INSIDE STANFORD MEDICINE

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Martha Bachmann, 100, has volunteered for more than half a century at Stanford Hospital.

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Advances made in brain-controlled typing

By Bruce Goldman

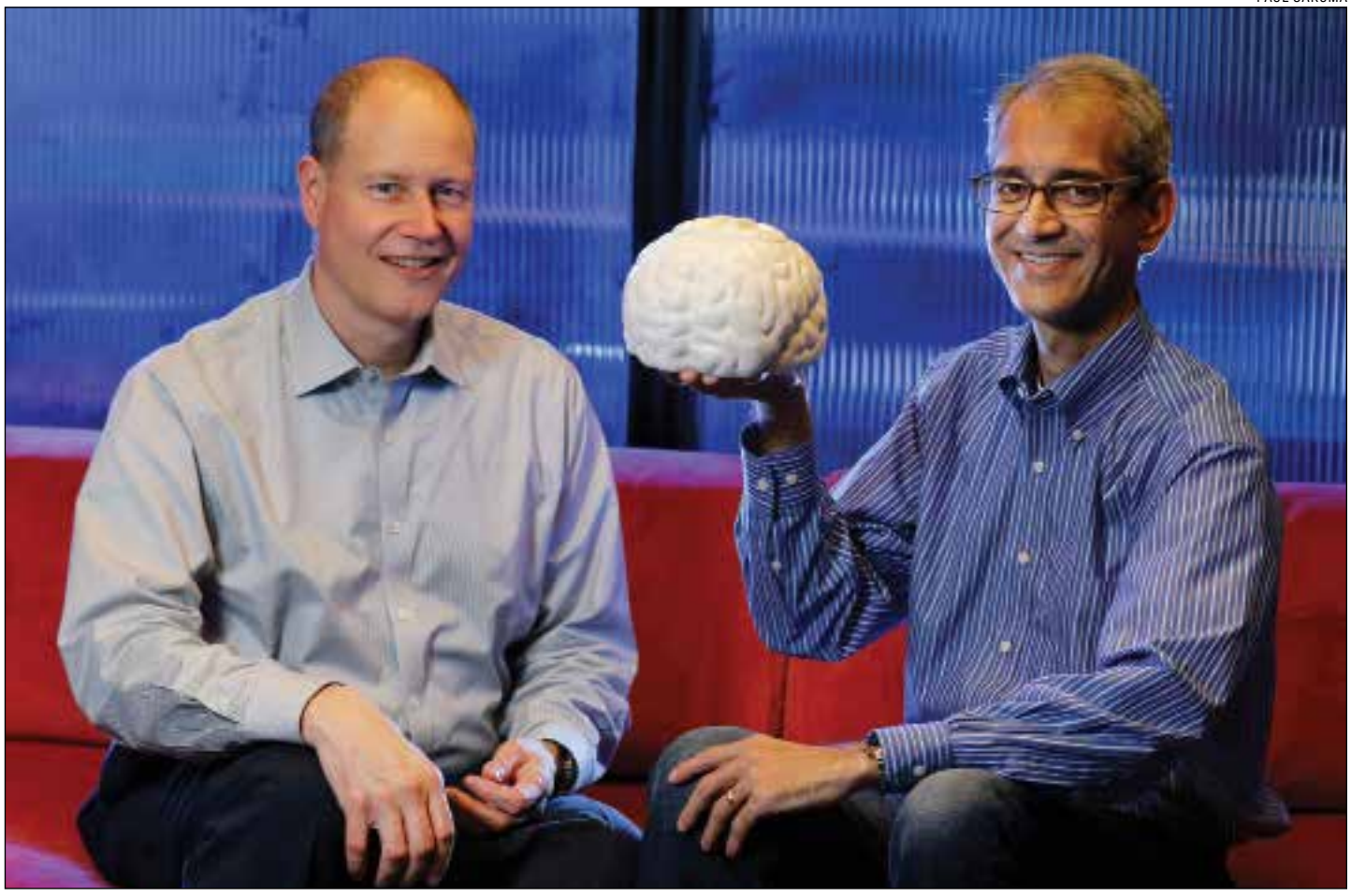
A clinical research paper led by Stanford investigators has demonstrated that a brain-to-computer hookup can enable people with paralysis to type via direct brain control at the highest speeds and accuracy levels reported to date.

The report involved three study participants with severe limb weakness — two from amyotrophic lateral sclerosis, also called Lou Gehrig's disease, and one from a spinal cord injury. They each had one or two baby-aspirin-sized electrode arrays placed in their brains to record signals from the motor cortex, a region controlling muscle movement. These signals were transmitted to a computer via a cable and translated by algorithms into point-and-click commands guiding a cursor to characters on an onscreen keyboard.

Each participant, after minimal training, mastered the technique sufficiently to outperform the results of any previous test of brain-computer interfaces, or BCIs, for enhancing communication by people with similarly impaired movement. Notably, the study participants achieved these typing rates without the use of automatic word-completion assistance common in electronic keyboarding applications nowadays, which likely would have boosted their performance.

One participant, Dennis Degray of Menlo Park, California, was able to type 39 correct characters per minute, equivalent to about eight words per minute.

PAUL SAKUMA



Neurosurgeon Jaimie Henderson and electrical engineer Krishna Shenoy are members of a consortium working on an investigational brain-to-computer hookup.

'A major milestone'

This point-and-click approach could be applied to a variety of computing devices, including smartphones and tablets, without substantial modifications, the Stanford researchers said.

"Our study's success marks a major milestone on the road to improving quality of life for people with paralysis," said Jaimie Henderson, MD, professor of neurosurgery, who performed two of the three device-implantation procedures. The third took place at Massachusetts General Hospital.

Henderson and Krishna Shenoy, PhD, professor of electrical engineering, are co-senior authors of the paper, which was published online Feb. 21 in *eLife*. The lead authors are former postdoctoral scholar Chethan Pandarinath, PhD, and postdoctoral scholar Paul Nuyujukian, MD, PhD, both of whom spent well over two years working full time on the project at Stanford.

"This study reports the highest speed and accuracy, by a factor of three, over what's been shown before," said Shenoy, a Howard Hughes Medical Institute investigator who's been pursuing BCI development for 15 years and working with Henderson since 2009. "We're approaching the speed at which you can type text on your cellphone."

"The performance is really exciting," said Pandarinath, who now has a joint appointment at Emory University and the Georgia See BRAIN CONTROL, page 6

Test developed to rank how toxic chemotherapy drugs are to the heart

By Krista Conger

Researchers at the School of Medicine used heart muscle cells made from stem cells to rank commonly used chemotherapy drugs based on their likelihood of causing lasting heart damage in patients.

Drugs known as tyrosine kinase inhibitors can be an effective treatment for many types of cancers, but they also have severe and sometimes fatal side effects. Using lab-grown heart cells, Stanford researchers were able to assess the drugs' various effects on heart muscle cells, including whether the cells survived, were able to beat rhythmically and effectively, responded appropriately to electrophysiological signals and communicated with one another.

The researchers found that their assay can accurately identify those tyrosine kinase inhibitors already known to be the most dangerous in patients. In the future, they believe their system may prove useful in the early stages of drug development to screen new compounds for cardiotoxicity.

"This type of study represents a critical step forward from the usual process running from initial drug discovery and clinical trials in human patients," said Joseph Wu, MD, PhD, director of the Stanford Cardiovascular Institute and a professor of cardiovascular medicine and of radiology. "It will help See CARDIOTOXICITY, page 4

Pancreatic islet cells can change character to produce insulin, researchers discover

By Krista Conger

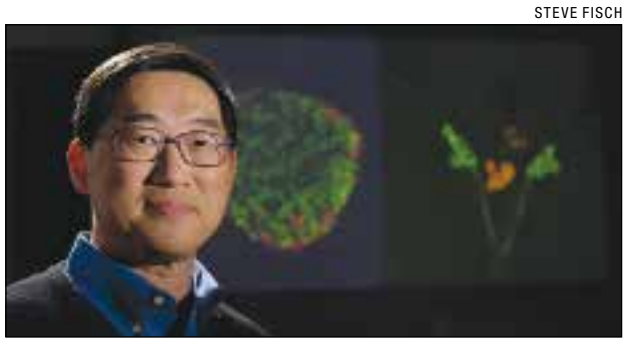
Alpha cells in the pancreas can be induced in living mice to quickly and efficiently become insulin-producing beta cells when the expression of just two genes is blocked, according to a study led by researchers at the School of Medicine.

Studies of human pancreases from diabetic cadaver donors suggest that the alpha cells' "career change" also occurs naturally in diabetic humans, but on a much smaller and slower scale. The research suggests that scientists may one day be able to take advantage of this natural flexibility in cell fate to coax alpha cells to convert to beta cells in humans to alleviate the symptoms of diabetes.

"It is important to carefully evaluate any and all potential sources of new beta cells for people with diabetes," said Seung Kim, MD, PhD, professor of developmental biology and of medicine. "Now we've discovered what keeps an alpha cell as an alpha cell, and found a way to efficiently convert them in living animals into cells that are nearly indistinguishable from beta cells. It's very exciting."

Kim is the senior author of the study, which was published online Feb. 16 in *Cell Metabolism*. Postdoctoral scholar Harini Chakravarthy, PhD, is the lead author.

STEVE FISCH



Seung Kim and his team were able to convert alpha cells from the pancreas into insulin-producing beta cells in mice. The findings may hold clues to developing treatments for diabetes.

Food's effect on glucose levels

Cells in the pancreas called beta cells and alpha cells are responsible for modulating the body's response to the rise and fall of blood glucose levels after a meal. When glucose levels rise, beta cells release insulin to cue cells throughout the body to squirrel away the sugar for later use. When levels fall, alpha cells release glucagon to stimulate the release of stored glucose.

Although both Type 1 and Type 2 diabetes are primarily linked to reductions in the number of insulin-producing beta cells, there are signs that alpha cells may also be dysfunctional See ISLET CELLS, page 7

Simple test may predict which children develop severe TB

By Ruthann Richter

A simple blood test commonly used in screening adults for tuberculosis could predict whether children infected with the TB bacteria are likely to progress to the active disease, according to a study by researchers at the School of Medicine and five other institutions.

In an analysis of medical data from more than 2,500 South African babies, infectious disease specialist Jason Andrews, MD, and his colleagues found that a test, known as the QuantiFERON-TB assay, was a valuable predictor of which infants carrying the bacteria would become sick. The test could be particularly useful in high-risk countries like South Africa, where hundreds of thousands of young children die of the disease every year and where screening tests for TB in children are ineffective, Andrews said.

"It could be highly valuable in determining which kids will develop TB disease," said Andrews, an assistant professor of medicine who is lead author of the study.

Andrews said he hopes the study will prompt changes in World Health Organization guidelines, which currently don't recommend use of the test in children.

"Given the high rates of TB and the difficulty of diagnosing it in kids, this can be something that could be done routinely in kids to identify the high-risk ones," he said. "You could imagine in a high-burden country that at a child's 12-month visit, they could also get a QuantiFERON test and, if it's high, they'd get aggressively investigated for TB."

Jason Andrews

The test is a type of interferon-gamma release assay, or IGRA, commonly used for TB screening, both here and abroad, as it is more accurate than the older skin test.

"These new findings confirm that the IGRA test for tuberculosis infection performs differently in young children compared with adults," said Mark Hatherill, MD, senior author of the study and senior clinical researcher at the South African Tuberculosis Vaccine Initiative. "More importantly, we now know that the IGRA test can be used to identify those children who are at highest risk of developing tuberculosis disease and who would benefit most from investigation and therapy."

The study was published online Feb. 10 in *Lancet Respiratory Medicine*.

Potentially fatal lung disease

TB is a potentially fatal lung disease caused by a bacterium that is airborne and readily transmitted by coughing. In 2015, it caused 1.8 million deaths worldwide and is one of the top 10 killers around the globe, according to the WHO. In South Africa, it is the leading cause of death among both adults and children, accounting for some 8.5 percent of the nation's fatalities, said Andrews, who has been studying the disease there for a decade.

He said young children are particularly vulnerable to TB, with up to 20 percent of those infected by the bacteria developing the active disease. While adults are commonly screened in South Africa using sputum testing, this method doesn't work in children, as they typically swallow their sputum after coughing, he said. And though children may be screened if their parents become ill, they also can become infected through contact with other infected individuals on buses, in churches, schools or other public places, he said.

So there is no effective screening tool for children, who often show up in clinics in a late stage of the disease, when it is more difficult to treat, he said.

"We really need a reliable screening test for children. It's so frustrating to see how little progress we've made," Andrews said.

Analyzing data from trial

In the hope of finding a viable testing method, Andrews and his colleagues analyzed data from a published trial of a potential TB vaccine that had raised high hopes but proved to be a disappointment. The trial was done by the South African Tuberculosis Vaccine Initiative between 2009 and 2012 in a rural area outside Cape Town, a city of 3 million people where about 30,000 TB cases are reported every year.

The trial included 2,512 babies who were all healthy and HIV-negative, with no known exposure to the disease. Half of them received the experimental vaccine, and half received a placebo.

The researchers in the trial used the QuantiFERON-TB test, also known as QFT, to measure infection in the children, who were all tested at the start of the trial and again at one year and two years.

The assay exposes whole blood cells to the TB antigen and then measures the amount of interferon gamma, a type of cell-signaling protein, released by certain immune system cells. If the response measures less than 0.35 international units per milliliter, the person is considered negative for the bacteria, while any result higher than that is considered to be positive.

Test results at one year

When the 2,512 children in the study were tested at a year, 172 of them — 6.8 percent — were found to be positive carriers of the bacteria, a very high rate of infection, the researchers reported. Of these, 30 had already been diagnosed and treated for the active disease.

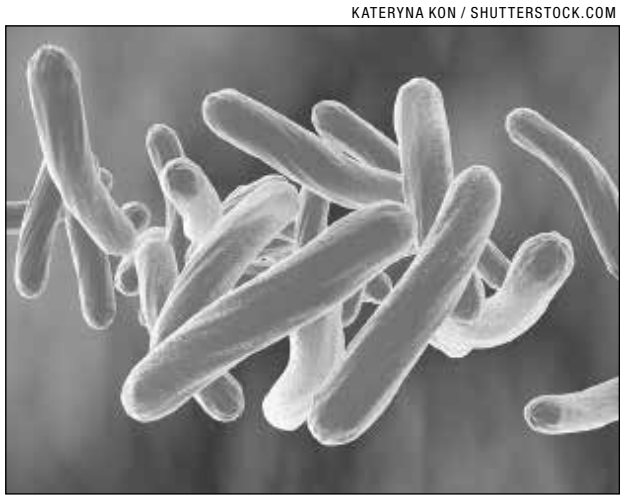
The researchers more closely examined the other 142 children who tested positive but hadn't yet developed TB. They found that among those whose test results were between 0.35 and 4.0 international units per milliliter, only 2.5 percent developed the active disease. But among those with values greater than 4.0 international units per milliliter, many more children — 28 percent — became ill. Only 0.7 percent of those with a negative test developed TB.

"We found that as your value goes up, your risk goes up, and the risk really begins to accelerate after a value of 4," Andrews said. "The children in the high-value group had a 40-fold higher risk of getting sick, which is a very powerful marker."

He said the study is the first to show that these higher numbers matter more.

"What we are hoping is that this will show the international community — the WHO, CDC and those creating guidelines — that QuantiFERON testing can be reliable in kids, and that the quantitative values may be important so we may need to look a different thresholds than we use in adolescents or adults," Andrews said.

KATERYNA KON / SHUTTERSTOCK.COM



Tuberculosis bacteria infected and killed over 1.8 million people in 2015. A simple blood test may help identify infected children who are likely to develop the disease.

He said the only drawback of the test is that it is moderately expensive and requires a well-equipped laboratory and trained personnel to perform. It may be viable in a country like South Africa, with its relatively advanced infrastructure, but would be less practical to use in poorer countries. The researchers are now exploring whether it could be cost-effective to scale up testing in South Africa, he said.

Other co-authors of the study are scientists from the London School of Hygiene & Tropical Medicine; the Desmond Tutu HIV Centre; the Jenner Institute at Oxford; and Aeras, a TB vaccine nonprofit in Rockville, Maryland.

The study was funded by the National Institutes of Health.

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

Needless shocks from heart devices can trigger extra health costs

By Devika G. Bansal

A team led by a School of Medicine researcher has discovered that shocks from implantable cardioverter defibrillators often trigger a cascade of health tests and interventions, even when the shocks they deliver are not needed.

A study describing the team's findings was published online Feb. 14 in *Circulation: Cardiovascular Quality and Outcomes.* The lead author is Mintu Turakhia, MD, assistant professor of cardiovascular medicine at Stanford.

Each month, more than 10,000 people in the United States with heart conditions get ICD implants. The devices are designed to keep track of heart rate, delivering an electric shock to control life-threatening rapid rhythms, especially those that can cause sudden cardiac arrest. Sometimes, however, the devices can deliver shocks that are unnecessary. In either case, the patients are expected to see their doctors for an evaluation afterward.

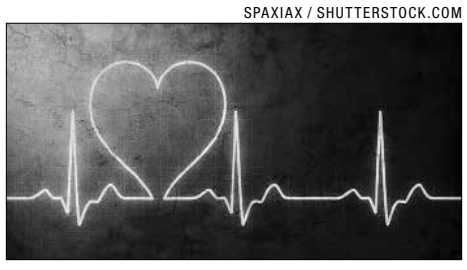
The study analyzed data from patients who were implanted with ICDs between 2008 and 2010. The health care costs of dealing with shocks from ICDs ranged between about $1,300 and $20,000 per patient for outpatient and inpatient care, regardless of whether the shocks were necessary, the team reported.

Unnecessary shocks can occur if there is a problem with the defibrillator system itself — for example, if a wire breaks, resulting in electrical noise that the system mistakes for an abnormal heart rhythm, or if the implant responds to abnormal heart rhythms that it's not meant to treat.

"Sometimes the defibrillator gets tricked, and it misinterprets what the rhythm is," said Matthew Reynolds, MD, a study co-author and cardiac electrophysiologist at the Lahey Hospital and Medical Center in Massachusetts.

"You're putting these in to do their job to save patients' lives," said Turakhia, who is also the senior director of research at the Stanford Center for Digital Health and a practicing cardiac electrophysiologist. "But we live in a bit of duality with implantable defibrillators."

SPAXIAX / SHUTTERSTOCK.COM



A cascade of health care use

Interested in trying to understand that contradiction, Turakhia and his colleagues began by tackling the challenge of linking implant data with electronic health records for 10,266 U.S. patients. The team took a freestanding data set of remote monitoring of ICDs and pacemakers and linked it to the patients' clinical information, making it one of the first and largest such studies of its kind, Turakhia said.

"That's one of the big innovations here, especially as we start thinking about big data and precision health," Turakhia said. "Linking data across multiple domains **See HEART, page 3**

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STANFORD MEDICINE

VANTAGE POINT

one in an occasional series of essays written by faculty, staff and students

In fighting for children's health care, we must engage with policymakers

By Lisa Chamberlain

I remember two things about my patient, Maria, a tiny baby who was born a little early. One was her large, beautiful eyes. The other was that when I put my stethoscope on her chest, I heard an enormous heart murmur. Maria had been born with a serious heart condition that would change her life and the life of her mom.

Good patient care at a time like this involves much more than treating a child's heart. At that first appointment, Maria (not her real name), her mother and I began a long journey punctuated by multiple hospitalizations, surgeries and procedures.

Maria was born at Lucile Packard Children's Hospital Stanford and lived with her mom in East Palo Alto. As her general pediatrician at Ravenswood Family Health Center, I came to know them both well. I focused on helping the tiny infant gain weight, so that she would be strong enough to undergo her heart surgeries. We brought in the Women, Infants and Children program to support her nutrition.

I explained to her mom what the surgeries would do. I reviewed what Maria's medicines were for, and when her mother couldn't pay for them I helped gain authorization from county staff, who were able to get them dispensed at the pharmacy. When I realized Maria's mom didn't have enough money for food (due to many absences at work), I made sure she applied for food stamps.

My experience with Maria coincided with my research at Stanford involving access to care for kids in California. As a result of the research, I spent part of my time in Sacramento, working with legislators on changes to the California Children's Services program. This program is critical to the care of low-income children with serious medical conditions. My research, which involved analyzing data on publicly insured pediatric care like Maria's, showed that access to high-quality care for low-income kids was pretty good in California compared with other states, but that there was variation among its 58 counties.

While working on the program's reform in Sacramento, I spent time in countless staff meetings, public hearings and hallway discussions. I often thought about Maria, whose life depended on CCS. The research data I brought to these negotiations were as important as sharing Maria's story — how her mother lost her job because of time spent caring for her fragile daughter, how the family sank more deeply into poverty and how services needed to be more focused on families. As changes to the CCS system were being discussed, I imagined how they would benefit or hinder Maria's care and her future.

Lisa Chamberlain

A foreign land

The health policy decisions made in Sacramento and Washington, D.C., impact health care programs, and these changes trickle down to communities where the results are deeply felt. Before spending time in Sacramento, I had been on the receiving end of seemingly capricious program shifts. I had spent my time at Stanford teaching, doing research and seeing patients in East Palo Alto. The policy arena was a foreign land, complete with its own calendar and language. But I came away very impressed with how hard elected officials and their staff members work. They are dedicated and smart. They ask good questions and scramble to understand the multiple, complex issues that confront them on a daily basis.

As a physician, I have experienced the scarcity of time firsthand. No matter how quickly I work, there never seems to be enough time. But legislators and their staff members have even more compressed days. The speed with which they meet, consider, decide and take action is exhausting. They are open to, and benefit from, the perspectives of parents, doctors and patients, and they value the work of advocacy groups, in this case Family Voices, a group that advocates for children with special needs. As California's legislators considered changes to the CCS program, this input helped to inform legislation to protect children and minimize the potential for unintended consequences.

I am happy to say that Maria is thriving. The talented pediatric surgeons and cardiologists at Lucile Packard Children's Hospital saved her life, and the network of community support systems and programs coalesced to make it all happen. She now is in elementary school, and her mom is back at work. Maria had access to the right care at the right time, and she wasn't dependent on her family's ability to pay. This is something to celebrate — the CCS program and the state of California enabled everyone to do their jobs and do them well.

The programs that support the most vulnerable kids like Maria cannot sustain significant changes without risking the well-being of children. Moreover, health policy that works well in communities cannot be created in a vacuum. Through my experience, I realized that bringing the voices, experiences and patient stories to the policymaking arena leads to policy shifts that have fewer unintended consequences. It is up to us all to engage with our dedicated policymakers to protect what is working while improving the systems so many depend upon. We need this engagement now more than ever. **ISM**

Lisa Chamberlain, MD, MPH, is an associate professor of pediatrics and director of the Pediatric Advocacy Program at the School of Medicine.

Heart

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— indirectly and without patient identifiers — is the wave of the future to understand disease, care and outcomes."

In the linked data, the team picked 963 patients who had received an ICD shock more than once. They found that over one-third of administered shocks were inappropriate and nearly half the patients who experienced a shock received some form of health care related to it.

But researchers were surprised to find that patients who got a shock were hospitalized one out of seven times. Patients often had to go through procedures like stress tests, cardiac catheterization and echocardiography. "It didn't really matter why the shock occurred," Turakhia said. "The very fact that any shock happened at all triggered all that stuff happening to the patient."

These findings indicate that reprogramming the devices so they are smarter and more selective about when to send shocks may help further reduce health care expenditures. At the same time, patients do better if doctors program the ICDs to shock less, or more conservatively, previous studies suggest. "Fortunately, the industry has made many advancements in this area," Turakhia said. "Even older-generation devices can be programmed to be smarter. The quality of care is no longer just an issue of whether an ICD was implanted in appropriate patients but also whether it was programmed in the best way possible."

The study was done in patients with ICDs implanted between 2008 and 2010, but because arrhythmia treatment practices have changed since that time, including more recent data might have affected the results of the study, Reynolds said. Further, he said it would be interesting to analyze this in a wider cohort of patients, because patients in the present study were all using defibrillators from a single manufacturer, Medtronic Inc.

Mintu Turakhia

Looking ahead, Turakhia hopes to use data from remote monitoring devices like defibrillators, as well as insurance claims and electronic health records and even smartphone, genetic and environmental data to take a precision health approach to predicting patient health.

"Right now, we're using very limited data relative to what's out there," he said. But by linking all of that data together, it may be possible to predict, for example, the risk of stroke in patients with certain types of arrhythmia, like atrial fibrillation. In addition, with that data, doctors could potentially predict the chance of someone getting admitted to the hospital with heart failure or the prospect of a patient getting a shock over the next month or so. And having that foreknowledge could help doctors intervene with drugs to better manage risks and save lives, Turakhia said.

Researchers at Hartford Hospital and Medtronic are also co-authors.

Turakhia is a consultant to Medtronic and St. Jude Medical Inc. and has received honoraria for speaking for St. Jude Medical; Reynolds is a consultant to Medtronic.

The research was funded by Medtronic.

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

Virtual reality imaging gives surgeons a better view of patient anatomy

By Erin Digitale

When Gina Milner needed a new heart valve, she was surprised to learn that a virtual-reality tool could help her get one.

Milner's doctors at the Adult Congenital Heart Program, a joint program of Lucile Packard Children's Hospital Stanford and Stanford Health Care, hoped to perform her valve replacement through a much smaller incision than usual. To figure out if this approach would be safe, surgeon Katsuhide Maeda, MD, used a new computer program that transformed Milner's CT scans into a three-dimensional image of her heart, lungs and chest cavity. He then donned a pair of 3-D glasses and stood in front of a special computer monitor that let him rotate and examine every layer of her cardiothoracic anatomy from any angle. The technology, called True 3D, helped Maeda anticipate what anatomic structures he would see behind a small surgical opening at each stage of Milner's surgery.

"For patients with very complex anatomy and a lot of variation from the normal cardiac structure, 3-D technologies are really helpful," said Maeda, a clinical associate professor of cardiothoracic surgery at the School of Medicine.

Milner, 46, was born with a heart defect called tetralogy of Fallot that was repaired in childhood, placing her in the group of patients for whom standard 2-D imaging may not give surgeons the information they want. "It can sometimes be very hard to understand how to put a path through the heart," Maeda said.

Milner's successful Dec. 2 surgery, the first at Packard Children's to use the new imaging technology, is one of many examples of how virtual-reality techniques are now helping patients. Her surgery is also one of many recent successes for the Adult Congenital Heart Program, which recently became one of the first in the country to receive formal accreditation from the Adult Congenital Heart Association as a comprehensive care center.

Big view through a small window

Last fall, Milner had difficulty breathing. Testing revealed that she had a leaky pulmonary valve. Blood was backwashing into the pumping chamber on the right side of her heart, making it work too hard. Milner's heart became dangerously enlarged, and her heart and lungs couldn't deliver enough oxygen to the rest of her body.

Most patients in this situation need an open-heart procedure to get a new heart valve, and Maeda wasn't sure if the minimally invasive surgery he wanted to perform instead was feasible. The 3-D technology helped him figure it out before he made a single incision.

"By looking at her CT scans in three dimensions, we were able to tell that we would have enough space to work with," Maeda said. The technology can also create 3-D images from MRI scans.

Some adult congenital heart disease patients have a lot of scar tissue inside their chests from prior surgeries; with the 3-D image, Maeda could see that Milner did not. "We could prepare in our minds, if we cut the bone this much, we can get access to this or that blood vessel," Maeda said. His team also consulted the 3-D images **See VIRTUAL, page 8**

Volunteer devotes more than half a century to Stanford Hospital

By Grace Hammerstrom and Jana Chow

Every Tuesday and Thursday afternoon, Martha Bachmann drives her 1989 Buick LeSabre sedan up to the front of Stanford Hospital, hands her keys to one of the valet attendants and comes inside to start her volunteer shift. Like clockwork, she arrives smiling, 20 minutes early, ready to stock the patient shopping cart and head out on the floors. At 100 years old, Bachmann has had the same routine for 54 years.

When Bachmann first volunteered as a Stanford Auxiliary "Pink Lady" in 1962, Stanford Hospital was known as Palo Alto-Stanford Hospital Center. Over her long career, she has watched the hospital expand dramatically. But one constant has remained: her shopping cart. For more than five decades, Bachmann has pushed the cart through the hospital's halls, bringing T-shirts, jackets, books, magazines, gum, candy, stuffed animals and toiletries to patients' rooms.

"The shopping cart is my heart and soul," said Bachmann, who shares the job with partners Betty Cowart and Pat Ricaud, her fellow Pink Ladies. "You get to meet the patients, their visitors and the hospital help. It's one of the best jobs anyone can have in the hospital. We don't stick. We don't poke. We just bring some happiness."

Her favorite part of the routine is visiting the newborns. Each shift, she pushes the cart to the maternity unit at Lucile Packard Children's Hospital Stanford to visit new parents, bringing every new baby a tiny, colorful beanie. She hand-knits the hats at home with help from her daughter and another volunteer.

Born in Germany in 1916, Bachmann came to the United States when she was 10, settling into the Lower East Side of New York with her family. After high school, she moved to California. She came to Palo Alto for a wedding in 1941 and rekindled a friendship with a young man she knew from her church choir. The two fell in love, married and had two daughters. In the early 1960s, with her children grown, Bachmann began looking for an opportunity to do charitable work with her extra time. Her friends from church invited her to join the Stanford Auxiliary and volunteer at the hospital. Today she is the longest-serving volunteer in Stanford Health Care's history and one of its last remaining Pink Ladies.

NORBERT VON DER GROEBEN

For more than 50 years, Martha Bachmann has been bringing a smile to Stanford Hospital patients as a "Pink Lady" volunteer.

'Not all days are easy'

With her smile and occasional hugs, Bachmann does her best to bring some happiness to the patients she sees each day. "Not all days are easy," she said. "It has its nice moments, and it has its sad moments. It's a hospital. Sometimes, patients ask, 'Would you just hold me for a minute?' When I find myself with tears, I sneak my tears away. You can't come to a place like this with a sad face. You can't bring your miseries here."

Bachmann is one of 850 active volunteers at the hospital. "We use her as a role model during volunteer orientation," said Linda Velez, director of Volunteer Services. "She is so kind and selfless and always has a smile on her face. Martha affects everyone she interacts with and brings a glimmer of sunshine to patients, staff and visitors."

While Stanford Health Care asks its volunteers for only a six-month commitment, Bachmann remains dedicated after 54 years and has no intention of retiring. Her biggest concern is that her driver's license will expire in a little over a year, so getting to the hospital could become a challenge. Her health remains strong, and Bachmann attributes her longevity to not smoking or drinking and to remaining active. In addition to walking the halls of the hospital twice a week, she walks to the store near her home.

"I like to keep going," she said. "I'm really blessed." **ISM**

Cardiotoxicity

continued from page 1

pharmaceutical companies better focus their efforts on developing safer drugs, and it will provide patients more effective drugs with fewer side effects."

A paper describing the research was published Feb. 15 in *Science Translational Medicine.* Wu, who holds the Simon H. Stertzer Professorship, is the senior author. Former graduate student Arun Sharma, PhD, is the lead author.

'Multiple measurements'

"We used multiple measurements to accurately predict which of the tyrosine kinase inhibitors were the most cardiotoxic," said Sharma. "The drugs with the lowest safety indices in our study were also those identified by the Food and Drug Administration as the most cardiotoxic to patients. Other drugs that are not as cardiotoxic performed much better in our assays."

STEVE FISCH

Joseph Wu and his colleagues used lab-grown heart cells to assess the effect of chemotherapy drugs on heart muscle.

Validating the researchers' cardiac-safety test on drugs with extensive clinical track records is necessary before the assay can be used to predict with confidence the likely clinical outcomes of drugs still under development.

Sharma, Wu and their colleagues created heart muscle cells called cardiomyocytes from induced pluripotent stem cells, or iPS cells, from 11 healthy people and two people with kidney cancer. They grew the lab-made cardiomyocytes in a dish and tested the effects of 21 commonly used tyrosine kinase inhibitors on the cells.

They found that treatment with drug levels equivalent to those taken by patients often caused the cells to beat irregularly and begin to die. The cells also displayed differences in the electrophysiological signaling that controls their contraction. The researchers used these and other measurements to develop a cardiac safety index for each drug.

They found that those drugs known to be particularly dangerous to heart function, such as nilotinib, which is approved for the treatment of chronic myelogenous leukemia, and vandetanib, which is approved for the treatment of some types of thyroid cancer, also had the lowest safety indices based on the assay; conversely, those known to be better tolerated by patients ranked higher on their safety index. Prescribing information for both nilotinib and vandetanib contains warnings from the FDA about the drugs' potential cardiotoxicity.

Activity increase in insulin responsive pathway

Six of the 21 tyrosine kinase inhibitors tested were assigned cardiac safety indices at or below 0.1 — the threshold limit at which the researchers designated a drug highly cardiotoxic. Three of these six are known to inhibit the same two signaling pathways: VEGFR2 and PDGFR. The researchers noticed that cells treated with these three drugs ramped up the activity of a cellular signaling pathway that responds to insulin or IGF1, an insulinlike growth factor.

This discovery, coupled with the fact that treatment with insulin or IGF1 is known to enhance heart function during adverse cardiac events such as heart attacks, led the researchers to experiment further. They found that exposing the cells to insulin or IGF1 made it less likely they would die due to tyrosine kinase inhibitors blocking the VEGFR2 and PDGFR pathways. Although more research is needed, these findings suggest it may be possible to alleviate some of the heart damage in patients receiving these chemotherapies.

The current study mirrors another by Wu's lab that was published in April 2016 in *Nature Medicine*. That research focused on the toxic effect of a chemotherapy drug called doxorubicin on iPS cell-derived cardiomyocytes. Doxorubicin, which indiscriminately kills any replicating cells, is increasingly being replaced by more targeted, cancer-specific therapies such as the tyrosine kinase inhibitors tested in the current study.

"The switch from doxorubicin is a result of the paradigm shift in cancer treatment to personalized, precise treatment as emphasized by President Obama's 2015 Precision Medicine Initiative," said Wu. "Moving even further, we're discovering that many tyrosine kinase inhibitors are themselves significantly cardiotoxic, and some have been withdrawn from the market. There is a critical need for a way to 'safety test' all drugs earlier in development before they are administered to patients. Our drug safety index is a step in that direction."

Other Stanford co-authors are Paul Burridge, PhD, a former instructor at the Cardiovascular Institute; graduate student Wesley McKeithan; postdoctoral scholars Praveen Shukla, PhD, Tomoya Kitani, MD, Haodi Wu, PhD, and Alexandra Holmström, PhD; instructors Nazish Sayed, MD, PhD, Elena Matsa, PhD, and Jared Churko, PhD; medical student Anusha Kumar; undergraduate student Yuan Zhang; assistant professor of medicine Alice Fan, MD; associate professor of medicine Sean Wu, MD, PhD; and professor of medicine Mark Mercola, PhD.

The research was funded by the American Heart Association, the National Science Foundation, the National Institutes of Health, the Lucile Packard Foundation for Children's Health, the Stanford Child Health Research Institute and the Burroughs Wellcome Foundation.

Mercola is on the scientific advisory board for Vala Sciences, a company offering high-content screening services, and Wu is on the scientific advisory board of Stem Cell Theranostics, a company using patient-specific iPS cells for drug discovery. **ISM**

Formerly conjoined twins Erika and Eva a step closer to going home

By Erin Digitale

LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD

(Left) Erika Sandoval was all smiles as she left Lucile Packard Children's Hospital Stanford on Feb. 13 with her mother, Aida, for the first time since the twins' separation surgery. (Right) Formerly conjoined twins Erika, front, and Eva take a wagon ride at the hospital.

Formerly conjoined twins Erika and Eva Sandoval, who were separated Dec. 6 at Lucile Packard Children's Hospital Stanford, are making good progress toward learning to live as two people, their caregivers report.

The 2½ -year-old sisters are happy, chatty and motivated to learn new skills, the caregivers said. The twins are working with the hospital's physical and occupational therapists and child psychiatrists to prepare them for their return home to Antelope, California.

"They're doing great," said Gary Hartman, MD, clinical professor of pediatric surgery at the School of Medicine, who led the 50-person team that separated the sisters. Erika was released from the hospital on Feb. 13 and is now staying nearby with her parents. Eva, whose surgery wound is healing more slowly, will stay in the hospital for several more weeks.

"It's happening," Aida Sandoval, the twins' mother, said as she walked with Erika in her arms through the hospital and readied her daughter for her first ride in a regular car seat. "It's surreal to be taking her out of the hospital for the first time as an individual."

Hartman and Peter Lorenz, MD, professor of plastic and reconstructive surgery, are evaluating whether a skin graft will be necessary to close Eva's wound. The girls' surgical sites were closed differently, which contributed to the time difference in healing.

Now that the twins are separated, each child has one kidney and one leg. Prior to surgery, Hartman had warned the twins' parents, Aida and Arturo Sandoval, that the girls might not be able to sit up on their own after separation. Because of the way they were joined, the twins lack the abdominal muscles usually used to maintain balance.

However, both Eva and Erika are already sitting up for short periods with support from their physical and occupational therapists, and are sometimes able to balance briefly on their own. "In this respect, they're way ahead of our expectations," Hartman said.

> **"I've been amazed with the progress they've been able to make in a short time."**

'Highly motivated and hard workers'

The team is also developing ways for the girls to play, reach for objects around them and adopt new movement patterns suited to their separate bodies. They will also be learning to eat more by mouth, since before separation much of their nutrition came from tube feeding.

"I've been amazed with the progress they've been able to make in a short time," said Kelly Andrasik, an occupational therapist at Packard Children's "For their age, they are highly motivated and hard workers, and that's going to carry them really far."

The caregivers are also enjoying seeing the sisters express their personalities. "They're very sweet and funloving," Andrasik said. "Eva loves it when we play with our wooden pizza set; she makes slices for everyone who comes into the room. Erika has also been really motivated by different things she wants to play with, such as bubbles and Mr. Potato Head. We're learning from her how she is best able to use her body."

At the same time, the hospital's child psychiatrists are using play therapy to help the girls work through their feelings about the separation.

"Before separation, they were truly never by themselves," said Michelle Goldsmith, MD, clinical assistant professor of child and adolescent psychiatry.

Most toddlers begin to understand that they are individuals around 18 months of age, but that process may have progressed differently for Eva and Erika because they had each other's constant company. To help the twins understand their new state, Goldsmith's team is encouraging each girl to play with a set of teddy bears that can either be joined together with Velcro to replicate the girls' presurgery anatomy, or separated to look more like the girls now.

"We're letting them know that it's OK to be apart," Goldsmith said. "We can say, 'Yay, this bear wants to read a book, and that one wants to have a tea party, and they can come back together later.'" Since young children don't have abstract conversations about their feelings, the play therapy gives the twins a concrete way to talk about their new reality.

"They do express preferences about whether they want the bears to be together or apart, and the play therapy normalizes that for them," Goldsmith said. "Neither girl seems to have trouble adjusting; they're both rolling with what's going on very well."

Once Eva is released from the hospital, they will both continue receiving physical and occupational therapy through an intensive outpatient or inpatient program near their family's home.

Eva and Erika's parents are ready for the next phase of the girls' recovery.

"One of the hardest parts of their being conjoined was not being able to give them the individual attention they needed at different times, like when one was playful but the other felt sleepy or sick," Aida said. "I am excited to have time with the girls separately and to bond with each." ISM

New issue of magazine looks at the arts, humanities in medicine

By Rosanne Spector

Imagine your doctor told you at the end of an exam, "I'm going to prescribe you an artistic experience." Would you be thinking, "Time to get a new doctor"?

Well, you might want to stick with the one you have. Taking part in art probably won't cure you, but, depending on your particular illness, it really could help. People with Parkinson's disease, for instance, benefit physically and psychologically from taking dance classes.

The winter issue of *Stanford Medicine*, produced in collaboration with Stanford's Medicine and the Muse program, features articles on the role of the arts and humanities in medicine, among them an article on Dance for PD, a program that offers dance classes to people with Parkinson's disease.

"The worlds of dance and medicine have been far apart for a long time. That is why this is so exciting," professor of neurology Helen Bronte-Stewart, MD, said in the article.

"As physicians, we stress the importance of physical activity, social interaction and mental stimulation to our patients with Parkinson's disease," Bronte-Stewart said. "Dance for PD gives them all three. But it is much more than a possible therapy or treatment; the PD dancers have told us this type of dance restores their self-image and brings them joy."

Also in the report:

- A physician-poet's essay on the movement to include the arts and humanities in medical education and practice.
- An article by an ophthalmologist explaining how our eyes help us perceive color, including strategies artists use, knowingly or otherwise, to create magical effects.
- A collection of stories about Stanford medical students who use art in a variety of ways to become better doctors.
- A Q&A with Max Aguilera-Hellweg, MD, a world-class photographer who earned a medical degree and then returned to photography to document the body during surgery and in everyday life.
- A story about children in chronic pain who use photography to convey their experiences to their families and doctors.

The issue also includes an article about a new paradigm for cancer research that looks beyond mutations as the cause of the disease, and a feature about a newborn's life-and-death battle that revealed the power of a few mutant heart cells to wreak massive damage.

The magazine is available online. Print copies are being sent to subscribers. Others can request a copy by calling 723-6911 or by sending an email to medmag@stanford.edu. ISM

Brain control

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Institute of Technology as an assistant professor of biomedical engineering. "We're achieving communication rates that many people with arm and hand paralysis would find useful. That's a critical step for making devices that could be suitable for real-world use."

Shenoy's lab pioneered the algorithms used to decode the complex volleys of electrical signals fired by nerve cells in the motor cortex, the brain's command center for movement, and convert them in real time into actions ordinarily executed by spinal cord and muscles.

"These high-performing BCI algorithms' use in human clinical trials demonstrates the potential for this class of technology to restore communication to people with paralysis," said Nuyujukian.

Life-changing accident

Millions of people with paralysis reside in the United States. Sometimes their paralysis comes gradually, as occurs in ALS. Sometimes it arrives suddenly, as in Degray's case.

Now 64, Degray became quadriplegic on Oct. 10, 2007, when he fell and sustained a life-changing spinal-cord injury. "I was taking out the trash in the rain," he said. Holding the garbage in one hand and the recycling in the other, he slipped on the grass and landed on his chin. The impact spared his brain but severely injured his spine, cutting off all communication between his brain and musculature from the head down.

"I've got nothing going on below the collarbones," he said.

Degray received two device implants at Henderson's hands in August 2016. In several ensuing research sessions, he and the other two study participants, who underwent similar surgeries, were encouraged to attempt or visualize patterns of desired arm, hand and finger movements. Resulting neural signals from the motor cortex were electronically extracted by the embedded recording devices, transmitted to a computer and translated by Shenoy's algorithms into commands directing a cursor on an onscreen keyboard to participant-specified characters.

The researchers gauged the speeds at which the patients were able to correctly copy phrases and sentences — for example, "The quick brown fox jumped over the lazy dog." Average rates were 7.8 words per minute for Degray and 6.3 and 2.7 words per minute, respectively, for the other two participants.

A tiny silicon chip

The investigational system used in the study, an intracortical brain-computer interface called the BrainGate Neural Interface System*, represents the newest generation of BCIs. Previous generations picked up signals first via electrical leads placed on the scalp, then by being surgically positioned at the brain's surface beneath the skull.

An intracortical BCI uses a tiny silicon chip, just over one-sixth of an inch square, from which protrude 100 electrodes that penetrate the brain to about the thickness of a quarter and tap into the electrical activity of individual nerve cells in the motor cortex.

Henderson likened the resulting improved resolution of neural sensing, compared with that of older-generation BCIs, to that of handing out applause meters to individual members of a studio audience rather than just stationing them on the ceiling, "so you can tell just how hard and how fast each person in the audience is clapping."

Shenoy said the day will come — closer to five than 10 years from now, he predicted —when a self-calibrating, fully implanted wireless system can be used without caregiver assistance, has no cosmetic impact and can be used around the clock.

"I don't see any insurmountable challenges." he said. "We know the steps we have to take to get there."

Degray, who continues to participate actively in the research, knew how to type before his accident but was no expert at it. He described his newly revealed prowess in the language of a video game aficionado.

"This is like one of the coolest video games I've ever gotten to play with," he said. "And I don't even have to put a quarter in it."

The study's results are the culmination of a long-running collaboration between Henderson and Shenoy and a multi-institutional consortium called BrainGate. Leigh Hochberg, MD, PhD, a neurologist and neuroscientist at Massachusetts General Hospital, Brown University and the VA Rehabilitation Research and Development Center for Neurorestoration and Neurotechnology in Providence, Rhode Island, directs the pilot clinical trial of the BrainGate system and is a study co-author.

"This incredible collaboration continues to break new ground in developing powerful, intuitive, flexible neural interfaces that we all hope will one day restore communication, mobility and independence for people with neurologic disease or injury," said Hochberg.

Stanford research assistant Christine Blabe was also a study co-author, as were BrainGate researchers from Massachusetts General Hospital and Case Western University.

The study was funded by the National Institutes of Health, the Stanford Office of Postdoctoral Affairs, the Craig H. Neilsen Foundation, the Stanford Medical Scientist Training Program, Stanford BioX-NeuroVentures, the Stanford Institute for Neuro-Innovation and Translational Neuroscience, the Stanford Neuroscience Institute, Larry and Pamela Garlick, Samuel and Betsy Reeves, the Howard Hughes Medical Institute, the U.S. Department of Veterans Affairs, the MGH-Dean Institute for Integrated Research on Atrial Fibrillation and Stroke and Massachusetts General Hospital.

Stanford's Office of Technology Licensing holds intellectual property on the intercortical BCI-related engineering advances made in Shenoy's lab.

Stanford's departments of Neurosurgery and of Electrical Engineering also supported the work.

CAUTION: Investigational Device. Limited by Federal Law to Investigational Use. ISM

For 15 years, working to create a brain-controlled prosthesis

By Elizabeth Svoboda

Billions of text messages and emails are sent around the globe each day. One seldom if ever pauses to think about the complex interplay of neurons, synapses and muscles at work as the brain transmits the thought to the fingertips that type and send messages into the world. But how this all works is a question of life-altering significance for those who are paralyzed or have severe movement disabilities — and one that electrical engineer and neuroscientist Krishna Shenoy, PhD, and his collaborators have long sought to understand.

Their goal for the past 15 years has been to create a brain-controlled prosthesis, a device that channels thoughts into words or movements. And after years of research with monkeys, Shenoy, a professor of electrical engineering, is part of a national consortium that has begun clinical trials in which a tiny electrical device was implanted into the brains of three movement-impaired people. Among other things, this device, about the size of a baby aspirin, allows these people to compose and send text messages merely by thinking about moving their hands. Neurosurgery professor Jaimie Henderson, MD, Shenoy's longtime friend and collaborator who performed two of the implant surgeries, keeps one such text message from a participant on his phone: "Let's see your monkey do that!" it reads.

The Stanford researchers recently published results from a clinical trial of the investigational technology. Behind those results lie years of efforts by an interdisciplinary team of neurosurgeons, neuroscientists and engineers who brought different scientific vantages together to solve challenges that would have stumped any single discipline. Institutional support was another key ingredient in this long-term effort aimed at ultimately helping people with paralysis affect the world around them using only their minds.

Though more work lies ahead, this ongoing research shows that new engineering and neuroscience techniques can be directly applied to human patients. The milestone is heartening for Shenoy, who has led the effort to create brain-controlled prosthetic devices since he came to Stanford in 2001. Integral to that success has been his 12-year partnership with Henderson, which Shenoy described as a professional marriage of engineering, science and medicine. "When you have a clear vision, you involve yourself in as many details as possible and you work with absolute mutual respect, as coequals, it's pretty interesting what you can do over a couple decades, he said."

A born tinkerer

Shenoy, director of Stanford's Neural Prosthetic Systems Laboratory, had dreamed of bringing the brain-controlled implant into being even before he came to Stanford. A born tinkerer with a desire to improve people's lives, he traces his motivation for the project back to memories of his childhood in Cedar Rapids, Iowa. "My mother's father suffered from multiple sclerosis for around 40 years. He was wheelchair-bound," Shenoy said. "It was not like I ever had a conscious epiphany, 'I want to help him,' but I think it subconsciously influenced me greatly."

Shenoy grew up thinking about a traditional engineering career, but changed that plan in college when he learned about the nascent field of computational neuroscience. For the first time, researchers were trying to figure out how the brain processes information, and Shenoy — then an undergraduate at the University of California-Irvine — knew he wanted to be part of that herculean effort. "I had that light bulb turn on," he said. "Small things, transistors, put together create computers. The brain is spectacular — how is it built from all its component neurons that are wired together?"

After completing his PhD in electrical engineering and computer science at the Massachusetts Institute of Technology, Shenoy headed to the California Institute of Technology to do a postdoctoral fellowship in neuroscience, an experience he likens to "another PhD." As he used electrodes to record signals from monkeys' brains, he toyed with the prospect of tapping into the brains of people with paralysis in order to give them entirely new prosthetic devices. Existing methods of helping such people interact, like eye-blink systems or pointers strapped to their heads to let them move a cursor on a computer screen, were slow and cumbersome — and they didn't work at all for people who didn't have enough muscle control to operate them. A device that translated thoughts into actions — a true brain-computer interface — would be far more efficient and intuitive, Shenoy figured. He kept returning to the same question: "How do we design systems capable of listening in on those neurons and interpreting their language?"

After becoming an assistant professor at Stanford in 2001, Shenoy devoted his research to answering that question. He recorded neural activity from hundreds of neurons at the same time while monkeys, whose brains are quite similar to human brains, performed a variety of arm and hand movement tasks. Generations of students, postdoctoral scholars and research staff in Shenoy's lab used the electrode-array recordings to explore how ensembles of neurons in the motor cortex prepare and guide hand and arm movements. Their goal was to understand the fundamental ways that these neural circuits control arm movements, and to then use this scientific knowledge to design mathematical algorithms for converting, or decoding, this language of the brain into electronic signals for controlling prosthetic devices such as keyboards or robotic limbs.

PAUL SAKUMA

Electrical engineer Krishna Shenoy began dreaming of developing a brain-controlled implant before coming to Stanford in 2001

Better and better

As Shenoy and his colleagues added detail and depth to their understanding of the brain, their decode algorithms kept performing better and better. That success encouraged them to start thinking about bringing this preclinical research to people. They got a major assist in 2004 when Henderson, then interviewing for a neurosurgery position at Stanford, arrived on campus for a round of meetings. Among other skills, Henderson was an expert at using medically approved electronic de-

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Islet cells

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in these disorders.

"In some cases, alpha cells may actually be secreting too much glucagon," said Kim. "When there is already not enough insulin, excess glucagon is like adding gas to a fire."

Because humans have a large reservoir of alpha cells, and because the alpha cells sometimes secrete too much glucagon, converting some alpha cells to beta cells should be well-tolerated, the researchers believe.

The researchers built on a previous study in mice several years ago that was conducted in a Swiss laboratory, which also collaborated on the current study. It showed that when beta cells are destroyed, about 1 percent of alpha cells in the pancreas begin to look and act like beta cells. But this happened very slowly.

"What was lacking in that initial index study was any sort of understanding of the mechanism of this conversion," said Kim. "But we had some ideas based on our own work as to what the master regulators might be."

Chakravarthy and her colleagues targeted two main candidates: a protein called Arx known to be important during the development of alpha cells and another called DNMT1 that may help alpha cells "remember" how to be alpha cells by maintaining chemical tags on its DNA. The researchers painstakingly generated a strain of laboratory mice unable to make either Arx or DNMT1 in pancreatic alpha cells when the animals were administered a certain chemical compound in their drinking water. They observed a rapid conversion of alpha cells into what appeared to be beta cells in the mice within seven weeks of blocking the production of both these proteins.

> "An important step toward realizing the therapeutic potential of alpha cell transdifferentiation."

To confirm the change, the researchers collaborated with colleagues in the laboratory of Stephen Quake, PhD, a co-author and professor of bioengineering and of applied physics at Stanford, to study the gene expression patterns of the former alpha cells. They also shipped the cells to collaborators in Alberta, Canada, and at the University of Illinois to test the electrophysiological characteristics of the cells and whether and how they responded to glucose.

"Through these rigorous studies by our colleagues and collaborators, we found that these former alpha cells were — in every way — remarkably similar to native beta cells," said Kim.

Testing the theory in human cells

The researchers then turned their attention to human pancreatic tissue from diabetic and nondiabetic cadaver donors. They found that samples of tissue from children with Type 1 diabetes diagnosed within a year or two of their death include a proportion of bi-hormonal cells — individual cells that produce both glucagon and insulin. Kim and his colleagues believe they may have caught the cells in the act of converting from alpha cells to beta cells in response to the development of diabetes. They also saw that the human alpha cell samples from the diabetic donors had lost the expression of the very genes — ARX and DNMT1 — they had blocked in the mice to convert alpha cells into beta cells.

"So the same basic changes may be happening in humans with Type 1 diabetes," said Kim. "This indicates that it might be possible to use targeted methods to block these genes or the signals controlling them in the pancreatic islets of people with diabetes to enhance the proportion of alpha cells that convert into beta cells."

Kim is a member of Stanford Bio-X, the Stanford Cardiovascular Institute, the Stanford Cancer Institute and the Stanford Child Health Research Institute.

Researchers from the University of Alberta, the University of Illinois, the University of Geneva and the University of Bergen are also co-authors of the study.

The research was supported by the National Institutes of Health; the California Institute for Regenerative Medicine; JDRF, an organization that funds Type 1 diabetes research; the Center of Excellence for Stem Cell Genomics; the Wallenberg Foundation; the Swiss National Science Foundation; the NIH Beta-Cell Biology Consortium; the European Union; the Howard Hughes Medical Institute; the H.L. Snyder Foundation; the Elser Trust; and the NIH Human Islet Resource Network.

Stanford's Department of Developmental Biology also supported the work. ISM

Collaboration

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vices to stimulate the nervous system for therapeutic purposes. To treat Parkinson's disease, for instance, surgeons often use deep-brain stimulation, a procedure in which they deliver tiny jolts of electricity to relieve the tremors that characterize the condition. Shenoy had the opposite goal: He wanted to read the brain's faint biochemical signals and translate these into electronic data.

But Gary Steinberg, MD, PhD, professor and chair of neurosurgery, had a hunch Shenoy and Henderson would get along. Steinberg made sure the electrical engineer got penciled into Henderson's interview schedule. During their first meeting at the Clark Center, the two hit it off. "It was chemistry," Shenoy said. "Two people who just clicked." When he told Henderson about his dream of creating a brain-controlled prosthetic system, Henderson responded, "Yeah, that's exactly the kind of thing I'd like to do."

Henderson's interest in surgical treatment of Parkinson's disease, coupled with Shenoy's expertise in recording from large numbers of brain cells simultaneously, led them to propose a joint project investigating brain activity during deep-brain stimulation surgery, using the sensor that Shenoy had been using in his laboratory. Those sessions marked the project's first tentative forays into human research and cemented the team, Shenoy recalled. "It started getting us thinking more deeply about how these [implants] could really work, if implanted for years," he said. Henderson's medical expertise helped the engineers figure out what approaches might work in a clinical setting. In turn, Henderson, who holds the John and Jene Blume–Robert and Ruth Halperin Professorship, learned about the finer points of computer control systems — how detailed algorithms allow for swift interpretation of messages coming from the brain.

> "It was one of the biggest operations I've ever done in my life."

Steinberg, the Bernard and Ronni Lacroute–William Randolph Hearst Professor of Neurosurgery and Neurosciences, was impressed by Shenoy and Henderson's teamwork. "They're not ego-driven," he said. "That allows them to build these collaborative programs, rather than feeling that as an individual they have to be the shining light." As he watched them make necessarily slow but fundamental and systematic progress in those early years of their collaboration, Steinberg told the researchers that when they were ready to start a clinical trial to bring this to people with paralysis, the university would provide the initial resources they needed. With Steinberg's financial backing and moral support, along with support from Stanford's interdisciplinary biosciences institute Bio-X, Shenoy and Henderson formed the Neural Prosthetics Translational Laboratory in 2009.

Improving system performance

But before the team felt that their technology would provide people with a nearly natural and enjoyable experience, they needed to improve overall system performance by refining their knowledge of movement intent embedded in brain signals. Much of that pioneering work fell to graduate students Paul Nuyujukian and Jonathan Kao. They trained monkeys to think about moving a cursor toward targets on a computer screen and kept track of how the neurons in the monkeys' brains formed this intention. That allowed them to develop new mathematical algorithms that continuously processed a monkey's brain signals into the movement commands that controlled the cursor.

In essence, they were decoding how the brain forms an intention and then carries out a movement. Over many such experiments carried out over several years, they steadily improved the algorithm. At first, the monkeys managed to hit one target every two to three seconds. By 2012, they were hitting a target a second because the algorithm was enabling them to make faster, straighter and more controlled movements. As Nuyujukian recalls, those kinds of results signaled that it was time to "take those techniques, try them in people with paralysis and ask the fundamental question, 'Does this actually work in the real world?'"

That same year, Henderson surgically implanted the first electrode array in a clinical trial participant at Stanford. The 50-year-old individual had suffered for years with amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, a degenerative condition that causes the loss of motor neurons and can ultimately make movement impossible. As part of the clinical trial process it was explained that there would be no personal benefit from participation. The individual chose to proceed to help advance the research. Henderson, a seasoned neurosurgeon, typically approached the operating room with calm and composure. Less so this time. "I was definitely hyped up," Henderson recalled. "It was one of the biggest operations I've ever done in my life." After the four-hour procedure, the team went out for burritos. Henderson slumped in his chair, exhausted.

PAUL SAKUMA

Jaimie Henderson has been collaborating with Krishna Shenoy on developing a brain-computer interface. He has implanted the experimental devices in two patients as part of a clinical trial.

Even then the researchers couldn't relax. They wouldn't know whether they had been successful for another month or so, when they brought the first participant back into the lab to see whether the implant could pick up electrical signals from the person's brain and correctly decode them into movement controls. During that first lab session, the data was a bit difficult to interpret — the team had to make some computing tweaks to ensure the participant's brain signals came through reliably. But it soon became clear that the surgery had been a success: The participant moved a cursor to an on-screen target just by thinking about it. "We definitely, as a lab, opened a bottle of Dom Pérignon," Henderson said.

The celebration was, of course, preliminary. Years more work lay ahead. Another participant was implanted at Stanford, and another at Massachusetts General Hospital as part of the multi-institutional BrainGate consortium, bringing to three the participants contributing to the present round of results. Testing the results required some creative on-the-spot adjustments. Nuyujukian, by then a postdoctoral scholar at Stanford, recalls visiting the participants' homes after the surgery with fellow postdoctoral scholar Chethan Pandarinath, now an assistant professor at Emory University and Georgia Institute of Technology. They would arrive with a cart filled with computers and electronic recording equipment. For a few minutes at a time, they would tell each participant to look at a cursor moving back and forth on a screen and pretend they were controlling it with their mind. This process was meant to calibrate the algorithms responsible for converting patterns of neural activity into computer cursor movements.

Nuyujukian recalls watching, awestruck, as study participants became proficient at moving the cursor from one letter to the next, tapping out words, then whole sentences, using only their brains. "To see that actually happen is unbelievable. It was hard to not display emotion on the spot," he said. From time to time, he and the participants would chat about how incredible all this was.

Now, 15 years into the effort and with many more years of development and testing ahead, team members think that collaborative problem solving remains the key to success. "This group was so careful and just laid out every step along the way," Nuyujukian said. Next, the team plans to test the implant in even more participants — and expand the types of devices people can operate. "The follow-on to this is allowing a person to use an off-the-shelf tablet device," Henderson said. "And to do so 24/7, so that the participant has access to assistive devices at any time."

For all of the success in getting to this point, Shenoy remains cautious, yet deeply optimistic.

"Neurotechnologies such as this will alter how we think about treating nervous system disorders," he said. "And perhaps even how we think about what it means to be human."

Shenoy, Henderson and Steinberg are members of Bio-X and the Stanford Neurosciences Institute. ISM

Researchers: Latest ban on U.S. global funding ignores science

By Ruthann Richter

In a commentary published Feb. 22 in *The New England Journal of Medicine*, two School of Medicine scientists make a case for lifting the ban on U.S. aid to international groups that support abortion-related activities, saying the policy harms women and ultimately could hurt the country's economic and security interests abroad. They argue that scientific evidence, not ideology, should guide policymaking in global health.

The so-called Mexico City policy bans funding to nongovernmental organizations that provide abortion counseling or referrals. The policy, initiated by President Reagan in 1984 during a United Nations conference in Mexico City, was reinstated by the Trump administration in January.

"The reinstatement of the Mexico City policy is a stark example of 'evidence-free' policy making that ignores the best scientific data, resulting in a policy that harms global health and, ultimately, the American people," wrote Nathan Lo, an MD-PhD student, and Michele Barry, MD, a professor of medicine.

Barry, director of the Stanford Center for Innovation in Global Health, had worked with the Obama administration to lift the restrictions in 2009. She said she was particularly disheartened to see the Trump administration take the policy one step further, banning funding to groups that promote maternal and child health, as well as HIV prevention efforts.

"It's very unfortunate to see all that good work unraveled," Barry said. "It not only impacts reproductive services, but the health of women and their children."

Nathan Lo

Michele Barry

In the commentary, the authors note that even when U.S. aid is provided to groups supporting abortion-related activities, the money is not used to directly pay for abortion services. Rather, the funds are used for reproductive counseling, education and contraception. Without health and reproductive services, more women suffer pregnancy-related complications and engage in unsafe sex, putting them at risk of contracting HIV, the authors said.

A 2011 Stanford study found that women living in countries most affected by the ban had 2.6 times the odds of having an abortion compared with those in countries not affected by the policy. This means the policy had the opposite of its intended effect. **ISM**

Virtual

continued from page 3

during surgery, taking brief breaks in the operating room to double-check the virtual-reality monitor.

Instead of the usual 6-inch incision, Maeda was able to perform Milner's operation through a 2.5-inch incision, enabling her to recover more quickly, causing less post-surgery pain and lowering her risk for complications, such as infection.

LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD

A computer system at Lucile Packard Children's Hospital Stanford allows medical images to be viewed and manipulated in three dimensions.

Many uses

The 3-D innovation will help many of the hospital's surgical patients, according to pediatric radiologist Frandics Chan, MD, who worked with the Mountain View-based company EchoPixel to develop the new virtual-reality tool using the HP Zvr Virtual Reality Display. (Chan has no financial relationship with either company.)

"In any situation with unexpected anatomy — either anatomical differences the patient was born with, those associated with tumors or those created by a prior surgery — this will be very helpful for both pediatric and adult patients," said Chan, an associate professor of radiology at the School of Medicine. The team that separated conjoined twins Erika and Eva Sandoval at Packard Children's in early December used the same virtual-reality technology to help navigate complex steps in the separation, Chan said.

The technique complements 3-D printed physical models of patients' anatomy, which the Stanford 3-D and Quantitative Imaging Laboratory produces for surgical planning. The virtual-reality approach has some distinctive advantages. "When you print an anatomical model, you can cut it open once and that's it," Chan said. "In virtual reality, you can put it back together, cut it again in a different place and magnify it with the flick of your hand."

Breathing easier

At home in Clovis, California, Milner's recovery is progressing. She's grateful that the new technology spared her a much larger incision. "For them to have not had to do that is just wonderful," she said.

She can already feel the benefits of her new heart valve, she added. "My breathing is so much better."

"We're going to use 3-D and other virtual-reality technologies more and more," Maeda said. "They have big advantages for our patients." **ISM**

OF NOTE

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

BETH BEADLE, MD, PhD, was appointed associate professor of radiation oncology, effective Jan. 1. She specializes in radiation therapy for head and neck cancers. Her research interests include improving patient outcomes through technology and developing automated radiation treatment techniques for low- and middle-income countries.

TINA COWAN, PhD, was promoted to professor of pathology, effective Jan. 1. She's a biochemical geneticist who is working to improve testing to diagnose and monitor patients with metabolic disorders.

MANISHA DESAI, PhD, was promoted to professor of medicine and of biomedical data science, effective Feb. 1. She is the founder and director of the Quantitative Sciences Unit, which supports researchers by providing expertise in biostatistics and informatics. She is developing team-based approaches to collaborate with clinical and translational investigators. Her research interests include the treatment of missing data, the processing and analysis of accelerometer data and the analysis of longitudinal studies.

DIANA DO, MD, was appointed professor of ophthalmology, effective Jan. 1. She is a retina surgeon, and her research interests include developing new treatments for age-related macular degeneration and diabetic retinopathy.

ANTHONY DOUFAS, MD, PhD, was promoted to professor of anesthesiology, perioperative and pain medicine, effective Dec. 1. His research focuses on pain responses and clinical opioid pharmacology in surgical patients suffering from sleep-disordered breathing.

MICHAEL JENG, MD, was promoted to professor of pediatrics, effective Jan. 1. His research and clinical practice focus on pediatric hematology. He is currently investigating histiocytic disorders, including Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis and vascular anomalies.

MARK MCGOVERN, MD, was appointed professor of psychiatry and behavioral sciences, effective Jan. 30. His research focuses on developing and implementing integrated behavioral health services for patients with psychiatric disorders or addiction disorders, or both, who present in general medical settings. He also conducts research on expanding access to addiction medications and improving outcomes for patients with opioid addictions.

QUAN DONG NGUYEN, MD, was appointed professor of ophthalmology, effective Feb. 1. He is a retina surgeon who specializes in the management of uveitis, ocular inflammatory diseases and vitreoretinal disorders. He has conducted clinical trials on macular edema, neovascular age-related macular degeneration and ocular inflammatory and uveitic diseases, as well as contributed to the development of several pharmacotherapeutic agents.

KAVITA SARIN, MD, PhD, was appointed assistant professor of dermatology, effective Jan. 1. Her research interests involve integrating genetic and clinical patient data to inform disease susceptibility prediction, stratify prognoses and direct treatments for dermatologic disease.

JAY SHAH, MD, was appointed associate professor of urology, effective Jan. 1. He will also serve as cancer-care program leader for genitourinary oncology. He is a urologic oncologist who focuses on bladder cancer and uses both robotic and open surgery to treat patients. He conducts outcomes research on patients undergoing bladder removal surgery.

GARY STEINBERG, MD, PhD, professor and chair of neurosurgery, was among the recipients of *Stroke*'s 2016 Progress and Innovation Award. He won third prize for the paper "Clinical outcomes of transplanted modified bone marrow-derived mesenchymal stem cells in stroke: a phase 1/2a study." The prize includes a $1,000 and travel award to attend the 2017 International Stroke Conference. Steinberg is the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences.

YANG SUN, MD, PhD, was appointed associate professor of ophthalmology, effective Feb. 1. His clinical work focuses on the medical and surgical management of glaucoma. His research interests include inositol metabolism and primary cilia signaling in eye development and disease. **ISM**

Beth Beadle

Tina Cowan

Manisha Desai

Diana Do

Anthony Doufas

Mark McGovern

Quan Dong Nguyen

Kavita Sarin

Jay Shah

Gary Steinberg

Yang Sun