

S T A N F O R D M E D I C I N E

Issue 1 / 2023

special report

REAL-WORLD HEALTH

How social factors
make or break us

No shelter

How health is determined by
more than medical care

Shhhh...

Breaking through the stigma
of having breast cancer

Equal opportunities for positive outcomes

A conversation with health equity
expert Alyce Adams

A long and happy life

Uncovering the mystery
of aging really well

Gulp

Troubles with water

plus

What makes collaborations work

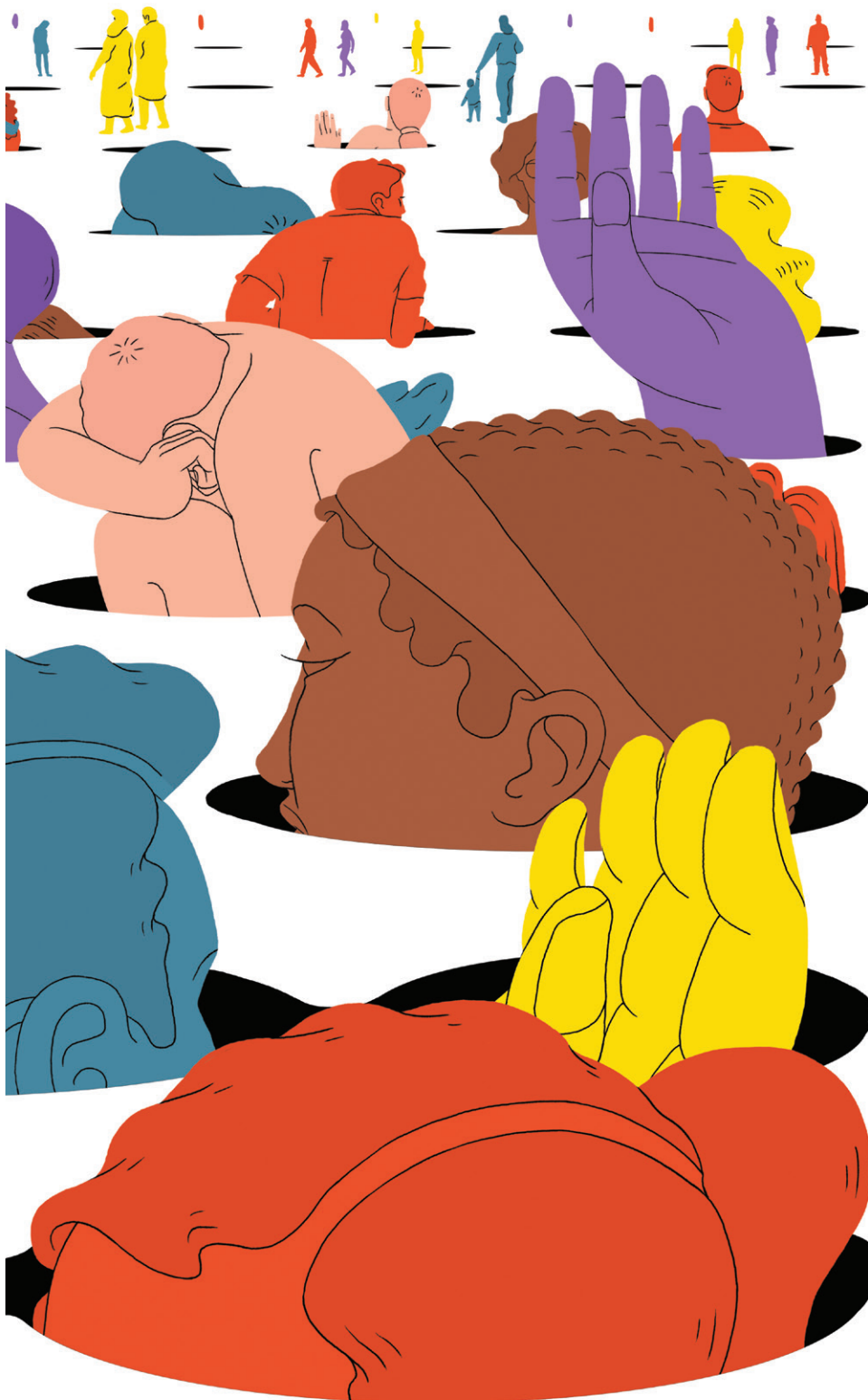
A conversation with Carolyn Bertozzi,
new Nobel laureate

Cult classic

A trippy '70s film about protein synthesis

Oh, you're so picky

The secret life of ribosomes



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NOBEL WINNER CAROLYN BERTOZZI

THERE ARE NO FAILURES —

ONLY OPPORTUNITIES IN UNEXPECTED OUTCOMES

Early on Oct. 5, 2022, Carolyn Bertozzi learned she was a 2022 recipient of the Nobel Prize in chemistry for her development of bioorthogonal chemistry — a technique that allows chemical reactions to be carried out in living cells.

The first person she called was her 91-year-old father, William Bertozzi, PhD, a retired physics professor from MIT. He was thrilled. Together, he and one of her sisters watched the broadcast of the announcement, which was streamed live from Stockholm, an hour later.

“It was a stunning, shocking moment of excitement and exhilaration,” the peanut butter lover and *Breaking Bad* aficionado recalled of the life-changing moment. Within a couple of hours, her family was already booking flights to Stockholm for the award ceremony in December.



Carolyn Bertozzi said she values and fosters diversity and inclusivity in her lab and hopes the people she mentors learn that it's OK to take risks in their research.

During her career at Stanford University, Bertozzi, PhD, the Anne T. and Robert M. Bass Professor in the School of Humanities and Sciences and a professor of chemistry, has been a prolific collaborator with researchers across the Stanford School of Medicine — exploring topics as varied as tumor biology, cancer immunotherapy and even COVID-19.

Bertozzi is also the Baker Family Director of Stanford University's Sarafan ChEM-H, which was created to explore the interface between chemistry and human biology. We caught up with her to learn more about how such interdisciplinary collaborations have shaped her work.

Why is collaboration in research important?

I realized the importance of collaboration in graduate school. This was the early days of interdisciplinary research that spans chemistry and biology, and we were learning to put our heads together.

If you want to be at the leading edge, it's important to realize that the big breakthroughs come in the convergence of different areas of science, and the solutions to big problems often come from very unexpected places. And no one lab is going to be able to make all the necessary connections.

What makes a collaboration successful?

The best collaborations have a certain ethos to them. First and foremost, both faculty members must be interested in the project. It can't be a one-way street.

Next, both labs have to have a person on the ground who is dedicated to the project and who can actually execute the idea, as well as the physical space and the bandwidth to dedicate to the project. It can't be just that I'm excited about an idea.

Finally, good communication is essential so each party understands and appreciates the other's hard work when it comes to reporting the findings.

How can diversity help with research?

Diversity in a lab can make a huge difference in science. If a lab has no women, no people of color, no queer people, it's going to be difficult to recruit those people later.

If the faces of science are primarily white dudes, researchers of other backgrounds will take their talent somewhere they don't feel so marginalized. And talent is a rare thing; there's not enough talent to go around for everyone who wants to hire that talent. So my approach has been to foster the most inclusive and welcoming lab that I can and to cultivate a diverse group of scientists.

What lessons do you hope your mentees learn from you?

I hope they learn to take risks and think outside the box. And when these high-risk endeavors fail, as they sometimes do, they don't get demoralized. Don't get too hung up on what you thought would happen; understand what did happen and make the best of that and be ready to pivot.

If the experiment was well thought out and designed, there really is no failure. It's just an outcome you didn't anticipate, and you have the chance to learn something new and unexpected. **SM**

BY KRISTA CONGER

S T A N F O R D M E D I C I N E

SPECIAL REPORT

Real-world health

How social factors
make or break us



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Health inequity is one of the most urgent challenges we face in health care and biomedicine.

We see evidence of it everywhere, from infant mortality to life expectancy.

We see it in disease prevalence and in how well conditions are managed. We see it in clinical trials that lack diversity and in the uneven distribution of resources, with COVID-19 vaccines serving as a recent example.

Despite widespread advances in prevention and numerous breakthroughs in therapies and drugs, for millions of people, a wide gap persists in realizing lifelong health.

While the underlying reasons for this gap are complex and deeply structural, the lived reality is this: The color of your skin, the community you belong to, and the place you call home remain the largest predictors of health and longevity. Far more than your doctor or what's written in your DNA.

These social and environmental factors are appropriately called determinants of health because their influence is so profound. And perhaps at no other time have they been so vividly and painfully on display, from the health effects of climate change to the devastating impact of structural racism during a global pandemic. As our latest issue of *Stanford Medicine* magazine uncovers, effectively engaging these issues demands that we view a patient's health in a completely different light.



There is a wealth of data on how structural racism has created neighborhoods that lock in health disparities. Communities of color, often burdened with substandard housing, are typically located far from the best schools, good jobs and quality hospitals or clinics. They lack access to nutritious food, clean air and green spaces. The barriers to good health are often literal: railroad lines and highways that cut off disadvantaged urban neighborhoods, or miles and hours of travel that isolate rural areas.

These are the realities that too many Americans, particularly people of color, must navigate every day.

Far too often, physicians treat patients and then send them back into the same environment that caused their illnesses. I'm encouraged that researchers and health care providers are broadening their scope to better identify the most acute factors impacting human health. Further research is vital to fully understand the complex relationships between non-medical factors and their impact on outcomes and, importantly, to identify solutions — in partnership with communities — to begin to correct generations of inequality.

Social determinants are integral to Stanford Medicine's vision of precision health. By embracing a holistic approach, precision health treats the individual and focuses on predicting and preventing disease before it strikes, and curing it — *precisely* — if it does. And to be precise, we must appreciate the full context of a patient's environment and all of the factors that shape the patient's health and well-being.

I am proud of the many Stanford Medicine community members who are pioneering ways to address social determinants, and I encourage you to learn more in these pages. I believe the insights and experience gained represent a critical opportunity to eliminate the unconscionable health disparities that plague our nation. Through concerted efforts across research, education, policy and patient care, we can build a more equitable health care system for all.

Sincerely,

Lloyd Minor, MD

Carl and Elizabeth Naumann Dean of Stanford School of Medicine
Professor of Otolaryngology-Head & Neck Surgery

upfront

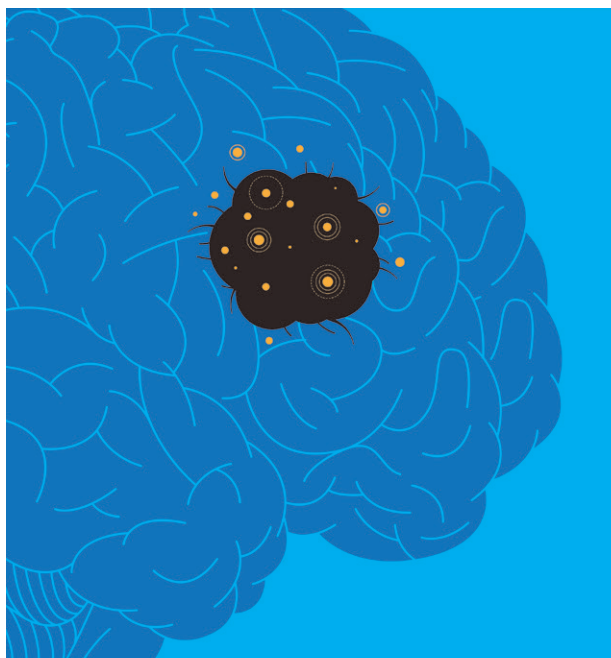
A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Brain tumor heat treatment

BRAIN TUMORS, such as glioblastomas, are among the most deadly and difficult-to-treat cancers, typically requiring open-skull surgery followed by chemotherapy or radiation. What if a brain tumor could be treated painlessly, without anesthesia, at home?

Stanford School of Medicine researchers have tested in mice a small device implanted between the skin and the skull that could do just that. The remotely activated implant uses infrared light to heat up nanoparticles that have been injected into the tumor — just enough to gradually kill cancer cells without damaging surrounding brain tissue.

In mice with brain tumors, 15 minutes of daily treatment over 15 days, as the



animals went about their normal activities, was enough to significantly increase survival times.

"The nanoparticles help us target the treatment to only the tumor, so the side effects will be relatively less compared with chemotherapy and radiation," said Hamed Arami, PhD, a former Stanford School of Medicine postdoctoral fellow who is now at Arizona State University. He is co-lead author of the study published in August 2022 in *Nature Nanotechnology*.

Unlike previous attempts at photothermal therapy, which required surgically exposing the tumor to the light source, the new device uses infrared light that can penetrate brain tissue to target tumors.

The researchers are confident they can scale up the device for human-sized brains. "In the next five years, we'll be able to develop devices that can generate even more optical powers for deeper tumors," Arami said.

[Retinal implant](#)

Stanford University researchers have designed an implantable retinal prosthesis with five times the resolution of the best devices being tested.

"Our implant provided not only the highest resolution, but it also shaped vision rather than just light sensitivity," according to Daniel Palanker, PhD, a professor of ophthalmology and senior author of an article published in November 2022 in *Nature Communications* describing the device.

The device was designed to restore vision loss due to age-related macular degeneration, which damages the retina, causing blurred center vision. After successfully testing the implant in rats, the researchers are now optimizing the device for clinical trials.



COVID- fat connection

OBESITY IS AN ESTABLISHED INDEPENDENT RISK FACTOR for SARS-CoV-2 infection as well as for the patients' progression, once infected, to severe disease and death. Possible reasons range from impaired breathing resulting from the pressure of extra weight to altered immune responsiveness in obese people.

But a new Stanford School of Medicine study provides a more straightforward reason: SARS-CoV-2 can directly infect fat tissue. That, in turn, cooks up a cycle of viral replication within resident fat cells and causes pronounced inflammation in immune cells that hang out in fat tissue. The inflammation converts even uninfected "bystander" cells within the tissue into an inflammatory state.

The researchers observed this in fat tissue excised from patients undergoing stomach and heart surgeries and later infected in a laboratory dish with SARS-CoV-2. They confirmed their findings in autopsy samples from deceased COVID-19 patients.

Fat tissue surrounds our hearts, guts, kidneys and pancreases, which can be adversely affected by tissue inflammation. Ominously, the scientists found infection capable of driving inflammation in virtually every SARS-CoV-2-infected fat-tissue sample they collected and analyzed.

"It's reasonable to infer that having a lot of infected fat could contribute to the overall inflammatory profile of severely ill COVID-19 patients," said Catherine Blish, MD, PhD, professor of infectious diseases, co-senior author of the *Science Translational Medicine* study published in September 2022. It could also contribute to the enduring post-infection symptoms collectively called long COVID, a hypothesis Blish and the study's other co-senior author, Tracey McLaughlin, MD, professor of endocrinology and of infectious diseases, are exploring.

"With more than 4 in 10 American adults overweight, this is a potential cause for concern," McLaughlin said.

Eyes on the OR

A SOPHISTICATED monitoring system has been installed in four operating rooms at Stanford Hospital to capture everything that happens during surgical procedures.

Stanford Hospital is the first to install the technology on the West Coast. Called OR Black Box, it is designed to improve training and promote a culture of safety. It records all activity during a procedure, including the surgical team's actions and performance, distractions in the room, patient vital signs, equipment malfunctions and

other factors that might affect the outcome of a procedure.

"I was inspired by aviation and what made aviation the safest form of transportation," said the technology's inventor, Teodor Grantcharov, MD, PhD, who recently joined the Stanford School of Medicine as a professor of surgery and associate chief quality officer for innovation and safety at Stanford Health Care.

"Our patients are not aircraft, but a lot of the methods — the culture, the approach to safety, the never-ending pursuit of 'safer' — is transferable," he said.

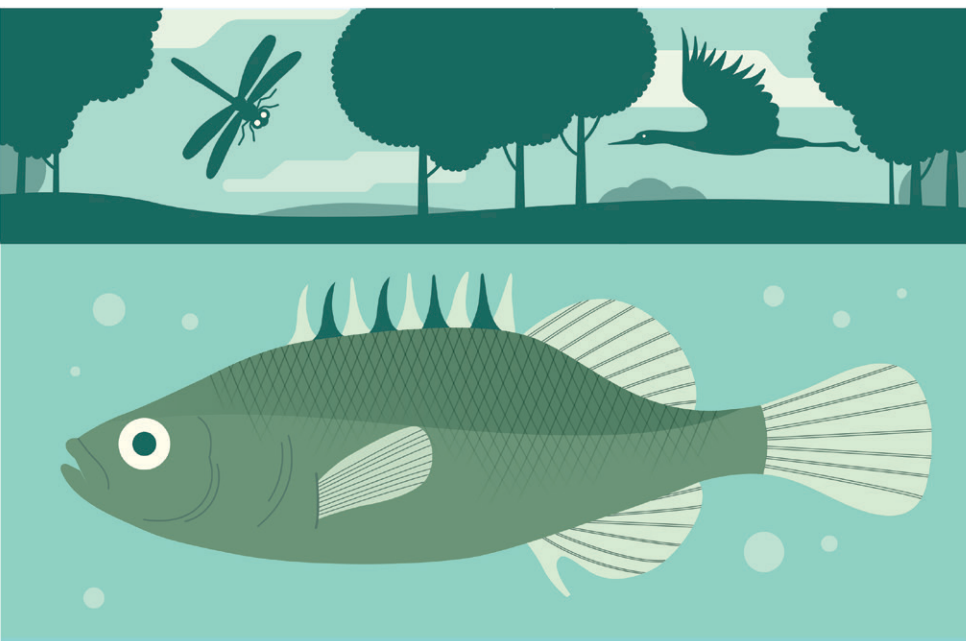
The information gathered by the technology will be used to pinpoint opportunities for improvements in efficiency, collaboration or safety.

Hopeful monsters

STANFORD MEDICINE RESEARCHERS have confirmed a long-standing assumption about natural evolution: Naturally occurring mutations can lead to the acquisition of major new structural traits that are beneficial for survival.

Research published in September 2022 in *Nature Ecology & Evolution* identified changes in a key developmental gene that increase the number and govern the length of the major defensive spines of a fish called the stickleback. New spine traits improve the two- to four-inch-long fish's survival — flying in the face of an assertion by anti-evolutionists that major changes will always leave animals unfit to survive in the wild.

"Scientists already know that changes in the regulation of this gene, called HOX, control the development of major body structures during development," said David Kingsley, PhD, professor of developmental biology, who led the study. "What's new is that we conclusively show that mutations in this gene produce major changes in wild animals — new features that help fish thrive in natural environments."



Sticklebacks evolve rapidly and dramatically in response to changing environmental conditions. For example, a lake rife with fish-eating insects often houses sticklebacks with fewer and shorter spines to grab, but a pond with larger fish or birds that swallow their fish sticks whole is likely to boast sticklebacks with longer, more numerous, throat-scratching spines.

"Our findings refute the common argument that these types of genes are so important, so fundamental, that animals with mutations in these regions wouldn't survive in nature — that if you play with master regulators, you're only going to make a hopeless monster," said Kingsley, a Howard Hughes Medical Institute investigator and the Rudy J. and Daphne Donohue Munzer Professor.

ILLUSTRATIONS BY HARRY CAMPBELL

Counteracting Alzheimer's

A MUTATION HAS BEEN FOUND that protects people who are genetically predisposed to Alzheimer's disease.

The mutation was identified by analyzing massive genetic data sets in an international collaboration of scientists led by Michael Greicius, MD, the Stanford School of Medicine Iqbal Farrukh and Asad Jamal Professor of neurology. Called the R251G variant, the mutation brings about a change in the makeup of a protein known as apolipoprotein E, or APOE — which is implicated in Alzheimer's.

"If we, as a field, can figure out exactly how the R251G mutation reduces risk, then maybe we can come up with a small molecule drug that gets into the brain and mimics what R251G is doing," said Greicius, senior author of the research published in May 2022 in *JAMA Neurology*.

Dueling diets

IN A HEAD-TO-HEAD comparison of two low-carb diets, ketogenic versus Mediterranean, the keto diet fell short in nutrient levels and ease of maintenance, according to a May 2022 study in the *American Journal of Clinical Nutrition*.

The ultra-low-carb, high-fat keto diet drastically restricts carbohydrate intake. The low-carb, moderately high-fat Mediterranean diet emphasizes vegetables, legumes, fruits, whole grains, olive oil and fish.

Both controlled blood glucose levels and aided weight loss, important benefits for people with or at risk of Type 2 diabetes.

But keto provided less fiber, thiamin, phosphorus and vitamins B6, C, D, and E, and was harder to follow. The takeaway?

"There's no reason to restrict heart-healthy, quality carbohydrate foods above and beyond," said Christopher Gardner, PhD, professor of medicine and the study's lead author.

RECKONING WITH HEALTH'S SOCIAL CONTEXT

Why zip codes, culture
and support networks matter

PHOTOGRAPHY BY LESLIE WILLIAMSON

ILLUSTRATIONS BY BRYCE WYMER

AS A NEURO-ONCOLOGIST, Reena Thomas, MD, PhD, takes care of patients with brain tumors and metastatic cancers that have spread to the brain — among the toughest cancers to treat. Her patients who are able to enroll in clinical trials for new, experimental therapies tend to have the best chances of survival. But clinical trial participants don't reflect the diversity of all the patients she sees.

"Unfortunately, as neuro-oncologists we're often dealing with diagnoses that do not have a cure," said Thomas, a Stanford School of Medicine clinical associate professor of neurology and neurological sciences. "The truth is, patients in clinical trials do better. There are more lines of treatment available to them beyond the standard-of-care options."

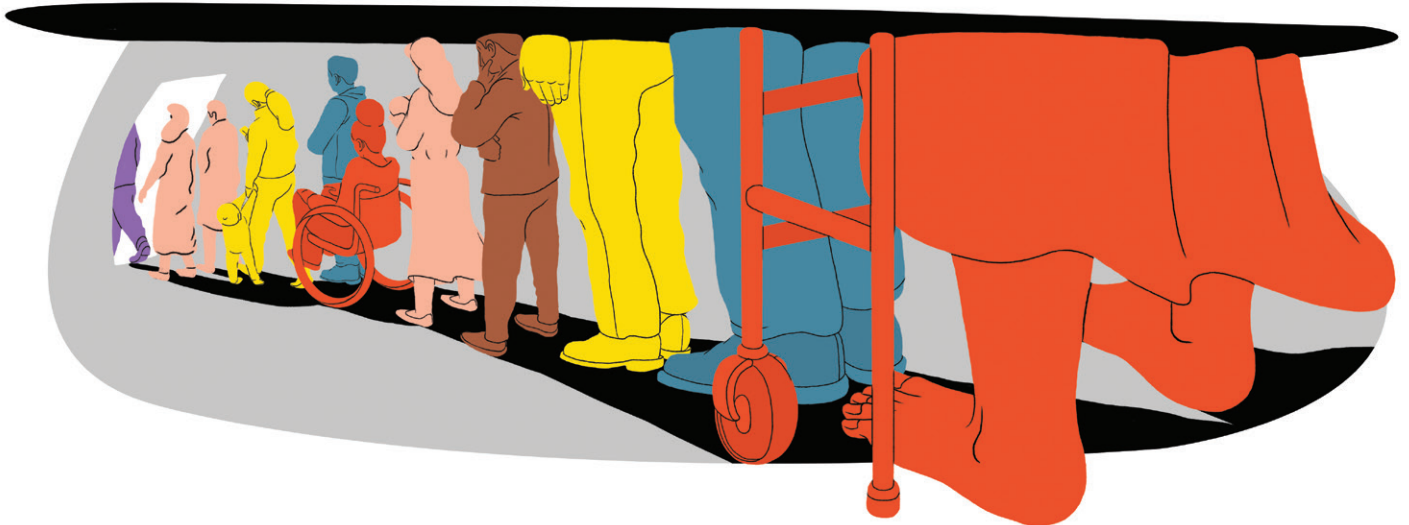
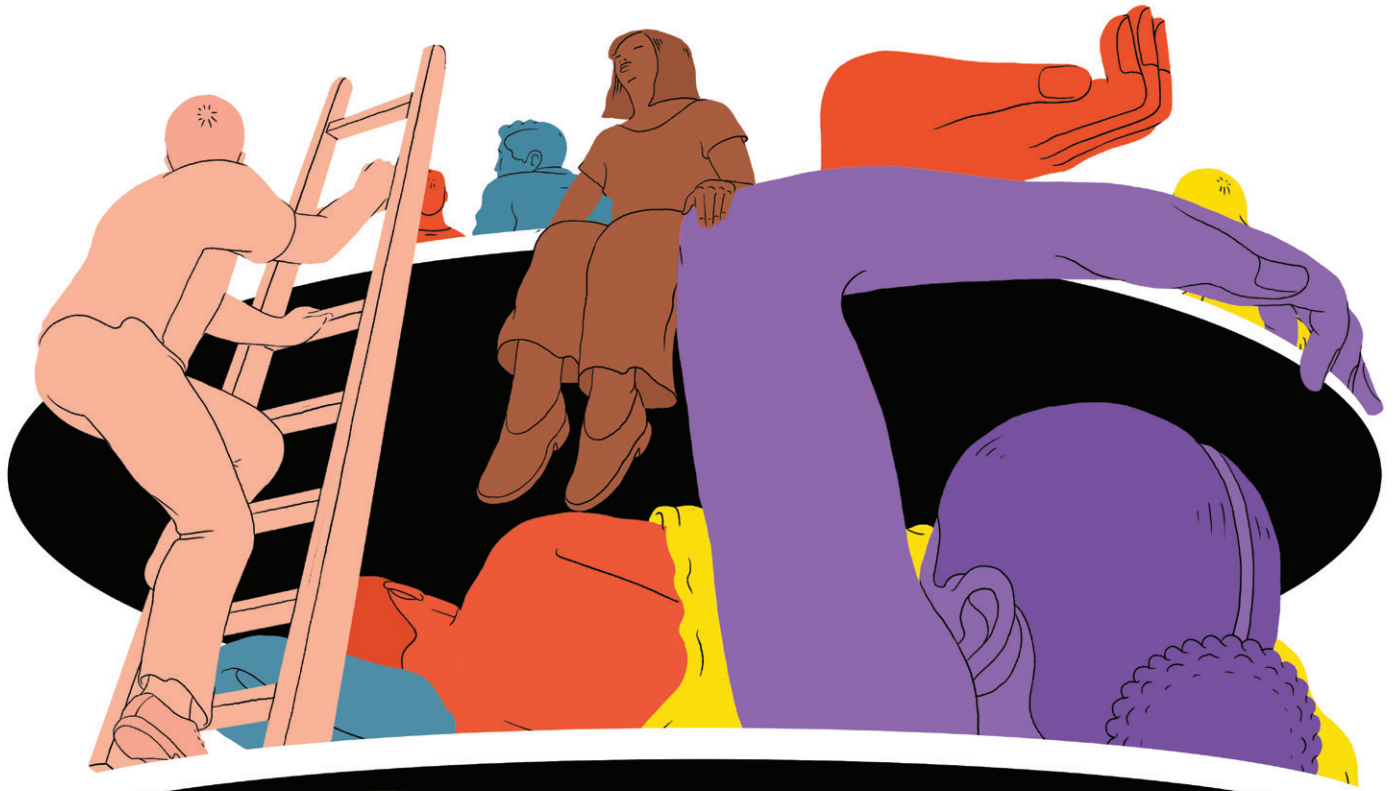
That means her patients' prognoses can be influenced by social determinants of health in addition to genetic variations or lifestyle choices.

Social determinants of health, as defined by the federal Centers for Disease Control and Prevention, are the conditions in the places where people live, learn, work and play that affect health and well-being. Income, education, housing, food insecurity, so-

cial support and discrimination are just a few examples.

Social determinants of health do not mean that any individual's health is dictated by their circumstances, but studies on a population level have revealed strong links to all kinds of health issues. They can influence behaviors like smoking, exercise, diet and sleep; increase exposure to pollutants and infectious diseases; and limit the time, energy and resources to access health care.

For Thomas' patients, for instance, participating in a clinical trial can feel like a full-time job. Trials can be difficult to understand, require numerous visits to the hospital, more oversight, more medications and more monitoring for side effects to ensure safety. Many pa-



tients lack the means of transportation, the support of friends or family, the language skills or simply the time to join a trial.

These socioeconomic factors originate far upstream of the diagnosis itself and are often overlooked in medicine, though that's beginning to change.

"You can see what's happening in the river right in front of you, but social determinants of health are what's upstream," said David Rehkopf, ScD, associate professor of epidemiology and population health and director of the Stanford Center for Population Health Sciences. "If the river starts to flood, would you only focus on scooping water out of the river in front of you, or would you go and see what the cause of the problem was upstream, and set up a dam or stop the leak?"

Rehkopf and other researchers are looking upstream. He studies how decisions made by governments and corporations, such as tax policy, can influence health.

"If you have a lower level of education, that constrains what kind of job you can have, and that constrains your earning ability, and that constrains where you live, and that constrains where your kids go to school," he said. "And this cascade of factors can act synergistically together to give people fewer opportunities to be healthy."

An upswing in research

FOR AS LONG AS POPULATION-LEVEL data on health have been collected, people have noted the impacts of work and living conditions on health. In the 1700s, studies showed that mortality rates in Parisian neighborhoods varied according to the poverty levels of their residents. By the early 1900s, public health work in the United States had collected data connecting pellagra — a disease caused by a vitamin B3 deficiency — and other diseases to poverty.

In 2008, the World Health Organization published a landmark report on social determinants of health, warning that "social injustice is killing people on a grand scale," and calling on countries to take action to close the health gap. More recently, the COVID-19 pandemic's disproportionate effect on communities of color and the murder of George Floyd at the hands of police have brought more urgent attention to the health implications of socioeconomic inequalities, Rehkopf said. Published research on social determinants of health has increased six fold over the past decade, with a steep rise since 2020.

Studies suggest that such issues outweigh medical care or lifestyle choices in their overall contributions to health. Though researchers who focus on these factors have often faced skepticism, said Rehkopf.

"The first objection was that it's too difficult to study these kinds of fundamental things in society: If you can't do random-

ized trials, then it's not amenable to scientific investigation," he said. In the past decade, however, new statistical methods and ways of collecting data have shown that randomized studies are not the only way to make causal inferences.

"The second thing that people say is, 'Well, we know they're important, but they'll never change,'" Rehkopf said. "The work that we and other people have done is to show these things can change over time." The federal earned income tax credit that provides tax breaks for people with low to moderate incomes, for example, has dramatically decreased child poverty in the United States and translated to improved health of children and their families, according to Rehkopf.

Clinicians like Thomas are taking into account how non-medical factors affect their patients' health. "Understanding that social determinants of health can limit a patient's ability to consider clinical trials, for example, allows us to attempt to dismantle those barriers, as an institution and as clinicians," she said. That includes providing the appropriate educational resources, having conversations around a patient's nonmedical concerns and recruiting a workforce that reflects the diversity of the patient population.

"Social determinants of health is an area that is underfunded and understudied," Thomas said. "The reality is, they are some of the most insurmountable challenges that we have facing clinical medicine."

At Stanford Medicine, a broad array of educational, clinical, research and community initiatives are addressing the challenges and opportunities presented by social determinants of health. From childhood screening for food insecurity to the first large-scale, nationwide study of LGBTQ+ health, from mobile apps that document health inequities to data sharing for population health research, these programs recognize that health begins outside the doctor's office. — NINA BAI

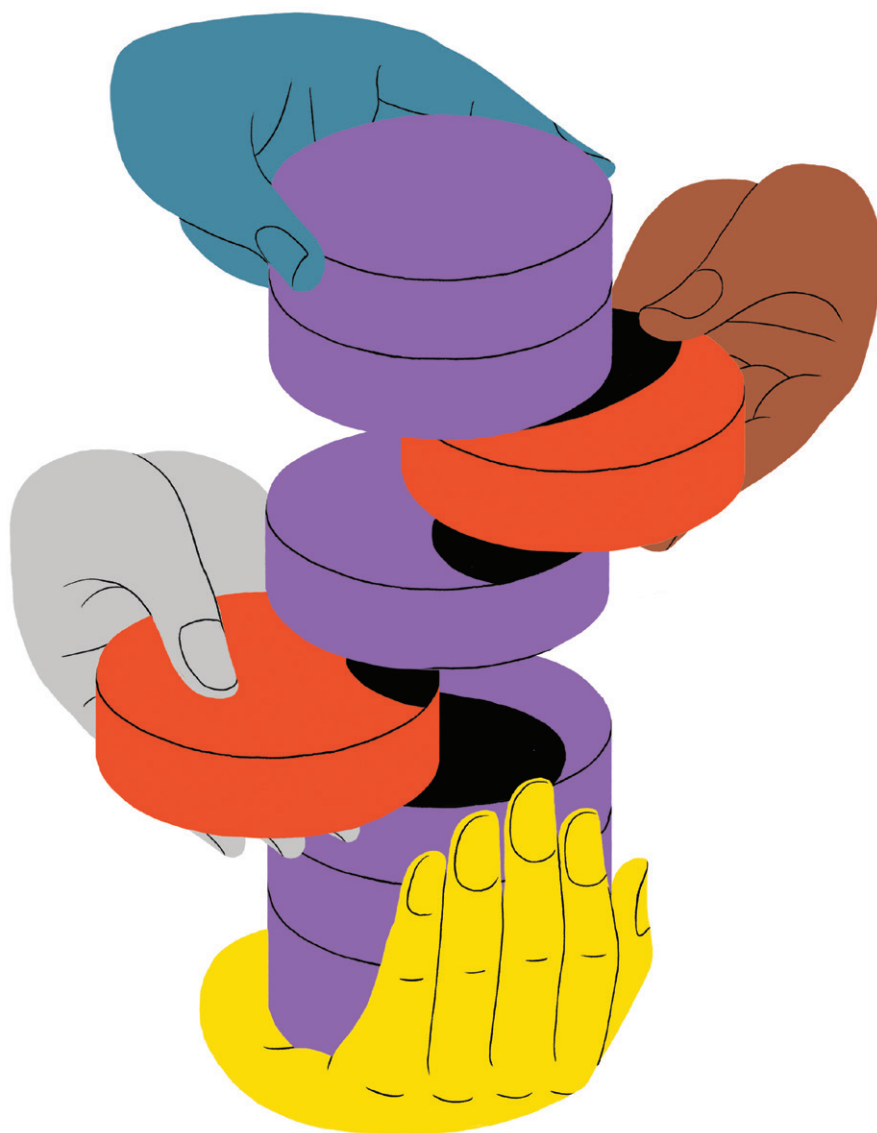
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AGENTS OF CHANGE

A program for medical students
has developed a host of leaders in fighting
health disparities

EDO IGHODARO WAS, AND STILL IS, fascinated by the brain, but she felt her studies didn't capture the complexity needed for well-rounded patient care.

"As a neuroscience undergraduate major, my classes tended to be more focused on the biological aspects of a person's



health,” said Stanford medical student Ighodaro. “But after volunteering at an immigrant community clinic, I decided I wanted to dedicate more time to exploring and studying the other aspects, including environmental and social factors, that could affect one’s health as well.”

While working as a care coordinator for pregnant patients in a Chicago clinic after graduation from college, Ighodaro witnessed socioeconomic factors that can discourage patients from seeking care. She further explored these factors when she entered the Stanford School of Medicine in 2022 and joined its Leadership in Health Disparities Program.

The program began in 1984 as the Early Matriculation Program, developed by professors Fernando Mendoza, MD, and Robert Cutler, MD, and administrator Ronald Garcia, PhD, to empower incoming minority medical students and others who were educationally disadvantaged to tackle health care inequi-

ties and obstacles their patients might face.

In 2007, the program opened to all medical students — though many still come from minority populations — and evolved to also teach skills needed to become faculty members or hold other leadership roles in addressing those inequities, said Felipe Perez, MD, the program’s director, who noted that graduates have become leaders at such places as MD Anderson Cancer Center, Harvard University and Johns Hopkins University.

During the summer quarter before medical school begins, the students in the program conduct a research project, take introductory courses in anatomy and clinical skills and participate in sessions to develop leadership skills and understand who they want to be as a doctor.

After the summer, students meet every quarter, join the previous year’s students for social gatherings and attend a two-year leadership seminar series.

“When you’re a minority student entering a medical school, having a cohort of students who are going to have your back is one of the greatest feelings,” said Perez. “When they show up for their first day, they have that group and that support. And I think that sense of belonging is going to help them go further in life.”

The force behind medical student Sofi Vergara’s decision to join the program is her

desire to become an agent of change.

“We infiltrate systems of power by training ourselves to enact change from within the communities,” said Vergara, a first-generation immigrant from Ecuador who has experienced poverty and health disparities firsthand as an international low-income student. Like Ighodaro, Vergara was seeking to break out of the lab and into communities.

“Seeing the medical students go through the program, you see them come in eager to change our health care system,” said Perez. “We get to hear their vision of what a better tomorrow looks like.”

Vergara’s research project examined skin color bias in the use of pulse oximeters — devices that clip onto a fingertip to measure the oxygen level in a person’s red blood cells by analyzing light that passes through the finger. Darker skin tones lead to overestimates of the oxygen level, an error that could mean the difference between receiving oxygen therapy or not.

The project doesn't end with the reporting of scientific results. With health disparities work, you must turn the results into outcomes, she said. "These findings are really not significant if you're not willing to work with those communities," said Vergara.

Fatima Al Rashed is another student in this year's cohort. Her research found that rural areas tend to lack policies to expedite stroke care. She wants to be a neurosurgeon, providing more access to previously underserved populations. But she also wants to raise the profession's consciousness about disparities.

"It's a very important topic that applies to all fields of health care," said Al Rashed.

"All health care professionals should be aware of what disparities they are dealing with within their own fields," she said.

That, Mendoza said, is the point of the program, which has graduated more than 400 students since 1984.

"We're not just going to send people back to the communities, which is important," said Mendoza, professor emeritus of pediatrics. "We're creating leaders who are going to change medicine. Just think about what it's going to look like in 20, 30 years from now." — EMILY MOSKAL

— Contact Emily Moskal at emoskal@stanford.edu

SPEAKING THEIR LANGUAGE

A critical need for more Latino physicians

A YOUNG WOMAN IN LABOR WAS in crisis and had a crucial decision to make. Her doctors at Lucile Packard Children's Hospital Stanford had discovered an infection in her placenta, a condition that required an urgent cesarean section. That procedure is most safely conducted with the patient awake and receiving an epidural — a pain-relieving injection of medication near the spinal cord often used during labor. The alternative would be general anesthesia, a riskier choice during a C-section for the woman and newborn.

Yet the patient was hesitant to have an epidural because she, like many women in her native country of Nicaragua, believed the procedure causes paralysis and permanent back pain. U.S. Latinas in general are 20% less likely to receive an epidural than their white counterparts, and that comes with an increased risk of maternal and newborn death, according to Cesar Padilla, MD, a Stanford Health Care obstetric anesthesiologist.

The woman, an immigrant to the United States, spoke little

English, but one of her doctors was Padilla, who speaks Spanish, and he told her of the low risk epidurals pose, especially compared with the larger risks of general anesthesia. She agreed to an epidural, but without a Spanish-speaking doctor who understands the cultural myths, she may have gone without it and had complications like bleeding and heart failure, said Padilla.

"It's hard not to see your loved ones when you're dealing with such cases because they are a microcosm of our communities," said Padilla, whose parents emigrated from Mexico. "I felt elated after her successful delivery. But what if I didn't have that cultural connection?"

A dearth of Latino physicians

MOST SPANISH-SPEAKING patients in the United States are not treated by Spanish-speaking physicians. The percentage of U.S. physicians who are Latino has remained roughly the same for 40 years: 6%, despite a growing Latino population of about 19%. In California, the portion of the population that is Latino is more than double that, according to the U.S. Census Bureau.

To recognize the need for more Latino physicians, Stanford Medicine physicians, students and colleagues launched National Latino/a Physician Day on Oct. 1, 2022. The campaign is the brainchild of Padilla and Stanford Medicine-trained pediatric hand surgeon Michael Galvez, MD, now at Valley Children's Hospital in Madera, California, who organized the day's promotion with an alliance of Stanford Medicine Latino physician faculty, Stanford Latino Faculty Advocacy Meetings, founded last year.

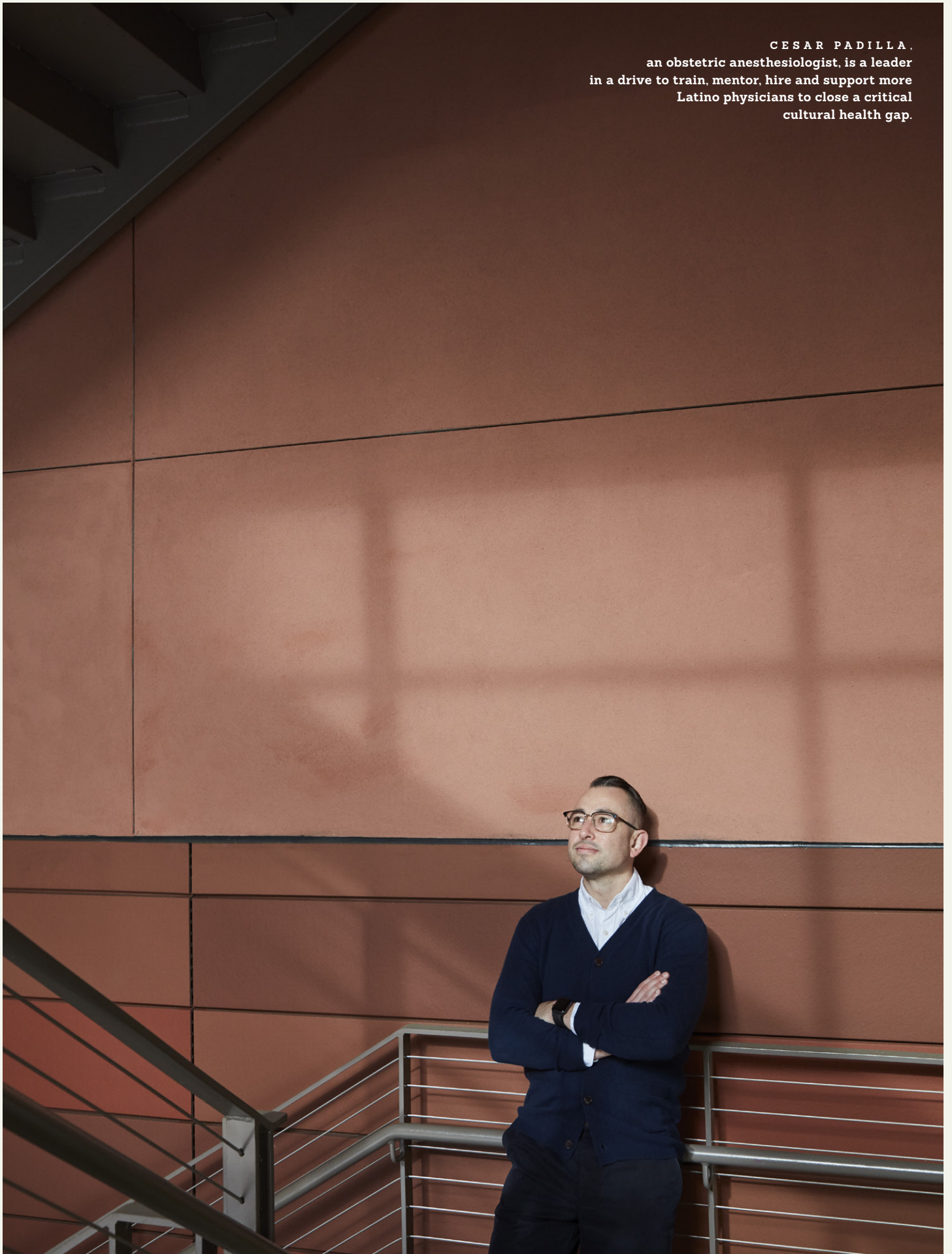
The organizers celebrated the day through social media, and more than a dozen health care organizations around the country ran in-person and online events. California Surgeon General Diana Ramos, MD, gave support through a Facebook Live event promoting the day. Southern California Kaiser Permanente organized the largest in-person event, called Super Saturday, in Los Angeles with roughly 200 people.

Padilla said his social media posts garnered more than 14 million views.

The sale of promotional T-shirts by MiMentor, a program dedicated to mentoring Latino pre-medical students and run by the Latinx Physicians of California, played a major role in outreach, with proceeds going to the same program.

At Stanford Medicine, Padilla and incoming obstetric anesthesiology fellow Lydiesther Martinez, MD, will lead courses for their colleagues on talking with Spanish speakers about epidurals. They hope to dispel myths and increase the number of Latinas having epidurals, which makes childbirth safer, according to Padilla. It's just one way, Padilla said, that Latino physicians can have a positive impact on patient care.

CESAR PADILLA,
an obstetric anesthesiologist, is a leader
in a drive to train, mentor, hire and support more
Latino physicians to close a critical
cultural health gap.



Padilla said that employing, mentoring, training and supporting more Latino physicians is critical.

“Six percent is not enough,” he said. “We’re here, but there needs to be more of us in order for clinics and hospitals to effectively care for our patients.”

Padilla hopes that this year the state will officially recognize National Latino/a Physician Day so more eyes will be on the movement and more Latino physicians will be hired and feel welcomed into the profession, he said. — EMILY MOSKAL

— Contact Emily Moskal at emoskal@stanford.edu

AFTER THE CURE

In rural California, one physician investigates how to get follow-up care for childhood cancer survivors

TODAY, MORE THAN 80% OF CHILDREN WITH cancer are cured. After months or years of surgeries, chemotherapy and radiation, survivors return to home and school, as their parents draw deep breaths. Instead of illness, kids focus on homework, friends, video games and swimming lessons. They scrimmage with their siblings. They grow up and lead relatively normal lives.

But the phrase “relatively normal” hides struggles. Survivors of childhood cancer face lingering health challenges and need regular checkups to detect late-onset effects of treatment, such as heart and lung problems that emerge years after chemotherapy and secondary cancers linked to radiation exposure.

Upon graduating from cancer treatment, each child is supposed to receive a treatment summary from their pediatric oncologist to guide long-term medical monitoring. The summary includes details such as the original cancer diagnosis, specific chemotherapy drugs and radiation protocols used in treatment, and which medical tests survivors should receive, on what schedule, to look for late side effects.

But when, as part of a recent research project, Stanford Medicine Children’s Health oncologist Stephanie Smith, MD, asked teen and young adult cancer survivors and their parents about these summaries, she learned that many hadn’t looked at theirs in years.

“The vast majority said, ‘All my records are in a backpack, but they just sit there,’” said Smith, an instructor of pediatric hematology-oncology at the Stanford School of Medicine. “Or people would tell us, ‘I don’t know what I would do with a summary if I had one.’”

Smith’s research aimed to identify the medical gaps faced

by adolescent and young adult cancer survivors, mostly of Mexican heritage, who live in California’s Salinas Valley, an agricultural region a few hours’ drive south of the Stanford Medicine campus.

“There is a huge gap between what science tells us should happen in terms of their long-term care and what is happening,” said Smith, whose research received funding from a Stanford Maternal and Child Health Research Institute grant program aimed at addressing structural racism.

Hidden barriers

MAKING THE SHIFT FROM pediatric to adult medical care can be tricky for anyone, even if they don’t have complex medical needs. These young people also grapple with economic and cultural factors that compound the challenge — which, until now, have gone mostly unrecognized.

“We’re not getting to the most vulnerable people,” Smith said.

Smith conducted the study in concert with Jacob’s Heart Children’s Cancer Support Services, a Watsonville, California-based community nonprofit that assists young cancer patients and their families. During cancer treatment, Jacob’s Heart meets families’ basic needs with financial assistance, a food pantry, transportation to medical appointments, and family support specialists, who are similar to hospital case managers. Staff members also foster community by offering a summer camp for kids with cancer, frequent social activities, art therapy, and support groups for patients, cancer survivors, parents, siblings and bereaved family members.

The board of Jacob’s Heart recently identified an additional need in its community: supporting childhood cancer survivors as they navigate their long-term medical risks. A mutual colleague introduced them to Smith and they soon began collaborating with her to help close this gap.

In their joint project in early 2022, Smith and her team conducted detailed interviews with seven Jacob’s Heart staff members, 12 cancer survivors and 11 parents, spending up to two hours with each person to get a detailed picture of the difficulties they have faced after completing cancer treatment.

“We realized their cancer history is, in some ways, the least of their concerns,” Smith said. Survivors and families described having unstable housing, financial and insurance barriers, and issues integrating into school after cancer — challenges they often saw as more pressing than medical follow-ups.

They also encountered cultural and language divides: One survivor had to rely on an older sibling who was more fluent in Spanish to bridge a language gap with their mother. She knew the details of the survivor’s early-childhood cancer but spoke



ONCOLOGIST and researcher Stephanie Smith (right) at the Jacob's Heart Watsonville facility with child cancer survivor Cole Rossi and Heidi Boynton, executive director.

less English than her kids.

Families expressed a strong desire to put their children's cancer behind them, saying things like, "We don't think about that. It was 15 years ago and my son is well now." Mexican American family support specialists at Jacob's Heart told the researchers that this may be partly because the Spanish word "cáncer" carries a strong connotation of death.

"There's so much stigma and negativity that families' reluctance to discuss it totally makes sense," Smith said.

In some cases, families worried that their child missing school for medical reasons could somehow draw attention from authorities that might result in a visit from U.S. Immigration and Customs Enforcement.

"Families are scared of Child Protective Services coming to say, 'Why isn't this kid in school?' for an unexcused medical reason, and then finding an undocumented family member and calling ICE," Smith said.

"It's just heartbreaking that this is the undercurrent these families are dealing with and emblematic that there is so much families don't tell me in clinic visits. If you don't talk to the community and have partnerships with them, you as a physician actually have no clue what people are dealing with."

Even those who attended follow-up appointments said they found that cultural and language barriers sometimes kept them from getting information they needed.

"People were really hesitant to question doctors or nurses," Smith said. "They often assume the doctor knows best, or feel they need to show respect for others, or think they didn't understand something only because of the language barrier."

Survivors also described mental-health challenges: lingering symptoms of emotional trauma or depression, worries about sacrifices their parents and siblings made while they were sick, and guilt at surviving when some of the friends they met during treatment did not.

"They said things like, 'Do I have to become a model person and do something amazing with my life?'" Smith said. "There's a lot of pressure."

Tapping the real experts

THE PROJECT'S NEXT STEP IS TO work with survivors and families to brainstorm and test strategies to help. Smith's expertise in community-engaged research will enable her to measure the impact of these ideas and help Jacob's Heart staff scale up the things that work.

For instance, having young adult survivors meet with Jacob's Heart case managers before medical appointments might enable them to brainstorm questions they need answered, as well as strategies to broach their concerns with physicians, Smith said. But

that's her idea; she anticipates that the best concepts will come from cancer survivors.

"We need to bring parents and young adults into the solutions we try to develop," she said.

Cole Rossi, a 24-year-old student at California State University, Monterey Bay, agreed. Diagnosed with a brain tumor at age 6, Rossi completed cancer treatment at Lucile Packard Children's Hospital Stanford, with support from the Jacob's Heart team, in 2004-05. Today, Rossi volunteers with Jacob's Heart's summer camps and teen groups.

Though he's long been cured and will graduate from college in the spring, the aftereffects of Rossi's diagnosis persist, often in ways that don't make sense to others. "It's a bear," he said, citing, for example, the challenge of getting his professors to understand why his energy levels and memorization skills differ from those of other college students.

Insider knowledge counts when it comes to navigating how to grow up after cancer, he added.

"It's never over," Rossi said. "Being someone who has lived through that takes a big toll on you." — ERIN DIGITALE

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MAKING CONNECTIONS

Closing the gap for people without internet access or experience

WHILE MANY PEOPLE TURNED TO video chats and social media to help overcome the isolation caused by the COVID-19 pandemic, those without internet access faced growing isolation — from community, health care and other types of much-needed support.

As telehealth became a go-to option for care, many community health organizations ventured into the unfamiliar territory of trying to build sustainable and equitable high-quality virtual care experiences for historically marginalized communities.

To aid that effort, one of Stanford Medicine's community-based faculty members at Roots Community Health Center, Tem Woldeyesus, MD, a clinical assistant professor at Stanford School of Medicine, co-developed a screening tool to identify needs and challenges in using telehealth services. This is one of several Stanford Medicine initiatives that aims to close the digital divide for patients.

During academic year 2021-22, volunteers screened by phone more than 100 Roots clinic patients, primarily in East Oakland, California, to assess their readiness for telehealth and



barriers to using telehealth-enabling devices — for example, lack of access to a computer or internet connection.

The screening survey found that 72% of participants had reliable internet access; 80% had access to a video-capable device; and 67% felt comfortable using video calling platforms.

Before the survey, Roots was not aware of the extent that lack of internet service was a barrier to accessing virtual care. Now, Roots and researchers can re-allocate their efforts to further understand this need and address it.

“The lack of internet can influence other factors affecting health, such as finding a job, applying to other programs, continuing education and connecting with others within their community,” said Mayra Reyes, clinical services coordinator at Roots.

The group of 12 Stanford and UC Berkeley student volunteers, including medical students and undergraduates, conducted the interviews. Then they co-developed, with the Roots telehealth patient advisory council, solutions for each

core area: digital literacy, device access and internet access.

“Students come up with solutions based on patient needs and prototype and demo them in front of patients to get their feedback to see how we can quickly iterate and operationalize them within the health center,” said Woldeyesus.

Stanford medical student Kalijah Terilli joined the effort after she learned from her mother, a physical therapist for children with development delays, about the problems the digital divide posed for her patients.

“At Stanford Medicine, there’s a lot of emphasis on the development of new technologies and all the possibilities that offers,” said Terilli, who helped analyze the survey results. “But many people still don’t have access to existing technologies. Without addressing that gap, we’ll continue to leave these communities out of the conversation and perpetuate inequities.”

The team partnered with EveryoneOn, an organization that trains community-based institutions to provide digital skills training and resources to advance digital equity, to host a six-week digital literacy class at Roots in March and April 2022. To address the needs of participants who said they didn’t have access to or couldn’t afford broadband

service, the student volunteers and staff researched low-cost internet options and provided instructions for getting connected.

“Existing telehealth services and technologies often exclude vulnerable and marginalized communities in the design and implementation process. This is a sobering reality because these are the communities that stand to gain the most,” said Woldeyesus. “We’re trying to flip that narrative with inclusion of patients in the design and implementation of our telehealth services and ancillary support programs to advantage those that are systemically disadvantaged.”

Woldeyesus said many community members have no email address, which is another barrier to using telehealth platforms or patient portals because the applications require people to register using one.

“It’s the little encounters like helping a participant walk through the steps of sending a text message and connecting with family members that make the work impactful,” said Reyes. “Other times it is assisting clients with password recov-

ery so they can find an email connecting them to our workshops or group visits.”

Roots is seeking resources to expand the program’s reach and impact.

Digital literacy, device access and internet access have also been a concern for the Stanford Health Care, Department of Patient Experience. Understanding that these factors drive health and health care access, Rachelle Mirkin, the executive director for health education, engagement and promotion, helped launch a pilot study with digital literacy nonprofit Community Tech Network. The organization is testing a program to provide devices, internet access and training to patients and families to help keep them connected and prevent social isolation.

Mirkin said that it’s a common assumption that people have internet access. “Reality suggests there are still gaps in connectivity, knowledge and confidence that we must overcome to ensure everyone has the ability to be cared for.” — EMILY MOSKAL

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CITIZEN SCIENCE FOR HEALTH EQUITY

Mobile app empowers community members
to capture data and catalyze health-
promoting changes

NEARLY A THIRD OF THE WOMEN who live in Bogotá, Colombia, work full time as unpaid caregivers. For decades, these women — numbering more than one million — have been deprived of educational opportunities, economic autonomy and equal access to health care, exacerbating gender inequalities.

In recent years, however, the city of Bogotá has established community centers to offer them resources including child care, education, job counseling, washing machines and workout equipment.

There’s just one problem: Getting to the community centers can be difficult and risky for many of the women, who live in neighborhoods without safe walking routes.

In the summer of 2022, Stanford University undergraduate Zakaria Doueiri visited Bogotá to collaborate with a research team from Universidad de los Andes in supporting community members to address this issue. Working together, the team utilized Our Voice — a technology-supported participatory research method that Stanford School of Medicine researchers

have been optimizing for a decade to help people from all walks of life improve their communities.

With the project team’s support, local caregivers used Our Voice’s mobile app to record photos and audio or text narratives about their experiences walking to a Bogotá community center. The goal was to have those experiences inform ideas for making their neighborhoods safer and encourage more people to visit the center.

“A lot of policymakers don’t necessarily have the time or resources to go into these communities and really understand the intricacies of living there,” said Doueiri. “We wanted to give the caregivers an opportunity to document their perspectives and bring their ideas to the forefront of the conversation.”

The Our Voice citizen science method was developed by Abby King, PhD, a Stanford School of Medicine professor of epidemiology and population health, and of medicine. It began when she and her postdoctoral fellows were helping a few California jurisdictions make their cities and streets safer, more accessible and more walkable. The team designed what has evolved into a multilingual mobile app to let people track facilitators and barriers to healthy living in their neighborhoods — identifying everything from dark alleys that might need lighting to food “deserts” and unkept parks. Users record geotagged photos and audio or text comments, along with positive and negative ratings. The data are captured in community maps and reports that the citizen scientists discuss and interpret and then use to activate change through collaboration with decision-makers.

“We believe that community members are often the people most equipped to understand and gather data about their local environments,” said King. “We called it Our Voice because we wanted to give a voice to people who traditionally have not had a say in local policy.”

The Our Voice method led to immediate successes in an initial research project in East Palo Alto, California, including repaired sidewalks and a community garden. The power of this method, King said, is that it captures the essence of a place and its people in a way that typical data sets often can’t, and the collective data can catalyze relevant and sustainable solution-building.

Humanizing data

SANDRA WINTER, PHD, a former postdoctoral fellow at the Stanford School of Medicine who worked on the early development of the platform, still gets emotional recalling one of the first times she participated in data gathering with the app, joining a wheelchair-bound citizen scientist who pointed out the intersection where he’d been hit by a car a few weeks earlier.

“It was so much more powerful to hear it in this man’s words, and hear how it impacted his life, rather than reading in a



spreadsheet that there have been 10 accidents at that intersection,” Winter said.

Winter is now an adjunct lecturer at the Stanford Prevention Research Center and executive director of Senior Coastsiders, an organization in Half Moon Bay, California, that provides resources for older adults. In recent years, she has used the Our Voice platform and method to help aging adults along the near-by coast generate and activate ideas about making their neighborhoods more accessible. As a result of one of the Half Moon Bay Our Voice projects, officials added a new bus stop and shelter that made it easier for older adults to get to the grocery store and cleaned up trails and updated signage to make walking safer and more accessible.

Over the past six years, King has worked with Ann Banchoff, director of community engagement for the Our Voice Initiative, to expand it from a handful of Stanford University-area projects to scores of citizen science projects across 18 U.S. states and more

than 20 countries. A 2016 Robert Wood Johnson Foundation grant helped King and her team launch a global network of Our Voice collaborators worldwide. One example is a project in Thailand, where villagers displaced by a previously constructed dam are getting a chance to speak about how the changing environment is affecting their lives. In Sweden, a project is probing how to encourage adolescents from diverse backgrounds to be more physically active. And in Colorado, a researcher is using the method to choose locations for vending machines that disperse naloxone — a medication to reverse opioid overdoses.

Meanwhile, projects continue to be launched on the Stanford University campus. Undergraduate and graduate student teams recently collected student opinions on preventing sexual violence and promoting gender equity. The students suggested expanding access to single-stall restrooms, increasing campus funding for safe, communal gathering spaces, and boosting diversity among professors and teaching assistants, among other things.

King said the student projects reflect a broader trend in expanding the initiative’s network of projects and collaborators. Her initial goals often revolved around making

people’s environments more conducive to physical activity and healthy eating — issues about which King is particularly passionate.

“Now, we’re using it for a much broader range of topic areas,” she said. “We have Our Voice efforts aimed at infectious disease, social problems, environmental justice, mental health and sustainability.”

Virtual reality advantages

THE TECHNOLOGY platform is also adding new features. In Colombia, for instance, Doueiri integrated a virtual reality feature into the Our Voice workflow. So, as the unpaid care workers brainstormed how to make it safer and easier to get to the community center, they could each don a pair of virtual reality glasses and experience the walks their peers had recorded.

“They were all able to see each other’s perspectives, which really helped them come together as a team,” said Doueiri.

At Stanford Medicine Children's Health, Baraka Floyd, MD, (right) helps families lacking reliable access to food, with assistance from Lindsay Stevens, MD, (left) on electronic health record enhancements and Kimberly Browne, executive director of patient and family services.



Now, he's testing the same virtual reality platform with school-aged children in Half Moon Bay to support them in working with others to make their walks to school safer. Using virtual reality glasses can help them more clearly visualize what solutions — like new traffic signals or crosswalks — would look like in their community.

“Our goal continues to be to get residents of all ages and walks of life involved in using their own data to come up with solutions that may work better than some of the things that policymakers might propose,” said King. “There are so many different issues that this type of community-facing, by-the-people citizen science can help address, and we’re always looking for new opportunities, both at Stanford and beyond.” —SARAH C.P. WILLIAMS

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ARE YOU GOING HUNGRY?

Pediatricians are adding food insecurity to their health checks

AS THEY CARE FOR CHILDREN AND TEENS, a big question lurks in pediatricians’ minds: “What don’t I know about patients’ lives that harms their health?”

Behind the scenes, many families struggle to afford food, rent or child care. They might have trouble arranging transportation to doctor appointments, getting a landlord to eliminate mold at home, or finding safe playgrounds for their kids.

“Patients have an entire life outside the hospital and our clinics,” said Baraka Floyd, MD, a Stanford Medicine pediatrician and clinical assistant professor of pediatrics. “What’s happening there makes so much more of an impact on their care than anything I can do in a medical visit.”

Though many pediatric caregivers at Stanford Medicine Children’s Health ask families about their circumstances, the organization has lacked a tool to make sure the questions reach every patient or to consistently lead families to helpful resources. That’s set to change.

Floyd leads a multidisciplinary team that is modifying the electronic health record system used by Stanford Medicine Children’s Health, called Epic, to incorporate a sequence of questions about social determinants of health into each patient’s record. After an initial screening, the responses will be easy for clinicians to find.

“Otherwise, a family might be asked the same question by

five or six different people over their time with us,” said Floyd, adding that parents feel stigmatized by repeatedly having to explain their child’s unmet needs. “It can make the experience that much harder, even traumatizing for families.”

Connecting to resources

THE FIRST TWO SOCIAL QUESTIONS IN the electronic health record focus on food insecurity. A health care provider asks whether, in the previous 12 months, a parent worried food would run out — or it did run out — before they had money to buy more.

If parents worry about where their next meal will come from, it’s hard to focus on their child’s medical needs.

“When we address that need, it not only allows us to provide better care to improve health outcomes. It also gives the parent space to put their attention on mutually agreed-on areas necessary for their child’s care,” Floyd said. “This is especially true for children with complex health situations, who are more likely than other kids to have unmet social needs too.”

In collaboration with the Office of Child Health Equity, part of Stanford Medicine’s Department of Pediatrics, Floyd and her colleagues are partnering with Second Harvest Food Bank. If a family reports experiencing food insecurity, the clinician can generate an electronic referral to the food bank, where an employee calls to offer resources, such as help applying for food stamps or receiving drop-offs of boxes of fruits and veggies or prepared meals.

Digital food insecurity screening tools became available to clinicians in August 2022 — with the nephrology and gastroenterology clinics among the first to use them. The team is spending 18 months troubleshooting the system and working with the food bank to make sure it’s ready to respond to lots of referrals, before expanding screening to every patient.

Ultimately, the team plans to add screening for other social determinants of health: Financial strain and transportation needs are next on the list.

Broader benefits

THE SCREENING QUESTIONS WILL NOT ONLY benefit patients but also boost the ability of clinicians to advocate for large-scale changes. Stanford Medicine researchers plan to analyze aggregate data — about how common food insecurity is among their patients, where those patients live, and other risk factors they might have — to inform new ways to reduce structural inequities in patients’ communities. Based on her work in Bay Area community clinics, Floyd estimates that over 40% of her patients lack consistent access to enough food, and she believes this is likely an underestimate, she said.

“My hope is that we are able to understand the burden of

food insecurity in our community to help target interventions,” Floyd said. “Thinking about it from an equity perspective allows you to learn about the drivers behind the problem. What is causing these needs? What can our institution do to address these drivers?”

The uptick in food insecurity during the COVID-19 pandemic, especially among families with kids, reinforced the need for this work, she added.

“The pandemic really laid bare inequalities. We can’t afford inaction anymore.” — ERIN DIGITALE

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HEALTH DATA ON DECK

An information trove that’s helping to reduce health inequities

WHEN HOLLY ELSE, MD, PHD, was a Stanford medical student, a patient with multiple sclerosis told her that heat made her MS symptoms worse. “It’s called Uhthoff phenomenon — when core body temperature increases, suddenly neurologic symptoms worsen due to demyelination,” said Elser, now a resident in neurology at the University of Pennsylvania. “That got me curious and wanting to study how a warming climate might adversely impact people with MS and other heat-responsive diseases.” But just how to study the connections between global warming and patient symptoms wasn’t clear.

About six months later, Elser and a group of colleagues from a variety of fields at Stanford and Columbia universities conducted what Elser said will be just the first of many of their studies about the health ramifications of the changing climate for onset and exacerbation of neurologic diseases. The study, published in *PLOS Medicine* in 2021, used a detailed, nationwide commercial and Medicare Advantage insurance-claims database to examine the relationships between anomalously warm weather and acute care visits for people with MS.

“If we had wanted to conduct our own longitudinal epidemiological study, it would have taken untold resources to recruit an adequate number of patients to follow over several years,” Elser said.

[A deep well of data](#)

What made her retrospective study possible was the Stanford Center for Population Health Sciences. It gave her and her colleagues access to powerful existing data sets full of precise de-

tails about the timing and location of inpatient, emergency department and outpatient visits, which enabled them to examine the risk of MS-related health care visits as a function of average monthly temperature data from those patients’ zip codes.

Elser’s was just one of hundreds of studies the center made possible in 2021. The center is currently fueling upwards of 2,800 projects with data sets and has 1,580 members.

It’s a truism of our digital age that data is power. And so-called “real-world” medical data — brimming with potential but collected by physicians, pharmacists and insurance providers without research specifically in mind — has been recognized as an awesome but underutilized resource. It is abundant but expensive; it generally must be purchased from institutions that collect it and must be curated, or changed from its original format into one useful to researchers.

Patient privacy also makes these kinds of data sets daunting to work with. The ramifications of leaking any private patient information could be profound, so data must be kept secure with strict protocols and are often converted into safe, or de-identified, forms (so that no information can be associated with a particular patient) before they can be used by researchers. Such oversight and conversions are time-consuming, technically demanding and expensive, creating a serious impediment for researchers working on their own.

[Using data to improve health equity](#)

SINCE ITS FORMATION IN 2015, the Stanford Center for Population Health Sciences has been a vehicle for smoothing access to such real-world data for researchers in the Stanford School of Medicine community and beyond.

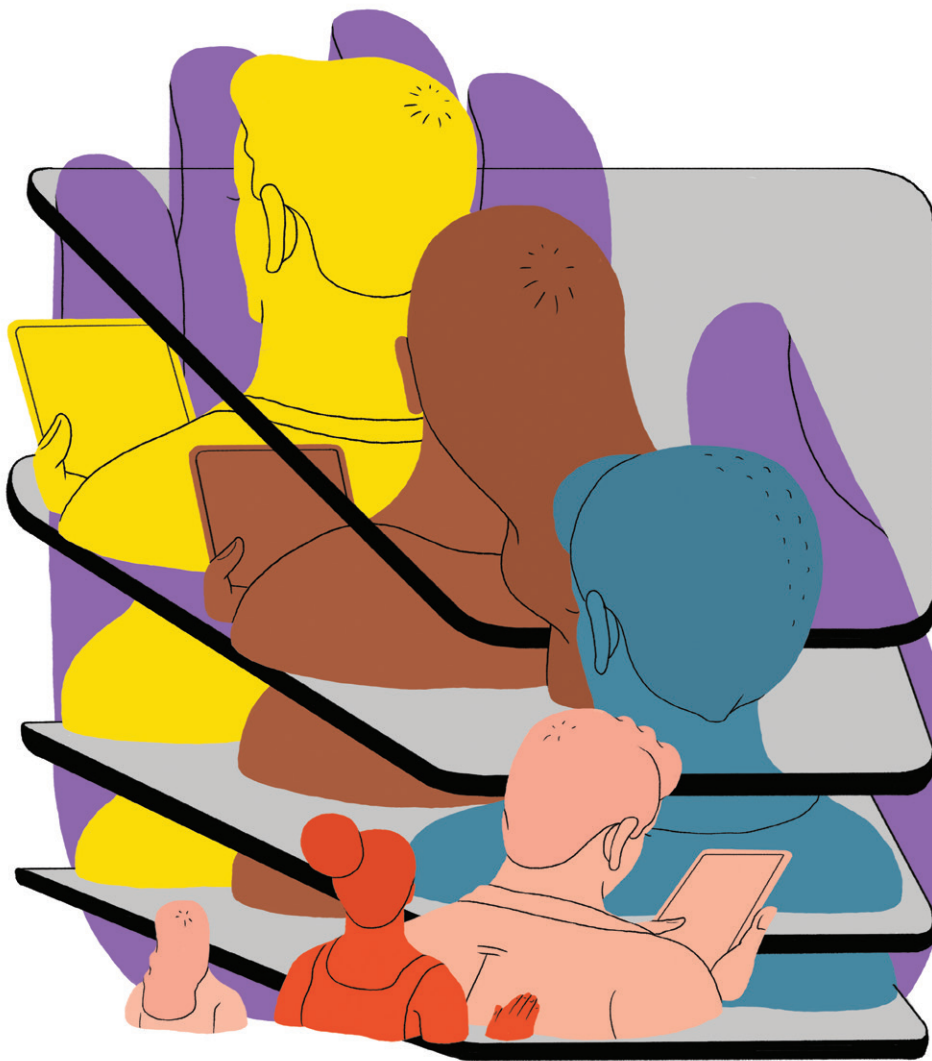
“Our focus on having a direct impact on the world beyond the publication — by influencing good new public health policy, for example — separates us from other data-oriented research centers,” said Executive Director Lesley Sept. “Reducing social and health inequalities guides everything we do.”

The center provides access to large databases full of useful details about its subjects’ health histories as well as administrative and organizational support to everyone from medical and graduate students to well-established multidisciplinary research labs, government agencies and nonprofits.

In the past year alone, the center has helped more than 1,000 users conduct more than 800 studies resulting in 326 journal publications.

These run the gamut from the particular, such as a clinical study of sociodemographic disparities in the management of pediatric thyroid nodules, to the big picture, such as measuring and combatting systemic racism at the county level.

The center offers users access to 72 different medical data



sets of various types. These include commercial databases such as MarketScan that tap into insurance claims, as well as messier, more broadly representative databases, including those shared by Medicaid, Medicare and the American Board of Family Medicine.

The latter provides longitudinal electronic health record data from primary care practices in all 50 states and includes detailed notes from primary care physicians that center director David Rehkopf, ScD, said are especially powerful.

“We can use those data to address pressing questions that can’t be answered in any other way,” said Rehkopf.

To ensure that researchers — even those without data-crunching experience — can tap into such powerful data, the center spent three years developing protocols and an internal infrastructure for curating data to keep patient information secure, and for optimizing databases for easy access.

The center is also a training ground for population health scientists. What’s more, it functions as a multidisciplinary commu-

nity incubator for developing, honing and testing study ideas, and it has an advisory team that helps translate study results into improved public health policy, said Rehkopf. “We work with people from the education, economics, sociology and psychology departments, from the School of Sustainability and, of course, with many from the medical school.”

The availability of so much data-research-related wisdom, as well the data sets themselves, were key to Elser’s research on the effects of global warming on patients with neurological disorders, she said.

“The center’s secret sauce is providing access to such a rich and diverse network of investigators,” she said. “I’m not an environmental epidemiologist or climate researcher, but I could rely on the center’s ecosystem of extraordinarily collaborative researchers.”

“The center is also a great equalizer,” said Elser. “You don’t have to be a tenure-track faculty member with an NIH-funded project to be able use these data to do important research.”

The center is also pursuing a grant for an 18-month project sparked by a request from the health officer for California’s Solano County to help identify and measure the health effects of structural racism countywide and to find policy or program changes that might mitigate it.

Another project is examining equity disparities in long COVID-19.

“The data we curate and provide at the center is equally useful for clinical projects in more generalizable and diverse populations, as well as projects that focus on the primary drivers of population health and health inequities,” said Rehkopf.

— GORDY SLACK

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To inquire about joining the Stanford Center for Population Health Sciences and getting access to its data and services, visit redivis.com/StanfordPHS or send an email to pbsdatacore@stanford.edu.

UNCHARTED TERRITORY

Surveying LGBTQ+ health to build the evidence base for medical care

AS MEDICAL STUDENTS AT the Stanford School of Medicine in the early 2000s, Juno Obedin-Maliver, MD, and Mitchell Lunn, MD, noted a void in research addressing many of the health and social issues that are unique to sexual and gender minorities throughout their lives.

“We were not finding many evidence-based outcomes about caring specifically for members of the LGBTQ+ community,” Obedin-Maliver said. “As members of this community ourselves, we noticed that sexual and gender minorities seemed to be having not just bad experiences with medical care but also worse outcomes. We saw a need to better understand the physical, mental and social health outcomes related to being an LGBTQ+ person.”

More than 7% of people in the United States identify as lesbian, gay, bisexual or transgender, according to a 2021 Gallup Poll. Yet a 2021 report by the Kaiser Family Foundation found that people who identified as LGBTQ+ were more likely than non-LGBTQ+ people to have their medical concerns dismissed or disbelieved and to be personally blamed for a health problem. All told, over one-third reported having negative encounters with health care providers as compared to fewer than 1 in 5 of non-LGBTQ+ people.

Putting participants first

IN 2015 OBEDIN-MALIVER and Lunn launched The PRIDE Study with colleagues at UC San Francisco, where they had both entered fellowship programs. It was the first large-scale, long-term national health study of LGBTQ+ people in the United States.

“We don’t believe being LGBTQ+ in itself dictates someone’s health, but the stigma and discrimination that sexual and gender minorities often experience can adversely affect a person’s health,” Obedin-Maliver said. “Loving and moving in a world that doesn’t see or value the experience of being LGBTQ+ can be a strain.”

For the ongoing study, the researchers built a national network of organizations to engage LGBTQ+ people in health research. “We want all types of diversity within the LGBTQ+ community,” Lunn said, “including people who are diverse in race, geography, education and income.” The PRIDE Study connects researchers and LGBTQ+ people via digital screening tools and questionnaires through a web-

site designed to be easily accessible.

“We made the study national and made it easy to participate online,” Lunn said. “Participants don’t have to travel to medical centers, which often remind them of negative experiences with health care providers. Instead, they can participate in the comfort of their own homes.”

More than 24,000 people across the country have signed up to participate in the study, which has published dozens of papers on topics as diverse as eating disorders, body dysmorphia, migraines, mental health, pregnancy and abortion among LGBTQ+ people.

“Traditional research tools can have different cutoffs or expectations for men and women based on the idea that people labeled as one or the other have different amounts of body water, muscle mass, liver size, etc.,” said Obedin-Maliver. “But this is problematic for transgender, nonbinary and gender diverse people. So how can science and medicine be more specific and accurate to meet the diversity of people as they really are rather than making assumptions that are not actually relevant to people’s health?”

Bringing results back to the community

COMMUNITY ENGAGEMENT IS a major focus of the study. Participants are treated as collaborators rather than study subjects, and research findings and next steps are shared among the participants before publication — in clear summaries without medical jargon.

“In the past, scientific and medical research has been extractive and separated from the communities it seeks to serve. This is not only unkind, it can be exploitative, and it makes for less than optimal clinical care,” Obedin-Maliver said. “If we want to impact health care for the better, we need to make sure what we’re finding comes back to our participants.”

Other researchers can also benefit from the study’s data. “Because we’ve created trust with the community, we’ve been able to generate more data than we can analyze ourselves,” Lunn said. “So we encourage researchers from other institutions and community investigators to approach us and help us analyze data on topics that interest them.”

Participants can choose which individual research projects they wish to be a part of and can opt out of the study at any time. But the researchers hope their collaborative approach will encourage people to continue their participation over time.

“Part of our work is making visible what has often been invisible in the past. People can come and go,” Obedin-Maliver said. “But we hope they come and stay.” — KRISTA CONGER

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THE PRIDE STUDY, launched by Juno Obedin-Maliver (left) and Mitchell Lunn, is 'making visible what has often been invisible in the past,' Obedin-Maliver said.

KEEPING BREAST CANCER SECRET

For South Asian women,
stigma stands in the way
of asking for support

WHEN ANU GUPTA HAD HER FIRST BOUT WITH BREAST CANCER AT AGE 29, she was reluctant to tell her parents.

“It was something that was never talked about in India when they were growing up,” said Gupta, a San Jose, California, resident. “There is this stigma in the South Asian community: What will society say if my daughter or mother has a breast cancer diagnosis?”

Gupta was taken aback by the diagnosis because she was unaware of any family history of the disease. But how could she really know? These matters were hidden.

Stigma can exert a powerful influence in the treatment and recovery of South Asian women with breast cancer, said clinical psychologist Ranak Trivedi, PhD, who specializes in understanding how social, cultural and interpersonal factors impact outcomes for chronically ill people.

The stigma may prompt those with breast cancer to delay care or to avoid seeking support from a community that is otherwise traditionally all-embracing, said Trivedi. That stigma was a common theme in a study she recently led on the psychosocial needs of South Asian breast cancer survivors and their caregivers living in the United States.

“Because of stigma, the individual may feel isolated because it’s not easy to share this as a diagnosis,” said Trivedi, a Stanford School of Medicine assistant professor of psychiatry and behavioral sciences. “There are many myths about breast cancer — that it is contagious or that a woman must be deserving of this disease. Girls may not be marriageable if a family member has had cancer. There are layers of stigma, depending upon how conservative the families are.”

BY RUTHANN RICHTER

PHOTOGRAPHY BY LESLIE WILLIAMSON

RANAK TRIVEDI'S MOTHER'S CANCER DIAGNOSIS CATALYZED HER CAREER FOCUS ON CAREGIVING ISSUES.





“Even when women know they have something horribly wrong, they don’t seek care because they don’t want to bare their breasts to doctors,” she said. “So people delay care and wind up dying from a disease that could have been prevented or managed.”

Easing the path to treatment

TRIVEDI, WHO HELPED CARE FOR her mother when she had breast cancer, said she undertook the study because so little is known about the kinds of care and support South Asian women need. Her goal was to help ease their treatment and recovery by improving their emotional and psychological support and making culturally relevant resources and services available to them. She said her mother’s cancer diagnosis 20 years ago became the catalyst for her career focus on caregiving issues, as she observed how her parents looked after each other.

“I saw how they both had the other person on their mind — the person they were caring for. That sparked my interest in how people manage chronic or serious illness at home and set the stage for all the work I’ve done since,” she said.

South Asians are among the fastest-growing ethnic minorities in the United States, and breast cancer rates are rising along with the population. Trivedi said incidence of the disease is increasing at a rate of 1.9% a year, with 1 in 8 South Asian women in the United States facing a lifetime breast cancer risk. Unique cultural influences can impact their care, she said, yet very few researchers have sought to document or understand their health care experiences.

Her study, called South Asian Family Approaches to Disease, or SAFAD, involved interviews conducted via video conference and follow-up surveys with 26 breast cancer survivors and caregivers in the United States. The researchers asked them about issues such as quality of life, depression and anxiety, pain management, their adaptation to American culture and their ability to navigate the health care system. The study was conducted between the fall of 2020 and the spring of 2022, but the results haven’t yet been published.

Trivedi noted that the culture in India is a collectivist one, meaning that when someone becomes ill, the community rushes to embrace the person and make his or her daily needs a group priority. But South Asian women who live in the United States lack this valuable communal support, so they often experience a sense of isolation, she said.

They might be fearful of sharing their diagnosis — some-

times even with older family members living in their home — so they do not have access to a broader network of people on whom they can depend for emotional and practical support.

“They felt that if they were in India, they would get a lot more help,” Trivedi said. “They would have more hired help to do laundry, wash dishes, help with cooking and clean the house. Here, it was falling on the nuclear family. With the woman sick, it ended up falling to other people who were not prepared to take on that role. We heard from the women survivors that they still had to care for other people.”

She said caregivers who were surveyed also reported feeling cut off from the community: “They were feeling ignored by the health care teams and by the friends and families too. People weren’t asking how they were doing.”

A need for culturally relevant resources

WHILE THE PARTICIPANTS SAID THEY TRUSTED THE MEDICAL CARE SYSTEM, they felt there was a lack of culturally relevant materials and resources, including information about the disease in their native language so they could refer to it and share it with family members.

“People want something they can take home, when they are not groggy or terrified, something that tells them what their treatment choices are,” Trivedi said.

Gupta, who was one of the study participants and said she received excellent medical care, echoed these sentiments.

Though she hesitated to call on her family for help during her first brush with cancer, she ultimately did so because she was so sick, she said. When she suffered a recurrence two years ago she alerted her parents, who now live in England, and they came to California to spend months taking care of her. They accompanied her to doctors’ visits, but Gupta had to explain what had transpired, which she found exhausting.

“My parents found it hard to digest the information coming to them,” she said. “Do I think it would have been useful for them to talk to someone in their language? One hundred percent. For my parents, it was hard to process all of that information in English. They would also have been inclined to ask more questions if they had been able to speak to someone in Punjabi or Hindi.”

Even the visit with the nutritionist did not seem culturally relevant, Gupta said. “It would have been helpful to customize that because our diet is very specific,” she said. “I know my

CONTINUES ON PAGE 50

**ANU GUPTA WAS RELUCTANT TO TELL HER PARENTS THAT SHE HAD BREAST CANCER —
THOUGH SHE ULTIMATELY DID, AND THEY CARED FOR HER FOR MONTHS.**

A CONVERSATION WITH
HEALTH EQUITY EXPERT ALYCE ADAMS

TOWARD EQUAL FOOTING

The passion Alyce Adams, PhD, has for improving health outcomes for people in marginalized communities was inspired by the suffering she witnessed of chronically ill elderly relatives in California, Oklahoma and Arkansas.

Adams' desire to understand how adults who had health insurance could have such catastrophic health outcomes eventually led her to Harvard University, where she earned a doctorate in health policy. She has since spent two decades at academic and research institutions conducting research to inform policies that address and prevent suboptimal treatment for people with multiple chronic conditions, particularly in minority and low-income communities.

Now, Adams, who holds the inaugural Stanford Medicine Innovation Professorship, is a leader in the Stanford School of Medicine's efforts to improve the quality of health care and outcomes for minoritized individuals and those from underserved communities.

In addition to teaching and mentoring, Adams co-directed the Stanford Medicine Commission on Justice and Equity's working group on health equity excellence. She is also the Stanford Cancer Institute's associate director for cancer health equity and the Department of Health Policy's associate chair for health equity and community engagement.

Priya Singh, Stanford Medicine's chief strategy officer and senior associate dean and a member of the Commission on Justice and Equity, recently talked with Adams about her health disparity discoveries and her vision for forging meaningful health equity advances at Stanford Medicine and beyond.

SINGH: What motivated you to do the work you do today?

ADAMS: Growing up, I saw the devastating impact that chronic conditions like diabetes had on my own family members. Worse still, I was troubled by the acceptance that these outcomes, such as repeat amputations and blindness, were just the consequences of being a Black person with chronic illness. It sparked my interest in health policy and its potential to improve health care and address these disparities.

SINGH: Why does chronic disease disproportionately affect marginalized groups? What can be done to help?

ADAMS: The drivers of disparities include factors at the patient, interpersonal, health system, community, societal and policy levels. For example, let's take medication adherence: Historical racial injustices toward Black patients have led many to distrust doctors and the treatments they prescribe. Similarly, physicians' personal beliefs about whether a certain patient can pay for newer medications may influence what is prescribed.

Health systems also might not have enough interpreters to help people who aren't fluent in English navigate their care options. Further, in some communities, the rising cost of housing and food can prevent a patient from being able to buy medications or follow through on their treatments.

Focusing on a single driver, such as access to high quality health care, is not enough to eliminate these disparities. We have to look at broader health and social policies as well — something we are doing at the new Department of Health Policy, where we take a multidisciplinary approach to developing policy solutions to address health inequities.

SINGH: Can you talk about how we can include more medically underserved people in medical research and why that's important?

ADAMS: At its core, impactful research involves asking the right questions and finding answers. To have the most impact, engaging with patients, communities and practitioners is critical. As scholars, we are experts at posing questions based on our theoretical understanding of the world and available evidence to support or refute those theories. However, people with lived experience and practitioners working to address their needs are better able to help us prioritize research questions with the greatest potential for impact. For example, community partners can identify environmental factors

that may contribute to disparities in cancer and other conditions.

Too often, the people who are selected as research participants or who volunteer to be part of the research team are not those who would most benefit from the research. Including people from communities affected by adverse health conditions enhances the quality of the work and its potential to improve health. We are partnering with community care providers and advocacy groups to educate communities about clinical trials and make patient participation easier.

In another collaboration, the Stanford Cancer Institute's clinical



HEALTH POLICY EXPERT ALYCE ADAMS (LEFT) WAS INTERVIEWED BY STANFORD MEDICINE CHIEF STRATEGY OFFICER AND SENIOR ASSOCIATE DEAN PRIYA SINGH (RIGHT).

trials office and Stanford Health Care are evaluating clinical trial proposals with an eye toward diversity, equity and inclusion. For example, we are encouraging scientists to consider opening trials to people who have more than one illness — who are typically excluded — to increase participation from patients who are more ethnically and geographically diverse.

SINGH: You have spoken about the need to have “equal opportunity for positive health outcomes.” Can you elaborate on this concept and explain how we can achieve it?

ADAMS: People with the greatest need are often the last to benefit from health care innovations. Therefore, in addition to improving access to high quality care, we need to identify strategies within and outside of health systems that can accelerate getting the benefits of treatment innovations to the most vulnerable patients.

The key to making this happen is building partnerships between researchers, patients, communities, practitioners and policymakers to create interventions that have equity at the forefront of innovation. For example, our research lab is working with cancer patients, survivors and clinicians to develop and evaluate an algorithm to identify which patients are at risk for chemotherapy-induced neuropathy. We are also working with these groups to understand patient perspectives on balancing the risks and benefits of chemotherapy.

SINGH: You mentioned using algorithms in cancer care. How else can new technologies such as artificial intelligence help address health disparities?

ADAMS: Exceptional scholars here in the Department of Health Policy and elsewhere have rightly drawn attention to the potential of algorithms to create or exacerbate bias in clinical care and outcomes. At a minimum, biomedical ethics should be applied to the development, deployment and adaptation of these algorithms to reduce potential harms and maximize potential benefits. Toward that end, we can ensure that the data used to train algorithms represents those affected by the algorithm, engage community and clinician partners in the development of workflows for implementation and monitoring of algorithms, and use artificial intelligence to augment rather than replace autonomous decision-making by patients and providers.

We are also paying attention to how these algorithms might inform the development of more equitable health care practices. Some of our work with colleagues at Kaiser Permanente, Harvard and Northeastern, for example, uses causal inference and machine learning to emulate randomized controlled trials to identify intervention combinations that might address underuse of clinically effective medications due to cost.

SINGH: Where are you seeing the most progress and what gives you hope?

ADAMS: I am heartened by the current focus on structural and systemic drivers of health inequities and efforts to improve research practices. As scientists, we have to be willing to cast a critical eye on our own work and change our approaches to acknowledge and address previously unacknowledged biases. For example, some journals are requiring publications of machine learning algorithms to include a discussion of potential biases toward minoritized subgroups.

In the same way that we have to be open to the possibility that our hypotheses are wrong, we have to be open to accepting where our methods may be flawed. That willingness to be introspective and curious about the future is at the heart of what we do. **SM**

WITH
DRINKING
WATER
OUT
OF
REACH
FOR
MANY
KIDS,
A
PEDIATRICIAN
PARTNERS
WITH
SCHOOLS
TO
GET
THEM
ACCESS

REAL-WORLD HEALTH
How social factors make or break us

Gulp

BY ERIN DIGITALE

ILLUSTRATION
BY
ANDREA
MONGIA

It was a few vocal middle-schoolers who set the course for Anisha Patel's research career.

In late 2006, Patel, MD, then a brand-new physician scientist, was working in Los Angeles middle schools to gather ideas for reducing childhood obesity. As part of a fellowship training program in community-based participatory research, she mapped barriers to obesity prevention — what food was available, how school cafeterias were set up, where and how much students could be physically active. Patel planned to take this information back to a community advisory board and her mentor at UCLA to develop an obesity-prevention strategy they could test.

But a few middle school students had a different idea for the young scientist.

“It was a really hot day out in the schools — these were low-income schools in low-income areas of Los Angeles — and we were observing the school cafeteria and the lunch line,” Patel, now a Stanford School of Medicine associate professor of pediatrics, said in a



recent interview for a Stanford School of Engineering podcast, *The Future of Everything*. “Students came up to us, and they said, ‘You know what? What we really need is, we need water.’”

Patel was taken aback. Students didn’t have water?

The nearest place to get a drink of water, she soon learned, was a porcelain fountain outside the cafeteria. It was not easily accessible to kids eating indoors, produced a feeble stream of lukewarm water and was clogged with leaves.

Even on a hot day, she thought, who would want to drink from that?

With that observation, Patel launched more than a decade of research and initiatives to improve access to a vital but overlooked component in children’s health: drinking water.

When she started, no one was aware that about half of California public school cafeterias lacked a place for students to get a free drink of water — and that was just one example of the problem. Safe, free, appealing tap water can help combat childhood obesity and dental cavities because water can replace sugary drinks kids otherwise consume, as Patel’s research is now demonstrating.

To make sure their findings have the maximum benefit, especially for vulnerable kids in low-income areas and communities of color, Patel and her collaborators have formed close ties with community members to inform the research, and with health policy and legislative experts to help translate their solutions into reality.

Community members as experts

DURING HER PEDIATRIC RESIDENCY AT Stanford Medicine, in the early 2000s, Patel realized she wanted to tackle kids’ health challenges at a larger scale than one-on-one doctor’s visits allow. Her fellowship training at UCLA was the logical next step.

Community-based participatory research, which she was learning to conduct, takes scientists outside ivory-tower isolation. Instead, researchers partner with community organizations to identify and articulate problems that affect real people. They collect data on the issues and solutions that community members suggest and promote their discoveries to people who have the power to change things.

It’s a method especially suited to investigating social drivers of health — poverty, racism, and the like — because it allows scientists to build studies that, from the start, account for insider knowledge in the communities where they work.

“The ideal scenario would be the community coming to us to say, ‘We want your help evaluating X,’ and then you work together to design the study you’re going to conduct,” Patel said. “It’s always action-oriented; communities don’t want you to

just describe the problem over and over. They want us to help them fix it.”

Traditional research takes, on average, 17 years to be translated into clinical practice, she noted. The goal of her work is to make changes much faster.

Not a drop to drink

AFTER HEARING STUDENTS’ INSIDER KNOWLEDGE — “Hey, we don’t have water” — Patel and her colleagues began examining water access in Los Angeles schools.

“A lot of the fountains were not in great shape, and students didn’t want to drink the water because of taste or quality concerns, or even safety concerns,” she said. “Bottled water was there for purchase, but it was next to all these more-enticing beverages, so even if you had the dollar to spend, you probably wouldn’t be getting water.”

At the time, vending machines in California schools were still selling beverages with added sugar, including juice, sodas and sports drinks. (Selling these drinks in schools has since been outlawed.) Sugary drinks increase the risk for obesity and dental cavities and cost money students don’t necessarily have.

Kids asked Patel’s team for free bottles of water with lunch, but a school district beverage contract with PepsiCo Inc. prohib-

ited offering students free bottles of beverages they might otherwise buy. To get around this restriction, Patel and her team designed a research project to test schools’ water for lead contamination, enlisting cafeteria staff to serve free, chilled tap water in dispensers at lunch. Kids could use cups or refillable water bottles to help themselves.

Patel refined the project with input from a community advisory board that included school district staff, teachers, parents, youth, the local public health department and others. At one of her presentations, Matt Sharp, who worked at a nonprofit then called California Food Policy Advocates, now known as Nourish California, heard her describe the dismal state of water access in Los Angeles schools.

“He said, ‘This is crazy,’” Patel recalled. Sharp enlisted Ken Hecht, LLB, a founder of the nonprofit,

“IT’S ALWAYS
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A CHAT WITH A FEW THIRSTY MIDDLE-SCHOOLERS LAUNCHED ANISHA PATEL'S DECADE-LONG QUEST TO GET CHILDREN EASY ACCESS TO SAFE, APPEALING WATER.

to raise the issue with state legislators he knew. Hecht is now policy director at the University of California Agriculture and Natural Resources' Nutrition Policy Institute.

The nonprofit sponsored a bill requiring California schools to offer water in their cafeterias, which passed both houses of the legislature but was vetoed by then-Gov. Arnold Schwarzenegger, who said the problem should be fixable without legislation, Hecht recalled. The veto prompted Hecht to call a colleague at the California Department of Education to ask for hard numbers on water access in school cafeterias. The department added a question about water to a school survey they were already conducting, and Hecht quickly had data to take back to

lawmakers: About half of California school cafeterias had no place for students to get a free drink of water.

The data changed Schwarzenegger's mind; among other details, Hecht recalls the governor saying in his famous Terminator accent, "I love water."

Schwarzenegger signed a new bill, CA SB 1413, into law in 2010. It reads, in part: "Schools participating in the school lunch program under this Act shall make available to children free of charge, as nutritionally appropriate, potable water for consumption in the place where meals are served during meal service."

The bill became a template for water provisions in the federal Healthy, Hunger-Free Kids Act of 2010, the first major revision to school food programs in more than 30 years. Both California and federal laws have also been changed to require free water in centers that participate in the Child and Adult Care Food Program, a federal program that funds food for child care and adult day care facilities.

Patel has collaborated with other researchers including Hecht and his wife, Christina Hecht, PhD, senior policy adviser at the University of California Agriculture and Natural Resources' Nutrition Policy Institute, to track how much the legislative changes improved students' water access. For instance, in a 2020 scientific paper in *Preventive Medicine Reports*, they showed that between 2010-11 and 2016-18, California schools doubled or

tripled the number of water sources in key locations such as food service areas, outdoor physical activity areas and classrooms; had more bottled water access; installed more fountains with appealing features such as refrigeration and filtration; and had more drinking fountains per student.

Tackling contaminants

AT UC SAN FRANCISCO, WHERE PATEL took her first faculty job, she launched a collaboration in 2014 with the Rural Community Assistance Corp., a national network of nonprofits that aid people in rural areas, to promote use of clean-water stations in

CONTINUES ON PAGE 50

unsheltered

INSIDE A CLINIC FOR HOMELESS PEOPLE IN SILICON VALLEY'S BIRTHPLACE

EVERY MONDAY, Crystal Unzueta, MD, a family medicine physician and clinical assistant professor who recently joined Stanford Health Care, works at a small Palo Alto clinic a five-minute drive from Stanford University's campus.

Her "most frequent patient," a 62-year-old man with poorly controlled diabetes, usually drops in on Monday mornings to have his pill box refilled. Mr. Issac, as Unzueta calls him, has been homeless for many years and doesn't want to risk carrying around all his medications.

Peninsula Healthcare Connection provides free health care to people like Mr. Issac who are homeless or at risk of becoming homeless. It's staffed by physicians from Stanford Health Care and the Palo

Alto Medical Foundation who take shifts a few times a month. Unzueta is from a Mexican American family and has spent the early years of her career working with lower-income, Spanish-speaking communities. In fact, it was the opportunity to work at a clinic like this that convinced her to move to Stanford Health Care.

Patients come to Peninsula Healthcare Connection with the same complaints as patients in any other clinic: diabetes, high blood pressure, allergies, sleep problems, stress from the slings and arrows of modern life. They come in to refill their prescriptions, to get their flu and COVID-19 vaccines, to seek help quitting an addiction, or to get a rash checked out.

But the fact that a large proportion of the clinic's patients have no home address stacks the odds against them. Some have been unhoused for decades. They live on the streets, in tents,

BY NINA BAI

PHOTOGRAPHY BY LESLIE WILLIAMSON

AN OPPORTUNITY TO WORK AT PENINSULA HEALTHCARE CONNECTION IS PART OF
WHY PHYSICIAN CRYSTAL UNZUETA CAME TO STANFORD MEDICINE.



in their cars, or move from one temporary shelter to another. Their lack of housing can exacerbate their health conditions, limit their access to care, and hinder their ability to make healthy choices.

Mr. Issac's diabetes is so poorly managed that it has put him in the hospital several times. "The first time I saw him he had just been released from the hospital. He was there because his sugar level was so high it was unreadable in clinic," Unzueta said. Having high blood sugar affects not only his physical health but also his mental state, often leaving him confused.

"It's really difficult for you to check your sugars when what's on your mind is, 'Where am I going to sleep tonight?' you know?" Unzueta said.

Recently, he had tried staying in a shelter recommended by clinic staff but left because of a loud snorer. He told Unzueta that he'd rather sleep outside by the train tracks.

The basic requirements of managing his diabetes — eating a low-carbohydrate diet, taking his pills and having insulin shots with regular meals — are often impossible for Mr. Issac to manage. He needs insulin shots twice a day, but the insulin needs to be kept in a refrigerator, which he doesn't have, though he tries his best by keeping it with an ice pack. Some nights he has dinner, some nights he has no food. When he can find a free breakfast program, it's usually pancakes or something similarly high in carbohydrates.

For the doctors who staff the clinic, the work can be rewarding and, for some, a reminder of why they went into medicine. They can make a real difference in their patients' lives and yet, as physicians, they cannot change the stark reality of their patients' homelessness, which often comes with broken social ties and past traumas. With no guarantee of shelter, food and safety, staying healthy is next to impossible.

Nowhere is it more clear that health is determined by more than medical care.

According to a 2022 survey, more than 10,000 people are experiencing homelessness in Santa Clara County, which bills itself as the "birthplace of Silicon Valley." Peninsula Healthcare Connection, located in the north end of the county, serves around 4,000 people a year, mostly from Palo Alto or East Palo Alto.

The clinic — two exam rooms, a tiny office and a chair in the entryway that serves as the waiting room — is part of the Opportunity Center, a nonprofit program

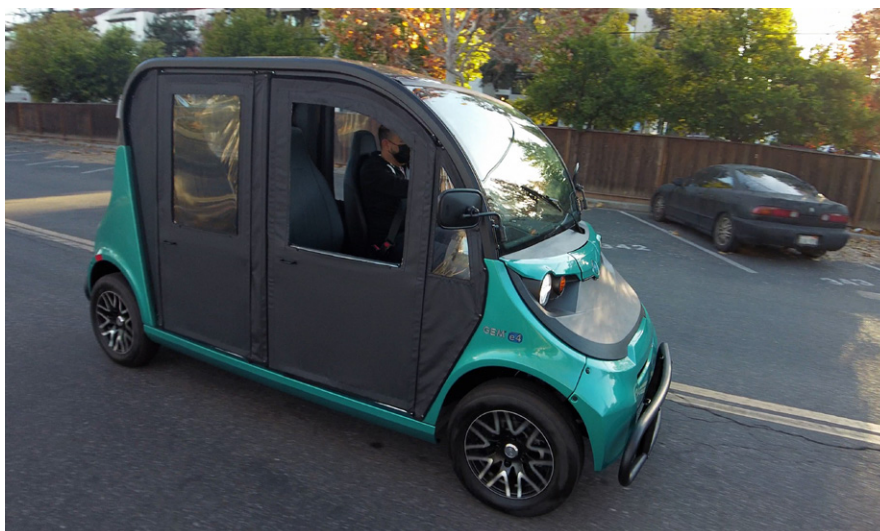
that provides permanent housing and services to previously unhoused people. Founded in 2006, the clinic is largely supported by federal and local grants, including funding through Stanford Health Care's Community Partnership Program.

Recently, a grant from Stanford Health Care allowed the clinic to purchase an outreach vehicle — a sort of semi-enclosed, street-legal golf cart — which will help address a common barrier for homeless patients: transportation. "It's a game changer," said Drew Navarro, the clinic manager and designated driver of the new vehicle. Many patients take multiple buses and trains to get to their appointments and even those with cars may not be able to afford gas. Having the new vehicle will enable Navarro to bring patients to the clinic, to a hospital appointment, or pick them up from the train station.

Navarro leads the clinic's outreach efforts, which include a street medicine team that goes out to encampments twice a month. The team is equipped to treat wounds, give out antibiotics, take blood pressure and blood sugar measurements, or even collect urine samples to take back to the clinic. "The whole point is to meet them where they are, because we know not everyone's going to come into a clinic," Navarro said.

He and outreach worker Michelle Myers are the familiar faces that can finally convince someone to get care at the clinic. They even do a bit of matchmaking between patient and physician to find the best fit.

"Drew and Michelle are really the heroes. They're the ones that really know the patients and the ones bringing folks in," said David Shi-Ann Chang, MD, an internist and clinical assistant professor who oversees the group of Stanford Health Care physicians at the clinic.



A NEWLY ACQUIRED GOLF CART PROVIDES CARE TEAMS AT PENINSULA HEALTHCARE CONNECTION A WAY TO GET PATIENTS WITHOUT HOUSING OR TRANSPORTATION TO THE CLINIC FOR THE SERVICES THEY NEED.

PRIMARY CARE PHYSICIAN DAVID SHI-ANN CHANG, WHO WORKS EXTENSIVELY IN COMMUNITY AND POPULATION HEALTH, TREATS MIRACLE, A PATIENT AT THE PENINSULA HEALTHCARE CONNECTION CLINIC.



At 10 o'clock on a warm Monday morning in November, the clinic was quiet. Unzueta checked her schedule for the day. She had only three appointments on the books, but Mr. Issac usually drops in without one.

The previous Monday, Mr. Issac showed up at the clinic feeling dizzy and looking extremely pale. His sugar levels were in the 500s — three times the normal level — so the clinic had to send him to the emergency room again. Unzueta wondered how he's doing this week.

The first patient on this day arrived for his appointment at 10:30 a.m. José, 59, is tall and has close-cropped, salt-and-pepper hair. He's there because his urine smells bad. Unzueta spoke with José in Spanish, his preferred language. This was his first visit with Unzueta, and he's animated and talkative. He tells her he has bipolar disorder, which makes him hallucinate voices and sinks him into depression most of the time. On Tuesdays, Wednesdays and Thursdays, he cares for and stays with his elderly mother, who has dementia. His siblings, worried about his bipolar disorder, won't let him be more involved. That means Mondays, Fridays and weekends, he's out of luck.

Families, Unzueta said, often don't know how to deal with mental illness in their loved ones.

Because José is considered partially housed, he doesn't qualify for a place in a long-term shelter. Four days a week, he sleeps in a tent on the street, where he's had his medications stolen, gotten into fights and been harassed by police. It's a difficult, depressing life out there, he told Unzueta, holding his head in his hands, but he's determined to stay as healthy as possible so he can take care of his mother.

Unzueta spent about 45 minutes with José, talking over his concerns, his medical history and his living circumstances. She

examined him and gave him a referral to a urologist at Stanford Health Care. Before he left, she also set him up to get a COVID-19 booster shot. Relatively long visits like this one are the norm at Peninsula Healthcare Connection, but a rarity in primary care clinics where patients are often filed in and out in 15 minutes. The slower pace allows physicians to build trust with their patients and learn about nonmedical circumstances — like housing, food and employment — that can affect their health.

"They don't teach you this in medical school," Unzueta said about accounting for the challenges of homelessness for her patients. She's worked a lot with low-income communities before, but never with so

many patients without housing. "Five years out of residency and I'm only now learning how a homeless shelter works," she said.

The truth is, not all physicians want to work with the homeless population. "There's still stigma associated with taking care of patients who are unhoused," Chang said. "Unless a clinic is set up with doctors and staff who understand that you need a lot of social services and wraparound support for these patients, it's not well equipped to take care of them."

Chang grew up in Palo Alto, known for its affluence. His homeless patients include former software engineers and a high school classmate. Working at the clinic has opened his eyes to how easily someone can lose their housing.

"It's sobering and also humbling to think all these environmental forces could have pushed anyone, really, onto this different pathway," he said.

Though most of the patients at Peninsula Healthcare Connection have a

case worker from the Opportunity Center to help connect them with social services, the physicians often find themselves in the role of patient advocate.

Angie Chen, MD, is a Stanford Health Care addiction specialist and clinical associate professor who works at the clinic every other Tuesday.

"Everybody is an amazing case of hope and effort and tragedy," Chen said of her patients.

Maggie, in her 50s, for example, had a thriving career in advertising before she became homeless in 2018. She takes buprenorphine for an opioid use disorder and Adderall for attention-deficit/hyperactivity disorder. After her psychiatrist died in

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longevity's secret sauce

IN NICOYA, COSTA RICA, where average incomes are among the nation's lowest, the average life span is 85 — among the world's highest. By comparison, a person in the United States can reasonably expect to live to just 77, according to federal census data.

So why is it that the people of Nicoya outlive so many others?

For a long time, scientists and demographers pointed to a handful of qualities seen in regions around the globe like Nicoya with extreme longevity: meaningful and plentiful social connections, consumption of unprocessed foods and living in communities in which walking is the main form of transport. It's a sensible observation, but it's short on scientific detail, said David Rehkopf, ScD, associate professor of epidemiology and population health and of medicine at the Stanford School of Medicine.

Rehkopf is uncovering those details. In the past 15-plus years, his studies in Nicoya have identified social factors, an immune system trait and chromosomal features — telomere length and methylation patterns — that correlate with longevity there. Now, he's studying other

regions of longevity in Greece and Italy and has found the same correlations.

"Our questions are, 'Can we figure out the social and biological reasons why people live so long in this area?'" said Rehkopf. (Maybe it's Nicoya's lack of grinding desk jobs that keeps their telomeres strong, or perhaps it's the absence of heavily processed cream-filled cookies that maintains dependable methylation.) "And 'What can we learn from that?'"

He's exploring how social factors influence those chromosomal features in Sardinia, Italy, and Ikaria, Greece — which along with Nicoya and Okinawa, Japan, comprise the four regions known as "blue zones" that are recognized for their populations' extreme longevity.

Blue zone, schmoo zone?

THE TERM BLUE ZONE was coined in 2000 by longevity researchers Michel Poulain, PhD, a senior researcher at the

A way of life that
keeps cells young in one
region of Costa Rica

BY HANAE ARMITAGE

ILLUSTRATION
BY
MICHAEL
PARASKEVAS

This illustration was inspired by a photograph of a five-generation family that lives in a small town in the mountains of Costa Rica's Nicoya Peninsula.



Estonian Institute for Population Studies at Tallinn University, Estonia; Giovanni Mario Pes, PhD, a senior researcher at the University of Sassari, Italy; and Daniel Buettner, a National Geographic fellow and one of Rehkopf's collaborators and friends.

The trio observed and described trends that seemed to exist in regions of the world where populations are longest lived, then marked them with blue circles on a map. But other academics doubted the scientific legitimacy of the trio's claims — particularly after other scientists and journalists claimed residents in other regions, such as areas in the Andes and Caucasus mountain ranges, also experienced exceptional longevity. (These claims were ultimately revealed to be based on incorrect information about residents' ages.)

Rehkopf, a molecular biologist-turned social epidemiologist, first heard about the impressively long lives of Costa Rican people when he was in graduate school at UC Berkeley. Even more intriguing to him was that the Costa Rican census and population-tracking system had stored generous amounts of meticulously gathered data from past decades. The information was systematically collected and verified via birth certificates, creating a trove of dependable, unmined data.

"That was key. It allowed for an unbiased approach to quantifying where people live the longest in Costa Rica and really let the data speak for itself," said Rehkopf. As his interest in Costa Rica grew, he met a like-minded Costa Rican demographer by the name of Luis Rosero-Bixby, PhD, who was a research collaborator of Rehkopf's postdoctoral mentor. Some 16 years later, Rehkopf and Bixby are still close collaborators as they continue to survey the people of Nicoya.

When Rosero-Bixby and Rehkopf first teamed up in 2007, Nicoya was not yet a sanctioned blue zone, and questions of the blue zones' legitimacy still lingered.

The research, which was conducted in collaboration with the Costa Rican Longevity and Healthy Aging Study, revealed a "spatial variation of longevity" in Costa Rica, meaning some regions throughout the country were home to an exceedingly high number of healthy old people.

"To my knowledge, that was one of the first studies that really showed strong evidence to support the phenomenon," said Rehkopf.

In that study, Rehkopf and colleagues showed that Nicoyan people who were around 60 years or older were about 29% less likely to die at that age than people in the rest of Costa Rica. They also found, in 2013, that men benefited from living in the Nicoya blue zone more than women did. Within Nicoya, men are seven times more likely to live to 100 than men living in

Japan, a country with a higher gross domestic product and a generally high overall average life span, their research showed.

The 2013 study also showed that rates of cardiovascular disease and high blood pressure — two ailments that disproportionately impact men — were significantly lower in Nicoyan men compared to Japanese men. "Or maybe it's because men just have more room to improve," Rehkopf said, referring to the comparatively lower life span of the average man.

The data was clear. Nicoya enjoyed a lower mortality rate than most the world. It was time, Rehkopf and Rosero-Bixby decided, to go molecular.

Time-telling telomeres

THE 2013 STUDY ALSO REVEALED the first clues into what underpinned this lavish longevity: telomeres. Telomeres are nubs of DNA that cap both ends of our chromosomes, the structures of bundled-up DNA that contain our genetic information. Telomeres act as a sort of molecular buffer zone: As chromosomes replicate and split, the DNA at the ends is at risk of fraying and tangling. So instead of our genes withering away, telomeres protect the genetic information from degrading.

Once telomeres have worn away, the cell dies. So the longer the telomere, the longer a cell can live. Rehkopf, Rosero-Bixby and colleagues pulled at that thread, conducting further studies of Nicoyan people to examine the length of these protective caps in immune and blood cells.

Multiple studies have shown that telomeres act as a molecular marker of stress. One study evaluated telomere length in a group of adults who were tending to sick family members. Telomeres in this population were shorter compared to the average person's, age and gender aside. But when the family member recovered or care was no longer needed, telomere length returned.

Nicoyans, it turns out, have exceptionally lanky telomeres. Rehkopf and Rosero-Bixby conducted another study in 2013 showing that, in immune cells, Nicoyan people have about 81 additional base pairs on their telomeres compared to people in the rest of Costa Rica. During replication, telomeres lose anywhere from 30 to 200 base pairs. Once the telomeres run out, the cell dies. So an extra 81 base pairs could mean a cell can undergo an additional three cycles of cell division before dying. "Telomere length can be seen as a measure of cellular age, which is different from a person's calendar age," said Rehkopf. And, according to their telomeres, Nicoyans are young on the inside.

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PHOTOGRAPH BY LESLIE WILLIAMSON

EPIDEMIOLOGIST DAVID REHKOPF AND A
LONGTIME COLLABORATOR HAVE
PIONEERED RESEARCH
INTO WHY AND HOW PEOPLE
IN CERTAIN REGIONS OF THE WORLD —
INCLUDING NICOYA, COSTA RICA —
LIVE ESPECIALLY
LONG AND HEALTHY LIVES.



DAWN OF THE 'SURPRISOSOME'

TRIBOSOMES, THE GENE'S TRANSLATORS, UPEND
THE CENTRAL DOGMA OF GENETICS

BY KRISTA CONGER

PHOTOGRAPHY BY LESLIE WILLIAMSON

A HIGHLY TRAINED ORCHESTRA CAN play any musical score set in front of it. But what if a simple swap of a flute with a piccolo limited the set list strictly to military marches, or the switch of a French horn for a clarinet meant listeners would be swaying in their seats to waltzes all evening?

It would be a whole different concert experience — and probably not one you signed up for when you bought your ticket.

"This is very unexpected," said Stanford School of Medicine associate professor of genetics Maria Barna, PhD.

Barna was, of course, not talking about orchestras, but about ribosomes — the cellular factories that turn genetic messages from our DNA into proteins responsible for nearly every function in our cells. They are the ultimate all-purpose machines; every protein in your body, in anybody's body, in fact, was birthed by one of the multitude of ribosomes bobbing in each cell's cytoplasmic soup.

They are also almost bafflingly ancient. The ribosome's core structure arose more than 3 billion years ago and is shared by every living organism. As a result, many researchers have believed for decades that ribosomes were mostly identical and largely indiscriminate; little mechanical pianos mindlessly reading any and all nearby genetic messages and obediently spewing out the encoded proteins into the cytoplasm like melodies in a concert hall.

Recently, though, Barna's work has illuminated a secret life for ribosomes that upends our fundamental understanding of how the genetic code gives rise to the cells and tissues in our bodies. Like that fickle orchestra, Barna has found, ribosomes are unexpectedly picky: Some prefer to latch primarily onto messages important to how a cell uses nutrients (polkas!), others to

messages that dictate how and when the cell divides and develops (tangos!). These predilections mean that ribosomes act as de facto gatekeepers, controlling in broad sweeps which genres of messages are made into proteins and freeing cells from micromanaging the relative levels of thousands of individual genes. In doing so, these ubiquitous factories play critical roles in cell fate and function and even control the earliest steps of embryonic development and how and where body parts are formed.

"This is a completely unexpected way to control body plan formation, and an entirely new frontier of study," Barna said. "We're learning that evolution bakes in layers of genetic regulation whenever and wherever possible to allow cells to quickly respond to changing environmental conditions or developmental demands."

"This is pretty spectacular data," said Robert Schneider, PhD, the Albert Sabin Professor of Molecular Pathogenesis at NYU Grossman School of Medicine.

“Maria has shown clearly that cells, which are smarter than we are, have ways to alter the composition of ribosomes in ways that impact the kinds of proteins they make.”

But not everyone has been happy with the ribosomes’ move from the wings to center stage. “Some scientists studying hardcore ribosome structure — how ribosomal proteins interact at a molecular or atomic level — and who favor a reductionist approach to ribosomal biology view these findings as controversial,” Barna said. “However, we’ve shown that ribosomes are dynamic, and each cell

can have its own constellation of ribosomes. This has critical implications for biomedical research.”

HIGH SCHOOL BIOLOGY students learn that genes are found on long stretches of DNA that make up chromosomes. These genes are selectively copied, or transcribed, into short stretches of messenger RNA that carry the assembly instructions for specific proteins.

Because only genes that are transcribed into RNA can become proteins, scientists have focused for decades on the process of transcription as the key arbiter

of when and where and which proteins are made. They’ve identified hundreds of specialized proteins called transcription factors that can dial the transcription of specific genes up or down based on other nearby DNA sequences. Other proteins act more globally, controlling the transcription factors’ access to longer stretches of DNA by either keeping it tightly packed or allowing it to unspool for rapid transcription.

These layers of control, or regulation, ensure that cells have enough of the right kinds of proteins at the appropriate times to carry out their specific tasks — a muscle cell might need plenty of energy-generating factories called mitochondria, for example, while a rapidly dividing cell might need to ramp up its production of molecules involved in the cytoskeleton that helps each new daughter cell hold its shape. But researchers, including Barna, have uncovered clues that the control of transcription isn’t the whole story.

“After the birth of messenger RNA, there are additional layers of gene regulation,” Barna said. “But these downstream steps are much less well understood. What we’ve come to realize is that the levels of transcription of a particular gene are a poor proxy for the amount of protein encoded by that gene that is actually made in the cell.”

Enter the ribosome

EVERY LIVING CELL has thousands or even millions of ribosomes crammed into their cytoplasm waiting to translate the instructions in messenger RNA molecules into proteins. These highly specialized machines are made up of 79 core proteins, clustered around a heart of four RNA molecules that NASA scientists recently confirmed evolved before life itself. Together, the proteins and RNA

MARIA BARNAL (LEFT) HAS DISCOVERED THAT RIBOSOMES CAN CALL THE SHOTS.



form two subunits, one that binds to and reads, or translates, the messenger RNA molecule and another that recruits the amino acids called for by the RNA blueprint and joins them together like popcorn on a string.

Ribosomes were first identified in 1955 by George Palade, who became intrigued by electron microscopic images that showed a profusion of tiny speckles peppering a cross section of rat pancreas. He was awarded the Nobel Prize in physiology or medicine in 1974 for his discovery that the ribosomes were solely responsible for protein synthesis in cells.

At first blush, all ribosomes seemed to be basically the same. Though some early hints emerged that ribosomal structure and composition may differ among species, that idea fell out of favor during the 1960s and '70s as scientists pushed to understand the genetic code and its expression in the broadest possible terms.

"Biologists tend to want to make things simple," said Schneider, "even though nature is not simple. Some people studying the control of translation pushed the idea that ribosomes are just big, lumbering machines that all translate every mes-

cleft palate. In contrast, North American Indian childhood cirrhosis specifically damages the liver. If ribosomes function identically in all tissues and cells, why were the disorders caused by the mutations so location specific?

Tails of two mice

IT WAS 1946. And mouse #289, a male, was about to meet his sister, mouse #291 — courtesy of the breeding program devised by researchers from the National Cancer Institute in Bethesda, Maryland. Breeding brothers to sisters keeps mouse lineages with genetic traits that scientists want to study pure from the influence of genes from other, unrelated mice.

This lineage, or strain, was known as strain C. And for 62 previous generations, these brother and sister matings had gone off smoothly. But this time there was a hitch. Or, rather, a kink: One of the resulting 18 offspring had an unusually short, kinked tail. And 3 of 26 pups from a subsequent mating between #289 and another sister, #292, also sported the strange appendage. Normally, a laboratory mouse's tail is about 4 inches long; the tails of these mutant mice

breeding program to learn more about the gene that might cause such mutations. But it would be decades before the root cause was discovered, by Barna, in 2011.

As an undergraduate at New York University, Barna majored in anthropology. But when she needed to fulfill a science requirement, she ended up in a graduate level course in immunology taught by NYU viral immunologist Carol Reiss, PhD. Soon, Barna was working in Reiss' laboratory, and by graduation she had published several peer-reviewed papers on viruses that infect the nervous system of mice.

Barna took some time off after her degree to work as a technician in a cancer genetics lab at Memorial Sloan Kettering. When she bred a mouse with strange looking limbs while investigating genes involved in leukemia, she sought out Lee Niswander, PhD, at Sloan Kettering for help. "I became really interested in these uncharacterized mouse mutants, and she was an expert in embryonic development," Barna said.

One of those mutants was the tail-short mouse identified decades earlier. Barna, who leapfrogged directly from graduate

'WE WANTED TO ANSWER THE QUESTION AS TO WHETHER ALL RIBOSOMES WERE THE SAME, OR IF THEY DID IN FACT VARY. WE STARTED TO SEE THAT NOT ALL THE PROTEINS WERE PRESENT IN ALL RIBOSOMES.'

senger RNA the same way, and that has stuck for decades."

But one conundrum was difficult to explain away: Several human diseases that are caused by mutations in ribosomal proteins, or in the proteins that direct the formation of intact ribosomes from their component proteins, manifest only in specific tissues or cells of the body. Diamond-Blackfan anemia, for example, hobbles cells in the bone marrow that make red blood cells and can also lead to skeletal defects such as a small jaw or a

ranged from a barely noticeable stub to around 1.5 inches.

The mice had another quirk: Many of them had a variety of skeletal abnormalities, including an extra set of ribs that replaced cervical vertebrae.

"Their entire skeletal system is jumbled up," Barna said. "It was very rare to see so many homeotic, or developmental, changes in a single mouse strain."

The researchers were intrigued.

They named the new mutant mouse strain "tail-short," and embarked on a

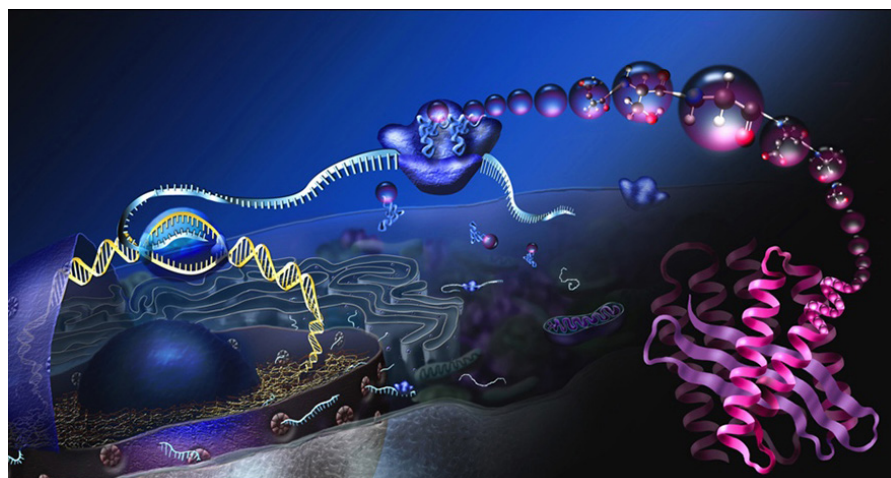
school at Cornell University to an independent researcher with her own lab at UC San Francisco, showed in 2011 that the tail-short mice owed their distinctive skeletal structure to a defect in a ribosomal protein called Rpl38.

"This result was a huge surprise," Barna said. "We expected to find a master regulator of gene packaging, or a transcription factor that influences gene expression levels. Instead, we found the first link between a ribosomal protein and the fundamental mammalian body plan."

At UC San Francisco, Barna benefited from a close association with developmental biologist Gail Martin, PhD, who was one of the first people to identify and isolate embryonic stem cells from mice. Their joint lab meetings helped Barna puzzle through her unconventional results.

Rpl38, they learned, is necessary to help the ribosome latch onto messenger RNAs that encode a group of proteins that regulate the formation of the skel-

A RIBOSOME (CENTER) TRANSLATES THE CODE ON A STRAND OF MESSENGER RNA (LIGHT BLUE) INTO A PROTEIN (RIGHT).



eton in mammals — ensuring that all the legs, arms and vertebrae end up in the right place at the appropriate time. The finding was the first to suggest that the presence or absence of specific ribosomal proteins might confer an unexpected selectivity in ribosomal function.

They also found that the genes for Rpl38 and several other ribosomal proteins vary considerably in their expression among tissue types and developmental stages — suggesting the composition of ribosomes is likely to be much more modular and dynamic than previously expected.

“We began to realize this could have critical implications for our understanding about how genes are regulated within the cell,” Barna said.

In 2012, Barna moved to the Stanford School of Medicine to continue her research. “When I started at Stanford I took a bold approach,” she said. “We wanted to try to answer the question as to whether all ribosomes were the same, or if they did in fact vary.”

Initially they looked at just 15 of 80 ribosomal proteins, using a special technique that compared the ratios of the proteins in embryonic stem cells. “We started to see that not all the proteins were present in all ribosomes,” Barna said. “So there must be some level of regulation going on. Each cell can have its own con-

stellation of ribosomes, and a new level of control of gene expression.”

They also found that ribosomes collect a variety of ribosome-associated proteins, or RAPs, that dangle off their outer shells like ornaments on a Christmas tree. Some of these RAPs are also components of key molecular pathways governing the cell cycle, energy metabolism and signaling between cells.

The RAPs, they learned, further fine-tune the ribosome’s preference for which messages they choose to translate — helping them to select from a vast library of messenger RNA floating in the cell’s cytoplasm. To extend the orchestra metaphor, perhaps one cues up square dances and classical scores while another prefers disco and swing. Each choice

results in a specialized panel of proteins that can direct cell fate.

The ribosome’s importance in embryonic development was cemented in 2022, when Barna and her lab showed that mutations in another ribosomal protein, Rpl10A, result in mouse embryos that one-up the tail-short mouse of the 1940s.

Mice with Rpl10A completely lack not just a tail, but a chunk of their body. “It is a striking body structure,” Barna said. “It’s as if a guillotine had chopped off all tissue after their hind limb, but the rest of the organs were completely normal.”

Further research showed that the mutations affected the ability of the embryos to make mesoderm — one of three primary tissue types, or germ layers, from which all other body parts arise. Rpl10A, they found, promotes the ability of ribosomes to translate messenger RNA molecules that encode members of the Wnt family of proteins — another group notorious for their roles in tissue patterning. Rpl10A also waxes and wanes dramatically in its abundance in ribosomes during early embryonic development in a pattern mirroring mesoderm development.

“This is likely to be the tip of the iceberg,” said Naomi Genuth, PhD, a former graduate student in Barna’s lab and the first author of a 2022 *Nature Communications* article describing the research.

“By meticulously measuring the composition of ribosomes as cells form different cell types, we found dozens of ribosomal proteins that change in their incorporation into the ribosome. This could lead to hundreds of different ribosome types,” said Genuth, who is now a postdoctoral scholar at UC Berkeley.

“Each of these studies is dragging ribosomes back into the limelight,” Barna said. “Until now, we would not have expected that ribosomes control the development of one of the body’s three germ

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'AND PROTEIN CHAIN OUTGRABE'

THE MAKING OF A '70s CULT CLASSIC THAT BRINGS PROTEIN SYNTHESIS TO LIFE

BY JANE GITSCHIER

'All mimsy was mRNA

That colored message unit array

... All mimsy was mRNA

And protein chain outgrabe'

Narration from the film *Protein Synthesis: An Epic on the Cellular Level*

WHILE TEACHING a high-school biology course recently, I found myself reflecting on a low-budget movie that had delighted me as a graduate student decades before. The quirky 13-minute film in question, *Protein Synthesis: An Epic on the Cellular Level*, was produced on the Stanford University campus in 1971, with colorfully clad students depicting the roles of mRNA, tRNA, ribosomes, amino acids and translation factors, all while dancing to the beat of a psychedelic improv band.

Soon, I was down the rabbit hole, discovering an archival copy of the movie on the web to show my students. I couldn't help but go deeper.

Protein Synthesis was the brainchild of Robert "Gabe" Weiss (MD '75), a first-year medical student at the Stanford School of Medicine at the time. Weiss had a background in moviemaking from his days as an undergraduate at UC San Diego. There, he was an integral part of the Senses Bureau, the film-production unit of the lab of chemistry professor Kent Wilson, PhD.

Though Weiss and Wilson are both deceased, I was able to interview the remaining ringleaders, including Weiss' wife, Jacquelyn (née Benington, BS '73, MA '75), and others who recalled with delight that singular time in their lives. Paul Berg, PhD, then chair of the Stanford School of Medicine's Biochemistry Department and the film's staid counterpoint to the gyrating bodies, also reminisced.

It was also a singular time in American history, as the nation was in an uproar over the Vietnam War. Gregory Redding (MD '74), a friend of Weiss' from UCSD and also a Stanford School of Medicine student, said they and their cohort opted for a future in medicine so they could qualify for the so-called "doctor draft." (Until 1973, medical students were allowed to defer being drafted into the military until they completed medical school and their residency training).

In the spring of 1971, they enrolled in a biochemistry class, the most popular course in the medical school. Also in the class was Gordon Norman (AB '70, MD '74, MBA '94) who was folded into the

close-knit UCSD group, playing lunch-time volleyball with Weiss and Redding and jamming with them, UC San Francisco medical student William Corey and his brother, Paul, in San Francisco.

Berg — who nine years later was awarded a 1980 Nobel Prize in chemistry — happened to be teaching the class that spring, and his lectures on protein synthesis ignited Weiss. Observed Norman, “I think he had been itching to make a movie about anything,” but when he saw Berg’s lecture, he knew this was his chance.

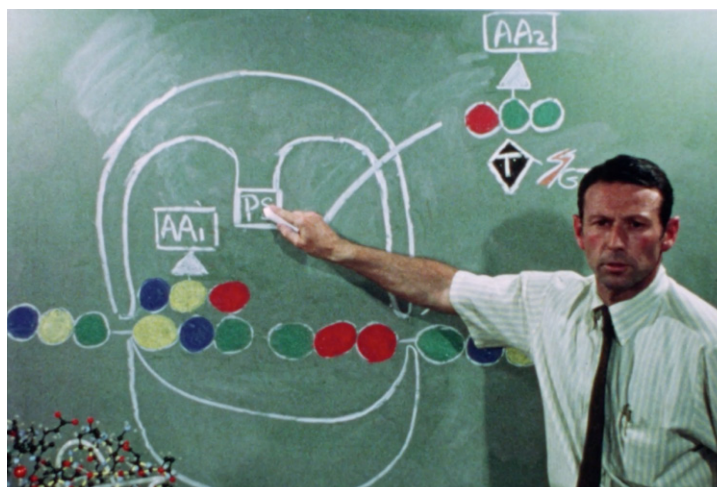
“Gabe was pretty cocky,” recalled Redding. “He told Berg that he needed to make the process more dynamic. And to his credit Paul said, ‘You think you can do better?’ We said, ‘Yeah.’ He said, ‘How are you going to do that?’ ‘We’re going to make a movie!’”

Weiss, Redding, Norman and Gregory O’Leary (MA ’72), another San Diego friend and Stanford University graduate student in English, organized a planning council and recruited others to help. “Gabe probably could have done this single-handedly, but he was inclined to do it as a collective activity. He was happy to have his friends involved,” said Norman. Ann Bailey (MA ’76, JD ’76), Norman’s girlfriend at the time and the film’s sweet-voiced narrator, put it more vividly. “Gabe was like a pied piper. You would follow this guy!”

Weiss envisioned depicting protein synthesis through the medium of dance and enlisted undergraduate Benington, a human biology major with extensive gymnastics, dance and performance experience, to join the project as its chore-

ographer. She recalled being captivated not only by the project but also by Weiss. “I was totally smitten,” she said.

Weiss collaborated with Wilson to help produce the movie, but to pull it off, they needed funding to buy film. They turned to Berg.



SCENES FROM:
PROTEIN SYNTHESIS:
AN EPIC ON THE CELLULAR LEVEL

TOP: PAUL BERG EXPLAINS HOW A RIBOSOME TRANSLATES A MESSENGER RNA STRAND INTO A CHAIN OF AMINO ACIDS TO MAKE A PROTEIN.

BOTTOM: DANCERS ENACT THE TRANSLATION PROCESS.

WATCH THE FILM AT
STAN.MD/PROTEIN-SYNTHESIS

“To put it in context,” said Berg, “you have to think about what was going on at Stanford at the time. In 1970-71, the campus was in an uproar about the Vietnam War. The students were skipping classes, out of the labs, attending sit-ins and protest marches. It was pretty grim.”

“I was chair of the [Biochemistry] Department, so I was engaged in all the departmental discussions about what was going on and how are we going to handle it. Many of us were sympathetic to what the students were doing, but we had to keep the ship going.”

When Weiss and Norman approached Berg, they told him they saw the process as being very dynamic, with molecules moving in and out of the ribosome and so on.

“I thought they were pulling my leg! I was sort of very standoffish for a bit. ‘How do you intend to do this?’ I asked. ‘With people playing the part of molecules, out on a big green, and filming from high above in one of the student dormitories,’ they said.

“To suddenly have something that had a flavor of the old-time high jinks, where people would do funny things ... maybe it could transform the mood on campus. So I said I would give them the money and to go ahead.”

Richard Palmiter, PhD, who was a pharmacology postdoc and played Elongation Factor 2 in the film, recalled when Weiss, whom he didn’t know, wandered into his lab seeking donations for the project. “I was intrigued with the idea. I think I gave him \$100, and somehow that made me a producer!”

With the concept in place, funding

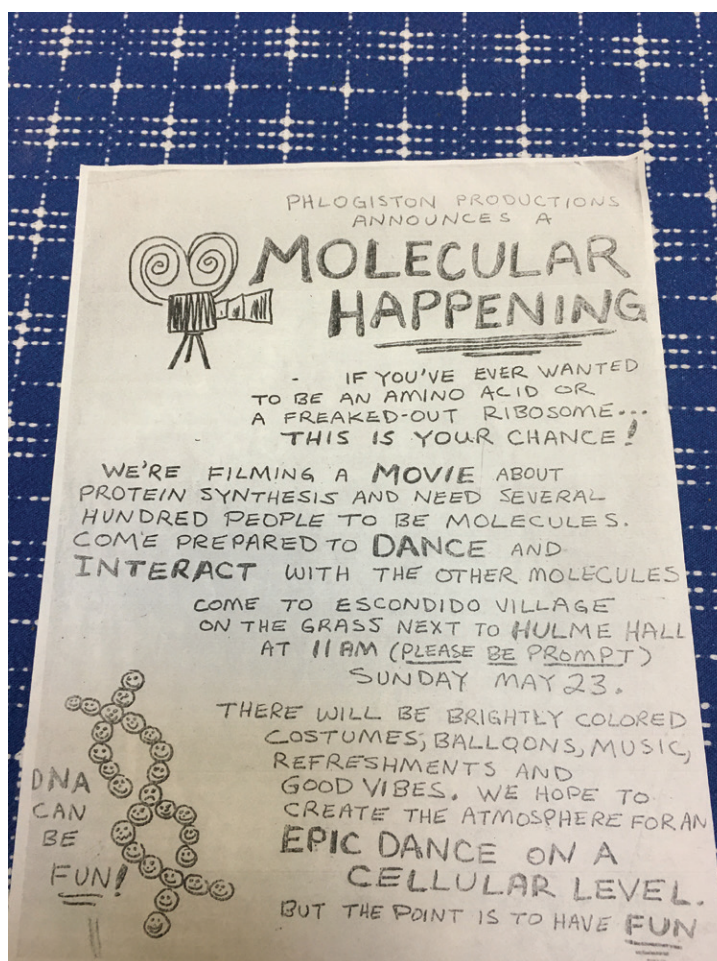
secured and a venue selected, the committee recruited students and friends as performers, but they needed a bigger crowd. So O'Leary turned to the student newspaper, the *Stanford Daily*, to get the word out. In it, Joanne Jacobs (BA '74) wrote, "Greg O'Leary and 15-20 fellow freaks hope to lure at least 200 people ... with molecular acting ambitions" to Hulme lawn in Escondido Village the following Sunday morning, noting that, "Nobody knows for sure how long it will take."

On May 23, a hoard of students arrived and the directors distributed assignments, costumes and brief instructions, saying, "Here, you're a ribosome, you're an amino acid, you're a tRNA," recounted Redding.

Berg was in attendance for the rehearsal. "They scheduled a teach-in," he said. "It was done like football practice, out on the field. They were teaching them the role they had in this process of protein synthesis." After this brief introduction, with costumes donned, bodies painted, and key dancers leading the way, the action and the filming began.

Jacquelyn Benington Weiss recalls racing to the top floor of Hulme Hall with cinematographer Noël Bartlett and Redding, knocking on doors of students who were studying for finals, to secure a balcony perch with a good view.

Once filming began, Gabe Weiss took his place on a ladder, barking through a bullhorn to control the human molecular traffic. With Bartlett secured on the balcony, cameraman Paul Savage filmed the ground shots, and Norman served as a cheerleader on the field.



"IF YOU EVER WANTED TO BE AN AMINO ACID OR A FREAKED-OUT RIBOSOME ... THIS IS YOUR CHANCE!"
GABE WEISS' HANDWRITTEN RECRUITMENT FLYER FOR THE PRODUCTION SOUGHT SEVERAL HUNDRED DANCERS TO BE MOLECULES.

FOR THE choreography, Benington had tapped into Stanford University's folk dance community, who formed the basis for the mRNA molecule. Three people, arms wrapped around each other and tethered by a rope, enacted triplet codons. Each base — guanine, adenine, uracil or cytosine — was identified by a colored pinny and matching balloon.

Three other dancers (the similarly arrayed triplet anticodons) depicted tRNA molecules, with coded amino acid dancers lashed together and prancing behind.

When the tRNA entered the ribosome and met its cognate, the codons and anticodons joined hands to symbolize hydrogen bonding. Meanwhile, amino acids, identified by red body paint, held hands once the peptide bond was formed and were instructed: "Don't let go!"

Jazz musician Jim Nadel (BA '72, who later founded the Stanford Jazz Workshop), drummer Steve Savage and bassist Mark Weimer (BA '92), kept the energy and beats going with what Nadel described as "very long jams" and "changing grooves to accommodate what was happening on the field."

A phalanx of flexible folks — garbed in drab blue scrubs "borrowed" from operating rooms — constituted the two ribosomal subunits,

30S and 50S. Tumbling into the ribosome complex, defined on the field by chalk, the subunits clamped onto the mRNA, setting into motion production of the protein, then tumbled back out after it was completed.

Protein synthesis requires a few other factors, of course, and eye-catching costumes were worn to help viewers follow their roles in the process. Benington, for example, wore an orange leotard and yellow tights while performing the role of Initiator Factor 2. Med student Hans Dankers (AB '70, MD '75) depicted GTP while wearing a red poncho and ski goggles. At Berg's suggestion, he shot puffs of chemicals from a fire extinguisher to represent energy during key parts of the protein synthesis process — the formation of the peptide bond and at the indexing step.

The "happening" came to a close after a spirited day of rehearsal, performance

and bacchanalia, but the filming wasn't finished. The planning committee wanted Berg to provide an introduction, and they needed his segment to take place the next day while the film crew from San Diego was still in Palo Alto.

"They invoked that I had to explain the process of protein synthesis first and lead the audience to understand it was going to be done in the 'dance idiom,' as they referred to it. I was given three minutes' time to present that whole story," he said.

"So the night before my filming, I wrote a description, and they laughed me out of it. They said I had to do it without a script. So we arranged to use idiot cards — pieces of brown paper with 30-second bits of what I wanted to say were written out and hung from the ceiling," Berg recalled. "My three minutes took me about seven hours! I made mistakes, I fumbled my words, I turned the wrong way to the blackboard and so on. It was a real joke."

The scholarly presentation was a straight-laced affair, in stark contrast to the exuberant scene it would preface. There is Berg in a button-down shirt and narrow tie, with two pens in his pocket, neatly outlining the process in colored chalk on a green board.

"Only rarely is there an opportunity to participate in a molecular happening," Berg began, playing the very model of an atomic age nerd. "You are going to have that opportunity, for this film attempts to portray symbolically, yet in a dynamic and joyful way, one of nature's fundamental processes, the linking together of ami-

no acids to form a protein. ... This film, with people portraying molecules, using the dance idiom, tries to animate these two processes, the programming and assembly of a protein."

RECALLING BERG'S filming of the introduction, Redding said, "He was a really good sport."

Moreover, because Berg would soon be internationally recognized during the debate over recombinant DNA, his contribution was probably crucial to the film's success.

"I think a lot of the credit of the film's long life goes to Dr. Berg for having embraced it and sanctioned it with the imprimatur of Stanford Department of Biochemistry," said Norman.

With the filming finished and the spring term behind them, the team retreated to UCSD to produce the final film by trimming down the dance scenes, adding graphics to call attention to the key players and steps, and laying down audio tracks that rival the video itself in capturing the spirit of the times. Gabe Weiss appropriated Lewis Carroll's *Jabberwocky* to spin the tale of protein synthesis, and Ann Bailey supplied the narration.

The group did not capture audio during the performance, so they produced a soundtrack, a '70s psychedelic improvisation, dubbed *Protein Jive Sutra*, on guitars, electric organ, drums, cowbell, a flute obbligato and occasional trumpet. And to top it off, Weiss bleated out the names of molecules as

they came into play, "T factor!" "Initiator Factor 2!" To this day, I cannot hear, or even read, the word "GTP" and not recall that voice.

Protein Synthesis: An Epic on the Cellular Level premiered at the Unicorn Theatre in La Jolla, California, in mid-fall of 1971 and was shown before the premiere of *The Andromeda Strain* the following January at Memorial Auditorium on the Stanford University campus, with author Michael Crichton in attendance. Though Berg was out of town, his wife, Mildred, reported that the audience was already giggling during Berg's explication in anticipation of what they were about to witness, especially as still shots of the whimsical dance had been inserted into his formal lecture.

After I rediscovered the film, I took a pilgrimage to Hulme Hall and the grassy field that still remain on the Stanford University campus and wondered how many people passing that way today have an inkling of the molecular happening that took place half a century ago.

I'm grateful to those who entrusted me with their memories of how this classic came to be. "I have to tell you, none of us were high for this," said Redding. Thank you for clarifying.

And as for my high-school students, they were wide awake. "Far out!" was the word that came to mind.

Jane Gitschier, PhD, is a freelance science writer and a professor emeritus of medicine and of pediatrics at UC San Francisco. Contact her at medmag@stanford.edu

'ONLY RARELY IS THERE AN OPPORTUNITY TO PARTICIPATE IN A MOLECULAR HAPPENING. YOU ARE GOING TO HAVE THAT OPPORTUNITY, FOR THIS FILM ATTEMPTS TO PORTRAY SYMBOLICALLY, YET IN A DYNAMIC AND JOYFUL WAY, ONE OF NATURE'S FUNDAMENTAL PROCESSES, THE LINKING TOGETHER OF AMINO ACIDS TO FORM A PROTEIN.'

FEATURE

Keeping breast cancer secret

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mum said, “We cook a lot in ghee and butter. Is that OK? What about the spices we use?”

Trivedi added that advising patients to eat more protein, like white meat chicken or lean red meat, is not helpful to an Indian who is a vegetarian. “There was a gap, at times, between what the individuals were looking for and what the care team was providing,” she said.

Trivedi recently presented the study results at the Society of Behavioral Medicine and the Gerontological Society of America and plans to submit the findings to a medical journal. The study was funded by the Cambia Health Foundation Sojourns Scholar Leadership Program.

“The biggest takeaway is that it’s a good start, and we learned a lot, but there is so much more we need to understand,” she said. **SM**

— Contact Ruthann Richter at medmag@stanford.edu

FEATURE

Gulp

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California’s San Joaquin Valley.

The valley, one of the state’s most important agricultural regions, has some of California’s worst drinking water, caused by naturally occurring contaminants such as arsenic and by introduced pollutants such as fertilizer nitrates and coliform bacteria in agricultural runoff. In some cases, public health advisories about how to make water safer (by boiling it to get rid of bacteria, for instance) can worsen other contamination concerns (boiling concentrates nitrates). Many households resort to buying bottled water.

To compound the problem, average per capita incomes among the region’s residents are about \$7,000 per year less than the state average. Every dollar residents spend to buy bottled water reduces their ability to meet other needs.

In a project called Agua4All, Patel and her colleagues tested two approach-

es for getting people to use free water stations, set up around their communities, that provided clean, uncontaminated drinking water.

“The goal was to saturate a community with safe public water sources so families could go and fill up there,” Patel said. The researchers compared one town that used minimal promotion of the stations, such as posters, to a second town where the community also implemented activities from a tool kit of promotional ideas. The larger package of community-driven promotion increased water-station use, the research showed. The work was published in *Preventing Chronic Disease* in 2019.

“We’re big believers in the human right to water; everyone should have affordable access to safe drinking water,” said Sarah Buck, Patel’s research partner at the Rural Community Assistance Corp. and a co-author on the scientific paper. The need is especially acute for kids because they’re small, growing, and thus especially susceptible to contaminated water, she added.

Since the project was completed, Buck has moved to the national office of the Rural Community Assistance Partnership, where she lobbies for water-system improvements in rural communities nationwide. The research she conducted with Patel has been valuable for securing funding for these projects from the Environmental Protection Agency and the private sector.

“We utilized the study as part of an example of what could potentially be done and why the EPA should be helping pay for it as part of the WIIN program,” said Buck, referring to the Water Infrastructure Improvements for the Nation Act of 2016’s Reducing Lead in Drinking Water grant program. “It has been a feather in our cap as far as proof of concept.”

Water first

Patel hasn’t lost sight of her early goals to reduce childhood obesity and, since arriving at Stanford Medicine in 2018, has built the evidence base for water’s role, especially around boosting kids’ water intake at school.

With a large NIH grant, Patel’s team has been conducting a study, called Water First, at 26 low-income elementary schools in the San Francisco Bay Area. Developed in concert with a community advisory board that included policy advocates, the California Department of Education, schools, parents and teachers, it provided participating schools with upgrades to their drinking water facilities and a six-month educational program about the health benefits of water for all fourth-grade students.

As part of the study, after randomly assigning the schools to act as intervention or control sites, each school in the intervention arm received three water fountains that deliver chilled, filtered water and serve as water-bottle filling stations. Often, the new fountains replaced old, poorly functioning porcelain models.

The entire school participated in a kick-off assembly, usually including a live performance by a local musician who had written a children’s song, with actions, about the benefits of drinking water. The students also learned about orderly use of the water fountains.

Research staff led eight weekly lessons for fourth-grade students about health, environmental and financial benefits of drinking water. Fourth-graders also received reusable water bottles to drink from at school, and presented projects — including posters, skits and puppet shows — to describe what they had learned. Family-engagement activities, such as worksheets to complete with a parent or guardian, were also part of the study.

The researchers conducted measurements at baseline, seven and 15 months later. They measured students’ body mass index, an obesity measure, as well as calorie intake from foods and beverages in 24-hour food diaries. Researchers also collected data on kids’ water intake at school during lunch, recess and PE and used the volume of water dispensed at the new fountains to estimate changes in students’ water consumption over time.

The study ran into challenges because participation by some schools was interrupted by the beginning of the COVID-19 pandemic in early 2020. But so far, the data

indicates that the work achieved some degree of overweight prevention, Patel said. Water intake increased, too. The report is under peer-review for publication. Patel has also shared data from the study in testimony for new California legislation that will require water bottle filling stations in public schools undergoing modernization or new construction.

Making a difference

Students and school officials report seeing benefits from participating in the study. Before Bay Elementary School, in San Lorenzo, California, joined the Water First study in the fall of 2019, the school had only old porcelain fountains, many of which didn't function, said Principal Bethanne Witzak. Students mostly drank water or juice from single-use plastic bottles, generating a lot of waste.

The water bottle filling stations changed that. Once the stations were installed, school leaders encouraged students to bring reusable bottles and started talking about the health and environmental benefits of doing so.

"Now it's just part of the culture," Witzak said. "When I walk into a classroom, at least 85 to 90% of kids have water bottles on their desks."

Parents get information about reusable water bottles in beginning-of-the-year information packets, and Witzak describes the water bottle filling stations at Back to School Night. In her slide show explaining to students how to behave at school, proper use of the water stations is part of the material, just like the rules about lining up when the bell rings.

The stations make filling water bottles fun, Witzak said, adding with a chuckle that it's become trendy: "It's this positive space, like, 'Oh, I'm going to go fill my water bottle!' 'You are?' 'Yeah!' 'Me, too!' And kids bring water bottles that are representative of themselves as humans; it's very sweet."

While the research was underway, students participating in water lessons frequently chatted with Witzak on the playground about what they'd learned, or she

overheard them reminding each other to drink less juice so they wouldn't get cavities.

As for Patel, she's planning how to translate the study's findings into still more action to build healthier communities.

The research shows that in addition to other strategies to improve children's health and reduce childhood obesity — fixing playgrounds, encouraging physical activity, providing free school meals for everyone — details like water fountains matter, just as the Los Angeles middle-schoolers told Patel years ago, she said.

"It's the combination of access, structural changes in the school and home environments and our neighborhoods, and education that makes a difference for kids' health," Patel said.

"You can't just educate this problem away without making investments in policies, school and home environments to make sure healthy options are accessible." **SM**

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FEATURE Unsheltered

CONTINUED FROM PAGE 37

November 2021, she found her way to the clinic, where she sees a psychiatrist and Chen. When Chen learned that Maggie was paying \$400 a month for medications she should have been getting for free, she called the pharmacy and told them that the drug costs were now covered by Medi-Cal, California's Medicaid program. Such oversights are not uncommon and can be the deciding factor in someone's ability to stay healthy. "Most pharmacists have no idea," Chen said.

Another of Chen's patients, Charles, is trying to quit drinking, but at a visit in October, he was panicked about a problem with his Social Security payments. Chen found him some information for a pro bono lawyer.

WEB EXTRA:

A video takes us inside the clinic and tells a patient's story at stan.md/unsheltered

The stress of losing steady income made him want to drink, he said, and staying sober had been that much harder. He was anxious and irritable. Nevertheless, he hadn't had a drink since the last time he saw Chen two weeks earlier. "It's a conscious effort. I appreciate that so much," Chen told him, giving him a fist bump.

Charles is 62 and had his first drink at age 6. His mother was an alcoholic, and he's estranged from his wife and kids. He didn't like staying in a shelter because he couldn't stand being around other people. He asked Chen if it was bad for him to be alone all the time. She told him about a study in which rats were given a choice between getting an addictive drug like heroin or playing with other rats. They chose the latter. Like the rats, "we are social creatures," said Chen.

For people who are homeless, a social support network is hard to find. Sometimes it's a matter of choosing between a housing opportunity that takes them away from the community they've managed to make or staying and living on the streets.

"People and relationships are essential to human health," said Laura Vaughan, MD, another Stanford Health Care physician who works at Peninsula Healthcare Connection. "It's common for us to see folks whose ties with family have been severed for whatever reason. They don't have a life raft to help them through harder times. They have nowhere to go and nowhere to turn."

"We provide the medical piece, but the social piece is really what matters, and that's harder," said Vaughan, an internist and clinical assistant professor. She sees it as part of her job to work with the case workers to figure out where medical care falls in a patient's hierarchy of needs. Oftentimes, social needs — like housing or transportation — are higher on their priority list than taking their blood pressure medication.

When Unzueta prescribes medications for her patients who have no housing, she keeps in mind that it may be the last time she'll see them. She'll choose the medication that has the least risk of side effects, for

example. Lately, she'd considered switching Mr. Issac to a new type of insulin that is administered only once a week. "Yes, he needs insulin because everything is just so uncontrolled. But it's not really practical for him, it's not really feasible," she said.

Mr. Issac didn't show up at the clinic that week. "You kind of always think, this patient may not be able to come back," Unzueta said. But the next Monday, he returned. And he came in with an empty pill box — a good sign that he'd remembered to take his medications. **SM**

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FEATURE

Longevity's secret sauce

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That doesn't mean that Nicoyan people feel no stress. But perhaps their social system and community is structured such that, when stressors arise, friends and family are nearby to support and weather the trouble together.

Maybe you're born with it, maybe it's methylation

Some four years after their initial telomere analyses, Rehkopf and others turned their attention to a molecular phenomenon called methylation, which helps to regulate gene activity.

During methylation, molecules called methyl groups, made of one carbon and three hydrogen atoms, latch onto various genes. These accessories can rev up or subdue the genes' activity, and having too much or too little activity can stir trouble. So can high variability, which equates to sloppy methylation. What's needed is methylation in moderation.

"When people age, two things happen: an increase in methylation variability, and a resulting imprecision in regulation of gene expression," said Rehkopf. That imprecision is what leads to aging and susceptibility to disease.

But not so much in Nicoyans: Elderly Nicoyans have a methylation pattern that reflects a younger person, particularly in

their immune cells. Subsequent studies to analyze methylation in blood cells revealed that same trend — younger methylation.

Methylation, overall, is not set in stone. Environmental occurrences can change one's methylation pattern. (Past studies have shown that people who have experienced trauma have altered methylation patterns.) So perhaps, suggested Rehkopf, a similar logic applies to communities in Nicoya, a rural place where societal norms are markedly different than say, a city in the United States: few cars, families who live together in multi-generational housing or in houses close to one another, and other ways of life that avoid big-city stressors.

Just last year, Rehkopf and others investigated how smoking impacts longevity in Nicoya, finding that people there who smoked had methylation patterns associated with accelerated aging.

Youthful methylation patterns among elders were thought to be unique to Nicoyans — until Rehkopf conducted a follow-up study in Ikaria and Sardinia, published in November 2022 in *Frontiers in Aging*, revealing that some of the same telltale methylation patterns persisted in these zones too.

Rehkopf's study also found that Nicoyans have different levels of CD8 T cells, a type of immune cell, which play a critical role in killing infected cells.

"Basically, the more mature CD8 cells a person has, the more wear and tear their immune system has seen," said Rehkopf. In other words, the immune systems of older Nicoyans are still fresh-faced and ready to take out infected or otherwise naughty cells.

Rehkopf plans to expand his sleuthing to the genetic realm. Past studies dismissed genetics as a root cause of the Nicoyan people's long life span. But Rehkopf and collaborator Michael Greicius, MD, a Stanford Medicine geneticist and neurologist, are teaming up to pressure test that idea. "I wonder whether past genetic studies of the population just weren't granular enough. We're using fine-grain sequencing to see if those find-

ings really hold up," Rehkopf said.

Make your own blue zone?

WHILE THE REST OF THE WORLD marvels at the extra years of life among blue zone residents, Rehkopf said, the people, at least in Nicoya, don't pay much attention to their superior mortality stats. "They're just living their lives — walking their kids to school, visiting family within the community, and cooking simple, unprocessed meals."

So are Nicoyans born inoculated with the elixir of youth? Or do they make their own longevity? The likeliest explanation is both, said Rehkopf. Folks who move to Nicoya around retirement age don't suddenly tack years onto their lives. (Rehkopf and others conducted a study in 2013 showing that Nicoyans who see extended life spans are born and raised in Nicoya and spend their adult lives there too.) Also, Nicoyans who are born and raised in the region but move to another place for adulthood don't get the blue zone effect.

But that doesn't mean other people can't take lifestyle tips by examining the rural peninsula's way of life. Physically active lives; simple, clean cooking and diets that are high in fiber and lean protein, and low in fat and unprocessed ingredients; and community ties and support can all contribute to a microenvironment that replicates the behaviors, and maybe even the effects, seen in blue zones.

Nicoya isn't full of marathon runners or vegans. But the days of those who live there are filled with movement — for example, sweeping the front porch in the morning, walking kids to and from school, working on the farm, raising cattle, laundering by hand and making visits to family on foot. And, in Costa Rica, primary care doctors make home visits to families, meaning annual checkups or appointments are infrequently missed or forgotten.

Those behaviors, even if they're not sole contributors to healthy aging, are vital — and it may even be possible to bundle them into a routine that creates one's own

micro blue zone, said Rehkopf. “The social behaviors seen in blue zones are things we can all integrate into our everyday.”

But even in Nicoya, some of them are starting to slip. “As more Western foods and modes of transportation become common in Nicoya, we’re seeing the blue zone effect become more tenuous,” said Rehkopf. It’s still there — but the life expectancy of the population born around the 1940s and 1950s is dipping.

“These people are losing the advantage seen by previous generations,” said Rosero-Bixby. “It’s not uncommon to see people in Nicoya live to be in their 90s, but we’re seeing that number slip back down into the 80s.” It’s not clear why, but levels of diabetes are increasing across Costa Rica — potentially one key indicator of change. If the trend continues, the “Nicoya effect” could be lost entirely over the next several decades.

That’s not to say that all blue zones are on the way out. Nearly 6,000 miles away, in Denmark, several new hot spots for longevity are emerging. A report in 2018 pointed to some regions of the country seeing statistically longer life spans, raising the question of whether more blue zones are yet to be identified. Rehkopf suspects persistent activity, as opposed to spurts of rigorous exercise, might play a big role. Biking is the main form of transportation in Denmark; it’s built into their culture and infrastructure.

“The four blue zones that exist weren’t the result of an exhaustive search,” said Rehkopf. “There may very well be others that aren’t even on our radar.” **SM**

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FEATURE

Dawn of the ‘suprisosome’

CONTINUED FROM PAGE 45

layers. These are some very unexpected functions for these ancient proteins.”

They’ve created a stir among fellow scientists. “As is often the case in science, Maria’s results were greeted by a gamut of responses and feedbacks,” said leading pro-

tein synthesis researcher Nahum Sonenberg, PhD, the Gilman Cheney Chair in Biochemistry at McGill University. “The findings are intriguing, but the general mechanism to explain exactly how the specificity is achieved is yet to be elucidated.”

“All the really cool ideas face controversy,” said NYU’s Schneider. “But this is actually based on a very old idea. Maria has the tools and excellent science background to address whether it’s true, and it very clearly is.”

An international conference is planned for fall 2023 to bring together researchers fleshing out the role of ribosome specificity as many other groups are now following this line of research. Barna is no stranger to weathering controversy with the help of staunch colleagues and collaborators.

“I didn’t come from a privileged background,” she said. “My family was very poor and my father didn’t want me to go to college. I was the first person in my family to go to university, and I was really lucky to have some incredible women mentors. It’s been great to have had, at an early stage in my career, strong women to teach me how to be the best scientist I can be.”

Barna’s mentors gave her the courage to pursue what was at first unlikely fodder for a career on the edge of biomedical science. “I had never imaged I’d be challenging the way ribosomes were thought to work in textbooks,” she said. “Now we have a road map for how ribosomes affect stem cell fate and embryonic development, and it’s really exciting.”

Barna’s focus on ribosomes is unlikely to wane soon.

“There’s an old joke that researchers tend to view cells as being made up of only the proteins or molecules they study,” she reflects.

“And it’s true. My lab members joke that the cell is just a sack of ribosomes. But 60% of a cell’s energy is devoted to making and maintaining ribosomes. To imagine they play no role in gene regulation and cell fate is just a little silly.” **SM**

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Stanford Medicine is published by the Stanford Medicine Office of Communications as part of an ongoing program of public information and education.



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HEALING GEL

IN STUDY, GENE THERAPY HEALS OPEN WOUNDS IN PATIENTS WITH BLISTERING SKIN DISEASE

Vincenzo Mascoli, 22, was diagnosed with a debilitating blistering skin condition when he was a toddler and has since had large intensely painful open wounds that can take months to heal or don't heal at all.

The rare genetic disease, called dystrophic epidermolysis bullosa, has no cure and treatments are generally limited to keeping the wounds clean and bandaged, managing pain and preventing further injury. In severe cases, even the friction of clothing can cause blisters.

Now, thanks to a gene therapy gel developed at Stanford Medicine, Mascoli is one of 31 patients in a late-stage trial of the drug who have seen dramatic progress in their wound healing. "After four months, I saw an improvement on a large wound on my back that I had for 20 years," said Mascoli, who lives in Italy and came to Stanford Medicine for the study. "After six months, the wound had healed completely and was much less painful."

Peter Marinkovich, MD, a pediatric dermatologist who directs Stanford Medicine's Blistering Disease Clinic and led the trial, said the results are life-changing for Mascoli: "Now he can bathe and sleep on his back. This treatment made a huge difference in quality of life for Vincenzo and other trial participants."



Vincenzo Mascoli, seen in Milan, Italy, with his parents and Peter Marinkovich (left), was treated with a gene therapy gel for a painful blistering disease.

An associate professor at the Stanford School of Medicine, Marinkovich was senior author of a study detailing the clinical trial results. Lead authors of the study, which published Dec. 15, 2022, in *The New England Journal of Medicine*, were Isin Sinem Baci, MD, a basic life research scientist at the school, and two pediatric dermatologists — one from Children's Health of Orange County, California, and the other from Florida-based Pediatric Skin Research.

In the double-blind, placebo-controlled trial, which included 19 patients who were 18 years old or younger, 67% of the wounds treated with the gel — applied to the skin during bandage changes — healed completely after six months of weekly applications. In comparison, 22% of the wounds treated with the placebo healed.

The experiment's results replicate a Stanford School of Medicine nine-patient trial published in March 2022. It was the first trial of gene therapy in pediatric epidermolysis bullosa patients.

The disease is caused by a genetic mutation that prevents the patients from making collagen VII, a protein that binds the middle and outer layers of the skin together. Without this protein, the layers of skin slide across each other, which results in blisters.

The new therapy gel works by delivering a copy of the missing collagen VII gene — by way of a modified herpes simplex virus — to the skin's surface, thereby stabilizing its structure.

Previous attempts at using viruses to deliver therapies have been thwarted by the body's rejection of them as foreign invaders. But the herpes simplex virus circumvents the human immune system, allowing patients to repeatedly apply the gel without having an immune reaction.

"We saw no inflammation, significant side effects or immune neutralization of the drug, even with repeated administration of the gel over the six months of the trial period," Marinkovich said.

If Marinkovich and his colleagues receive Food and Drug Administration approval for use of the drug — called B-VEC — to treat dystrophic epidermolysis bullosa, it would be the first topical gene therapy treatment approved for use in the United States. — BY KRISTA CONGER

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The kids are all right

NO CONNECTION FOUND BETWEEN A CHILD'S PHONE OWNERSHIP AND WELL-BEING

Surprise! A Stanford School of Medicine study showed no meaningful links between children's well-being and the age at which they received their own mobile phone — a result researchers credit, in part, to parents being thoughtful about timing.

"One possible explanation for these results is that parents are doing a good job matching their decisions to give their kids phones to their child's and family's needs," said senior author Thomas Robinson, MD, the Irving Schulman, MD, Professor of Child Health and a professor of pediatrics and of medicine.

The study, published in September 2022 in *Child Development*, followed 250 low-income Latino children for five years, during which time researchers tracked their well-being as they transitioned into phone ownership. Little prior research has focused on technology acquisition in non-white or low-income populations, the researchers said.

Over the five years, each child and one of their parents took part in baseline and annual assessments. At each point, parents reported whether and when their child got a phone, the child's recent grades, and their sleep patterns and daytime sleepiness.

When deciding to give a child a phone, parents typically weigh many factors, such as the child's need to contact a parent or maintain social connections, how much the phone may distract the child, and whether the child can handle exposure to cyberbullying.



More than half the children were given a phone between 10.7 and 12.5 years of age, but the average was 11.6 years old. (The children ranged from 7 to 11 years old when the study began, and 11 to 15 when it ended.)

During the check-ins, children filled out assessments for depression. For a week after check-ins, the children wore accelerometers on their right hip to determine when and how long they slept.

In addition to finding no measurable link between phone ownership and a child's well-being, researchers found there was no "golden rule" about timing, said the study's lead author Xiaoran Sun, PhD, a former postdoctoral scholar at Stanford Medicine and Stanford Data Science.

"These results," Robinson concluded, "should be seen as empowering parents to do what they think is right for their family."

BY ERIN DIGITALE

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