

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

Fall 2018

special report

THE DIGITAL EDGE

Forward-thinking
Technology transforming
human health

Surgical skills
A superstar student reinvents training

Electronic health records
There's a lot of good in there

Car nirvana
Keeping you healthy in body and mind

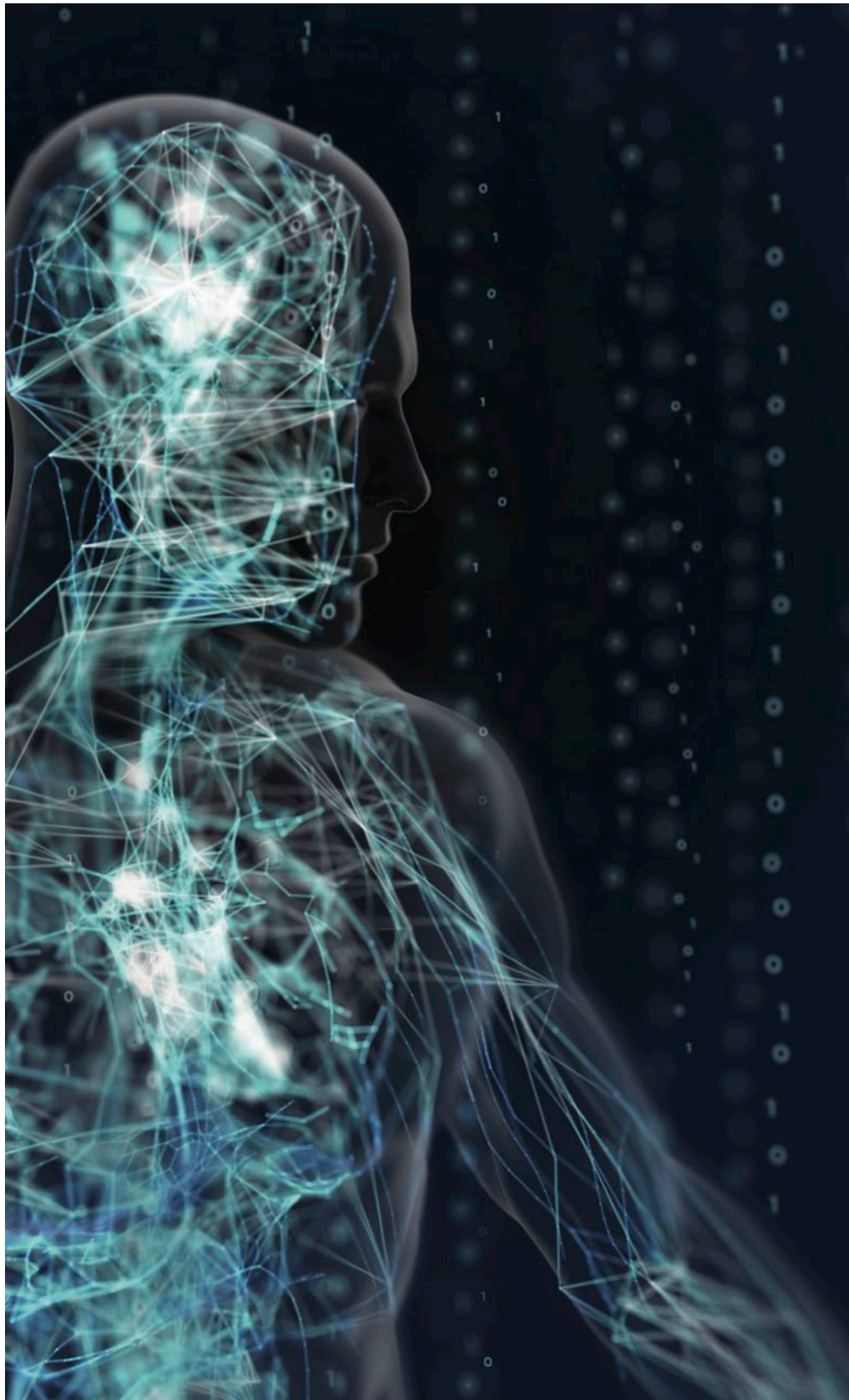
Digital hippocampus
Recreating the brain's memory maker

Innovator
Advancing the science of touch

plus

Transgender
Scientist Ben Barres tells his story

A little more time
Treating babies with severe
congenital defects



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

Fall 2018



HANDS ON

SURGEON, EDUCATOR AND INVENTOR BUILDS ON COLLABORATIONS TO ADVANCE THE SCIENCE OF TOUCH

When describing the inspiration for her life's work, Carla Pugh, MD, PhD, recalled her time as a medical student and surgical resident. "Before I could operate on a tumor, I needed to know how densely it was attached. A CT scan couldn't tell me — the only way I'd know was through my hands," said Pugh. "I realized I wouldn't truly learn how to diagnose with my hands just by watching my instructors, and I wanted to find a better way."

Today, Pugh is an international expert in the science of touch. She has created sensor technologies to quantify clinicians' hands-on skills and combined those tools with educational concepts that, together, help medical students and residents learn to more effectively use touch when treating their patients.

After completing her surgical residency at Howard University, Pugh enrolled as a doctoral student in the Stanford Graduate School of Education, where she began to explore optimal training methods in the medical environment and to develop the sophisticated sensor, video and motion-tracking technologies that would be key



Surgeon Carla Pugh, an international expert on touch sensor medical technology, displays mannequin heads and touch sensors — both plastic and fabric — that she and her team design and use to evaluate diagnostic and treatment skills.

to capturing haptic — or touch-sensing — information.

"It really all started at Stanford 17 years ago," said Pugh, who received a PhD in education in 2001 and now holds three patents on the use of sensor and data-acquisition technology to measure and characterize hands-on clinical skills.

Since returning in December — to take a dual role at Stanford Medicine as professor of general surgery and director of the Technology Enabled Clinical Improvement Center — Pugh has created collaborations across campus and beyond that are bringing the new field of touch technology and training to the next level.

On the technology side, for example, the Pugh lab has partnered with the Israel Institute of Technology to develop a fabric force-sensor bra that captures clinical data during a breast examination. Pugh is also exploring the creation of new touch-sensing tools with Stanford faculty members Allison Okamura, PhD, professor of

mechanical engineering, an expert in haptics as well as virtual environments and simulators, and Zhenan Bao, PhD, professor of chemical engineering and of materials science engineering, who builds stretchable flexible sensors.

Pugh is working with colleagues in the Graduate School of Education, including Dean Daniel Schwartz, PhD, and Karin Forssell, PhD, on the training half of the equation.

"In terms of the best approach to training students to use haptic data," she explained, "we need to know: How much of this should be learned while using your hands in context, or on a computer? Does this learning objective require a haptic display, or virtual reality? How much data can you collect during the process of care, right in front of the patient, and get real-time feedback that goes directly to a database?"

Pugh and her colleagues plan to engage industrial and systems engineers, social scientists and other experts in answering these critical questions about using the growing quantity of haptic data in the training.

"Nationwide, trainees are telling us they want this information," said Pugh. "There's a lot more work to be done — but the audience is ready." — STEPHANIE BRUZZESE

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



Emotional intelligence
page 6

SPECIAL REPORT

The digital edge

- 6 **High-tech health** *By Tracie White*
HOW DIGITAL MEDICINE IS IMPROVING PATIENT CARE
- 12 **Superstar** *By Ruthann Richter*
YOUNG SCIENTIST HELPS DESIGN AI SOFTWARE THAT MEASURES
A SURGEON'S SKILLS
- 18 **On the record** *By Amy Jeter Hansen*
MEET A NEW MEMBER OF THE HEALTH CARE TEAM: THE ELECTRONIC
HEALTH RECORD
- 24 **Computer memory** *By Bruce Goldman*
CAPTURING THE BRAIN'S LEARNING AND RECALL MOTOR IN SILICON
- 28 **The happy commute** *By Hanae Armitage*
NEW TECHNOLOGY COULD MAKE YOUR DRIVE THERAPY TIME

A virtual hippocampus
page 24



PLUS

- 34 **Deciding to change**
AN EXCERPT FROM THE AUTOBIOGRAPHY OF BEN BARRES,
A TRANSGENDER SCIENTIST
- 36 **Compatible with life?** *By Erin Digitale*
DOCTORS AND FAMILIES GRAPPLE WITH WHAT'S NEXT WHEN A SEVERE
GENETIC DISORDER IS DIAGNOSED DURING PREGNANCY

More time
page 36



DEPARTMENTS

- Letter from the dean 2
- Upfront 3
- Backstory 42

You can Google your symptoms, Skype your worried mom and Uber to the hospital, but you might have to ask your doctor to fax your medical records.

Technology has dramatically changed our lives — from the way we learn, to the way we communicate, to the way we travel. But when it comes to our health care, progress has been uneven.

However, that's changing. With Stanford Medicine at the vanguard, the digital transformation of health care is underway. And we've embraced this transformation in every regard — identifying “digitally driven” as one of three pillars in the new integrated strategic plan that will inform and guide our strategy for the future of Stanford Medicine.

One sign of the times is that more and more physicians are embracing electronic communications and finally junking the fax machine, a central recommendation of Stanford Medicine's recent white paper on the future of electronic health records.



Based on the input of industry experts who spoke at our EHR National Symposium and hundreds of physicians who participated in our Harris Poll survey, this white paper outlines what it will take to make EHRs the backbone of an information revolution in health care. Learn more in this issue of *Stanford Medicine* magazine and read the white paper in full at <http://med.stanford.edu/ehr/whitepaper.html>.

I'm a strong proponent of fixing what's broken about EHRs because I believe they have game-changing potential. Amy Jeter Hansen's story shows some of these possibilities, such as how EHRs can help diabetic patients manage their blood sugar levels and NICU workers manage phototherapy for preterm babies with jaundice.

Of course, the great hope of these new digital tools also comes with the risk that health care will lose something essential in the process — the human touch. In her story, Tracie White shares four ways that we at Stanford Medicine are pioneering advances that are high-tech as well as high-touch. Google Glass headsets are helping children with autism learn to read emotions and facial expressions. Stanford's MyHeart Counts app is prompting people to get moving. Holograms are helping surgeons remove breast tumors with greater precision. And an e-curriculum is teaching basic health care skills to people in remote areas of Haiti and India.

But it's not only our patient care mission that technology is upending. The way we train future physicians, many of whom have never seen a paper chart, is also changing. Don't miss Ruthann Richter's story about an artificial intelligence technology, developed in part by a remarkable high school student participating in an internship program here at Stanford, that may revolutionize how we teach surgeons by establishing a best-practices curriculum as well as providing real-time feedback.

I'm inspired by this issue, and I think you will be inspired, too. The future of health — proactive and personalized care — is a future that will be made possible by a revolution in digital technology. And it's happening here 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

Killer waves

OFTEN WHEN A CELL DIES, its demise comes in a wave, propelled by killer proteins that strike one after the other in something scientists call a trigger wave, new research suggests.

Trigger waves transmit information quickly and continually, and have long been associated with normal tissue development. But until now it wasn't clear that they're instrumental in a form of cell death called apoptosis — a natural, and mostly pre-determined, part of healthy cell regulation that also kicks in to kill damaged or diseased cells.

"This work is another example of how nature makes use of these trigger waves — things that most biologists have never heard of — over and over again," senior author James Ferrell, MD, PhD, professor of chemical and systems biology and of biochemistry, said of the study published Aug. 10 in *Science*.

He and the lead author, postdoctoral scholar Xianrui Cheng, PhD, used *Xenopus* frog eggs, which are giant single cells, to observe how death spreads through a cell. In the eggs, cell death



occurred with constant and steady progress, indicating that trigger waves propagate the process.

"Sometimes our cells die when we really don't want them to — say, in neurodegenerative diseases. And sometimes our cells don't die when we really do want them to — say, in cancer," Ferrell said. "And if we want to intervene, we need to understand how apoptosis is regulated."

5 million people die each year in low- and middle-income countries from poor-quality health care — five times more than global deaths annually from HIV/AIDS and three times more than from diabetes. More at <https://stan.md/2Dsk4rW>

Sugar bombs

A STANFORD RESEARCHER whose team showed that blood-sugar levels spike more than previously thought, even in healthy people, is encouraging everyone to undergo annual continuous glucose monitoring.

"There are lots of folks running around with their glucose levels spiking, and they don't even know it," said Michael Snyder, PhD, professor and chair of genetics and senior author of the findings published online on July 24 in *PLOS Biology*.

Prolonged, high blood-sugar levels can contribute to cardiovascular disease risk and a tendency to develop insulin resistance.

Sociability boost

ACTIVATING THE RELEASE of a mood-regulating chemical into a single brain circuit in mice that were genetically altered to exhibit autismlike symptoms can make the mice more sociable, a new Stanford study reported.

"This points to a previously understudied brain mechanism that contributes to an inability to derive pleasure from social interactions," said Robert Malenka, MD, PhD, professor and associate chair of psychiatry and behavioral sciences, and senior author of the study published Aug. 8 in *Nature*.

Autism spectrum disorder is marked by severe social deficits, which researchers were able to reverse in mice by manipulating the release of serotonin, a chemical and neurotransmitter that regulates, among other things, mood and social behavior.

"Mice aren't little human beings," Malenka said. "We can't ask them how they're feeling about their social lives. But they provide insights into the human brain. They can be very useful for studying relatively primitive mechanisms governing social behavior."

Malenka said that drugs designed to activate a particular subtype of receptor for serotonin found predominantly in the brain's nucleus accumbens — a region that helps control reward and motivation — could improve sociability in people with autism and other disorders that lead to social withdrawal.

Magnetic pull

RESEARCHERS HAVE FIGURED OUT how to employ a magnetic wire to detect up to 80 times more free-floating cancer cells in blood than can be found through simple blood tests.

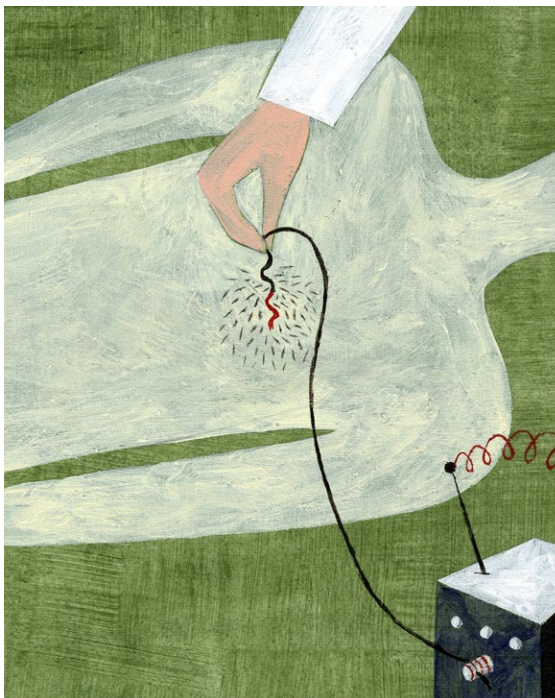
The technology has been used only in pigs, but researchers believe it could eventually enhance cancer detection, diagnosis and even treatment in humans, according to a study published July 16 in *Nature Biomedical Engineering*.

A typical blood test involves drawing about 5 milliliters of blood, an amount so small that few of the cancer biomarkers would likely show up, said study senior author Sanjiv Gambhir, MD, PhD, professor and chair of radiology, and director of the Canary Center at Stanford for Cancer Early Detection.

"We estimate that it would take about 80 tubes of blood to match what the wire is able to sample in 20 minutes," Gambhir said.

The procedure involves injections of magnetic nanoparticles that glom on to floating cells that have sloughed off cancerous tumors. The magnetic wire then is inserted into a vein and, before long, the magnetized cells start sticking to it and can be extracted for analysis.

Gambhir imagines the magnetic wire could be used not only for early cancer detection but as a treatment — by leaving it in the vein longer. "That way, it almost acts like a filter that grabs the cancer cells and prevents them from spreading to other parts of the body," he said.



BLUES CLUE

CLINICALLY

DEPRESSED PEOPLE have lower levels of a naturally occurring amino acid that helps our bodies produce energy, a collaborative study reported.

The findings, published July 30 in the *Proceedings of the National Academy of Sciences*, mirror results of rodent research into the potential link between depression and levels of the substance, acetyl-L-carnitine.

Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences, called the findings "an exciting addition to our understanding of the mechanisms of depressive illness," but said large-scale, robust clinical trials are needed to determine any potential role in treatment.

Depression affects 8 to 10 percent of the general population at any given time.

Rasgon shared senior authorship of the study, which analyzed blood samples from 71 adults treated for depression at either of two New York City hospitals. Compared with 45 adults without depression, levels of acetyl-L-carnitine were lower in people with depression symptoms and lowest in people with more severe symptoms.

Stalling salmonella

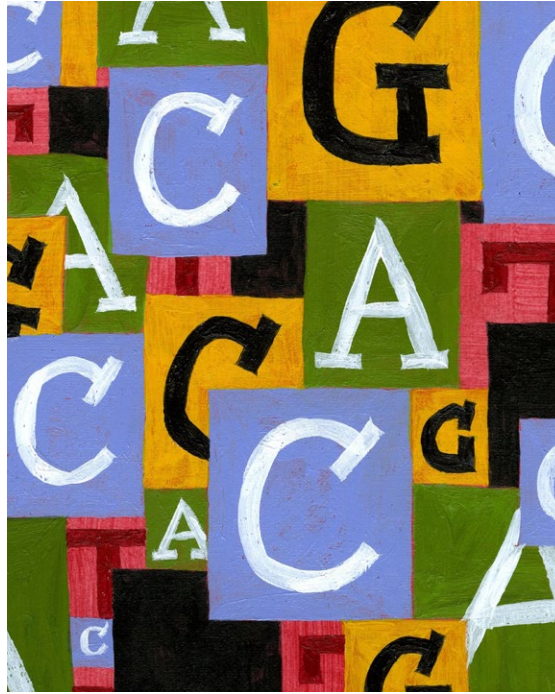
A MOLECULE CALLED PROPIONATE SLOWS THE spread of salmonella poisoning in mice, a Stanford study showed, offering promise for new treatments. Different levels of the naturally occurring molecule could explain why some people who ingest the food-borne pathogen don't get sick.

Salmonella brings on diarrhea, fever and abdominal cramps. It causes about 1.2 million illnesses and 450 deaths in the United States a year, according to the Centers for Disease Control and Prevention.

"It has been a real mystery to understand why we see these differences among people," said Denise Monack, PhD, professor of microbiology and immunology and the senior author of the study of how gut variability might contribute to responses, published July 26 in *Cell Host and Microbe*. "Our finding may shed some light on this phenomenon."

"Human evolution has given us big and active brains and a remarkable cognitive capacity. But a side effect of this could be an increased risk for other, less desirable outcomes."

DAVID KINGSLEY, PHD



Hidden DNA stutter

THE RELATIVELY RAPID EVOLUTION OF OUR BRAINS could explain why humans suffer from schizophrenia and bipolar disorder, which aren't found in other animals, according to a Stanford study.

Researchers were scrutinizing regions of the human brain that differ from our closest animal relatives, such as primates, when they found a series of repeated DNA sequences unique to humans within a small stretch of DNA that was previously linked to schizophrenia and bipolar disorder.

"Human evolution has given us big and active brains and a remarkable cognitive capacity," said professor of developmental biology David Kingsley, PhD, senior author of the study. "But a side effect of this could be an increased risk for other, less desirable outcomes."

The repeated sequences represent a kind of genomic stutter that is difficult to detect and, as a result, stayed hidden from researchers looking for genetic causes for mutations that contribute to risk for the diseases, according to the study published Aug. 9 in the *American Journal of Human Genetics*.

Previous research implicated genes involved in calcium transfers to and from brain cells in response to external signals. The stutter occurs in a non-coding region of one such gene.

These calcium channel genes are responsible for many critical biological processes. Researchers hope that existing drugs that effectively regulate the channels, used to treat high blood pressure and cancer, can be used to treat the psychiatric illnesses.

The finding could help identify people at risk for the disorders and identify clinical interventions that work long term for the about 3 percent of people who are bipolar or schizophrenic.

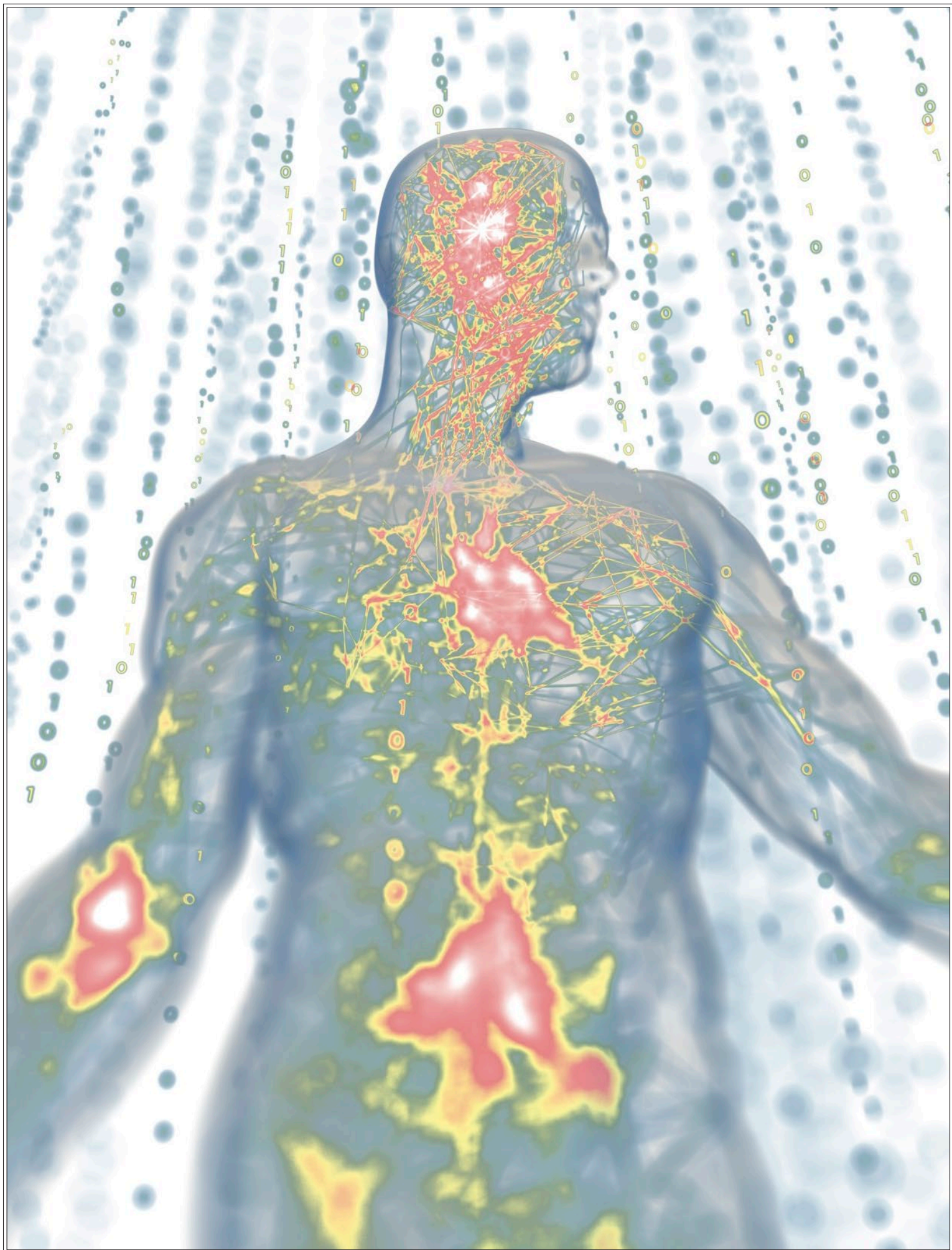
Cancer canary

PEOPLE WITH FREQUENT common skin cancers could have a higher risk of developing other cancers, a preliminary study shows.

Over 10 years, researchers followed 61 Stanford Health Care patients treated for unusually frequent basal cell carcinomas, 21 of whom reported developing additional cancers, including blood cancer, melanoma, prostate cancer, breast cancer and colon cancer. Researchers found similar results when analyzing a medical insurance claims database that included more than 13,000 people with six or more basal cell carcinomas over the 10-year period.

Kavita Sarin, MD, PhD, assistant professor of dermatology and senior author of the study published Aug. 9 in *JCI Insight*, said the findings help pinpoint candidates for more frequent and intensive cancer screenings.

Mutations in a panel of proteins responsible for repairing DNA damage are the likely cause of increased susceptibility, researchers found.





H I G H - T E C H

H E A L T H

HOW
DIGITAL MEDICINE
IS IMPROVING
PATIENT
CARE

As digital technology has become more portable, easy to use and affordable, it has begun to capture the minds of medical researchers. From new imaging tools to mobile devices, Stanford researchers are exploring how to use technologically advanced tools to fill gaps in patient care. And it's begun to make a difference.

The following four stories show ways researchers at Stanford are exploring the use of new technologies to solve old problems. An emergency room physician uses tablet computers to train community health care workers in underserved rural areas of Haiti and India. Radiologists transform holograms to assist in breast tumor removal. Heart doctors are dovetailing with society's obsession with smartphones to try "pinging" people off the couch and onto their feet. And researchers are using Google Glass to provide at-home therapy for children with autism.

"There is a revolution in health care that is in large parts driven by technology," said Michael Halaas, associate dean for industry relations and digital health. "There are a lot of great ideas emerging about how to transform health care that are digitally driven, but they need to be validated and thoughtfully introduced. We remain focused on developing digital health tools that can improve health while keeping the human element that is vital to care delivery."

E - C U R R I C U L U M

Years ago, Ayesha Khan's grandfather was hit by a semitruck as he rode a bicycle along a road in rural Pakistan. With no emergency response system in place — no 911, no ambulance service — he lay severely injured by the side of the road until someone eventually drove by

B Y T R A C I E W H I T E

ILLUSTRATION BY BRYAN CHRISTIE • PHOTOGRAPHY BY TIMOTHY ARCHIBALD

and delivered him to the hospital. After 30 more minutes, he died in the waiting room without receiving care.

Now Khan, MD, a Stanford emergency medicine physician, uses digital devices to address these kinds of voids in care in the developing world. Working first in Haiti and now in rural India, Khan and her team have developed an app-based curriculum to train community members in basic health care delivery — from half a world away at Stanford.

“My grandfather, he died in this sort of unceremonious way,” said Khan, Stanford Medicine clinical assistant professor of emergency medicine, who immigrated to the United States from Pakistan when she was 3. “Where my family comes from has somewhat inspired me. I’m passionate about health equity.”

By studying animated, spoken lesson plans accessed on digital tablets, completing a work book and passing the tests provided on the tablet, health care workers with limited education have been successfully trained in first-line treatment for acute complaints. These providers are now controlling bleeding, and stabilizing airway obstructions and seizures. They diagnose and treat urinary tract infections, sexually transmitted diseases, broken limbs, skin infections, fever, upper respiratory infections, diarrhea and high blood pressure. They care for severe wounds. And they triage patients toward more intense levels of care when necessary.

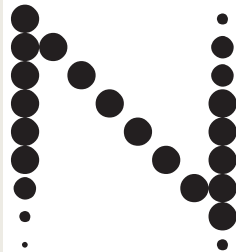
“My desire was that the program we created not rely heavily on people flying back and forth; that’s just not sustainable,” Khan said. “We developed an e-curriculum so that the program was not dependent on live trainers.”

Currently, five health care workers ages 19 to 21 who grew up as orphans are providing first-line care for patients within their community of 28,000 in Haiti. In rural India, 54 women from the states of Uttar Pradesh and Bihar provide care to patients in the 54 villages where they live and now work. Four local facilitators in India used the app to train the women, who are considered past childbearing age and are seen as a burden in their communities.

“This project has a twofold advantage,” Khan said. “It provides health care to communities without it, and it employs people marginalized within their own communities.” The workers are paid through the community where they work, and a Stanford grant helped fund their training. “Now

that we see the program working, I’m so eager for the chance to grow,” said Khan, adding that she’s exploring opportunities to expand into Kenya. “There is so much scope for it to help around the world.”

READING MINDS



- nine-year-old Alex, who has a high-functioning form of autism, has always had difficulty making eye contact and understanding social cues, traits that are typical of someone with his disorder. Making friends has been a challenge, particularly on the playground.

“In preschool, he was hit with a mallet and kicked in the face by children. They were upset with him, and he couldn’t see it coming,” said his mother, Donji Cullenbine. “Children were very scary for him.”

About a year and a half ago, Stanford researchers hooked Alex up with a Google Glass visual headset, which he thought was really cool. It helped teach him how to read other people’s emotions through their facial expressions.

The new form of behavioral therapy uses a Stanford-designed app paired with Google Glass to help children distinguish between eight classical facial expressions indicating happiness, sadness, anger, disgust, surprise, fear, contempt or neutral. The wearable computer links to the smartphone app through the local wireless network. The device has a glasses-like frame with a camera to record the view of the person wearing it, a small screen and a speaker for verbal cues.

‘NOW THAT WE SEE
THE PROGRAM
WORKING,
I’M SO EAGER FOR
THE CHANCE TO GROW.
THERE IS SO MUCH
SCOPE FOR IT
TO HELP AROUND
THE WORLD.’

BEFORE USING GOOGLE GLASS AND AN APP THAT HELPED HIM DISTINGUISH EIGHT DIFFERENT FACIAL EXPRESSIONS, ALEX, 9, COULDN’T ALWAYS UNDERSTAND SOCIAL CUES, MAKING INTERACTIONS WITH OTHER CHILDREN DIFFICULT.



BY THE END OF A STUDY USING GOOGLE GLASS AND APPS THAT HELPED HIM READ FACIAL EXPRESSIONS THROUGH ALERTS LIKE THE ONE IN THE INSET PHOTO, ALEX, 9, TOLD HIS MOTHER, DONJI CULLENBINE, 'MOMMY, I CAN READ MINDS!'

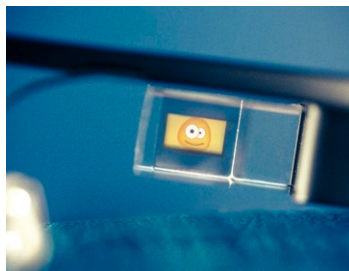
Researchers designed three different formats to help engage kids. The first is “free play,” which gives auditory clues about the emotions of others. The other two are games — “Guess My Emotion,” in which parents act out emotions for the child to guess what they are, and “Capture the Smile,” in which the child tries to elicit a certain emotion from the parent or other caregiver. Alex particularly liked the “Guess My Emotion” game and free play. The app seemed to his mother to make a difference.

“Within a couple of weeks, he started to flick glances at me,” said Cullenbine, who agreed to have Alex participate in a clinical trial in 2017 to test the new home-based therapy. “I had tried for years to get him to engage with my face, but he never stayed for more than a second.”

The clinical trial included 14 families, each with a child who had been clinically diagnosed with autism. The children used the Google Glass setup over a 10-week period, according to the study, which was published in *Digital Medicine* in August.

One-on-one treatment with a trained therapist has been shown to be effective in treating autism, but a shortage of therapists means many children aren’t being treated early enough, said Dennis Wall, PhD, the study’s senior author and Stanford Medicine associate professor of pediatrics and of biomedical data science.

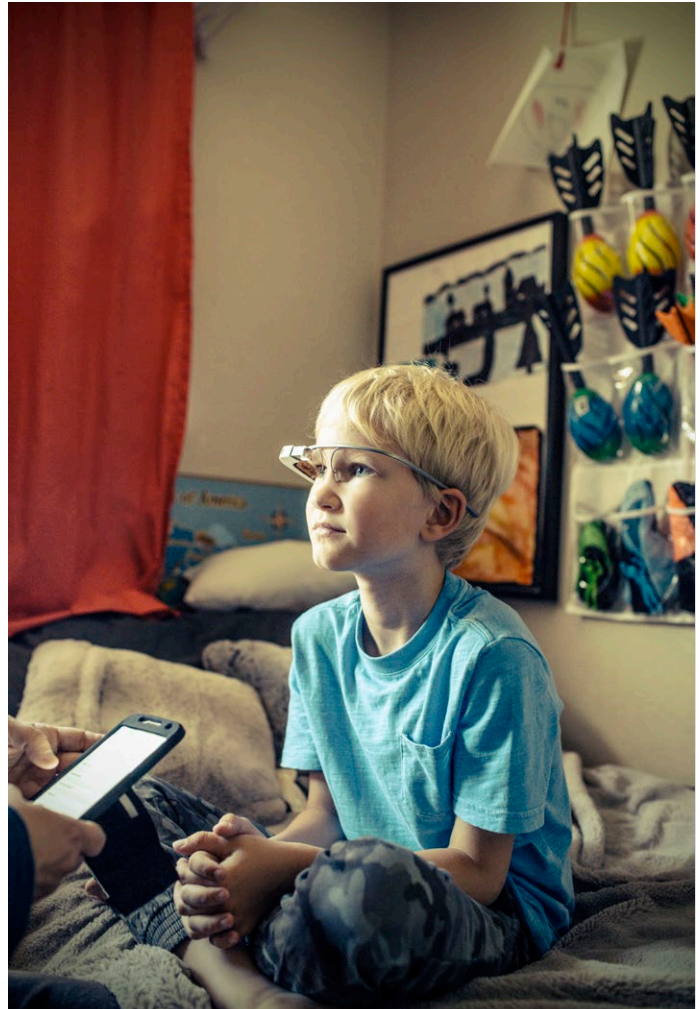
A window of opportunity is being missed, and that’s where Wall hopes this new digital health-based therapy can step in.



“The only way to break through the problem is to create reliable, home-based treatment systems,” he said. “It’s a really important unmet need.”

Results from early clinical trials have been overwhelmingly positive, Wall said.

“We’re seeing improved eye contact, emotional awareness, an ability to understand and appreciate emotions,” he said. And comments from parents have reflected this early success. “Parents said things like, ‘A switch has been flipped; my child is looking at me.’ Or, ‘Suddenly the teacher is tell-



ing me that my child is engaging in the classroom.”

By the trial’s end, Alex recognized emotions so well in others that one day at home he exclaimed: “Mommy, I can read minds!”

“I thought, ‘He got it!’” his mother said. “He understands there is information on people’s faces that he can interpret.”

COUCH POTATOES

Doctors know exercise helps prevent heart disease, but trying to motivate people to get off the couch is no easy task. MyHeart Counts, an iPhone app developed by Stanford researchers, not only collects massive amounts of research data from smartphone users to study cardiovascular health, it also pings them when it’s time to stand up.

“We are giving them customized prompts to encourage them to exercise,” said Anna Shcherbina, a graduate student in biomedical informatics on the MyHeart Counts team. “We’re trying to determine which prompts work the best to encourage exercise.”

If a user sits for more than an hour, for example, the Stanford MyHeart Counts app sends a reminder to get up even if just for a moment. Users who set daily goals of 10,000 steps will get a friendly prompt on the days they fall short, such as, “You are at 115 steps now, and you need 9,885 more to reach your goal. Walking to your next appointment will help you reach your step goal.”

The app also presents users with graphs that show how they compare with other users in terms of daily step counts, how happy they are, how much they sleep and even how many vegetables they are eating.

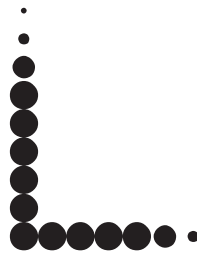
“Consumer adoption of smartphones really has opened up this whole new world,” said Steve Hershman, PhD, a member of the MyHeart Counts team and director of mHealth in cardiovascular medicine at Stanford Medicine. “It’s amazing the volume of information researchers can get from these apps. And they’re also just sort of fun to use. They help make research more human.”

The app, which now collects such data as daily activity levels, blood pressure, cholesterol and cardiovascular health from 50,000 users in the United States, Hong Kong and the United Kingdom, was designed in 2015. It was one of the inaugural mobile health apps launched on Apple’s ResearchKit platform.

Researchers published their first study based on data collected from 49,000 MyHeart Counts app users in *JAMA Cardiology* in December 2016. The study found that use of apps for collecting large amounts of health care data could transform cardiovascular research. Results also showed that among groups of subjects with similar activity levels, those who were active throughout the day, rather than in a single, relatively short interval, reported better levels of cardiovascular health with lower rates of chest pain, heart attacks and atrial fibrillation. The next research study is expected to be ready for publication soon, Hershman said.

Today’s 2.0 version of the app also includes an added consent module that allows users who have a 23andMe account to securely share their genetic information with Stanford researchers. “At first it was just a way to collect data for medical research,” Hershman said. “Now we’re really hoping to change people’s health.”

H O L O G R A M S I N S U R G E R Y



Looking to increase precision during the surgical removal of breast tumors, a Stanford research team developed a technique that brings holographic images into the operating room.

Surgeons refer to MRI images on computer displays to help guide their incisions, but there is still quite a bit of guesswork because tumors come in various three-dimensional shapes and sizes.

As a result, either too much tissue gets removed or too little, said Bruce Daniel, MD, professor of radiology and director of IMMERS, the incubator for medical mixed and extended reality at Stanford.

“The surgeon can’t always tell what’s what,” Daniel said. The team developed a mixed-reality system using Microsoft’s HoloLens headsets to reflect a three-dimensional image of a patient’s tumor, based on MRI scans, directly on the diseased breast. The surgeon looks through the headset, which includes a holographic computer, and aligns a floating holographic image of the tumor onto the surgical site. The goal is to use the tools to increase the precision of the removal of the entire tumor, leaving as much of the healthy breast tissue as intact as possible, said Brian Hargreaves, PhD, Stanford Medicine professor of radiology and of electrical engineering and co-director of IMMERS.

“It gives me X-ray vision,” said Amanda Wheeler, MD, clinical associate professor of surgery who is participating in a pilot clinical research study of 10 patients that uses the new system. Prior to surgery, Wheeler puts on the headset, then uses markers to sketch the reflection of the hologram onto the patient’s breast. “It helps me plan the surgical site, making sure I’m getting as much accuracy as possible. I love it.”

Among the 300,000 women who are diagnosed yearly with breast cancer, about half are eligible for radiation and a lumpectomy that removes the tumor and leaves the remainder of the breast intact, the American Cancer Society reported. But deciding whether to have a lumpectomy rather than a mastectomy — total breast removal — is often difficult. It’s further hampered by the fact that 20 percent of women who have lumpectomies require a second surgery because the surgeon didn’t remove all the cancerous tissue the first time.

“Because this new method helps surgeons determine exactly where to cut out the cancerous breast tumor, it should reduce the number of second surgeries,” Daniel said. **SM**

— Contact Tracie White at traciew@stanford.edu



AMY JIN, 18, IS A RECENT HIGH SCHOOL GRADUATE WHO LOVES HIP-HOP DANCE, THE VIOLIN AND ENGLISH LITERATURE. But it's her passion for computer science that has made her a superstar in the exploding field of artificial intelligence.

Jin has been intrigued by AI since the sixth grade, when students at The Harker School in San Jose, California, chose research projects that challenged them to show how they'd use computer programs to tackle real-world problems.

But her passion for the subject was ignited when she was a high school freshman and she heard an IBM scientist describe how the Watson supercomputer could help extend human capabilities in medicine and other fields through artificial intelligence, the ability to teach machines to “think” and “see.”

“That was really fascinating to me — that Watson could become like a second pair of eyes for a doctor,” the soft-spoken teen said in a re-

S U P E R

cent interview. “I thought artificial intelligence was a really promising field, with so many cross-disciplinary connections.”

Since then she's become part of a new generation of young science enthusiasts who are making waves in artificial intelligence, one of the hottest fields today in computer programming. The same technology behind the self-driving car, AI has the potential to change medical practice in myriad ways, from helping diagnose disease early to improving treatment and ensuring patient safety in the hospital and at home.

Over the past two years, Jin has worked with mentors at Stanford to produce a new software program that can measure a surgeon's technical skill. It works by “watching” a video of a surgery and tracking the movement and timing of instruments used during a procedure. The creation of the stunning piece of technology by Jin and researchers from Stanford's medical and engineering schools won the top research prize at a major international scientific symposium on artificial intelligence where Jin presented it in December.

AMY JIN AND HER MENTORS AT THE STANFORD ARTIFICIAL INTELLIGENCE LAB AND THE SCHOOL OF MEDICINE DESIGNED A SOFTWARE PROGRAM TO ASSESS SURGICAL SKILLS.

STAR

YOUNG
SCIENTIST HELPS
DESIGN
AI SOFTWARE
THAT
MEASURES A
SURGEON'S SKILLS

BY RUTHANN RICHTER

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

Arnold Milstein, MD, PhD, director of Stanford Medicine's Clinical Excellence Research Center, predicts the approach will break new ground in objectively assessing clinicians' manual skills in diverse clinical activities.

"This could make a big difference when manual skills matter," said Milstein, a co-author of a paper describing the work. "It provides a path for tailoring the duration of surgical training to how quickly residents learn. And it opens the way to a more objective approach to periodically certifying a surgeon's technical skill or alerting a surgeon when he or she needs a restorative break during a long procedure."

THE PROJECT GREW OUT OF A 6-year-old partnership between Milstein's group and researchers at the Stanford Artificial Intelligence Lab, led by Fei-Fei Li, PhD, a professor of computer science at Stanford. The scientists are developing forms of AI to help ensure that best practices in health care are reliably applied. They initially focused on increasing staff adherence to patient safety protocols in intensive care units, improving hand hygiene in hospitals and monitoring frail seniors at home by assessing such things as how steady they are on their feet.

"Then one of the CERC fellows said, 'I think we should do this with surgical skills,'" said Milstein. "The American Board of Surgery has long sought an objective test of surgeons' technical skills."

Those hands-on skills are critical, said Stanford general surgery resident Jeff Jopling, MD, the former CERC scholar who proposed tracking surgical skills with computer technology. Jopling naturally gravitated to the project, as he had done graduate studies in Georgia in both engineering and medicine. He came to Stanford six years ago because he wanted to work with Milstein and Tom Krummel, MD, then chair of the Department of Surgery, to improve health care systems around the country.

Safety issues in health care became a focal point after the National Academy of Medicine issued its 1999 report on the high rate of deaths and disability that resulted from human errors in medicine. Afterward clinicians tried to minimize preventable complications with solutions such as surgical safety checklists, a series of detailed steps for clinicians to follow to

help avoid mistakes, Jopling said.

Then a 2013 study of 20 bariatric surgeons in Michigan highlighted a missing variable in the picture: surgeon proficiency. The study, published in *The New England Journal of Medicine*, showed that if a surgeon did well — as measured through blind ratings by peers of videos of surgeons' hand movements — so did the patient; if the surgeon faltered, the patient was more likely to suffer complications, undergo repeat operations and have emergency room visits.

"Until then, there had been so much focus on improving the system, but here it showed that people and their skills matter, too," said Jopling, one of the authors of the latest AI paper with Jin.

Yet, in the course of their training, surgeons are sometimes unable to get a good sense of how they are performing, he said.

"Even when I do the 1,000 operations for my training, I get very little feedback on most of those surgeries," Jopling said. "I was surprised by that as a trainee. I thought it would be like a sport or music, where you have a coach saying, 'Do this. Don't do this.' Exceptional teachers provide that, but not everyone does. Not everyone can explain what you are doing well or not doing well."

While Jopling was mulling the new surgery project, Amy Jin was busy adjusting to the demands of high school. The second child of Chinese immigrants, both PhDs in physics, she had long been keen on computer science and was already a whiz at math, but she had never done any programming. So as a freshman she



SERENA YEUNG, PHD, LEFT, AND STANFORD SURGICAL RESIDENT JEFF JOPLING

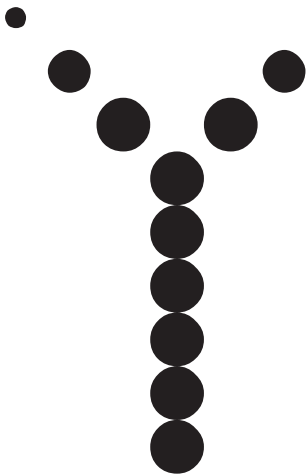
signed up for an AP computer science class and joined the school's Women in Science, Technology, Engineering and Math Club (she later became the club's president). There, she heard about an opportunity at the Stanford Artificial Intelligence Lab's Outreach Summer Program, which is designed to entice young women into science careers.

In the program, she was paired with Serena Yeung, PhD, then an up-and-coming doctoral student, who mentored her. Yeung is also the daughter of Chinese immigrants, and the two shared a passion for science and a desire to help others. Yeung had long been interested in medicine — her father is a family physician — but as a Stanford undergrad she realized she was an

'EVEN WHEN
I DO
THE 1,000 OPERATIONS FOR
MY TRAINING,
I GET VERY LITTLE
FEEDBACK ON MOST OF
THOSE SURGERIES.'



engineer at heart. She became immersed in AI, doing internships in the field at Facebook and Google. While searching for a doctoral project, she met Milstein and became captivated by the idea of using the technology to improve medical practice.



● YEUNG INTRODUCED JIN TO one of the group's AI in medicine projects — a hand-sanitizing initiative designed to control the spread of infection, a significant problem among hospitalized patients. For the project, Yeung, Jopling and colleagues at CERC, the Department of Pediatrics and the AI lab received permission to install depth and thermal sensors

outside a transplant unit at Lucile Packard Children's Hospital Stanford, where hand hygiene gel dispensers are located. They used AI to program the sensors to monitor personnel — shown only as outlines of human shapes to protect their privacy — as they passed by the dispensers.

Their algorithm was able to predict with more than 95 percent accuracy whether staff members were using proper hand hygiene, the researchers reported at the Machine Learning for Healthcare Conference in 2017. They are now using the algorithm to measure hand-hygiene compliance in other hospitals and see whether interventions, such as real-time alerts, can improve these practices, said Yeung, who is expected to join the Stanford faculty in early 2019.

Jin was enthralled by her work on the project and was eager to learn and do more. Yeung figured the budding surgery project was the perfect new opportunity for her.

"We could scope it to a level that Amy could start with. Obviously, she surpassed all of our expectations," Yeung laughed. "It became much more than a high school project, which was great."

Jin fit in the work between a demanding school schedule, club meetings, and orchestra and dance rehearsals. She audited a Stanford undergraduate course in computer vision to learn more about how to train computers to "see" and understand the visual world, with Yeung coaching her through. On her own, Jin dug up dozens of related studies in the medical and computer science literature, which she shared with the team.

Jopling took her under his wing to introduce her to the

world of surgery. He showed her laparoscopic surgical techniques in the Goodman Surgical Education Center at Stanford Hospital.

The trio met every other week, and sometimes more often, at the Stanford Artificial Intelligence Lab across the road from the university's medical center. The glass-walled laboratory is a hive of activity, as dozens of hoodie-wearing students peer intently at screens displaying colorful computer code and then discuss problems, often well into the night. The three researchers also frequently texted and emailed each other, as Jin was dependent on her mother to drive her to meetings.

The challenge of the project, which was officially launched in the summer of 2016, was to "teach" the computer to recognize and follow the path of surgical tools as the clinician guided them through the body. This is a form of object detection, a field that has been rapidly advancing in recent years, in part because of contributions from Li's lab.

The method involves developing an algorithm that teaches the computer to learn as it is fed thousands of data points. With each bit of data, the computer gradually adjusts until it reaches a stage where it can form an accurate picture of the object — in this case, a surgical tool. The process is enabled by the growing ability of computers to rapidly digest vast amounts of data. Jin refined some of the techniques of object detection to apply it to surgery, Yeung said.

"The general idea was that if we are able to track and recognize instruments in videos, we would be better able to analyze tool usage patterns and movements," something that Jin said has been shown to be an effective building block for measuring and assessing a surgeon's skill.

● OR SIMPLICITY, the researchers focused on gallbladder-removal surgery because it is a common, standardized procedure that typically uses seven instruments at most, including clippers, graspers and scissors. They obtained 15 videos of procedures done at the University Hospital of Strasbourg and labeled some 2,500 individual frames, attaching a value to each one so the computer could build a visual picture of the tools and locate them within the surgical field. They used metrics to track the timing of tools — which instrument was used when, and for how long — and produced maps of the pathway of each tool. In addition, they created heat maps that showed how far the tools ranged within the

'THE INSIGHTS INTO HOW THE MACHINE RATED THE DIFFERENT SURGERIES CORRELATED WITH THE SURGEONS' INSIGHTS INTO HOW THEY RATED THE VIDEOS.'

surgical field, as better surgeons tend to handle instruments in a focused area.

"With that, we could gain a sense of a surgeon's performance overall," Jin said over iced tea at a Starbucks near her home.

From the visuals and statistics, the researchers were able to gauge multiple aspects of the clinicians' performance, including their economy of motion, how often they switched back and forth between instruments, and their efficiency at each step of the procedure. They then asked three Stanford surgeons to watch the videos independently and rate the surgeons on a scale of 1 to 5, based on widely accepted criteria: their efficiency, their dexterity with both hands, their depth perception and their handling of the tissue.

"The insights into how the machine rated the different surgeries correlated with the surgeons' insights into how they rated the videos," Yeung said.

For instance, there is a critical step in a gallbladder-removal surgery where the clinician has to clip and cut both the cystic artery, which supplies blood to the organ, and the cystic duct, which carries bile in and out of it. When done properly, this step prevents bleeding and leakage of bile during and after the procedure. If the clips are in the wrong place or come loose, the patient can suffer devastating complications, including damage to the bile duct.

A good surgeon does this efficiently, with economy of motion. In one case, a videotaped procedure showed the deft skill of the surgeon, with the clipper and grasper placed just right. Another video showed a surgeon struggling to put an extra clip in place, then later taking some time to pry it loose. The computer detected the discrepancy in skill levels by viewing not only the placement and the pathway of the

implements, but also the elapsed time of the procedure.

With the analysis in hand, the group submitted their results to the Workshop on Machine Learning for Health, part of the conference on Neural Information Processing Systems in December 2017 in Long Beach, California. The conference is one of the biggest AI meetings in the world, involving 7,000 researchers, graduate students and industry professionals. Yeung listed Jin as the first author of the paper, an extraordinarily generous move on her part considering doctoral candidates eager for publication credits typically claim this spot themselves, Milstein said.

In the workshop, the paper was selected from more than 120 submissions as one of 10 worthy of a spotlight talk. Jin, attending her first-ever conference, presented her work to the distinguished audience and it was then published in the conference proceedings.

When the choice of best paper was announced, Jin was casually scrolling through her laptop, barely listening since she didn't expect she'd know the authors.

She was stunned when her name was called. "I was just kind of half there and was really surprised," she said, her face lighting up with a smile. She immediately sent a text message to Yeung and Jopling, who said it was a surreal moment.

Jopling called Jin an "inspiration to all of us," and Yeung marveled that a high school student had both submitted a paper to the conference and won the top award.

So how did Jin do it? "It's definitely a combination of luck and opportunity, I guess," she said. And hard work? "Hard work, yeah, from everyone," she laughed.

Jopling said the next step in the project is to amass as many as 1,000 videos recorded from several different surgeries. The Stanford researchers will collaborate with colleagues at the Utah-based Intermountain Healthcare, a 22-hospital system with large surgical volume, to analyze the videos and refine the evaluation tool. The future work will take into consideration the complexity of surgical cases, as some gallbladder removals, for instance, may be quite straightforward, while others might be more challenging because of a patient's multiple medical problems, Jopling said.

He said the technology will be particularly helpful in surgical training, noting that it's labor-intensive for a surgeon to sit for hours and review the videotaped performance of a trainee. The automated system could do this for them, and could alert surgeons, in real time during a procedure, if they are starting to lose their edge, said Milstein.

CONTINUES ON PAGE 39



on the record

**meet a new member
of the health care team: the electronic
health record**

BY AMY JETER HANSEN

ILLUSTRATION BY JOHN HERSEY

Brian Dickson was installing shelves and moving boxes around his garage over President's Day weekend in San Jose when the familiar seasick feeling washed over him. Shaky. Sweaty. Fight or flight. He dropped what he was doing and went into the house. Sat down in front of a fan, drank a glass of water and tested his blood sugar.

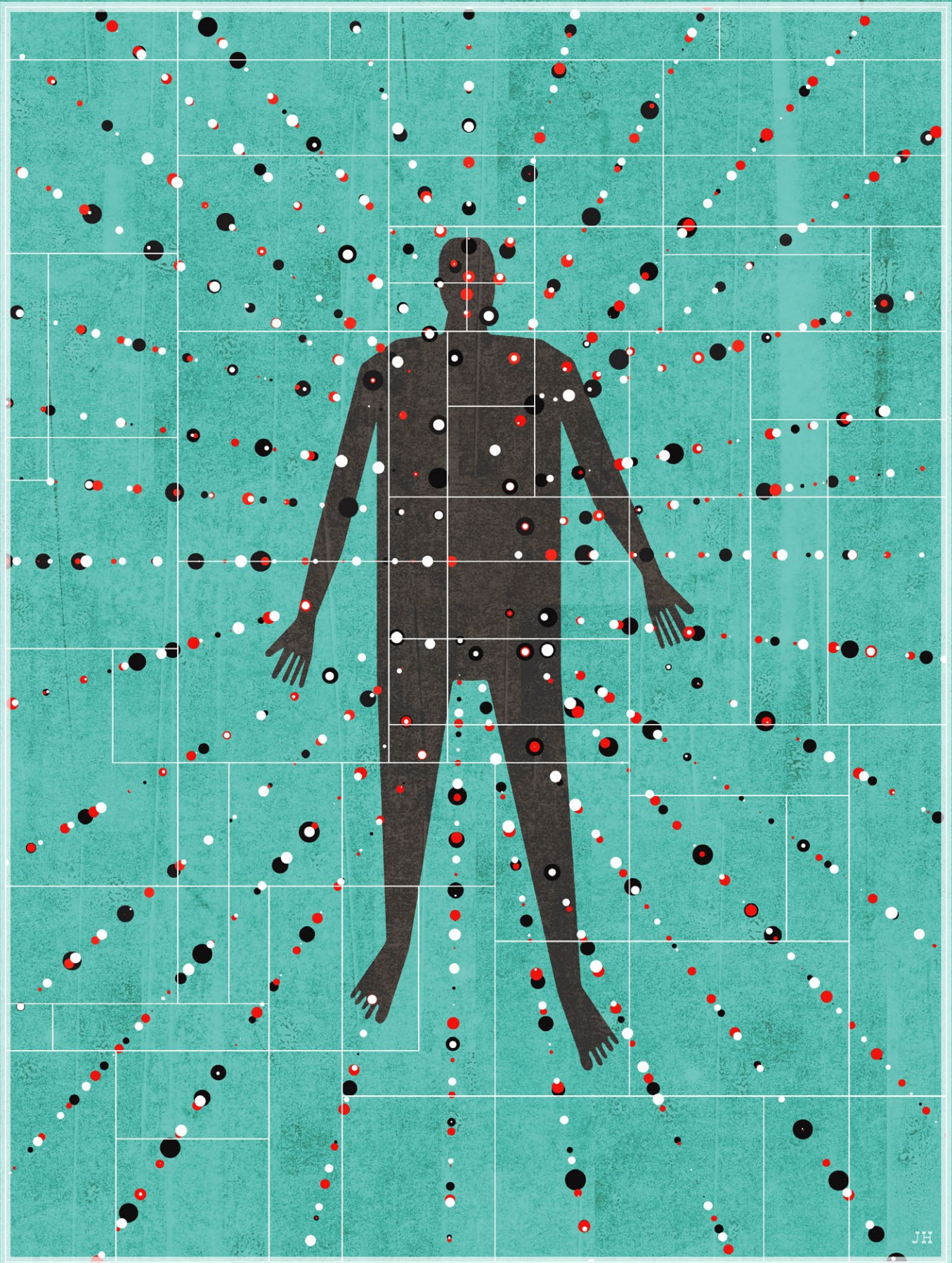
The glucometer confirmed his suspicion: His level had dropped below 70 milligrams per deciliter, an undesirable reading for Dickson, 52, who has type 2 diabetes. He took a glucose tablet and ate a cheddar and raspberry jam sandwich, then spent the rest of the weekend trying to get back on track.

At 1:15 p.m. on the following Tuesday, an email notification floated across Dickson's phone as he worked from his home office.

"Hi Brian," wrote Nancy Shin, PharmD, a clinical pharmacist at Stanford Primary Care in Santa Clara, in the message. "I got a few alerts over the weekend that your blood sugar was in the 60s. Wanted to see if you were doing OK."

She reminded him of how to take his three medications around meals and asked if anything unusual had caused his blood sugar to drop. She offered to talk.

Dickson felt reassured. Shin was there for him. Like a coach on the field. "It was as if she said, 'You fumbled the ball, so now you need to come up with a new play for



JH

TECH-SAVVY
DOCTORS WHO STEPPED
IN TO HELP WITH IT
TROUBLESHOOTING ARE NOW
SEASONED LEADERS,
MANY OF THEM
BOARD-CERTIFIED, IN THE
EMERGING FIELD OF
CLINICAL INFORMATICS.

how to prevent that from happening,” he said.

Flowing securely into his electronic health record, Dickson’s readings had triggered a pre-programmed alert for Shin. Such remote monitoring of chronic conditions is just one way computerized systems are moving beyond replicating paper medical files to improve how health providers do their jobs.

Gone are the days of the late-night pilgrimage to track down a chart for an early morning procedure, or managing a complex case in the emergency room while the patient’s medical file languishes on an unknown cart.

Also in the past are large-scale transitions to massive documentation systems and classroom tutorials on basic keystrokes and menus. Tech-savvy doctors who stepped in to help with IT troubleshooting are now seasoned leaders, many of them board-certified, in the emerging field of clinical informatics. Each year, new trainees emerge who have never seen a paper chart.

MOVING PAST EARLY FRUSTRATIONS

• • • • • n this moment — deemed “the second inning of a nine-inning game” by one medical informaticist — doctors are working through early frustrations, communicating with each other more seamlessly about individual patients, and identifying potential new uses for their digital collections of medical numbers and notes. Health leaders are exploring remedies for procedural inefficiencies. Researchers are building records-based tools to aid clinical care at the bedside. And patients are collaborating electroni-

cally with providers about their health in real time.

At Stanford Medicine, physicians are moving beyond workflow challenges to design innovative ways for electronic health record systems to enhance patient care.

Lloyd Minor, MD, dean of the School of Medicine, believes the time is right to capitalize on the potential of digital documentation.

“We can dramatically improve the care we deliver to patients,” he said at the recent Electronic Health Records National Symposium at Stanford, “if we’re better able to derive information from the vast amounts of data that oftentimes sit trapped inside electronic health records.”

Pioneering providers began using electronic systems for medical documents as far back as the 1960s, attracted by the prospect of more efficiently storing patient information. As technology evolved, other potential benefits emerged: more sophisticated tracking of individual and population health, easier communication with patients, improved safety and cost savings. For years, though, the cost of installing the systems, along with privacy concerns and substantial technical and logistical challenges, remained largely insurmountable.

Incentives changed on a grand scale in 2009 with the passage of the national stimulus bill. The American Recovery and Reinvestment Act provided \$27 billion for an incentive program to help doctors and hospitals adopt and use electronic health records systems, and billions more was later set aside for training and assistance.

By 2016, the government reported that more than 97 percent of hospitals and 70 percent of office-based physicians participating in the incentive program were using electronic health record systems. Both Stanford Health Care and Stanford Children’s Health had transitioned by the mid-2000s, adding functions over subsequent years.

Christopher Sharp, MD, chief medical information officer for Stanford Health Care, said a crucial part of the process was convincing doctors to embrace the far-reaching change. “We called it driving adoption,” he told the audience at the EHR symposium.

Though few wish to return to paper files, the medical world’s transition to electronic records generally has been rocky. Some of the struggle comes simply from learning to navigate a complicated new software system and related programs. But other challenges arise from increased — and changing — documentation requirements from payers and the government, along with decreased opportunities to delegate.

Adding to the frustration, doctors report spending more time navigating digital files than interacting directly with their patients. In a Stanford Medicine survey, conducted with The Harris Poll in March 2018, primary care physicians across the nation said that of 31 minutes they devoted to a patient on average, they spent 19 minutes — or 61 percent of the overall time — interacting with electronic health records during or outside a visit.

In a separate needs assessment conducted in late 2015, more than a year after Stanford Children's Health installed a new system that brought ambulatory care clinics on board, physicians there said they spent five hours a week, on average, using electronic records systems after clinic hours.

The results were eye-opening. "They were trying to be as efficient as they could, and still it wasn't good enough," said Tzielan Lee, MD, the associate chief medical information officer for Stanford Children's Health and a pediatric rheumatologist and clinical associate professor.

A team led by Lindsay Stevens, MD, used the assessment, along with user data from the system and direct observations, to create personalized learning plans. They rolled out the plans in one-on-one sessions over nine months in 2016, naming the training Home 4 Dinner. Stanford Health Care has a similar program called Epic Concierge.

Tandy Aye, MD, was one of more than 370 health care providers to complete the Home 4 Dinner training. In years of practicing medicine, Aye, a pediatric endocrinologist and associate professor, was accustomed to structuring her notes a certain way. She found the pre-formatted templates in the new electronic records system frustrating and was pleased to learn how to create customized templates for her notes — for example, having a different plan and counseling advice for an 11-year-old versus a 16-year-old.

"Home 4 Dinner made it a lot more efficient," Aye said.

Others who completed the program reported similar results. A follow-up survey showed a significant improvement in providers' comfort with the system's tools and in their feelings about control of their workload, said Stevens, a clinical assistant professor and medical director for training and communications at Stanford Children's Health. "One of the biggest things that this program did was make people feel heard," she said.

Now that most providers have completed the training, Stevens has turned her attention to developing a version for new hires.

Still, Aye and others are not completely pleased with elec-

tronic records. For example, the system automatically pulls in pronouns — or even patient names — that are incorrect for young transgender patients she treats. Aye must override the automated information to correct the errors, which takes time.

Lee said requests for such sophisticated changes in software are more common now that clinicians are more adept with the system.

"I definitely think there is a learning curve," Lee said. "Now, instead of questions like 'Where is that button?' we hear 'How can I use the system to improve my whole job?'"

IMPROVING CARE THROUGH INNOVATION

Teams of doctors and nurses at Stanford Health Care and Stanford Children's Health devote hours outside their clinics to answer precisely that question. They work with Stanford IT staff, as well as vendor representatives dedicated to supporting Stanford, to design and implement solutions for requested improvements, such as displaying upcoming operating room staffing assignments on mobile phones or integrating drug infusion pumps with the electronic health record system so dosages in patient files are automatically updated.

"We have all these ways of continuously checking how the system is working. Where are the issues coming up? What can we do to make the system better?" said Natalie Pageler, MD, chief medical information officer for Stanford Children's Health.

Some researchers are pursuing more far-reaching advancements, such as using speech recognition and machine learning technology to automatically generate a progress note, or designing a way for physicians with difficult cases to query electronic health records data for information on the care of similar patients.

Each year, two new scholars take on a challenge related to electronic records, or health information systems generally, through Stanford's two-year clinical informatics fellowship program, which in 2014 became the first in the country to be accredited by the Accreditation Council for Graduate Medical Education.

Jonathan Palma, MD, the program director, sees innovation in clinical informatics as a way to extend the functionality of electronic records. "I think of it in three buckets: to improve the patient experience, to improve provider workflow or satisfaction, and then the holy grail, which is

to improve care with the data you're generating and analyzing," he said.

That kind of breakthrough is the goal for an EHR tool developed at Stanford for the neonatal intensive care unit. Premie BiliRecs helps clinicians decide when preterm babies should receive phototherapy for jaundice. The calculus about whether to take the measure is not easy. The yellow tint of a jaundiced baby's skin and eyes is the result of a buildup of bilirubin, a substance formed when red blood cells break down. Too much bilirubin in the blood, a condition called hyperbilirubinemia, can cause brain damage when the substance circulates in a baby's tissue. Light absorbed through the baby's skin helps eliminate excess bilirubin. Phototherapy is a well-proven treatment, but too much too early carries its own risks, particularly for preterm babies.

"In the well-baby nursery, we rely on bilirubin levels as a function of postnatal age to identify those that needed treatment and closer scrutiny," said Vinod Bhutani, MD, a Stanford neonatology professor. "But a number of factors make premature babies more vulnerable. A bilirubin value that is not toxic to a term baby becomes extremely toxic to a baby at 28 weeks."

A tool had already been created to guide clinicians through treatment for babies born after 35 or more weeks of gestation, an effort led by Christopher Longhurst, MD, a pediatrician and former chief medical information officer at Stanford Children's Health. Bhutani, who is renowned for his research and clinical expertise in treating hyperbilirubinemia in babies, wanted a similar application for infants who arrive early.

Premie BiliRecs would be more complicated because data are limited by preterm infant fragility and the wide variability of their health concerns. Bhutani, Palma and Yassar Arain, MD, who was then a neonatology scholar at Stanford, used linear algebra to flesh out recommendations Bhutani had co-authored, matching a baby's age — adding gestational age and days since birth — with a threshold bilirubin level for beginning phototherapy or, in serious cases, exchange transfusion, in which an infant's damaged blood is replaced. They then worked with Joshua Faulkenberry, a senior web applications engineer with Stanford Children's Health, to build the tool.

The recommendation and related data from Premie BiliRecs deploy automatically in the electronic record of preterm babies. Previously, nurse practitioners and residents turned to a table in the 450-page neonatal intensive care unit guide with less precise values. Arain used a screenshot of the page bookmarked to his phone.

"Clinicians are making tens if not hundreds of decisions a day, and that's just one less decision," Arain said. "With the

click of a button, they can move on with their day."

As Bhutani sees it, the benefits of Premie BiliRecs are twofold. First, because it was designed to collect data, it can eventually be used to inform evidence-based standards after gathering sufficient information from enough users. Secondly, with a more detailed source at their fingertips, clinicians are more likely to follow the established guidelines with ease and trust. Early results in a study by Palma and Arain have borne this out. Previously, doctors and nurses in the NICU were more cautious about treatment, initiating phototherapy earlier than the guidelines in more than 50 percent of cases. With Premie BiliRecs, that number dropped to under 30 percent with no adverse effects.

"I was always concerned whether people would conform to recommendations from a 'black box' because we all trained as capable individuals and are keen to rely on our individual intellect," Bhutani said. "We respect that individual judgment, and you don't want to supplant their decision-making process."

Lance Downing, MD, an assistant professor in biomedical informatics research, has looked at clinicians' reactions to some EHR-based decision support tools and witnessed pushback against what has been termed "cookbook medicine."

"The flip side," he said, "is that it has been shown to really improve care on the whole."

ENGAGING PATIENTS MORE

ut digital reminders are not confined to physicians in the new era of electronic health data. Through Bluetooth-compatible devices and special apps, patients' vital measurements can transfer directly into their medical files — available for view and comment from their health care providers in near real time.

Shin, the clinical pharmacist at Stanford's primary care clinic in Santa Clara, manages patients' diabetes and hypertension drug therapies, and is involved in a clinical trial that examines how patients' hypertension management is affected when they wear a blood pressure cuff that automatically transmits data into their electronic record.

Regular reports on blood sugar readings for diabetic patients, like Dickson, and on blood pressure for hypertensive patients have been helpful, she said.

"This is information that we want to know anyway," Shin said. "Chronic diseases occur outside the clinic."

Downing, the principal investigator for the virtual hypertension management study, said the hope is to use devices in a way that's more effective for patients and more efficient for them and providers. "Those are two important themes," he said, "using electronic health records and IT infrastructure to connect data generated by patients, and moving away from a hospital-centric model into these other models of remote monitoring and care."

One concern is ensuring that providers have sufficient time to track the data flowing in from the field. For Shin, scanning a handful of reports a day hasn't been burdensome. What's more, she's found that periodic review of health data on chronically ill patients saves time during clinic visits — when she'd normally be pulling the readings — and it allows for a quicker assessment of the effects of medication changes and other adjustments.

The increased interaction outside of the clinic also fosters trust with patients. For some, like Dickson, the system flags readings that are particularly high or low, and Shin responds by reaching out with emails for routine situations or check-in phone calls for more serious concerns.

Dickson finds the communication reassuring: "It makes me a little bit more aware," he said. Knowing that Shin sees his blood sugar measurements between visits also makes him more accountable. And he's had fewer readings outside the acceptable range.

"It's improved my health," said Dickson, a network and software engineer. "I'm aware of what's going on and I can do a better job of planning my lifestyle, in terms of food and exercise and everything else." **SM**

— Contact Amy Jeter Hansen
at ajeterhansen@stanford.edu

The promise of electronic health records

INSIGHTS FROM A NATIONAL SYMPOSIUM

BY FRED GUTERL

••••• The health care industry hadn't been known to move quickly — then electronic health records came along. In 2009, when the federal government spent billions of dollars to encourage a switch from paper records, only 1 in 10 physicians used electronic records; now 9 in 10 do. "We have made a colossal transformation in a relatively short period of time," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "But we have not realized the potential benefits of electronic health records."

That was the consensus at Stanford Medicine's Electronic Health Records National Symposium in June, where attendees discussed the problems and potential of electronic records, and made recommendations for bringing home a vision of digital health care enabled by the technology.

That vision is for the electronic record to recede into the background, even as it enhances the ability of physicians to focus on their patients. Information would flow seamlessly to all parties who handle a patient's progress through the health care system. Physicians would have, at their fingertips, a synthesis of the patient's history, relevant medical literature and the histories of similar patients in anonymized, aggregated form. In other words, electronic health records would enrich care decisions with knowledge and context.

Today, the technology is viewed, at best, as an optimized storage medium and, at worst, as a major distraction from patients. Few physicians regard the electronic record as a tool to support clinical decision-making. To get there, symposium participants offered ideas about best practices and ways to improve the electronic health record experience. The ideas were captured and discussed in detail in a white paper released in September and available online at <http://med.stanford.edu/ehr/whitepaper.html>.

Here is a sampling of the key takeaways:

TRAINING: Many physicians feel burdened by EHRs. But organizations that emphasize teamwork and training — and devote higher-than-average amounts of time to training physicians — report higher levels of physician satisfaction.

COMMON STANDARDS — FROM PATIENT DATA TO PAYMENT: Common standards for patient data are needed to enable seamless data sharing within and across organizations. Moreover, payers need to agree on a common set of data and formats for reimbursement and quality reporting. This would greatly reduce the bureaucratic burden on practices.

OPEN-SOURCE SOFTWARE TOOLS: EHR developers must move away from building "walled garden" ecosystems toward something akin to today's smartphone app store. Open-source software programming can help accelerate this in the future, promote data sharing, and nurture a community of third-party developers who are better positioned to customize electronic records to serve the many stakeholders who rely on them, including patients.

ARTIFICIAL INTELLIGENCE: Machine learning has the potential to help physicians quickly get up to speed on a patient's clinical history and make notes during the patient visit, and could suggest actions for clinicians to take, based on established clinical guidelines. Through various initiatives, researchers are bending artificial intelligence toward these aims.

JUNK THE FAX MACHINE: A third of the nation's physicians still rely on this antiquated device to communicate with each other, patients, payers, staff and others, gumming up an already overly bureaucratic system. Federal and private payers can help by providing incentives for using their websites instead of a fax machine. It would help, too, if all physicians embraced electronic payment systems.



CAPTURING
THE
BRAIN'S
LEARNING
AND
RECALL
MOTOR
IN
SILICON

C O M P U T E R

memory

BY BRUCE GOLDMAN

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

In 1953, a 27-year-old Montreal man who'd had frequent seizures ever since getting a nasty smack in the head at age 7 underwent surgical removal of brain tissue containing the site where his seizures originated. The excised tissue included both of his hippocampi.

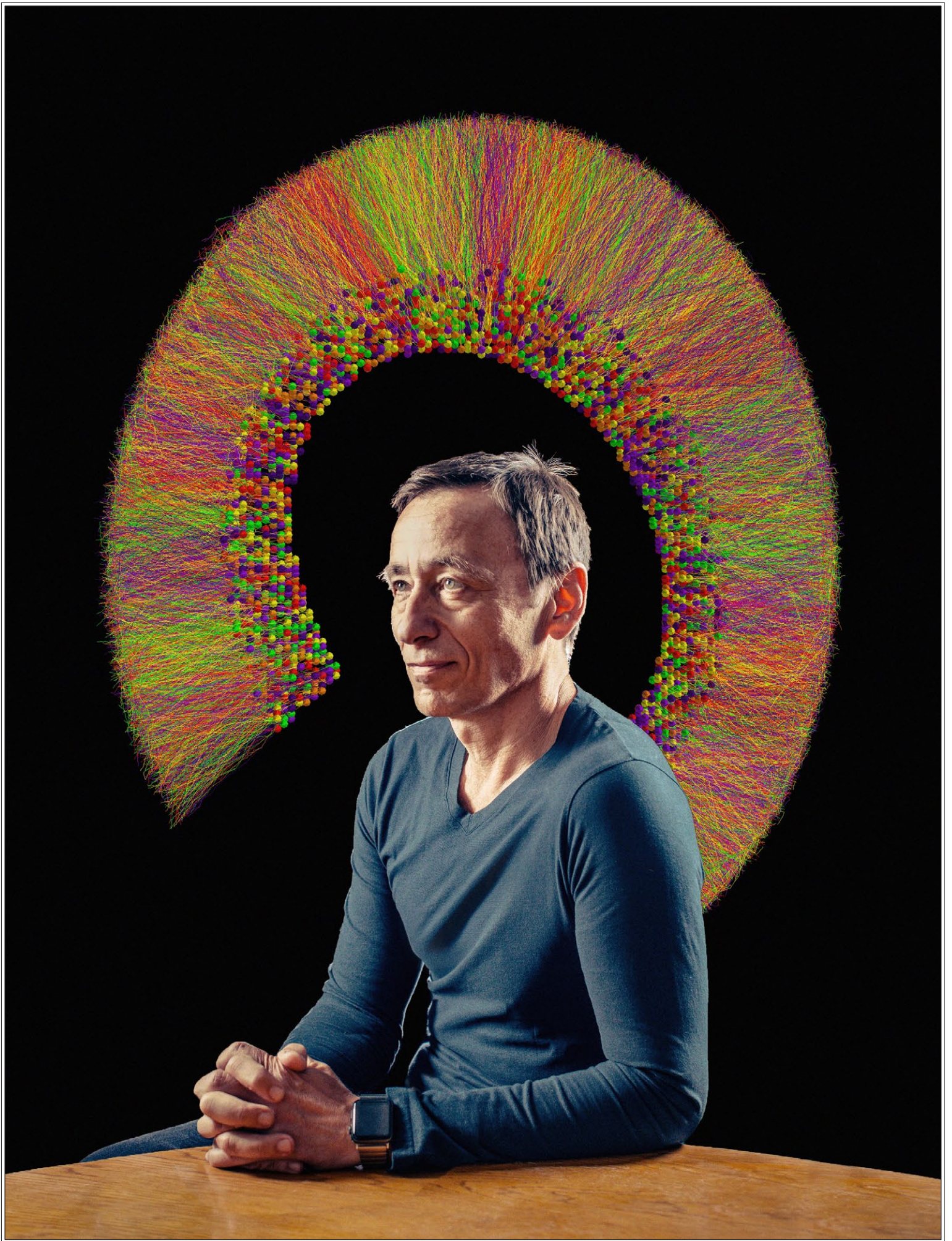
The hippocampus is a little horn-shaped structure found on each side of the brain's midline just above the ears. If you spend enough time staring at a cross section of it on a slide, you may eventually come to see it as resembling a seahorse, which is what the Latin terms *hippo* and *kampos* roughly translate to.

In the 1950s, not much was known about the role of the hippocampus — or any other brain structure. The plight of the patient, Henry Molaison — referred to as H.M. — is widely known among neuroscientists as both a cautionary tale and a wake-up call.

Sure enough, his seizures did subside. But for the rest of his long life (he died in 2008 at 82), he could not remember anything new — not a single thing — for more than 30 seconds. His pre-existing biographical memories were unaffected.

“You could have a perfectly lucid conversation with him, walk out of the room to get coffee, come back in and have the same exact conversation all over again,” said Ivan

NEUROSCIENTIST IVAN SOLTESZ, FRAMED BY AN ENLARGED IMAGE
OF THE VIRTUAL DENTATE GYRUS HE CREATED.



Soltesz, PhD, professor and vice chair of neurosurgery at the Stanford School of Medicine. “For H.M., it was always as if for the first time.”

H.M. could learn new motor skills just fine but couldn’t remember learning them. Plus, his spatial memory was shot. He couldn’t get around on his own.

From his experience and many thousands of unrelated experiments, brain scientists and brain surgeons have learned that the hippocampus is both indispensable for learning and memory and, often, the seat where epileptic seizures are initiated.

These features, along with some anatomical and physiological ones that make it easy and exciting to study, have propelled the once-mysterious hippocampus to the fore as arguably the most thoroughly researched part of the brain. Much of this learning has come about by carefully taking the hippocampus apart and analyzing the activities of its components and connections.

But Soltesz, who has devoted more than 30 years to understanding how brain circuits work (or don’t), has gone a step further, taking to heart a thought attributed to the late, famed Caltech physicist and Nobel laureate Richard Feynman: If you can build it, you can understand it.

Soltesz, Stanford Medicine James R. Doty Professor of Neurosurgery and Neuroscience, and his teammates are building a full-scale virtual model of the hippocampus. But unlike a wooden airplane you might see hanging from a 12-year-old’s bedroom ceiling, this model lives in a computer, in the form of mathematical depictions of neuronal types and their electrochemical components and connections that drive the reception, propagation and handoff of nerve impulses.

The resulting mathematical constructs mimic the component processes that go into a neuron firing off an impulse or its failure to fire one. As a result, the properties of any given individual virtual neuron, or its connections with other virtual neurons, are very similar to what you’d find in its biological counterpart.

“Anything we feed into the model is based on hard experimental evidence,” Soltesz said. “If we’re telling the computer that ‘the firing frequency, strength and duration of this neuron-to-neuron connection should be *this* much,’ it’s because that’s what we’ve observed in biological systems. We don’t make stuff up.”

They’ve completed two of its most important sections — about half of the entire structure — and used them to illustrate what goes on inside

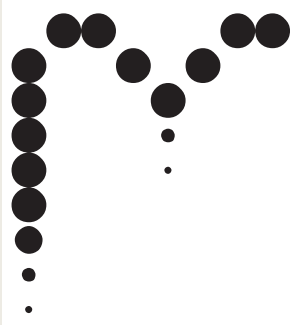
their flesh-and-blood counterparts. The project, funded by the National Institutes of Health and the National Science Foundation, is steaming along, with plans to complete the model within two or three years.

That, in turn, will enable neuroscientists to get a better handle on how the hippocampus does the immensely important things it does: namely, ruling over two crucial cognitive processes. The first is episodic memory (what I had for breakfast), and the second is spatial memory (where I parked the car).

The ability to run virtual experiments may also speed the much-sought understanding of why the hippocampus is so vulnerable to normal aging — leading us to forget what we ate for breakfast and where we parked the car — and is so particularly prone to the biological deterioration set in motion by Alzheimer’s disease.

It may even lead to better understandings and treatments of a wide range of neurological conditions. And, of course, it’s the next step to the logical final outcome: a virtual brain.

REPLICATING ANATOMY

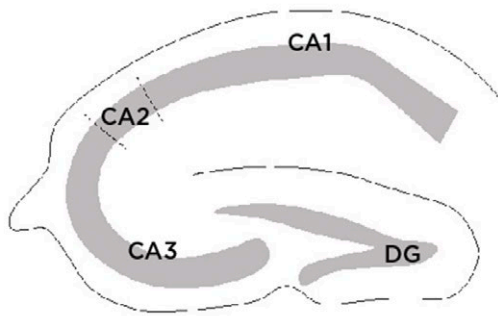


Modeling the hippocampus at such a level of biological realism is a tall order. Like all brain regions, it’s mostly a complicated tangle of individual neurons. The average neuron in the hippocampus is in communication with something like 1,000 other neurons, so the circuit diagram quickly gets crazy complicated. Making matters more daunting, not all neurons are alike.

About 80 percent of hippocampal neurons are excitatory: Their output signals have a stimulating effect on neurons they contact. Neuroscientists have divided the hippocampus into four or five serial compartments whose boundaries are roughly defined by where each compartment’s excitatory neurons pass along information to their downstream partners. The first of these compartments is called the dentate gyrus, which plays a crucial role in the transfer of information. That’s followed by compartments known as CA3, CA2 and CA1. (CA2 is very small and somewhat underexplored.)

Most of the remaining neurons in the hippocampus are inhibitory, with their outputs exerting an impulse-stifling effect on downstream neurons.

The average neuron in the hippocampus is in communication with something like 1,000 other neurons, so the circuit diagram quickly gets crazy complicated.



NEUROSCIENTISTS HAVE DIVIDED THE HORN-SHAPED HIPPOCAMPUS INTO COMPARTMENTS THAT ARE ROUGHLY DEFINED BY WHERE EXCITATORY NEURONS — STARTING WITH THE DENTATE GYRUS — TRANSFER INFORMATION THAT IS ESSENTIAL TO FORMING MEMORIES.

Unlike excitatory neurons, their reach is almost entirely restricted to other neurons within their own compartments. So, the hippocampal inhibitory neurons are also known as interneurons. An interneuron can impinge on both excitatory neurons and other inhibitory interneurons, forcing anyone trying to parse the logic of compartmental circuitry to cope with cascades of double and triple negatives.

“It would be valuable, from both medical and strict scientific standpoints, to know what will happen if — say, as a result of illness or trauma — the hippocampus loses 20 percent of one or another particular population of neurons,” said Soltesz. But in the majority of cases, there’s no known way to experimentally manipulate the activity of a specific neuronal subtype.

“That’s where we come in,” said Soltesz, referring to his virtual hippocampus.

EXPLOITING THE MODEL

• • • In 2017, the Soltesz lab published a report in *eLife* on its virtual model of a rat’s hippocampal compartment CA1 replete with 338,740 neurons, most of them excitatory. The minority of inhibitory interneurons are crucial, though. Of the many actual interneuronal subtypes known to inhabit CA1 (they differ in how hard and how quickly they inhibit and which part of their target neurons they contact), the model captures the majority of those whose characteristics and connections are well-known. The model features an astounding 5.7 billion neuron-to-neuron connections.

The numbers involved are so gigantic that a four-second simulation of CA1 activity takes four hours to run on Blue Waters, a powerful supercomputer hosted by the University of Illinois at Urbana-Champaign. Blue Waters’ operating speed is measured in the number of mathematical calculations it can perform in one second: 10 to the 15th power, the equivalent of stringing a few hundred thousand high-performance laptops together to work in tandem.

Modeling the functions of a *human* hippocampus — 100 times bigger, with an accordingly astronomical number of neurons and connections among them — would crash any existing computer, however super. Besides, there’s much more experimental data available about rodents because you can do experiments with them that can’t be done on humans.

Soltesz’s CA1 model exists in isolation. But he and his colleagues have approximated the placement, strength and timing of the inputs that this compartment’s real-life biological counterpart would have received from an estimated 454,700 neurons coming into it from elsewhere.

Intriguingly, the researchers have found that this model spontaneously reproduces some important rhythmic firing patterns seen in real neurons in the CA1. Soltesz thinks different phases of these rhythms serve a multiplexing function, like different channels on a TV, allowing separate streams of information to be processed in parallel and then routed to the right destination. When the timing is off, information is misrouted or loses its meaning. Researchers can maximize these rhythms by keeping the total level of input stimulation within a certain range.

Among the most prominent rhythms in the brain are so-called theta waves, which arise in the hippocampus. These occur when a mammal (including the human kind) is learning, moving around or dreaming. It turns out that the peak incoming-stimulation level for optimizing theta rhythms in Soltesz’s CA1 model duplicates what’s been determined using an isolated rat CA1 in a dish.

“The result we got almost numerically mimicked what happens in the biological brain,” Soltesz said. “It’s mind-blowing.”

Soltesz’s team went beyond merely recapitulating experimental findings and performed some simulations whose outcomes couldn’t be predicted based on previous experimental experience. In their model, for instance, several different types of inhibitory cells needed to be transmitting impulses to recipient excitatory neurons at just the right time, frequency, speed and power or else the theta rhythm would collapse.

CONTINUES ON PAGE 40



PABLO PAREDES, STANDING,
AND GRADUATE STUDENT
PETER WASHINGTON
TEST STRESS MITIGATION
TECHNOLOGY IN STANFORD'S
VOLKSWAGEN AUTOMOTIVE
INNOVATION LAB.

T H E H A P P Y

NEW TECHNOLOGY
COULD MAKE YOUR DRIVE
THERAPY TIME

PABLO PAREDES SAT IN A DOCTOR'S OFFICE, watching his family member scrutinize a photo of himself. Paredes knew what he was thinking: *My chin is too big*. They were there for the sixth appointment that month, arranged by Paredes in the hopes of arming his relative with tools to overcome a form of obsessive compulsive disorder that led him to agonize over his chin, which he believed was larger than normal.

The doctor took the picture of the relative's face and drew a line around the chin, exaggerating its size. He was using a tactic called exposure therapy, which initially exposes the patient to the source of anxiety in high doses. Paredes' relative fidgeted uneasily. The strategy, however uncomfortable at first, works by allowing the patient to become accustomed to the stressor, diminishing angst over time.

Paredes took the picture from the doctor. "I have another idea," said Paredes, a graduate student of electrical and computer engineering at the time. He uploaded a digital version of the photo to an editing application on his laptop and altered the image, expanding the chin to twice its normal size, and showed it to his family member. "This is what you would look like with an enlarged chin," Paredes said.

His relative winced at the digitally doctored photo, but the repetitive exposure worked as planned, and eventually, his angst subsided.

It wasn't revolutionary technology, nor was it a definitive fix, but to Paredes' relative, it was an effective, albeit initially distressing, strategy to blunt his anxiety. It was then, Paredes said, that he realized just how powerful technology could be in aiding mental health.

More than a decade later, Paredes is an instructor of radiology and of psychiatry and behavioral sciences at Stanford Medicine. His career was one he never foresaw — in a former life, he'd been a Latin rock band's bass guitarist, a thriving entrepreneur and a high-level business manager at Intel in Brazil. But from his family member's struggle, Paredes found inspiration

BY HANAE ARMITAGE

P H O T O G R A P H Y B Y T I M O T H Y A R C H I B A L D



C O M M U T E





ROAD TRIP

TURNING YOUR
DRIVE TIME
INTO A RESPIRE FOR
CHANGING
YOUR
STATE OF MIND

STEPHANIE BALTERS, TOP LEFT, AND PAREDES DISCUSS 'MINDFUL COMMUTE' TECHNOLOGY. BALTERS, AT RIGHT, MONITORS AN EVALUATION WITH PAREDES IN THE DRIVER'S SEAT. OPPOSITE: PAREDES, BALTERS AND STUDENT MADDY BERNSTEIN SET UP FOR THE TEST, WHICH INCLUDES POSITIONING SEVEN CAMERAS: FOUR TO OBSERVE THE DRIVER AND THREE TO CAPTURE DRIVING BEHAVIOR.

for a new career — applying his engineering expertise to elevate the mental health of an entire population.

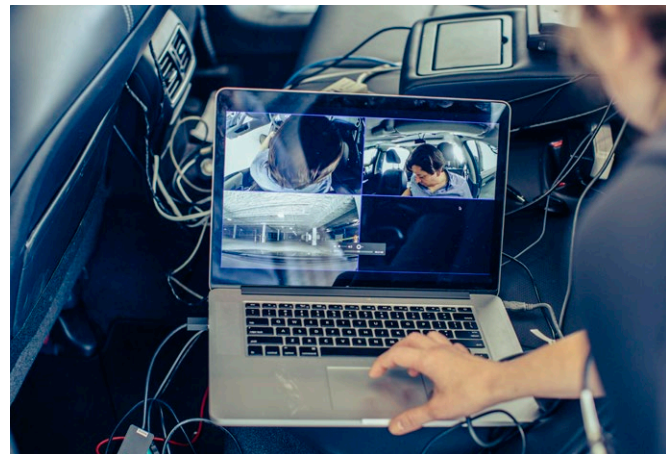
THE MECHANICS OF WELL-BEING

••• or now, it's early days for Paredes' work, and he's sussing out how to tackle such a complex issue. "Understanding how to best influence mental health through engineering will take serious time; there's no manual to follow. We're figuring it out as we go," said Paredes. "Eventually, our experimental data will point us to a more narrow path, which we will then investigate more deeply."

In 2003, Paredes, originally from Ecuador, went to Georgia Institute of Technology on a Fulbright scholarship. After earning a master's in electrical and computer engineering and an MBA, he spent several years managing product teams at various companies in South America before pursuing a new career in mental health technology. In 2010, he went back to being a full-time student at the University of California-Berkeley, joining a lab that used sensors and actuators to identify, measure and mitigate stress. Five years later, he graduated with a PhD, and moved south to Stanford, joining James Landay, PhD, a professor of engineering, as a postdoctoral scholar.

Now in his own lab at Stanford, Paredes leads the development of more than a dozen digital interventions that could one day provide millions of people the means to champion their own well-being. He designs technologies for the places we frequent the most — the office, car and home.

There's the "haunted desk," a sit-stand desk that lifts and lowers of its own accord to encourage movement throughout the workday; chairs that remind you, with a gentle wiggle, to stand; LED lights that saturate entire rooms in a single color to alter mood; and even a "dogbot" — a small circular robot that barks, growls or whines in sympathy with the gripes of



its owner, offering comfort in the same way a pet would.

With his inventions, Paredes is after answers to one overarching question: How do you improve and measure emotional well-being? His goal is to implement and engineer technologies to help people grapple with mental health challenges while collecting data that show the biological changes linked to fluctuations in mental well-being.

"Broadly speaking, there've been few people taking a physiological approach to well-being and really looking at the underlying biology associated with why and how we feel better," said Mark Cullen, MD, director of Stanford's Center for Population Health Sciences and senior associate dean for

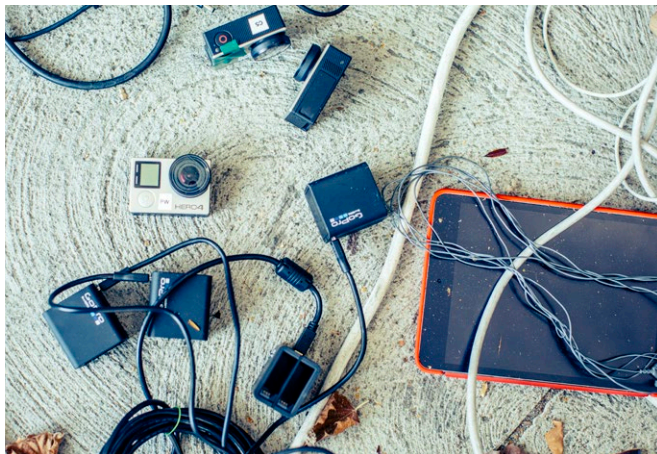
research at the School of Medicine. “The idea that we could develop some integrative physiological measures of well-being is greatly appealing — it’s part of beginning to foster a real science around positive health outcomes.”

And that’s what Paredes is doing. His technology tracks different combinations of breathing rate, heart rate and cortisol levels (all of which are scientifically linked to a person’s mental state, stress level or anxiety), among other parameters, to gauge how well the interventions dampen stress and promote mental health upkeep.

THE WELL-BEING-MOBILE

• • • • • f his many projects, one takes to the road. • Its strategy is to transform a notoriously stressful part of the day that holds millions of Americans captive to a bucket seat: the commute. After all, almost 117 million people in the United States spend about an hour a day ferrying themselves to and from work. Why not use that time for a little self-care?

This effort, deemed “the mindful commute,” aims to passively sense stress and enable people to use their commute



time to mold their mental state — like turning the drive home from work into a cool-down or de-stress period.

“You can do something very simple — do breathing exercises, have a humorous moment, or simply reflect on something that encourages self-compassion,” said Paredes. These actions, he said, aren’t like triggering an immediate switch; a moment of gratitude won’t instantly erase the weight of a nerve-racking week, but it can initiate a “change of gears” and help dissipate built-up stress as you make your way home.

“We hope to change the commute with our inventions so that people don’t see it as a waste of time, but instead as a really transformative part of their day, where they can begin to

detach and reattach to and from work,” said Paredes.

With Paredes’ inventions, after a long day, you could hop in a car that could sense your stress and recommend personalized digital de-stressors. For a handful of these sensing and intervention technologies, Paredes has published scientific papers that establish validity and set the stage for future investigation.

Those in the mood to talk might choose to hash out a tense situation with one of Paredes’ chatbots — a cadre of robots using various therapeutic tactics to help a driver cope with the situation at hand. (For instance, one bot prompts users to think about the problem as if they were giving advice to a friend. Another encourages the “glass half-full” approach and helps find positive aspects of the situation.) While the data collection process has only just begun, 40 people have demoed the chatbots — half in a car, and half in a driving simulation — and Paredes is continuing to collect data on which bots are best suited for stress relief. Overall, participants have reported enjoying the therapeutic variety and generally said they’d prefer to hash out stress with a non-judgmental robot than a real person.

If you’re more of the silent type, you might opt for technologies Paredes created that help you train your breathing to



‘IT’S PART OF BEGINNING TO FOSTER A REAL SCIENCE AROUND POSITIVE HEALTH OUTCOMES.’

DRIVING US SANE

IN A LITERAL TEST DRIVE, I CHATTED WITH EXPERIMENTAL ROBOTS THAT HELP MANAGE STRESS — HERE'S HOW IT WENT



ablo Paredes, PhD, a Stanford Medicine instructor, is the mastermind and engineer behind what he calls “the mindful commute.” It’s a collection of gadgets — including chatbots, steering wheels that sense stress and car seats that vibrate in sync with your heartbeat — that aim to transform the daily schlep to and from the office into a sanctioned time to cultivate your mental well-being. I had a chance to demo the various technologies installed in Paredes’ well-being-mobile, as I fondly dubbed it, one of which had me chatting with a suite of kindly robots. At their core, these bots are like robot therapists. The idea: You tell them what’s ailing you; they help you think it through or come to a solution. I tested a few, each of which takes a different approach to curtailing stress. One — my personal favorite, Sir Laughs-A-Bot — helps you find something humorous about the situation; one encourages you to engage in positive thinking; another helps you sleuth out the root of the stress.

When I arrived at Paredes’ lab for the chatbot demo, Hiroshi Mendoza, the lead graduate student on the project, gave me the rundown.

“You’ll take that car and drive it around campus. When you leave, the chatbot will talk to you,” he said. “And you’ll talk back.”

Easy enough. Buckled in and ready to divulge my biggest stresses to a little robot, I took the car out for a spin. As I turned out of the lab, the bot spoke up.

“Hi! I’m Sir Laughs-A-Bot. I’m here to help you deal with your stress. Can you tell me a little about a recent event that’s making you stressed?”

There was a hot spell that week, so I went with the first thing that came to mind. “I’m on the second floor of an apartment that’s in sunlight all day — without air conditioning it really heats up.” After sharing a few more details, Sir Laughs-A-Bot responded.

“That does sound stressful! Let’s try looking at this situation in a different light. I want you to take a few minutes to come up with a joke about this situation.”

A joke? On the spot? Sir Laughs-A-Bot seemed to sense my apprehension. “Don’t worry about it being the best joke, just think of something humorous about the situation.”

I stumbled through a made-up anecdote about me being so sweaty and smelly I’d forget the temperature outside. It was barely a joke. But Sir Laughs-A-Bot gave a good-natured giggle anyway.

“Hehe! You’re funny,” the bot chirped. “Humor can be found in many situations. Did that help you find something good or at least funny about the situation?”

I’ll admit, I giggled, too, when the robot gave me a pity laugh. And maybe it didn’t solve the problem, but it did make me chuckle and think about the situation differently, which Paredes said is half the battle in dealing with stress. — HANA E ARMITAGE

slow down or persuade your heart into an optimal resting rate. (Some studies by others suggest a person’s heart can sync up with an external beat if exposed to its rhythm in the right way.)

Both tactics use machinery embedded in the seatback on the driver’s side to create vibrational patterns. In the breathing exercise, one buzz cues inhalation; another, exhalation. The vibrations of the heart rate exercise, on the other hand, turn the driver’s seat into a soft, thumping subwoofer.

“Some of these strategies could even work in reverse,” said Stephanie Balters, PhD, a postdoctoral scholar in Paredes’ lab who’s just begun recruiting participants for the guided breathing project. “There’s something called power breathing, or fast-paced breathing, and it’s been shown to heighten alert-

ness.” Something, perhaps, to shake off Monday blues or wake up a drowsy driver.

For the day that we’re touted about by self-driving cars, Paredes has built a virtual reality experience that puts a deep-sea spin on meditation. In this open-ocean VR excursion, drivers-turned-divers plunge through ocean trenches, tag along with schools of fish and can even find themselves eye to eye with a giant humpback whale.

To assist your inner ear, Paredes has added something called “kinesthetic congruence,” to the virtual reality experience, which allows the movement of the car to dictate the movement of the virtual world: If the car turns left, the whale turns left, and so does your field of vision, helping mitigate any car (or sea) sickness.

“One key aspect of meditation is being present and focused on one thing — maybe it’s your breathing, maybe it’s a repeated saying. That’s what a lot of meditation apps try to get people to do,” said Paredes. But with these more traditional apps, people benefit only insofar as they are able to focus on one thing without losing concentration or getting bored.

That’s where the humpback comes in. So far, 15 virtual whale watchers have participated in a preliminary test of the in-car tech. Survey data combined with physiological measurements that track relaxation (heart rate and skin conductance) showed that all the participants were less stressed when virtually swimming with whales than when using a more traditional virtual reality meditation app. And, while a few felt a bit woozy, no one got sick. The plan, Paredes said, is to see whether larger cohorts confirm these findings.

Today’s self-driving cars aren’t ready for this technology just yet — riders still need to be awake and able to take the wheel should circumstances go awry — but Paredes said that one day when autonomous cars are dependable enough that its occupants can go to sleep, it’ll be a green light for up-close, in-car whale watching.

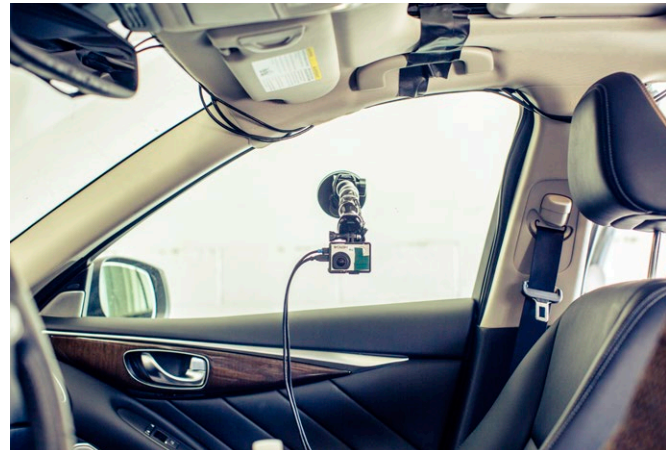
ON THE PULSE OF MENTAL HEALTH

hattering bots and tranquil whales are well and good, but what makes Paredes’ gadgets transformative are real-time measurements that report how the user interacts with them. Tactics like surveys and recorded feelings are typically the go-to methods to evaluate mental well-being, but Paredes purposefully strays from conventional self-reporting.

“We’re not the first to use lights to sway mood or chatbots to talk to people, but companies working in this vein don’t have the science behind it — that’s what’s missing.” That, Paredes said, is why his lab is looking into it — to figure out how to passively assess stress and alter the lights or engineer the chatbots to support mental health based on data and scientific evidence.

“My deep desire is to use technology to understand the biology behind mental health issues so we can either prevent people from reaching a breaking point or help them manage mental ailments, long or short term,” he said. It’s a drive kindled by his anxiety-battling family member, his unsung hero, he said. “I doubt I’d be in this type of research if it weren’t for him.” **SM**

— Contact Hanae Armitage at harmitag@stanford.edu



A ‘DOGBOT,’ TOP LEFT, LIGHTS UP IN REACTION TO A COMMENT FROM A DRIVER DURING A TEST OF TECHNOLOGY DESIGNED TO REDUCE STRESS FOR COMMUTERS. A CAMERA, TOP RIGHT, RECORDS A DRIVER’S REACTIONS. WASHINGTON AND PAREDES, AT RIGHT, INSIDE A ROOM EQUIPPED WITH LED LIGHTS THAT SATURATE THE SPACE IN A SINGLE COLOR TO ALTER MOOD.



plus

EXPLORING THE REALMS OF MEDICINE AND HEALING



NEUROSCIENTIST BEN BARRES WAS ACCLAIMED FOR HIS DISCOVERIES OF THE ROLES PLAYED BY GLIAL CELLS.

Deciding to change

AN EXCERPT
FROM THE
AUTOBIOGRAPHY
OF A TRANSGENDER
SCIENTIST

STANFORD NEUROSCIENTIST BEN BARRES HAD AN UNUSUAL LIFE. He began it as a girl, one of four children in a financially struggling New Jersey family, earned an MD and PhD, and became a successful researcher as a woman in a male-dominated field. Barres eventually garnered acclaim for waking up neuroscience to the role of glial cells, the brain's unsung heroes. At midlife Barres changed his gender to become male, continued to make path-breaking discoveries about glia and became an advocate for gender equality in science. Then, at 61, he learned he had advanced pancreatic cancer. In the foreword to Barres' new book, *The Autobiography of a Transgender Scientist* (MIT Press, 2018), friend and scientist Nancy Hopkins, PhD, said that many people had urged Barres to get his extraordinary life down on paper, to no avail. But in the months before his death at 63 in December 2017, he committed his story to print.

In this excerpt from the resulting autobiography, Barres described making the decision to transition from female to male, about four years after joining Stan-

ford Medicine's neurobiology faculty. As a child and young adult, he wrote, he was too ashamed about his gender incongruity to speak of it to a single person. It caused him emotional pain, leading him to consider suicide. He learned of the possibility of changing gender, by chance, while reading a newspaper article about a transgender man. Barres was 40 at the time. The increasing awareness and openness about the topic amazed him in his later years. "Whenever I see videos of parents talking openly and supportively with their (pretransition) transgender children, I weep," wrote Barres. "Much progress is left to be made, but I marvel at how far the world has come in recent years."

EXCERPT

FELT AN IRRESISTIBLE DESIRE TO TRANSITION FROM FEMALE to male from the moment I was offered that possibility. But I thought about it for several weeks because I was worried about what the repercussions might be for my career. Even though I was already tenured and so did not have to worry about being fired — a frequent outcome for transgender people in other professions at the time (in many states, transgender people are still not legally protected from being fired) — there was much to consider.

I did not know of any successful transgender scientists, and I worried whether, if I transitioned, I would be able to get any more grants (it was already nearly impossible). Would new students or postdocs wish to join my lab? Would my colleagues reject me? Would I still be invited to meetings and so forth? Reading about the experiences of other folks in other professions who had transitioned, I strongly feared that a transition would end my career. For about a week, I was almost unable to sleep from the stress as I pondered whether I should transition or commit

suicide. I finally decided to open up to three friends whose opinion I valued very much: David Corey, Martin Raff and Louis Reichardt. For the first time, I opened up to them about my gender confusion and told them that I was considering changing sex. Did they think that the repercussions would be so bad that it would harm my career? To my great relief, all three were immediately and strongly supportive. Based on their support, I decided to transition. I sent out the following letter to my colleagues, family and friends late in December of 1997 to let them know of my gender dysphoria and my decision to transition.

*Dear friends,
I am writing to disclose a personal problem that I've been struggling with for some time. It is important for me to talk about it now in order that I can finally move forward.*

Ever since I was a few years old, I have had profound feelings that I was born the wrong sex. As a child, I played with boys' toys and boys nearly exclusively. As a teenager I could not wear dresses, shave, wear jewelry, makeup or anything remotely feminine without extreme discomfort; I watched, amazed, as all of these things came easily to my sisters. Instead I wanted to wear male clothing, be in the Boy Scouts, do shop, play sports with the guys, do auto mechanics and so forth. Since childhood, I have been ridiculed and shunned by women and by men. At the age of 17, I learned that I had been born without a uterus or vagina (Mullerian agenesis), and that I had been exposed prenatally to masculinizing hormones. Despite plastic surgical correction of my birth defect, throughout my life I have continued to have intensely strong feelings of non-identity with women. Perhaps most disturbingly, I feel that I have

the wrong genitals and have had violent thoughts about them. My lack of female identity was brought home vividly to me recently after having bilateral mastectomies for breast cancer. This surgery, rather than being an assault on my female identity as it was for my mother, felt corrective as my breasts never seemed like they should be there anyway; the thought of reconstructive surgery has been repellent to me. Since the surgery, people who do not know me often call me sir; but that doesn't bother me, either. It is not that I wish I were male, rather, I feel that I already am.

It would be difficult to describe the mental anguish that this gender confusion has caused me. Although I have never been clinically depressed, it has been the source of strong feelings of worthlessness, intense isolation, hopelessness and self-destructive feelings. I have never been able to talk to anyone about it because I felt so ashamed

Ever since I was a few years old, I have had profound feelings that I was born the wrong sex. As a child, I played with boys' toys and boys nearly exclusively.

and embarrassed by it. It seemed that it must be my fault, that somehow I should be able to make myself be a woman. This is how things stood until two months ago, when I read in the newspaper about the existence of a gender clinic at Stanford. They found that I have a condition known as gender dysphoria. To my amazement, I learned that I am not alone and that my story is stereotypical of all of those who have this condition.

So what is gender dysphoria (also known as being transgendered or as gender identity disorder)? Those who have it feel, from childhood, a strong mismatch between their anatomical sex and their brain sex (gender identity). The cause is unknown but is thought to be biological, as some cases are clearly associated with a history of hormone exposure during development. Although it is not treatable by psychotherapy, the dysphoria is substantially lessened by a change in gender role. Treatment with testosterone

CONTINUES ON PAGE 41

Compatible with life?

DOCTORS AND FAMILIES GRAPPLE WITH WHAT'S NEXT WHEN A SEVERE GENETIC DISORDER IS DIAGNOSED DURING PREGNANCY

By Erin Digitale

ILLUSTRATION
BY JEFFREY FISHER

IN THE SPRING OF 2015, in the midst of a cross-country move to California, Kristin and Patrick Flor learned the baby they were expecting had trisomy 18, a genetic abnormality. It was halfway through what had seemed a picture-perfect pregnancy, and the couple had been excited to welcome another sibling for their two small boys.

The diagnosis was awful news. The condition, also called Edwards syndrome, is characterized by three copies of the 18th chromosome in most or all of the body's cells. Most affected fetuses die before birth, and about half of babies born alive die during their first week. Children with trisomy 18 have many physical problems — heart defects are common — as well as neurological deficits and profound developmental delays. Fewer than 10 percent of them survive to their first birthdays.

"We were devastated," Kristin Flor said. "We were grieving immediately. We had just been told we were going to have our first girl and assumed she would be healthy. We had dreams of raising a daughter along with our two sons." Although they could have terminated the pregnancy, the Flors, who are Episcopalians, felt that was the wrong choice for them. They really wanted to meet their daughter.

"Pat and I are big people of faith and we wanted to focus our energy on finding a purpose for her life, focused on love," Flor said.

Trisomy 18 and a similar diagnosis, trisomy 13, are among a few congenital syndromes traditionally described in the medical literature as "incompatible with life." Trisomy 18 occurs in 1 in 5,000 live births, and trisomy 13 in 1 in 16,000;

survival statistics for both diagnoses are equally poor. Most of these newborns struggle to breathe and eat, and survivors are severely disabled. Because of the dire prognosis, many women decide to end their pregnancies. Those who don't terminate, who hold out hope to meet their child alive, have usually been told that little can be done.

But today, some families want more options for their babies' treatment, a shift that raises complicated questions: How should medical caregivers help families navigate painful situations? When should potentially life-length-



ening procedures *not* be offered? And most of all: How do the words, stories and philosophical framework that experts use to think about disease shape how they approach it?

EXTENDING SURVIVAL RATES

AMONG THOSE whose thinking has shifted is Thomas Collins, MD, clinical associate professor of pediatrics and of medicine at Stanford Medicine, and a pediatric cardiologist at Lucile Packard Children's Hospital Stanford. Last year, Collins published a study comparing babies with trisomy 13 or 18 who had heart surgery with those who did not have surgery. The study, which drew on a national database, included babies born between 2004 and 2015 at 44 children's hospitals across the United States.

"I went into the study expecting that we would see no difference in survival," Collins said. Heart surgeries carry risks and cause pain. Before conducting the study, Collins believed the surgeries would harm these babies. "I was against doing things 'to' children as opposed to doing things 'for' children," he said. "My goal was to prevent people from doing surgery just because they could, without real benefit."

The data upended his expectations. Though a small proportion of infants in the study received cardiac surgery — 7 percent of the 1,480 study subjects born with trisomy 13 or 18 and heart defects, for a total of 100 surgery recipients — the surgeries seemed to help. For instance, in trisomy 18 patients, 84 percent of those who had heart surgery lived to go home with their families, compared to 66 percent of those who did not receive surgery.

Collins wonders what this means for our understanding of the limits of life in babies with trisomy 13 or 18. "We base our life span estimates mainly on the natural, un-operated history," of infants with these birth defects, he said. "We don't know what the life span would be if we addressed their issues."

The right amount of intervention depends on what feels acceptable to the family, Collins added. Most quickly grasp the severity of the disabilities a child with trisomy 13 or 18 would face, but they reach different conclusions. "I've seen families who have said, 'I love my child and want to do everything I can to help her live' and other, similar families who love their kids just as much who have said 'In our family that is not living; it's torture,'" he said.

The Flors had their first sign that something was wrong at a 20-week prenatal ultrasound scan in June 2015. It was the Friday before they planned to start driving from Illinois to the Bay Area, where Patrick Flor had a new job. The scan revealed that the baby was small and there were cysts on her brain, prompting Kristin Flor's obstetrician to ask the family to delay the trip for follow-up testing. "Then I knew it was serious," Flor said.

Over the weekend, they searched the internet and realized the brain cysts could be a marker of a severe form of trisomy. Or the cysts could resolve spontaneously and the baby could be fine. They hadn't named their two sons, Elijah, then 5, and Joshua, then 2, until later in pregnancy, but the uncertainty they were facing made choosing a name feel urgent. They decided on Julia Elizabeth.

Monday's follow-up testing revealed that, in addition to brain cysts, Julia had

a heart defect. On Tuesday, the Flors departed for California. They were in Denver when their genetic screening results came back: Julia almost certainly had trisomy 18. By the time they reached the Grand Canyon, they decided to tell Elijah the news about Julia. He'd picked up on his parents' distress.

"We talked to him about the fact that she had trisomy 18, and tried to tell him what that meant in kid terms," Flor said. "He knew that there was a chance that she was not going to live, a chance that when she was born we would have to say goodbye right away."

MAKING DIFFICULT DECISIONS

MANY PHYSICIANS are uncomfortable proposing invasive procedures such as heart surgery for trisomy 13 and 18 patients, even at parents' request.

"My biggest concern is that a family might think that heart surgery is going to increase their child's long-term survival more than it likely is," said Louanne Hudgins, MD, professor of pediatrics and director of perinatal genetics at Packard Children's. There is a risk of death during surgery, she said. Also, many infants with trisomy 13 and 18 die because their brains don't consistently prompt them to breathe, and cardiac surgery doesn't repair the brain. Hudgins worries that surgery raises false hopes.

Collins is planning a study to identify which infants with trisomy 13 or 18 tend to benefit from heart surgery. Do surgeries work best for those born with a specific type of heart defect? For those who have or lack other specific medical problems? Or are born past a certain time in pregnancy or above a certain birth weight? If doctors knew the answers, it would be easier to help families make realistic plans.

'My goal was to prevent people from doing surgery just because they could, without real benefit.'

“We’re trying to create a data-driven rubric so the best surgical patients can be selected,” Collins said. “We’re not yet satisfied that we have helped people make the right decisions for all of these patients.”

Into this climate of uncertainty, medical teams must help families navigate decisions about how to achieve their goals for their children’s lives.

“The best version of this is all of us compassionately and transparently providing all that we know, giving explanations of what we don’t know, and supporting a family as they understand how their life is going to be changed and how they can absorb it,” said Danton Char, MD, a faculty member at the Stanford Center for Biomedical Ethics and assistant professor of anesthesiology, perioperative and pain medicine.

With respect to invasive procedures, he added, “families need to think not just for themselves but also for their child, to make sure the balance of suffering from surgery is not greater than letting the natural course progress.”

And doctors can’t ignore that emerging literature suggests trisomy 13 and 18 are perhaps less hopeless than the traditional descriptors such as “incompatible with life” and “lethal” indicate.

“Does ‘incompatible with life’ mean simply that they will not live beyond birth? That’s not true,” said Collins. “The median age is 10 days, and 10 days is life in a real way.”

“I believe this language is a self-fulfilling prophecy in medicine,” Char said. “So much literature has described these conditions as universally fatal, and we have let these children go for almost a generation.”

PREPARING FOR THEIR OPTIONS

EVEN BEFORE THE FLORS arrived in California, they began arranging

appointments at Packard Children’s. Through the rest of the pregnancy, they worked with the maternal-fetal medicine, genetic counseling, neonatology, medical social work and chaplaincy teams through the hospital’s Fetal and Pregnancy Health Program to plan for Julia’s life. They wanted her to feel loved. They hoped to meet her alive. They did not want her to suffer.

“In every situation like this, we have iterative discussions about how things may play out for the baby and the family,” said neonatologist Susan Hintz, MD, the program’s medical director, who was one of Flor’s caregivers, along with obstetrician Gaea Moore, MD.

The experts did their best to evaluate the diagnostic information they had, present scenarios that could happen before, during and after Julia’s birth, and explain the family’s options in each case.

They discussed the family’s goals for Julia together: whether they wanted oxygen or other resuscitation measures to be offered if she had trouble breathing, how to handle issues and options related to feeding, and whether they would consider heart surgery if she lived long enough. (Julia had a relatively mild heart defect, for which surgery would not be needed until 4 to 6 months of age.)

“It’s not a paternalistic approach to developing a care plan,” Hintz said. “We are focused on understanding what a family’s desires and goals are and doing everything we can to make them happen.”

Central to the plan was the idea that the Flors were welcoming a new family member.

“We always acknowledge the diagnosis, but the baby is not a diagnosis,” Hintz said adamantly. “Julia is their daughter. Julia is a precious child.”

A PHILOSOPHICAL SHIFT

BENJAMIN WILFOND, MD, a bioethicist and pediatric pulmonologist at Seattle Children’s Hospital, is a long-time advocate for broader interventions for children with trisomy 13 and 18. In 2003, he wrote a commentary for the Hastings Center Report called “Lethal Language, Lethal Decisions” to probe how doctors’ use of the word “lethal” shapes families’ choices about their children’s lives.

“We said that, often, a condition was called lethal when there were a lot of medical issues and neurological problems as well,” Wilfond said. “The idea was that if you have neurological issues and medical complexity, you call it lethal and don’t do anything about it, and then patients will die.”

Many trisomy patients have such severe problems that no medical intervention would help, while a few others survive without major interventions, Wilfond said.

In the middle are a group for whom the right interventions sometimes lengthen life.

Recently, one of Wilfond’s trisomy 18 patients in Seattle had chronic respiratory failure and a heart defect called a ventricular septal defect. The heart defect couldn’t be repaired unless the child grew, which wasn’t possible unless she could breathe. She received a tracheostomy and spent several months on a ventilator. Eventually, she could breathe on her own and was healthy enough to receive surgery. She’s now 3.

“That would not have happened years ago,” Wilfond said. “She would have died from her ventricular septal defect, or we never would have thought of putting her on the ventilator and she would have died from respiratory failure.”

WELCOMING BABY JULIA

AS FLOR’S PREGNANCY progressed, the couple asked for close monitoring so they would know if Julia was

In every situation like this, we have iterative discussions about how things may play out for the baby and the family.

struggling. By 37 weeks of pregnancy, Julia had stopped growing, and the family and medical team decided it was time to deliver. Although they'd initially planned for a vaginal birth, Julia was breech. Because their goal was to meet their baby alive, they asked for a C-section to increase the chance Julia would survive birth.

On Oct. 21, 2015, at 11:48 a.m., Julia Elizabeth Flor came into the world at 3 pounds, 11 ounces and 15.5 inches long. Flor couldn't see past the drape that had been set up across her middle for the surgery.

"She was not crying, and I remember asking the nurse, 'Is she alive?'" she said. "The nurse said, 'She is alive, she's moving, but she's not making any sounds yet.'"

Flor was shaking from the anesthetic, so the nurse gave Julia to her father, who held her on his wife's chest. "She did start to make little kitten sounds," her mother said.

They moved to a recovery room, where 16 waiting friends and family members joined them for Julia's baptism. "It was wonderful, such a great moment," Flor said. That evening, in their hospital room, they held a small birthday party for Julia. Her brothers, grandparents and other extended family members were all there. Everyone sang "Happy Birthday," ate cupcakes and took turns holding the newest member of the Flor family.

That night, Flor heard Julia struggling to breathe. Her husband was asleep on the couch in her hospital room. "I said to him, 'Get up, get up!'" He flipped Julia over and patted her back. She coughed up a bunch of fluid. "After that she breathed so much more easily," Flor said. "But it was one of many times she turned blue."

Over the next few days, it became apparent that, like many babies with trisomy 18, Julia couldn't swallow. Her parents learned to feed her with a naso-

gastric tube. Otherwise she did better than expected, and they were excited and surprised when they were able to take her home at 5 days old.

"To be quite honest, I did not expect her to live," her mother said. "We had prepared more for her death than for her life." They'd chosen a dress for Julia to wear to her funeral, but hadn't picked a pediatrician.

At home, life with Julia was both "pretty normal and also really stressful," Flor said. Julia was on hospice care right away. Her parents fed her as a team to reduce the chance that she would choke, and made sure someone was awake and holding her 24 hours a day. But they also changed her diaper, read books to her, took walks to the park and dressed her as Tinker Bell for Hal loween. (Elijah and Joshua were Peter Pan and Captain Hook.) She was still alive at Thanksgiving. She went on the family outing to pick a Christmas tree.

Shortly after Thanksgiving, Julia caught a cold. "It was just too much for her body," her mother said. "Her lungs filled. We tried to keep her as comfortable as possible with medicines." Julia died Dec. 4, 2015. She was 43 days old.

Had Julia lived longer, the Flors might have considered surgery for her heart defect, but they knew it wasn't what ended her life. Looking back, they say that although their goals for their daughter were met, something else happened, too. Julia, always a newborn, able to express herself only with her deep gaze and tiny cries, drew people together.

"She brought a lot of love to our family," Flor said. "It was a privilege to be able to have her." **SM**

— *Contact Erin Digitale at digitale@stanford.edu*

FEATURE Superstar

CONTINUED FROM PAGE 17

"It's really important for the patient's outcome to know when those moments

of fatigue and deterioration set in," he said. "Knowing when it's time for a lead surgeon to take a break and allow the assistant to take over is analogous to a baseball coach deciding when a dip in accuracy and pitching speed indicates that a pitcher needs relief."

Milstein has shared the work with Mary Hawn, MD, professor and chair of surgery at Stanford, who was also enthusiastic about presenting the model, once it's perfected, to the American Board of Surgery as a possible addition to current board certification exams.

However, not all surgeons are enthused about the idea of having a machine second-guess their skills, Jopling said.

"I had one surgeon tell me, 'When that day comes, that's the day I'm going to retire,'" he said. But, Jopling added, "There are always things you can work on and improve. It's like having a tennis coach that watches every single swing you take over the course of your career, but without blinking or getting tired — there is always something you can improve, but in surgery, you often don't get that feedback."

The AI technology could have broader applications in many aspects of medicine, Yeung noted. For instance, the group has been testing it to monitor the movements of patients in intensive care units — when, for example, they get in and out of bed or a chair — and to ensure that caregivers are following steps to keep patients safe. The technology is also being tested to monitor frail seniors at home, measuring their activities and mobility, and alerting others to a fall or other mishap that requires immediate attention.

"Clinicians, nurses and other health care providers are so overwhelmed now, and the problem is going to get worse as the baby boomer generation gets older," Yeung said. "I think AI has great potential to provide an untiring, constant awareness of what is happening, which can be used to assist health care provid-

ers and prevent cognitive overload.”

But, the work will go on at Stanford without Jin, who is now a freshman at Harvard, following the path of her brother, also a science whiz, who is a senior there. She said it was hard to say goodbye to her Stanford coaches after two years of intensive work, but she’s excited — and a bit nervous — about what may come next. Although she has not settled on a major, it’s no surprise that she’s considering computer science. And that, said Yeung, could be a boon to the profession.

“It’s great to have people like Amy who excel in computer science,” Yeung said. “It’s one of the problems AI is trying to address — that we don’t have enough women in the field and the number decreases at every stage. So we hope Amy will continue in the field and be a good role model for others.” **SM**

— *Contact Ruthann Richter at medmag@stanford.edu*

FEATURE

Computer memory

CONTINUED FROM PAGE 27

This finding doesn’t prove that the same thing would happen in a living animal’s hippocampus, but it generates a hypothesis that can in some cases be tested.

“I don’t care if the model’s predictions are proved true or false,” Soltesz said. “The point is to make experimentally testable predictions. The model is a tool, not a be-all and end-all.”

Playing around with an early, much simpler 10,000-cell model of another hippocampal compartment, the dentate gyrus, generated an intriguing hypothesis that not only was borne out but also could have huge implications for people with epileptic seizures.

“We became intrigued by a small population of cells in the dentate gyrus, called mossy cells,” said Soltesz. If neurons were airports, mossy cells would be JFK or LAX, he said. “These mossy neurons were especially hublike

— each connects with many thousands of other neurons in the dentate gyrus.” His team wondered if the loss of some significant fraction of these sparse but densely connected neurons might increase the likelihood of symptomatic epileptic seizures.

Because mossy cells, which are inhibitory, hook up with both excitatory and other inhibitory neurons, trying to predict what will happen when you silence some of them is a toss-up. In a study published in *Science* in early 2018, Soltesz’s group succeeded in getting a clear answer. Their experiments in live mice showed that a die-off of mossy cells did trigger a rise in the spread of seizures originating in the dentate gyrus throughout the mice’s brains. It also reduced the mice’s ability to recall spatial information.

Mossy cells are especially delicate and vulnerable to pressure as well as to decreased oxygen supply, which occur in brain injury or stroke. Concussions and stroke are known risk factors for increased seizure susceptibility. A drug aimed at protecting mossy cells could have major clinical possibilities.

Soltesz’s models, which he makes freely available, have been used by labs all over the world for research on memory storage and retrieval, antiepileptic drug effects, genetic models of disease and more. He makes available all the experimental data his team has fed into the model, so the data can be funneled into any new, improved model that comes along. He’s even giving away software to investigators inclined to tinker with the model.

“What’s most impressive about Ivan’s CA1 model,” said Angus Silver, PhD, a professor of neuroscience at University College London and a Fellow of the Royal Society, “is that it’s full-scale. He and his team have combed the literature for all the information available about this part of the hippocampus, they’ve put it all together and, amazingly, it exhibits several key properties of the real CA1, without

your having to tweak it. It certainly gives you hope that this approach is useful.”

Meanwhile, Soltesz and his team are forging ahead with a full-scale model of the rodent dentate gyrus (1 million cells in all, three times as many as in CA1), which Soltesz expects to complete in less than a year. Next on the to-do list are CA3, then models of nearby structures that send inputs to the hippocampus. In the longer term, he wants to model the entire brain region that includes the hippocampus — the temporal lobe.

But why stop there? Other well-funded groups, such as the Allen Institute for Brain Science in Seattle and the Human Brain Project in Switzerland, are also building representations of various parts of the brain.

“We’re not working in a vacuum,” said Soltesz. “I can imagine that in 20 years or so we’ll have full-scale models of mouse and human brains at single-cell resolution.” It may someday be possible, Soltesz speculated, to build customized, patient-specific models of the entire brain based on advanced noninvasive imaging and recording techniques, so the effects on any patient’s brain of a given drug or other intervention can be tested.

When a model has as much resolution as the thing it’s modeling, is it still a model? Or is it a working copy?

“That’s an excellent question,” Soltesz said. “Luckily, we’re nowhere near being able to answer it. It’s pure fantasy right now. But we humans are busily working our way toward that quandary. We’ll deal with it when we get there.” **SM**

— *Contact Bruce Goldman at goldmanb@stanford.edu*

PLUS

Deciding to change

CONTINUED FROM PAGE 35

induces normal male secondary sexual characteristics within six to 12 months. Most patients also opt for mastectomies, which I

have already had, and hysterectomy, which nature has already done for me. In my case, testosterone treatment would have the added benefits of substantially lowering my chance of new or recurrent breast cancer; because it lowers estrogen levels, and would block the osteoporosis and menopausal symptoms that will otherwise follow when I have my ovaries removed because of my cancer susceptibility mutation.

After much reflection, I have made the decision to take testosterone. I will thus become a female to male transsexual. This has been a difficult decision because I risk losing everything of importance to me: my reputation, my career, my friends and even my family. Testosterone is a far from perfect solution; I'm still not going to be "normal" and social isolation will undoubtedly continue. But testosterone treatment offers the possibility that, for the first time in my life, I might feel comfortable with myself and not have to fake who I am anymore. I know that I am making the right decision because whenever I think about changing my gender role, I am flooded with feelings of relief. I will begin taking testosterone in February. A change in my appearance will not be visible for several months. By summer, I will begin to dress in men's clothes and will change my name to Ben. Throughout this process I will continue to work normally and to conduct myself in all ways as usual (except that I will only use single-occupancy bathrooms). Although the idea of my changing sex will take some time for you to get used to, the reality is that I'm not going to change all that much. I'm still going to wear jeans and T-shirts and pretty much be the same person I always have been — it's just that I am going to be a lot happier.

Many transsexuals change jobs after their "sex change" in order to retain anonymity, but anonymity is obviously not an option for me — nor is it one I desire. I am tired of hiding who I am. More importantly I owe it to others who unknowingly endure this condition, as I did, to be visible. Despite my seven years of medical training, which I undertook to understand what was wrong with me, until two months ago, I had never heard of gender dysphoria (oddly, I somehow picked

the right organ to study!). Had it not been for the transsexual who allowed himself to be the subject of the news piece I read, I would still not know about it. Sure I knew that sometimes there were male-to-female transsexuals, but I had thought that these people were perverts. I am not a pervert; I don't seek pleasure — only relief from pain. Most transsexuals hide because of shame and fear; perpetuating ignorance and oppression about their condition. Their suicide rate is so high that some experts have called gender dysphoria a lethal disease. This is why I cannot hide.

In my heart I feel that I am a good scientist and teacher. I hope that, despite my trans sexuality, you will allow me to continue with the work that, as you all know, I love. I am happy to answer any questions.

Sincerely,
Barbara A. Barres

DESPITE SUPPORT FROM DAVID, MARTIN AND LOUIS, sending out this letter was still very scary. I found that my family was immediately supportive and so were all of my colleagues. I heard back from many of them very quickly. Here is the very first response that I received. It is from Chuck Stevens at Salk, a colleague I had long admired for his science and his wonderfully generous mentorship of so many young scientists:

Dear Barbara,
Thanks for the letter and the personal info. I have always been fond of the person in there and the gender makes zero difference to me — I expect you will find the same with all of your friends. Let me know when to change to "Ben."

Best regards,
Chuck

ALL OF THE OTHER responses I received were similarly supportive. And there it was: This shameful secret I had held inside of me for 40 years was out, and within a few months I had transitioned to Ben ... My career went on as before without a hitch. I am not aware of

Executive Editor:

PAUL COSTELLO

Editor:

ROSANNE SPECTOR

Associate Editor:

PATRICIA HANNON

Art/Design Direction:

DAVID ARMARIO DESIGN

Director of Print and Web Communication:

SUSAN IPAKTCHIAN

Writers:

HANAE ARMITAGE
STEPHANIE BRUZZESE
KRISTA CONGER
ERIN DIGITALE
BRUCE GOLDMAN
FRED GUTERL
AMY JETER HANSEN
RUTHANN RICHTER
TRACIE WHITE

Copy Editor:

MANDY ERICKSON

Circulation Manager:

ALISON PETERSON

Stanford Medicine is published four times a year by the Stanford University School of Medicine Office of Communication & Public Affairs as part of an ongoing program of public information and education.



© 2018 by Stanford University Board of Trustees.

Letters to the editor, subscriptions, address changes and correspondence for permission to copy or reprint should be addressed to *Stanford Medicine* magazine, Office of Communication & Public Affairs, 3172 Porter Drive, Palo Alto, CA 94304.

We can be reached by phone at (650) 723-6911, by fax at (650) 723-7172 and by email at medmag@stanford.edu.

To read the online version of *Stanford Medicine* and to get more news about Stanford University School of Medicine visit <http://med.stanford.edu>. For information from the Stanford University Medical Center Alumni Association visit <http://med.stanford.edu/alumni/>.

a single adverse thing that has happened to me in the past 20 years as a result of my being transgender, but there was the immediate relief of all emotional pain as a result of my transition. Never did I think of suicide again and I felt much happier being myself (Ben), no longer having to pretend to be a woman. It is hard to explain how much relief I felt and how much happier I became. It was as if a huge weight had suddenly been lifted from my shoulders. **SM**

GOING STRONG

GENETIC SCREENING COULD PROVIDE AN EARLY CHANCE TO COUNTER BONE WEAKENING

More than 2 million people in the United States are affected by osteoporosis every year. Many of them are in their 50s or 60s and aren't aware they have the disease until they break a bone. New research, however, suggests that genetic screening could predict much earlier in life who is most susceptible, giving them a fighting chance to prevent it. Osteoporosis, or porous bone, causes a reduction in bone mass, especially in older people, and elevates the risk of fractures. It accounts for \$19 billion in annual health care costs, according to the National Osteoporosis Foundation. People who have it are more likely to break a bone if they fall, or even during routine daily activities.

The disease is diagnosed through a bone mineral density test that measures the amount of minerals, such as calcium, in a person's hip, spine or heel.

But testing is usually done only for people who have a family history of the disease or who have already fractured a bone — a factor that Stuart Kim, PhD, an emeritus professor of developmental biology at Stanford Medicine, contended hampers the ability to predict disease risk before fractures occur in the first place.

That's why he believes genetic screening might provide a better opportunity for predicting the disease early and mitigating the effects as people age and bone mass decreases.

"There are lots of ways to reduce the risk of a stress fracture, including vitamin D, calcium and weight-bearing exercise," said Kim, whose study was published July 26 in *PLOS ONE*. "But currently there is no protocol to predict in one's 20s or 30s who is likely to be at higher risk, and who should pursue these interventions before any sign of bone weakening. A test like this could be an important clinical tool."

Kim first approached his study of bone mineral density to help elite athletes and military personnel determine their risk of bone injury during strenuous training.

For his study, he used health and genetic data from 400,000 people in the UK Biobank, a vast collection of information that is available to health researchers around the world. Kim gathered data on bone mineral density, age, height, weight, gender and genome sequence for each participant.

Then he performed a genomewide association study to pinpoint genetic differences among people with low bone mineral density, leading him to 899

regions in the human genome associated with bone mineral density, 613 of which had never been identified.

He then used a machine-learning method called LASSO, developed by Stanford professor of biomedical data science and of statistics Robert Tibshirani, PhD, to hone the data and develop a predictive algorithm to assign a score to indicate each person's risk of low bone mineral density; further analyses showed that those in the bottom 2.2 percent of the scores were 17 times more likely to have been diagnosed with osteoporosis and nearly twice as likely to have had a bone fracture.

The knowledge makes it possible to use genetics to pinpoint who is at risk and provide early intervention against the disease, Kim said.

"This is one of the largest genomewide association studies ever completed for osteoporosis, and it clearly shows the genetic architecture that underlies this important public health problem," Kim said. — KRISTA CONGER



JH

Stanford University
School of Medicine
Office of Communication and Public Affairs
3172 Porter Drive
Palo Alto, CA 94304

Change Service Requested

Snake weather

CLIMATE STUDY SHOWS UPTICK IN BITES AFTER RAINY SEASONS AND DROP FOLLOWING DROUGHTS

If you're terrified of being bitten by a snake in California, you might not want to plan a hike just after a stretch of rainy weather. That could be tough to swallow considering it's commonly believed that snakes are more active in dry, hot weather. But a study led by Grant Lipman, MD, clinical associate professor of emergency medicine at Stanford Medicine, proved otherwise.

Lipman routinely treats people with venomous snakebites in the emergency room. But his inspiration for finding out how climate affects bite numbers didn't strike at work; rather, it came when he saw a 3-foot-long rattlesnake on a trail where he was running in the brown hills near the Stanford campus during a severe drought. "I wondered if there are more snakebites during droughts," he said.

So he and two other researchers — one from the University of Colorado-Boulder and one from the University of California-San Francisco — examined 20 years of snakebite data from every phone call made to the California Poison Control System from 1997 to 2017. Details included dates, times and sites where the calls were made; patient ages and genders; where the bites occurred on the body; treatments; and medical outcomes.

In all, 5,365 snakebites — five of them fatal — were reported, all from rattlesnakes. The median patient age was 37, and the patients were mostly male.

Looking at reports of the wettest and driest years during the 20-year period, researchers



found that precipitation was a strong predictor of bites, with the number peaking following the heavy precipitation years of 2006 and 2011. But the number of bites dropped during two periods of extreme drought between 2002 and 2005, and from 2007 to 2010. From 2015 to 2016, the most severe drought on record in California, the number of bites reached their lowest, according to the study, published Sept. 5 in *Clinical Toxicology*.

"We can predict a big snakebite season because of prior wet winters and have antivenom in places where there are a lot of hikers or trail runners," Lipman said. "It's important information for people who work and play in California."

The researchers theorized that the reason for more bites after rain is that wet weather results in more shrub growth and, with that, an increase in rodents — the snakes' primary food source.

"More food, more snakes, more snakebites," Lipman said. — TRACIE WHITE

JOEL SARTORE

TO SUBSCRIBE
TO STANFORD MEDICINE
email medmag@stanford.edu
or call (650) 723-6911.