INSIDE STANFORD MEDICINE

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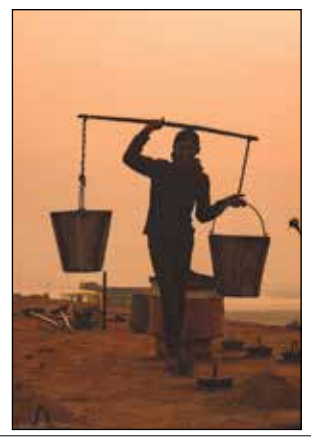

Researchers aim to save lives in Bangladesh by encouraging cleaner brick production.
Page 4

# Ovarian cancer patients undertested for mutations that could guide clinical care

By Krista Conger

STEVE FISCH

Allison Kurian helped to lead a study of women with breast and ovarian cancer that revealed significant gaps between national guidelines for genetic testing and actual testing practices. The study looked at roughly 83,000 women in California and Georgia in 2013 and 2014.

Fewer than a quarter of breast cancer patients and a third of ovarian cancer patients diagnosed between 2013 and 2014 in two states underwent genetic testing for cancer-associated mutations, according to a study by researchers at the School of Medicine and several other organizations.

The findings indicate that substantial gaps exist between national guidelines for testing and actual testing practices. In particular, the findings show that too few women with ovarian cancer are tested for the presence of mutations that could be used to guide health care decisions.

The study looked at about 83,000 women diagnosed with breast or ovarian cancer in California and Georgia in 2013 and 2014.

"We initiated this study — the largest population-based study of multigene testing in breast and ovarian cancer patients — because we wanted to see what cancer genetic testing and results looked like in the real world," said Allison Kurian, MD, MSc, associate professor of medicine and of health research and policy at Stanford. "Now we can see that women with ovarian cancer are dramatically undertested. We also learned that between 8 and 15 percent of women with breast or ovarian cancer carry cancer-associated mutations that could be used to drive care decisions and influence family members' health care and screening choices."

Kurian shares lead authorship of the study, which was published online April 9 in the *Journal of Clinical Oncology*, with Kevin Ward, PhD, MPH, assistant professor in epidemiology at Emory University. Lynne Penberthy, MD, MPH, associate director for the National Cancer Institute's Surveillance Research Program, and Steven Katz, MD, MPH, professor of medicine and of health management and policy at the University of Michigan, are co-senior authors.

### Changing guidelines

Researchers have known for decades that inherited mutations or variations in certain genes, notably BRCA1 and BRCA2, increase the risk of developing breast and ovarian cancers. Genetic tests for mutations in BRCA1 and BRCA2 have been available for several years. But since 2013, genetic tests have incorporated many more potential cancer-susceptibility genes, and results have become much more complicated.

"Integrating genetic counseling and testing into the management of cancer after diagnosis has become much more challenging for patients and their clinicians," Katz said.

National guidelines recommend See CANCER, page 6

# Scientists use CRISPR for possible 'bubble boy' therapy

By Hanae Armitage

Very rarely, a boy is born with a mutation that renders his immune system barren — devoid of any and all immune cells. The disease, X-linked severe combined immunodeficiency, or SCID-X1, often is referred to as the bubble boy disease. It affects only males and is lethal if not treated in the first year of life.

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Now, scientists at the School of Medicine and their collaborators have used the gene-editing system CRISPR-Cas9 to devise a new treatment to replenish immune cells in mouse models of SCID-X1. The results are promising, the scientists said, because they believe the treatment could potentially work in humans, as well.

SCID-X1 affects about 1 in 50,000 male births. Those with the disease suffer from a debilitating mutation in a single gene, IL2R gamma. When this gene is defective, the immune system never develops.

The standard treatment for patients with SCID-X1 is a bone marrow transplant, which supplies them with stem cells that will give rise to a working immune system. But the transfer process is tricky and not guaranteed to work. So, Matthew Porteus, MD, PhD, professor of pediatrics, came up with a new idea: correct the genes in the patients' own cells.

Through CRISPR-Cas9, Porteus and his team have done just that. Using cell samples that came from people with SCID-X1, the researchers genetically altered the class of stem cells that give rise to blood and immune cells. Their approach got the gene working again.

Each mouse that received the edited cells began generating new immune cells and displayed no detectable adverse side effects. "To our knowledge, it's the first time that human SCID-X1 cells edited with CRISPR-Cas9 have been successfully used to make human immune cells in an animal model," said postdoctoral scholar Mara Pavel-Dinu, PhD.

A paper describing the work was published online April 9 in *Nature Communications*. Porteus is the senior author, and Pavel-Dinu is the first author.

### Editing in a solution

Gene-based therapy for SCID is not new. In the 1990s, scientists began to dabble in gene therapies that used a virus to deliver a new, functional IL2R gamma gene. "It was very effective, but about 25 percent of the patients developed a leukemia because the virus integrated into an erroneous gene," Porteus said. "It showed both the promise of what gene therapy could do and highlighted the area that needed to See CRISPR, page 6

# Drug reduces risk of kidney failure in people with diabetes

By Amy Jeter Hansen

A new landmark clinical trial shows that a drug lowers the risk of kidney failure by a third in people with Type 2 diabetes and kidney disease.

"For the first time in 18 years, we have a therapy for patients with Type 2 diabetes and chronic kidney disease that decreases kidney failure," said Kenneth Mahaffey, MD, professor of medicine at the Stanford See KIDNEY, page 7

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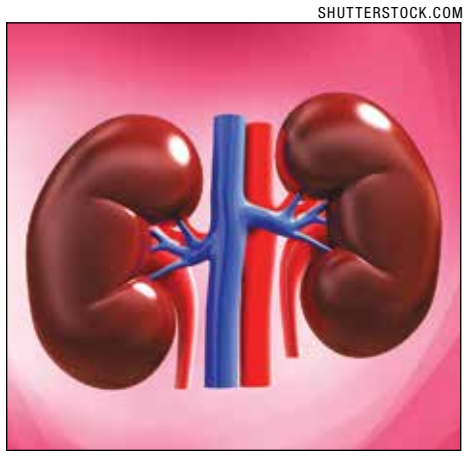

# Scientists help parse molecular changes in twin astronauts

**By Hanae Armitage**

NASA

The International Space Station, where astronaut Scott Kelly spent a year, as seen from the space shuttle Discovery in 2009.

A new NASA-led study comparing the biology of twin astronauts Scott and Mark Kelly details the range of immune and molecular stresses outer space imposes on the human body.

Among the 26 institutions that collaborated with NASA to conduct the analyses, the Stanford University School of Medicine led an effort to characterize the twins at the molecular level, focusing on protein production, immune response, metabolism and the efficacy of vaccines in space.

Details of the study were published April 11 in *Science*. Michael Snyder, PhD, professor and chair of genetics and the Stanford W. Ascherman, MD, FACS, Professor in Genetics, and Emmanuel Mignot, MD, PhD, professor of psychiatry and behavioral sciences and the Craig Reynolds Professor in Sleep Medicine, are two of the senior authors of the study.

### A stressful situation

Snyder and a team of researchers characterized the molecular shifts in both Scott Kelly, the brother who traveled to space and lived on the International Space Station for a year, and Mark Kelly, his twin, who remained on the ground. In particular, the researchers focused on immune-, metabolic- and protein production-related stresses imposed by space capsule launch, zero gravity and re-entry to Earth. Blood samples from Scott taken when he was in space showed heightened levels of immune-related molecules called cytokines, which flag inflammation and bodily stress.

"We looked at a panel of 62 cytokines and saw that 50 of them were changing in some manner associated with flight, about half of which were elevated," said Tejaswini Mishra, PhD, a postdoctoral scholar at Stanford and one of the study's lead authors. The overall takeaway, she said, is that the immune system is revved up under the stressors of space flight.

Astronauts on the station periodically sent frozen vials of blood back to Earth via unmanned spacecraft. Blood samples taken at different time points revealed that Scott Kelly's cytokine-spike pattern was not uniform: Levels of some cytokines rose before takeoff, some rose while in space and some rose upon return to Earth. Six months after Scott Kelly's return to Earth, the majority of his cytokine levels were back to normal.

### Intriguing associations

Although it's still unclear exactly how cytokine fluctuation tracked with Scott Kelly's overall health, Snyder's team did find intriguing associations. These connections, while interesting, are only associations at this point, and more extensive studies will be needed to understand exactly how space flight changes human health.

Despite the dips and spikes in inflammatory markers, Mignot, who was responsible for assessing the efficacy of vaccines in space, said that Scott Kelly's body handled the flu vaccination no differently than his brother's body back on Earth.

> "Our studies show that vaccination in space is feasible and effective."

"The challenges of keeping our immune system up to date and heathy during space travel are likely to become critical," Mignot said. "Our studies show that vaccination in space is feasible and effective."

All of this data, Snyder said, will begin to help "work out the circuitry of the immune system in response to this unusual environment."

Outside the immune system, Snyder and Mishra saw a change in the ratio of two particular proteins known as apoB and apoA-1. Studies within the past decade have suggested that the apoB to apoA-1 ratio can predict cardiovascular disease even more accurately than cholesterol levels. According to these studies, a decreased apoB to apoA-1 ratio predicts a lower risk of cardiovascular disease. When analyzing Scott Kelly's protein-production levels after a year in space, Snyder and Mishra saw that his ratio of apoB to apoA-1 had increased. While that doesn't directly equate to an increase in heart disease risk, Mishra said, it's a potential factor to watch for in future studies of the effects of long-term space exposure on humans.

Ling Lin, MD, PhD, a research associate at Stanford, and Brian Piening, PhD, a former postdoctoral scholar at Stanford, are also lead authors of the study.

The study was supported by NASA, the National Institutes of Health, the National Science Foundation, the German Aerospace Center, the Vallee Foundation, the WorldQuant Foundation, the Pershing Square Sohn Cancer Research Alliance and the Bill and Melinda Gates Foundation. ISM

# Artificial intelligence identifies risk of cholesterol-raising genetic disease

**By Hanae Armitage**

A new algorithm can determine whether a patient is likely to have a cholesterol-raising genetic disease that can cause early, and sometimes fatal, heart problems, reports a new study conducted by researchers at the School of Medicine and their collaborators.

The disease, known as familial hypercholesterolemia, is often misdiagnosed as garden-variety high cholesterol.

"We think that less than 10 percent of individuals with FH in the United States actually know that they have it," said Joshua Knowles, MD, PhD, assistant professor of cardiovascular medicine at Stanford. It's a serious oversight, he added, because an FH patient with high cholesterol is three times more likely to develop early heart disease than someone who has high cholesterol but not FH. A person with FH faces 10 times the risk of heart disease as someone with normal cholesterol.

Knowles and Nigam Shah, MBBS, PhD, associate professor of medicine and of biomedical data science, have come up with a solution to help catch more cases of FH: a computer algorithm that flags patients who are likely to have the disease. In test runs of the algorithm, it correctly identified 88 percent of the cases it screened. Theoretically, if the algorithm were used in a clinic, any patient it flagged as having FH could undergo further genetic testing to verify the algorithm's calculation.

Nigam Shah

Joshua Knowles

Without intervention, around 50 percent of men with FH have a heart attack by age 50 and about 30 percent of women by age 60. But swift, early diagnosis and treatment of the disease can essentially neutralize this threat, Shah said. The trick is to catch it before it's too late, and this is where Knowles and Shah think their algorithm could make an impact.

One diagnosis could even help multiple people, Knowles said. Because FH is genetic, if one family member has the disease, it's likely that other relatives have it too. "So screening family members of FH patients is really important, just like it would be with breast cancer or any other genetically linked illness," he said.

A paper describing the research was published online April 11 in *npj Digital Medicine*. Shah and Knowles, who is the director of the FH clinic at Stanford Health Care's Center for Inherited Cardiovascular Disease, share senior authorship. Juan Banda, PhD, a former research scientist at Stanford, is the lead author.

The project is part of a larger initiative called Flag, Identify, Network, Deliver FH, or FIND FH, a collaborative effort involving Stanford Medicine and the nonprofit Familial Hypercholesterolemia Foundation that aims to identify and engage individuals and families affected by the disease by leveraging machine learning and big data.

### Identifying FH

People with FH carry a mutation that hinders their bodies' ability to clear harmful LDL cholesterol that collects in arteries and clogs them. Hypothetically, anyone who walked into a hospital could have genetic testing and know whether they had inherited an FH mutation.

Unfortunately, Shah said, hospitals don't have the means to sequence patients on such a large scale, even as prices for genome sequencing drop. "The problem is, the chance that someone seen in the cardi-

See CHOLESTEROL, page 3

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STANFORD MEDICINE

# Viruses help protect harmful bacteria in cystic fibrosis patients

**By Erin Digitale**

Chronic bacterial infections in the lungs of cystic fibrosis patients are worsened by a previously unappreciated biological agent: a group of viruses that infect the bacteria.

The viruses form a biofilm that sequesters antibiotics away from bacteria, potentially contributing to the development of antibiotic resistance in CF patients' lungs, a new study from the School of Medicine has found.

A paper describing the study, which involved 110 children and adults with CF, was published April 17 in *Science Translational Medicine*. It is the first to explore how filamentous phages, which are stringy bacteria-attacking viruses, can contribute to lung disease. Understanding how the viruses work could lead to better CF therapies.

"Phages haven't been thought of as pathogens that affect humans," said lead author Elizabeth Burgener, MD, an instructor of pediatrics at Stanford. "This is a whole new paradigm of thinking about them."

The study's co-senior authors are Paul Bollyky, MD, PhD, assistant professor of medicine and of microbiology and immunology, and Carlos Milla, MD, professor of pediatrics. Milla and Burgener are pediatric pulmonologists at Lucile Packard Children's Hospital Stanford, where they treat CF patients.

Because phages infect only bacterial cells, scientists have assumed that the viruses do not act on human health. The new study's findings contradict this assumption: CF patients with phage-infected bacteria in their lungs fared worse than those with uninfected lung bacteria.

Elizabeth Burgener

"We saw that phage infection of the lung bacteria is associated with more antibiotic resistance in patients," Burgener said. Scientists have struggled to understand how an aggressive bacterial species, Pseudomonas aeruginosa, persists in the lungs of CF patients who are receiving antibiotics, she added. "We think the virus is helping Pseudomonas to establish chronic infection in CF patients' lungs and potentially making patients sicker over time."

### Sticky substances

Cystic fibrosis is a genetic disease that causes the lungs to produce unusually thick, sticky mucus. Over time, patients tend to develop chronic bacterial infections, which can lead to respiratory failure and death. By adulthood, the lungs of about half of CF patients are infected with Pseudomonas. The infection is linked to worsened prognosis.

"When somebody first grows Pseudomonas, we try to eradicate it with antibiotics," Burgener said. Patients inhale high doses of antibiotics directly into their lungs. But the bacteria often keep growing.

To see how the phages and bacteria might work together, the researchers took advantage of a quirk of the biology of filamentous phages: When these phages infect the bacteria, they do not kill them; rather, the still-living bacteria incorporate the phage DNA into their own DNA and begin churning out lots of viral particles.

The researchers looked at genetic analyses of Pseudomonas bacteria from the lungs of 34 CF patients in Denmark. The patients had had their bacterial DNA sequenced repeatedly over time, allowing the researchers to see whether phage DNA had been persistently incorporated into the bacterial genomes. Patients were more likely to develop consistent phage infections as they got older, supporting the idea that the virus-infected bacteria come to dominate CF patients' lungs over time. The average age of patients without the phages was 13, while the average age of phage-infected patients was 19.

Burgener and her colleagues also collected sputum samples from 76 people with CF, both adults and children, who were receiving treatment at Stanford. The team tested the sputum for genetic signatures from Pseudomonas and filamentous phages and found that 58 people had Pseudomonas infection. The researchers studied information from the patients' medical records on lung function, what bacteria had been growing in their lungs over time and other health indicators.

Among the Stanford patients, carrying phage-infected Pseudomonas was more common as patients got older. Phage-infected Pseudomonas bacteria were more likely than bacteria without the virus to be resistant to three antibiotics commonly used to treat CF — aztreonam, amikacin and meropenem — but not to another antibiotic, ciprofloxacin.

"The thing that really stood out was that patients with phage and Pseudomonas had significantly more antibiotic resistance than patients that didn't have phage," Burgener said.

### How does antibiotic resistance happen?

The researchers previously showed that phage particles glom together into a liquid-crystal structure, a slimy biofilm, which grabs onto antibiotic molecules. In the new study, they tested whether this could prevent antibiotics from diffusing to bacteria. The phage biofilm sequestered aztreonam, amikacin and meropenem away from bacteria, the team showed.

"We think the biofilm is protecting Pseudomonas," Burgener said. As the biofilm sequesters antibiotics, the bacteria sees subtherapeutic levels of the drugs, allowing individual drug-resistant bacteria to grow and gradually take over in the lung.

> "It's shocking how much effect the phages have on the host immune system."

The researchers think the physical properties of the different types of antibiotic molecules — such as whether the drugs have charged or neutral surfaces — may explain why some antibiotics get stuck in the phage biofilm and others do not.

"If we're able to confirm these results, it may affect how we choose antibiotic therapy for patients who have CF and Pseudomonas," Burgener said.

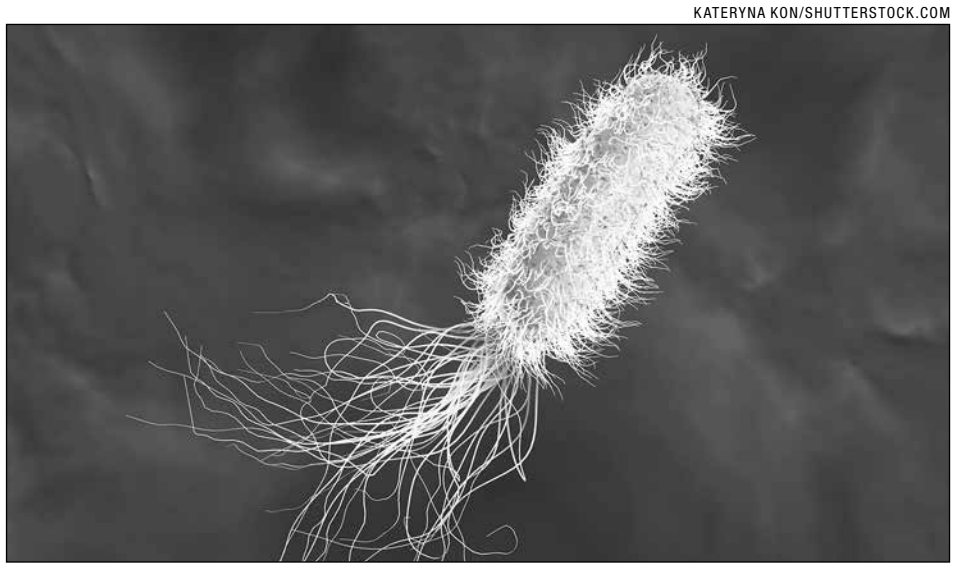
The next step is to understand how CF patients' bodies respond to the phages, Burgener said, adding, "It's shocking how much effect the phages have on the host immune system."

Bollyky recently led another study that suggests it may be possible to vaccinate against the phage.

"Ideally, we'd be able to give a vaccine to CF patients when they're young," Burgener said. "Hopefully we can prevent Pseudomonas infection."

Other Stanford co-authors of the study are graduate **See PHAGE, page 6**

KATERYNA KON/SHUTTERSTOCK.COM



An illustration of Pseudomonas aeruginosa. The bacteria infects the lungs of about half of all patients with cystic fibrosis by the time they reach adulthood.

# Cholesterol

**continued from page 2**

ology clinic has this genetic condition is somewhere around 1 in 90, or 1 in 100, so it doesn't make sense to sequence every single person," he said.

So Shah and his fellow researchers designed an algorithm that works like a sieve, filtering out only those who are likely to have the disease. "Theoretically, when someone comes into the clinic with high cholesterol or heart disease, we would run this algorithm," Shah said. "If they're flagged, it means there's an 80 percent chance that they have FH. Those few individuals could then get sequenced to confirm the diagnosis and could start an LDL-lowering treatment right away."

To create the algorithm, the team used data from Stanford's FH clinic to learn what distinguishes an FH patient in an electronic health record. The researchers trained the algorithm to pick up on a combination of family history, current prescriptions, lipid levels, lab tests and more to understand what details signal the disease.

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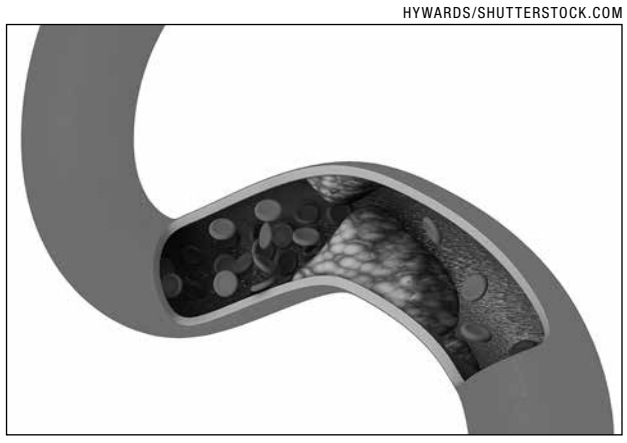

Familial hypercholesterolemia is caused by a mutation that hinders the body's ability to clear LDL cholesterol, which can collect in arteries and clog them, causing heart attacks and strokes.

Shah compared it to training a spam filter that catches fishy emails. Instead of simply applying rules, such as "must mention money," spam filters learn what to flag by using actual spam emails as examples of what to capture — just as the FH algorithm learns by looking at information about real FH patients.

The scientists built the algorithm's foundation using data from 197 patients who had FH and 6,590 who did not, allowing the computer program to learn the difference between the two.

"In the end, you get a ranking that shows who is most likely to have the disease," said Shah. "Those who rank at the top have the highest likelihood and, as you move toward the bottom, the likelihood tapers off."

While the software could fill a gap in FH diagnoses, Knowles and Shah acknowledge that it's not a surefire solution to catch all cases. "Not everything can be solved by an algorithm," Shah said. "We're also thinking about how we can work with the FH Foundation to implement networks of family screening to reach more patients who might have the disease and not know it."

### Toward AI in the clinic

Once the algorithm was trained, the team moved on to the testing phase, initially running it on a set of roughly 70,000 de-identified patient records it had never encountered. From the patients flagged, the team reviewed 100 patient charts, extrapolating that the algorithm had detected patients who had FH with 88 percent accuracy.

Next, the researchers teamed up with the Geisinger Healthcare System to test the algorithm on 466 FH patients and 5,000 non-FH patients. "The predictions came back with 85 percent accuracy, and we knew that many of the Geisinger patients had a confirmed FH diagnosis with genetic sequencing," Shah said. "So that's how we convinced ourselves that yes, this indeed works."

Now, Knowles and Shah are working on ways to implement the algorithm in doctors' offices, something they're actively pursuing for Stanford's FH clinic.

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.

Shah is a member of Stanford Bio-X, the Stanford Cancer Institute and the Wu Tsai Neurosciences Institute at Stanford. Knowles is a member of Bio-X, the Stanford Cardiovascular Institute and the Stanford Maternal & Child Health Research Institute.

Other Stanford co-authors of the study are medical fellows Ashish Sarraju, MD, and Justin Parizo, MD; clinical assistant professor of medicine Fahim Abbasi, MD; clinical instructor of pediatrics Mitchel Pariani, MD; genetic counselors Hannah Ison and Hannah Wand; visiting researcher Elinor Briskin, MD; former graduate student Sebastien DuBois; and research scientist Kenneth Jung, PhD.

Researchers from Atomo Health in Texas, the University of Pennsylvania, Yale University and Georgia State University also contributed to the work.

The study was funded by the American Heart Association and Amgen. **ISM**

# Stanford global health researcher helps lead effort to e

**By Rob Jordan**

When Stephen Luby, MD, first arrived in Dhaka, Bangladesh, in 2004, he barely registered the hazy atmosphere. The 45-year-old epidemiologist from Nebraska had spent several years in Karachi, Pakistan, where soot-choked air was as predictable and intractable as open sewers and rutted roads. It didn't distract him then from his mission to save lives with modest, affordable health interventions, such as hand-washing training and directions to local clinics. It wasn't going to distract him now.

Luby was focused on his new job with the U.S. Centers for Disease Control and Prevention, where he would be investigating emerging infections in a region considered a global hot spot. "I believed in what I was doing."

As Luby, his wife, Jeni, and their four children moved into their U.S. embassy-furnished house in a quiet enclave of Dhaka, they found a rattling electrostatic air purifier the size of a small refrigerator.

"I thought, 'Where is the data showing that thing has any effect?'" recalled Luby, now a professor of medicine at Stanford and director of research at the university's Center for Innovation in Global Health. "I turned it off. It stayed that way for eight years."

Over time, though, Luby became aware of a catastrophic airborne health threat facing tens of millions of people, and a likely culprit was the production of a ubiquitous building material: the humble brick. The realization forced Luby to rethink basic medical assumptions, and to challenge development community dogma that was failing to address the issue.

Now, after more than eight years of research, analysis and on-the-ground negotiations, Luby is poised to launch a plan to transform the brick kiln sector in Bangladesh and, ultimately, across South Asia.

## Silent killer

Consistently ranked among the world's least livable cities, Dhaka is a cacophonous overflowing sprawl of more than 10 million people, with a population density of 44,500 per square kilometer. While other metrics of misery have declined in the face of the country's burgeoning economy, air pollution remains a scourge during the dry, winter months. Dhaka's air quality index, a representation of pollutant concentration over a specified period of time, hovers above 150 — a level considered unhealthy for all groups — but often spikes much higher between November and February.

"When you open the door to go out in the morning, there's a haze of smoke that hits your face," said Alex Yu, MD, a postdoctoral scholar in infectious disease who works in Luby's Stanford lab. "You have a chronic low-grade cough. We call it Dhaka lung. People don't want to go out, but life has to go on."

Still, when a Bangladeshi colleague of Luby's suggested they install air particulate sensors in Dhaka households as part of a 2011 influenza and pneumonia study, Luby was skeptical. "I was looking at it primarily through the lens of the pathogen — what organism was causing problems," Luby said. "I was not attuned to air quality. I hadn't really thought about the science."

The findings were stark: Air pollution had a huge impact on respiratory infections, but indoor air pollution — the focus of most related public health community efforts — wasn't the only culprit. It turned out that the most important determinant of indoor air quality was outdoor air quality. Surprised, Luby shifted his focus to the environment's effect on health.

"It's different from a medical model that says let's wait until they get sick and treat them in clinic," he said. "We need to think like a physician about how we can treat the environment."

Air pollution is among the largest contributors to mortality worldwide, hastening the deaths of more than 7 million people a year, according to the World Health Organization. Although the model-based WHO estimate is contested by some health experts, pollution's damaging impacts are clear. Microscopic particles of soot, ash and other pollutants can penetrate deep into lungs and bloodstreams. Resulting long-term inflammation and organ damage can lead to pneumonia, heart disease, strokes, premature births, early onset lower respiratory infection in children and a host of other ailments.

HTTP://INSTAGRAM/NAVAISM

Workers remove fired bricks from a kiln in Bangladesh, while smoke billows out of other kilns in the background.

Luby realized that if he could determine what was driving the outdoor air pollution in Dhaka, he might be able to lift the curse of pneumonia, the leading killer of children under the age of 5 globally.

## To the source

Once Luby began looking for a pollution source that might be causing such deadly infections, his research quickly led him to brick kilns. As Bangladesh's population and economy has grown, so has its need for building materials. In a land of few trees and minimal manufacturing capacity, bricks fit the bill. Primarily burning coal, thousands of kilns ringing Bangladeshi cities turn out about 25 billion bricks a year. It's a familiar story throughout South Asia. Brick kilns across the region have a global warming impact equivalent to that of all U.S. passenger cars.

In Bangladesh, a single brick kiln spews up to 53 tons of carbon monoxide in one season, the annual equivalent of more than 180 passenger cars in the United States. The country's 5,000 or so kilns are responsible for about 40 percent of airborne particulate matter during winter. (Kilns operate only during rainless winter months so bricks can be left outside to dry).

Perhaps unsurprisingly, hundreds of thousands of people who live downwind from kilns face an elevated risk of cardiovascular and respiratory disease, and tens of thousands of adults die from pollution-related illnesses each year, according to modeled estimates.

Research by Allison Sherris, a graduate student in Stanford's Emmett Interdisciplinary Program in Environment and Resources, suggests a correlation between spikes in airborne particulate matter and increased rates of pneumonia among children in Dhaka. Sensors reveal a strong signal of sulfate, a chemical common to coal burning, in the city's air.

"I had given brick kilns very little thought," Luby said. "Now, I can talk for days about kiln designs, technology, regulation, combustion. I can find specific data that substantiate the problem, then hold onto them like a bulldog."

But good data about the magnitude of the problem is hard to find. Yu and graduate student Nina Brooks are trying to fill that gap and quantify the adverse health effects that can be attributed to brick kilns. They are comparing rates of asthma, chronic obstructive pulmonary disease and other air-related illnesses in communities with and without kilns.

"This is about saving people's lives," Brooks said. "Human-generated waste is what's killing so many people — mostly poor people. It's preventable."

As research continued, Luby's team found mounting evidence that the global development community's approach to mitigating health effects of air pollution was systematically flawed. For years, funders poured hundreds of millions of dollars into improving people's health by targeting indoor air quality and advocating for cleaner-burning cookstoves. After more than three decades of promoting the stoves in Bangladesh, less than 2 percent of households were using them.

To Luby, it was a self-perpetuating cycle of failure that had overlooked the key connection between outdoor and indoor air pollution. "Money comes available when an idea gets a certain amount of currency," Luby said. "People will do things because funding is available."

The pattern is familiar to people trying to solve health problems in the developing world. "The solu-

HTTP://INSTAGRAM/NAVAISM

A worker carries coal used to fuel a kiln. Sensors around Dhaka reveal a strong signal of sulfate, a chemical common to coal burning, in the air.

# encourage cleaner brick production in Bangladesh

NORBERT VON DER GROEBEN

Stephen Luby sees a way to quell an airborne health threat affecting millions.

tions that seem like they should be the most sustainable, effective and beneficial to people and the environment are not always feasible on the ground," said Erin Mordecai, PhD, an assistant professor of biology who studies the ecology of infectious disease. "For example, improving access to clean, reliable, piped water would lift billions of people out of poverty, improve quality of life and reduce transmission of disease. But aid often focuses only on stopgap solutions like medicines and treatments once people are infected, which leave them vulnerable to reinfection after the initial treatment wears off or aid programs dry up."

"It was clear people preferred their old cookstoves," Luby said. "They cooked their chapatis better. I never thought it was going to be easy to change the way several thousand kilns make bricks, but I thought it's got to be easier than changing the way 40 million households cook their meals."

### Teaming up

Luby was at a point where he was ready to lay the groundwork for a plan of attack, which coincided with his 2012 hiring at Stanford, where he is also a senior fellow in the Stanford Woods Institute for the Environment.

To start, he gathered a team of Stanford researchers, including renowned political scientist Francis Fukuyama, PhD, and geophysicist Howard Zebker, PhD. Fukuyama, who, like Luby, is a senior fellow at the Freeman Spogli Institute for International Studies, helped Luby understand governance issues and formulate a politically effective message to incentivize kiln owners to switch to cleaner technologies. Zebker, a professor of electrical engineering and of geophysics, is an authority on developing space-borne radar systems and using remote sensing data to study earthquakes and other phenomena. He laid the groundwork for a satellite imaging program to pinpoint kiln locations, something that's difficult to do using unreliable government records.

"This problem seems to be one in which you could have a huge payoff both locally and for the world as a whole if you could get to the proper solution," Fukuyama said. "Most problems promise to improve life much less."

Luby and his colleagues burned through iteration after iteration. "We definitely pursued some dead ends," he said.

Among the team's biggest failures was a pollution-scrubbing technology they spent months developing. At the invitation of a member of India's parliament, Luby traveled across the state of Punjab to pitch the idea to industry leaders. Without an incentive to install the $5,000 device, kiln owners balked.

Eventually, a game plan began to materialize. Luby and his team used the satellite data to start building a website that gives people information about nearby kilns, and teaches them how to nudge kiln owners toward making their operations more efficient and profitable. The site will help users pinpoint kilns that violate local ordinances and design standards, and join a larger discussion among public- and private-sector stakeholders.

Working with Greentech Knowledge Solutions, a Delhi-based leader in improving brick kiln efficiency, Luby's team formulated affordable technology options, such as transitioning from a fixed chimney to a zigzag kiln, in which the flames from the kiln's fire and a mechanized coal feeder circulate around the circumference of the kiln to take advantage of natural air drafts. The method improves combustion efficiency — a major incentive for kiln owners whose primary expense is coal — and reduces black carbon emissions by more than 80 percent.

The plan also includes a mechanism to provide loans for the cost-saving upgrades, a significant step for an industry that mostly operates in an informal economy. Seasonal and with few fixed assets, brick making is considered by the Bangladeshi government to be temporary, and therefore ineligible for government-backed bank loans.

"When we initiated this project, I saw that everyone, including the government and media, was blaming brick manufacturers for generating air pollution," said Debashish Biswas, a Bangladeshi anthropologist working with Luby. "But thinking from the kiln owners' perspective is important. Rather than impose changes on them, we need to identify the best viable strategy to solve the problem."

By tracking emission reductions, the initiative could earn credits from global climate change funds. These credits, one for each ton of $CO_2$ kept from the atmosphere, could then be traded or sold to industrialized countries trying to meet emission reduction targets. The earnings could then be used to finance kiln upgrades and ongoing oversight of measures to meet efficiency and climate objectives.

"We're doing something completely novel here," Luby said.

The plan was in place, but Luby still lacked a key ingredient: a resourceful and influential partner to facilitate and oversee the initiative. The perfect candidate turned out to be nearby.

> **"We need to think like a physician about how we can treat the environment."**

Founded in 1972 to help refugees after Bangladesh's war for independence from Pakistan, Building Resources Across Communities is the world's largest nongovernmental organization. Luby was familiar with its numerous, respected branches because he taught classes at the organization's school of health for several years.

With training from Greentech, the BRAC construction group could provide technical expertise to kiln owners on improving manufacturing practices, including support for construction and management upgrades. Its small-enterprise program could provide loans to kiln owners for upgrades, while ensuring adherence to standards and repayment. Its presence in tens of thousands of communities across Bangladesh made it an ideal partner.

HTTP://INSTAGRAM/NAVAISM

HTTP://INSTAGRAM/NAVAISM

(Left) A worker on the outskirts of Dhaka carries newly fired bricks to transport trucks. (Right) Workers remove newly fired bricks from a kiln.

Luby was mindful that the project's fate rested on his pitch, so he approached the director of BRAC, Fazle Abed, with trepidation. When they met, Abed held up his hand to signal his need to speak first. "I really appreciate what you've done for our school, and what you've done for Bangladesh," Abed told Luby. BRAC would join the effort.

"It struck me how much these big decisions are based on trust and relationship," Luby said.

The lesson is not lost on colleagues of Luby's, such as Desiree LaBeaud, MD, an associate professor of pediatrics at Stanford who has conducted extensive epidemiological field work in Kenya. "For the successes we have had, our trusted long-term relationships across sectors have been the driving force for sustainable improvements in our communities."

### Unlikely allies

There was just one major sticking point left.

"As in many policy problem areas, the chief issue is to build a stakeholder coalition in favor of the kind of reforms that are necessary, and to find ways to get around those players who are opposed to change," Fukuyama said. "In the case of the brick kilns, it was assumed that the existing kiln owners would not accept the medical evidence that what they were doing was harmful."

Luby's anxiety over this possibility came to a head in January 2013. He had invited influential stakeholders, including representatives from government agencies, nongovernmental organizations and brick-dependent construction firms, to a dialogue in a Dhaka convention center aimed at gathering feedback on kilns' health hazards, as well as incentives for change. Would the kiln owners come? If so, what would they say? Would they protest or demand major concessions? Jamil Hussain, vice president of Bangladesh's national brick manufacturing association, told Luby he likely would not show. He was wary of bad press and criticism for his already maligned industry.

Luby hired professional meeting facilitators and barred media coverage. Hussain showed up at the last minute. So far, so good. Luby braced himself for reaction to a colleague's presentation about the health impacts of kilns. There was a long moment of silence, then Hussain rose and asked to address the audience. "I was at the edge of my seat," Luby said. "I thought this could be a shouting match. It could go off the rails."

Instead, Hussain told the crowd, "We don't dispute anything you just said. Brick kilns do damage the environment and human health. What I'm asking for is your help in solving this problem. I'd like you to help us so that people don't hate us."

Luby was stunned. And, now, instead of having to advocate for the project, he could focus on finding a solution.

Luby's concept, with its various incentives, had struck a chord for Hussain and other kiln owners wary of complicated and expensive pollution-reduction systems pushed by the central government. "If the new technology is economical and environment-friendly, if it's not harmful to our business, everyone should be interested," Hussain said. "This approach makes it possible for us to follow the regulations of the government and maintain our business. That's why we listened to Dr. Luby."

Working closely with kiln owners is another way Luby butts up against what he considers a systemic bias toward top-down solutions in the global development community. "We often get pushback," Luby said. "'Why are you working with these guys? These guys don't wear ties. They're not educated.'" Luby's answer is simple: "'These guys have 85 percent of the market. Why don't we work with the market leaders? They have a business model that works.' It pushes against this idea that we should leapfrog to the modern, that we should do it like we do in North Carolina or wherever."

Luby's team hopes to pilot various technological interventions at Bangladeshi kilns to generate results that would nudge kiln owners, government regulators and others toward change. He's seeking funding of $4 million to $8 million for pilots at about 10 Bangladeshi kilns this spring and at another 30 to 45 kilns two years later. Eventually he'd like to see the industry transformed, which he estimates would cost $30 million to $80 million.

Luby's ready for an uphill battle. "Problem-defining research is most highly rewarded in academia," he said. "One step that donors interested in a sustainable future can make is to fund solution-oriented research and reward leading researchers who engage in it.

"We know the problem," Luby said. "People get rich by destroying the Earth or human health. If we can't figure out how to change that incentive system, we will destroy our future." ISM

# Persis Drell to give keynote speech at medical school diploma ceremony

Stanford Provost Persis Drell, PhD, the James and Anna Marie Spilker Professor and professor of physics and of materials science and engineering, will be this year's keynote speaker at the School of Medicine's diploma ceremony.

The ceremony will be held from 1-3 p.m. June 15 on Alumni Green, next to the Li Ka Shing Center for Learning and Knowledge. No tickets are required.

Drell is a physicist who has served on the Stanford faculty since 2002. She is the former dean of the Stanford School of Engineering and former director of the U.S. Department of Energy's SLAC National Accelerator Laboratory at Stanford.

> Now provost, Drell joined the Stanford faculty in 2002.

Drell earned a bachelor's degree in mathematics and physics from Wellesley College in 1977 and a PhD in atomic physics from the University of California-Berkeley in 1983. She then switched her research focus to high-energy experimental physics and worked as a postdoctoral scholar at the Lawrence Berkeley National Laboratory. She joined the physics faculty at Cornell University in 1988.

In 2002, Drell joined the Stanford faculty as a professor and director of research at SLAC. In her early years there, she worked on the construction of the Fermi Gamma-Ray Space Telescope. She was named SLAC's deputy director in 2005 and its director in 2007. She led the 1,600-employee national lab until 2012 and is credited with helping broaden the focus of the laboratory, increasing collaborations between SLAC and the main Stanford campus and overseeing transformational projects.

Persis Drell

Among the projects Drell oversaw was the transition of SLAC from being a laboratory dedicated primarily to research in high-energy physics to one that is now seen as a leader in a number of scientific disciplines. In 2010, the laboratory began operating its Linac Coherent Light Source. LCLS is the world's most powerful X-ray free electron laser, which is revolutionizing the study of the atomic and molecular world.

After serving as the director of SLAC, Drell returned to research and teaching at Stanford, focusing her research on technology development for free electron lasers and particle astrophysics.

In 2014, Drell was named the dean of the Stanford School of Engineering, where she catalyzed a collaborative, schoolwide process, known as the SoE-Future process, to explore the future of engineering education and research.

She became university provost on Feb. 1, 2017.

In addition to her administrative responsibilities, Drell teaches a winter-quarter companion course to introductory physics each year for undergraduate students who had limited exposure to the subject in high school.

Drell is a member of the National Academy of Sciences and the American Academy of Arts and Sciences, and is a fellow of the American Physical Society. She has been the recipient of a Guggenheim Fellowship and a National Science Foundation Presidential Young Investigator Award.

Drell is married to SLAC accelerator physicist James Welch, PhD. They have three children. **ISM**

## Cancer

**continued from page 1**

that all women with the most common type of ovarian cancer be tested for the presence of cancer-associated mutations; guidelines for testing breast cancer patients have been less expansive. Although the guidelines for genetic testing have expanded to include more patients diagnosed with breast or ovarian cancer and the more extensive multigene panel tests, it's not been clear to what degree these guidelines are followed in real-world clinical settings. Furthermore, the prevalence of known cancer-associated mutations in breast and ovarian cancer patients who are racial or ethnic minorities, as well as in the overall population, is unknown.

> "We wanted to see what cancer genetic testing and results looked like in the real world."

For the study, the researchers tapped the National Cancer Institute's Surveillance, Epidemiology and End Results Program, which tracks cancer diagnoses and outcomes in large populations across the United States. They linked data on cancer cases in California and Georgia with data from four laboratories conducting the majority of cancer genetic testing from 2013 to 2014. They found that only 24.1 percent of 77,085 women diagnosed with breast cancer and 30.9 percent of 6,001 diagnosed with ovarian cancer underwent any genetic testing.

### Disparities in genetic testing

The researchers also observed disparities in testing, particularly among ovarian cancer patients. Although nearly 34 percent of non-Hispanic white women were tested, only about 22 percent of black women and 24 percent of Hispanic women were tested. Income and insurance status played a role in the prevalence of testing among women with ovarian cancer from all racial and ethnic groups, the researchers found. About 20 percent of patients with Medicare were tested compared with about 34 percent of patients with other forms of health insurance. Testing prevalence decreased to about 20 percent in areas where residential poverty equaled or surpassed 20 percent, and it was about 38 percent in regions where the poverty level was less than 10 percent.

The researchers found that among women with breast cancer in the study who underwent testing for a panel of guideline-designated genes, the prevalence of mutation variants of unknown significance was much higher in minority patients: 28.5 percent, 26.6 percent and 19.3 percent in African-American, Asian and Hispanic patients, respectively, versus 14.5 percent in non-Hispanic whites. The prevalence of pathogenic variants also varied along racial and ethnic lines.

"These differences underscore the need to improve the clarity of genetic test results, especially for racial or ethnic minority patients," Kurian said.

Researchers from Information Management Services Inc. and the University of Southern California, as well as other researchers from the National Cancer Institute, also contributed to the work.

The research was supported by the National Institutes of Health, the California Department of Public Health, the Centers for Disease Control and Prevention and the Cancer Registry of Greater California.

Stanford's departments of Medicine and of Health Research and Policy also supported the work. **ISM**

## CRISPR

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be improved."

Porteus' approach uses CRISPR-Cas9 to create a double-stranded break in DNA to insert a healthy copy of the IL2R gamma gene in the stem cells that create immune cells.

Using the gene-editing system, scientists tweaked cells from six people with SCID-X1 and then transplanted those cells into mouse models of SCID-X1. Those mice were then not only able to make their own immune cells, but many of the edited cells retained something called "stemness," meaning that they maintained their ability to continually create new cells.

"The idea is that these modified stem cells will give rise to the blood system and the immune system for the entirety of the patient's life, which we hope is 90 or more years," Porteus said. "And we see evidence for that in our study."

LUCILE PACKARD FOUNDATION FOR CHILDREN'S HEALTH

Using the gene-editing system CRISPR-Cas9, Matthew Porteus and his colleagues replaced the mutated gene underpinning SCID-X1 in a mouse model of the devastating immune disease.

### Popping the bubble

"We've showed that this is a novel and effective strategy to potentially treat this disease, but the other big thing here is safety," Porteus said. "We don't see any abnormalities in the mice that receive the treatment. More specifically, we also performed genetic analyses to see if the CRISPR-Cas9 system made DNA breaks at places that it's not supposed to, and we see no evidence of that." That's crucial, Porteus said, because it ensures that other healthy genes aren't being erroneously tampered with.

Translating lab research to a patient population takes time, Porteus said, but he's optimistic that if larger mouse studies are successful, the CRISPR-Cas9 gene therapy could be piloted in human patients in the next year or two through the Stanford Center for Definitive and Curative Medicine.

Other Stanford co-authors of the study are postdoctoral scholars Volker Wiebking, MD, and Camille Sindhu, PhD; research assistant Beruh Dejene; graduate student Waracharee Srifa; medical student Sruthi Mantri; lab manager Camencita Nicolas; former flow cytometry research assistant Nivedita Saxena; and professors of pediatrics Maria Grazia Roncarolo, MD, and Kenneth Weinberg, MD.

Researchers from Rice University, the University of Texas-Dallas, the University of California-Irvine and the National Institutes of Health contributed to this research.

The study was funded by the California Institute for Regenerative Medicine, the National Institutes of Health, the Laurie Kraus Lacob Translational Research Fund, the Amon Carter Foundation and the Sutardja Family Fund.

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

## Phage

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students Johanna Sweere, Michelle Bach and Naomi Haddock; former postdoctoral scholar Xiou Cao, PhD; Lu Tian, ScD, associate professor of biomedical data science; and biostatistician Laurence Nedelec, PhD.

Bollyky is a member of Stanford Bio-X and the Wu Tsai Neurosciences Institute at Stanford. Bollyky and Milla are members of the Stanford Maternal & Child Health Research Institute.

Scientists from the University of Montana, Copenhagen University Hospital and the University of Copenhagen also contributed to the research.

The Stanford scientists involved in the research were supported by the Stanford Maternal & Child Health Research Institute; the Stanford Training Program in Pulmonary Biology, part of a grant from the National Heart, Lung and Blood Institute; a pilot grant from Stanford's Translational Research and Applied Medicine Program; the Ross Mosier Laboratories Gift Fund; the National Institutes of Health; the Cystic Fibrosis Foundation; and the Dr. Ralph and Marian Falk Medical Research Trust Bank of America. **ISM**

# Two medical students awarded 2019 Soros Fellowship for New Americans

Two second-year medical students, Harriet Kiwanuka and Shamik Mascharak, have been awarded 2019 Paul & Daisy Soros Fellowships for New Americans.

Paul Soros, who died in 2013, and his wife, Daisy Soros, established the fellowship program in 1997 to support graduate study for immigrants to the United States and their children.

Harriet Kiwanuka

Each fellow receives as much as $90,000 for tuition and living expenses over two academic years. Recipients are selected for fellowships based on merit, with an emphasis on creativity, originality, initiative and sustained accomplishments. They can study in any degree-granting graduate program in any field at any university in the United States.

Kiwanuka will use the award to support work toward her medical degree. Her parents emigrated from Uganda, and she was born in Norwood, Massachusetts. She traces her passion to pursue medicine to the time her parents were severely injured in a house fire.

Kiwanuka is a member of the Gurtner laboratory, which is interested in the mechanism of blood vessel growth following injury, and how pathways of tissue regeneration and fibrosis interact in wound healing. Her research is focused on CRISPR-cas9 engineered stem cell burn therapy. She hopes to become a plastic and reconstructive surgeon specializing in burn management.

Shamik Mascharak

Mascharak, who earned a bachelor's degree in bioengineering at Stanford, will use the award to support his work toward an MD-PhD in stem cell biology and regenerative medicine.

He was born in Santa Cruz, California, to parents who emigrated from India.

As an undergraduate, Mascharak did research in the Heilshorn biomaterials group, where he explored new grafting materials to be used in vascular bypass surgery, which relies on grafts to reroute blood flow. Current graft materials are notorious for integrating into the vascular system very slowly — if at all — and often fail, requiring more surgery. In the lab, Mascharak used a particular recombinant protein, called elastinlike protein, to manufacture a family of biomaterials that could one day be used as vascular grafting materials — research that resulted in his honors thesis.

Mascharak is a member of the Longaker laboratory, where he is working alongside surgeons to better understand the complex biology of wound healing and tissue regeneration. **ISM**

# Women getting C-sections best judge of own pain-medication needs, study finds

**By Erin Digitale**

When doctors ask, women scheduled for cesarean sections know in advance whether they will need low, medium or high levels of pain medication, and are happier with their pain-management experience if given a choice about it, a Stanford-led study has found.

"It makes sense: You know your body and have had previous pain experiences," said Brendan Carvalho, MD, professor of anesthesiology, perioperative and pain medicine and lead author of the work, which was published online March 13 in *Regional Anesthesia & Pain Medicine*. "Instead of physicians trying to predict what the patient will need, this study says we should get the middleman out and let the patient decide."

The research tested an approach that was different than what anesthesiologists have traditionally done to control pain during and after a C-section. Barring medication allergies, every woman coming to a hospital for a C-section usually gets the same anesthetic and postoperative painkillers — an approach that is typical for patients having other surgeries, too.

Before the current standardized approach was instituted, doctors used their personal judgment to plan anesthesia, with variation between physicians. The shift to a uniform, evidence-based standard protocol was better than having each doctor do something different, but it doesn't account for individual patient needs.

In the study of 160 participants who were scheduled to have C-sections, women were randomly assigned to "choice" or "no-choice" groups for their plan for pain management during surgery and in the following 48 hours. The 40 women in the "no-choice" group got the standard pain-management protocol, while the 120 women in the "choice" group specified whether they wanted "medium" pain management — the same as the current standard — or lower or higher doses of pain medication.

In the "choice" group, 18% chose the low level of pain management, 68% chose the medium level and 14% chose the high level of pain management.

The researchers asked study participants in the "choice" group why they sorted themselves into their chosen groups. Women who picked the lowest doses of pain medication were concerned about side effects from opioids, such as itching and nausea. Women who chose the highest doses said they knew they needed more pain relief, and their predictions were correct. Regardless of which level of medication they had picked, these women were more satisfied with their pain relief plan than those in the "no-choice" group.

The results, which are consistent with earlier work by the same team, suggest that more studies are called for to test how to accommodate patients' self-reported pain-relief needs, Carvalho said. Patients' preferences must always be balanced with safety concerns, such as the potential need for more respiratory monitoring in patients who get higher doses of opioids, he said. **ISM**

# Conference to highlight advances in immune monitoring technology and bioinformatics

A two-day conference will focus on new technologies, analytic methods and areas of focus for human immunology and bioinformatics.

The Human Immune Monitoring Technology and Bioinformatics Conference is scheduled for 8:30 a.m.-6:30 p.m. May 2 and 8:30 a.m.-5:30 p.m. May 3 in Berg Hall at the Li Ka Shing Center for Learning and Knowledge.

Speakers will include more than a dozen Stanford faculty members, as well as researchers from the University of California-San Francisco, UC-Berkeley, Harvard University, the University of Oxford, the National Institutes of Health, the Fred Hutchison Cancer Research Center, the Broad Institute, the Dana-Farber Cancer Institute, the Karolinska Institute, the Institute for Systems Biology, the Ragon Institute and the Bill and Melinda Gates Foundation.

The event is sponsored by the Stanford Human Systems Immunology Center and the Stanford Institute for Immunity, Transplantation and Infection.

Attendance will be limited to 300. The event costs $150 but is free to Stanford community members with a SUNet ID.

To register or learn more about the conference topics, agenda or speakers, visit https://tickets.stanford.edu/iti2019#link. **ISM**

## Kidney

**continued from page 1**

University School of Medicine and co-principal investigator of the trial. "Now, patients with diabetes have a promising option to guard against one of the most severe risks of their condition."

The trial involved 4,401 participants in 34 countries.

The drug, canagliflozin, improves on a nearly two-decades-old therapy that is currently the only treatment approved to protect kidney function in people with Type 2 diabetes. In the trial, canagliflozin also was found to reduce the risk of major cardiovascular events.

Canagliflozin increases the excretion of glucose through the kidneys. It has already been approved by the Food and Drug Administration to lower blood glucose in patients with Type 2 diabetes and to reduce the risk of major adverse cardiovascular events in patients with Type 2 diabetes and existing heart disease.

A paper describing the findings of the CREDENCE trial was published April 14 in *The New England Journal of Medicine* and presented at the International Society of Nephrology's World Congress of Nephrology in Melbourne. Mahaffey, who is director of the Stanford Center for Clinical Research, is the study's senior author. The lead author is Vlado Perkovic, MBBS, PhD, executive director of The George Institute for Global Health Australia, and a professor of medicine at the University of New South Wales in Sydney.

Kenneth Mahaffey

### 'Definitive trial result'

"People with diabetes and kidney disease are at extremely high risk of kidney failure, heart attack, stroke and death," Perkovic said. "With this definitive trial result, we now have a very effective way to reduce this risk using a once-daily pill."

Participants in the trial received the best care available for kidney disease under current guidelines, a type of therapy called renin-angiotensin-aldosterone system, or RAAS, blockade. In addition, half were randomly selected to receive canagliflozin, while the other half were given a placebo.

The primary results of the study found that participants who took canagliflozin were 30 percent less likely than the placebo group to develop kidney failure or die from either renal failure or cardiovascular disease. Their risk of kidney failure or death from kidney failure was reduced by 34 percent, and the risk of hospitalization for heart failure or death due to cardiac causes decreased by 31 percent.

### 'Eagerly sought' treatment

People with diabetes can develop kidney disease because prolonged high blood sugar harms blood vessels in the kidney. In addition, diabetes often causes high blood pressure, which can stretch and weaken blood vessels in the organ.

For the past two decades, physicians have largely relied on RAAS blockade to prevent the deterioration of kidney function in diabetic patients. Although RAAS blockade lowers blood pressure and delays progression of kidney disease, patients undergoing this treatment remain at a high risk for renal failure and cardiovascular disease, as well as death from these conditions.

Given that the number of people with Type 2 diabetes worldwide is estimated to rise by 20 percent to 510 million in 2030, "a drug like canagliflozin that improves both cardiovascular and renal outcomes has been eagerly sought by both patients with Type 2 diabetes and clinicians caring for them," Mahaffey said.

Other Stanford researchers assisting in the trial were Glenn Chertow, MD, professor of medicine, and Tara Chang, MD, assistant professor of medicine, who were national co-leads; and Sun Kim, MD, associate professor of medicine, who was a site investigator.

The work was funded by Janssen, which manufactures canagliflozin, and led by an independent steering committee.

Stanford's Department of Medicine and the Stanford Center for Clinical Research also supported the work. **ISM**

# Sylvia Plevritis appointed chair of biomedical data science

**By Hanae Armitage**

Sylvia Plevritis, PhD, professor of biomedical data science and of radiology, was appointed chair of the Department of Biomedical Data Science, effective April 1.

Sylvia Plevritis

"An accomplished scientist, researcher and educator, Dr. Plevritis' collaborative vision, depth of expertise and leadership skills make her uniquely qualified to lead the department as it develops novel computational and statistical methods that transform health," said Lloyd Minor, MD, dean of the School of Medicine. "Dr. Plevritis has focused her research on computational modeling of cancer biology and cancer outcomes, and her findings have forged new pathways that have advanced the medical community's understanding of the disease."

She replaces Carlos Bustamante, PhD, the department's inaugural chair, who is taking a leave of absence from Stanford to join a venture capital firm that invests in health care, life sciences and technology.

Plevritis is the director of the Stanford Center for Cancer Systems Biology and of the Cancer Systems Biology Scholars Program, and a principal investigator of the Cancer Intervention and Surveillance Modeling Network. She has served as the co-section chief of Integrative Biomedical Imaging Informatics at Stanford for the past 10 years.

Outside Stanford, she serves on the scientific advisory board of the National Cancer Institute and is a fellow of the American Institute for Medical and Biological Engineering and a distinguished investigator with the Academy of Radiology Research.

Plevritis earned a PhD in electrical engineering, with a concentration on MRI imaging of tumors, at Stanford in 1992 and a master's degree in health services research, with a focus on cancer screening evaluation, at Stanford in 1996.

Her lab investigates cancer systems biology, parsing the molecular mechanisms of cancer progression and cancer outcomes through integrative computational modeling.

As the new chair, Plevritis said she has two overarching goals that she wants to pursue in collaboration with the faculty of the department: further enhance the educational mission through direct connections with the biomedical informatics graduate program, and continue to deepen collaborative research opportunities for the department as a whole.

"As biomedical research increasingly turns to data sciences for answers, there's an opportunity to build new approaches to analyze, visualize and derive insights from complex data sets," Plevritis said. "Right now, we're at the center of a tremendous revolution where we can use these data and insights to think about the whole person, how to maintain health, quickly identify early signs of disease and treat disease with the right therapies at the right time." ISM

# NIH awards $12 million grant renewal for flu vaccine research

**By Bruce Goldman**

The National Institutes of Health has awarded the Stanford Institute for Immunity, Transplantation and Infection a five-year, $12 million renewal of a grant for the study of how people respond to influenza vaccination.

With the renewal, the total amount granted for this project has exceeded $69 million since the first award was made in 2003.

"This represents a milestone in efforts to understand the human immune system, an area that has been sorely neglected but is a major part of anyone's health," said the grant's principal investigator, Mark Davis, PhD, director of the institute and professor of microbiology and immunology. "It also represents a new 'team science' model and a breakout from decades of thinking that mice were the only species worth studying."

The project's primary goal, Davis said, is to better understand the human immune system, how it varies and why, using new technologies, new ideas and new ways to improve an influenza vaccine that "is so ineffective in many people, especially the elderly, that it is one the top priorities for improvement."

Much of the work is being done through Stanford's Human Immune Monitoring Center, directed by Holden Maecker, PhD, professor of microbiology and immunology. Davis, who holds the Burt and Marion Avery Family Professorship, praised the center as having created "the world's best high-tech engine of human immune discovery, gathering huge amounts of data from carefully constructed clinical studies and subjecting these data to rigorous analysis."

Mark Davis

In 2008, Davis wrote a controversial essay asserting that human immunology wasn't making much progress and suggesting that it needed to focus less on mice and more on direct human studies, and to do so using systems-biology approaches.

"But having these ideas of what's wrong is not the same as having acknowledged solutions, so my colleagues and I have spent the time since then figuring out how to implement these ideas and advance the field," he said. "This latest renewal is an acknowledgement that Stanford is making unique and valuable contributions in this area."

The center also received a separate $50 million grant from the Gates Foundation in 2015. ISM

## OF NOTE

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

**NICHOLAS GIORI**, MD, PhD, was promoted to professor of orthopaedic surgery, effective March 1. His research examines orthopaedic biomechanics and assesses the design and function of joint replacements. His work also uses large medical databases to investigate important questions relating to joint replacement surgery.

**RICHARD HOPPE**, MD, the Henry S. Kaplan-Harry Lebeson Professor of Cancer Biology and professor of radiation oncology, received the Rodger Winn Award from the National Comprehensive Cancer Network. He is the founding chair of the network's guidelines panel for Hodgkin lymphoma and is a member of two additional panels. He was recognized for expert judgment and commitment to excellence in service of the guidelines, and for his collegial and respectful manner, compassion, thoughtfulness and preparedness. The award is in memory of the first leader of the guidelines program.

**ANDREI IAGARU**, MD, was promoted to professor of radiology, effective Feb. 1. His research interests include early cancer detection using positron emission tomography, magnetic resonance imaging and computed tomography; clinical translation of PET radiopharmaceuticals; and peptide-based diagnostic imaging and therapy. He is chief of the division of nuclear medicine and molecular imaging.

**ANITA KISHORE**, MD, clinical associate professor of psychiatry, was awarded a 2019-20 Fulbright U.S. Scholar Program grant. The two-year, $32,750 scholarship will support her work to build, strengthen and enhance collaborative mentorship programs and networks for medical students interested in child psychiatry in the Netherlands, Australia and India. The goal is to increase access to child psychiatric services worldwide.

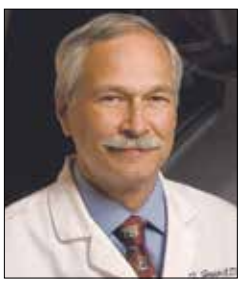
**RUTH LATHI**, MD, was promoted to professor of obstetrics and gynecology, effective March 1. She is the director of the recurrent pregnancy loss program and specializes in reproductive endocrinology and infertility. Her research interests include genetic causes of miscarriages and the prognostic value of genetic testing related to miscarriage; the role of preimplantation genetic diagnosis; and the long-term outcomes of fertility treatments.

**KYLE LOH**, PhD, assistant professor of developmental biology, and **BO WANG**, PhD, assistant professor of bioengineering, are on separate research teams that will each receive a grant from the international Human Frontier Science Program. The three-year, $250,000-per-year grants are awarded to teams of researchers from different countries. Wang's team will study how an immune response can shift from being beneficial to being harmful. Loh's team will study the role of vasculature in the development of brain tissue.

**CAROLYN RODRIGUEZ**, MD, PhD, was promoted to associate professor of psychiatry and behavioral sciences effective March 1. Her research investigates the neurobiology of obsessive-compulsive disorder and related mental health conditions, with the aim of developing targeted, rapid-acting treatments that relieve suffering.

**MICHAEL SNYDER**, PhD, the Stanford W. Ascherman, MD, FACS, Professor in Genetics, chair of genetics and director of the Stanford Center for Genomics and Personalized Medicine, will receive the 2019 George W. Beadle Award from the Genetics Society of America. The award recognizes significant, sustained service to the genetics community. He was recognized for developing and disseminating widely used technology for the simultaneous analysis of thousands of genes, RNA molecules and proteins. ISM

Nicholas Giori



Richard Hoppe

Andrei Iagaru

Anita Kishore

Ruth Lathi

Kyle Loh

Bo Wang

Carolyn Rodriguez

Michael Snyder