no evidence for the utility of testing in adult populations.” Fed up, she decided to gather that evidence herself and teamed up with Waung to recruit patients from the Manetti Shrem Clinic for a study that’s now underway.

Examining the athlete, So observed a “pattern of muscle weakness in the lower extremities” and “very active reflexes.” His chart also noted bladder and bowel issues. “When we put all that together, I wondered about adult polyglucosan body disease,” So said. She prescribed a test for another dozen or so genes. If that, too, led to a dead end, then they could “look at rarer things,” she told him.

“Sometimes it’s a quick road, but sometimes it takes longer,” she said.

Plot twist

Then there was Mary. She and her husband had driven five hours early that morning from their home in the Sierra foothills to get to the clinic. Seated beside him in the exam room, she wore a billowy flowered dress and nail polish in various shades of blue.

For most of her adult life, Mary had chalked up her bad back and other baffling symptoms to the car accident she was in as a teenager. Then one day, about 20 years ago, a cousin casually mentioned that he and his children had been diagnosed with myotonic dystrophy, a rare heritable disease that causes the muscles to slowly waste away.

At first, Mary didn’t think much of it. But over the years, as more family members came forward with the same diagnosis, she grew convinced she must have the disease, too, and decided to get tested. “I needed to know if I could have passed it on to my grandchildren,” she told me.

Genetic disorders, So says, usually have telltale flags, including atypical onset, progressive or unrelenting symptoms, complications involving multiple body systems, and a family history. But many doctors don’t know to look for those patterns. “On one end of the spectrum, physicians will see a patient with neurological issues that develop over decades and not have even a lick of suspicion that there could be a genetic basis,” she says. “On the other end, there’s over-suspicion, where people try to ascribe everything to genetics.”

Mary’s case ticked all the boxes. Plus, she had the luck of already knowing her relatives’ mutation. For So, that was the obvious place to start. The week before Mary’s appointment, however, her test for myotonic dystrophy had come back negative.

“I truly was shocked,” Mary says.

So was too. “I have to tell you, this is a real puzzle,” she said to Mary in the exam room. In fact, she and Biswas, the genetic counselor, had been so certain the result was a mistake that Biswas had persuaded the lab to rerun her blood sample, but no dice.

Still, So knows genetic diseases can be tricky. The same mutation, for instance, can cause vastly different symptoms: For example, mutations in the SCN2A gene, which So herself has studied, can variably give rise to seizures, coordination disorders, intellectual disability,



autism, and schizophrenia. Conversely, syndromes that look like the same disorder can stem from different underlying mutations, even within the same family. “We see families with multiple genetic disorders all the time,” So told me. Perhaps Mary was another unicorn.

Before investigating other suspect genes, though, So wanted to send a new sample to a different lab to see if it might catch something the first lab had missed. In the meantime, she advised Mary to see Waung, who could test her muscle fibers for other clues.

“We’ll get to the bottom of this one way or another,” she promised.

How cases are cracked

When Waung and her colleagues were planning the clinic, they’d assumed that most cases would be like Mary’s – peculiar plights that would demand a Sherlock Holmes-level of deductive ingenuity. “Going in, we suspected they were all going to be these very complex, rare conditions,” Josephson says. “There’s a lot of those, but there’s also a lot of patients who, it turns out, have very common neurological diagnoses.”

Why they weren’t easily identified elsewhere, Josephson believes,

comes back to the widespread deficit of neurologists as well as a lack of proficiency among medical providers generally in assessing neurological problems. “Neurology is one of those fields that non-neurologists find particularly mystifying,” he says.

Jessamyn Conell-Price, MD ’15, MS, one of the clinic’s neurologists, says that about 30% of her cases end up being “just an atypical presentation of things I know well.” Many, for instance, have been unusual forms of Parkinson’s. While the disease is most easily recognized by tremors, subtler signs can include bad constipation and frequent fainting. Previous diagnoses and treatments can also be confounding, Conell-Price says.

“You have to tease out the side effects and complications from other diseases that might be obscuring the picture.”

Sometimes, the clinic’s neurologists work out what’s wrong with a patient before even seeing them. “We spend a long time going over the history and prior workups,” says Min Kang, MD, who specializes in neuromuscular diseases. These records, which the clinic’s administrative staff meticulously compile, often span decades and multiple institutions. Their comprehensiveness, Kang says, is extraordinary. Referrals to her general practice, by comparison, can be laughably cryptic – merely “back pain,” for example – in which case she must fill in the backstory herself and redo tests she can’t easily track down. “It’s a dream to have all the pieces already assembled for you,” she says.

Other times, the key to unlocking a difficult diagnosis is simply a detailed physical evaluation, says Alexandra Brown, MD, another staff neurologist and the medical director of outpatient neurology at Zuckerberg San Francisco General Hospital. “Neurology is the only medical specialty where we examine literally head to toe.” Done well, she says, this takes 20 minutes or more – time that doctors today rarely have. “It’s an art that, sadly, medicine is losing.”

When I spoke with her in January, Brown, who holds another of the Manetti Shrem Professorships, had just resolved a case that proved her point. Eric Zhang, a 59-year-old grocery clerk in San Mateo who’d had a series of falls, had been searching for an explanation unsuccessfully for two years. One doctor had suspected Parkinson’s. Another guessed multiple sclerosis. Yet another wondered if he’d inherited a rare spastic disorder.

“He’d gotten the million-dollar workup,” Brown says. “But at the end of the day, all he really needed was for someone to do a thorough



neurological exam.” Tapping and pricking and inspecting every inch of his body, she detected a subtle change in sensation within a narrow strip of skin that extended all around his upper chest and back. This meant something was probably compressing his spinal cord at that level. “Most neurologists doing a cursory exam would have easily missed it,” she says. Sure enough, an MRI scan revealed a mass, which a surgeon removed.

“I feel pretty good,” Zhang told me five weeks after the surgery. “In the afternoons, I go outside and take a walk and do some exercises” – activities he hadn’t been able to enjoy for years. “Dr. Brown is an excellent doctor,” he wanted me to know. “She found the root cause of my condition after so many others couldn’t.”

“He’d gotten the million-dollar workup, but at the end of the day, all he really needed was for someone to do a thorough neurological exam.”

—Alexandra Brown, MD

The long game

Before I left the clinic, Waung told me about one last case, which she was preparing to present at an upcoming neurology conference.

About a year ago, a Bay Area couple named Maureen and David Costello had brought in their adult son, Daniel, who lives with them. As a child, Daniel had been slow to walk and never learned to speak beyond simple phrases. He had a knack for math but struggled with attention and spatial reasoning. Occasionally he’d explode in rage, though he was otherwise sweet and kind. Despite years of evaluations by countless doctors, nobody could tell them what troubled their son. “I really thought we would never have an answer,” Maureen told me later.

Surmising a rare genetic disorder, Waung offered to enroll Daniel in the study she’s doing with So. This would allow their research team to parse his entire genome for suspicious DNA changes, including lesser-known ones, as the study would take care of the testing costs, which Daniel’s insurance wouldn’t cover.

When the team reviewed the data, one result stood out: a “variant of unknown significance” in the SATB2 gene. Several mutations in this gene are associated with Glass syndrome, which causes symptoms like Daniel’s. But this mutation was a new clinical discovery. It was also new to his family – neither parent had it.

The Costellos got the diagnosis last August, on Daniel’s 31st birthday. “To be able to pinpoint this as what he has, and it just pertains to him – it was just a huge relief,” David says. At the time, their daughter was eight months pregnant. They didn’t have to worry whether their grandchild might have inherited the disease.

What Waung likes about this case is that it shows the value of persistence. Even when doctors “take a deep dive into a case and try to leave no stone unturned,” she says, they often will abandon it when

they don’t find anything. But patients’ stories are constantly evolving, and science is constantly revealing new stones to turn over. When Daniel was growing up, the tools and knowledge to identify his mutation didn’t yet exist. If the Costellos hadn’t kept up the search for 31 years, who would have?

Once a year, Waung and her staff review the clinic’s unsolved cases to see if a new discovery or test might lead to a new break. Although many patients still don’t have a definitive diagnosis, Waung thinks they shouldn’t have to continue on their odysseys alone. “The whole idea is that we’re going to keep looking,” she says.

When I last heard from Mary, she was still optimistic about her own case, despite its stubborn perplexity. A second myotonic dystrophy test had also come back negative, and Waung’s assessment of her muscles confirmed no electrical signature of the disease. Waung had recommended she repeat the muscle exam in a few months and referred her for an MRI to look for marks of nerve damage and autoimmune disease.

I thought Mary would be discouraged, but she wasn’t. “It wasn’t like, ‘Oh, this test was negative – sorry, there’s nothing we can do for you,’” she says of Waung and her colleagues. “I really believe they’re going to figure it out.”

ARE THE NEW *WEIGHT LOSS* DRUGS TOO GOOD TO BE TRUE?

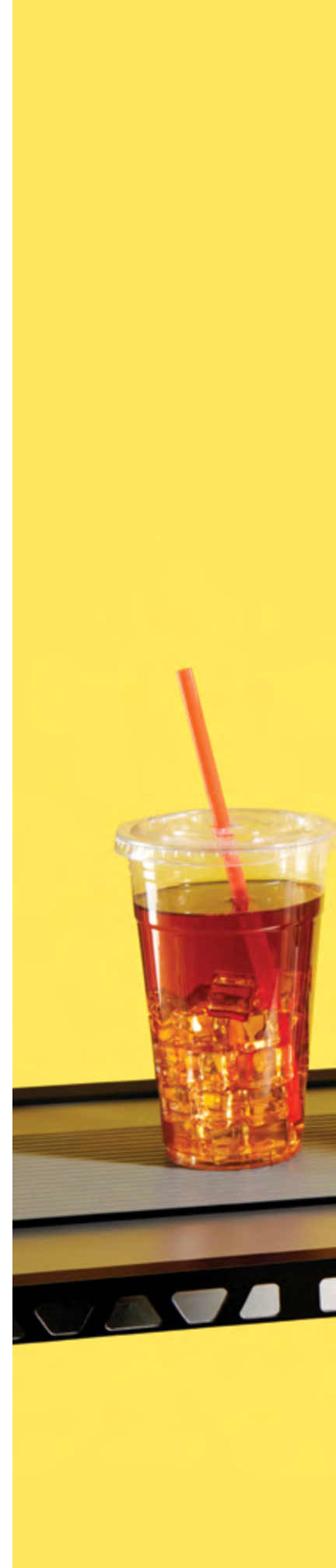
Whether you view the latest weight loss drugs as a miracle or a menace, the hype around them is impossible to ignore. Ozempic seized the spotlight first; a weekly injection intended to treat diabetes, it was quickly repurposed by people trying to trim down. Then came Wegovy, a high-dose version officially marketed as an obesity treatment. The drugs have proven so popular that the market value of the Danish company behind them recently exceeded the entire economy of Denmark. In November, Eli Lilly's Zepbound joined their ranks.

The medications have inspired a lot of hope but also intense debate. Do they deepen our bias against fat and make life more miserable – draining patients not just of money but also dignity and joy? Or are they the cure that people with obesity – roughly 40% of American adults – have been waiting for? Before you make up your mind, consider what UCSF experts have to say about the new wave of weight loss drugs.

The real answer isn't "yes" or "no." Here are six things you need to know.

By Elizabeth Daube

Conceptual photograph by David Arky





PROF STYLIST: KELLIE MURPHY

1

So far, they seem much better than the get-thin-fast drugs of yore.

The history of weight loss medication is littered with drugs that seemed like impressive, easy solutions – at first. Chemist Derek Lowe, PhD, summarized the decades-long quest to find a cure for obesity as, “for the most part, a bottomless pit into which people shove money and time.” The demand for this kind of drug is overwhelming, according to Suneil Koliwad, MD, PhD, UCSF’s chief of endocrinology and metabolism and an expert in diabetes and obesity.

“This can lead to less scrutiny and caution after a weight loss drug gets initial approval from the U.S. Food and Drug Administration,” Koliwad says. “There used to be fen-phen billboards, remember? Then five to 10 years later, we started seeing vascular and cardiac issues. They just needed time to manifest.”

Fen-phen, a combination of fenfluramine and phentermine, was a popular diet drug in the '90s. But it's far from the only pharmaceutical failure. For example, amphetamines were once widely prescribed for weight loss, until they were linked to high blood pressure, heart complications, anxiety, and aggression. Did we mention amphetamines – street name “speed” – are addictive?

So there's good reason for skepticism. But Koliwad – who holds UCSF's Grodsky/JAB and Woeber-Mount Zion Distinguished Professorships – says the latest treatments really might be the solution some patients have been hoping for. The drugs work by mimicking a hormone called glucagon-like peptide-1 (GLP-1), which curbs hunger. GLP-1 also slows down the movement of food from the stomach to the small intestine – hence a feeling of fullness – and increases insulin production, lowering blood sugar. Patients with diabetes have been taking older versions of GLP-1 agonists for almost 20 years.

The drugs work by mimicking a hormone called glucagon-like peptide-1 (GLP-1), which curbs hunger.

The gist? GLP-1 drugs make you eat less. Over time, obese patients lose roughly 12% of their body weight on Wegovy (semaglutide) and about 18% on Zepbound (tirzepatide, which targets GLP-1 and another gut hormone, GIP.) Diana Thiara, MD, medical director of the UCSF Weight Management Program, says the results can be “amazing and life-changing” for people with obesity, a condition linked to a host of health risks.

Recent studies have shown that semaglutide also helps people with obesity lower their high blood pres-

sure and reduce their odds of heart attacks or strokes. Michelle Albert, MD, MPH, UCSF's Haas-Stern Professor of Cardiology and past president of the American Heart Association, says it's unclear exactly how semaglutide prevents heart attacks and strokes, and it's uncertain whether the drug has a similar impact on patients who don't have heart disease already. Still, she's excited about the news.

“It's a big deal because cardiovascular disease is the number-one killer globally,” Albert says.

Early evidence suggests the drugs might also improve depression and substance abuse disorders. Because the drugs seem to dampen inflammation in the brain, they're now being studied as a possible way to prevent neurological diseases like Parkinson's and Alzheimer's, too.

2

They come with risks that we're still learning about.

The potential side effects of GLP-1 drugs are no fun: nausea, vomiting, fatigue, diarrhea, constipation. Most patients nudge up to the recommended dose, slowly adjusting to the drugs to minimize discomfort. Thiara, who is also an assistant professor of clinical medicine, says some patients stick to a lower dose because they can't tolerate more GLP-1 medication, which is fine. What she worries about are the patients who feel pressure to power through.

“We're living in a world that values thinness so much,” she says. “There are patients watching GLP-1 TikTok videos and thinking vomiting and extreme nausea are normal, and they're not.”

Albert agrees that the side effects, while mild or temporary for many, can't be underestimated. Some people find the drugs unbearable.

“Someone I know was put on semaglutide,” says Albert. “They’re older, and they became severely dehydrated and experienced an exacerbation of their atrial fibrillation [irregular heart rhythm]. They went off the drug. It might have helped with their diabetes and weight loss. But as people age, they’re thinking not just about quantity but also quality of life.”

For others, GLP-1 agonists can slow digestion to a problematic degree. Patients have sued the drugmakers after developing dangerous conditions, such as stomach paralysis and bowel obstructions. Koliwad says these complications are incredibly rare, but it’s important for patients to know they’re a possibility.

“The stomach contents are retained sometimes for days on GLP-1s,” Koliwad says. “People facing surgery have fasted for 24 hours so they can safely get anesthesia. And physicians find there’s still food in their stomachs.”

Thiara also says the risks of taking GLP-1 medication during pregnancy haven’t received nearly enough attention, given that the majority of patients on the drugs are women.

“We’re living in a world that values thinness so much. There are patients watching GLP-1 TikTok videos and thinking vomiting and extreme nausea are normal, and they’re not.”

– Diana Thiara, MD



They’re not meant for everyone. People have figured out how to get the drugs anyway.

The new weight loss medications are approved by the Food and Drug Administration (FDA) only for obesity, which the agency defines as a body mass index of 30 or greater. The FDA makes exceptions for patients who don’t quite meet that threshold but have a related condition, like high blood pressure. Insurers tend to have similar criteria. Of course, that doesn’t stop providers from writing “off-label” prescriptions for people willing to pay out of pocket for them.

“There are different reasons why people want to lose weight,” Koliwad says. “One is that, medically, the weight loss will allow them to be healthier. But depending on the individual, the most powerful reason might be cosmetic.”

The soaring demand for GLP-1s has created shortages across the country. In response, semaglutide and tirzepatide were added to the FDA Drug Shortages Database,

“There are different reasons why people want to lose weight... But depending on the individual, the most powerful reason might be cosmetic.”

– Suneil Koliwad, MD, PhD

allowing compounding pharmacies to produce generic versions. In turn, telehealth companies began selling the drugs at prices far lower than the average \$1,300 per month paid for brand-name GLP-1s.

New Yorker writer Jia Tolentino – who wears a size 4 – documented her experiment buying the drugs on a telehealth site. It cost her just \$250 for a three-month supply: “I expected to be caught out during the Zoom appointment that I assumed was coming. Instead, a nurse practitioner named Nicole sent me a direct message laced with cheerful emojis.... I asked if she would help me manage the side effects but got no reply.”

Koliwad and Thiara are both concerned that telehealth companies rarely provide meaningful medical supervision for patients prescribed GLP-1s. In this common scenario, people are injecting the drugs at home and hoping for the best.

“We see a lot of them having problems with side effects. They show up in the emergency room or urgent care or come to specialists like me,” Koliwad says. “We have to undo problems that they have from medicines that they got in random ways.”

It’s unlikely the drugs will stay on the FDA’s shortage list forever. Eventually, the supply and demand should stabilize. When the new GLP-1 drugs come off the list, compounding pharmacies are supposed to stop selling semaglutide and tirzepatide, which will send many off-label patients scrambling for affordable medication. Some are already shifting to older, less expensive GLP-1 agonists.

The people who need weight loss medication the most are still having trouble getting it.

The shortages have made it difficult for some people to get GLP-1 agonists – even those with health insurance coverage for the drugs. Thiara says patients had to track down doses at far-away pharmacies last year, sometimes driving hours to retrieve a prescription.

“We still have delays, and lots of people do give up,” says Thiara, who is planning a study about health disparities in accessing GLP-1s for weight loss.

Shortages aside, many insurers still won’t pay for GLP-1 agonists unless the patient has been diagnosed with diabetes or cardiovascular disease. A 2003 law currently prohibits Medicare from covering drugs for weight loss alone. Meanwhile, states get to decide whether to cover the drugs under Medicaid. The net result? A lot of people struggling with obesity can’t afford the most effective treatment. Obesity rates are highest among Black and Latinx adults, people in rural areas, and people with low incomes.

“The populations that would benefit most haven’t even been included in the trials in significant numbers,” Albert says. “They often can’t get the drugs now because they’re expensive. And the injection alone is not a solution. It has to be partnered with lifestyle changes.”

To be clear, eating a lot less does drop the numbers on the scale. But exercise is still important – for your heart, bones, brain, and more. And the nutritional quality of your food matters, not just the quantity. Talya Kurzion, MS, RD, a clinical dietitian with UCSF Health, says patients taking GLP-1s should prioritize fruits and vegetables; whole grains; lean protein; and the healthy fats found in olive oil, nuts, and seeds.

Of course, it’s tough to put all that advice into practice. For people with low incomes – many juggling multiple jobs, caring for young children or elderly relatives, or living in areas where fresh produce is hard to come by – the hurdles are much higher.

“The time and effort component of cooking healthy meals is a big barrier,” Kurzion says. “Still, these medications do offer meaningful help. People taking them have fewer cravings. They don’t feel the calling for fast food so much.”

Legislative efforts to expand insurance coverage for GLP-1 medications are already underway. Even if those initiatives fail, the cost of the blockbuster weight loss medications is expected to come down in the future. Additional GLP-1s might enter the market in a few years. Several contenders are already in development, as pharmaceutical companies race to find better drugs for weight loss. For example, AstraZeneca recently spent \$2 billion to license an experimental pill that might have fewer side effects than the injectable treatments.

“These medications do offer meaningful help. People taking them have fewer cravings. They don’t feel the calling for fast food so much.”
– Talya Kurzion, MS, RD

GLP-1 weight loss might not look – or feel – the way you expect.

While the health benefits of GLP-1s have gotten plenty of press, their potential to help people transform themselves aesthetically has received even more attention. Until recently, it only took typing “oze” into Instagram for the suggestion “ozempick [sic] before and afters” to pop up. With it came countless makeover images – primarily of women – and tips on how to deal with “Ozempic face” (shorthand for the bitter realization that a skinnier face sometimes reveals one’s advancing age).

In short: A lot of people taking GLP-1s want to look better, and they’re toting around hopes that might not match reality. Despite setting expectations before patients start GLP-1s, Thiara says many still believe the drugs will enable them to reach their ideal weight.

“People who’ve been on Wegovy for a year or so will come to me and say, ‘Well, now I’m plateauing. What else can we do?’” Thiara says. “I’ve had this conversation like seven times in the last week. A 12% drop in body weight falls within the average. But for some people, there’s this idea of how they want to look. They’re disappointed.”

Online, speculation runs wild on what the rise of GLP-1s will mean for American culture and, in turn, our mental health. Are we devolving to a ’90s-era obsession with thinness? Will the drugs destroy the movement for body acceptance?

Jason Nagata, MD ’13, an eating-disorders expert and associate professor of pediatrics, says social pressure to look thin never really went away. Studies of teenage girls across the U.S. suggest that two out of three are trying to lose weight. For adolescent boys, the results are more complex – with a third wanting to lose weight and another third hoping to bulk up with muscle. Nagata is concerned that some people taking GLP-1s might fixate on weight loss at any cost.

“Eating disorders affect people of all sizes,” Nagata says. “We have often seen people considered overweight or obese who start with a weight loss journey that is well

intentioned. Then it becomes an obsession and gets out of control. They can lose such a significant amount of weight in such a short period of time that they develop complications from starvation and have to be hospitalized.”

Nagata suggests that patients taking GLP-1s check in regularly with a physician or nutritionist who can monitor their progress and flag unhealthy behaviors. Thiara and Koliwad, who both prescribe GLP-1s, do this. Part of what they look for is too-rapid weight loss – which, in addition to straining vital body functions, can accelerate muscle loss. Thiara’s clinic also offers counseling. Dropping a lot of weight can stir up unexpected psychological challenges.

“You can see some people mourning their previous selves,” Thiara says. “A patient told me, ‘People used to be so mean in public.’ Now, they’ve lost weight and society is treating them better. But they’re struggling with it.”

For example, when writer Elna Baker lost 110 pounds, she got a lot of attention and affirmation – but it felt flimsy. Her story on the podcast *This American Life* unpacked the questions that haunted her long after the dramatic makeover was complete. Did her new partner like *her*, or did he just like her new body? She still longed to be loved exactly as she was, fat or not.

“Eating disorders affect people of all sizes.”

– Jason Nagata, MD ’13



how many people relax, celebrate, socialize. For example, Thiara described a patient who asked if she could stop her medication for a week or two; she wanted to enjoy decadent meals and drinks during a birthday trip. Taking a break is OK, Thiara says. But if you stay off the drug, expect cravings to return with full force.

In the future, Koliwad thinks it’s possible that many people might use GLP-1s for a time, adjust their eating and exercise habits, then maintain their new weight with an “off ramp” of coaching or other support. He anticipates studies pairing GLP-1 medication with lifestyle modification programs.

“Maybe five years after they stop taking the drug, people would need another two-year course to sustain the effects,” Koliwad says. “But that would still be a lot cheaper than taking it for their whole life.”

Thiara isn’t so optimistic. Researchers have been investigating and tweaking exercise and diet interventions for many years. Obesity has surged anyway. About a decade ago, adult obesity rates of 35% were unheard of in the U.S. A couple of years ago, 22 states exceeded that rate.

“We can’t put someone on GLP-1s for only two years and expect them to maintain,” Thiara says. “We know that doesn’t work.”

The factors fueling excess weight are complex: social, environmental, genetic. But big picture, biologically, humans evolved in scarcity. If our ancestors’ brains didn’t urge them to eat – ravenously, whenever an opportunity arose – they probably didn’t live long enough to pass along their genes. For many Americans today, food is abundant and cheap. But it’s still wildly difficult for most of us to walk away from, say, a warm cookie or a juicy cheeseburger. Some research suggests that common, highly processed foods – packed with sugar, fats, and other potentially harmful ingredients – might be almost as addictive as cocaine.

“We live in a food environment that is constantly pressuring people to make indulgent decisions,” Thiara says. “On top of that, genetics predispose some people to having excess weight.”

GLP-1 medications have the potential to usher in much-needed nuance in how Americans understand obesity. Some believe that conversation – even amid the endless ads and op-eds and Instagram “before and afters” – is already happening.

“We’ve shifted away from attributing the problem to individual willpower,” Koliwad says. “For decades, we didn’t emphasize that. People thought that failures to lose weight were their fault when the game was rigged against them. Now the question is, how do we create a more even playing field?”

Once you start taking GLP-1s, the drugmakers suggest you stay on them. Forever.

The downsides of GLP-1 medication might not seem so daunting if you only took it temporarily. Unfortunately, the existing studies are clear: People who go off the drugs eventually regain much of their lost weight. Still, insurers and many patients remain eager to define an end point for the treatment.

“The most common question patients ask me is, ‘When can I stop it?’” says Koliwad. Even patients who tolerate GLP-1 treatment just fine don’t necessarily *enjoy* the medication’s effects. Indulgence is, for better or worse,

“We live in a food environment that is constantly pressuring people to make indulgent decisions.”

– Diana Thiara, MD



Genetic Testing Is the Key to Our Health Secrets

Our genome may one day serve as a passport guiding our health care – from cradle to grave.

By Jaimie Seaton
Illustrations by Keith Negley





Erin Fusco loves to visit Disneyland. She's had an annual pass since she was 18 years old and has visited hundreds of times. But there was a stretch when her regular trips to the happiest place on earth were put on hold. When Fusco, now 37, was in her 20s, she was living in the Bay Area with her boyfriend, Adam, and working as an artist in the video game industry while running her own design business.

Life was good.

But when she was 27, Fusco started experiencing symptoms that seemed abnormal, such as acute stomach pain after eating; severe nausea after one glass of wine; and floating, white stools. Something felt off, but the doctors she consulted told her not to worry.

In 2018, at age 31, Fusco finally found a doctor who took her symptoms seriously and ran a series of tests, culminating in an MRI the following year. The image showed a mass on her pancreas. It would have to be biopsied, and Fusco's doctor sent her to UC San Francisco for the procedure.

As Fusco was waking up at UCSF Medical Center, Barry Tong, MS, MPH, a genetic counselor with the UCSF Cancer Genetics and Prevention Program, was standing next to her bed with Adam, who was by then her husband, and her parents. Tong was there to talk with Fusco about genetic testing, which he said needed to be done immediately. The testing could disclose if she had a genetic mutation that could impact her treatment.

The biopsy revealed that Fusco had pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, which has an average five-year survival rate of 12%.

"The second the surgeons confirmed that it was pancreatic cancer, they messaged the oncology team, who then messaged us to say, 'Hey, we need genetic testing as fast as possible,'" recalls Tong. "So her blood was drawn while she was in the recovery room. I got consent from her partner and her parents, and I literally walked the sample down the street to a genetic testing lab five blocks away."

Genetic testing was required to meet national guidelines and, due to Fusco's young age, to rule out a genetic mutation as the cause of her cancer. Fusco was on board with the testing from the moment she was fully awake and discussing it with Tong.

"I was actually really excited to participate in [the genetic testing] and see if [it was] going to make a difference in my treatment," Fusco says.

Uncovering the mysteries in our genes

At its most basic, genetic testing looks for changes – referred to as variants or mutations – in a person's DNA that may affect their health, but that simple definition belies the far-reaching and extraordinary impact such testing has on health care and health outcomes. It's almost a magic key that can unlock the body's secrets. Genetic test-

ing, which is typically done on blood or saliva, can alert individuals to hidden health risks – knowledge that can help patients make better-informed decisions and that can guide clinicians as to what treatment approaches and medications will be most effective – and we are still in the early days of this medical revolution.

"Genetic testing can be integrated into every aspect of health care, from preconception through senescence," explains Aleks Rajkovic, MD, PhD, chief genomics officer at UCSF and a Lindsay Professor of Experimental Pathology. While genetic testing already plays a pivotal role in diagnostics, Rajkovic says, "we are definitely in the early stages of taking an individual's genome into account and using it to make preventive decisions about their health needs."

Rajkovic says the cost of such testing has dramatically decreased over the years and now ranges from a few hundred to a few thousand dollars, depending on the depth and breadth of the analysis. Insurance coverage varies widely, though, which is a barrier to large-scale genetic testing.

Additionally, genetic testing is more likely to be available at academic medical centers like UCSF than at smaller or rural facilities.

Genetic testing can be beneficial across the entire life span, beginning even before conception. Many people choose to have carrier screening done before they become pregnant or during pregnancy to learn whether they carry a genetic mutation for hereditary diseases such as cystic fibrosis or

spinal muscular atrophy. If both parents are carriers of the same genetic disease, there's a 25% chance that their children will have the disorder.

Next comes genetic screening and diagnostic testing, which is available to anyone who is pregnant. These tests look for inherited disorders and chromosomal abnormalities in the fetus that can cause diseases such as Down syndrome. In the past, prenatal testing was often associated with finding out the health status of a fetus in order to decide whether to terminate a pregnancy, but innovations in neonatal care – including gene therapies, stem cell transplantation, and intrauterine surgery – give parents today a far larger range of options, says Mary Norton, MD, the Thorburn Professor of Perinatal Medicine and Genetics at UCSF's Prenatal Diagnostic Center.

Newborn screening is now standard for certain genetic, endocrine, and metabolic disorders, as well as for hearing loss and serious congenital heart defects. However, in critically ill babies for whom current testing can't yield a diagnosis, rapid whole-genome sequencing is becoming the standard of care at UCSF and other academic medical centers, Rajkovic says. UCSF Health is the only system in Northern California to provide this test for both fetal and newborn patients.

"Genetic testing can be integrated into every aspect of health care, from preconception through senescence."

– Aleks Rajkovic, MD, PhD

Then, throughout our lives, predictive and presymptomatic testing can be used to determine whether we are predisposed to certain hereditary conditions – like cardiovascular disease, diabetes, or cancer, as well as genetic abnormalities – and to diagnose adult-onset genetic conditions like heart disease or diabetes.

Joyce So, MD, PhD, UCSF's Epstein Professor of Human Genetics, points out that the availability and types of genetic testing have changed significantly over the lifetimes of today's adults. "Even if they were seen as a child for something that was thought to be genetic," she says, "if they didn't have a diagnosis and they came back now for genetic evaluation, there's a much higher likelihood that we would find a diagnosis because the testing has changed so much over the last 15 to 20 years."

So works in psychiatric genetics, looking at the impact of rare genetic conditions on psychiatric and neurogenetic patients: that is, patients who appear to have a primary psychiatric condition but actually have an underlying genetic condition (such as DiGeorge syndrome or porphyria) that's causing their psychiatric symptoms.

The effectiveness of many drugs, including psychiatric drugs, depends on our underlying genetic makeup. That's where the field of pharmacogenetics – which screens patients for adverse reactions to certain drugs, as well as for differences in how they metabolize drugs, to guide prescribing and dosing recommendations – comes in. UCSF is the first hospital system in California and one of the first in the country to provide drug-gene testing. This is fast becoming a crucial part of health care, because adverse drug reactions are the fourth-leading cause of death in the U.S.

Tumor testing is another kind of common genetic testing. It's done with certain cancers to aid in diagnosis; identify variants susceptible to drugs; predict progression, recurrence, and metastasis; and guide oncology treatments and therapeutics.

A guide on our genetic journey

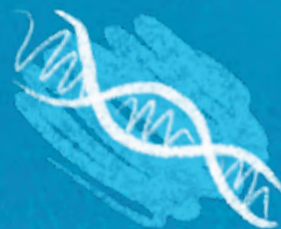
Fusco says she didn't know much about genetic testing – or genetic counseling – before Tong spoke with her in the recovery room. She had heard of the BRCA mutation, which is often associated with breast cancer, but "until I got the testing, I wasn't really aware of it impacting my life at all."

Norton explains that "genetic counseling is really an opportunity for patients to find out more about genetic testing before deciding whether or not to have it done."

The purpose of genetic counseling is multifold, Tong says. One is gathering information about the patient's personal and family history, determining the likelihood of a hereditary predisposition or hereditary risk of disease, and looking at the guidelines to determine whether genetic testing is appropriate.

"The counseling side of [genetic testing] in the pretest setting is talking with the patient about what the testing entails, what you learn, what you don't learn, what the risks and benefits are, and helping the patient come to a decision whether or not they want to do the genetic testing – making an informed decision about it," Tong says.

The ABCs of DNA: A Genetic Glossary



DNA

DNA is the molecular structure in every living thing containing that organism's genetic code; it's a long strand of nucleotides twisted into a double helix shape. Medical genetic testing doesn't require visualizing DNA with microscopy but instead uses laboratory techniques and bioinformatics to analyze nucleotide sequences in specific, targeted regions on the strand.

Gene

A gene is a discrete segment of DNA that carries the information needed to make a specific protein. Each protein, in turn, directs a particular bodily function. Abnormal (or mutated) genes cause genetic conditions. Genetic testing is done when a specific gene or set of genes is suspected to be the culprit behind a disease.

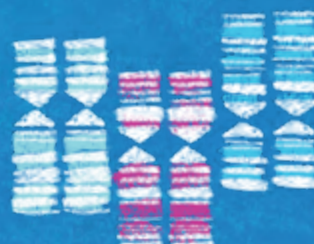


Chromosome

Human genes are organized into 23 pairs of thread-like structures called chromosomes; we inherit one set of chromosomes from each parent. Some genetic conditions, such as Down syndrome, result when there are too many or too few chromosomes due to errors during cell division. In other cases, such as cystic fibrosis and sickle cell anemia, a mutation in a single gene on a specific chromosome can cause the disease.

Cell

A cell is the most basic unit of life. The process of genetic testing requires DNA to be extracted from the patient's cells. First, a chemical reaction breaks down the cell membranes. Then the DNA is separated from the other cellular components through a series of purification procedures.



Genome

An organism's genome is its complete set of DNA. Variations in our genome influence our risk of developing genetic diseases, as well as our responses to medications. Whole-genome sequencing involves analysis of an individual's entire genome and can be done when the cause of a disease or disorder is unclear.

He adds that there are no medical risks to genetic testing. But testing could reveal information the person wasn't seeking, there could be family implications, or the person might not be psychologically prepared for the information learned from the testing. This is why the third part of the process, interpreting and explaining the results to the patient, is so critical.

Amie Blanco, MS, clinical services director for the Cancer Genetics and Prevention Program, says that post-test genetic counseling is a process of shared decision-making and that the role of the counselor is particularly important when delivering a positive test result because information in a vacuum doesn't necessarily lead to action.

"If our goal is to reduce the burden of cancer, we hope that patients take action on these positive test results to ultimately reduce their risk of cancer or find it as early as possible," Blanco says.

"By building this relationship with patients through shared decision-making and motivational interviewing and other tools to really help patients feel supported in their decision-making processes, we hope to get patients to where they are taking the necessary steps to reduce their risks," she adds.

This is one reason it's important to distinguish between genetic tests ordered by a doctor and those offered by direct-to-consumer companies such as 23andMe. The direct-to-consumer commercial tests are far more simplistic than medical tests, and though some companies offer genetic counseling, the advice should be taken with a grain of salt.

"Sometimes the commercial laboratories will provide genetic counseling, but they obviously have a huge conflict of interest if [they] work for a lab to say you should have this test," Norton says.

Further, commercial companies don't usually offer clinician support or follow-ups. "So we end up with a lot of these patients who were given certain risks, and they want to know what to do with this information," Rajkovic says.

And that leads to the subject of ethics.

The Genetic Information Nondiscrimination Act (GINA) prohibits health insurers from using genetic information to set rates or offer or withhold policies and prohibits employers from using it in employment decisions. But GINA's protections don't apply to long-term care insurance, life insurance, or disability insurance, nor do they apply to the military, which is allowed to use genetic information in employment decisions.

Nadav Ahituv, PhD, director of the UCSF Institute for Human Genetics, says an ethical dilemma can arise when genetic testing yields what's known as a variant of unknown significance (VUS). These are variants that are quite rare and have not yet been connected to a health condition.

"So those are very hard to interpret, and [counselors] really try to make sure that if they provide results, they're reliable," Ahituv says.

Additionally, certain minority groups are suspicious of genetic

testing because of historical abuse of such information. The eugenics movement, for example, advocated selective breeding (once theoretical, but now possible). Bogus science has often been used to justify racism. Then there's the case of Henrietta Lacks, a young Black woman whose cancer cells were taken without her consent in 1951. The cells were cultured, and what is now known as the HeLa cell line has been used in medical research ever since.

"As medical professionals, we must ensure that genetic testing is conducted ethically, equitably, and with sensitivity to the historical context that may affect trust among minority groups," Rajkovic says. "Our goal is to make genetic testing accessible and fair for all individuals, irrespective of their ethnicity or race, and to actively address and work to overcome the barriers created by past misuses of genetic science."

With knowledge comes power

Eighteen days after Tong walked Fusco's blood sample down the street, the results came back. Fusco, it turned out, has a BRCA2 mutation, meaning one of her BRCA2 genes doesn't work properly. We all inherit two copies of the BRCA1 and BRCA2 genes, whose functions are to produce proteins that help repair damaged DNA and suppress cancer. People who inherit a mutation or variant in either BRCA1 or BRCA2 are at greater risk of developing several cancers, notably breast and ovarian, and of developing cancer at a younger age.

Tong says the mutation is the primary cause of Fusco's cancer. After receiving the test results, he met with Fusco's parents and then tested them, her brother, and her sister. Her father also has the BRCA2 mutation.

BRCA mutations are probably the most widely known among the public because a number of high-profile people who have them have gone public, including actors Christina Applegate and Angelina Jolie. Both women have a family history of breast cancer, and upon learning of their BRCA mutation, each woman had a double mastectomy. They opted for the surgery as a preventive measure, though only Applegate had breast cancer (and only in one breast).

Blanco says half of the Cancer Genetics and Prevention Program's referral volume is patients who don't have cancer but do have a family history of the disease. "And really, our goal here is to identify those patients that do have an inherited cancer risk and inherited gene mutation because then we can implement screening programs that can identify cancer as early as possible, and in some cases [implement] risk-reducing medications [or] surgeries to prevent cancer from happening altogether."

Knowing that Fusco had the mutation was crucial to her treatment because there is data suggesting that BRCA-mutated cancers are more sensitive to certain types of chemotherapy. Fusco had six months of platinum-based chemotherapy, which has been shown to improve survival rates for patients with BRCA-mutated PDAC, before undergoing an operation called a Whipple procedure to remove her tumor and part of her pancreas. Following surgery, Fusco was cancer-free for nine months, but the cancer returned. Since then, she's been on targeted chemotherapy and other standard-of-care treatments.

Genetics is only one part of health. Environment, education, socioeconomic status, and other variables also play a role.

A genetic revolution

We are living in the midst of a genetic revolution, but it's still in its infancy, and it has its limitations.

Ensuring equitable access to genetic testing remains a challenge. And currently, there is much more genomic information about people of European ancestry than of any other demographic group. In order for more people to benefit from the revolution, it's essential for research studies to include more individuals of non-European ancestry.

Additionally, no one test can detect every genetic condition, nor is every test definitive. A negative result could mean that the wrong test was done, that there is not yet a test for that specific condition, or that there simply isn't a genetic cause for the person's illness.

It's also important to remember that genetics is only one part of the health equation. "Genetics is not simple and does not in itself determine our health. Our health is a confluence of genetics, environment, education, socioeconomic status, and other variables," Rajkovic says.

Still, countless people like Fusco have benefited from genetic testing – and there will no doubt be many more in the future.

After all, says Rajkovic, we understand only 1.5% of the genome that codes for proteins and even less about the noncoding part of the genome.

One area that is quickly gaining traction is epigenetics – the study of how behavior and environment can cause changes in the way our genes work. "Epigenetics is increasingly used to classify tumors and predict the course of cancer syndromes," Rajkovic explains, adding that because epigenetic signatures are so specific to tissue and tumor type, companies are exploring ways to use them to screen individuals for cancer.

"Similar to how a Pap smear is used to detect precancerous or cancerous cells, there is a growing effort to use epigenetic markers to identify early signs of cancer elsewhere in the body. This could enable early detection and treatment, potentially improving outcomes for patients," Rajkovic says.

Studies also are looking at the impact of sequencing the genomes of every newborn, thus creating a genetic passport that can be used during their lifetime. Rajkovic says the likelihood of such a practice increases as costs decrease and as the benefits of early intervention become clearer. However, he emphasizes that significant research is still needed to establish the clinical value of such an approach, particularly its ability to reduce suffering and bring about positive health outcomes. "To validate the effectiveness and benefits of creating genetic passports for newborns, a large-scale study will be necessary. We expect considerable developments in this area within the next decade. Success in this endeavor will likely require government support," Rajkovic says.

"This could revolutionize preventive health care, allowing for early detection and intervention for countless conditions. It can also lead



"This could revolutionize preventive health care, allowing for early detection and intervention for countless conditions."

– Aleks Rajkovic, MD, PhD

to the development of whole new classes of therapeutics to prevent disease manifestations," he adds.

Five years after her surgery, Fusco says she's doing well and taking things one day at a time. In 2020, she and Adam moved to Southern California, and Fusco got her dream job producing for the video game *Diablo IV*. Her current care team consults with her oncologist at UCSF, and she and Tong stay in touch through social media. Though she recently learned that her cancer is spreading, Fusco's optimism hasn't waned.

"I think the genetic testing has prolonged my life, absolutely," she says, adding that her options for treatment continue to be state-of-the-art because of the genetic testing, and she is currently investigating clinical trials for targeted treatment. "Given everything I've been through, I mean, my life is awesome and I'm really glad to be alive still. So I kind of take the good with the bad."

She adds that on her weekends off from chemotherapy, she and Adam go to Disneyland.

TREASURE CHEST

The orbs await your exploration. They peer from within UCSF's Rare Book Collection, a trove of health sciences history in the Kalmanovitz Library. More than 21,000 books line shelves next to artifacts like a trachea kit used in World War II and decades-old nursing uniforms. Here are a few gems from the collection to pique your curiosity and perhaps prompt a visit.



┌ A tonic made in San Francisco in the 1800s.



┌ Oculist Phil Danz donated this collection of blown glass pathological eye specimens to the School of Medicine. They were made in the 1880s by his uncle, Amandus Mueller.



De Humani Corporis Fabrica Libri Septem (On the Fabric of the Human Body in Seven Books), by 16th-century physician Andreas Vesalius. Published in 1543, it is considered the landmark text of modern human anatomy.



A scalpel with an ivory handle owned by UCSF founder Hugh Toland, MD.



The homeopathic medicine kit of Florence Nightingale Ward, MD (1860-1919), a prominent San Francisco surgeon, obstetrician, and gynecologist.



Maybe a sense of calm comes with a walk in the woods surrounded by birdsong or during the quiet of your morning meditation or evening prayer. Maybe the rhythm of knitting or the earthy smell of gardening clears your head.

Science backs up what we know intuitively: Time we spend in nature or on calming practices or hobbies can benefit our mental and physical health. These activities rejuvenate us, right down to our body's living building blocks: our cells.

A UC San Francisco-based team led by Alexandra Crosswell, PhD, and Elissa Epel, PhD, has woven together their own research and studies by others in various fields to connect the experience of, say, painting or practicing yoga to shifts in the nervous system and, subsequently, within our cells. To make this transition, our bodies and minds require certain conditions. But once these are met, the result, they say, is *deep rest*.

This truly restorative state – one never described before – confers benefits unattainable through routine rest and relaxation. In putting forward this concept, the team highlights the regenerative biological processes that protect us as we age.

“Deep rest is something our bodies need and deserve,” says Epel, a professor of psychiatry and vice chair of psychology. “With it, we improve our chances for healthy longevity.”

Perpetual stress runs us down.

But a truly restorative state that alters our bodies at the cellular level can counter this deterioration.

A NEW DEFAULT HOW CHRONIC STRESS CAUSES HARM AT THE CELLULAR LEVEL

To understand the benefits of deep rest, we must confront its counterpoint: stress. Surveys by the American Psychological Association suggest Americans experience plenty of this stomach-churning state. Almost half of adults who responded to a 2023 survey agreed at least somewhat with the statement “My stress makes going to work [or] school increasingly difficult.”

Stress, though it can interfere with our ability to function, originated in physiological mechanisms to help us meet challenges – whether escaping a pack of wolves or facing fallout from a major work mistake. Just like the fear of being eaten, the threat of losing your colleagues' respect can put your body on high alert, triggering a cascade of responses.

Your nervous system hands over control of unconscious processes like breathing and digestion to its in-house crisis response coordinator: the sympathetic nervous system. This shift kicks off a series of energy-demanding changes that prime your body and mind for action. Your heart beats faster. Blood flow increases to your skeletal muscles, which tense up. Your production of hormones, such as cortisol and other energizing chemical messengers, surges. Your alertness intensifies.

By Wynne Parry

Illustrations by Marine Buffard

Cell illustration by Farah Hamade

THE POWER OF DEEP REST

Together, these and other shifts help ready you to fight or flee – even if you’re just anxiously awaiting a reply to your apologetic email while imagining dire scenarios.

A certain degree of stress is inevitable in life, Crosswell points out. “After years of studying stress, it became clear to us that we have to stop trying to get rid of it,” she says. “Stressful events are often outside our control, and our bodies’ response to them is natural and helpful.”

Too much stress, however, can cause harm. She and her colleagues argue that many Americans spend most of their waking hours in a moderately stressed-out state, driven by feelings of uncertainty about the future and lack of control. While no surprise to many of us, the idea the team explores – that we experience continual stress – represents a new direction in scientific thinking, which has traditionally considered relaxation the default human state.

Ideally, a stress-inducing crisis comes to a quick, clear ending. Maybe your apology at work is accepted, the mistake quickly forgotten. But problems in modern life often don’t come to quick, complete conclusions. Your boss may repeatedly deny requests for remote work. You and a loved one may frequently argue. You may struggle financially for years. Under such circumstances, stress can attenuate to a more moderate level, but it doesn’t stop.

While less taxing, residual stress still drains you. Maintaining an elevated heart rate or pumping out more cortisol than usual requires extra energy. This energy takes the form of molecules known as ATP, or adenosine triphosphate. Cellular organelles called mitochondria make ATP by using oxygen from the air we breathe to harvest energy from fats, proteins, and glucose derived from food we eat.

“Mitochondria are the source of the vital force that brings a cell to life and ultimately gives us our conscious mind, our emotions,” says Martin Picard, PhD, director of the Mitochondrial Psychobiology Group at Columbia University and one of Epel and Crosswell’s collaborators.

“Everything we experience is powered by the energy flow inside our cells,” he says, “and that flow takes place in mitochondria.”

While a single cell can contain hundreds of mitochondria, the organelles can generate only so much ATP – for reasons that remain unclear. So when your body goes on alert, a cell diverts its limited ATP supply to carry out the urgent functions the stress response demands, such as contracting the heart or synthesizing hormones. This robs it of energy for more routine but necessary tasks.

What’s more, studies have linked diseases, including diabetes, heart disease, and neurodegenerative disorders, with poor mitochondrial health. Picard suspects psychological stress has a similar effect, with mitochondria sustaining damage and becoming less productive when someone is under chronic strain.

Some prior studies and his own research with mothers caring for children on the autism spectrum, a source of chronic stress, support this idea. In a study led by Epel and described in *Biological Psychiatry*, Picard and others found that mitochondria in the mothers’ white blood cells had a reduced ability to transform energy into ATP. Cells face another potential consequence of damaged mitochondria: increased production of a potentially toxic byproduct of making ATP – chemicals known as reactive oxygen species (ROS). If not neutralized, ROS can harm our cells.

The effects of chronic stress extend to our genetic material as well. At the tips of chromosomes, repeating segments of DNA form telomeres. With assistance from proteins, telomere “caps” protect the integrity of these packets of genetic code – for as long as they can.

Each time a cell copies its genetic material so it can replicate, its telomeres lose a little DNA and shorten. Research started 20 years ago by Epel, with UCSF colleagues Nobel laureate Elizabeth Blackburn, PhD, and Jue Lin, PhD, shows that chronic psychological stress further shortens telomeres. This loss is a consequence of exposure to ROS, the release of hormones like cortisol, and inflammation. Molecular studies of cells substantiate this connection: By mimicking long-term exposure to the stress hormone cortisol, Picard has shown that cells respond by revving up their metabolisms, which shortens telomeres and hastens cell death.

Over time, such processes can have big consequences for our health. The deterioration of telomeres leads cells to stop dividing and to send out signals promoting more inflammation. Old cells with short telomeres and compromised mitochondria build up. The cumulative damage leaves us more prone to cancer and degenerative diseases, according to Epel.

“The crux is that the rushed pace of modern life without sufficient time for restoration is a formula for accelerating our aging,” she says.

HITTING THE SWITCH

WHAT IT TAKES TO TURN STRESS OFF

Run-of-the-mill leisure activities, like spending time with friends or watching a movie, can provide some relief. Such pursuits may shut off your mind’s looping replays of, say, a relationship conflict or poor exam performance.

But whatever distraction they provide, these experiences probably won’t generate the restorative state that slows the biological clocks ticking in our cells, the team contends. Our unconscious mind can hold onto stress, and our body’s stress response may linger even into sleep.

STATES OF THE CELL

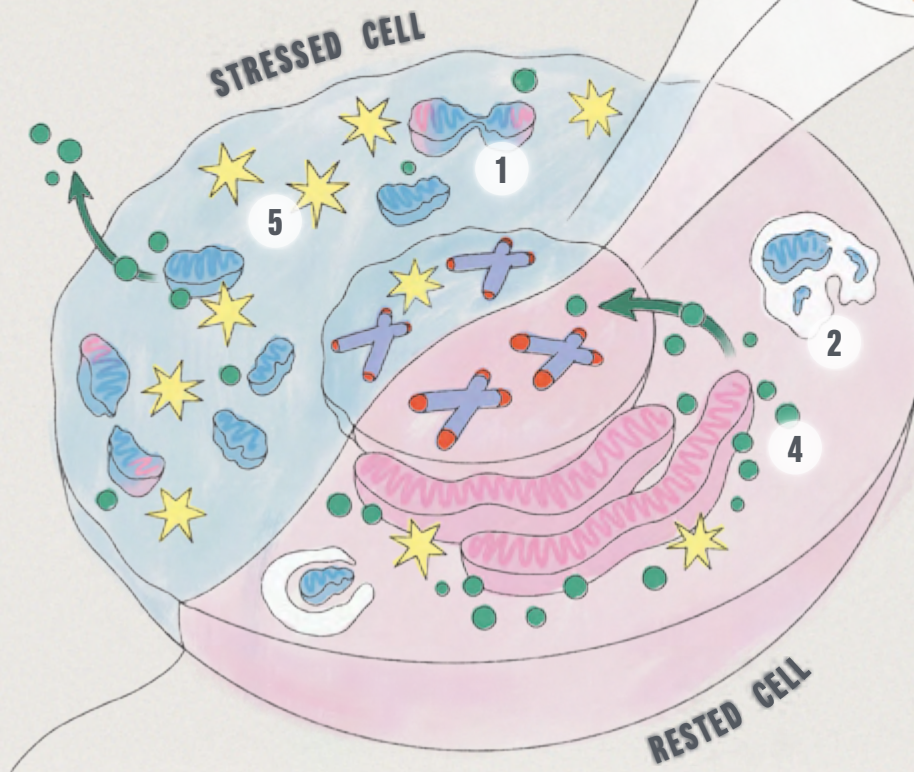
HOW STRESS – OR DEEP REST – MAY CHANGE OUR BODY’S MOST FUNDAMENTAL UNITS

1 MITOCHONDRIA

Mitochondria produce the energy our cells use. Over time, however, stress can damage these powerhouse organelles, leaving defective bits behind.

2 CELLULAR RECYCLING

When stressed, cells neglect routine maintenance, accumulating damage and detritus. Researchers think that during deep rest, a process called autophagy resumes, recycling useless cellular components – including defective mitochondria.



3 TELOMERES

Telomeres are protective tips on chromosomes, and they shrink a little each time a cell divides. Stress appears to accelerate this deterioration, leading to cellular aging. Telomerase, an enzyme that reverses telomere loss, may become active during deep rest.

4 ENERGY USE

Cells power our activities with ATP molecules made by mitochondria. Stressed cells divert ATP from routine to survival-related activities like increasing heart rate. Cells burn more energy and age faster when they are stressed for long periods: Their telomeres shorten, they promote inflammation, and they die sooner. Researchers think that during deep rest, cells redirect ATP toward restoration – and overall energy expenditure drops.

5 REACTIVE CHEMICALS

At normal levels, highly reactive chemicals called ROS contribute to cells' health. But damage to mitochondria and inflammation during stress may increase ROS to levels that harm cellular structures, including telomeres. Deep rest may protect against excessive ROS.

But deep rest can effectively counter stress, the team argues. In their definition, deep rest is a psychological and physiological state during which our bodies can recover on a cellular level. In deep rest, formerly stressed cells restore themselves by performing the maintenance needed to keep such a complex machine, the human body, in working order.

Certain practices – those that cultivate inner well-being and quiet our minds – can open the door to this fully restorative state. Meditation and yoga are two of the most recognized contemplative practices, but many others exist.

Prayer, spiritual reading, the Japanese practice of therapeutic relaxation in nature known as forest bathing, and movement-based practices like tai chi and qigong can similarly calm and focus mind and body. And they don't have to be quiet; drum circles or other group rituals offer comparable benefits. Other people may find hobbies like knitting or painting contemplative and soothing.

Regardless of form, these practices send signals telling their practitioners they're safe, the researchers say. The practices turn off our subtle anticipation of threats like physical harm or emotional pain, including those brought on by others' judgment or our own thoughts. They often accomplish this by tapping into our senses – the aroma of incense during a religious ritual, for instance. Likewise, caressing prayer beads during meditation or doing yoga in a candlelit room can convey safety by activating internal systems that have evolved to allow our bodies to rest. So, too, can the sights, sounds, and scents of a walk in nature.

Social safety cues also matter. Chanting in unison or listening to a calming voice may appeal to our auditory systems and social brains. A sense of belonging or a bond with others also fosters a feeling of safety. However, such perceptions can vary. Those who have experienced various types of discrimination may feel more at ease among others who share their social identity, for instance.

Beyond these external cues, such practices often look inward. Many encourage an awareness of the body through movement and measures like mentally scanning the body during mindfulness meditation. They may also emphasize focusing attention and managing emotions. In doing so, they free the mind from roiling thoughts and feelings.

And that's not all. Either deliberately or as a side effect, contemplative practices also slow our breathing, a cardinal safety cue with potentially wide-ranging effects on our physiology, according to Epel.

"Having a slow, full exhalation is unique to a relaxed state. We don't usually fully exhale as we're rushing around our day feeling stressed," she says.

The brain responds to slowed breathing, as well as other cues from contemplative practices, the researchers posit, thus prompting physiological changes that make true rest possible.

The commonalities across many contemplative practices mean that if you are considering starting one, you have plenty of choices, notes Crosswell, who conducted the research as an assistant professor at UCSF.

"For probably the past 10 years, a myth has been circulating that your only choice for managing stress is to meditate daily," she says. "But we're saying there are many ways to reach the same state of deep rest and combat stress. I hope that feels freeing for people."

INTRODUCING DEEP REST IT MAY RESTORE OUR VERY CELLS

Once received, safety signals prompt a shift in your nervous system, which switches off the ready-for-action sympathetic mode, the manager of the stress response. Then its neurological partner, the calming parasympathetic nervous system, takes over.

The unconscious changes that occur during this transition likely feed on themselves, according to the researchers. Slowing your breathing initiates a sense of calm and slows the heart rate. The vagus nerve, which passes information between the brain and internal organs, lets the brain know of this change. Your brain then switches off the stress response, allowing the parasympathetic nervous system to dominate, reinforcing the shift. Your heart rate continues to drop, digestion increases, your muscles relax. Meanwhile, your sense of ease grows, and you feel at peace. You may also experience a sense of deep connection – to yourself, the world at large, or a higher power.

You have now entered a distinct state – deep rest. The researchers introduced the concept in January 2024 in the journal *Psychological Review*. Though the term "deep rest" had previously been used for certain relaxation techniques, Crosswell and Epel's concept ventures more deeply into

our bodies' physiology. Once in deep rest, they propose, our cells can redirect energy, in the form of ATP, to restoring themselves, from both the stress response and mundane wear and tear.

Cellular recycling is among the housekeeping activities that resume, they believe. Known as autophagy, that process occurs when our cells gather up old, damaged, malfunctioning parts, which are broken down by structures called lysosomes. The lysosomes then release the components to build fresh molecules and structures. The stress response interferes with this recycling process, which also declines as we age.

One form of autophagy focuses on sweeping up damaged mitochondria. Removing and replacing them not only ensures ATP production but also reduces the output of reactive ROS. This helps protect our cells from the damage ROS can cause. Studies have linked glitches in recycling mitochondria with numerous diseases, including Alzheimer's and cardiovascular disease.

Likewise, deep rest may help protect our invaluable genetic material, according to Epel. Though aging and stress wear down the telomeres on our chromosomes, our cells also possess an enzyme called telomerase that adds DNA back onto those "caps." By lengthening telomeres, telomerase prolongs their ability to protect chromosomes and the health of our cells. Studies show, says Epel, that telomerase's activity increases during recovery from intense stress, whether the stress lasts for minutes or hours. Research also suggests that telomerase tends to increase during meditation retreats that take place over days or weeks, as well as after taking meditation classes for a month or more.

The new paradigm the team proposes – that contemplative practices signal safety to mind and body, triggering a truly restorative state whose benefits extend down to the level of cells – relies on their interpretation of years of studies in multiple scientific fields. Yet their synthesis of this research also points to a major oversight in our understanding of health and aging.

"Most of the focus has been on stress and disease," says Epel, noting that the restorative processes that slow our cellular clocks and maintain our well-being over decades have received comparatively little attention. She describes the team's work as "a call for action" for more research on deep rest as a key to healthy aging and healing.

The revitalization that occurs during sleep and the newly defined state of deep rest is "critically important" to healthy aging, she says. "It's the other half of the equation."





FOUR QUICK WAYS TO TRULY REST

Deep rest is best achieved in prolonged practices that relax the body and quiet the mind, such as a yoga class or meditation retreat. But you can also combat stress within seconds by activating your parasympathetic nervous system. Here are a few approaches to making this biological shift quickly.

1 SLOW YOUR BREATHING

Entering a state of deep rest requires the mind and body to feel safe. Cues that indicate safety can come from the body itself, most notably through breathing. Slowing your breathing, particularly lengthening your exhalations, calms your mind and body by activating the vagus nerve. “You’re intentionally switching on a state of calm,” notes Crosswell. Even a few deep, slow breaths taken repeatedly throughout the day can help, she says.

2 PLEASE YOUR SENSES

Stimulating your senses in enjoyable and relaxing ways can also activate your parasympathetic nervous system. Crosswell recommends intentionally triggering your senses by, for example, smelling essential oils, arranging flowers, putting your bare feet in grass or sand, enjoying a view of the horizon, or cooking. These sensory-rich activities can move your focus from your mind to your body, reducing stressful thoughts while easing you into a state of rest, she says.

3 PAY ATTENTION TO NATURE

According to the biophilia hypothesis, humans are drawn to natural environments due to having evolved within nature. Studies have shown that the sensory stimulation nature provides can aid recovery from stress. To take advantage of this connection, visit a natural setting, perhaps as close by as your yard, and pay attention to the sights, sounds, and scents. Try touching leaves or petals. Be curious about what you see, touch, feel, smell.

4 LOOK OUTSIDE THE BOX

If you want to try a contemplative practice, know you have options beyond yoga and meditation. Less recognized practices include drum circles, prayer, and spiritual reading, such as the Christian practice of *Lectio Divina*. Crosswell recommends treating the activity as a way to connect with your spiritual life or cultural heritage – or to try something new, since novel experiences are associated with a greater sense of well-being. She says enjoyable pursuits that tap into the senses and require focus, such as knitting, art, or playing music can also lead to deep rest. If you have the luxury of trying a residential meditation retreat, these can offer larger resets for your nervous system, according to Epel.

ALUMNI HUB

They're helping us age with dignity, fixing problems with patient care, founding biotech companies, and more. Meet five thought leaders who are sparking conversations and changes that are improving the world of health.

Illustrations by John Jay Gabuay

GRADUATE DIVISION

Sebastian Bernales, PhD '06, Postdoc Alum

Inspiring Innovation through Connection

IDEAS AND ADVENTURES

Bernales has spent years bringing scientists together for conversation and collaboration and uniting funders with scientists who have promising ideas. While a graduate student and postdoc studying cell biology at UCSF, he and a mentor – Pablo Valenzuela, PhD, co-founder of the biotech company Chiron – would take groups of students and faculty members to Chile, Bernales' home country. They would discuss science with students and colleagues and explore Patagonia and the Atacama Desert. "It was a way to put Chile on the scientific map," says Bernales, the Graduate Division's Alumnus of the Year. Over the years, more than 200 scientists from UCSF made the trip. His networking would become a sort of subspecialty of his career.

A BRAIN FOR BIOTECH AND LEADERSHIP

After his time at UCSF, Bernales joined the biopharmaceutical firm Medivation. One of the co-founders, David Hung, MD '84, participated in the Chile trips. Bernales opened a lab in Chile, where he helped develop Xtandi, a blockbuster drug for prostate cancer. "I saw firsthand how an idea could transform into something that was helping people," he says. In 2016, Pfizer acquired Medivation for \$14 billion. After the buyout, Bernales co-founded Praxis Biotech with another mentor, Peter Walter, PhD, a UCSF professor emeritus. Bernales also served as that company's CEO and then co-founded the gene-editing company Metagenomi.

SPARKING NEXT-LEVEL SCIENCE

Bernales is now a general partner at the Humboldt Fund, a venture capital firm he co-founded in 2020. He's invested in research and startups in areas as varied as gene editing, antibiotic resistance, longevity, the gut-brain axis, mitochondrial diseases, and cell-based therapies. The work allows him to meet with and learn from scientists in many different fields, something that he loves – and that follows naturally from his inclination to connect.

INVESTOR-MENTOR

"It's not only about giving them money and then calling them three years later to see what happened," he says. "It's also being involved, helping them, trying to contribute – basically knowing and relating to where they're coming from."

■ *Dora Dalton*



SCHOOL OF DENTISTRY

Jennifer Perkins, DDS, MD, Resident Alum

Envisioning a More Humane Dentistry Education

GOING DENTAL

Perkins spends part of her working hours immersed in her clinical practice as an oral and maxillofacial surgeon, focused on caring for head and neck cancer patients after radiation. She loves the work, especially expanding access to high-quality care. But the majority of her time is dedicated to transforming dental education at UCSF. Dental students, unlike medical students, aren't required to do a residency, so in just four years, they need to acquire both the knowledge and the hand skills to do delicate microsurgery. "You have to take them from point A to a distant point B quickly and support them along the way," she says.

STUDENT TEACHERS

Her mission to humanize dental education leads Perkins down many pedagogical pathways. She is leading a faculty team in revising the School of Dentistry's predoctoral curriculum, incorporating more interactive learning, shadowing, and lessons on bedside manner. She is the director of the clinical oral surgery courses for dental students. And she is an award-winning instructor, teaching classes on the basics, like physiology, to the more specialized, like the administration of local anesthesia. The question that always guides her in such efforts, she says, is "How can we use our curricular time to help breed the inquisitiveness, the self-directed learning, the resilience, the curiosity to go in whatever direction the field takes them?"

SHOULDERS TO STAND ON

"The largest driver of my wanting to be in dental education is that I didn't particularly enjoy my own dentistry training," says Perkins, a first-generation college student. "I went into health care because I wanted to help people, and my time in dental school didn't really help me sustain that desire. Trying not to grind that out of students is really important for their well-being and for furthering everything they're capable of doing."

■ *Kira Goldenberg*



Jarmin Yeh, PhD '20, MPH, MSSW

Creating a Better Aging Process

THRIVING WHILE AGING

Yeh works at the intersection of aging and environment, studying the resources needed to improve the golden years we all hope to reach. “What do we have in our places and spaces to let us live the life we want?” Yeh asks. “It’s activities, it’s transportation, it’s people.” She is not just theorizing in an ivory tower; Yeh partners with community organizations to help people as they grow older in their homes and communities. One project offers training for in-home dementia caregivers and studies the impact on health system resources. Another, co-created with those it serves, is a day program for LGBTQIA older adults that provides a safe place and specialized care.

BUILD ME UP

Yeh entered gerontology by happenstance. She was completing an MPH/MSSW, studying how cities impact health and quality of life, when she interned at the New York Academy of Medicine. There, she undertook a national initiative to bolster the portion of the social work workforce focused on aging. “It solidified the direction I started to study,” she says. Today, Yeh is co-director of UCSF’s Emancipatory Sciences Lab, which approaches research, practice, and teaching through an anti-oppression lens. She also teaches leadership theory and practice to UCSF students who are pursuing master’s degrees in health care administration.

JUST A NUMBER

“I’m really interested in the ways our social policies do or don’t support people’s abilities to age in place with dignity and autonomy and to make decisions for themselves,” Yeh says. “We’re all aging. My work is to try and make the future a better place to grow old.”

■ *Kira Goldenberg*



SCHOOL OF MEDICINE

Amin Azzam, MD, MA, Resident Alum

Instilling a Thirst for Lifelong Health Care Learning

WELCOME TO THE TRENCHES

When Azzam was approached by UCSF's Medical Alumni Association about mentoring a high school student from a community under represented in medicine, he immediately signed up to be paired with Noe Lopez, 17, a senior at Mission High School in San Francisco. "We are the inaugural pilot, just the two of us, for this proof of concept," Azzam says. Lopez has shadowed Azzam, both at teaching and at clinical sessions, and the teen is researching brain tumors under his mentor's guidance. "It's cool that I'm comfortable with a doctor," says Lopez, who is on track to be the first person in his family to attend college. "This mentorship definitely has reaffirmed my interest in the medical field."

STUDENT-LED LEARNING

Azzam is so passionate about health professions education that he teaches at three universities – UCSF, UC Berkeley, and Samuel Merritt University – implementing his ongoing research into student led learning. "What I love about teaching is the privilege and opportunity to help young professionals become the best version of themselves," he says. His commitment to that work focuses both on best teaching practices and on expanding access to opportunity. It has led him to study topics like the use of artificial intelligence avatars in mental health training to give large student populations exposure to realistic scenarios to supplement and standardize their training. Azzam also teaches a class in writing for Wikipedia to improve public access to high quality medical information.

FROM STUDENT TO SELF-TEACHER

"How do you help students be active thinkers rather than passive recipients of our knowledge?" he says. "If we help young health professionals learn to be lifelong learners, that is the environmentally sustainable fuel that will stimulate perpetual growth."

■ *Kira Goldenberg*

Pamela Schweitzer, PharmD '87

Advocating for Person-Centered Health Care

NEVER GIVE UP, NEVER RETIRE

Schweitzer's government career arc – from delivering direct patient care for the Indian Health Service to helping implement the Affordable Care Act for the Centers for Medicare and Medicaid Services – shaped her fundamental belief that health care should be widely accessible and patient centered. "I'm big on gauging the community, getting everybody on the same page, and having them work together – the businesses, the different institutions. And on giving people the information and letting them make their own choices," she says.

She retired in 2018 after four years as the U.S. assistant surgeon general and chief pharmacist officer in the United States Public Health Service Commissioned Corps. But Schweitzer, the first woman to hold the latter role, is hardly resting. Her days are filled with health consulting projects as she seeks to leverage her hard won wisdom. "I love it when there's a problem, because then I can package it, and I know right where to send it to get it fixed."

PEOPLE OVER PROFITS

Schweitzer spent 19 years as a pharmacist in the Indian Health Service as a USPHS Commissioned Corps Officer. The service provides some government funded health care for Indigenous Americans. She learned there how different top down health policy can be from the actual needs of a population. "It's about caring about the community," she says. "You hear the medical system say, 'We're going to do this,' but nobody talked to people to make sure that's what they wanted."

A MODEST PROPOSAL

"We should all be able to get basic health care," Schweitzer says. "It shouldn't be so difficult. It shouldn't be the haves and the have nots." And, she adds, "we need to take care of our providers."

■ *Kira Goldenberg*



My Olympic Reflections

By Rhonda Watkins, MD, MPH, as told to Paula Hermann

Olympic magic is unfolding in Paris this summer, and I am unapologetically giddy. The Games evoke a worldwide spirit of competition, outsized patriotism, and for me, nostalgia. Every time I watch Olympic track and field events, I relive the extraordinary opportunity I had to represent Trinidad and Tobago in Beijing in 2008.

The opening ceremonies were surreal. The grandness of it all struck me as I walked into the most majestic track and field venue I'd ever seen and heard 90,000 cheering fans. It took my breath away. As the only female long jumper representing my country, I felt a powerful desire to make Trinidad and Tobago proud.

I flashed back to watching my first Olympic track and field events on television when I was 9 and proudly declaring to my family, "Someday, I will bring home gold." As I was standing in the Beijing stadium, I was no longer pursuing my Olympic dream – I was living it.

I began running track at age 10 and moved to field events in high school – my 5-foot-11-inch frame was well-suited to the long jump and high jump. While perfecting my skills, I sustained injuries multiple times, affecting my knee, ankle, and back. Injuries can take you down or make you stronger. I chose the latter, ultimately winning gold at the World Championships and qualifying for the Olympics.

I worked hard to become an elite athlete while battling recurring injuries. I earned a track scholarship to UCLA, and on one of my frequent visits to the training room, I met a sports medicine doctor who shared his experience as a track athlete. He knew what I was feeling physically and emotionally. That interaction inspired me to work toward one day delivering authentic care to young athletes.

As a pre-med student-athlete, I studied at night and trained several times a day to prepare for the Olympics. I didn't sleep much. As the Games approached, I was still nursing injuries, and when I arrived on the biggest stage in sports, I wasn't performing to my fullest potential.

I know from the moment I take off down the runway whether it will be a good jump. Everything stops for a split second as I sail through the air – it feels like flying. I had only three chances to advance to the final round; all three fell short.



At age 19, Rhonda Watkins participated in the 2008 Olympics in Beijing. The former world-class track and field athlete is now a pediatric sports medicine physician at UCSF Benioff Children's Hospitals.

It was devastating. I had given everything I had that day despite being limited by my injury. However, it was such a special opportunity just to be there, so I felt like I'd still realized my dream.

The Olympics only come around every four years, and the path to get there is arduous. I knew that despite a yearslong journey to medical school looming, I wanted to try again. I trained for two more years but eventually focused solely on medical school, and I have no regrets. Thanks to my injuries and experiences on the track, I can give my patients a lived perspective, listen empathically, and assure them that better days lie ahead.

My daughter, Semira, was born in March. I'm looking forward to raising a strong female minority, watching the Olympics together, helping her achieve her aspirations, and showing her how to be a boss on the runway.

PHOTO: PAUL KITAGAKI JR./SACRAMENTO BEETHRIBUNE NEWS SERVICE VIA GETTY IMAGES



Celebrating Remarkable UCSF Alumni

In April, UCSF honored 13 alumni for their extraordinary ingenuity, compassion, and global and community impact. Now, we are seeking nominations for 2025. **If you or someone you know is a UCSF alum deserving of recognition, we want to hear from you.**



Visit tiny.ucsf.edu/award25 or scan the QR code to learn more about our 2024 honorees and tell us briefly about a UCSF alum who inspires you. We will contact you with the next steps for an official nomination.

Alumni Award winners will be honored at Alumni Weekend, April 25-26, 2025, at UCSF's Mission Bay campus.

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