INSIDE STANFORD MEDICINE

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Technologies invented by Stanford Biodesign trainees have been used in the care of more than 1.5 million patients.

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App, Google Glass help kids with autism read facial expressions, investigators say

By Erin Digitale

STEVE FISCH

Alex took part in a pilot study in which a smartphone app paired with Google Glass was shown to help children with autism understand emotions conveyed in facial expressions. The study's findings were published online Aug. 2 in *npj Digital Medicine*.

Children with autism were able to improve their social skills by using a smartphone app paired with Google Glass to help them understand the emotions conveyed in people's facial expressions, according to a pilot study by researchers at the School of Medicine.

Prior to participating in the study, Alex, 9, found it overwhelming to look people in the eye. Gentle encouragement from his mother, Donji Cullenbine, hadn't helped. "I would smile and say things like, 'You looked at me three times today!' But it didn't really move the bar," she said. Using Google Glass transformed how Alex felt about looking at faces, Cullenbine said. "It was a game environment in which he wanted to win — he wanted to guess right."

The therapy, described in findings published online Aug. 2 in *npj Digital Medicine,* uses a Stanford-designed app that provides real-time cues about other people's facial expressions to a child wearing Google Glass. The device, which was linked with a smartphone through a local wireless network, consists of a glasses-like frame equipped with a camera to record the wearer's field of view, as well as a small screen and a speaker to give the wearer visual and audio information. As the child interacts with others, the app identifies and names their emotions through the Google Glass speaker or screen. After one to three months of regular use, parents reported that children with autism made more eye contact and related better to others.

The treatment could help fill a major gap in autism care: Right now, because of a shortage of trained therapists, children may wait as long as 18 months after an autism diagnosis to begin receiving treatment.

'Really important unmet need'

"We have too few autism practitioners," said the study's senior author, Dennis Wall, PhD, associate professor of pediatrics and of biomedical data science. Early autism therapy has been shown to be particularly effective, but many children aren't treated quickly enough to get the maximum benefit, he said. "The only way to break through the problem is to create reliable, home-based treatment systems. It's a really important unmet need."

Autism is a developmental disorder that affects 1 in 59 children in the United States, with a higher prevalence in boys. It is characterized by social and communication deficits and repetitive behaviors.

The researchers named the new therapy "Superpower Glass" to help make it appealing to children. The therapy is based on applied behavior analysis, a well-studied autism treatment in which a clinician teaches emotion recognition using structured exer- See AUTISM, page 6

Clinical depression linked to low blood levels of acetyl-L-carnitine

By Bruce Goldman

People with depression have low blood levels of a substance called acetyl-L-carnitine, according to a School of Medicine scientist and her collaborators in a multicenter study.

Natalie Rasgon

Naturally produced in the body, acetyl-L-carnitine is also widely available in drugstores, supermarkets and health food catalogs as a nutritional supplement. People with severe or treatment-resistant depression, or whose bouts of depression began earlier in life, have particularly low blood levels of the substance.

The findings, published online July 30 in the *Proceedings of the National Academy of Sciences*, build on extensive animal research. They mark the first rigorous indication that the link between acetyl-L-carnitine levels and depression may apply to people, too. And they point the way to a new class of antidepressants that could be freer of side effects and faster-acting than those in use today, and that may help patients for whom existing treatments don't work or have stopped working.

Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences at Stanford, described the findings as "an exciting addition to our understanding of the mechanisms of depressive illness."

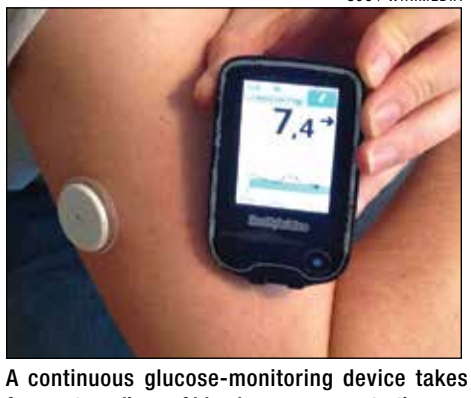
"As a clinical psychiatrist, I have treated many people with this disorder in my practice," she said.

Depression, also called major depressive disorder or clinical depression, is the most prevalent mood disorder in the United States and the world, affecting 8-10 percent See DEPRESSION, page 6

Diabetic-level glucose spikes seen in healthy people, researchers find

By Hanae Armitage

SJÖ / WIKIMEDIA



A continuous glucose-monitoring device takes frequent readings of blood-sugar concentrations.

A device that keeps extra-close tabs on the ups and downs of blood glucose levels reveals that most people see only a partial picture of the sugar circulating in their blood, according to a study by researchers at the School of Medicine.

It turns out that the level of sugar in an individual's blood — especially in individuals who are considered healthy — fluctuates more than traditional means of monitoring, like the one-and-done finger-prick method, would have us believe. Often, these fluctuations come in the form of "spikes," or a rapid increase in the amount of sugar in the blood, after eating specific foods — most commonly, carbohydrates.

"There are lots of folks running around with their glucose levels spiking, and they don't even know it," said Michael Snyder, PhD, professor and chair of genetics at Stanford and senior author of the study. The covert spikes are a problem because high blood sugar levels, especially when prolonged, can contribute to cardiovascular disease risk and a person's tendencies to develop insulin resistance, which is a common precursor to diabetes, he said.

"We saw that some folks who think they're healthy actually are misregulating glucose — some- See GLUCOSE, page 7

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Deep-brain stimulation for drug-resistant epilepsy

Devices that administer deep-brain stimulation, or DBS, are now in widespread use for the treatment of Parkinson's disease and other movement disorders. They also are used for the treatment of obsessive-compulsive disorder. In April, the Food and Drug Administration approved such a device for the treatment of patients with recurring epileptic seizures that don't respond to existing drugs. That approval was based largely on clinical trial results published in 2010 in Epilepsia *and led by Robert Fisher, MD, PhD, professor of neurology at the School of Medicine.*

Fisher, who holds the Maslah Saul, MD, Professorship, has been studying the use of deep-brain stimulation for epilepsy since 1990. Science writer Bruce Goldman interviewed him about the trial's findings and the FDA's action.

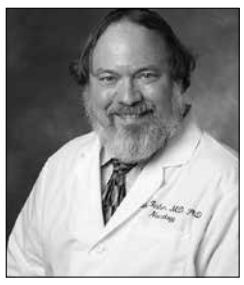
1 What is epilepsy and how common is it?

FISHER: Epilepsy is a brain disease characterized by vulnerability to spontaneous, recurrent seizures. It affects about 1 percent of all people in the world. A seizure, in simple terms, is an electrical storm in the brain arising from excessive or abnormally synchronous neuronal activity. Different types of seizures can produce symptoms ranging from mild tingling or twitching to loss of awareness to falling and shaking. Epilepsy can result either from brain injury or from a genetic predisposition. More than half of adults with the condition have so-called focal-onset seizures, meaning these seizures originate in a particular spot in the brain — although they can spread throughout the brain. Anti-seizure medications work well for only about 2 of 3 people with epilepsy. The number left with seizures is very large, and their epilepsy can seriously interfere with their health and quality of life.

2 What is deep-brain stimulation, and how can it be used to treat seizures?

FISHER: DBS entails sending electrical signals to a location in the brain. This is done by implanting electrodes in the brain and supplying power to these electrodes via fine wires threaded to a pulse-generating device placed under the skin of the chest. For this therapy, the wires are placed in the part of brain called the anterior thalamus, which can influence widespread regions of brain.

I led a trial in 2010 that showed DBS in the anterior thalamus can reduce seizures in epilepsy patients for whom other therapies have failed. Compared with surgery to remove parts of the brain, which can also eliminate or reduce the frequency of recurrent, drug-refractory seizures, DBS is adjustable and reversible. And it spares brain tissue. However, surgery may be more effective in some cases.



Robert Fisher

3 Can you briefly discuss the clinical trial you led in 2010?

FISHER: The trial was performed at 17 centers on 110 patients with medication-resistant focal-onset seizures that occurred, on average, about 20 times per month. Half of these patients were randomized to active stimulation and half to placebo stimulation. Patients could not feel the stimulation so could not tell which group they were in. Active stimulation reduced seizures by 40 percent, whereas placebo reduced seizures by 15 percent — a significant difference. There were fewer seizure injuries in the active group. This was the first proof in a large, controlled trial that electrical brain stimulation could reduce seizures.

In 2015, another study I led showed that the long-term results of this procedure were very favorable. Over time, numbers continued to improve, reaching a 70 percent reduction of seizures. About 15 percent of the participants receiving active stimulation became seizure-free for at least six months. And a study assessing the cognitive and psychological outcomes confirmed the positive findings. In April of this year, the FDA approved the device's use for epilepsy. Exactly how DBS works is only partially understood.

4 Now that the FDA has approved this device for this indication, is it commercially available?

FISHER: It's marketed by Medtronic but is not yet approved for reimbursement by American insurance companies. It should be available at experienced epilepsy centers by early 2019. About 30 other countries have already been using DBS to treat uncontrolled seizures for several years.

5 How would you categorize Stanford's academic and clinical strengths regarding the application of DBS for treating neurological disease?

FISHER: Stanford is the world leader in neurostimulation for epilepsy, and one of the leaders for neurostimulation in a variety of other neurologic and psychiatric diseases. Martha Morrell in the Stanford Comprehensive Epilepsy Program led the successful trial for the FDA-approved responsive neurostimulation therapy for epilepsy, which stimulates by a different method from DBS that is applicable to some epilepsy patients. I led the U.S. trial of the latest generation of vagus nerve stimulators for epilepsy at Stanford. Our neurosurgeons Jaimie Henderson, Casey Halpern and Lawrence Shure have developed important techniques for stimulation. Peter Tass, a research neurosurgeon at Stanford, is pioneering a better method to deliver stimulation. Helen Bronte-Stewart, a neurologist here, is a leader in using DBS to treat movement disorders such as Parkinson's disease.

Until we find definitive cures for epilepsy, neurostimulation is an important new option, and Stanford stands at the forefront of its development. **ISM**

Osteoporosis and fracture risk predicted with genetic screen

By Krista Conger

A new genetic screen may predict a person's future risk of osteoporosis and bone fracture, according to a study by a researcher at the School of Medicine.

Specifically, the study, one of the largest of its kind, identified 899 regions in the human genome associated with low bone-mineral density, 613 of which have never before been identified.

People deemed to be at high risk — about 2 percent of those tested — were about 17 times more likely than others to develop osteoporosis and about twice as likely to experience a bone fracture in their lifetimes. In comparison, about 0.2 percent of women tested will have a cancer-associated mutation in the BRCA2 gene, which increases their risk of breast cancer to about six times that of a woman without a BRCA2 mutation.

Early identification of people with an increased genetic risk for osteoporosis could be an important way to prevent or reduce the incidence of bone fracture, which according to the National Osteoporosis Foundation affects 2 million people each year and accounts for $19 billion in annual health care costs.

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

Kim is the sole author of the study, which was published online July 26 in *PLOS ONE*.

Bone-mineral density as predictor

Kim originally approached his investigation as a way to help elite athletes or members of the military learn if they are at risk of bone injury during strenuous training. Once he had compiled the results, however, he saw a strong correlation between people predicted to have the highest risk of low bone-mineral density and the development of osteoporosis and fracture.

Osteoporosis, or porous bone, is a disease that results in a reduction in bone mass due to bone loss or defects in bone production, or both. It's correlated with a high incidence of bone fracture because the weakened bone is less able to withstand the stress of slips and falls, or sometimes even normal daily activity. It affects millions of Americans and is responsible for as many as 1 in 2 fractures in women and 1 in 4 in men over the age of 50.

Stuart Kim

Two previous studies have shown that there is a genetic component to osteoporosis; you're more likely to develop it if you have a family history of the condition. In addition to genetics, your behaviors, including the frequency and type of exercise you prefer and your diet, as well as your weight and gender, also play a large role in bone health. Recently, genetic studies on large groups of individuals have shown that hundreds of genes are likely involved, each making its own small contribution to either increased or decreased risk of the disease.

Osteoporosis is often diagnosed with a bone-mineral density test that uses X-rays to measure the amount of minerals, such as calcium, in a person's hip, spine or heel. But bone-mineral density tests are usually only performed on people with a family history of osteoporosis or those who have experienced a recent fracture from a simple fall.

"The most common clinical algorithm used to detect or predict osteoporosis is called FRAX," Kim said. "But the catch is that the two largest components of the FRAX algorithm are bone-mineral density and prior fracture. So it's kind of a circular argument."

Developing an algorithm

Kim analyzed the genetic data and health information of nearly 400,000 people in the UK Biobank — a vast compendium of de-identified information freely available to public health researchers around the world. For each participant, Kim collected data on bone-mineral density, age, height, weight and sex, as well that participant's genome sequence. He then developed a computer algorithm to identify naturally occurring genetic differences among people found with low bone-mineral density.

Using the algorithm, Kim was able to identify 1,362 independent differences, or single-nucleotide polymorphisms, that correlated with low bone-mineral density readings. He then used a machine-learning method called LASSO, developed in 1996 by Stanford professor of biomedical data science and of statistics Robert Tibshirani, PhD, to further hone the data.

The resulting algorithm assigned a score to each of the nearly 400,000 participants to indicate their risk of low bone-mineral density; subsequent analyses showed that those in the bottom 2.2 percent of these scores were 17 times more likely than their peers to have been diagnosed with osteoporosis and nearly twice as likely to have experienced a bone fracture.

"The analysis worked really well," Kim said. "This is **See FRACTURE, page 3**

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STANFORD MEDICINE

Gut bacteria byproduct protects against Salmonella, study finds

By Kimber Price

Researchers at the School of Medicine have identified a molecule that serves as natural protection against one of the most common intestinal pathogens.

Propionate, a byproduct of metabolism by a group of bacteria called the Bacteroides, inhibits the growth of Salmonella in the intestinal tract of mice, according to the researchers. The finding may help to explain why some people are better able to fight infection by Salmonella and other intestinal pathogens and lead to the development of better treatment strategies.

A paper describing the work was published July 26 in *Cell Host and Microbe*.

The researchers determined that propionate doesn't trigger the immune response to thwart the pathogen. Instead, the molecule prolongs the time it takes the pathogen to start dividing by increasing its internal acidity.

Salmonella infections often cause diarrhea, fever and abdominal cramps. Most people recover within four to seven days. However, the illness may be severe enough to require hospitalization for some patients. Salmonella causes about 1.2 million illnesses, 23,000 hospitalizations and 450 deaths nationwide each year, according to the Centers for Disease Control and Prevention. Most cases are caused by contaminated food.

Denise Monack

Different responses to exposure

"Humans differ in their response to exposure to bacterial infections. Some people get infected and some don't, some get sick and others stay healthy, and some spread the infection while others clear it," said Denise Monack, PhD, professor of microbiology and immunology and the senior author of the paper. "It has been a real mystery to understand why we see these differences among people. Our finding may shed some light on this phenomenon."

For years, scientists have been using different strains of mice to determine how various genes might influence susceptibility to infection by intestinal pathogens. But this is the first time that researchers have looked at how the variability of gut bacteria in these mice might contribute to their different responses to pathogens.

"The gut microbiota is an incredibly complex ecosystem. Trillions of bacteria, viruses and fungi form complex interactions with the host and each other in a densely packed, heterogeneous environment," said Amanda Jacobson, the paper's lead author and a graduate student in microbiology and immunology. "Because of this, it is very difficult to identify the unique molecules from specific bacteria in the gut that are responsible for specific characteristics like resistance to pathogens."

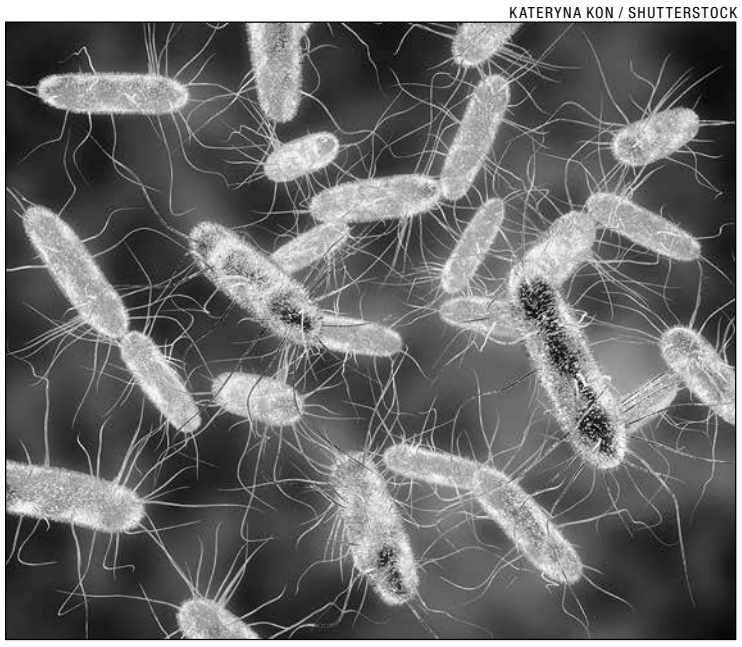
From mice to men

The scientists started with an observation that has been recognized in the field for years: Two inbred strains of mice harbor different levels of Salmonella in their guts after being infected with the pathogen. "The biggest challenge was to determine why this was happening," Jacobson said.

First, they determined that the differences in Salmonella growth could be attributed to the natural composition of bacteria in the intestines of each mouse strain. They did this by performing fecal transplants, which involved giving mice antibiotics to kill off their usual composition of gut bacteria and then replacing the microbial community with the feces of other mice, some of whom were resistant to Salmonella infection. Then, the researchers determined which microbes were responsible for increased resistance to Salmonella infection by using machine-learning tools to identify which groups of bacteria were different between the strains.

They identified a specific group of bacteria, the Bacteroides, which was more abundant in mice transplanted with the microbiota that was protective against Salmonella. Bacteroides produce short-chain fatty acids such as formate, acetate, butyrate and propionate during metabolism, and levels of propionate were threefold higher in mice that were protected against Salmonella growth. Then, the researchers sought to figure out whether propionate protected against Salmonella by boosting the immune system like other short-chain fatty acids do.

KATERYNA KON / SHUTTERSTOCK



An illustration of Salmonella bacteria. A new study identified a molecule that offers natural protection against the microbe, which causes about 1.2 million illnesses a year.

The scientists examined their Salmonella model for the potential impact of propionate on the immune system but found that the molecule had a more direct effect on the growth of Salmonella. Propionate acts on Salmonella by dramatically decreasing its intracellular pH and thus increasing the time it takes for the bacterium to start dividing and growing, the study found.

"Collectively, our results show that when concentrations of propionate, which is produced by Bacteroides, in the gut are high, Salmonella are unable to raise their internal pH to facilitate cellular functions required for growth," Jacobson said. "Of course, we would want to know how translatable this is to humans."

Reducing the impact of Salmonella

"The next steps will include determining the basic biology of the small molecule propionate and how it works on a molecular level," Jacobson said. In addition, the researchers will work to identify additional molecules made by intestinal microbes that affect the ability of bacterial pathogens like Salmonella to infect and "bloom" in the gut. They are also trying to determine how various diets affect the ability of these bacterial pathogens to infect and grow in the gut and then shed into the environment. "These findings will have a big impact on controlling disease transmission," Monack said.

The findings could also influence treatment strategies. Treating Salmonella infections sometimes requires the use of antibiotics, which may make Salmonella-induced illness or food poisoning worse since they also kill off the "good" bacteria that keep the intestine healthy, according to Monack. Using propionate to treat these infections could overcome this limitation. "Reducing the use of antibiotics is an added benefit because overuse of antibiotics leads to increased incidence of antibiotic-resistant microbes," Monack said.

Other Stanford co-authors of the paper are postdoctoral scholar Manohary Rajendram, PhD; graduate students Lilian Lam, Fiona Tamburini, Will Van Treuren, Kali Pruss, Jared Honeycutt and Kyler Lugo; Trung Pham, MD, instructor of pediatrics and infectious diseases; life science researcher Russel Stabler; Donna Bouley, DVM, PhD, professor emeritus of comparative medicine; José Vilches-Moure, PhD, assistant professor of comparative medicine; senior research scientist Mark Smith, PhD; Justin Sonnenburg, PhD, associate professor of microbiology and immunology; Ami Bhatt, MD, PhD, assistant professor of medicine and of genetics; and KC Huang, PhD, associate professor of bioengineering and of microbiology and immunology.

Bhatt, Huang, Monack, Sonnenburg and Vilches-Moure are members of Stanford Bio-X. Bhatt, Huang, Monack and Sonnenburg are faculty fellows at Stanford ChEM-H. Bhatt, Bouley and Vilches-Moure are members of the Stanford Cancer Institute. Bhatt and Monack are members of the Stanford Child Health Research Institute. Vilches-Moure is a member of the Stanford Cardiovascular Institute. Bouley is an affiliate of the Stanford Woods Institute for the Environment. Sonnenburg and Huang are Chan Zuckerberg Biohub Investigators.

The study was funded by the National Institutes of Health, the Paul Allen Stanford Discovery Center on Systems Modeling of Infection and the National Science Foundation.

Stanford's Department of Microbiology and Immunology also supported the work. **ISM**

Fracture

continued from page 2

one of the largest genomewide association studies ever completed for osteoporosis, and it clearly shows the genetic architecture that underlies this important public health problem."

Kim is now planning to arrange a clinical trial to investigate whether elite athletes and select members of the military identified by the algorithm as being at high risk for osteoporosis and potential fracture can increase their bone-mineral density with simple preventive measures. He's also interested in conducting a similar study among younger people with no obvious clinical symptoms of bone weakening.

"Fifteen million people in this country have already accessed their genome sequences using direct-to-consumer testing services," Kim said. "I think this analysis has the potential to become the standard of care in the coming years. It would be a relatively simple measure to identify those who should have their bone-mineral density tested and perhaps take steps at an early age to ensure their future bone health."

The study is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

The research was supported by the National Institute on Aging.

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

Protein key for making stem cells identified

By Krista Conger

Researchers at the School of Medicine have identified a new protein critical to the production of induced pluripotent stem cells, or iPS cells.

The protein, NKX3-1, has previously been shown to play a role in prostate development and tumor suppression. It can substitute for one of the four proteins first identified in 2007 by stem cell researcher Shinya Yamanaka, MD, PhD, as sufficient to prod mature cells like those in the skin or blood to become iPS cells — a transformation known in the stem cell world as reprogramming.

The discovery creates a peephole into the black box of cellular reprogramming and may lead to new ways to generate iPS cells in the laboratory. It was made possible by the use of a unique laboratory model for reprogramming that tightly synchronizes the earliest steps of the process.

"This is a crucial regulator that would not have been discovered any other way," said Helen Blau, PhD, professor of microbiology and immunology. "It appears within two hours of the initiation of reprogramming, and then it's gone. But it's absolutely critical. If we eliminate it, reprogramming doesn't happen."

Blau, the Donald E. and Delia B. Baxter Foundation Professor and director of the Baxter Foundation Laboratory for Stem Cell Biology, is the senior author of the research, which was published online July 16 in *Nature Cell Biology*. Postdoctoral scholar Thach Mai, PhD, is the lead author.

The ability to reprogram mature cell types, such as skin cells, into pluripotent stem cells by the addition of just four proteins, called Yamanaka factors, captivated the scientific world and led to a Nobel Prize in 2012 for Yamanaka. Since then, countless researchers worldwide have used the technique to create iPS cells for study or potential clinical use.

Hopes for safer reprogrammed cells

The four Yamanaka factors — Oct4, Sox2, cMyc and Klf4 — were identified because they are highly expressed in embryonic stem cells in mice and humans. Exposing mature cell types to these factors makes them regress in their development and, eventually, behave like **See CELLS, page 5**

Study: Nonclinician effective in end-of-life talks with patients

By Amy Jeter Hansen

Patients with advanced cancer who spoke with a trained nonclinical worker about personal goals for their care were more likely to talk with doctors about their care preferences, report higher satisfaction with their care and incur lower health costs in their final month of life, School of Medicine researchers report.

STEVE FISCH

Manali Patel created a curriculum to train a nonclinical health worker on conducting goals-of-care conversations.

The findings, from a pilot study of 213 patients, suggest that patients with a serious illness are more at ease with decisions about their care and more likely to mention their care preferences to health care providers when they discuss those preferences soon after their diagnosis, and on an ongoing basis, with someone outside the medical context, said Manali Patel, MD, assistant professor of medicine at Stanford and the study's lead author.

She and her colleagues employed a lay health worker to conduct conversations with patients about their personal desires for care and to encourage them to share this information with providers. The intervention was based on prior research conducted by Patel, when she was a fellow at Stanford's Clinical Excellence Research Center, in which patients expressed a preference for having these discussions with nonclinical workers. Though more research is needed, the new study suggests it is a promising approach for improving the quality of end-of-life cancer care while lowering the costs, she said.

"A goals-of-care conversation is not about prognosis. It's a holistic approach to understanding the patient's wishes and how they want to experience their life," Patel said. "You don't need higher-level training to have that conversation. You just need a very supportive ear."

The study was published July 26 in *JAMA Oncology*. Its senior author is Kate Bundorf, PhD, associate professor of health research and policy at Stanford.

Conversations about goals of care

Patel and her fellow researchers followed patients at the Veterans Administration Palo Alto Health Care System for 15 months after they were diagnosed with stage-3 or -4 cancer or with recurrent cancer. Half were randomly assigned to speak with a lay health worker about goals of care over a six-month period.

The lay health worker had participated in a training curriculum created by Patel that included an 80-hour online seminar, as well as four weeks of observational training with the hospital's palliative care team. During several telephone and in-person conversations, the worker led patients through a structured program that addressed questions, such as, "What is your understanding of your cancer?" "What is important to you?" "Have you thought about a time when you could be sicker?" "How would you want to spend your time in that situation?" Together, they also established care preferences, identified a surrogate decision-maker and filed an advance directive.

"We trained the worker to address these questions over multiple time periods and to revisit the conversation when unexpected events occurred, such as an emergency department visit or bad scan results," Patel said. "How a patient feels and what they express as their desires today may be different from how they may feel a week from now, if they had a really horrible side effect from the chemotherapy that they're receiving and they're finding themselves in the hospital for two weeks rather than spending the time with their family."

Patients in the study who participated in conversations with the lay health worker were more likely to have documentation of end-of-life care preferences in their electronic health records within six months of those conversations starting (92 percent compared with 18 percent in the control group). Researchers used this documentation to gauge whether patients had discussed the topic with their doctors.

Patients in the intervention group also rated their oncology care higher, giving it an average satisfaction score of 9.16 out of 10, compared with the average of 7.83 from the control group. They also posted higher satisfactions scores when queried about their care-related decision-making.

"This indicates that patients in the intervention were having a better experience with their providers despite having been prompted and activated to discuss really difficult topics," Patel said. "This is consistent with what other studies have shown indicating that patients value honest and open communication regarding their prognosis."

"You just need a very supportive ear."

Use and cost of health care

The researchers also monitored health-care costs and use among patients in the two groups.

They found few significant differences over 15 months; however, for patients who died during the study, the final 30 days diverged markedly. Those who discussed goals of care with the lay health worker were six times less likely to visit the emergency department or be hospitalized than members of the control group, and twice as likely to use hospice services. Their median health care cost within 30 days of death was $1,048, compared with $23,482 for the control group.

Overall, patients who participated in conversations with the lay health worker used hospice at higher rates than the control group — a finding that tracks with other research, Patel said.

"Consistently, patients who understand that they have an incurable cancer are more likely to choose less aggressive care, and we see that same result here," she said. "Communication and listening to patients seem to be the common theme because when providers listen to patients and they're receiving care that's concordant with their goals, they seem to have better outcomes, especially at the end of life."

Other Stanford co-authors of the study are biostatistician Vandana Sundaram; Manisha Desai, PhD, professor of medicine and of biomedical data science; VJ Periyakoil, MD, associate professor of medicine; James Kahn, MD, professor of medicine; Jay Bhattacharya, MD, PhD, professor of medicine; Steven Asch, MD, professor of medicine; and Arnold Milstein, MD, professor of medicine.

Patel is a member of the Stanford Cancer Institute.

The research was funded by the California Health Care Foundation, Veterans Affairs Office of Healthcare Transformation Specialty Care and the National Institutes of Health.

This work was also supported by Stanford's departments of Medicine and of Health Research & Policy. ISM

Med school communications office wins four national awards

The medical school's Office of Communication & Public Affairs earned four national awards from the Council for Advancement and Support of Education for work produced in 2017.

Stanford Medicine magazine earned one of two silver awards for periodical staff writing (the other silver award went to *Stanford Magazine*). Judges for CASE's annual Circle of Excellence Awards said the magazine stories were "highly readable from a non-specialist's perspective, and we noted how well the articles spoke to a wide range of audiences from physicians to policy makers to the general public." The magazine's editor is Rosanne Spector.

The five stories in the staff-writing entry were:

- "Of mice, men and women," by Krista Conger, published in the spring 2017 issue, which examined efforts to embrace and account for sex and gender differences in research.
- "Transgender," by Erin Digitale, also published in the spring issue. The story featured a family that shared its experiences of having a transgender child and included commentary by caregivers who discuss their approach to working with such children and their families.
- "Two minds," by Bruce Goldman, also published in the spring issue. The story explored the question of whether the brains of men and women are wired differently.
- "The fearful eye," by Goldman, published in the summer issue. The story described how researchers are using frightening virtual reality experiences to understand the neuroscience of fear.
- "No place to call home," by Digitale, published in the fall issue. The story focused on how a growing number of pediatricians are addressing the social problems, such as difficulties in finding an affordable place to live in the expensive Bay Area, that have a direct bearing on the health of their young patients.

A photo in the magazine won a silver award. Brian Smale's photo of Jeffrey Goldberg, MD, professor and chair of ophthalmology, accompanied a story about Stanford's efforts to combat vision loss. "The juxtaposition of the soft image through the glass and the sharp focus on the eye was dramatic and interesting," the judges wrote.

A video that accompanied the magazine story about transgender youth received a bronze award in the news and research category. Video director Mark Hanlon produced the video, which told the story of a transgender teen and his family. "The video frames Dani's struggles and joys as part of the broader issue of gender research and care of transgender patients for which Stanford Medicine is at the forefront," the judges wrote.

The news releases produced by the office received one of two bronze awards in the research, medicine and science news writing category. Judges said the releases "are compelling examples of scientific advancements being made that inform and impact the general public. The writing explained highly technical research in a way that is understandable and appealing to lay readers." The news releases were edited by John Sanford.

The news releases in the entry were:

- "Study finds first possible drug treatment for lymphedema," by Tracie White.
- "In northern humans, evolution favored shorter bones," by Conger.
- "Small drop in measles vaccinations would have outsized effect," by Digitale.
- "Regular marijuana use linked to more sex," by Goldman.
- "Neuroscientist Ben Barres dies at 63," by Goldman

CASE is a professional organization for those in the fields of communications, alumni relations and development at educational institutions. It includes more than 3,600 colleges, universities, and independent elementary and secondary schools in 82 countries. To recognize the best work in these fields, CASE sponsors its annual Circle of Excellence Awards. ISM

BRIAN SMALE

This photo of ophthalmologist Jeffrey Goldberg received a silver award in the annual competition sponsored by CASE.

Stanford Biodesign technologies reach over 1.5 million patients

By Stacey Paris McCutcheon

Medical technologies invented by fellows and students over the past 18 years at the Stanford Byers Center for Biodesign have been used in the care of more than 1.5 million patients, leaders of the center say.

The center teaches a process for solving problems in health care through technology innovation.

"The successful translation of these technologies into patient care reflects Stanford Biodesign's focus on solving real-world problems, as well as the determination of our trainees to not only develop solutions but bring them to the market," said Paul Yock, MD, the center's founder and director. "Health care is an extremely challenging field for innovation because there are many different stakeholders — from doctors to patients to regulators to insurers — who have a say in whether a new technology is adopted."

To help aspiring health care innovators succeed, Stanford Biodesign teaches a need-driven innovation process that involves interdisciplinary collaboration, project-based learning and hands-on mentoring from experts across Silicon Valley. In the yearlong Biodesign Innovation Fellowship, for example, the fellows spend a full six weeks in hospitals, clinics and other environments observing the delivery of care to identify unaddressed problems that could benefit from technology-based solutions. After determining which problems represent the most compelling opportunities, the teams use everything they learn over the course of the year to develop solutions.

The innovators who contributed to the 1.5 million-plus patient milestone have addressed a wide range of problems, from surgical infections to prostate disease to heart arrhythmia and essential tremor. But they all have one thing in common: a story about a patient encounter that inspired them to try and make things better. Following are a few of those stories.

Rush Bartlett: End-of-life planning

In their first week of clinical immersion, biomedical engineer Rush Bartlett, PhD, MBA, and the other members of his 2012-13 fellowship team — Stanford pulmonologist Ryan Van Wert, MD, and electrical engineer Frank Wang, PhD — sat down with an emergency physician at Stanford Hospital. They asked him to describe the worst part of his job. The physician replied almost immediately: "Giving CPR to a 90-year old woman, breaking her ribs and then finding out later that was not what she or her family wanted."

After learning that this scenario repeated almost weekly, the team decided to investigate further. Explained Bartlett, "We learned that, while advance care directives are common, far too often this information isn't readily available to the care team, especially in emergency situations. The advance care directive is filed away with an attorney or taped to the patient's refrigerator. What was missing was a way for doctors to rapidly access the patient's directive in a crisis if they are unable to personally communicate their wishes."

The team solved this issue by directly linking advance care directives and other critical end-of-life information to electronic medical records, and by making it available to health care providers across the care continuum. Information about the team's experience and project is available online at https://youtu.be/OgQV3ffCrCg.

Fletcher Wilson: Deep vein failure

A 2009-10 fellowship team that included mechanical engineer Fletcher Wilson was motivated to develop a better solution for treating deep vein valve failure after meeting a robust, physically active man debilitated by repeated venous leg ulcers that manifested as open wounds.

"They tried everything to help him," said Wilson, who had a background in medical device development. "Unfortunately, the blood clot he'd experienced years ago had destroyed the vein valves throughout his thigh. On his most recent clinic visit, he was told that compression therapy was the best option available to control the swelling and pain. I caught him in the hall as his face turned red, unable to hold back tears. 'Tight socks?' he asked in frustration. 'That's the best they can prescribe for me?' That's when I committed myself to solving this problem."

The technology Wilson and his team invented represents the first minimally invasive approach to deep vein valve failure. The solution allows physicians to create new vein valves for patients who are unable to efficiently pump blood from their legs back to their heart.

COURTESY OF THE STANFORD BYERS CENTER FOR BIODESIGN

Michael Carchia, Todd Murphy and Brownwyn Harris were 2014-15 Stanford Biodesign fellows. They worked together on developing a system to enable better management of childhood asthma.

Bronwyn Harris: Childhood asthma

Bronwyn Harris, MD, a pediatric cardiologist, was a fellow in 2014-15. Her experience caring for children with asthma, both as a doctor and as a mother, inspired her to help caregivers manage this frustrating disease. "Pediatric asthma is a chronic disease with no good measures of control," she said. "It's hard to tell how a child is doing, and what might trigger a flare-up. The unpredictability of the condition leaves parents feeling as though asthma is controlling their lives."

Harris' team developed a system that uses environmental data and outputs from sleep sensors to detect changes in asthma control, identify potential triggers and provide insights to families and their physicians that enable more comprehensive management of the disease. The results so far have been promising.

As an example of what drives her to keep advancing the technology, Harris told the story of a 9-year-old boy she met during a clinical study: "He was having an asthma exacerbation roughly once a month. In the prior year, his flare-ups were so severe that he had been to the emergency room twice and was hospitalized once. But by the third month of using our service, he was symptom-free, and his mother felt more knowledgeable and empowered to manage his asthma."

A need-driven approach

Yock, an interventional cardiologist and renowned medical device innovator, founded Stanford Biodesign in 2000 as part of both the School of Medicine and the School of Engineering. The center's focus on deeply understanding the need first, rather than starting with an idea for a new technology, has become a model for health technology training programs around the world. Recognizing this contribution, the National Academy of Engineering awarded Yock the 2018 Bernard M. Gordon Prize for Innovation in Technology Education.

To date, 47 companies have been founded by the center's trainees based on technologies they initiated during their training. Other alumni have gone on to drive innovation initiatives within larger medical-technology companies, launch innovation training programs at other universities, or pursue technology innovation within their clinical practice. Information about the center is available online at biodesign.stanford.edu. **ISM**

Cells

continued from page 3

stem cells, even beginning to express Oct4 on their own. There are concerns about this process, however, because cMyc and Oct4 are oncogenes that can cause cancers when overexpressed in normal cells. Researchers believe an understanding of how reprogramming occurs might allow them to identify new ways to generate stem cells that are safer for clinical use.

Unfortunately, much of what goes on during the first hours of reprograming has remained a mystery, in part because only about 1 in 1,000 cells treated with the factors successfully undergoes the transition. Furthermore, those that do, do so on their own erratic schedule.

"It's been difficult to get a handle on early regulators of reprogramming to pluripotency," Blau said. "The process is highly heterogeneous and asynchronous, so the earliest events have been hard to study."

To overcome this limitation, Mai turned to a cell fusion model used successfully by Blau in the 1980s to show that specialized human cells, such as those in the liver and skin, could express muscle-specific genes when joined with mouse muscle fibers. At the time, the results provided the first evidence that adult cells could be coaxed under the right conditions to assume entirely different cell fates.

Helen Blau

In the new study, Mai fused human skin cells called fibroblasts to mouse embryonic stem cells. After fusion, factors in the developmentally flexible stem cell quickly and efficiently reprogrammed the fibroblast nucleus along a predictable, research-amenable timeline. The fused cells are called heterokaryons, and they enabled Mai and his colleagues to closely track patterns of gene expression and DNA modification during the first 24 hours of reprogramming.

Using the heterokaryon model, the researchers discovered that NKX3-1 is expressed within about two hours of the initiation of reprogramming but quickly dissipates. If the protein's expression is blocked, the Yamanaka factors are no longer able to reprogram the human fibroblasts, indicating NKX3-1's crucial role in the conversion of adult cells to stem cells. The researchers also found that externally added NKX3-1 can replace Oct4 to reprogram cells without any loss of efficiency.

Finally, they also showed that NKX3-1 expression was necessary to trigger the cells' expression of their own Oct4 protein and to promote other genetic changes that facilitate reprogramming.

Delving deeper

Now Blau and her colleagues, in collaboration with assistant professor of genetics and of computer science Anshul Kundaje, PhD, plan to continue their studies into the earliest steps of reprogramming to pluripotency using a multipronged "omics-based" approach.

"Our goal is to study all facets of the regulatory logic, or 'grammar,' that underlies cellular reprogramming to pluripotency," Blau said. "Reprogramming completely changes a cell's fate. We want to understand the mechanistic and signaling pathways that mediate such a remarkable change."

Other Stanford co-authors are postdoctoral scholars Glenn Markov, PhD, and Adelaida Palla, PhD; former postdoctoral scholar Jennifer Brady, PhD; senior research scientist Hong Zeng, MD, PhD; and assistant professor of obstetrics and gynecology Vittorio Sebastiano, PhD.

Blau is a member of Stanford's Institute for Stem Cell and Regenerative Medicine, Bio-X, Cardiovascular Institute, Child Health Research Institute, Cancer Institute and Neurosciences Institute.

The research was supported by the National Institutes of Health, the California Institute of Regenerative Medicine, the National Science Foundation, Bio-X, the GSK Sir James Black Program for Drug Discovery and the Baxter Foundation.

Stanford's Department of Microbiology and Immunology also supported the work. **ISM**

Autism

continued from page 1

cises such as flash cards depicting faces with different emotions. Although traditional applied behavior analysis helps children with autism, it has limitations: It must be delivered one-on-one by trained therapists, flash cards can't always capture the full range of human emotion and children may struggle to transfer what they learn to their daily lives.

Eight core facial expressions

Wall's team decided to try using applied behavior analysis principles in a way that would bring parents and everyday situations into the treatment process. They built a smartphone app that uses machine learning to recognize eight core facial expressions: happiness, sadness, anger, disgust, surprise, fear, neutral and contempt. The app was trained with hundreds of thousands of photos of faces showing the eight expressions, and also had a mechanism to allow people involved in the study to calibrate it to their own "neutral" faces if necessary.

Typically developing children learn to recognize emotions by engaging with people around them. For children with autism, it's different. "They don't pick those things up without focused treatment," Wall said.

In the study, 14 families tested the Superpower Glass setup at home for an average of 10 weeks each. Each family had a child between the ages of 3 and 17 with a clinically confirmed autism diagnosis.

The families used the therapy for at least three 20-minute sessions per week. At the start and end of the study, parents completed questionnaires to provide detailed information about their child's social skills. In interviews, parents and children also gave feedback about how the program worked for their families.

The researchers designed three ways to use the face-recognizing program: In "free play," children wear Google Glass while interacting or playing with their families, and the software provides the wearer with a visual or auditory cue each time it recognizes an emotion on the face of someone in the field of view. There are also two game modes. In "guess my emotion," a parent acts out a facial expression corresponding to one of the eight core emotions, and the child tries to identify it. The game helps families and researchers track children's improvement at identifying emotions. In "capture the smile," children give another person clues about the emotion they want to elicit, until the other person acts it out, which helps the researchers gauge the children's understanding of different emotions.

Good reviews from families

Families told the researchers that the system was engaging, useful and fun. Kids were willing to wear the Google Glass, and the devices withstood the wear and tear of being used by children.

Twelve of the 14 families, including Alex's, said their children made more eye contact after receiving the treatment. A few weeks into the trial, Alex began to realize that people's faces hold clues to their feelings.

"He told me, 'Mommy, I can read minds!'" Cullenbine said. "My heart sang. I'd like other parents to have the same experience."

Families whose children had more severe autism were more likely to choose the game modes rather than free play, the researchers reported.

The children's mean score on the SRS-2, a questionnaire completed by parents to evaluate children's social skills, decreased by 7.38 points during the study, indicating less severe symptoms of autism. None of the participants' SRS-2 scores increased during the study, meaning nobody's autism symptoms worsened. Six of the 14 participants had large enough declines in their scores to move down one step in the severity of their autism classification: four from "severe" to "moderate," one from "moderate" to "mild" and one from "mild" to "normal."

STEVE FISCH

Clinical research coordinator Jessey Schwartz (left) with Alex and his mother, Donji Cullenbine.

> "My heart sang. I'd like other parents to have the same experience."

The results should be interpreted with caution since the study did not have a control arm, Wall said. However, the findings are promising, he added.

Parents' comments in interviews helped illustrate the improvements, he said. "Parents said things like 'A switch has been flipped; my child is looking at me.' Or 'Suddenly the teacher is telling me that my child is engaging in the classroom.' It was really heartwarming and super-encouraging for us to hear," Wall said.

His team is currently completing a larger, randomized trial of the therapy. In addition, they also plan to test the therapy in children who have just been diagnosed with autism and are on a waiting list for treatment. Stanford University has filed a patent application for the technology.

Information about the project is available online at http://autismglass.stanford.edu.

The study's other Stanford authors are clinical research coordinators Jena Daniels and Jessey Schwartz; graduate students Catalin Voss and Peter Washington; postdoctoral scholar Nick Haber, PhD; software engineer Azar Fazel; software developer Aaron Kline; Carl Feinstein, MD, professor emeritus of psychiatry and behavioral sciences; and Terry Winograd, PhD, professor emeritus of computer science.

Wall, Feinstein and Winograd are members of Stanford Bio-X and the Stanford Child Health Research Institute. Wall is also a member of the Stanford Neurosciences Institute.

The research was funded by grants from the National Institutes of Health, Stanford's Clinical and Translational Science Award, the David and Lucile Packard Foundation, the Beckman Center for Molecular and Genetic Medicine, the Wallace H. Coulter Foundation, Stanford's Walter V. and Idun Berry Postdoctoral Fellowship Program, the Stanford Child Health Research Institute, the Dekeyser and Friends Foundation and the Mosbacher Family Fund for Autism Research, as well as an individual gift from Peter Sullivan. The researchers received an in-kind gift from Google of 35 Google Glass devices as well as technical assistance from the company, and an in-kind grant of Amazon Web Services Founder Support.

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

Depression

continued from page 1

of the general population at any given time, with every fourth person likely to experience the condition over the course of a lifetime.

"It's the No. 1 reason for absenteeism at work, and one of the leading causes of suicide," Rasgon said. "Worse, current pharmacological treatments are effective for only about 50 percent of the people for whom they're prescribed. And they have numerous side effects, often decreasing long-term compliance."

Rasgon shares senior authorship of the study with Bruce McEwen, PhD, professor and chief of the Laboratory of Neuroendocrinology at The Rockefeller University in New York City. The lead author is Carla Nasca, PhD, a postdoctoral scholar in McEwen's lab.

> "We've identified an important new biomarker of major depression disorder."

Results in animal studies

"In rodent experiments led by Dr. Nasca both here at Rockefeller and elsewhere previously, a deficiency of acetyl-L-carnitine was associated with depression-like behavior," McEwen said. Oral or intravenous administration of acetyl-L-carnitine reversed the animals' symptoms and restored their normal behavior, he said.

In those studies, the animals responded to acetyl-L-carnitine supplementation within a few days. Current antidepressants, in contrast, typically take two to four weeks to kick in — in animal experiments as well as among patients.

Nasca's animal studies suggest that acetyl-L-carnitine, a crucial mediator of fat metabolism and energy production throughout the body, plays a special role in the brain, where it works at least in part by preventing the excessive firing of excitatory nerve cells in brain regions called the hippocampus and frontal cortex.

The new study, also initiated by Nasca, recruited 20- to 70-year-old men and women who had been diagnosed with depression and, amid episodes of acute depression, had been admitted to either Weill Cornell Medicine or Mount Sinai School of Medicine, both in New York City, for treatment. These participants were screened via a detailed questionnaire and assessed clinically, and their blood samples and medical histories were taken. Twenty-eight of them were judged to have moderate depression, and 43 had severe depression.

In comparing their blood samples with those of 45 demographically matched healthy people, the depressed patients' acetyl-L-carnitine blood levels were found to be substantially lower. These findings held true for both men and women, regardless of age.

Lowest levels = worst symptoms

Further analysis showed that the lowest levels occurred among participants whose symptoms were most severe, whose medical histories indicated they were resistant to previous treatments, or whose onset of the disorder occurred early in life. Acetyl-L-carnitine levels were also lower among those patients reporting a childhood history of abuse, neglect, poverty or exposure to violence.

These patients, who collectively account for 25-30 percent of all people with major depression disorder, are precisely the ones most in need of effective pharmacological interventions, said Rasgon, who performed the bulk of the advanced data analysis for the study.

But she cautioned against rushing to the store to pick up a bottle of acetyl-L-carnitine and self-medicating for depression. "We have many previous examples of how nutritional supplements widely available over the counter and unregulated by the Food and Drug Administration — for example, omega-3 fatty acids or various herbal substances — are touted as panaceas for you-name-it, and then don't pan out," she said.

Big questions remain, she added. "We've identified an important new biomarker of major depression disorder. We didn't test whether supplementing with that substance could actually improve patients' symptoms. What's the appropriate dose, frequency, duration? We need to answer many questions before proceeding with recommendations, yet. This is the first step toward developing that knowledge, which will require large-scale, carefully controlled clinical trials."

Rasgon is a member of the Stanford Neurosciences Institute.

Researchers at Weill Cornell Medical College, the Icahn School of Medicine at Mount Sinai, Duke University and the Karolinska Institute in Stockholm, Sweden, also contributed to the work.

Stanford University shares in a multi-institutional agreement concerning intellectual property generated by this research.

The study was funded by the Hope for Depression Research Foundation, the Pritzker Neuropsychiatric Disorders Research Consortium and the Robertson Foundation.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. ISM

Social reward circuit in the brain impaired in kids with autism

By Erin Digitale

Children with autism have structural and functional abnormalities in the brain circuit that normally makes social interaction feel rewarding, according to a new study from the School of Medicine.

The study, which was published July 17 in *Brain,* documented deficits in children with autism in a crucial reward circuit, called the mesolimbic reward pathway, that's buried deep within the brain. The degree of abnormality in this pathway predicted the degree of social difficulty in individual children with autism, the study found.

The findings help clarify which of several competing theories best explains the social impairments seen in children with autism. The discoveries, made via MRI brain scans, support the social motivation theory of autism, which proposes that social interaction is inherently less appealing to people who have the disorder.

"It's the first time we have had concrete brain evidence to support this theory," said the study's lead author, Kaustubh Supekar, PhD, a research scientist at Stanford's Translational Neurosciences Incubator. Disrupting the mesolimbic reward pathway in mice reduces their social behavior, prior research has shown, but no one knew how closely the pathway was tied to social skills in people. "This is the first neurobiological evidence in children that this mechanism might explain their social impairments," Supekar said.

"Human social cognition is complex," said the study's senior author, Vinod Menon, PhD, professor of psychiatry and behavioral sciences. "We were surprised we could trace deficits in social skills to a very simple, almost primordial circuit."

> "Our findings suggest that this is a brain system that should be targeted early in clinical treatments."

A vicious cycle

The brain difference could launch a vicious cycle that makes it hard for children with autism to acquire complex social skills, according to the researchers.

"Social interaction is usually inherently rewarding. If it's not rewarding enough to a child with autism, that could have cascading effects on other brain systems," said Menon, who is the Rachael L. and Walter F. Nichols, MD, Professor. In order to develop social-communication skills and the ability to infer others' thoughts and feelings, children must interact with other people. If they don't find those interactions rewarding, they seek fewer opportunities to develop complex social skills, he said. "Our findings suggest that this is a brain system that should be targeted early in clinical treatments," he added.

Vinod Menon

Children with autism have difficulty with social interaction and communication, and show repetitive behaviors and restricted interests. The Centers for Disease Control and Prevention estimates the developmental disorder affects 1 in 59 children.

To conduct the study, the researchers collected MRI brain scans of 40 children with autism and 44 children without autism. They examined brain wiring in 24 children with autism and 24 children who didn't have it, and functional connections in the brain in 16 children with autism and 20 children without the disorder as they looked at social or nonsocial images — pictures of faces or of scenery — while having their brains scanned.

The team also conducted MRI scans of brain wiring on an additional 17 children with the disorder and 17 children without it to see if the results from the first groups could be replicated in a second, independent cohort. All of the children studied were 8-13 years old. Children with autism had their diagnosis confirmed by standard clinical testing for the disorder, and all children had their IQ tested.

The density of nerve-fiber tracts in the mesolimbic reward pathway was lower in children with autism than in those without; there were no differences between the children with and without autism when researchers examined an emotion-related brain pathway as a control. Among the children who had autism, lower density of nerve-fiber tracts was linked to greater social impairment on a standard clinical evaluation of their social skills. The results were the same in the second, independent cohort of children the team studied. Children with autism also had weaker functional connections in the mesolimbic reward pathway than did typically developing children. The degree of functional deficit was also correlated to social impairment.

Findings could aid treatment search

The research provides a useful link between prior work in animal models of autism and human data, the researchers said, and is especially strong because the findings were replicated in two groups of research participants. Next, the researchers want to determine whether the same brain deficits can be detected in younger children with autism.

The discovery also provides a good starting point for future studies of autism treatments. Some existing, effective autism therapies use various rewards to help children engage in social interaction, but it is not known if those treatments strengthen the brain's social reward circuits.

"It would be exciting to conduct a clinical intervention study to determine whether the structural and functional integrity of this pathway can be altered through a reward-based learning paradigm," Menon said.

The study's other Stanford authors are graduate student John Kochalka; former visiting scholar Marie Schaer, MD, PhD; former research assistant Holly Wakeman; Shaozheng Qin, PhD, former instructor; and Aarthi Padmanabhan, PhD, academic program professional. Menon is a member of Stanford's Child Health Research Institute, the Stanford Neurosciences Institute and Stanford Bio-X.

The research was supported by the Brain & Behavior Research Foundation, the National Institutes of Health, the Stanford Child Health Research Institute, the Autism Science Foundation, the Swiss National Foundation, and the Simons Foundation for Autism Research.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. **ISM**

Glucose

continued from page 1

times at the same severity of people with diabetes — and they have no idea," Snyder said.

The insight came to him after he and collaborators at Stanford gave study participants a continuous glucose-monitoring device, which superficially pokes into the surface layer of the skin and takes frequent readings of sugar concentrations in the blood as it circulates. With the frequent readouts providing more detailed data, Snyder's group saw not only that glucose dysregulation is more common than previously thought, but they also used the data to start building a machine-learning model to predict the specific foods to which people spike. The goal is to one day use the framework to compile data from an individual and, based on their continuous glucose readout, direct them away from particularly "spikey" foods.

The study was published online on July 24 in *PLOS Biology*. Graduate student Heather Hall, research dietician Dalia Perlman and postdoctoral scholar Alessandra Brechi, PhD, share lead authorship.

Some are 'spikier' than others

Most people who periodically check their blood sugar levels do so with a quick lance to the finger and a device that reads out the blood glucose concentration. The problem with this method is that it captures only a snapshot in time. The amount of sugar in a person's blood is not a constant; it ebbs and flows depending on what the person has eaten that day, down to the specific kind of carbohydrate. (For instance, rice, breads and potatoes are all different kinds of carbohydrates, yet people often digest them differently.)

To get a better read on glucose levels, Snyder fitted 57 people with a device that continuously took blood glucose readings over about two weeks. Most of the participants were healthy or showing signs of prediabetes, and five had Type 2 diabetes. Data sent back to the lab showed that there were multiple types of spikers, which were classified into three overarching "glucotypes." The glucotype categories — low, moderate and severe — are basically rankings of spike intensity.

"We're very interested in what it means to be 'healthy' and finding deviations from that," said Snyder, who holds the Stanford W. Ascherman, MD, FACS Professorship in Genetics. These glucotypes, he said, are subject to change based on diet. The researchers ultimately have two goals for their work: When people spike, catch it early; and understand what makes a person spike, and adjust their diet to bring the glucotype into the "low" range.

Often people who are prediabetic have no idea they're prediabetic. In fact, this is the case about 90 percent of the time. It's a big deal, Snyder said, as about 70 percent of people who are prediabetic will eventually develop the disease.

"We think that these continuous glucose monitors will be important in providing the right information earlier on so that people can make changes to their diet should they need to," he said.

Blame it on the cornflakes

In getting at the subtleties of spiking, Snyder conducted a sub-study in which 30 participants using the continuous glucose monitor alternated between three breakfasts: a bowl of cornflakes with milk, a peanut butter sandwich and a protein bar.

LEE ABEL

Michael Snyder and his colleagues found that glucose dysregulation is more common than previously thought.

The trio of tests yielded some fairly startling results: After eating one or more of the meals, more than half of the group — whose prior blood sugar tests showed that they were "healthy" — spiked at the same levels as those of people who were prediabetic or diabetic.

What's more, nearly everyone spiked after eating the cereal.

"We saw that 80 percent of our participants spiked after eating a bowl of cornflakes and milk," Snyder said. "Make of that what you will, but my own personal belief is it's probably not such a great thing for everyone to be eating."

Still, the variables that elicit spikes in an individual — genetics; the population of microbes that live in our bodies; and epigenetics, or changes to gene expression — are critical to understanding glucose dysregulation and the foods that cause glucose spikes. Those parameters are not set in stone, which is why Snyder encourages everyone — including those who think of themselves as healthy — to check their blood sugar with continuous glucose monitoring about once a year.

"Right now we have information about people who do and don't spike, or are super-spikers, but we need to get smart about why it's happening," Snyder said. "I think understanding the microbiome and manipulating it is going to be a big part of this, and that's where our research is headed next."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford co-authors of the study are Ryan Kellogg, PhD; former research coordinator Patricia Limcaoco; and professor of medicine Tracey McLaughlin, MD.

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

The study was supported by the National Institutes of Health and the National Science Foundation.

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

Prizewinner wants to create malaria vaccine for pregnant women

By Beth Duff-Brown

Malaria claims nearly a half-million lives worldwide each year, yet scientists still know little about the immunology of the disease that has plagued humanity for thousands of years.

There were 216 million cases in 2016, according to the World Health Organization. Sub-Saharan Africa carries 80 percent of the global burden of this mosquito-borne infectious disease, which devastates families, disrupts education and promotes the cycle of poverty.

It is particularly brutal to pregnant women, who are three times more likely to suffer from a severe form of the disease, leading to lower birthweight among their children and higher rates of miscarriage, premature birth and stillbirth.

"Pregnant women and their unborn children are more susceptible to the adverse consequences of malaria, so we are working to investigate new strategies and even lay the foundation for a vaccine to prevent malaria in pregnancy," said Prasanna Jagannathan, MD, an assistant professor of medicine and this year's recipient of the Dr. George Rosenkranz Prize for Health Care Research in Developing Countries.

The Freeman Spogli Institute for International Studies and Stanford Health Policy gives the $100,000 prize each year to a young Stanford researcher who is trying to improve health care in underserved countries. It was established in 2009 by the family of George Rosenkranz, PhD, a chemist who first synthesized cortisone in 1951, and later progesterone, the active ingredient in birth control pills.

Jagannathan, an infectious disease specialist who is also a member of Stanford's Child Health Research Institute, said the prize will allow his lab members to ramp up their research in Uganda. His team is particularly interested in how strategies that prevent malaria might actually alter the development of natural immunity to malaria.

"With support from the Rosenkranz Prize, we hope to identify maternal immune characteristics and immunologic targets that are associated with protection of malaria in pregnancy and infancy," Jagannathan said.

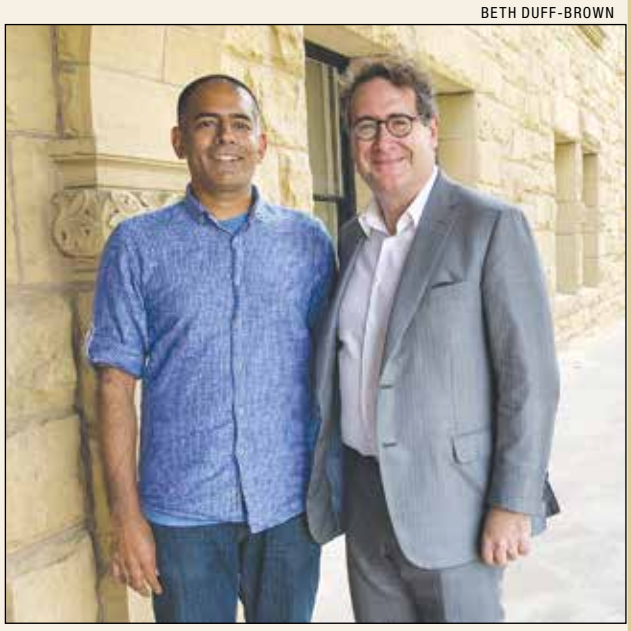
Goal: Vaccine for pregnant women

Jagannathan has been traveling to Uganda for a decade to study malaria. He's seen firsthand the relentless, gnawing impact the disease has on daily life.

"Before I went to Uganda I really didn't understand the burden that malaria causes in communities — and it's just incredible," he said.

Jagannathan and his collaborators at the University of California-San Francisco and in Uganda are currently conducting a randomized controlled trial of 782 Ugandan women who are receiving intermittent preventive treatment with a fixed dose of dihydroartemisinin-piperaquine, or IPTp-DP, a medication that has dramatically reduced the risk of maternal parasitemia, anemia and placental malaria. Their preliminary data suggests that among 684 infants born to these women, maternal receipt of IPTp-DP may lead to a reduced incidence of malaria in the first year of life.

BETH DUFF-BROWN



Prasanna Jagannathan (left) received the 2018 Rosenkranz Prize. The prize was established by Ricardo Rosenkranz (right) and his family in honor of his father, the late chemist George Rosenkranz.

"Having the discretionary support of the Rosenkranz Prize will allow us to generate some preliminary ideas from this trial that could lead to larger studies to push this agenda further along," Jagannathan said.

That agenda is to create a vaccine that prevents malaria in pregnant women and by extension, their infants, giving them a better start in life. ISM

OF NOTE

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

JULIA CHANDLER, MD, a resident in general surgery, has been named the Ernest and Amelia Gallo Endowed Postdoctoral Fellow by the Stanford Child Health Research Institute. Chandler will receive $105,000 to support her study of screening and secondary prevention for post-traumatic stress in pediatric trauma patients.

GREGORY CHARVILLE, MD, PhD,was appointed assistant professor of pathology, effective July 1. He specializes in the classification and study of disorders related to the gastrointestinal and hepatopancreatobiliary systems, and has a special interest in the diagnosis of rare tumors that derive from bone and soft tissues.

EDWARD DAMROSE, MD, was promoted to professor of otolaryngology-head and neck surgery, effective June 1. His research focuses on laryngeal physiology and function, with a particular interest in the use of advanced imaging techniques to study vocal fold physiology. He is the chief of staff at Stanford Health Care.

ROBERT DODD, MD, PhD, was promoted to associate professor of neurosurgery and of radiology, effective May 1. He specializes in endoscopic skull base surgery, with a clinical focus on minimally invasive techniques to treat brain tumors and cerebrovascular disease. His research interests include pituitary tumors and stroke.

IRIS GIBBS, MD, professor of radiation oncology, was elected as an American Society for Radiation Oncology Fellow. The ASTRO Fellows program annually recognizes individuals who have made significant contributions to radiation oncology through research, education, patient care and service to the field.

SABINE GIROD, MD, DDS, PhD, was promoted to professor of surgery, effective June 1. Her clinical and research interests are maxillofacial surgery and computer-aided surgery, especially in the reconstruction of complex craniofacial injuries and deformities of the face and jaws. She is the chief of the oral and maxillofacial surgery service.

ESTHER JOHN, PhD, was appointed professor (research) of medicine, effective May 1. Her research focuses on the epidemiology of cancer, with an emphasis on causes and outcomes of common cancers, such as breast and prostate cancer, in racial and ethnic minority populations, and on addressing cancer-health disparities. She co-leads the Stanford Cancer Institute's population sciences program.

PURVESH KHATRI, PhD, was promoted to associate professor (research) of medicine, effective May 1. His research focuses on developing new bioinformatics approaches to improve clinical care related to autoimmunity, infection and inflammation

ALEX MACARIO, MD, professor of anesthesiology, perioperative and pain medicine, was elected to the board of directors of the American Board of Anesthesiology. He will chair the ABA Research Committee and serve as a member of the Maintenance of Certification, In-Training Examination and Objective Structured Clinical Examination committees.

ROBBIE MAJZNER, MD,instructor of pediatric hematology and oncology, received a $330,000 grant from the St. Baldrick's Foundation. The three-year grant will fund his work to develop multi-specific chimeric antigen receptor T cells for pediatric high-grade gliomas (brain tumors) and use new cell-engineering methods developed at Stanford to introduce the receptors into the cells.

STEPHEN MONTGOMERY, PhD, was promoted to associate professor of pathology and of genetics, effective July 1. His research focuses on understanding the effects of genetic variation on molecular and cellular phenotypes, as well as on the molecular modeling of disease using genomics.

LISA GOLDMAN ROSAS, PhD, MPH, was appointed assistant professor (research) of health research and policy and of medicine, and the associate director of the Stanford Center for Population Health Sciences, effective May 1. She is also the associate faculty director for the center's Office of Community Engagement. Her research focuses on reducing the prevalence of obesity and related chronic diseases among low-income minority communities and on effectively engaging these communities in research to improve health.

VITTORIO SEBASTIANO, PhD, assistant professor of obstetrics and gynecology, and **KATJA WEINACHT**, MD, PhD, assistant professor of pediatrics, were awarded $865,292 by the California Institute for Regenerative Medicine. The grant will support their research on generating thymic tissue from induced pluripotent stem cells to help children born with a severe form of DiGeorge syndrome — a condition caused by the loss of a small piece of DNA on chromosome 22.

NATALIE TOROK, MD, was appointed professor of medicine, effective July 1. Her research focuses on understanding the molecular pathways that cause inflammation and fibrosis in the liver, particularly those leading to nonalcoholic and alcoholic steatohepatitis. ISM

Julia Chandler

Gregory Charville

Edward Damrose

Robert Dodd

Iris Gibbs

Sabine Girod

Esther John

Purvesh Khatri

Alex Macario

Stephen Montgomery

Lisa Goldman Rosas

Vittorio Sebastiano

Katja Weinacht

Natalie Torok