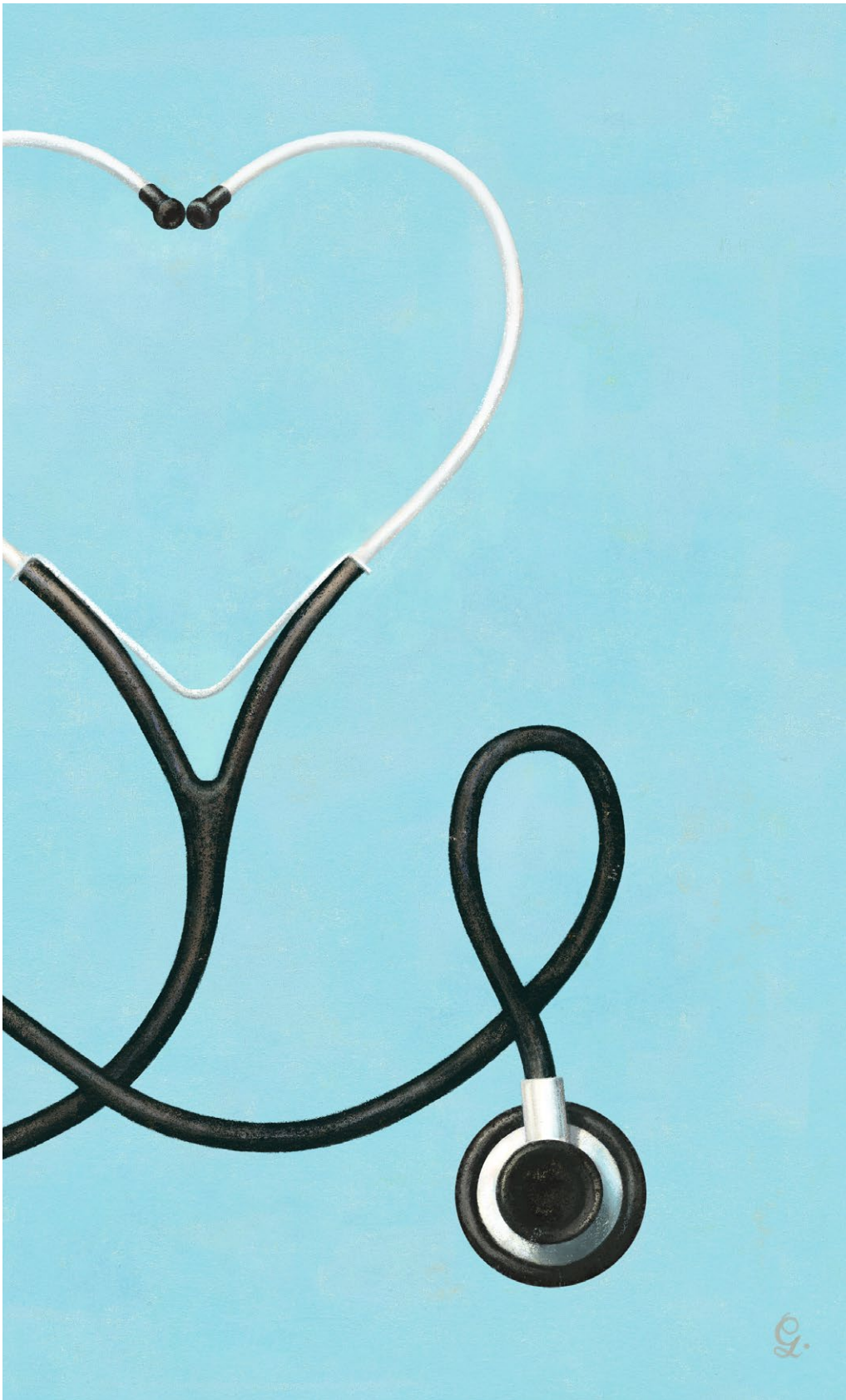
S T A N F O R D

M E D I C I N E

Summer 2019

special report

VALUE FOCUSED



STANFORD MEDICINE

Summer 2019

BANKING BIOLOGY

NEXT-GENERATION BIOBANKING IS BRIDGING THE GAP BETWEEN RESEARCH AND PATIENTS

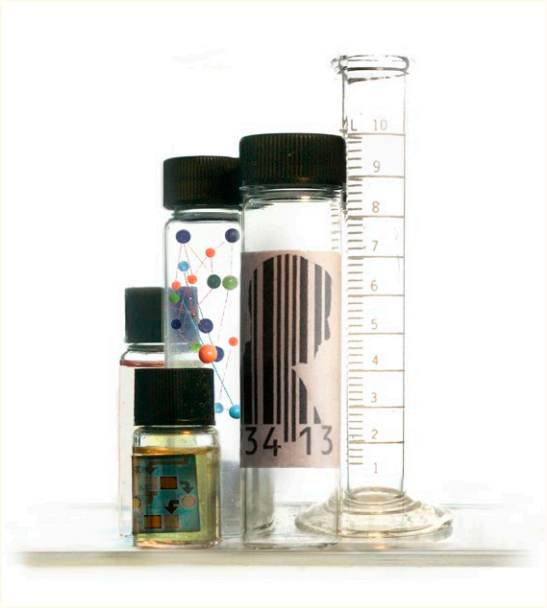
There's a new bank at Stanford that scientists are using to store some of their most coveted resources — and it's got nothing to do with money. This is a biobank, a repository of biological research specimens, such as tissue, saliva, blood and stool.

The facility holds data from nearly 200 research projects, all of which harness biological samples to probe the molecular roots of disease, understand disease progression or develop treatments.

Biobanks are not new, but in 2017 Stanford revamped its approach, adding new on- and off-campus freezer storage and streamlined sample tracking systems that capture clinical data annotations in real time. Another addition: a secure portal allowing scientists to share and access data from different samples and freely apply it to their research. For now, only Stanford scientists can access the samples and data, which are stripped of personal patient information to protect privacy.

It's an unconventional approach for academic medical organizations, said Rohit Gupta, who co-founded the biobank with Mark Cullen, MD, senior associate dean for research.

"The new biobank is right at the crossroads of patient care and molecular data," said Gupta, who has since begun serving as chief biobank officer at UC-San Francisco. "The goal is to bridge the gap between clinical care and research."



The Stanford biobank enabled Anne Chang, MD, associate professor of dermatology, to pursue a new avenue of investigation. She runs the high-risk skin cancer clinic, and in her work, she takes samples of patients' skin to monitor their conditions. But Chang wanted to get a more precise sample analysis by sussing out the molecular details of single cells. As a Stanford postdoc, Ansuman Satpathy, MD, PhD, co-developed a tool that enabled this research with graduate student Kathryn Yost in the lab of Howard Chang, MD, PhD, professor of cancer genomics and of genetics.

"With many of those skin cancer biopsies just sitting around, there was a big missed opportunity for deeper analysis," said Anne Chang. She and Satpathy wanted to apply the technology to her samples but neither had labs and personnel to conduct that work.

"It wasn't feasible for one lab to get the samples from the clinic and process them day and night as patients come in — especially in a way that enables smooth downstream analysis," said Satpathy, who is now an assistant professor of pathology at Stanford.

Biobank staff helped with that, making possible the examination of hundreds of samples to reveal more about how immune cells infiltrate skin cancer tumors and respond during immune-based treatments.

Dozens of other scientists entrust the facility with the seeds of their research: Using blood samples, Mark Davis, PhD, professor of microbiology and immunology, probes human immune function, using "disturbances" such as the flu vaccine to uncover system-level details of immune biology. Jennifer Frankovich, MD, clinical associate professor of pediatrics, uses blood samples to understand pediatric acute-onset neuropsychiatric syndromes, which can change the personality and behavior of a child within days. There's also discussion of using the biobank to host miniaturized living organ models, known as organoids, to enable scientists to better understand tissue-specific diseases and treatments.

"It's almost like you're working with another academic lab," said Satpathy. "It's that type of true collaboration, with both parties equally invested, and that's what makes this biobank such a valuable resource."— HANAE ARMITAGE

POLLY BECKER

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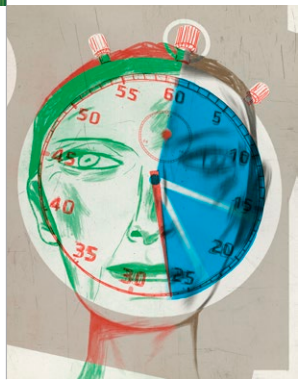


DEPARTMENTS

COVER: GÉRARD DUBOIS

letter from the dean

The stealthiest impediment to progress may well be conventional wisdom. "This is the way we've always done it" — consciously or not — helps determine what problems we address and which solutions we consider.

The U.S. health care system is not immune. Health care is resistant to change because of its complexity, byzantine structure and, most importantly, the high stakes involved: life and death.

Stanford Medicine is changing that.

Precision health refocuses biomedical research and patient care to predict and prevent more diseases, and, if they do strike, cure them precisely. It dramatically broadens the factors we consider during diagnosis and treatment and employs game-changing tools, such as big data and artificial intelligence. It challenges the status quo. With the same mindset, we're examining everything we do.

This issue of *Stanford Medicine* magazine explores what progress looks like across our clinics, hospitals, research labs and classrooms. Enhancing quality while driving down cost has long been the goal of health care reform in the United States, and that is also our goal here at Stanford. But for us, value is much more than an equation — quality divided by cost. It is about promoting precision health and sharing our pioneering solutions with patients everywhere.

GLENN MATSUMURA

With open minds, we are not only creatively solving the obvious problems but also identifying and overcoming hurdles we didn't realize were slowing us down.

Examples multiply as the full ingenuity and resourcefulness of the Stanford community comes to bear. Computer simulations of staffing and patient flow revealed a solution to a shortage of post-surgical recovery beds at Lucile Packard Children's Hospital Stanford — and the resulting change improved efficiency at the Bass Center for Childhood Cancer and Blood. Progress snowballs.

Academic medical centers like Stanford Medicine have come a long way from providing one-size-fits-all medicine, but we still have far to go to ensure each patient gets the right care at the right time. Personalized medicine means we can modify care down to an individual's genome. And a better understanding of the social determinants of health — everything from our behavior to our environment — means we have the opportunity and duty to treat each person individually.

That's why Stanford Medicine's Humanwide pilot project is so important and so exciting. Engaging a diverse cohort of 50 patients at Stanford Medicine's Primary Care 2.0 clinic in Santa Clara, Humanwide took a comprehensive, data-driven and collaborative approach to health care. Over the course of a year, care teams identified previously undiagnosed and overlooked health risks, and worked with patients on treatment plans to avert potential serious medical problems.

This shift in focus to detecting disease earlier, strengthening patient-provider relationships and deploying the latest health technology not only enhances value, it also demonstrates the power and promise of precision health.

Change is underway, and it is beginning at Stanford Medicine.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head & Neck Surgery

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

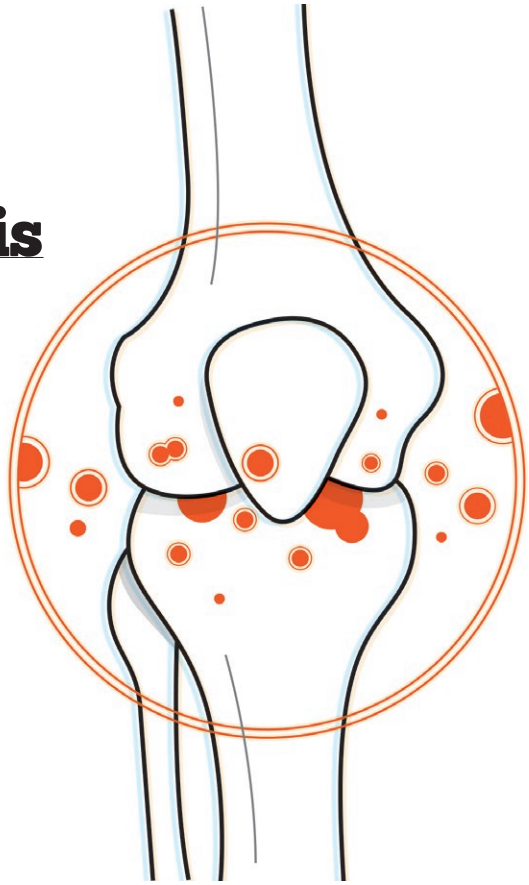
Banishing osteoarthritis

IMMUNOLOGIST WILLIAM ROBINSON, MD, WOULD LOVE TO figure out how to prevent people from getting osteoarthritis — one of the world's most common causes of pain and immobility. And he has a lead.

He and a group of colleagues recently found a link in mice between a class of immune cells — called mast cells — and the development of the condition. The discovery is unlikely to lead to a cure, but it gives researchers a potential way to design drugs to prevent it.

Mast cells produce the histamine and other molecules responsible for allergy symptoms, including hay fever and food-triggered anaphylaxis. But they also produce a degradative protein, tryptase, which can rip up collagens and other molecules that form the cartilage in joints, causing joint swelling and stiffness.

In a study published May 14 in *eLife*, the scientists discovered that blocking mast-cell activation or disabling tryptase protected mice from developing osteoarthritis. The results were supported by findings in human cells and tissues.



HARRY CAMPBELL

By age 60, the chances of humans exhibiting osteoarthritis symptoms exceed 30%. By age 80 or 90, the risk is nearly 100%.

"Almost all of us will ultimately suffer from osteoarthritis if we live to be old enough," said Robinson, professor of immunology and rheumatology and the study's senior author.

He wants to identify drugs that have excellent safety profiles and can prevent, rather than treat, osteoarthritis. "These drugs will have to be safe enough for large numbers of people to take for decades without problems," he said.

The new Stanford Hospital will double in size to 824,000 square feet. Read more in our fall issue and get a sneak peek at stanfordhealthcares.com

WEB EXTRA: READ MORE ON THESE TOPICS AT STAN.MD/MOREUPFRONT

No concealer needed

WHEN SURGEON Dana Lin, MD, told Karina Torres she could be the first Stanford patient to have her thyroid removed without leaving a visible scar, Torres loved the idea.

A hair stylist and makeup artist, Torres knows how to mask flaws. But this was different.

"A scar on the neck — that's something you can't really cover up," said Torres, who had a transoral thyroidectomy — thyroid removal through the mouth — April 16.

Besides leaving no scar, Lin said the procedure, which is done in only a handful of U.S. clinics, could reduce nerve injury risk and recovery pain.

upfront

Cancer screening gaps

SOME GROUPS OF women with ovarian cancer are far less likely to have genetic screening than national guidelines recommend, according to research by Allison Kurian, MD, a Stanford breast and gynecologic cancer specialist, and colleagues at Emory University and the University of Michigan.

The findings point to gaps in how well, or how widely, clinics follow guidelines, and to the role race and income levels play in testing disparities, researchers said.

Fewer black or Hispanic women were tested than non-Hispanic white women, fewer Medicare patients were screened than women with other insurance, and fewer patients living in high poverty areas were screened.

Kurian said the results, published April 9 in the *Journal of Clinical Oncology*, are significant because genetic testing results can guide patient care decisions, and can influence health care and screening choices of family members.

Researchers linked data on cancer cases in California and Georgia with data from laboratories conducting the bulk of cancer genetic testing from 2013 to 2014. Only 24.1% of 77,085 breast cancer patients had genetic screenings; and only 30.9% of 6,001 ovarian cancer patients did so — though guidelines recommend that all with the most common kind of ovarian cancer be screened.

Baby brain science

NEW RESEARCH COULD MAKE IT possible to drastically reduce the odds that premature babies will suffer brain damage from hypoxia, or episodes of low oxygen.

Studying brain spheroids — pinhead-sized balls of brain cells grown in culture that mimic structural and functional aspects of the developing human brain — researchers found the cells that are most susceptible to hypoxia damage and discovered a clue for reversing the damage. Premature babies can have dips in oxygen levels because their lungs and the brain center that controls breathing are immature. Resulting brain injuries can lead to neurological and psychiatric disease, said Anca Pasca, MD, lead author of a study published May 6 in *Nature Medicine*.

"In the past 20 years, we've made a lot of progress in keeping extremely premature babies alive, but 70% to 80% of them have poor neurodevelopmental outcomes," said Pasca, assistant professor of pediatrics and a neonatologist at Lucile Packard Children's Hospital Stanford.

After growing the brain spheroids until their development was similar to human brain tissue midway through gestation, Pasca's team exposed them to low oxygen for 48 hours, then restored oxygen levels. Changes occurred after 24 and 48 hours in genes that respond to hypoxia. And at later stages, hypoxic stress disrupted the development of neurons.

The researchers also found that the experimental drug ISRIB could prevent hypoxia-induced changes, indicating that drug treatments for preemies' brain injuries are possible.

Flagging chronic fatigue

A BLOOD TEST that reveals variations in how the immune systems of chronic fatigue syndrome patients respond to stress provided the first-ever biomarker for the debilitating illness, a pilot study showed..

Ron Davis, PhD, professor of biochemistry and of genetics, said patients can suffer for decades without answers as routine diagnostic tests typically come back normal.

"Too often, this disease is categorized as imaginary," said Davis, senior author of a paper on the findings published April 29 in *Proceedings of the National Academy of Sciences*.

Researchers used salt to simulate stress, studying the resulting changes in the flow of electricity in blood samples of 20 people with chronic fatigue syndrome and 20 without. Spikes in current occurred only in the chronic fatigue syndrome patients.

Symptoms of the syndrome include exhaustion, sensitivity to light and unexplained pain.

HARRY CAMPBELL; OPPOSITE: COURTESY OF STANFORD CHILDREN'S HEALTH

WEB EXTRA: READ MORE ON THESE TOPICS AT STAN.MD/MOREUPFRONT

CHRISTOPHER DAWES,

LONGTIME CEO OF PACKARD CHILDREN'S HOSPITAL, DIES AT 68

Christopher Dawes, who served as chief executive officer of Lucile Packard Children's Hospital Stanford for 18 years, died June 29 of amyotrophic lateral sclerosis, also called Lou Gehrig's disease. He was 68. Dawes guided the hospital during its formative years into a renowned center for advanced children's care. He was beloved by the hospital community for his leadership, warmth and humble nature; his advocacy for children's health; and his ability to listen.

He directed a $500 million program to build centers of excellence in several medical specialties; developed Stanford Children's Health — a regional network of care for children; and oversaw an expansion of the hospital into a technologically advanced, 361-bed facility that opened in 2017.

"We went from being a very lovely community hospital, nicely designed and family-friendly, to a world-class children's hospital drawing patients from across the United States and around the world," said Susan Packard Orr, a longtime member of the hospital's board of directors and daughter of hospital founder Lucile Packard.

Dawes was also an advocate at the national level, ensuring safe and healing environments for children and helping to create guidelines for coverage of children under the Affordable Care Act.

Lloyd Minor, MD, dean of the Stanford School of Medicine, said Dawes will be remembered for his enormous contributions to maternal and child health. "Chris was a tireless advocate for children's health. Through his passion and dedication, he helped bring extraordinary advances in clinical services to our young patients," Minor said.

Dawes, Minor and David Entwistle, president and CEO of Stanford Health Care, collaborated to create the Stanford Medicine integrated strategic plan. "It was wonderful to partner with an outstanding leader like Chris as our two hospitals and the medical school worked in concert to determine our collective future direction and how best to get there," Entwistle said.

"Beyond his effective leadership, what I will remember most about Chris are his kindness and dedication to the mission of helping children in need," said Stanford President Marc Tessier-Lavigne, PhD.

"He was very approachable and warm," said David Stevenson, MD, senior associate dean of maternal and child health at the School of Medicine. "He had a fatherly disposition that was very welcoming and supportive. His hardest problem was saying no. He always wanted to be helpful and responsive."

A native of Great Britain, Dawes grew up in California. He earned a bachelor's in public administration from San Diego State University and an MBA from the McLaren School of Business at the University of San Francisco. He was in senior positions at Pacific Presbyterian Medical Center in San Francisco, Santa Clara Valley Medical Center in San Jose and Stanford Health Care before joining Packard Children's as chief operating officer in 1995. He became CEO of the hospital in 1997, and retired in 2018.

Paul King became CEO of Lucile Packard Children's Hospital-Stanford Children's Health in January. "He understood at a fundamental level the profound difference that we could make in the lives of children and families when we come together in teams to share better ideas and better practices — that when applied consistently create the magic and miracle of healing," King said.

Dawes' survivors include his wife, Elizabeth (Beth) Dawes; sons Matthew and Scott Dawes (daughter-in-law Brittney Dawes); and daughter Sara Dawes Hughes (son-in-law Caleb Hughes). — RUTHANN RICHTER

PREDICT, PREVENT, CURE— PRECISELY

The Humanwide project integrates detailed health data with team-based care to better understand each patient

BY AMY JETER HANSEN

ILLUSTRATION BY GÉRARD DUBOIS PHOTOGRAPHY BY BRIAN SMALE

IN AN OLD FAMILY SNAPSHOT, three women and a man perch on a yellow couch, flanked by three men standing behind them. They look introspective, as if the photographer missed the moment when they smiled for the camera.

Eugene Celis pointed to a short-haired woman whose hands are neatly clasped. "My Auntie Lourdes," he said. "She died at the age of 80 of a stroke."

He touched the image of the man behind her in a patterned shirt. "My Uncle Edgardo. He died at the age of somewhere in the 60s range, of heart attack.

"My Uncle Alberto." A serene man in white. "He died of complications of diabetes."

The list stretched on and included several relatives who died before age 60 either of a heart attack or complications of diabetes. Celis' grandfather died of a heart attack. His father passed away in his 50s. His brother, sister, cousins: "They all have high triglycerides," Celis said. "Just like me."

At 42, Celis was already worried. During annual checkups, his doctor would say his blood pressure was fine. But when Celis used his mother's at-home blood pressure cuff, the readings were sometimes high.

All of it — the high triglycerides, family history, blood pressure — nagged at Celis like a persistent, unscratchable itch. He knew medication could help, but was reluctant to use it because triglyceride medication

harmed his liver years ago. Was he on the road to early heart disease?

"Most of my family on my dad's side, they don't even reach the age of 60," Celis said. "I don't want to be in the same situation. I want to see my grandkids."

A business supply chain analyst living in San Jose, California, Celis longed for objective answers to his health questions. Last year, after he mentioned concerns about his triglyceride level and medication, his primary care doctor invited him to participate in a Stanford Medicine project called Humanwide.

The yearlong pilot, which concluded in December, involved 50 patients and demonstrated a new approach to primary care, using information from genetic screenings, at-home digital monitoring devices and detailed wellness assessments to address current health concerns and lessen future risks. In a paper published in May in the *Annals of Family Medicine*, Humanwide's architects found that patients and clinicians embraced the new tools for preventive care, and care teams identified — and started treatment for — previously undiagnosed health conditions in several participants. Such insights provide a starting point for future care models based on analytics from individual patients, they wrote.

Lloyd Minor, MD, dean of the Stanford School of Medicine, said Humanwide offers a glimpse into a future when medicine can be more proactive and focus on averting disease through personalized care.

"Our vision of precision health is to predict, prevent and cure — precisely," Minor said. "With Humanwide, we have begun to realize that vision in a clinical setting. The information gathered in this pilot suggests approaches to primary care that may ultimately benefit many thousands of people."

MEGAN MAHONEY

Seeing her family struggle to obtain services for her sister, who had multiple sclerosis, drove Mahoney to pursue a career in medicine.

Seeds for Humanwide were planted in 2015, when Stanford Medicine leaders set out to craft a new way of delivering primary care. They were responding to national trends showing that patients increasingly required complex care for multiple ailments and that physician burnout was accelerating. Over 18 months, a group of clinicians and executives studied clinics around the country, commissioned interviews, synthesized information into a design for running a clinic, and refined the model based on feedback from patient and physician advisory groups.

The resulting Primary Care 2.0 model reconfigured the teams delivering care, assigning three to four medical assistants to the role of care coordinators who support a physician and an advanced practice provider, such as a nurse practitioner or physician assistant. The model also brought other health professionals on-site, including a clinical pharmacist, behavioral

HUMANWIDE'S ARCHITECTS FOUND THAT PATIENTS AND CLINICIANS EMBRACED THE NEW TOOLS FOR PREVENTIVE CARE, AND CARE TEAMS IDENTIFIED — AND STARTED TREATMENT FOR — PREVIOUSLY UNDIAGNOSED HEALTH CONDITIONS IN SEVERAL PARTICIPANTS.

health clinician and dietitian. Everything from the clinic's physical layout to the schedule of daily and weekly meetings emphasized collaboration and communication on each patient's care. In June 2016, Stanford Medicine's Santa Clara clinic started providing care using the Primary Care 2.0 model.

The next step was to develop a way to collect key health data for individual patients, and to integrate that information into their care. Megan Mahoney, MD, took the lead on the design, which would eventually become Humanwide. She'd arrived at Stanford Medicine in 2014 with a track record of establishing and revamping health care practices: She'd co-founded one of the first U.S. clinics to serve both HIV-infected patients and their family members in San Francisco, and she'd helped with an overhaul of California's prison health system.

Mahoney's drive to improve primary care came from a personal place. She was 11 years old when her older sister, Cindy, was diagnosed with multiple sclerosis. Over the next two decades, Mahoney watched her family struggle to navigate a fragmented health care system to get what Cindy needed, from securing Medicare coverage to obtaining a wheelchair. The experience motivated Mahoney to set aside aspirations to study economics and instead pursue medicine. Her sister died in 2007 at the age of 38.

EUGENE CELIS
Celis looked to the Humanwide project for objective answers to questions about his health.

"She did not have a medical ally — somebody who was going to walk that journey with her," said Mahoney, who is now Stanford Medicine's chief of general primary care. "When I see a patient, I like to say that 'it's an honor to walk this journey with you.'"

Those kinds of trusting, long-term relationships are at the heart of Primary Care 2.0, which frees physicians to spend more time with patients by distributing case management duties among the core members of the care team.

With Humanwide, Mahoney gave the teams another tool for personalizing patient care: data. Lots and lots of data. Beyond the usual questionnaire, this compilation included information captured from wearable devices and gleaned from genetic tests — results that patients often learn at home from consumer products but don't necessarily share with their providers.

It also included evaluations of how each patient's genetic makeup influences their medication responses, and answers to in-depth questions about sleep, stress, exercise, nutrition and weight. The care team assembled all of this information into individual portraits of each patient's health, which they used to develop plans for accomplishing personal goals.

For the pilot, Mahoney sought a diverse group of participants. They were men and women from ages 24 to 86, who came from varying racial and ethnic backgrounds and had a range of medical circumstances. More than half of the participants were obese, and more than half had a major cardiovascular risk factor. Three patients were being treated for cancer, one was awaiting a kidney transplant and another had already undergone a kidney transplant. Three patients had severe heart disease, and one had received a heart transplant.

"We saw this as an opportunity to bring in more data that was previously not available, giving us an unprecedented understanding of our patients' risks," Mahoney said. "It gave

CONTINUES ON PAGE 36

VALUE FOCUSED

RESEARCHERS ARE HARNESSING MILLIONS OF DE-IDENTIFIED PATIENT RECORDS FOR THE ULTIMATE CONSULT

data dealers

DOCTORS FACE ALL SORTS OF CONUNDRUMS. A patient might have troubling symptoms but no clear diagnosis. Medical guidelines may recommend one thing while intuition points to another. And the question that's perhaps most central: What's the best treatment for my patient?

When bloodwork, medical literature and one-off case studies don't turn up an answer, doctors often seek something called a curbside consult, the "phone a friend" lifeline of medicine. Now, there's a service at Stanford Medicine that does the curbside consult one better.

How? By scaling up — replacing one consult with a thousand.

This is the concept behind the new Clinical Informatics Consult service, which is being spearheaded by biomedical data scientist Nigam Shah, MBBS, PhD. The idea is to draw on patient records from across the country and use them to help answer medical questions.

His team's technology — part mega-search engine, part powerful data analysis — brings a deluge of data to bear on inquiries too thorny or in the weeds to answer based on established guidelines. Shah hopes the service, while currently available only to Stanford physicians, will one day extend to hospitals and academic centers across the country, even to patients themselves.

BY HANAE ARMITAGE

ILLUSTRATION BY HARRY CAMPBELL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At the core of the service is a one-of-a-kind search engine that scours a trove of anonymized health data. Records of lab test results, prescriptions, written medical histories, vital signs, surgeries and more accumulate by the millions, creating a wealth of information for the search engine to sort through. To protect the patients' privacy, all personal identifiers in their data have been stripped.

A doctor's query could be as simple as asking how many kids have run a fever in the past year. Or it could be as complicated as asking how an approved drug for a heart condition will interact with a blood pressure medication a patient is already taking. The federal approval process for a new drug tests the safety and efficacy of the therapeutic, but whether that drug plays nicely with others is often left blank.

"Our idea was to build something that answers these sorts of questions by sifting through millions of patient records and looking for information relevant to each specific case," said Shah.

RETHINKING THE PATIENT CONSULT

USING PAST RECORDS TO INFORM CURRENT CASES IS NOTHING NEW or controversial — in fact, the earliest attempts date back to the 1970s. But it took some finesse for Shah and his team to do it on such a large scale.

When Shah first joined Stanford in 2011, one of his colleagues had a tough patient case and thought other medical records of similar cases could help point her in the right direction. So the colleague pulled the files herself, which caused some concern among the medical school's leaders: Stanford had not yet established guidelines for accessing old patient records, even if it was for a good reason.

"I'd heard about what she did and I started chatting with a couple of colleagues, and we thought, 'This isn't something she should have had to do manually in order to help a patient,'" said Shah. And it pointed to a new opportunity: "What if we could treat these questions as a research project and come up with a way to learn from these cases systematically?"

Shah teamed up with Christopher Longhurst, MD, then-chief medical information officer of Lucile Packard Children's Hospital Stanford, and Robert Harrington, MD, professor and chair of medicine, to create a vision for using patient records of similar cases to successfully conduct the big-data-based consults on a large scale. Over three years, Shah's team rifled through thousands of records, carried out these steps — identifying symptoms, making note of timelines, compiling treatment information and more. Then they completed a few trial runs.

Their efforts served as a proof of concept to show that the process could be valuable for treating future patients.

"This service is not for the times when doctors absolutely know what they should be doing, nor is it for the times when they absolutely know what not to do. It's for the times when we don't know the answers, when a patient population hasn't been studied, or a disease condition has a twist that makes it different from what's been previously reported. And these are often the majority of cases and questions that we see," said Harrington, the Arthur L. Bloomfield Professor of Medicine.

"The service doesn't tell physicians what to do; it provides another set of information and data for clinicians to put into the context of everything else they know to better guide decision making."

Before the Clinical Informatics Consult service became a full-fledged operation offered to Stanford doctors, Shah called the concept the Green Button, he said, explaining: "We thought, 'Wouldn't it be great to have a button within the patient electronic health records system that, with one click, could comb through past patient records and spit out a report with data-based conclusions?'"

Over the next several years, the group built on the momentum of the initial test cases, devising strategies to streamline and, in some cases, automate the work necessary to conduct each consult. They needed a search engine for patient records — software that could efficiently and effectively scan patient records to pull out only those that fit certain criteria.

In true Silicon Valley style, Shah gathered venture backing for a startup, hoping to develop the idea into a company. The team, however, closed shop after two years, still needing time to perfect the search engine software. So Shah invited colleagues still interested in the project to Stanford, where they continued to refine the technology as a research project.

Vladimir Polony, PhD, senior research engineer and the driving force of the software's search engine, came first, followed by instructor of pathology Saurabh Gombar, MD, PhD, and research scientists Alison Callahan, PhD, and Ken Jung, PhD. Together, they formed the squad that trans-

formed the concept into what it is today. The informatics consult service is technically still research, but after five years of development and approval from the board that oversees Stanford research on human subjects, it opened to all Stanford physicians at the beginning of last year. As far as Shah knows, it's the first such service at an academic medical center.

"We wanted to make sure that this was a service provided, not a self-serve type of thing," said Shah. "If you look at the history of medical technology, anytime something complicated enough comes along, a new specialty is born. Doctors don't do their own MRIs; a radiologist does. We don't have primary care doctors analyze disease tissues; we have pathologists. So why would we expect a doctor to do their own data digging?"

'DOCTORS DON'T DO THEIR OWN MRIs; A RADIOLOGIST DOES. WE DON'T HAVE PRIMARY CARE DOCTORS ANALYZE DISEASE TISSUES; WE HAVE PATHOLOGISTS. SO WHY WOULD WE EXPECT A DOCTOR TO DO THEIR OWN DATA DIGGING?'

For doctors, Gombar is the first line of contact and focuses on what they want to know. Callahan and Jung then translate requests into code that the search engine will understand. Guided by the query, the search engine hunts for medical records with compatible information, whittling down the population until all that remains is data from individuals who, medically, look like the patient in question.

Then the group performs data analysis, drilling into the particulars (such as the time span of recovery or the efficacy of drug A versus drug B), and finally, summarizes the takeaways. The team is usually able to get doctors a full report within 72 hours.

To date, the service has filled more than 130 requests from Stanford doctors in a wide range of specialties, mining data from the Stanford hospitals and from two insurance claims databases that include patient records from across the United States, which is, in part, what makes the service so powerful. If one patient fares better on drug A, that could be a fluke, but if a thousand patients benefit more from drug A, that's something to pay attention to, said Shah.

The informatics service is also poised to supplement clinical trials, especially those that are highly specific. Take a well-studied field like cardiology: About 20% of evidence-based medical guidelines have their foundations in randomized clinical trials, but if you ask a doctor how often a patient who walks through the door matches the people who were in that clinical trial, the answer is less than a quarter of the time.

In addition, treatments recommended by a clinical trial are not always a sure thing. For instance, a patient could be allergic to the drug or taking another medication that doesn't mix well with the recommended therapeutic.

"So you're looking at about a 4% chance that there's a guideline with trial-based evidence that applies," said Shah. "By and large, doctors are extrapolating from evidence produced for people who are not like the person in front of them."

The consult service offers doctors an opportunity to learn from other patients similar to their own.

PUSHING THE BUTTON

When Shah first offered the consulting service at Stanford, he expected to get mostly "drug-A versus drug-B" types of questions. But his team has researched a variety of inquiries, some seeking treatment guidance, some that pertain to research, some aiming to help streamline administrative tasks. Most often, doctors want to know how often a particular medical outcome occurs.

In one of the earliest consultations, Matthew Wheeler, MD, assistant professor of cardiovascular medicine, asked the group to investigate the difference between two treat-

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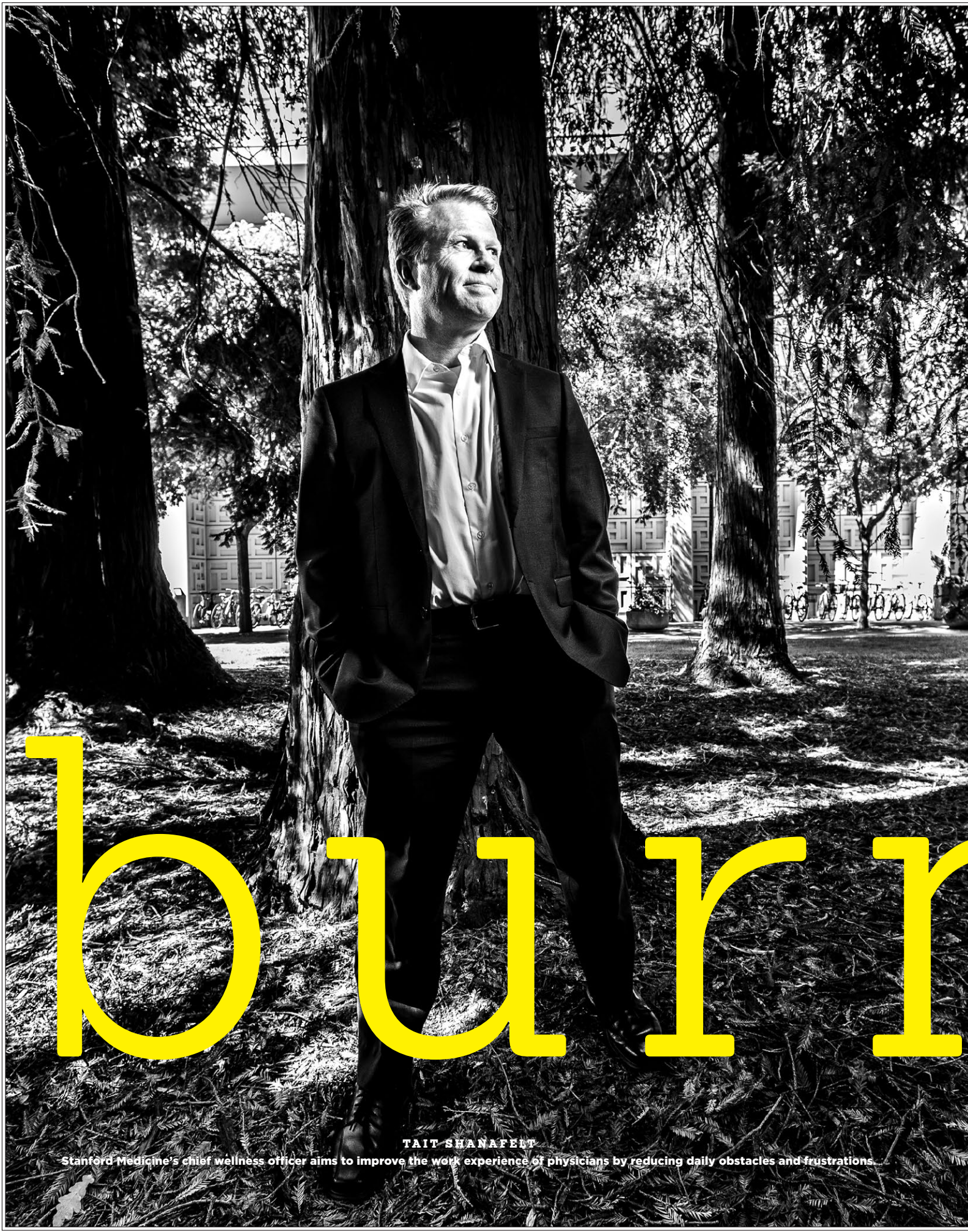

burn

TAIT SHANAFELT

Stanford Medicine's chief wellness officer aims to improve the work experience of physicians by reducing daily obstacles and frustrations.

BATTLING burnout

BY RUTHANN RICHTER

PHOTOGRAPHY BY BRIAN SMALE

VALUE FOCUSED

PROGRAMS THAT ADDRESS THE STRESSES OF BEING A PHYSICIAN BEGIN TO SHOW RESULTS

PEDIATRIC SPECIALIST RYAN WALSH, MD, REACHED A BREAKING POINT IN 2012. He was so physically and emotionally exhausted from work that he considered leaving Stanford and his lifelong home in Palo Alto.

Then chief of a major clinical program at Stanford Medicine, he felt overwhelmed by the relentless demands of his job, said Walsh, who asked that his real name not be used. He began to have sleep problems and anxiety attacks and had trouble focusing.

Walsh had classic signs of burnout, and he's not alone. Nearly half of the nation's doctors report feeling emotionally exhausted and ineffective, and having lost a sense of meaning in their work, according to studies by Tait Shanafelt, MD, Stanford's chief wellness officer.

But Stanford Medicine, under the leadership of Lloyd Minor, MD, dean of the School of Medicine, is out front nationally in combatting the trend with a campaign to confront the myriad issues that lead to burnout and implement programs to improve physicians' well-being.

The goal of the Stanford program, considered a national model, is to increase professional fulfillment by improving the work experience and building an efficient, high-quality system that promotes teamwork and work-life integration, among other things. Although not the primary

focus, it also aims to support physicians' efforts to take care of themselves, through offerings such as peer support and mindfulness training. A key to the program is data collected from daily practice records as well as from surveys about Stanford physicians' work satisfaction and wellness, which enables the team at WellMD, Stanford's physician wellness center, to identify problems and work with Stanford Medicine's leaders to solve them.

The 2019 survey of 1,437 Stanford physicians (about two-thirds of eligible physicians) shows the effort is starting to make a difference. In it, clinicians reported slightly fewer burnout symptoms on average, compared with the most recent previous survey, in 2016, when 34% had signs of distress. Concerted efforts to bring about change resulted in faculty members in six departments experiencing a dramatic improvement, Shanafelt said. Physicians in nine departments reported little or no difference, while those in two departments reported that symptoms had worsened, according to the survey. The center now plans annual surveys.

"Your experience at Stanford depends on which of those departments you are in," Shanafelt said. "There is much more work to be done, but we are encouraged by the progress of the departments that have made improving professional fulfillment a top priority. Their experience illustrates what is possible when departments actively focus on this issue, and we are actively engaging the other departments with the hopes they embark on improvement in a deeper way."

Doctors may experience burnout when faced with crushing work demands, lack of control, a toxic workplace and burdensome paperwork. Inefficient work processes, like clinics or operating rooms that don't function smoothly, also can be major contributors. The toll is enormous: Clinicians suffer from higher rates of alcohol and substance abuse and suicide than other professionals. Moreover, when doctors suffer, so do their patients. Studies link burnout to patient dissatisfaction, higher costs, poor patient results and medical errors.

"When people have higher burnout, the unprofessional behavior and the caustic way that people treat one another often increases. There is less teamwork," Shanafelt said. "There is also higher turnover among physicians. That results in access issues for patients, and it erodes continuity of care" as patients lose doctors who are familiar with them and their health situations.

As doctors leave or reduce their hours, the cost of care increases sharply, according to a new study in the *Annals of Internal Medicine* by investigators from the Stanford WellMD Center as well as Harvard and the American Medical Association. They found burnout-related physician turnover costs the nation $5 billion annually, or about $7,600 per physician per year.

Shanafelt, a national leader in developing initiatives to counter burnout, began exploring the issue nearly two decades ago when he was a senior resident in medicine at the University of Washington and noticed a disturbing tendency among the interns he supervised.

"I was watching people who I knew went into practice with altruistic values. They'd become quite cynical and were talking about their patients in ways that were incongruent with those values," said Shanafelt, a hematologist and the Jeanie and Stew Ritchie Professor at Stanford. He decided to launch a study of burnout trends among medical residents in December 2000, which showed for the first time that their suffering was linked to quality of care and patient health. Its publication in early 2002 in the *Annals of Internal Medicine* launched the issue of physician burnout into the national spotlight. Shanafelt moved to the Mayo Clinic, where he established a center to study the problem and develop interventions, conducting groundbreaking research that continues today.

At Stanford Medicine, faculty members began mobilizing around the issue a decade ago by forming a physician wellness committee, led by Bryan Bohman, MD, associate chief medical officer at Stanford Health Care. Bohman said it was clear that physician wellness was vital to the future of medical practice. He and his colleagues built the case for a full-fledged center, which eventually became the WellMD Center, and with major support from Minor and leaders at the two hospitals they recruited Shanafelt in September 2017 to be its first director.

PHYSICIAN, HEAL THYSELF

Bohman said that for too long, physicians have shouldered the burdens of an increasing workload and clerical demands with a kind of stoic heroism.

"They may be unable to get their work done and take good care of their patients without extraordinary, superhuman efforts, so they will go ahead and make those extraordinary, superhuman efforts, even at the cost of their own health and well-being," he said. "If you lose sight of when selflessness transitions into self-abuse, you ultimately may damage yourself, your patients, your co-workers and the whole system of care."

Moreover, when things go wrong, he said, physicians tend to blame themselves, rather than a flawed system. A powerful force behind burnout is the pervasive feeling among physicians that they have to be perfect and work excessively hard to feel a sense of self-worth, he said.

"When you make a mistake, do you beat yourself up or do you see it as, 'Hey, I'm human. I can make mistakes like anyone, but how do I mitigate that? How do I make sure those mistakes don't harm the patient? How do I learn from this mistake and turn it into a positive?'" Bohman said.

Stanford Medicine has offered self-compassion training to physicians, which helps them reframe their thinking so they learn to be as kind and compassionate to themselves as they would be to a good friend. Clinicians also can opt for mindfulness training to help minimize their stress and enable them to focus on the moment without being distracted by frustration, worry and negative thoughts. Surveys show that these skills can buffer against burnout and lead to professional fulfillment, Bohman said.

But no amount of self-compassion or mindfulness can shield physicians from basic inefficiencies in the system — daily obstacles and irritations that can turn a clinic day into a frustrating slog.

Shanafelt said the goal is to bring about wholesale culture changes in the organization and practice environment, beginning with a commitment to wellness from leaders.

As part of the effort, WellMD in July launched a multimillion-dollar project funded by the California Medical Association to reduce physician burnout by providing support to doctors statewide. The initiative will also bring new resources to Stanford physicians.

"Addressing the systemic issue of physician burnout is essential to not only increasing physician well-being but ultimately delivering better patient care," Minor said. "I'm confident that this comprehensive project that incorporates research-driven strategies developed at Stanford Medicine will help get to the core of the problem." Minor and the two hospital CEOs are fully behind the effort to make physicians' professional fulfillment a priority, Shanafelt said. From there, it's critical for each department to wage its own fight.

"The dean can't fix it for you. The WellMD Center can't fix all the problems across our hospitals and clinics," Shanafelt said. "So many of the friction points are unique to each specialty and department. That's why we are engaging departments and local leaders and partnering with them to begin to help each department address the specific changes that are the biggest local irritant."

Nearly all of the 18 clinical departments now have a well-being director charged with identifying and leading efforts to address sources of inefficiency and discontent. The surgical and anesthesia specialties, for instance, are tackling operating room scheduling and delay issues.

> 'IF A SURGEON IS WAITING AN HOUR AND A HALF BETWEEN CASES AND GOING HOME at 8 p.m., we can't ask them to meditate for an hour and a half between cases. We have to change the workload and staffing levels so everybody is getting home at a reasonable time.'

"If a surgeon is waiting an hour and a half between cases and going home at 8 p.m., we can't ask them to meditate for an hour and a half between cases," Shanafelt said. "We have to change the workload and staffing levels so everybody is getting home at a reasonable time."

The Department of Pediatrics has undertaken several initiatives in partnership with the WellMD Center, including one to help division chiefs strengthen leadership qualities that are important to the department's physicians. Previous studies led by Shanafelt at Mayo Clinic and subsequently confirmed in studies of Stanford physicians show these supervisor behaviors are a major factor in physicians' professional fulfillment.

In the past year, the department faculty members answered an anonymous survey to evaluate their division chiefs on a series of behaviors, such as providing helpful feedback, acknowledging a job well done, assisting with career

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WEB EXTRA: HEAR A CONVERSATION WITH TAIT SHANAFELT AT https://stan.md/2N9EPM9

stroke

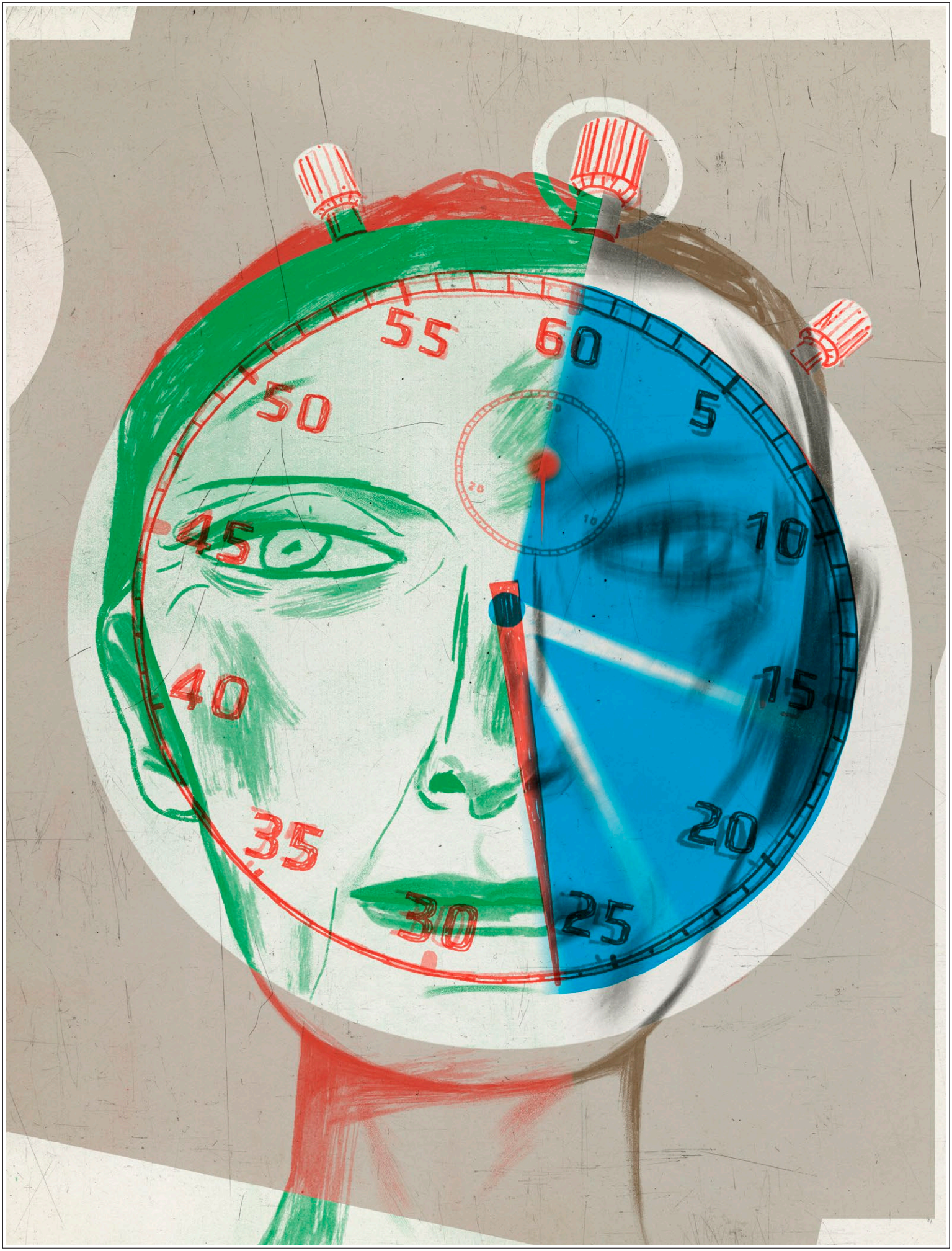
TREATING BLOOD CLOTS IN THE BRAIN GOES FROM FAST TO FASTER TO FASTEST

By the time the man arrives at Stanford Hospital's emergency bay doors, paramedics have already called in vital information: He is unable to move his right arm and his speech is garbled, suggesting a stroke. His blood glucose is normal, ruling out hypoglycemia as the culprit.

As soon as the ambulance rear doors open, at 3:47 p.m., a clerk leans inside to record the man's name, then runs back to the registration desk to enter his information into the system. A few yards beyond the ambulance bay a crowd of physicians, nurses and a pharmacist are waiting. The paramedics lift the man (a composite Stanford stroke patient created for the scenario described here) onto a hospital gurney. With the press of a button, the gurney records the patient's weight (let's call him David Williams), and the crowd wheels him into the computed tomography room.

BY MANDY ERICKSON

ILLUSTRATION BY JEFFREY DECOSTER PHOTOGRAPHY BY BRIAN SMALE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'DURING A STROKE, 1.9 MILLION NEURONS DIE EVERY MINUTE. WHEN WE ARE ABLE TO ADMINISTER TPA QUICKLY, THAT TRANSLATES INTO SAVED NEURONS, SAVED INDEPENDENCE AND SAVED HEALTH CARE COSTS.'

They quickly transfer him onto the CT bed, positioning his head inside the doughnut-shaped scanner. One of the paramedics, meanwhile, calls out his medical information: "Right-side facial droop, aphasia. Age 82. Last OK was 2:30."

While the scanner takes detailed X-ray images, the medical team stands behind a glass partition, eyes on computer screens. They are watching for telltale signs of bleeding in the brain, which would appear in the form of white, shapeless masses. Once the scan is complete, as cross-sectioned images of Williams' head flow onto the screens, nurses insert an intravenous line into his arm and draw his blood. Out in the hall, a pharmacist searches for Williams' medical information in Stanford's records.

The physicians need to decide, quickly, if tissue plasminogen activator would help. The medication will dissolve a stroke-causing blood clot, but it will worsen and may provoke cerebral bleeding. If tPA is warranted, they must give it immediately, in the scanner room: Minutes saved in stroke treatment can make the difference between walking and not walking, living alone and relying on caregivers.

The pharmacist finds that Williams is not taking any medication nor does he have a medical condition that could lead to bleeding. The neurologist orders tPA, the pharmacist hands a nurse the correct dose in an IV bag and the nurse sets the pump to deliver the medication. A quality assurance nurse checks his watch: 4:02 p.m. Fifteen minutes have passed from the moment the ambulance bay doors opened until the tPA entered Williams' vein.

"During a stroke, 1.9 million neurons die every minute," said Nirali Vora, MD, an associate professor of neurology and a stroke specialist. "When we are able to administer tPA quickly, that translates into saved neurons, saved independence and saved health care costs."

Seven years ago at Stanford Hospital, the average door-to-needle time — starting when a stroke patient arrives at the emergency department and ending when they receive tPA — was 66 minutes, typical for a U.S. hospital. Today, at Stanford, it's 26 minutes, with an all-time record of nine. Shaving so much time from a process, in a department already primed for quick action, required months of research, years of changing work habits and a good dose of diplomacy.

Developing new stroke protocols

THE RAPID STROKE PROTOCOL AT THE BUSTLING EMERGENCY DEPARTMENT got its start at Stanford's Clinical Excellence Research Center. CERC's office lies in the oak-studded hills about a mile south of the center of campus, reached by a winding, single-lane road.

CERC is the brainchild of Arnold Milstein, MD, an economics major who entered medical school and specialized in psychiatry and care quality before turning his attention to the rising cost of U.S. health care. Funded by grants and private foundation gifts, CERC generates research on lowering health care costs while preserving or improving quality.

Every year, CERC accepts and funds four to seven fellows, early career professionals with an interest in health care value. Most fellows work in the medical field, though some come from the business and engineering worlds. Split into two groups, they spend 11 months tackling two challenges that Milstein chooses. "I work backward," Milstein said. "I ask, 'Where is America spending the most on health care?' Then I pick a plausible target." CERC fellows have developed recommendations for such aspects of health care as outpatient surgery, prescription medication, spine pain treatment and ICU care.

During the second year of the program, 2012 to 2013, one of the teams took on stroke care, the leading cause of disability in the United States. The fellows started out "in a sort of innovation camp," according to Waimei Amy Tai, MD, who was one of the stroke fellows and is now a neurologist at Christiana Care Health System in Delaware. They learned about the economics of medicine as well as lean process management, a manufacturing approach that maximizes

customer value by minimizing waste. They pored over the scientific literature on stroke care innovation and visited health care facilities to observe treatment protocols. They took a field trip to Hillsboro, Oregon, to learn how Intel reduces waste in its microchip fabrication plant.

Their research completed, the fellows devised three proposals to lower spending by improving stroke care: coaching patients to better manage their blood pressure, avoiding long hospitalizations for stroke patients whose symptoms disappear before or during emergency department visits, and sharply reducing door-to-needle times.

In the next step of CERC fellowships, the fellows pitch their proposals to health care organizations and share them at medical conferences, hoping to find buyers for their ideas. Virginia Mason Medical Center in Seattle and Allina Health in Minneapolis took on the second proposal, avoiding long hospitalizations. Kaiser Permanente's Northern California hospitals adopted the third proposal, reducing door-to-needle times, as did Stanford Health Care.

NIRALI VORA
After taking on stroke care oversight in the hospital's emergency department, Vora closely observed ER stroke protocol to find ways to speed treatment further.

Shaving off the minutes

STANFORD'S NEW DOOR-TO-NEEDLE PROTOCOL WAS INSPIRED BY A STROKE TREATMENT innovation at Helsinki University Central Hospital; the CERC fellows uncovered it in a Scandinavian medical journal. In the Helsinki hospital, staff reduced their average time from nearly two hours to less than 20 minutes, largely by eliminating unnecessary steps and starting evaluations while stroke patients were traveling to the hospital.

But simply telling the staff at Stanford Hospital's emergency department to follow the Finns wouldn't bring lasting changes. "You have to understand how attached people are to their sense of mastery," Milstein said. "They are grounded firmly in how they currently do their work."

The task of reducing door-to-needle times fell, in part, to Tai, who stayed at Stanford for two years after the fellowship ended. Like Milstein, Tai was an economics major. "I've always had an interest in quality improvement," she said. "I applied to CERC because I wanted to take a look at health care from a value perspective."

Tai, Vora and other physicians, as well as nurses and CT technicians, began their project by observing. Whenever the charge nurse issued a stroke code — a text message alerting on-call nurses, pharmacists, registration clerks and physicians that a stroke patient is on the way — they watched.

They identified a few steps that were unnecessary, such as running an electrocardiogram and assigning a room, and eliminated them. They also realized that some steps, such as inserting an intravenous line and running lab work, could take place after the scan. They saved time by ensuring everyone on the stroke code team knew in advance the role they'd play in getting the patient to the CT scanner and, ultimately, treatment.

Like actors rehearsing for a play, they ran mock stroke codes with one staff member playing patient and everyone else acting out their assigned roles. When they found snags, they fixed them and ran more mock stroke codes, shaving off minute after minute.

"There was a lot of resistance initially because we were

changing people's habits," Tai said. She employed a host of management tactics, but perhaps her most effective tool was humility.

"At a meeting, I would suggest inserting the IV while we were waiting for CT scans, and no one would say anything," she said. "Then I would email reference papers around, and someone at the next meeting would say, 'Why can't we insert the IV in the CT scanner?' and I'd say, 'That's an awesome idea!'"

When Tai left Stanford in 2015, Vora took on the job of overseeing stroke care in the emergency department. At that time, stroke patients arriving by ambulance received speedy treatment, but those who showed up on their own were put through the old, slower process.

Like Tai, Vora spent a lot of time hanging out in the emergency department, waiting for potential stroke patients to walk in. When they did, she tried to blend into the background, timer in hand. Suspected stroke patients now have a bed reserved for them near the CT rooms — it signals that they need immediate testing — and triage nurses are empowered to call a stroke code. So are the security guards, who Vora ensured were trained to recognize a possible stroke. "Patients often tell the security staff their symptoms," she noted.

A little competition also helped drive the numbers lower: The stroke team started issuing buttons that display the minutes it took from a patient's arrival to the administration of tPA. If the door-to-needle time is impressive, under 30 minutes or so, stroke code team members pin them to their white coats and badge lanyards.

SIGNS OF A STROKE

- Sudden numbness or weakness in the face, arm or leg, especially on one side of the body
- Sudden confusion, trouble speaking or difficulty understanding speech
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking, dizziness, loss of balance or lack of coordination
- Sudden severe headache with no known cause

Call 911 right away if you or someone else has any of these symptoms.

SOURCE: U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

Continuing to improve

Eric Bernier, RN, was typing an email early this year when his cell phone flashed: "Stroke code adult: Emergency room ambulance bay ETA-10." He put on his white coat and walked upstairs to the emergency department. As a quality director for Stanford Health Care, his job is to keep the door-to-CT and door-to-needle times low and to ensure that all the steps in the stroke protocol are followed. "I'm the grumpy guy in the basement who asks why things are taking so long," he said.

On this day, he observed as the emergency crew ran through its well-practiced choreography and started the CT: It took just five minutes, one less than average. The process played out as it should, except, he noticed, an emergency technician failed to record the patient's weight. He made a note to speak with her supervisor. "Every stroke code is an opportunity to find something to improve on," he said.

Soon after the CT, the patient answered questions and was able to move her leg, so the neurology fellow on duty, Adam MacLellan, MD, decided against giving her tPA. "I'm more suspicious it's a seizure," he said. The lanyard holding MacLellan's Stanford Hospital badge is covered in buttons with his door-to-needle minutes: 21, 25, 17.

Only about a third of stroke codes result in a stroke diagnosis — a migraine, low blood sodium, fainting, even reactions to Novocain from a dental procedure can look like a stroke. But because a stroke can be so devastating, Bernier said, "We'd rather activate way over. We say call often and call early" whenever a stroke is suspected.

And only about one-eighth of stroke codes end with tPA being administered. But the speedy system also helps patients with a stroke that tPA can't treat: Quick diagnosis leads to rapid treatment — such as removing a clot with a device or repairing a damaged vessel — which means more brain tissue is protected.

If a door-to-tPA time is overly long, Bernier said, it's usually because it took time to confirm information about the patient. Stroke patients often can't speak, and family members or caregivers frequently don't know what medications they're taking. It can also take a while to determine when the stroke occurred; after 4½ hours, tPA is likely to cause more harm than good. In one case, the physicians determined the last time a patient was OK by reading a post on the patient's Facebook page.

ERIC BERNIER
As quality director for Stanford Health Care, Bernier says he's "the grumpy guy in the basement" asking why door-to-needle treatment for stroke patients in the ER took so long.

But if a patient's record is readily available, the door-to-needle time can drop significantly: "When we had that nine-minute code, we had all the information on hand," Bernier said. "Everything was in perfect alignment."

A patient's perspective

Malinda Mitchell, retired CEO of Stanford Health Care, was speaking with her mother, Rosina Might, in her kitchen when Might's face started to droop. Mitchell, a former nurse, suspected a stroke and called 911. While she was on the phone, her mother collapsed, wouldn't answer questions, and was unable to move one of her arms and one of her legs. An ambulance arrived in minutes.

By the time Mitchell and her sister, who was visiting along with their mother from Atlanta, made it to Stanford's emergency department, Might was undergoing a CT scan. Seventeen minutes after her arrival, she received tPA — a record at the time, 2015.

"The coordination and how synchronized they all were," Mitchell said, "was really an amazing thing to experience from the patient side."

Might, then 92, spent two days in the hospital and flew home two days later. "It was clearly a fairly massive stroke," Mitchell said. "But the next morning she was talking in full sentences and moving her arm and leg."

Might died last year at 95. Without effective stroke treatment, Mitchell said, her mother could have spent the last years of her life unable to speak, possibly paralyzed, relying on round-the-clock care.

Instead, Mitchell said, "She lived a very productive, active three years. It was as if nothing had happened." **SM**

— Contact Mandy Erickson at merickso@stanford.edu


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valuable addition

mathematical models to improve how hospitals are run

BY KATHARINE MILLER

ILLUSTRATION BY HARRY CAMPBELL

IN 2016, ANGIE KOPETSKY WAS IN CHARGE OF ASSESSING WHETHER THE PEDIATRIC OUTPATIENT CANCER TREATMENT UNIT AT LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD COULD TAKE ON MORE PATIENTS FROM ELSEWHERE IN THE HOSPITAL.

She had reviewed historical data showing that the unit, where patients come by appointment for hours-long chemotherapy infusions, was using only 40% of its capacity. But it was also true that activity in the infusion center was very dynamic, with some treatments running longer than scheduled, others shorter, some needing to be canceled for various reasons and others needing to be added at the last minute. "We knew we couldn't hit 100% utilization there," said Kopetsky, executive administrative director of the Bass Center for Childhood Cancer and Blood Diseases at the children's hospital. "But we wanted to find the sweet spot we should be hitting."

For help, Kopetsky turned to mathematicians from Stanford's Management Science and Engineering Department, including graduate student Allison Esho. Esho and her team created computer simulations to identify ways to increase use of the center's capacity. Based on the simulations, it seemed clear

that the center could take on more patients — specifically those who received other types of infusions in beds elsewhere in the hospital — and that doing so would open up those beds for patients recovering from surgery.

But the center's staff resisted. Patient care manager Merian van Eijk remembers thinking, "We're full! How can we do this?" Van Eijk, a nurse, had been on the 10-bed unit for 12 years and, at first, the analyses and simulations by Esho didn't convince her that the center could handle more patients. So van Eijk set about collecting her own data — only to discover that the analyses were right.

"My perception was that we were always busy, but the reality was that it was in a very inefficient way," she said. "I thought, 'OK, we're going to do this, because we need to take care of these patients.'"

Van Eijk said the mathematicians' work gave her powerful insight and has since proven itself.

SINCE WHEN DO HOSPITALS USE ADVANCED MATHEMATICAL APPROACHES TO REORGANIZE INTERNAL OPERATIONS? MOST DO NOT. BUT IN 2015 PACKARD CHILDREN'S HIRED DAVID SCHEINKER, WHO HAS A PHD IN MATHEMATICS, to apply mathematical, statistical and computational tools to optimize the experience of those who receive care at the hospital and of those who work there. Scheinker, director of systems design and collaborative research for Packard Children's and a clinical associate professor of pediatrics, directs Systems Utilization Research For Stanford Medicine, known as SURF. Esho was one of his students and received her PhD in 2018.

Originally focused on the children's hospital, but now Stanford Health Care as well, Scheinker works closely with various hospital staff, like Kopetsky, who have identified areas where his expertise may be helpful. He then supervises SURF master's and doctoral students as they use advanced mathematical and computational approaches to chip away at operational problems, fine-tuning staffing levels and improving scheduling efficiency, as well as addressing the challenge of serving more patients without compromising the quality of care.

SURF typically has five to 15 projects going at any one time. In addition to helping the Bass Center adapt to handling more patients, several of the team's projects have made it possible for families to schedule heart surgeries at Packard Children's sooner; others have helped ensure appropriate staffing levels for the hospital's recent expansion and will do the same for the new Stanford Hospital, opening later this year. Another project will make better use of data to identify the sickest diabetes patients and provide them with the additional attention they need. Still another will help families understand what to expect during a stay at the children's hospital.

Essentially, SURF is trying to do for health care what Amazon did for shopping, Kayak did for travel planning and Uber did for getting from point A to point B, Scheinker said. These companies didn't invent anything. "All they did was design better ways of organizing supply and demand to provide a high-quality experience for consumers and providers," he said.

Bringing a mathematician on board was "a bit of an experiment," said Kristin Petersen, vice president of operations, procedures and diagnostic services for Packard Children's and executive sponsor and director of strategy for SURF.

So far, she said, the experiment has worked: SURF has successfully completed multiple projects at Packard Children's. Now, at the request of the hospital's CEO, Paul King, Petersen is working with the SURF team to create a detailed mathematical simulation of ideal patient flow through the hospital. The simulation will help develop a long-term strategy for more efficiently providing high-quality, predictable care for as many patients as possible. "It's a new, big project," she said, "and it's a first for any hospital."

By building a rich, detailed simulation model of the hospital, Scheinker hopes his team will identify compelling opportunities to redesign care delivery. For significant change to happen, he said, "you need very, very convincing evidence of the benefit to the institution, patients, and doctors and nurses."

CHANGE IS HARD

AT THE BASS CENTER, EVEN THOUGH VAN EIJK SAW THE VALUE OF THE SURF TEAM'S DATA ANALYSIS, OTHERS WERE RESISTANT. The patients whose care would shift to the Bass Center were children and teens who came frequently for infusions, van Eijk said. That would include kids with Crohn's disease or other rheumatological diseases who required regular one-hour infusions of infliximab to tamp down inflammation, kids with organ transplants who

frequently need six-hour immune suppressant infusions, and immunology patients who will need monthly infusions of medication for the rest of their lives. For years, these patients had received their treatments at the hospital's short stay unit — a space that was in high demand for other uses, including surgical recovery. Although getting infusion appointments in the short stay space was increasingly challenging, these patients had established relationships with nurses there. They weren't happy about having to adapt to a new location with unfamiliar staff.

Employees weren't happy either. The unit's nurses would miss their patients, and the nurses at the Bass Center would have to learn procedures for treating patients with other categories of illness.

"It was a big deal for us," said Jill Becchetti, RN, a nurse who had worked at the Bass Center for 15 years. Oncology nurses are highly trained, with national certifications in oncology and bone marrow transplant, she said. "I felt like an expert, and then when those patients came over, I felt like I went back to being a beginner." It also took a while for the oncology nurses to build connections with the doctors in the other specialties such as gastroenterology, rheumatology and endocrinology, she said.

But the benefits of increasing use of the Bass Center were clear as well. Sending infusion patients there would make more short stay beds available for surgical recovery, allowing the hospital to schedule more operations for more sick kids. In addition, moving patients to the Bass Center would decrease the challenges of scheduling infusion patients around surgical patients' needs. As things were, van Eijk said, "People were struggling to get their medications."

It's all about providing more access to care, Petersen said. "By improving the efficiency of our operations, we can actually get more patients in. There are fewer barriers, and wait times go down."

USING A FLOW CHART ESHO PROVIDED, BASS CENTER SCHEDULERS ENCOURAGED PATIENTS TO OPT FOR THE EARLY AND LATE TIME SLOTS. FOR EXAMPLE, BECAUSE MORNING HOURS WEREN'T AS BUSY AS OTHER PARTS OF THE DAY, PATIENTS WERE LESS LIKELY TO HAVE TO WAIT FOR A BED. AFTERNOON SLOTS PREVENTED KIDS FROM HAVING TO MISS SCHOOL, VAN EIJK SAID.

In preparation for the influx of new patients, Scheinker and Esho worked closely with the Bass Center team. "I did a lot of shadowing and interviewing of folks to understand their process," Esho said. Although the unit was open from 7 a.m. to 7 p.m. Mondays through Fridays, she found that relatively few beds were used before 11 a.m. and after 4 p.m. That's because patients dictated their arrival times, with many of them wanting to come at the same time, Esho said.

With guidance from Kopetsky and other hospital staff, Scheinker and Esho designed simulations to test various alternative scheduling plans as well as options for increasing the clinic's hours of operation, including adding Saturday hours. The simulations accounted for such constraints as the duration and frequency of infusion appointments, whether the patient's doctor needed to be on hand, and whether the patient needed lab tests before treatment.

Esho was looking for approaches that were both effective and relatively easy to implement using a clear set of rules.

The simulations helped Scheinker and Esho get buy-in from the Bass Center staff. They showed that adding Saturday hours would spread the burden of adding more patients, and they demonstrated that schedulers could arrange appointments more tightly by filling one room at a time while consistently striving to leave open the largest possible blocks of time rather than carving the day into short, potentially unusable segments. Using a flow chart Esho provided, Bass Center schedulers encouraged patients to opt for the early and late time slots. For example, because morning hours weren't as busy as other parts of the day, patients were less likely to have to wait

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plus

EXPLORING THE REALMS OF MEDICINE AND HEALING

JEFFREY DECOSTER

Dream weaver

AN IMAGE OF A MESA THAT CAME TO A SCIENTIST IN HIS SLEEP SPARKS INSIGHT INTO A DEADLY HEART DISORDER

By Bruce Goldman

JIM SPUDICH ISN'T THE KIND OF AVID READER who devours a book in two days and moves immediately to the next on his nightstand. He just reads himself to sleep on evenings when he wants to reroute his brain from thinking about his work. Which he thinks about most of the time.

"Creative research is not a job — it's a full-time, almost childlike obsession driven by the curiosity that all kids have," said Spudich, PhD, professor of biochemistry at Stanford. "I see myself as a kid who's never had to grow up."

Yet even scientists have to sleep. Spudich, 77, ordinarily gets his fair share — close to eight hours a night. But when he needs some help winding down, a good murder mystery will do it, especially if it's set in the American Southwest, where he spent several years as a child and whose mesa-strewn terrain he's flown over many times in the pilot's seat of a small plane.

Flying is the perfect escape for Spudich, the Douglass M. and Nola Leishman Professor in Cardiovascular Disease. "I can go out once every couple of weeks for an hour, climb up into the clouds and get some perspective as everything down below disappears," he said. His taste in bird's-eye views favors mesas, which look like what you'd get if you sawed the top off a mountain.

One evening, in December 2014, Spudich's wife of 54 years, Anna, who knows his tastes well, slipped him a murder mystery. Spudich knocked off a few chapters before falling asleep, only to awaken in the dark with the germ of a vision that would solve a mystery he'd been brooding over for more than a year.

"It's not so unusual that we scientists go to bed dreaming about our research," Spudich said. "What was different about this dream was that it changed the entire course of our work."

DYING YOUNG

When he was 5, Spudich moved with his family from Illinois to Phoenix because his older sister had severe heart trouble, and her doctor had warned that she'd never make it through another cold winter. In the warm, dry Arizona climate, she survived for five more years before dying from a heart attack.

The heart beats because it's made of muscle cells that rhythmically shrink in sync and then relax, pumping blood throughout the vascular system. Since 1969, Spudich has zeroed in on a pair of proteins that make all muscular contraction possible. His interest has led him to focus on a particular disorder called hypertrophic cardiomyopathy.

"HCM, as we often call it, was first recognized as a genetics-based disease only about 25 years ago," Spudich said. "It's epitomized by the phenomenon of young athletes in their prime keeling over from sudden death when nobody even knew anything was wrong with them."

HCM's defining clinical symptom is a hypercontractile heart. "It's as if you're out for a short run," Spudich said. "The problem is, you're doing that 24 hours a day, every day of your life."

In response, the heart muscle thickens and eventually stiffens, choking off blood flow through the organ. The progression can end in sudden death.

One in every 500 people is affected by HCM. "The number of patients keeps getting bigger," Spudich said. "We used to have no idea how many there were, because people weren't checking." But with the discovery that HCM could — and usually did — arise from genetic mutations, intensive gene screening has turned up hundreds of different mutations — mostly in a small number of the proteins of the muscle-contraction machinery — that can cause the disorder.

A riddle that has stymied Spudich for years is this: "We usually think of mutations as causing a protein not to work as well as the unmutated version does; they're messing with what was a beautiful evolutionary design," he said. "But HCM mutations are doing the opposite. They're somehow causing the protein to work 'better.'" The result is a heartbeat that's too powerful.

'It's as if you're out for a short run. The problem is, you're doing that 24 hours a day, every day of your life.'

More than a third of those mutations occur in the gene coding for a protein that's intimately involved in every move we make and every beat of the heart. Spudich knows a thing or two about that protein, called myosin. He won the coveted Lasker Award in 2012, largely for inventing ways to study individual myosin molecules and their interactions with another protein called actin.

Of the 40 or so nearly identical versions of myosin produced in every cell of the body, Spudich pays the most attention to cardiac myosin, the version produced and used by heart muscle cells. In fact, Spudich's eight-person lab is one of the few in the world bearing down on human cardiac myosin in a serious way, he said. "So, I have an obligation to keep working on this until we cross the finish line."

Current HCM therapies leave much to be desired. Physicians rely on conventional heart drugs that, for example, slow the heartbeat. The ultimate treatment comes later: open-heart surgery to cut away excess heart muscle. "You can only do this once," Spudich said.

LOOKING FOR CLUES

A myosin molecule's general structure, known since the 1960s, resembles a two-headed monster: two large globular "heads" protruding from a stalk-like tail. It's long been known that myosin sometimes adopts a posture in which its heads fold over and snuggle up against its tail, reminiscent of a sleeping flamingo with its head tucked under a wing.

"But the relevance of this to HCM was essentially unknown," Spudich said.

To see why it's important, it helps to know how healthy muscles contract. Spudich has played a major role in explaining this in precise molecular detail.

A cardiac muscle cell contains perhaps a hundred repeating structural subunits called sarcomeres, arranged one after another in a series. A sarcomere is composed of myosin-rich "thick filaments" alternating with parallel "thin filaments" made of actin.

Closer inspection reveals that each thick filament is knitted from the bottom halves of myosin molecules' tails. In response to electrical impulses traversing the heart, the myosin heads protruding from the

thick filament chomp down on the nearest actin filament, then tug against it like sailors tugging in tandem on a rope, pulling the sarcomere walls closer together and making the muscle fiber contract, before relaxing again.

That's a heartbeat. And if those myosin sailors are tugging too hard on those actin ropes? That's hypercontractility, the hallmark of HCM.

But why would this happen?

About 35% to 40% of all known HCM-inducing mutations are in cardiac myosin, making it an obvious candidate for intense scrutiny. But until about a dozen years ago, nobody could study the effects of cardiac myosin mutations, Spudich said, because the biotechnology for making significant amounts of it that would work didn't exist yet.

Then one of his frequent collaborators at the University of Colorado figured out a way to pull it off. Spudich dropped everything else he'd been doing and began systematically characterizing the effects of HCM-inducing mutations on the function of cardiac myosin molecules, asking: Why would so many diverse mutations all cause myosin to be hypercontractile?

Most of these mutations pop up on the molecule's head. Another big batch are in the top part of its tail. Spudich hypothesized that the mutations somehow made each individual cardiac myosin molecule faster moving or more forceful than normal.

"But in the many mutations we studied, neither molecular speed nor strength were accounting for mutation-induced hypercontractility," he said. "We were missing something."

DREAMING

ON DEC. 14, 2014, after many months of not getting expected results, Spudich lay awake in bed late at night wondering what clue he'd been overlooking.

"For just one night, stop thinking about your work," his wife told him when she gave him *The Haunted Mesa* by Louis L'Amour. The book's plot unfolds in the setting of a Southwestern mesa similar to many Spudich had spied from above during his airborne sojourns.

He nodded off about 20 pages in, awakening hours later from a vivid dream in which the image of a mesa morphed into a myosin molecule.

It was 5:30 a.m. Aflame with inspiration, Spudich jumped out of bed and beelined to his computer, a new hypothesis in his head.

Protein molecules are born as linear sequences of chemical building blocks called amino acids, but that one-dimensionality doesn't last long. Almost as soon as each molecule is produced in a cell, it folds up into a characteristic three-dimensional shape it will retain for the rest of its working life.

With molecular-modeling software now widely available, researchers can speedily rotate a molecule of interest in any of three dimensions onscreen. Viewed from the right perspective, one part of the myosin head's surface is a broad expanse, as flat as the mesa of the dream that had just awakened the sleeping scientist.

Those who study myosin have known about this mesalike surface since 1993, Spudich said. But until now, nobody had given much thought to its significance.

Every amino acid sequence of a protein molecule is specified by the gene encoding that particular protein. There are 20 different amino acid varieties to choose from, each with its own distinctive biochemical quirks: for example, a negative versus positive versus neutral electrical charge. One typical type of mutation results in the substitution of one amino acid for another.

Spudich's team had previously generated computer models flagging points along cardiac myosin's linear sequence where a mutated amino acid had been found to cause HCM. These mutations' locations seemed to be scattered pretty randomly along the molecule.

But viewed on the properly folded molecule, as Spudich was now doing, many of these mutations could be seen to fall somewhere on the mesalike surface of the head of myosin. Many others fell along the part of the tail against which the head rested when the molecule was assuming its "sleeping" position.

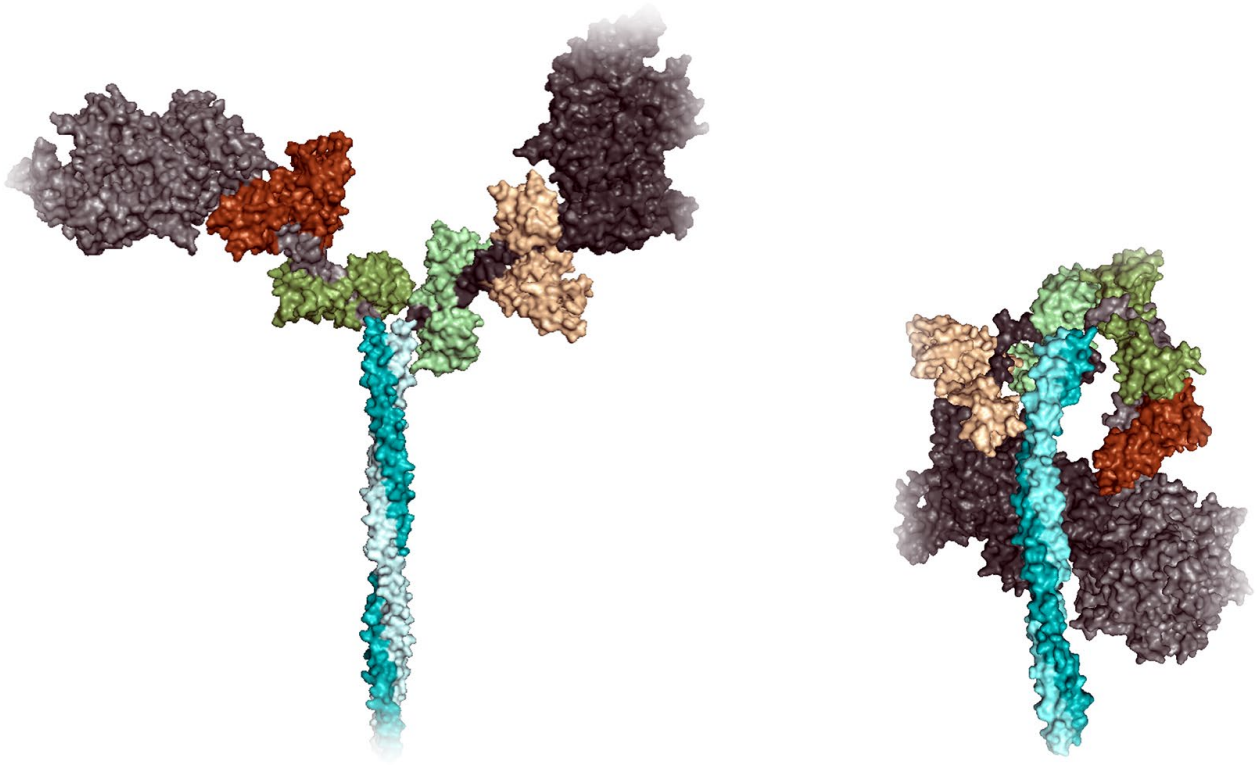
ALL HANDS ON DECK

SPUDICH'S GROUP HAD been studying 15 or so of the most common HCM-inducing cardiac myosin mutations. They knew that most of those mutations had the effect of changing or eliminating the electrical charge the amino acid in the unmutated molecule would have had.

Now it hit him: Opposites attract. Surfaces with lots of positive charges on them are drawn to surfaces with lots of negative charges on them. Any mutation that reduces this charge opposition could result in the myosin head's spending less time tucked up against its tail and more time on duty tugging on its nearby actin filament. These mutations aren't changing myosin molecules' strength or speed; they're just making more heads available to do the tugging.

What Spudich and others had been overlooking was this: Most of the time, many of the myosin heads in the thick filament are on break — at least in healthy heart muscle. Thick fibers normally host a huge reserve army of loafing myosin heads, which is a good thing; those loafing heads can be recruited by normal physiological responses when needed. But HCM mutations effectively nudge them back on the job, even when they're not needed.

A sarcomere's contractile force, Spu-



MYOSIN MOLECULES ARE ILLUSTRATED IN THE OPEN POSITION, LEFT, AND IN A CHARACTERISTIC THREE-DIMENSIONAL FOLDED POSITION.

COURTESY OF JIM SPUDICH

dich reasoned, is proportional to the number of myosin heads that are "grabbing" onto the actin filament at any given moment. Normally, the surface of a cardiac myosin molecule spends much of its time in coordinated proximity with a portion of the "tail" section, sequestering the head so it can't grab the actin filament.

Looking at the folded cardiac-myosin molecule on his computer screen, Spudich realized that by weakening the overall attraction between a myosin molecule's head and tail, HCM-inducing mutations were freeing up myosin heads to grab onto a neighboring actin filament, increasing the number of myosin heads actually pulling their weight at any one time. Hence, the hypercontractile heart. Not quite proof, but a hypothesis with a bright future.

Spudich's group has since shown that mutations at these suspect sites do actually alter cardiac myosin's posture and put more heads in play. A 2018 paper in *Proceedings of the National Academy of Sciences* co-authored by Spudich suggested that a drug called mavacamten, now in phase 3 clinical trials for HCM, may be successful in reversing the hypercontractility induced by a wide range of HCM-inducing mutations on the myosin mesa.

All patients in two earlier trials of mavacamten showed significant improvement. These trials have been sponsored by a South San Francisco-based biotechnology company, MyoKardia Inc., that Spudich co-founded in 2012 to speed the translation of his findings into drugs that could be used in clinical practice to treat HCM. Mavacamten was the fruit of this discovery effort.

"The drug is pushing available heads into the unavailable state — the opposite of what I believe most of these mutations are doing," Spudich said. (Interestingly, mavacamten's mode of action is the opposite of that of a heart-failure drug now in clinical trials sponsored by Cytokinetics, a company Spudich founded in 1998.)

In principle, this approach might apply to most HCM-causing mutations.

As for *The Haunted Mesa*, Spudich eventually finished it and, he said, enjoyed it. But the thing that sticks with him was that image of a mesa and its prophetic power, as revealed in his dream that night.

What if Spudich's wife hadn't given him that book to read that night? "I think someone else would have stumbled on the same idea," he said. "The dream just jump-started it, accelerating progress by a number of years."

For this, all hail Morpheus. "Sleep is amazing," Spudich said. "You've been thinking and thinking and thinking about something for such a long time. Then suddenly the dream solves the puzzle for you." **SM**

— Contact Bruce Goldman at goldmanb@stanford.edu

Making connections

CHILDREN WITH AUTISM ARE MORE SOCIAL WHEN TREATED WITH THE HORMONE VASOPRESSIN

By Erin Digitale PHOTOGRAPHY BY BRIAN SMALE

ANTONIO HARDAN AND KAREN PARKER ARE TRYING TO SOLVE THE MYSTERIES OF WHY CHILDREN WITH AUTISM STRUGGLE SOCIALLY.

SCHOOL WAS A STRUGGLE FOR BENNETT WALKER WHEN HE STARTED FIRST GRADE IN THE FALL OF 2012. Bennett's parents were surprised and worried. They knew their 7-year-old was bright: April Walker had started reading to Bennett when he was an infant, and he began memorizing children's books at 14 months. When he was 2, he soaked up information about World War II, learning facts about military machines and details of key battles. (Bennett and his family are identified by pseudonyms in this story.)

"He has an amazing ability to focus for long periods of time on a topic, and then, for reasons unbeknownst to us, he switches and starts drilling in on a new topic," said his mother. Every weekend, she took him to their local public library and they brought home 30 to 50 books. At 3, he was reading to her.

But in the first weeks of first grade, Bennett's teachers said something was wrong.

"He was getting bullied," his mother said. "They asked us, and we said, 'He's fine at home, we don't have any problems at home.' But he was acting out at school." When she and her husband asked Bennett what was going on, their son told them, "Nobody cares about what I do or who I am."

"He was desperately unhappy," she said.

Seeking more answers, the Walkers arranged for their son to have a clinical

evaluation that included several types of cognitive testing. The results held a shock: Though his symptoms were of mild severity, Bennett had autism.

"We took about a week to process and grieve that his test results meant the death of a future that didn't exist anymore," said his mother. Then she and her husband, Jacob, began aggressively pursuing interventions for their son: speech therapy, occupational therapy, academic tutoring and participating in clinical trials of autism treatments.

"Jacob and I are both very much boots-on-the-ground type of people," Walker said. "We were taking any and every action we could find."

A SOCIAL GAP

THE WALKERS FOUND THEMSELVES facing a challenge that confounds parents and researchers alike: Bennett struggled to navigate social situations.

Medications for the disorder's core features, including social problems, are high on the wish list of autism experts, and Stanford scientists are working to address that. In particular, they're enthusiastic about two hormones: oxytocin and vasopressin.

Bennett's social struggles didn't stem from lack of intelligence. Some aspects of his cognitive abilities were almost off the charts — his vocabulary test scores were in the 97th percentile for a child his age.

But social logic eluded Bennett. For instance, the last two weeks of the elementary school year — when classroom routines gave way to a frenzy of field trips, pool parties, movies and kickball games — were confusing and overwhelming for him. With buy-in from school officials, Bennett's parents took to keeping him home in early June. Though a workable coping strategy, this didn't explain why Bennett's brain was overloaded by activities his classmates enjoyed.

The mystery of why children with autism struggle socially has been equally challenging for researchers. Scientists and clinicians know what autism looks like from the outside, what behaviors fit the disorder's core features of social and communication difficulties, as well as restricted and repetitive interests or behaviors. They know that 1 in 59 children are affected, with four or five boys diagnosed for every girl, and that the disorder is on the rise. But autism's underlying biology is still mysterious, which makes it hard to treat.

"At least some individuals who have mild symptoms of autism say, 'I really want friends, I really miss this,' and have depression and anxiety that are attributable — through their eyes — to not being able to connect socially," said Karen Parker, PhD, associate professor of psychiatry and behavioral sciences.

The best available treatments consist of behavioral therapies to teach specific skills, such as understanding facial expressions or using words to express one's wants and needs.

> 'We took about a week to process and grieve that his test results meant the death of a future that didn't exist anymore.'

To try to develop medications that could add to the treatment options, Parker and her colleagues are studying the actions of hormones that regulate sociability. A recent pilot study, in which Bennett participated, showed improvements in social abilities in 30 children who were given vasopressin. They're now testing whether the results can be repeated in a larger group.

"If we have a neuropeptide that we could administer to allow people to understand social cues, or that is socially motivating, maybe it would work for children who have these social impairments," Parker said.

QUESTIONING THE 'LOVE HORMONE'

OXYTOCIN AND VASOPRESSIN ARE tiny, nearly identical hormones, each made of nine amino acids. Manufactured by the hypothalamus, a small region at the base of the brain, the hormones have similar three-dimensional shapes.

Oxytocin release aids many types of social behavior in animals and people, including mother-infant bonding and bonding between mates.

Starting in the 1990s, small studies suggested that deficiency of oxytocin, sometimes called the "love hormone," might explain autism in children. Through subsequent research, Parker and her colleague Antonio Hardan, MD, professor of psychiatry and behavioral sciences, have shown that reality is more complicated. In addition to his research role, Hardan directs the Autism and Developmental Disorders Clinic at Lucile Packard Children's Hospital Stanford, where he treats children and teens with autism.

In research published in 2014, Parker and Hardan compared blood oxytocin levels in three large groups of children: those with autism, their siblings without autism, and unrelated typically developing kids who had neither an autism diagnosis nor an autistic sibling.

Blood oxytocin levels varied within each of the three groups, with some children having low, medium and high levels. Overall, children with higher oxytocin had greater social abilities.

"It didn't matter if you were a typically developing child, a sibling or an individual with autism: Your social ability was related to a certain extent to your oxytocin levels, which is very different from what people have speculated," Hardan said. "The previous hypotheses saying that low oxytocin was linked to autism were maybe a little bit simplistic.

It's much more complex: Oxytocin is a vulnerability factor for social functioning that has to be accounted for, but it's not the only thing leading to the development of autism."

The team followed up with an oxytocin treatment trial in which they gave daily doses of intranasal oxytocin or a placebo to 32 children with autism. In the study, which was published in 2017, the hormone modestly improved social behaviors, but only in children with low initial oxytocin levels.

Research published this year by the Stanford researchers adds another interesting wrinkle to the story. Yawning in response to another person's yawn is thought to be an indicator of empathy, but studies of whether the contagious yawn response was absent in people with autism had mixed results. The Stanford team found that children with autism failed to yawn contagiously only if their oxytocin levels were low.

"These findings suggest that only a biologically defined subset of children with autism spectrum disorder exhibits reduced empathy, as measured by the impaired contagious yawn response," the scientists reported.

Parker and Hardan have collaborated for more than 10 years on applying basic laboratory research to clinical investigations. Their recent oxytocin research underscores the idea that the disorder is not one autism but many autisms.

"Because of the heterogeneity of the disorder, we need to start doing clinical trials not to see *if* there will be a response, but more to see *who* will respond to possible treatments," Hardan said.

The National Institutes of Health is funding a large, multicenter oxytocin treatment trial, which is expected to publish soon. Parker and Hardan weren't involved in that study but are eager to see its findings. If their pilot study results are replicated, it will suggest that clinicians should check oxytocin levels in kids with autism and consider prescribing the hormone if baseline levels are low.

'These findings suggest that only a biologically defined subset of children with autism spectrum disorder exhibits reduced empathy, as measured by the impaired contagious yawn response.'

OXYTOCIN'S FRATERNAL TWIN

Alongside the team's oxytocin work, Parker has been following a hunch that stemmed from her dissertation research. As a graduate student in the late 1990s, she studied social behavior in tiny mammals called meadow voles. Parker discovered that vasopressin helps facilitate pair-bonding and fathering behavior in the males. Meanwhile, other scientists had shown that the females' pair-bonding and mothering requires oxytocin release, a finding that holds in many mammalian species.

As she considered autism, Parker wondered if the vole findings held a clue to the disorder's biology.

"I was thinking that maybe there are things that protect females or make males vulnerable," she said. "We didn't find that oxytocin was a smoking gun for autism; it looked like a universal regulator of social function, not an indicator of whether you have autism or not. Since autism is strongly male-biased, I wanted to go back and look at vasopressin."

The highlights of her findings include a 2015 paper seeking a link between vasopressin levels in children with autism and performance on a test of theory of mind, the ability to recognize that other people's thoughts differ from one's own. Autistic children with lower vasopressin scored worse on the theory-of-mind test.

In a study published in 2018, Parker's team based at the California National Primate Research Center at UC-Davis investigated what male rhesus monkeys could reveal about vasopressin signaling. Monkeys that were naturally the least social had less vasopressin in their cerebrospinal fluid — which bathes the brain — than the most social monkeys. A comparison of vasopressin levels in the fluid from human boys, using samples from seven children with autism and seven without, uncovered a similar vasopressin deficit in children with autism. A follow-up study of 36 children with autism and 36 non-autistic children found that lower vasopressin levels in the spinal fluid were associated with more severe autism symptoms among children with the diagnosis.

The vasopressin research was painstaking work: Collecting cerebrospinal fluid requires invasive lumbar punctures. But Parker knew it was important to measure the hormone's levels in the fluid that bathes the brain because it has different roles and potentially different regulation in blood.

"Karen has really rolled up her sleeves and done the hard work of trying to understand the biological baseline," said John Spiro, PhD, deputy scientific director of the Simons Foundation, which supports autism research and has contributed funding to several of Parker's vasopressin projects.

The next step was to do a pilot study to see if giving vasopressin to children with autism improved social function. In this initial phase, Hardan and Parker recruited 30 participants, who received daily doses of vasopressin or placebo nasal sprays for four weeks. The children's social behavior and other autism symptoms were assessed before and after the four-week period.

The trial, which the NIH and the Stanford Maternal & Child Health Re-

search Institute supported, was blinded, meaning the participants, their parents and researchers didn't know which children were receiving vasopressin and which were receiving a placebo.

April and Jacob Walker heard about the trial from Stanford's clinical trials registry. "I don't think we had any reason to think it was going to work," Bennett's father said. But they enrolled Bennett, then a third-grader, reasoning that even if the hormone didn't work, going to Stanford and interacting with the researchers might stretch Bennett's brain in a positive way.

The Walkers wanted to avoid making him feel stigmatized, so have never told Bennett about his autism diagnosis — but he was enrolled in so many therapies that he didn't seem surprised to be participating in a Stanford study.

"I saw his brain as an ever-closing door," said April Walker, who sought as many opportunities as possible to combat this. "The most flexibility he had in rearranging his brain was when he was young, and it went away every single day."

AN OPEN DOOR?

After the treatment period, the Walkers met with Hardan and answered detailed questions about their son's behavior. Bennett was acting about the same as before the trial, they agreed. Hardan asked the Walkers if they wanted to guess which treatment group they had been in. "We said, 'Either it doesn't work or we got the placebo,'" Bennett's mother recalled.

"That was the placebo," Hardan told them. As is standard for this type of research, the Walkers were offered four weeks of vasopressin after the blinded phase of the trial ended.

"When he had the real vasopressin, it was stunning — the difference in the amount of eye contact he would make and the initiative he would take," Jacob Walker said. "The thing that shocked the crap out of me was when he walked up and randomly talked to someone at Safeway. I have never seen that from him, except during that month."

'The thing that shocked the crap out of me was when he walked up and randomly talked to someone at Safeway. I have never seen that from him, except during that month.'

The Walkers' experience mirrors the trial results: Compared with children in the placebo group, those receiving vasopressin had more gains in social behavior. They also had less anxiety and fewer repetitive behaviors.

"We saw this across multiple measures independently," Parker said. "It is really compelling."

The Walkers believe there was a lasting boost in Bennett's social abilities after the month of vasopressin treatment. "For about three years, there was a noticeable change," Jacob Walker said. "That month gave him social gains that did not go away." They enquired about continuing to give Bennett vasopressin after his monthlong treatment but had difficulty obtaining it. There is no vasopressin nasal spray on the market approved for autism.

Now in eighth grade, Bennett's social skills are still about two to five years behind his peers, depending on the situation, his parents said. However, Bennett was able to navigate a school trip to Japan last summer without his mom and dad. A teacher chose him for the trip because he's so organized and reliable.

The Walkers aren't sure if the social gains from the brief vasopressin treatment have stuck with Bennett. Like all kids, he grows and changes. Now in middle school, he is facing different social challenges than those he encountered when he was taking vasopressin in third grade. "Now he's adapting to whole new problems," his mother said.

The researchers are cautiously optimistic about vasopressin's future as an autism therapy. "We might finally, hopefully, have an agent that will target these core features that are very hard to treat," Hardan said. "But at the same time, we have to be careful not to get too excited before we finish the larger trial that we are currently conducting." That trial, also funded by the NIH, is underway now and includes 100 children.

If the findings hold up, the scientists will validate the safety of the hormone in large populations in a multisite trial and then study which aspects of social behavior are most improved by vasopressin, Hardan added. "Is it motivation, affiliation, attachment? Ability to understand others' mental states or read facial expressions or body language?" he asked.

If treatment continues to show promise, researchers will also face challenging questions about how the hormone might help shape the autistic brain over time. Vasopressin is unlikely to be a magic bullet, they said.

Rather, it may open the door for brain-molding social experiences that come naturally to most kids: giggling at their parents during peek-a-boo, pointing to a sippy cup to ask for water, forming early friendships in preschool, negotiating on-the-fly rules for games with their buddies.

The possibilities are keeping the Stanford team motivated as the work advances. "Our pilot trial showed that vasopressin moves the needle," Parker said. "Hopefully a large swath of children with autism can benefit." SM

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CONTINUED FROM PAGE 9

us the ability to proactively take care of them in a way we've never had before."

SETTING PERSONAL GOALS

On March 6, 2018, Celis pulled into the tree-lined parking lot of the one-story Stanford Medicine Primary Care 2.0 clinic for his Humanwide intake appointment with nurse practitioner Debra Hummel. He underwent a one-hour wellness assessment that included a family history questionnaire to determine whether further genetic testing for disease risk was appropriate. He swabbed the inside of his cheek to supply DNA for an evaluation of gene interactions with medications, and he received personal health tracking devices. Data from these devices — an at-home glucometer, scale, blood pressure cuff and pedometer — would automatically flow into his electronic health record for the care team to monitor remotely.

During the wellness assessment, Celis mentioned his stress at work and his concerns about high triglycerides and heart disease. Asked about overall personal goals, he thought of his two young daughters and imagined when they'd have children of their own.

"Being able to see my grandchildren," Celis responded. "Being active. Always being able to travel."

Armed with his newly issued digital devices, Celis tracked his health information at home with interest. Sure enough, before long he saw high blood pressure readings: 140 over 90, 160 over 100.

During an appointment at the clinic, he discussed the numbers with Hummel. They found nothing out of the normal range in a review of his in-office readings but, based on his readings from home, his care team decided he should undergo a more formal 24-hour test. Over the course of a day and night, he wore a blood pressure cuff attached to a monitoring device that took numerous readings.

The readings confirmed the diagnosis: hypertension.

Despite his predisposition for the condition, Celis struggled to accept it. He wanted to believe that the stress of his work, his mother's illness and a visit from an aunt could all have made the day unusual. In the end, however, he decided the numbers told the truth.

"It's not like I was stressed only for one week, and I only have one week of data," he said. "I have more data accumulated over time."

Meanwhile, other pieces of Celis' health puzzle pointed to a high risk of cardiovascular disease. As he suspected, his family history was notable, his doctors said. Additionally, they said, while his inherited health didn't signal any risks that could be tested by genetic screenings, his Filipino-American heritage was a factor to consider.

"Because of his family history, and because of his personal history of high triglycerides, and because I knew that Filipinos were more prone to early heart disease given my research, it was clear to me that he was on the higher end of the risk continuum, and we should act accordingly," said Latha Palaniappan, MD, who led Humanwide's genetic component and is Stanford Medicine's scientific director of precision genomics and pharmacogenomics in primary care.

She referred Celis to the preventive cardiology clinic, where he underwent a CT scan that generated detailed X-ray images of his heart. The scan revealed calcifications that suggested early atherosclerosis, a disease in which deposits of fat, cholesterol, calcium and other substances build up in the arteries.

The amount of deposits was high for a person Celis' age. In fact, 42 was too young to even be on the chart; and among 45-year-old men, he was in the 85th percentile, meaning most of his peers would have a lower amount of calcifications than he did.

Left untreated, Celis' condition could lead to heart attack or stroke. Luckily, both his hypertension and the calcium deposits could be managed with medication. But he had qualms about taking prescription drugs because of the side effects he had experienced years before.

"I hate taking medication if I don't have to," Celis said.

Pharmacogenomic testing — another genetic screening through Humanwide — helped Celis' doctors identify two drugs that would work best for him, meaning that his body would process them in the intended way, at the intended rate. Rosuvastatin would help control his triglyceride level and cholesterol without side effects. Losartan would help regulate his blood pressure without causing dizziness or adversely affecting his kidneys.

The pharmacogenomics test also helped determine which drugs would best prevent blood clotting for Celis if he were to have a heart attack.

"We were able to think ahead," Palaniappan said, "and map out which direction to take if he were to face potential health situations, given his risk factors."

Serving as a health coach, Mahoney met with Celis over five 20-minute sessions, and they added goals to improve his habits: Increase exercise by walking 30 minutes up and down a hill more than once a week. Walk before or after dinner. Cut down on salt in his diet.

WEB EXTRA

Read more about Humanwide and meet participants in the project at https://stan.md/2YqYDgq

Celis told Mahoney he would try to make changes. He, his wife and daughters would make an effort to eat healthier food. However, he said, "I'm not yet addicted to workouts. It takes a long time for someone to get used to that daily routine."

Although Humanwide has ended, Celis still checks his blood pressure at home on occasion, and he continues to benefit from insights gained through the project. He said he appreciated that the comprehensive approach helped him identify and address his most pressing health concerns in a systematic way — "not just guessing," he said.

> 'With Humanwide, we're able to focus on the whole human: who they are when they're working, who they are when they're playing, who they are when they're at home. I feel like this is just the beginning of where medicine will be going.'

Mahoney said she was gratified that Humanwide made such a substantive difference for Celis: "We're aggressively addressing his cardiovascular risk, and that was really important for him."

Celis' experience in Humanwide wasn't unique, she said.

The team flagged a number of undiagnosed conditions and overlooked or "rising" health risks. That included a very high risk of breast cancer for five patients — the clinicians recommended ongoing, enhanced monitoring for them. Pharmacogenomics screening resulted in more than a dozen changes in medication prescriptions or dosages, including, in one case, identifying an adverse reaction to a narcotic pain reliever.

Continual readings from home-based devices also helped providers detect and address early diabetes or hypertension in several patients, as well as refine medication dosages for others with chronic illness.

In an initial evaluation of Humanwide, patients and providers said they liked its holistic focus, the care-team model and the longer interactions it allowed, said Steven Asch, MD, vice chief of primary care and population health, who led the analysis.

Hummel, the nurse practitioner on Celis' care team, said she and her patients enjoyed learning more about their health. "Having the opportunity to do an extensive intake and really getting to know the patient story is always very beneficial," she said.

Five more studies related to Humanwide are in the works, examining implementation of the digital health, genetics and pharmacogenomics components, among other subjects. Because the pilot was a small project focusing on patient and provider engagement in the approach, there aren't plans to analyze potential costs, Mahoney said. However, she is exploring how to most effectively integrate elements of Humanwide into care for patients at varying levels of health. For example, patients who are chronically ill or have medically complex conditions like cancer would likely benefit from more-intensive remote monitoring than patients without those types of conditions.

"With Humanwide, we're able to focus on the whole human: who they are when they're working, who they are when they're playing, who they are when they're at home," Mahoney said. "I feel like this is just the beginning of where medicine will be going." SM

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FEATURE

Data dealers

CONTINUED FROM PAGE 13

ments for a heart condition known as hypertrophic cardiomyopathy. The disease can hinder the heart's ability to pump blood effectively, particularly when the heart rate is elevated. It leads to thickening of the heart wall, which can block blood flow. Small clinical trials from the 1960s and 1970s established beta blockers — drugs that slow the rate of heart contractions and therefore the thickening of the heart walls — as the go-to drug for the condition. But other studies from the 1970s and 1980s suggested calcium channel blockers might work just as well, if not better. Early trials that favored beta blockers monitored patients for a year, which Wheeler didn't think was long enough.

"No one's ever really looked at calcium channel blockers across very large data to see what happens over five to 10 years," Gombar said. "So we searched it in our data and, actually, when the patient population is large enough and monitored for long enough, the data showed that calcium channel blockers did effectively treat the heart condition." In fact, patients who were on calcium channel blockers did better than patients on beta blockers. The finding, Wheeler said, could challenge the current standard of beta blockers as the first-line drug.

Although the data is compelling, consult team members make it clear they're laying out a summary of what happened to other patients, not making recommendations for medical courses of action. Having findings that favor calcium channel blockers doesn't mean Wheeler and other cardiologists should abandon beta blockers, for example, but they do point to a new avenue for research and could even prompt a re-evaluation of current guidelines.

In another example, Douglas Blayney, MD, professor of medicine and a cancer specialist, contacted Shah's team because he wanted to compare two drugs he might prescribe to patients with tumors that have spread to bone tissue and who have an increased risk for fractures and bone-related injury. Blayney can treat the patient with a generic drug or he can use an antibody-based drug, which is more expensive. There's some evidence that the antibody-based drug works better to protect patients' bones from cancer erosion, but it's not convincing enough to solely favor it. Plus, if the cheaper drug works just as well, that's a huge advantage for whoever's paying.

According to the data the service provided, the costlier antibody-based drug was about 20% more effective in breast cancer patients at protecting against bone injury.

"That's a real difference, and bigger than we were expecting," said Blayney. "Does it mean we will exclusively use the more expensive drug from here on out? Not necessarily, but it's a clear sign that there's more investigation to be done."

Blayney and his colleagues are now proposing a new study to confirm the data analysis. "We would have had to muddle through 900 records to find this information on our own," he said.

The informatics consult service is stirring interest outside of Stanford, too. "This data-based 'consult' idea has been out there for some time, but what makes this project so novel is that last mile that Shah and his group have traversed. It's turned the idea into something that's actually operational," said Kevin Johnson, MD, professor and chair of biomedical informatics at Vanderbilt University Medical Center.

"What I really love about this is that a computer scientist by training merged the traditional MD train of thought — use a consult — with a newfangled data science approach," said Johnson. "I've been watching the project evolve, trying to learn more about it so that we might be able to implement it here at Vanderbilt."

Shah's plan is to make that a reality, but not just for Vanderbilt. He's put together a "playbook" about how to properly harness the search engine and data analysis software, which is open-source. That way anyone can access the code, technology and step-by-step instructions to run it themselves.

"Basically there are three things that you need for this to be successful: the data, the software and the people to run the service," said Shah. "I say, if you're an academic center and have the data, we'll give you the technology for free — all you have to do is find the people." SM

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FEATURE

Battling burnout

CONTINUED FROM PAGE 17

development and empowering the physicians to do their jobs. Division chiefs received the results, along with training and professional coaching to improve their skills, said Daniel Murphy Jr., MD, a professor of pediatrics at Stanford who helps lead the group of departmental well-being directors.

"This is about respect, empowerment, encouragement and recognition, and you can train people to do that," Murphy said. "This is the culture that makes people feel really fulfilled and can make their practices smoother and more effective." This investment in leadership development ultimately will be offered to clinical departments throughout the medical center, Shanafelt said.

In addition to encouraging the department-specific initiatives, the WellMD Center is making available some resources and programs to boost well-being across the medical center.

To help faculty gain better work-life integration, for example, the center has collaborated with the chief information officers of both hospitals to develop a tool to measure "work after work" — the time doctors spend logging in at home to complete increasing amounts of paperwork. The center now has real-time data on every division, clinic and department at Stanford Medicine, Shanafelt said.

'This is about respect, empowerment, encouragement and recognition, and you can train people to do that. This is the culture that makes people feel really fulfilled and can make their practices smoother and more effective.'

"We are looking at what is working in clinics that are doing well, where we need to focus and what groups need resources," Shanafelt said. "We are putting this data on the trends in the hands of each chair and chief, so they accurately understand the magnitude of the hidden work, recognize the variability across their clinics, and begin to implement system changes to drive improvement. We can't just blame EPIC [the electronic medical record system] when we have profound variability in our own clinics."

That data is also being reported to the hospital leaders as well as to the hospital boards, so there is accountability to spur improvement at the highest levels.

Some departments and clinics are now using scribes to minimize paper-

work. For instance, in a recent clinical appointment at Lucile Packard Children's Hospital Stanford, a scribe stood in a corner behind a portable computer while pediatric ophthalmologist Scott Lambert, MD, examined the eyes of a young patient. Lambert concluded that the boy needed glasses, and he filled out a new prescription online.

The scribe transcribed the encounter and retrieved a printed copy of the new prescription from the computer. Lambert never had to take a note or turn his attention away from the patient.

"It's really a painful part of my day to spend a couple of hours working on my notes," said Lambert, who is chief of the division of pediatric ophthalmology. "So a scribe makes life much more pleasant." A number of other departments are now evaluating the possibility of adding scribes to reduce work after work.

Besides robbing them of personal time, the crush of digital paperwork also isolates doctors from the community they crave.

"I attended a conference on physician wellness and one of the speakers asked each table to come up with the most important thing contributing to burnout. The consensus was that it was the demise of the doctors' lounge, which gave us a sense of camaraderie," said obstetrician-gynecologist Harise Stein, MD. "That is one of the things that keeps you going."

Stein directs the Physician Resource Network, a newly revitalized peer support program overseen by the WellMD Center that offers confidential help for clinicians who need someone to talk to, whether it's about an adverse event, career obstacle, feeling burned out or challenges with work-life integration. Faculty members who use the program are paired with a Stanford physician who does not know them, who has been trained as a peer supporter and who is volunteering time to help colleagues.

"We provide listening, coping support, perspective, resources and options," Stein said. "Our main job is not to tell somebody what to do, but to help them figure out what they want to do and help them find the resources to do that."

In 2018, the WellMD Center helped several departments start programs to build camaraderie, bringing small groups of doctors together to meet over dinner and reflect on a given question. For instance, they may be asked what makes their work meaningful, despite its challenges; or reflect on the repercussions of their work on family members.

Earlier this year, Stanford family practitioner and clinical professor of medicine Eva Weinlander, MD, met with a handful of colleagues from different departments and at various stages of their careers. Over a dinner of pasta with clams at a Palo Alto restaurant, they talked about how they show appreciation and gratitude toward their families.

"We work in silos and we don't know what other people are going through," said Weinlander, director of faculty wellness for the division of primary care and population health. "Getting together over dinner brings back the humanity and connects us with the people around us whom we don't get to know except superficially. Having them share their stories is a good reminder of your own purpose and meaning."

Simply connecting with colleagues has helped clinicians feel more fulfilled in their work lives, according to research studies and a survey of the 116 faculty who took part in the dinner meetings in 2018. The WellMD Center is now helping five other interested departments launch similar groups.

The comprehensive approach of Stanford's WellMD Center has sparked a proliferation of similar programs around the country as leaders have come to recognize that helping physicians remain healthy and fulfilled is not only good human relations policy but can also save organizations money. Every dollar spent on wellness brings in a $3 to $6 return on investment as a result of reduced medical errors, less physician turnover, improved patient satisfaction and improved quality of care, according to an October 2018 commentary in the journal *Health Affairs* by Minor, Shanafelt and 13 authors from other institutions.

'Getting together over dinner brings back the humanity and connects us with the people around us whom we don't get to know except superficially. Having them share their stories is a good reminder of your own purpose and meaning.'

"Many of the things that make practice easier may also save money in the long run," Murphy said.

As for Walsh's bout with burnout, he said he regained his equilibrium through mindfulness, counseling and a transition into a different job at Stanford that he loves. He still meditates and does breathing exercises to help him remain calm and focused. "Two years ago, I thought I'd be retired by today, but the work is too compelling," he said. "I think the lesson is that health care is important but difficult work for physicians, and the stresses inherent in that put us at risk for burnout. But the good news is that it's not inevitable or permanent." **SM**

— Contact Ruthann Richter at medmag@stanford.edu

FEATURE

Valuable addition

CONTINUED FROM PAGE 27

for a bed. Afternoon slots prevented kids from having to miss school, van Eijk said.

"The schedulers are fantastic puzzlers who make it as efficient as possible," van Eijk said. As a result, the Bass Center is now able to accommodate most of the patients who had traditionally received infusions in the short stay unit. Saturday hours result in fewer parents having to take time off work for their children's routine infusions. And, the center is now using 64% of its bed space, with fewer spikes in population in the middle of the day and a better ability to accommodate same-day add-ons of patients with urgent needs.

> 'SURF's work helps us have a more predictable day. There's this balance we're trying to achieve, and we can't do it without the math. Nearly every modern organization does it, but not health care.'

To ensure a smooth transition out of the short stay unit, van Eijk reached out to affected patients and families: "I spoke with every individual family to make it work for them," she said. And she held in-service trainings to bring her own staff up to speed.

At first, Becchetti said, the families from the short stay unit questioned whether the oncology nurses knew what they were doing. But now, she said, "I think we have won over all of our families. They know that our nurses are just as competent, friendly and skilled as the short stay nurses."

A teenage boy with Crohn's disease who had often missed school for appointments was nervous the first time he came to the Bass Center because he didn't know the nurses, van Eijk recalled. But by his second infusion at the center, he seemed happy with the new location.

"He didn't have to miss school and he liked the nurses," she said. "The patients moved over and embraced our unit as much as our nurses embraced them."

A MORE PREDICTABLE DAY

Surgical scheduling also went under SURF's microscope. In the past, surgeons at Packard Children's from any of nine different specialties could pick available date and time slots that most appealed to them and their patients (within windows designated for their specialties), estimate how long the surgery would take, then block it out on the schedule.

Day to day under this system, Scheinker said, "the numbers of planned surgical admissions jump around like crazy."

During the morning, there might be more staffers than were needed relative to the number of patients, while at midday all of the beds could be occupied at the same time, causing nurses to be stressed. For many reasons, variability could also lead to delays in surgical appointments — essential equipment might be in use in another operating room, post-anesthesia recovery or acute care beds might be full, or urgent cases might bump other patients from the calendar.

Unlike a manual scheduling system, Scheinker said, the tools he uses, such as machine learning and mathematical optimization, can take variability and uncertainty into account — and plan for it. For example, Scheinker and his team have used machine learning to better predict the time it takes to perform various types of surgery, information now used by schedulers.

In addition, to help guide surgery scheduling and reduce bottlenecks, they created a mathematical model of patient flow through the post-anesthesia care unit, developed a system to ensure that operating rooms were stocked with the correct surgical supplies, and created an electronic system for dealing with cancellations. The new system makes sure operating room slots are filled and equitably selects which surgeries to bump when cancellations are unavoidable.

"SURF's work helps us have a more predictable day," said Petersen. "There's this balance we're trying to achieve, and we can't do it without the math. Nearly every modern organization does it, but not health care."

DATA FROM WEARABLES

Having a mathematician on the team also offers an opportunity to make greater use of data collected from patients' health-related wearable devices. For example, to stabilize glucose values for Type 1 diabetes patients, parents can capture real-time data from continuous glucose monitors — devices a little bit smaller than an Oreo cookie with a sensor that reads a patient's glucose level every five minutes. However, only 30% to 35% of Type 1 diabetes patients use the monitors. And for those who do use them, "the data aren't being leveraged for the best possible care," Scheinker said.

David Maahs, MD, PhD, professor of pediatric endocrinology at Stanford, hopes that will change with help from SURF. Packard Children's recently launched a program to start children on the devices in the first week after a diabetes diagnosis. Glucose readings are beamed

to cloud storage and then down to a parent's phone, so he or she can respond to give a child more insulin (if the level is too high) or a snack (if it is too low).

"The monitors improve safety and provide the ability for patients and families to achieve tighter glucose control, which is important for long-term health," Maahs said.

But in patients' quarterly visits to the clinic, the data — more than 25,000 readings over the previous 90 days — gets short shrift. "It would be very time-consuming to look at all of the data for all of the patients," Maahs said. So Scheinker's team is devising a way to analyze the data and identify patients who need attention from the health care team.

'The monitors improve safety and provide the ability for patients and families to achieve tighter glucose control, which is important for long-term health.'

Scheinker's team has analyzed 2 million hours of glucose data for about 200 patients. Once they can identify which signals merit an alert to a health professional, the hospital can design a new workflow to take advantage of that information as it comes in from patients.

Scheinker envisions a tool that would notify caregivers of, say, the 10 patients most in need of a call on any given week.

"If you have an algorithm trained to recognize: 'Hey, your patient Jane, who's done really well before, it looks like her breakfast and dinnertime glucose is really elevated,' then maybe it's as easy as the care team making a quick call to chat with the patient," Scheinker said.

THE VALUE OF MATH

Operational change is certainly possible without the help of machine learning and computer simulations, but the math allows better, faster access to information that can enable change. Case in point: Before Scheinker came to Stanford, Andrew Shin, MD, clinical associate professor of pediatric cardiology and now medical director for SURF, used a manual, data-driven approach to determine reasonable goals for such things as the number of days a patient will spend in the intensive care unit and the hospital.

The goals were developed for congenital heart disease surgeries at Packard Children's and are now taped to patients' beds. In addition to ensuring transparent communication with families, the project reduced the average length of patient hospital stays — a remarkable success achieved without advanced mathematical modeling.

But because of the labor involved, the approach has been slow to roll out to other surgical procedures. To speed up that process, SURF has developed an automated tool that, in a proof of its worth, successfully and instantaneously reproduced virtually the same goals for six procedures, each of which took Shin's team four months to identify. Using this tool, the hospital can now more quickly develop goals for other surgical procedures.

Despite SURF's many successes, Scheinker is under no illusion that change will be easy.

"Health care is notorious for how long it takes to adopt new things, especially if they require people to change their workflows," he said. Yet current electronic health records make possible the redesigns and improvements that other industries have shown can lead to transparency, efficiency, fewer errors, fewer delays and overall higher quality, Scheinker said.

"That's the reason a mathematician was hired to do this." **SM**

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TOUGH TALKS

LEARNING HOW TO BREAK BAD NEWS

As a doctor in the cardiovascular intensive care unit at Lucile Packard Children's Hospital Stanford, Loren Sacks, MD, sometimes has to give parents awful news about their child's health. It's always heart-wrenching, but especially so when the child is dying.

"Part of what I love about working here is that we're able and willing to try things that may actually let a kid live," said Sacks, clinical assistant professor of pediatric cardiology at the Stanford School of Medicine. "But hand in hand with that is the acknowledgement that some of the things we do are not going to work."

It's difficult to tell parents there's nothing more to be done to save their child, but Sacks takes to heart the responsibility of lifting "some minuscule amount of burden off of a mother and father." That includes ensuring that the whole care team knows how to help families navigate through the worst experience of their lives.

"The way we communicate, the words we choose, the tone we use and the emotion we're able to get across can help shape the family's perspective and their experience," said Marcos Mills, MD, a pediatric cardiology fellow who works with Sacks. "That is, to me, as powerful as anything else we do, because this is a time in this patient's life that's going to be remembered forever."

JEFFREY DECOSTER

Sacks, Mills and several other colleagues are working with the Menlo Park-based company STRIVR on a virtual reality program that allows doctors to practice giving people bad news while getting live feedback from educators like Sacks.

The project is one of several at Stanford that aim to improve doctors' skill at communicating with patients.

A team that includes Sacks, Mills and Anne Dubin, MD, professor of pediatric electrophysiology, began creating the training in 2017. Trainees strap on a virtual reality headset and practice conversations with parent avatars. As the scenarios play out, background information and tips are displayed within the trainees' sight line — such as case background, parents' names, what the next part of the conversation should include and suggested responses to questions.

The team has developed three scenarios so far: telling parents their child has a terrible injury and won't recover, telling a parent it's time to disconnect an artificial heart pump that is keeping a child alive, and telling family members that a transplant team has decided their child can't have a heart transplant. The reactions of the simulated parents vary by scenario.

During a pilot, 20 pediatric cardiology trainees tested the program: 95% of them said the simulation generated emotional stress similar to what they'd expect in a real patient encounter, and 98% said they'd be willing to try the program again. Many also said they'd like to practice at home, without the in-person scrutiny of an instructor. Recording the sessions — including the language used, some visual cues, hand positions and body posture — allows participants and instructors to review the sessions for feedback.

The team plans to conduct a randomized trial to compare patient encounters for people who have standard fellowship training, the VR training or both.

Sacks hopes the program can help doctors comfort patients' families in their grief.

"I can't think of any more poignant validation of that desire than if a person whose family member has just passed away can still look at you and thank you for helping them with that," Sacks said. — PATRICIA HANNON

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Flavor danger

HARMFUL EFFECTS OF E-CIGARETTES ARE HEIGHTENED BY CINNAMON, MENTHOL AND OTHER FLAVORINGS

Though vaping is thought by some to be safer than smoking cigarettes, new research suggests that the flavorings in the liquid inhaled by users present heart-damaging risks beyond the negative effects of nicotine.

To conduct the study, a Stanford-led team of researchers generated endothelial cells, which line the interior of blood vessels, from stem cells. They then tracked the effects on these lab-grown cells of six popular e-liquid flavors — cinnamon, sweet butterscotch, fruit, menthol, tobacco, and sweet tobacco with caramel and vanilla. They studied the impact of these e-liquids with nicotine levels of 0, 6 and 18 milligrams per milliliter.

While several of the liquids were moderately toxic to the endothelial cells, cinnamon- and menthol-flavored e-liquids significantly decreased the viability of the cells, even in the absence of nicotine.

Further research showed that the e-liquids also increased the production of molecules that can cause DNA damage and cell death. Some also compromised the cells' ability to form tubes associated with the growth of new blood vessels, and some impaired migration — which enables endothelial cells to heal wounds or scratches.

Some of the effects of exposure to the various e-liquids were dependent on nicotine concentration. Others — like impaired cellular migration and decreases in cell viability — were independent of nicotine, suggesting a combined effect of nicotine concentrations and flavoring components.

"Until now, we had no data about how these e-liquids affect human endothelial cells," said Stanford cardiologist and stem cell researcher Joseph Wu, MD, PhD, who was senior author of an article about the research in the May 27 *Journal of the American College of Cardiology.* The lead authors were former postdoctoral scholars Won Hee Lee, PhD, and Sang-Ging Ong, PhD.

"This study clearly shows that e-cigarettes are not a safe alternative to traditional cigarettes," said Wu, director of the Stanford Cardiovascular Institute. — KRISTA CONGER

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