INSIDE STANFORD MEDICINE

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The new issue of *Stanford Medicine* magazine reports on the ways digital technology is transforming health care.

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The engineer who wants to drive us sane

By Hanae Armitage

Pablo Paredes sat in a psychologist's office. He watched as a family member, Alex (a pseudonym), scrutinized a photo of himself. Paredes knew what he was thinking: "My chin is too big."

They were there for Alex's sixth appointment that month, arranged by Paredes with the goal of providing 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 psychologist took the picture of Alex'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. Alex fidgeted uneasily. The strategy, however uncomfortable at first, works by allowing the patient to habituate to the stressor, diminishing angst over time.

Paredes took the picture from the doctor. "I have another idea," said Paredes, who at the time was a graduate student in electrical and computer engineering at the Georgia Institute of Technology. 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 Alex. "This is what you would look like with an enlarged chin," Paredes said.

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

It wasn't revolutionary technology, nor was it a definitive fix. But for Alex, it turned out to be an effective, albeit initially distressing, strategy to blunt his anxiety. It was then, Paredes said, that he realized just how powerful technology could be as a tool for improving mental health.

TIMOTHY ARCHIBALD

Pablo Paredes (left) and graduate student Peter Washington test car-based stress-mitigation technology.

Today, more than a decade after that psychologist's appointment, Paredes is an instructor of radiology and of psychiatry and behavioral sciences at the School of Medicine. His career was one he never foresaw; in a former life, he'd been the bass guitarist in a Latin rock band, a thriving entrepreneur and a high-level business manager at Intel in Brazil. But from his family member's struggle, Paredes found inspiration for a new career — one in which he would apply his engineering expertise to broadly improve mental health.

The mechanics of well-being

It's still early days for Paredes' work. "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," Paredes said. "Eventually, our experimental data will point us to a more narrow path, which we will then investigate more deeply."

In 2003, Paredes, who's originally from Ecuador, went to Georgia Tech on a Fulbright scholarship. After earning a master's degree in electrical and computer engineering and an MBA there, 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 enrolled as a graduate 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 the lab of James Landay, PhD, a professor of engineering, as a postdoctoral scholar.

Now with his own lab, Paredes leads the development of more than a dozen digital interventions that could one day provide millions of people the means to improve 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 wig-

See PAREDES, page 4

Gut microbiome variance linked to dietary lifestyle in four Himalayan populations

By Helen Santoro

The gut bacteria of four Himalayan populations differ based on their dietary lifestyles, according to a new study by researchers at the School of Medicine and their collaborators.

All four populations — the Tharu, the Raute, the Raji and the Chepang — are longtime residents of the Himalayan foothills, with similar languages, cultural practices and ancestry. Where the four diverge is in their dietary history: The Tharu have practiced agriculture for the past 250 to 300 years; the Raute and the Raji have practiced agriculture for the past 30 to 40 years; and the Chepang are hunter-gatherers. The study found that the composition of the gut microorganisms, or gut microbiome, of each population differed based on whether and how long ago it had departed from a hunter-gatherer lifestyle.

AASHISH JHA

Researcher Yoshina Gautam collects data in a Chepang village for a study on the dietary lifestyles of four Himalayan populations.

"This study indicates that human microbiomes may have changed gradually as human lifestyle

See HIMALAYAS, page 6

Surgery should remain the first-line treatment for appendicitis, study says

By Tracie White

Treating appendicitis with antibiotics as an alternative to surgical removal of the inflamed organ was found to be more costly in the long term and result in higher rates of hospital readmissions, according to a study by researchers at the School of Medicine.

"People treated with antibiotics alone have a higher chance of coming back needing further treatment for appendicitis-related problems, such as abdominal abscesses," said Lindsay Sceats, MD, a surgical resident and lead author of the study. "They also have a higher risk of having a reoccurrence, and the cost is no lower."

The study was published Nov. 14 in *JAMA Surgery*. Kristan Staudenmayer, MD, associate professor of surgery, is the senior author.

Appendicitis is an inflammation of the appendix, a finger-shaped pouch that projects from the colon on the lower right side of the abdomen. Acute appendicitis, if left untreated, can result in a ruptured appendix that can spread infection throughout the abdomen and be life-threatening. It occurs in about 5 percent of the United States population, according to

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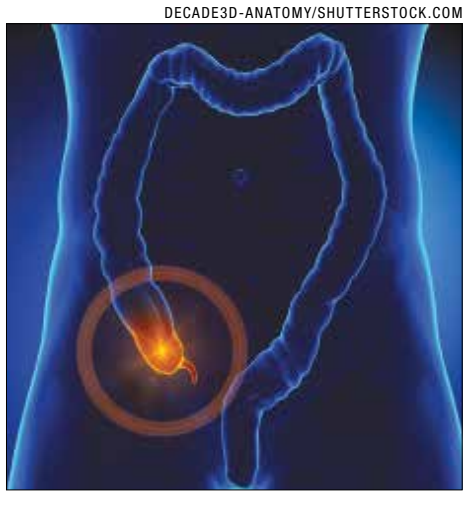

Appendicitis is the inflammation of the appendix, a finger-shaped pouch that projects from the colon.

See APPENDICITIS, page 7

For 7-year-old with failing bone marrow, a lifesaving transplant

By Amy Brooks

Seven-year-old Ikkei Takeuchi likes to say he has two birthdays: the day in April when he was born, and the day in July when he got a whole new blood system.

Ikkei was living in Japan when he started experiencing fevers and nosebleeds and lost a lot of his usual energy, according to his parents, Shojiro and Natsuko Takeuchi. When the family moved to the Bay Area and the symptoms still hadn't improved, Ikkei's pediatrician referred him to the Bass Center for Childhood Cancer and Blood Diseases, at Lucile Packard Children's Hospital Stanford, to find out why.

That's where he met Bertil Glader, MD, PhD, a pediatric hematologist.

"My first impression of Ikkei was that he was as cute as can be, and he only got cuter the more I got to know him," recalled Glader, professor of pediatrics at the School of Medicine.

Glader tested Ikkei's blood and found that it didn't have enough of three types of cells: platelets, which are necessary to prevent bleeding; red blood cells, which carry oxygen; and white blood cells, which help fight infections.

The dwindles

It was clear that Ikkei's bone marrow was failing. Despite running every test in the book, Ikkei's doctors couldn't figure out exactly why this was happening, making Ikkei one of a rare group of kids with unexplained bone marrow failure. One thing was clear, however: Ikkei's bone marrow wasn't repairing itself. Instead, it was starting to show signs of increased stress.

CRIS GEBHARDT

Bertil Glader with Ikkei, who received a bone marrow transfusion.

"We gave Ikkei occasional blood transfusions to keep his energy levels up, but he was going through what we call 'the dwindles,' when his blood counts continue to get worse. We knew it was time for a bone marrow transplant," Glader said.

Bone marrow transplantation would replace Ikkei's defective bone marrow, which would allow Ikkei to make new blood cells, give him more energy, stop his frequent nosebleeds and help him better fight infections. Ikkei was lucky to find a perfect donor match in his 4-year-old brother, Senshu.

"Since Senshu is 4 years old, he didn't understand everything that was going on. But we told him, 'You can help your older brother,' and he understood that," Natsuko, the boys' mother, said. "He never said he didn't want to go to the hospital, and he never cried, either."

Even with a perfect donor match, a bone marrow transplant is a serious procedure. Shojiro said the hospital staff worked to help ease the family's fears.

CRIS GEBHARDT

Ikkei (left) with his brother and bone marrow donor, Senshu, at Lucile Packard Children's Hospital Stanford.

"When we were told Ikkei needed to have a bone marrow transplant, we felt we would face a very, very, very hard time. We could not imagine how difficult it would be," Shojiro recalled. "However, the doctors explained everything to us so we could make the right decision. And everyone at the hospital was so supportive and gave us energy. They helped us get rid of our anxiety around unfamiliar medical terminology and made boring hospital days happy for Ikkei."

> "Everyone at the hospital was so supportive and gave us energy."

Ikkei's bone marrow transplant — overseen by Sandeep Soni, MD, clinical associate professor of pediatrics, and aided by Agnieszka Czechowicz, MD, PhD, assistant professor of pediatrics, and the stem cell transplant team — went smoothly.

"His blood counts are back to normal, and he's continuing to recover and build out a healthy immune system," Czechowicz said.

Energy and ice cream

Ikkei was able to return home a few weeks after his transplant. His parents say he already has more energy and is eating all of his favorite foods, including ice cream.

"He was very excited to be home. He was playing with his younger brother, running around and sweating," Natsuko said. "We were worried he would have a fever again, but he didn't. He just acted like a normal kid."

Ikkei is excited to spend more time playing basketball and football. He's a huge fan of the Golden State Warriors and the San Francisco 49ers.

For his parents, the transplant represents a new chapter in Ikkei's life.

"He had a lot of restrictions before the treatment," Natsuko said. "Whenever he had a fever, he wasn't able to do anything and had to save energy. In the future, I'd like him to do things he likes. He can act like a healthy, normal child."

Between the move and the transplant, it has been a whirlwind few years for the family. They are looking forward to calmer times ahead.

"We moved from Japan, and Ikkei received treatment in the United States, so he thinks he was saved by the United States," Shojiro said. "He really likes this country. We believe Ikkei is healthy now thanks to all the support we got from the hospital, and we're so thankful to the staff." ISM

How artificial intelligence could help veterinarians code their notes

By Hanae Armitage

As artificial intelligence continues to make inroads into human medicine, James Zou, PhD, assistant professor of biomedical data science at the School of Medicine, has found another use for it: animal medicine.

When pets visit an animal hospital, veterinarians type out notes in paragraph form to document the visit. There's no systematic or widespread infrastructure in place for pet electronic health records. And while hand-captured notes work fine to document one visit, in one clinic, it limits how the data can be used and shared.

"Unlike human electronic health records, there aren't standardized ways to map free text typed on a computer into codes that denote a specific type of disease," Zou said. "So there are millions of vet clinical records that are essentially wasted because they're so cumbersome to work with. Clinics don't have the infrastructure to extract information from these medical records, but there's a lot of really interesting information in them, and they might even come to bear on human health."

> "AI is now much better at understanding human languages and being able to respond to them."

Now, Zou and his team have devised a solution, DeepTag, rooted in artificial intelligence. DeepTag is an algorithm that essentially reads the typed-out notes from a vet and predicts specific diseases that the animal may have. It boils down the paragraph of medical notes into codes that represent certain ailments, symptoms or diseases.

Scanning for key words

A paper describing DeepTag was published Oct. 24 in *npg Digital Medicine*. Allen Nie, a machine learning researcher, and research scientist Ashley Zehnder, DVM, PhD, share lead authorship.

There's been a tremendous amount of progress in the ability of AI to understand and apply natural language, Zou said. "AI is now much better at understanding human languages and being able to respond to them, and we're leveraging that progress to build algorithms that can scan across the paragraph to actually read the clinical notes and interpret each word," he said. "We're not explicitly telling the algorithm what words are associated with what disease. Instead, it's finding the key words that are associated with specific diagnoses."

In training the algorithm, Zou collaborated with the College of Veterinary Medicine at Colorado State University, where a group of veterinary experts annotated more than 100,000 clinical notes, assigning disease codes to each case. Nie used that data set to "teach" the algorithm the types of notes that paired with a particular disease. Then, the group further vali- **See DEEPTAG, page 3**

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STANFORD MEDICINE

Puzzle of a mutated gene lurking behind many Parkinson's cases

By Bruce Goldman

Genetic mutations affecting a single gene play an outsized role in Parkinson's disease. The mutations are generally responsible for the mass die-off of a set of dopamine-secreting, or dopaminergic, nerve cells in the brain involved in physical movement.

Suzanne Pfeffer

The pathogenic variants of the gene, LRRK2, share a common tendency: They cause the protein it encodes to run in constant overdrive, upsetting the delicate balance of a healthy cell.

What ties defective LRRK2 so strongly to Parkinson's has puzzled researchers. Now, a study led by scientists at the School of Medicine appears to have pieced together a major part of that puzzle.

Suzanne Pfeffer, PhD, professor of biochemistry and the Emma Pfeiffer Merner Professor in Medical Sciences, is the senior author of the study, which was published Nov. 6 in *eLife*. The lead authors are postdoctoral scholars Herschel Dhekne, PhD, and Izumi Yanatori, PhD.

Randomness of Parkinson's disease

Most cases of Parkinson's are sporadic, meaning the condition seems to hit individuals at random rather than run in their families. But even in sporadic cases, genetic mutations can figure in.

Of the numerous LRRK2 variants suspected of predisposing people to Parkinson's, so far five have been solidly identified as boosting Parkinson's risk. Taken together, these LRRK2 mutations have been implicated in about 10 percent of inherited cases and 4 percent of sporadic cases among Caucasians. Just a single one of those mutations is responsible for about 40 percent of familial Parkinson's cases and 13 percent of sporadic cases among Ashkenazi Jews.

Drugs targeting the LRRK2 protein are already in clinical trials for Parkinson's, despite the absence of a real understanding of its role in the disease.

Pfeffer and her colleagues have previously reported that mutant LRRK2 renders some classes of nerve cells deficient in their ability to create an important subcellular structure called the primary cilium, which acts analogously to a radio receiving tower, except that instead of sucking in waves of electromagnetic radiation, the primary cilium slurps up signaling substances from its surrounding environment.

It's easy to imagine how a cell lacking such a receiving tower could go astray. But Pfeffer's team wanted to know why the defect preferentially leads to Parkinson's disease as opposed to a number of other neurodegenerative disorders.

A complicated molecular explanation

In the new study, the researchers unraveled a complicated molecular explanation: First, cells lacking primary cilia are unable to respond to a powerful chemical messenger known as sonic hedgehog. Second, the scientists learned, the types of cells that can't make a decent primary cilium when their LRRK2 protein is in overdrive include a set of cholinergic nerve cells, so named because they secrete acetylcholine rather than dopamine or other substances that signal nerve cells.

These cholinergic cells have a close working relationship with the dopaminergic cells implicated in Parkinson's disease. When the dopaminergic cells need some help, they pump out sonic hedgehog. Cholinergic cells with functioning primary cilia respond by triggering the secretion of a molecule that keeps dopaminergic cells healthy. Without that molecule, dopaminergic cells become more vulnerable to dying.

So an LRRK2 protein in overdrive leads to no primary cilia, which leads to no response to the sonic hedgehog signal, which leads to no chemical help for the dopaminergic cells and, therefore, to their death.

Could the breakdown of that support system underlie the unrelenting loss of dopaminergic cells in Parkinson's? Pfeffer's lab is now hard at work studying that very question.

Another Stanford co-author is graduate student Rachel Gomez. Researchers from the University of Dundee in Scotland; the Parkinson's Institute in Sunnyvale, California; and the Max Planck Institute of Biochemistry in Germany also contributed to the work. The work was funded by the National Institutes of Health, the Michael J. Fox Foundation for Parkinson's Research and the Medical Research Council.

Stanford's Department of Biochemistry also supported the work. ISM

DeepTag

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dated the algorithm's accuracy by testing it on pet clinical data collected from private veterinarian offices.

Broadly speaking, DeepTag would allow veterinarians to track the prevalence of disease in pets, and in the future could be a tool to track clinical trials for animals.

A win-win

Before a drug makes it to clinical trial in humans, it's typically tested in mice or rats for efficacy and safety. But the biology of small rodents can be quite different from that of a person. A dog, larger in size and in some ways more reflective of human biology, could more accurately indicate how a human might respond to a treatment, once the hypothetical treatment passed the "rodent stage."

"Dogs, which were the majority of patients that we documented using DeepTag, are very good candidates for many of the drugs scientists develop for humans," Zou said. "And there's a growing interest in pharmacology and biotechnology to try to test, for example, new cancer treatments in dogs — it could be a win for both humans and their pets."

Likewise, just as is the case for sick people, there's sometimes a lack of sanctioned options to treat disease in pets, and clinical trials would be their best bet at recovery. But until now, there's been little infrastructure to keep tabs on how animals fair on new therapies.

U.S. AIR FORCE SENIOR AIRMAN RITO SMITH

Scientists have developed an algorithm called DeepTag that would allow veterinarians to track the prevalence of disease in pets, and in the future could be a tool to track clinical trials for animals.

Since the paper published, Zou has been discussing applying the DeepTag algorithm to large veterinary clinics around the country, and locally in the San Francisco Bay Area. Soon, Zou said, his team will have a publicly available platform that veterinarians anywhere in the world can use. "Once the platform is online, any veterinarian could go and use the platform to annotate their notes and see the results in real time," he said.

Other Stanford co-authors include postdoctoral research scholar Arturo Pineda, PhD; assistant professor of biomedical science, Manuel Rivas, DPhil; and professor of biomedical data science and of genetics Carlos Bustamante, PhD.

Researchers from Colorado State University and Tsinghua University in Beijing, China, also contributed to the work. ISM

$6 million grant will support study of preeclampsia, atherosclerosis links

Preeclampsia affects 5 to 10 percent of all pregnancies — more than 8 million a year worldwide — and claims the lives of 76,000 mothers and a half-million babies each year.

The condition causes hypertension and an abnormal amount of protein in the urine, which can lead to organ failure, stroke and brain damage, and has few effective preventive or therapeutic strategies. The clinical abnormalities usually resolve completely after delivery, but recent research shows that women who have had preeclampsia have higher rates of heart disease later in life for reasons that are poorly understood.

That's where Mark Hlatky, MD, and Virginia Winn, MD, PhD, come in. They were recently awarded a $6 million grant from the National Heart, Lung and Blood Institute to study the links between preeclampsia and the subsequent risk of atherosclerosis, the buildup of plaque in and on artery walls, in women as they grow older.

"The goal of this study is to improve cardiovascular health in women, by learning how pregnancy affects heart disease later in life," said Hlatky, a Stanford Health Policy fellow and professor of medicine and of health research and policy. "We hope that shedding new light on these links can lead to better prevention and treatment."

The interdisciplinary study is called Effect of Preeclampsia on Cardiovascular Health, or EPOCH. It could eventually help millions of women.

Hlatky and Winn, an associate professor of obstetrics and gynecology, note that a history of preeclampsia doubles a woman's risk of future heart disease and stroke, and triples her risk of hypertension. And these adverse consequences occur at younger ages than they do among women who never developed the condition during pregnancy.

"The dramatic physiologic changes that happen during pregnancy are indeed remarkable," Winn said. "This study highlights how complications that occur in pregnancy impact women's health beyond pregnancy."

The four-year grant will support a research team across eight Stanford departments. The study will enroll three cohorts of participants: one group of pregnant women with preeclampsia; one group of middle-aged women who had preeclampsia; and one group of older women who had the disorder. ISM

Paredes

continued from page 1

gle, 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.

TIMOTHY ARCHIBALD

Washington and Paredes in a room with lights that saturate the space in a single color to alter mood.

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

Of 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," Paredes said. 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," Paredes said.

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 nonjudgmental robot than a real person.

If you're more the silent type, you might opt for technologies Paredes created that help you train your breathing to slow down or persuade your heart into an optimal resting rate. (Some studies 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 has 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 alertness." Something, perhaps, to shake off the Monday blues or wake up a drowsy driver.

For the day that we're ferried about in self-driving cars, Paredes has built a virtual reality experience that

TIMOTHY ARCHIBALD

One of several cameras used to record a driver's reactions as part of Paredes' research, which focuses on improving mental health.

Stanford Medicine magazine reports on the ways digital techno

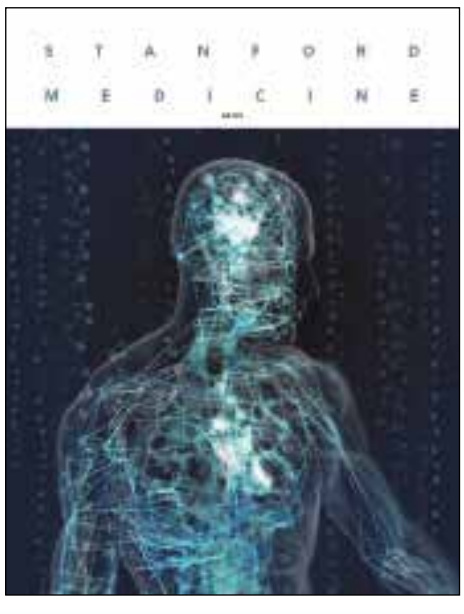
By Patricia Hannon

Digital technology permeates our lives. Smartphones that operate like mini-computers give us easy access to email, news, bank accounts and social networking apps. Even our well-being is in the game: Many of us use digital devices and apps to track our movement, sleep, blood sugar levels or heart rates.

At Stanford Medicine, that's only the beginning. The new issue of *Stanford Medicine* magazine explores how technology is transforming health education, research and patient care around the globe.

"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," Lloyd Minor, MD, dean of the School of Medicine, wrote in his letter introducing the issue.

An integral part of that strategy is ensuring that the human touch, an essential part of health care, not be lost, he said. To that end, Stanford Medicine has embraced a mission that takes advantage of the best elements of the latest technology to ensure a health care future that is both proactive and personalized.



Several stories in the issue explore ways clinicians are using high-tech tools to improve care. For example, more clinicians are tapping electronic health records to gather up-to-date information about disease and treatments, and using the technology to improve communication with patients and each other.

The issue also examines ways artificial intelligence, machine learning and technology have created opportunities for innovation in medical education, diagnostics and clinical skill assessment, and to better understand what makes our bodies and minds tick:

• Four programs highlight how Stanford Medicine uses digital technology to fill in gaps in care: An emergency room physician uses tablet computers to train community health care workers in underserved areas of Haiti and India; radiologists transformed holograms to facilitate more precise removal of diseased breast tissue; heart doctors are collaborating with Apple on the MyHeart Counts app and program that they hope will advance cardiovascular research — and get us off the couch; and researchers developed an app that uses Google Glass to help children on the autism spectrum better read facial expressions.

• A San Jose high school student worked with mentors at the Stanford Artificial Intelligence Lab and the School of Medicine to design a software program that measures surgical skills to fine-tune training and provides real-time feedback to surgeons.

• Many physicians have moved past

logy is transforming health care

early frustrations about electronic health records to take full advantage of their ability to enable better collaboration with each other and with patients to improve care. Also, a national symposium on EHRs found physicians brainstorming ways to update health-record technology to enhance clinical decision-making.

• One researcher creates digital interventions for use in our cars, homes and workplaces with the aim of empowering us to champion our own mental well-being. *(A version of this story appears on page 1 of this publication.)*

• A Stanford neuroscientist and his colleagues are building a virtual hippocampus to gain a better understanding of the area of the brain that helps us form and retain memories, and to find better treatments for a host of neurological conditions.

• A surgeon, educator and innovator shares her inspiration for developing sensor-enabled training tools, designed to advance the use of touch in diagnostics, for students and trainees.

This issue also includes an excerpt from the autobiography of transgender neurobiologist Ben Barres, who died last year. In the book, Barres describes the emotional process of transitioning to male in midlife.

In addition, the story of an infant born with an extremely rare genetic disorder at Lucile Packard Children's Hospital Stanford illuminates the difficult decisions doctors and families face when such conditions are diagnosed during pregnancy.

The magazine is available online at http://stanmed.stanford.edu/2018fall.html. Print copies are being sent to subscribers. Others can request a copy at 723-6911 or by sending an email to medmag@stanford.edu. **ISM**

STEVE FISCH

Air Cube touches down at hospital

The first commissioned art piece was recently installed on the garden floor of the new Stanford Hospital. Weighing in at almost 1,000 pounds, Ned Kahn's *Air Cube* was hoisted onto the third floor roof by crane, uncrated and bolted into its final position in the garden.

puts a deep-sea spin on meditation. In this open-ocean VR excursion, you plunge through ocean trenches, tag along with schools of fish and can even find yourself 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," Paredes said. 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.

"We're figuring it out as we go."

Where the humpback comes in

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 their occupants can go to sleep, it'll be a green light for up-close, in-car whale watching.

Chattering 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," he said. That, Paredes said, is why his lab is looking into 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." **ISM**

A version of this article appears in the fall issue of Stanford Medicine *magazine.*

TIMOTHY ARCHIBALD

Postdoctoral scholar Stephanie Balters monitors Paredes as he tests technology from his lab in the driver's seat of a car.

Relieving stress with Sir Laughs-A-Bot

By Hanae Armitage

Pablo Paredes, PhD, an instructor of radiology and of psychiatry and behavioral sciences, 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 time to cultivate 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, and 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.

Behind the wheel, ready for therapy

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. **ISM**

Ultrasound releases drug to alter activity in brain areas of rats

By Bruce Goldman

School of Medicine scientists have developed a noninvasive way of delivering drugs to within a few millimeters of a desired point in the brain.

The method, tested in rats, uses focused ultrasound to jiggle drug molecules loose from nanoparticle "cages" that have been injected into the bloodstream.

In a proof-of-principle study, the researchers showed that pharmacologically active amounts of a fast-acting drug could be released from these cages in small areas of the rats' brains targeted by a beam of focused ultrasound. The drug went to work immediately, reducing neural activity in the targeted area — but only while the ultrasound device was active and only where the ultrasound intensity exceeded a certain threshold. By modifying the strength and duration of the beam, the investigators could fine-tune the neural inhibition.

While the drug used in this study was propofol, an anesthetic commonly used in surgery, in principle the same approach could work for many drugs with widely differing pharmacological actions and psychiatric applications, and even for some chemotherapeutic drugs used to combat cancer.

By turning up the ultrasound intensity and monitoring brainwide metabolic activity, the researchers could also observe the drug's secondary effects on distant downstream brain regions receiving input from the targeted area, said Raag Airan, MD, PhD, an assistant professor of neuroradiology. In this way, the researchers were able to noninvasively map out the connections among disparate circuits in the living brain.

A paper describing the study's findings was published online Nov. 7 in *Neuron*. Airan is the senior author. Lead authorship is shared by Jeffrey Wang, a student in the MD-PhD program, and postdoctoral scholar Muna Aryal, PhD.

A kindred technology known as optogenetics, pioneered by Karl Deisseroth, MD, PhD, a Stanford professor of bioengineering and of psychiatry and behavioral sciences under whom Airan completed his PhD work a decade ago, uses invasive gene delivery to render specified classes of nerve cells vulnerable to precise experimental manipulation. Airan's approach employs noninvasive pharmacological methods to achieve similar control of neural activity.

"This important work establishes that ultrasonic drug uncaging appears to have the required precision to tune the brain's activity via targeted drug application," said Deisseroth, who wasn't involved in the study. "The powerful new technique could be used to test optogenetically inspired ideas, derived initially from rodent studies, in large animals — and perhaps soon in clinical trials."

'We're optimistic'

The new technology could not only speed advances in neuroscientific research but move rapidly into clinical practice, Airan said. "While this study was done in rats, each component of our nanoparticle complex has been approved for at least investigational human use by the Food and Drug Administration, and focused ultrasound is commonly employed in clinical procedures at Stanford," he said. "So, we're optimistic about this procedure's translational potential."

Harmless at the low intensities routinely used for imaging bodily tissues, high-intensity focused ultrasound is approved for the ablation, or deliberate destruction, of certain tissues, including portions of a central brain structure called the thalamus to treat the condition known as essential tremor.

For the new study, "we turned down the dials" on the ultrasound device, Airan said. The intensity of the ultrasound used in these experiments was about 1/10th to 1/100th of the intensity used in clinical ablation procedures. The ultrasound in these experiments was delivered in a series of short staccato pulses separated by periods of rest, giving the targeted brain tissue plenty of time to cool off between pulses. Rats exposed numerous times to the experimental protocol showed no evidence of tissue damage from it.

The nanoparticles, which Airan has been perfecting for several years, are biocompatible, biodegradable, liquid-filled spheres averaging 400 nanometers (about 15-millionths of an inch) in diameter. Their surfaces consist of a copolymer matrix in which the drug of choice is encaged. Roughly 3

See ULTRASOUND, page 7

Himalayas

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changed, and those changes can happen within a human's lifetime," said Aashish Jha, PhD, a postdoctoral scholar at Stanford and lead author of the study.

The findings were published Nov. 15 in *PLoS Biology*.

Past research has identified stark differences between the gut microbiomes of indigenous populations in Africa and South America and those of industrialized Western populations in Europe and the United States. However, this study is the first to show a change in gut microbiome compositions between closely related populations living within the same geographic area.

An evolving gut

Within our intestines lives a community of trillions of bacteria that make up our gut microbiome. These bacterial communities are essential for digesting foods and regulating our immune system. They begin to colonize immediately after birth and develop at an astounding rate once we start to interact with our environment. As we grow, our exposure to breast milk, soft foods and eventually solid fruits, vegetables and meats helps the gut establish a complex microbiome that plays a crucial role in maintaining human health.

AASHISH JHA

A Chepang child and woman in Nepal.

For most of human history, our guts were exposed only to the wild foods available in our environment. Beginning some 1.8 million years ago, during the time of Homo erectus, humans were a nomadic, hunter-gatherer species whose diet consisted of fish and meat, along with seasonal seeds, nuts, roots, vegetables and berries. It wasn't until around 10,000 years ago that we transitioned to farming, radically altering our diets, cooking techniques and way of life.

To examine whether this change in lifestyle affected gut microbiome compositions, the researchers collected stool samples from 56 individuals across the four Himalayan populations and from 10 individuals in a control group of North Americans of European descent. These samples were collected over the span of two months. The researchers also gathered information on individuals' demographics, dietary practices, health status, medications, use of tobacco and alcohol, and several other environmental variables to determine the degree to which the lifestyle variances across the four Himalayan populations correlated to differences in their gut microbiomes.

An analysis of the samples' contents revealed four distinct types of gut microbiome. Even more exciting, these distinctions paralleled the populations' transition from hunter-gatherers to farmers. The researchers found that subdivisions of bacteria, including Ruminobacter and Treponema, that are abundant in foraging groups like the Chepang, decrease as populations depart from the hunter-gatherer lifestyle. In fully industrialized populations, such as those in North America, these bacteria are rare or completely absent. Conversely, strains of other bacterial phyla such as Actinobacteria and Verrucomicrobia are rare or nonexistent in hunter-gatherers but appear as farming and industrialization take hold.

With the Raute and the Raji having transitioned to farming within the past 30 to 40 years, these results also suggest that pronounced changes in human gut microbiomes can occur within decades of a population's departure from a hunter-gatherer lifestyle.

Our microbial identity

A 2017 study in *Science* led by Justin Sonnenburg, PhD, associate professor of microbiology and immunology at Stanford, also showed significant gut microbiome changes in a society of hunter-gatherers called the Hadza. Specifically, the researchers found that the Hadza's gut bacteria were linked to their seasonally varying diet. Together with the current study, these findings "really speak to the power of diet in driving change to the microbiota," said Sonnenburg, senior author of the new paper.

> "We know that we have this microbial identity, and that microbial portion of our biology is malleable."

With the gut microbiome so easily influenced, Sonnenburg wonders what this means for our definition of human biology.

"We have always thought of humans as human DNA and the collection of humans cells that we walk around with," he said. "But now we know that we have this microbial identity, and that microbial portion of our biology is malleable. It can change over really short time periods."

The investigators are still working to uncover which dietary factors and other factors contribute to this transformation. So far, they have strong evidence suggesting a correlation between the villages' drinking water sources and differences in gut bacteria. This information can be valuable for future studies that aim to examine direct environmental influences on gut health.

The next step is to develop a more detailed survey that will pinpoint particular dietary components in each of the four Himalayan populations that are associated with changes in the gut microbiome.

AASHISH JHA

A couple belonging to a settled community of Raute people. Another group of Raute is still nomadic.

Jha feels a sense of urgency to conducting this research. "As the world is urbanizing rapidly, our microbiomes are also changing rapidly," he said. "So, if we don't study the traditional societies today, 20 years down the road we may be too late."

Other Stanford co-authors of the paper are postdoctoral scholars, Katharine Ng, PhD, and Gabriela Fragiadakis, PhD; professor of statistics Susan Holmes, PhD; and professor of biomedical data science and of genetics Carlos Bustamante, PhD.

Researchers from several other institutions are co-authors of the work and are listed in the paper.

Sonnenburg is a member of Stanford Bio-X, a faculty fellow of Stanford ChEM-H and a Chan-Zuckerberg Biohub investigator.

The research was supported by Stanford's Center for Human and Evolutionary Genomics and the National Institutes of Health.

Stanford's departments of Microbiology and Immunology, of Statistics and of Biomedical Data Science also supported the work. **ISM**

Old therapy superior to new one for oropharyngeal cancer

By Krista Conger

A drug increasingly used in combination with radiotherapy to treat a type of cancer that forms in the tonsils or the base of the tongue is inferior to a previously favored option, according to a large, multicenter clinical trial led by School of Medicine researchers that tracked patient survival and disease progression.

Patients randomized to receive the newer drug, cetuximab, had poorer outcomes than those who were randomized to receive the older drug, cisplatin, the trial found. Both drugs were administered in combination with radiotherapy.

The results of the trial, which included nearly 1,000 participants at 182 health care centers across the country, were published online Nov. 14 in *The Lancet*.

The trial was sponsored by the National Cancer Institute and conducted through NRG-Oncology, which is part of the National Clinical Trials Network. Patients from across North America were enrolled by NRG-Oncology researchers.

"Although one prior study suggested that cetuximab may provide survival benefits of similar magnitude as cisplatin when combined with radiation but with fewer long-term side effects, these two regimens have not been compared head to head in such a large study before. The result of our study showed that this is not the case," said Quynh-Thu Le, MD, professor and chair of radiation oncology. "Unfortunately, this means we are back to square one. We have to figure out a better way to reduce toxicity for these patients."

Le, who also holds the Katharine Dexter McCormick and Stanley McCormick Memorial Professorship and chairs the head and neck cancer committee of NRG-Oncology, is the senior author of the study. Maura Gillison, MD, PhD, professor of thoracic/head and neck medical oncology at MD Anderson Cancer Center in Houston, and Andy Trotti, MD, a professor of radiation oncology at Moffitt Cancer Center in Florida, share lead authorship.

HPV-positive cancer

The trial focused on patients with oropharyngeal cancers that are positive for the presence of human papillomavirus, or HPV. It's long been known that infection with specific subtypes of HPV confers an increased risk for cervical, anal and oropharyngeal cancers arising in the soft palate, the base of the tongue and the tonsils. The National Cancer Institute estimates that about 70 percent of oropharyngeal cancers are caused by HPV infection.

Quynh-Thu Le

Fortunately, many of these cancers are highly treatable with radiation and chemotherapy. But because many of these patients are diagnosed at a relatively young age, it is particularly important to minimize any toxic, long-term side effects of their treatment. Although effective in promoting survival, cisplatin can cause potentially lasting adverse effects, including hearing loss and kidney damage. Physicians have increasingly been turning to cetuximab plus radiotherapy after one study suggested cetuximab conferred a survival benefit of similar magnitude as cisplatin when combined with radiation but with fewer side effects.

Le and her colleagues conducted a randomized, prospective multicenter trial to determine whether the drugs were equally effective at treating HPV-positive oropharyngeal cancer. From June 2011 to July 2014, 987 people with the disease were enrolled and randomly assigned to receive either cetuximab or cisplatin, both in combination with radiotherapy. (Some patients were subsequently deemed to be ineligible.)

The researchers found that the estimated five-year overall survival of the 399 patients assigned to receive cetuximab was 77.9 percent, compared with 84.6 percent for the 406 patients who received cisplatin.

Another measure of effectiveness is progression-free survival, or the period of time after treatment during which the cancer does not progress. The researchers estimated that 67.3 percent of the patients in the cetuximab group would achieve five years of progression-free survival, compared with 74.8 percent of those who had received cisplatin.

In addition, the proportions of patients who suffered short-term and long-term toxicity as a result of their treatments were not significantly different between the two groups.

Assumption 'did not pan out'

"Unfortunately, our assumption that cetuximab would be less toxic but confer similar survival advantages did not pan out," Le said. "Cisplatin should still be the standard of care for most of these patients while we investigate other potentially less toxic treatments, such as immunotherapy."

Another Stanford author of the article is Dimitrios Colevas, MD, professor of medicine. Other co-authors are researchers from the University of Michigan, the University of Wisconsin, the Cleveland Clinic Taussig Cancer Institute, the Yale School of Medicine, the Fox Chase Cancer Center, the University of Toronto, the Imaging and Radiation Oncology Core Group, Case Western Reserve University, Ohio State University, the University of Oklahoma, Emory University, the Sutter Cancer Research Consortium, the James Graham Brown Cancer Center, Kaiser Permanente, the University of Alabama-Birmingham and the University of Chicago. **ISM**

Ultrasound

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million molecules of a drug typically dot the surface of one of these nanoparticles.

Each nanoparticle encloses a droplet of a substance called perfluorocarbon. Buffeted by ultrasound waves at the right frequency, these liquid cores begin shaking and expanding until the copolymer matrix coating the surface ruptures, setting the trapped drug molecules free. Propofol, like all psychoactive drugs, easily diffuses through the otherwise formidable blood-brain barrier. But having crossed this barrier, the drug is quickly soaked up by brain tissue, so that it never gets farther than about a half-millimeter from the capillary where it's been released.

Airan and his colleagues injected these particles intravenously into rats and explored focused ultrasound's potential for targeted drug delivery.

Initially, they measured nerve cells' activity in the visual cortex, an area in the back of the brain that's activated by

STEVE FISCH

Raag Airan and his colleagues used focused ultrasound to pry molecules of an anesthetic loose from nanoparticles in rats' brains.

visual stimuli, in response to flashes of light aimed at the rats' eyes. Focusing the ultrasound beam on that brain area, they watched electrical activity there plunge while the beam was being transmitted, then recover within about 10 seconds after the device was shut off. This drop-off in the visual cortex's electrical activity, which is what you'd expect from the release of an anesthetic there, grew more pronounced with increasing ultrasound intensity, and didn't occur at all when the rats had been injected instead with drug-free nanoparticles.

In contrast, activity in the motor cortex, a brain area not involved in vision, in response to light flashes directed at the rats' eyes was not diminished when ultrasound was applied there. But ultrasound targeting the lateral geniculate nucleus, a brain area that relays visual information to the visual cortex, did reduce electrical activity in the visual cortex. This showed that propofol release in one brain structure can produce secondary effects in another, distant region receiving inputs from that structure.

Brainwide metabolic response

Next, Airan's team monitored the brainwide metabolic response to focused ultrasound by using positron emission tomography to measure brainwide uptake of a radioactive analog of glucose — glucose is the brain's chief energy source — in the rats. When the injected nanoparticles were blanks, there was no effect in ultrasound-exposed areas. But with propofol-loaded nanoparticles, the metabolism dropped, meaning there was reduced neural activity in these ultrasound-exposed regions. This inhibition increased with increasing ultrasound intensity. Cranking the ultrasound level high enough also triggered selectively diminished activity in distant brain regions known to receive inputs from the ultrasound-exposed area.

"We hope to use this technology to noninvasively predict the results of excising or inactivating a particular small volume of brain tissue in patients slated for neurosurgery," Airan said. "Will inactivating or removing that small piece of tissue achieve the desired effect — for example, stopping epileptic seizure activity? Will it cause any unexpected side effects?"

Other study co-authors are postdoctoral scholar Qian Zhong, PhD, and medical student Daivik Vyas. **ISM**

Appendicitis

continued from page 1

the National Institutes of Health, and is most common before the age of 30.

While appendectomy, the surgery to remove the appendix, has long been the standard treatment, some physicians have begun offering drug therapy as an alternative, primarily to patients who are poor candidates for surgery, following the publication of several European studies showing positive outcomes.

"More and more patients in the Stanford emergency room have been asking about whether they can just take antibiotics when they come in with appendicitis instead of having surgery," Sceats said. This study was designed, in part, to help answer that question.

Analyzing claims data

To conduct the study, researchers used claims data from a private insurance database to compare patients admitted with appendicitis from 2008 through 2014. Of the 58,329 patients with appendicitis, 55,790, or 95.5 percent, underwent appendectomy. The remaining or 4.5 percent were treated with drug therapy alone.

Results showed that, surprisingly, overall costs were 5.5 percent higher for patients who didn't have the surgery. The average cost of care was $14,932 for these patients. For patients who underwent the surgery, the average cost of care was $14,186.

"Even if the initial hospitalization is cheaper, when you look at long-term cost, which our study did, it ends up being more expensive," Sceats said. The study collected medical care data for patients after treatment for up to an average of three years.

"People treated with antibiotics are more likely to come back and be hospitalized for any sort of belly pain," Sceats said. "Doctors may also be more cautious when the appendix isn't removed. This extra caution can be expensive."

The study also found slightly higher rates of abdominal abscess post-treatment for those who didn't have surgery.

The study did show that the recurrence rate of appendicitis is only 3.9 percent among those treated with antibiotics alone and pointed out that surgery comes with its own risks of postoperative complications, but the authors concluded that overall results suggest appendectomy should remain the first-line treatment for most people with appendicitis

"These results tell us that, in most cases, surgery is still the best strategy," Sceats said. "For your average, healthy 30-year-old, the alternative treatment is no cheaper, and it's easier to have the surgery. You also no longer have an appendix, so you're no longer at risk of having appendicitis again."

Other authors included biostatician Amber Trickey, PhD; Arden Morris, MD, professor of surgery; and Cindy Kin, MD, assistant professor of surgery.

The study was funded by the National Institutes of Health.

Stanford's Department of Surgery also supported the work. **ISM**

Four faculty members appointed to endowed professorships

ANDRA BLOMKALNS, MD, professor and chair of emergency medicine, was appointed the Stanford Medicine Professor in Emergency Medicine, effective Oct. 8. Her academic work has focused on clinical innovation, and evaluating and improving the process for technology development and commercialization within medicine. She also has studied cardiovascular emergencies, obesity and dietary influences on health and disease.

Andra Blomkalns

The professorship was established in June using funds from the Department of Emergency Medicine, the School of Medicine Dean's Office and Stanford Health Care.

GERALD GRANT, MD, professor of neurosurgery, was appointed the Endowed Professor in Pediatric Neurosurgery, effective Oct. 16. He specializes in brain tumor and epilepsy surgery in children, and his laboratory is working to improve the delivery of drugs past the blood-brain barrier to reach brain tumors in children.

Gerald Grant

The professorship was established in 2015 to support a faculty member in pediatric neurosurgery. Funders include Jeffrey Chambers and Andrea Okamura; Roelof Botha and Huifen Chan; and the Schow Foundation.

DAVID KINGSLEY, PhD, professor of developmental biology, was appointed the Rudy J. and Daphne Donohue Munzer Professor in the School of Medicine, effective Oct. 16. His research examines the molecular mechanisms that underlie evolutionary traits and common diseases in vertebrates.

David Kingsley

The professorship was established in 1990. Rudy Munzer was the president and chairman of Petrolane, and Daphne Munzer volunteered with numerous Southern California organizations, including the Children's Dental Health Clinic and the Long Beach Public Library.

CRYSTAL MACKALL, MD, professor of pediatrics and of medicine, was appointed the Ernest and Amelia Gallo Family Professor, effective Oct. 16. She is the founding director of the Stanford Center for Cancer Cell Therapy and directs the Parker Institute for Cancer Immunotherapy at Stanford. Her research focuses on enhancing the effectiveness of T cell-based cancer immunotherapies.

Crystal Mackall

The professorship was established in October with a gift from the Ernest Gallo Foundation in honor of Ernest and Amelia Gallo, as well as matching funds from an anonymous donor. Ernest Gallo co-founded E&J Gallo Winery in 1933. **ISM**

OF NOTE

reports on significant honors and awards for faculty, staff and students

Thomas Anderson

Fred Baik

Jan Carette

Timothy Cornell

Vasu Davi

Lisa Giocomo

Natalie Gomez-Ospina

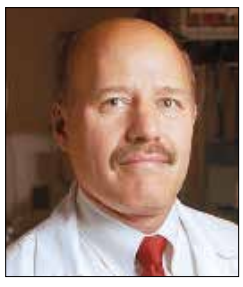
Harry Greenberg

Claire Gustafson

Sean Miller

Joel Neal

Tait Shanafelt



Ronald Pearl

Matthew Porteus

David K. Stevenson

THOMAS ANDERSON, MD, PhD, clinical associate professor of anesthesiology, perioperative and pain medicine, received a mentored research training grant from the Foundation for Anesthesia Education and Research. With this two-year, $250,000 grant, he plans to study the modulation of acute and chronic pain using focused ultrasound on the peripheral nervous system.

FRED BAIK, MD, was appointed assistant professor of otolaryngology-head and neck surgery, effective Sept. 16. He specializes in surgical care for patients with head and neck cancer, particularly squamous cell carcinoma and melanoma. His research interests are focused on advancing tumor imaging to aid in preoperative and intraoperative decision-making.

JAN CARETTE, PhD, was promoted to associate professor of microbiology and immunology, effective Oct. 1. His research uses genetic approaches to understand the molecular mechanisms of virus-host interactions, ranging from pathogenic viruses to viruses used in gene therapy.

TIMOTHY CORNELL, MD, was appointed professor of pediatrics, effective Sept. 1. His research interests include exploring the role of epigenetics in the regulation of inflammation, developing precision health techniques for treating critically ill children, and examining the role of molecular biomarkers in pediatric systemic inflammatory response and sepsis.

VASU DIVI, MD, was promoted to associate professor of otolaryngology-head and neck surgery, effective Oct. 1. As a cancer and reconstructive surgeon, his clinical focus is on treating high-risk and advanced skin cancers, oral cavity cancers and osteoradionecrosis of the head and neck. He specializes in using 3-D modeling to customize reconstruction of the jaw following surgery.

LISA GIOCOMO, PhD, assistant professor of neurobiology, received a Young Investigator Award from the Society of Neuroscience. The $15,000 award recognizes outstanding achievements and contributions by a young neuroscientist who has demonstrated scholarly independence. Her research focuses on the cellular and molecular mechanisms underlying the organization of cortical circuits important for spatial navigation and memory.

NATALIA GOMEZ-OSPINA, MD, PhD, was appointed assistant professor of pediatrics, effective Sept. 1. Her research focuses on diagnosing and managing genetic diseases, including improving therapies for children diagnosed with lysosomal storage disorders and developing point-of-care testing for children and families who have metabolic disorders with hyperammonemia.

HARRY GREENBERG, MD, the Joseph D. Grant Professor in the School of Medicine and professor of medicine and of microbiology and immunology, was elected to give the 2018 Jean Cohen Lecture at the 13th International Double Stranded RNA Virus Symposium in Houffalize, Belgium, in September. His talk was titled "The generation and function of innate and acquired immunity to rotavirus infection in vitro and in vivo."

CLAIRE GUSTAFSON, PhD, a postdoctoral scholar in immunology and rheumatology, was awarded a 2018 Irene Diamond Fund/AFAR Postdoctoral Transition Award in Aging from the American Federation for Aging Research. The two-year, $120,000 award will support her work to study T follicular helper cells in mucosal immune aging.

SEAN MILLER, PhD, postdoctoral scholar in neurology and neurological sciences, was awarded a 2018 Glenn Foundation for Medical Research Postdoctoral Fellowship in Aging Research from the American Federation for Aging Research and the Glenn Foundation for Medical Research. The one-year, $60,000 award will support his work to study the effects of the protein Norrin on the blood-brain barrier.

JOEL NEAL, MD, PhD, assistant professor of medicine, and **TAIT SHANAFELT**, MD, the Jeanie and Stew Ritchie Professor, professor of medicine and director of the WellMD Center, have received young investigator awards from the ECOG-ACRIN Cancer Research Group for 2018 and 2017, respectively. The award recognizes extraordinary scientific achievements and research leadership in the field of oncology by investigators younger than 46.

RONALD PEARL, MD, PhD, the Richard K. and Erika N. Richards Professor and professor and chair of anesthesiology, perioperative and pain medicine, was elected president-elect of both the Society of Academic Associations of Anesthesiology and Perioperative Medicine and the Association of Academic Anesthesia Chairs. This is a two-year term, after which he will become president for a two-year term in 2020.

MATTHEW PORTEUS, MD, PhD, was promoted to professor of pediatrics, effective Oct. 1. His research interests include using genome editing to better understand diseases that affect children, and developing genome editing by homologous recombination as curative therapy for children with genetic diseases.

DAVID K. STEVENSON, MD, Harold K. Faber Professor in Pediatrics and senior associate dean for maternal and child health, has been named the 2019 recipient of the John Howland Award, the top award given by the American Pediatric Society. The award honors Stevenson's contributions as a longtime leader, clinician and mentor in neonatology and pediatrics. He has co-authored more than 600 articles, and his research on the biology of neonatal jaundice has led to new technologies and standards of care for jaundice treatment. **ISM**