The engineer who wants to drive us sane

By Hanae Armitage

Pablo Paredes sat in a psychologist’s office. He watched a family member, Alex (a pseudonym), scrutinize 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 felt uneasy. The strategy, however, is not always effective. Alex’s anxiety subsided.

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 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.

“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.

“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.”

The mechanics of well-being

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

By Tracie White

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

“People treated with antibiotics alone need further treatment for appendicitis-related problems, such as abdominal abscesses,” said Lindsay Scents, MD, a surgical resident and lead author of the study. “They also have a higher risk of having a recurrence, 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 the 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 the National Institute of Health.

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.

All four populations — the Tharu, the Raute, the Raji and the Chepang — are longterm 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. "This study indicates that human microbiomes may have changed gradually as human lifestyle and dietary lifestyles of four Himalayan populations.

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

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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, Shoijyo 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 dwindle

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 decay.

"We gave Ikkei occasional blood transfusions to keep his energy levels up, but he was going through what we call 'the dwindle,' 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 got it," 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. Shoijyo said the hospital staff worked to help ease the family's fears.

"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," Shoijyo 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."

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.

"We moved from Japan, and Ikkei received treatment in the United States, so he thinks he was saved by the United States," Shoijyo said. "He really likes America. He has 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.

"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.

"As long as we have him, I want to do anything to keep him healthy. We want to do what's best for him," Natsuko said. "We are just happy to have him back."

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

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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.”

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.

The team’s algorithm is a testament 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.”

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Send letters, comments and story ideas to John Sanford at 723-8390 or at jsanford@stanford.edu. Please also contact him to receive an e-mail version of Inside 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 dopami-
nergic, nerve cells in the brain involved in physical movement.

The pathogenic variants of the gene, LRRK2, share a common tendency: They cause the protein it encodes to run in con-
tact with the dopaminergic cells implicated in Parkinson’s? Pfeffer’s lab is now hard at work studying that task.

Suzanne Pfeffer, PhD, professor of biochemistry and the Emma Pfeiffer Merner Professor in Medical Sci-
ences, is the senior author of the study, which was pub-
lished Nov. 6 in Cell. The lead authors are postdoctoral scholars Herschel Dheke, PhD, and Izumi Yanaroti, PhD.

Randomness of Parkinson’s disease

Most cases of Parkinson’s are sporadic, meaning the cause of the disease appears to be 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 to-
gether, these LRRK2 mutations have been implicated in about 6 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 ab-
sence 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 analogy to a radio receiving tower, except that instead of sucking in waves of electromag-
netic radiation, the primary cilium shunts up signaling substances from its surrounding environment.

It’s easy to imagine how a cell lacking such a receiv-
ing 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 neurodegenera-
tive disorders.

A complicated molecular explanation

In the new study, the researchers unraveled a compli-
cated molecular explanation: First, cells lacking primary cilia are unable to respond to a powerful chemical mes-

denger known as sonic hedgehog. Second, the scientists learned, the types of cells that can’t make a decent pri-
mary cilium when their LRRK2 protein is in overdrive include a set of cholinergic nerve cells, so named be-
cause they secrete acetylcholine rather than dopamine or other substances that signal nerve cells.

These cholinergic cells have a close working relation-
ship with the dopaminergic cells implicated in Parkin-
son’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 be-
come more vulnerable to dying.

So an LRRK2 protein in overdrive leads to no pri-
mary 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 un-
derlie the unrelenting loss of dopaminergic cells in Par-
kinson’s mellitus 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 Bio-
chemistry 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 sup-
ported the work.

DeepTag

DeepTag continued from page 2

dated the algorithm’s accuracy by testing it on pet clinical data collected from pri-

care veterinarians.

Broadly speaking, DeepTag would allow veterinarians to track the preva-

dence 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 biol-

gy of small rodents can be quite differ-
ent 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 treat-
ment passed the “rodent stage.”

A win-win for both humans and their pets.

“Dogs, which were the majority of pa-
tients that we documented using Deep-
Tag, are very good candidates for many of the drugs scientists develop for hu-

mans,” Zou said. “And there’s a growing interest in pharmacology and biotech-
nology 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 sanc-
tioned 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.

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 bio-

medical 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.

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

Preeclampsia affects 5 to 10 percent of all preg-
nancies — 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 abnor-
mal 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 af-

ter 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 atheroscle-
rosis, the buildup of plaque in and on artery walls, in women as they grow older.

“The goal of this study is to improve cardiovas-
cular health in women, by learning how pregnancy affects heart disease later in life,” said Hlatky, a Stan-
ford Health Policy fellow and professor of medicine and of health policy, who says an as-

hedging new light on these links can lead to better prevention and treatment.

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.

Pregnancy’s toll can be significant, and claims the lives of 76,000 mothers and a half-
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Pregnancy’s toll can be significant, and
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 sync with the voice of the 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

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 fartying 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 nervous-wracking worry. “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 pattern 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 seat-back on the driver’s side to create vibrational patterns. In the breathing exercise, one buzzes inhalations; another, exhalations. 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

Stanford Medicine magazine reports on the ways digital technologies permeate our lives. Smartphones that operate like laptops to fine-tune training and provide real-time feedback to surgeons.

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 personal.

Several stories in the issue explore ways clinicians are using high-tech tools to improve care. For example, most 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, diagnosis 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: an Emergency Room physician uses tablet computers to do a breathing test to slow down people who are having a heart attack, and a software program that measures surgical skills to fine-tune training and provides real-time feedback to surgeons.

• Many physicians have moved past...
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. “But, the brain these more traditional apps, people benefit only insofar as they are able to focus on one thing without losing concentration or getting bored.

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 conduc-
tance), 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 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 stray from conventional self-reporting.

“We’re not the first to use lights to sway mood or change touch or perception, 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 engi-

neer the charbots to support mental health based on data and scientific evidence.

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

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 charbots, 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 men-
tal well-being.

I had a chance to demo the various technologies in-
stalled in Paredes’ well-being mobile, as I fondly dubbed it, one of which had me charting with a suite of kindly ro-

bots. 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 clear out the stress of the root.

When I arrived at Paredes’ lab for the charbot demo, Hiroshi Mendoza, the lead graduate student on the proj-

ect, gave me the rundown. “You’ll take the car and drive it around campus. When you leave, the charbot will talk to you,” he said. “And you’ll talk back.

Easy enough. Buckled in and ready to divulge my big-
gest stress 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 condi-
tioning 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 situ-

ation 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 be-
ing so sweaty and smelly I’d forget the temperature out-
side. 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 some-
thing good or at least funny about the situation?”

I admit, I giggled, too. “When the robot gave me a piny laugh. And maybe it didn’t solve the problem, but it did make me chuckle and think about the situation differ-
ently, which Paredes said is half the battle in dealing with stress.”

Technology 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 sympo-

sium on EHRs found physicians brain-

storming ways to update health-record technology to enhance clinical decision-

making.

• One researcher creates digital in-

terventions for use in our cars, homes and workplaces with the aim of empower-
eting patients to change our own mental well-being. (A version of this story appears in page 3 of this publication.)

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

• A surgeon, educator and innova-
tor 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 dis-

order at Lucile Packard Children’s Hos-

pital Stanford illuminates the difficult decisions doctors and families face when such conditions are diagnosed during pregnancy.

The magazine is available online at http://mag.stanford.edu/201811.

Print copies are being sent to subscribers. Others can request a copy at 723-6911 or by sending an email to medmag@stanford.edu.
Ultrasound releases drug to alter activity in brain areas of rats

By Bruce Goldman

School of Medicine scientists have developed a non-invasive way of delivering drugs to within a few micrometers 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 when the ultrasound intensity exceeded a certain threshold. By modifying the strength and duration of the beam, the investigators were able to noninvasively map out the connections among disparate circuits in the living brain.

A paper describing the study’s findings was published Nov. 7 in Neuron. A senior author is Airan, a student in the MD-PhD program, and postdoctoral scholar Mana 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 alter behavior using light. Airan is currently developing similar noninvasive pharmacological methods to achieve similar control of neural activity.

In the new work, the researchers implanted ultrasound devices into the brains of rats, each component of their nanoparticle complex has a specific function and works together to treat the condition known as essential tremor.

For the new study, “we turned down the dial” on the ultrasound device, Airan said. “We exposed the rats to a series of ultrasound exposures that alternated 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 1/50 of a millionth of an inch) in diameter. Their surfaces consist of a copolymer matrix in which the drug of choice is encaged. Roughly 3

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

Himalaya

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changed, and those changes can happen within a human 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 astonishing rate once we start to interact with our environment. As we grow, our exposure to breast milk, solid foods and eventually solid fruits, vegetables and meats helps the gut establish a complex microbiome that plays a crucial role in maintaining human health.

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 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 different 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 Bacteroides 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 becomes more widespread.

With the Raute and the Raji having transitioned to farming within the past 30 to 40 years, these results also suggest that pronunciation 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 and the institute’s director of the Human Microbiome Project, found that 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 seasonal diet. Together with the current study, these findings “realistically 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,” Sonnenburg said.

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 somatic cell-induced tissue. We have 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 the factors that contribute to this transformation. So far, they have strong evidence suggesting a correlation between the villagers’ 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. 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 ultrasound engineer Amr Elsayed, PhD; Asiri Al-Tamimi, PhD, a research scientist at the Advanced Imaging and Diagnostics Laboratory; Torcilla Ng, PhD; and Gabriela Fragadis-Kish, PhD, professor of statistics Susan Holmes, PhD, 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.
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 too often a previously favored option, according to a large, multicenter clinical trial led by School of Medicine researchers that tracked patients for a median of 5 years after treatment.

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 from 182 health care centers across the country, were published online Nov. 14 in The Lancet. The trial was sponsored by the National Cancer Institute, through a mechanism known as 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 that showed 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 and improve outcomes.”

Le, who also leads the Karthein 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 Cullison, 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 tissues at 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. Fortunately, many of these cancers are highly treatable with radiation and chemotherapy. But because many of these patients are 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 similar to that of 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 77.4 percent, compared with 86.6 percent for the 406 patients who received cisplatin.

More evidence of progression-free survival, or the period of time after treatment during which the cancer does not progress. The researchers estimated that 67.9 percent of the patients in the cetuximab group and 78.4 percent of those in the cisplatin group had no evidence of disease for 3 years or more. This is compared with 42.1 percent of the patients in the cetuximab group and 58.9 percent of those in the cisplatin group who had no evidence of disease for 2 years or more.

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 Dimitriou 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 University of Washington, and the Case Western Reserve University, Ohio State University, the University of Oklahoma, Emory University, the Surrey Cancer Research Consortium, the James Graham Brown Cancer Center at the University of Louisville, the University of Alabama-Birmingham and the University of Chicago.

Ultrasound

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million molecules of a drug typically dot the surface of one of these nanoparticles. Each nanoparticle shows a droplet of a substance called perfluorocarbon. Buffered by ultrasound waves at the right frequency, these liquid cores begin shaking and expanding until the copolymer matrix coating the surface ruptures, setting the true free drug molecules free.

Propofol, like all psychoactive drugs, easily diffuses through the otherwise formidable blood-brain barrier. But having crossed this border, the drug is quickly soaked up by brain tissue, so that it is almost immediately neutralized. But ultrasound targeting of a targeted drug delivery.

Researchers led by Airan and his colleagues injected these particles intravenously into rats and explored focused ultrasound’s potential for drug-free nanoparticles. Brainwide metabolic response

As a new type of targeted drug delivery, ultrasound offers the potential to “turn on” or “turn off” a specific brain region to change neural activity in real time. In recent years, the technique has been used to activate or remove that small piece of brain that is causing a seizure disorder.

In the new study, researchers at Stanford and the University of Alabama-Birmingham collaborated to use ultrasound to focus brainwide metabolic changes in rats to study responses to a targeted drug delivery device.

According to the researchers, there are two primary advantages of ultrasound compared with more traditional pain medication, such as calcium channel blockers, for the treatment of chronic pain.

Appendicitis

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

While appendicitis, 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. The average cost of care was $14,932 for these patients.

Old therapy superior to new one for oropharyngeal cancer

By Krista Conger

After many patients in the Stanford emergency room have been asking whether they can just take antibiotics when they come into the emergency room instead of having surgery, Seacat 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 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,” Seacat 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,” Seacat said. “Doctors may also be more cautious about having appendicitis instead of having surgery,” Sceats said. This study was designed, in part, to help answer that question.

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People treated with antibiotics are more likely to come back and be hospitalized for any sort of belly pain,” Seacat said. “Doctors may also be more cautious about having surgery.”

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.

“This tells us that, in most cases, surgery is still the best strategy,” Seacat 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 it burst or become infected.”

Other authors included biostatistician 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.
Four faculty members appointed to endowed professorships

ANDREA BLOMKALNS, MD, professor and chair of emergency medicine, was appointed the Stanford Medicine Professor in Emergency Medicine, effective Oct. 16. 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 federal emergency, obesity and dietary influences on health and disease.

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.

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

NATALIA GOMEZ-OSPINA, MD, PhD, was appointed assistant professor of pediatrics, effective Sept. 1. Her research interests include exploring the role of epigenetics in the regulation of inflammation, developing precision health techniques for treating sepsis.

VENUS DOU, MD, was promoted to associate professor of otorhinolaryngology-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, PhD, 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 pedi atric inflammatory responses and sepsis.

FRED BAIK, MD, was appointed assistant professor of otorhinolaryngology-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.

DAVID KINGSLLEY, PhD, professor of developmental biology, was appointed the Rudy J. and Daphne Domohue Munner Professor in the School of Medicine, effective Nov. 1. His research examines the molecular mechanisms that underlie evolutionary traits and common diseases in vertebrates.

The professorship was established in 1990. Rudy Munner was the president and chairman of Petro lane, and Daphne Munner 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 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.

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.

OF NOTE

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

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 otorhinolaryngology-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.

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VENUS DOU, MD, was promoted to associate professor of otorhinolaryngology-head and neck surgery, effective Oct. 1. As a cancer and reconstructive surgeon, his clinical focus is on treating tumors Oct. 16. A cancer and reconstructive surgeon, his clinical focus is on treating tumors.

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 Joan 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.”

RICKY JUASTAFSON, PhD, a postdoctoral scholar in immunology and rheumatology, was awarded a 2018 Irene Diamond Fund/AFAF 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 SHANAFAELT, MD, the Jeanie and Stew Ritchie Professor, professor of medicine and director of the WeilMed 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 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 the Association of Academic Anesthesiology 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. He is also 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 long-time 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.