Ovarian cancer patients undertested for mutations that could guide clinical care

By Krista Conger

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 85,000 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 Karp, 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
Scientists help parse molecular changes in twin astronauts

By Hanae Armitage

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 General Medicine, 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, they 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 inflame and bolster 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 take-away, she said, is that the immune system is revved up under the stress 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. For example, 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.

“The challenges of keeping our immune system up to date and healthy 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 help to “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 Piensing, 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 Valex Foundation, the WorldQuant Foundation, the Pershing Square Sohn Cancer Research Alliance and the Bill and Melinda Gates Foundation.

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 really 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.

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 are 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 non-profit 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 cardiology clinic, any of these institutions, could be affected is 1 in 500,” he said.
Familial hypercholesterolemia is caused by a mutation that hinders an LDL-lowering treatment right away. "When somebody first grows 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

ogy 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 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 drives the disease.

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 makes fishy emails. They then 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. They then ran a larger 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," Shah said. "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 and other organizations 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, training 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 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 staff bioinformatician at Stanford Bio-X, the Stanford Cancer Institute and the Wu Tsai Neurosciences Institute at Stanford. Knowles is a member of Bio-X, the Stanford Cancer Institute and the Wu Tsai Neurosciences Institute at Stanford. Research co-authors of the study are graduate students Lisa E. Bollyky and Frederick A. Bollyky recently led another study that suggested 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 students Elizabeth Burgener and Kenneth Jung, PhD.

"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 is a pediatric pulmonologist 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 who have phage-infected bacteria in their lungs fared worse than those with uninfected lung bacteria.

"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 aeruginosa. The infection is linked to worsened prognosis.

"Once somebody first grows Pseudomonas, we try to eradicate it with antibiotics," Burgener said. Patients inhale antibiotic solutions directly into their lungs. But the bacteria often keep coming back.

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 aerugi- nosa 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 germline. Patients were more likely to develop persistent 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 15, 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 infections with phage DNA. 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 roughly equally likely than bacteria without virus to be resistant to three antibiotics commonly used to treat CF — aztreonam, amikacin and meropenem — but not necessarily to tigecycline.

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

How does antibiotic resistance happen?

The researchers previously showed that phage production can be a competitive advantage for bacterial colonies in 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 seemed to protect the bacteria from antibiotics 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.

The researchers think the physical properties of the different types of anti- biotic molecules — such as whether the drugs have charged or neutral surfaces or may adsorb to or displace antibiotics — 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 phage bacteria and whether it’s shocking how much effect the phages have on the host immune system.”

Bollyky recently led another study that suggested 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 students See PHAGE, page 6

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. See 3
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 intracatable 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 revelation 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 pollutants 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.

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 fill the bill. Primarily burning coal, thousands of kilns ringing Bangladesh’s 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.”

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

"We need to think like a physician about how we can treat the environment."
Cancer
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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 with ovarian cancer and the mouse and human models of ovarian cancer patients who are racial or ethnic minorities, as well as the overall population, is unknown.

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 just 24.1 percent of 77,085 women diagnosed with breast cancer and 36.9 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 25 percent of patients with other forms of health insurance. Testing prevalence decreased to about 20 percent in areas where test-treatment equity 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.

“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 North Carolina at Chapel Hill and 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.

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 transfected those cells into mouse models of SCID-X1. Those mice were then not only able to make their own IL2R gamma gene, but the edited cells retained something called “stemness,” meaning that the mice successfully used the transplanted cells 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. “We don’t see evidence for that in our study.”

Popping the bubble

“We showed that this is a novel and effective strategy to potentially treat this disease, but the other big thing is, it’s safer,” Porteus said. “We didn’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.

Targeting 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 Wiecking, MD, and Leonid Plakhov, MD, PhD; research assistant Beruh Dejene; graduate student Waracharee Srit; medical student Stuthi Marni; lab manager Camenecia 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-Dalлас, the University of California-Irvine and the National Institutes of Health also contributed to this research.

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

Stanford’s Department of Pediatrics also supported the work.

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 Electrical Engineering and Computer Science, 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 Stanford Institute for the Science and Engineering of Matter, or SLAC, the University of California-Irvine and the National Institute of Standards and Technology.

Now provost, Drell joined the Stanford faculty in 2002.

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students Johanna Sweere, Michelle Bach and Natasha Haddock; former postdoctoral scholar Xiou Cao, PhD; Lu Tian, ScD, associate professor of biomedical and genomic sciences; and bioinformatician Laurence Nedelec, PhD.

Bolinsky is a member of Stanford Bio-X and the Wu Tsai Neurosciences Institute at Stanford. Bolisky and Milia 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 Laboratorios Gift Fund; the National Institutes of Health; the Cytec Fibrous Foundation; and the Dr. Ralph and Marian Falk Medical Research Trust Bank of America.

Persis Drell

LUCILE PACKARD FOUNDATION FOR CHILDREN’S HEALTH

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

Kiwanuka, who died in 2013, and his wife, Daisy Soros, established the fellowship program in 1975 to support graduate study for immigrants and their children.

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

Kiwanuka and Mascharak both worked in medical research. Together they established the Mascharak Research Education Fund, which supports students who wish to support work toward their medical degree. Her parents emigrated from Uganda, and she was born in Norwood, Massachu-

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 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 and pain medicine and lead author of the work, which was published in Anesthesiology.

The study’s findings support a possible, yet unproved, trend toward offering patients choices in pain management, and echo recent guidelines that suggest informed consent and patient choice are fundamental to pain treatment.

Carvalho’s team randomly assigned 294 women scheduled for cesarean sections to either a "no-choice" group, where they were told they would receive 120 milligrams of "standard pain medication" based on their pain history, or a "choice" group, where patients were given three options: 60 milligrams, 120 milligrams or 180 milligrams. They were told these doses would be selected based on the level of pain they anticipate, and that the dose would be adjusted if needed.

Patients in the "no-choice" group had significantly higher pain scores during surgery and the following 48 hours than those in the "choice" group. 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 well women and men independently self-report 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.

"Women get C-sections best judge of own pain-medication needs, study finds

Two medical students awarded 2019 Soros Fellowships for New Americans

Harriet Kiwanuka and Shamik Mascharak have been awarded 2019 Paul & Daisy Soros Fellowships for New Americans.

Kiwanuka, who died in 2013, and his wife, Daisy Soros, established the fellowship program in 1975 to support graduate study for immigrants and their children.

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

Kiwanuka and Mascharak both worked in medical research. Together they established the Mascharak Research Education Fund, which supports students who wish to support work toward their medical degree. Her parents emigrated from Uganda, and she was born in Norwood, Massachu-

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By Erin Digitale

When doctors ask, women scheduled for cesarean sections know in advance whether they will need low, medium or high 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 and pain medicine and lead author of the work, which was published in Anesthesiology.

The study’s findings support a possible, yet unproved, trend toward offering patients choices in pain management, and echo recent guidelines that suggest informed consent and patient choice are fundamental to pain treatment.

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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 complications of the disease."

The trial involved 4,401 participants in 34 countries.

Canagliflozin increases the excretion of glucose through the kidneys. It has already been approved by the Food and Drug Administration for the treatment of glucose through the kidneys. It has already been approved by the Food and Drug Administration for the treatment of Type 2 diabetes worldwide is estimated to be around 20% to 30% lower when canagliflozin is taken, compared to placebo.

"Definitive trial result" of canagliflozin

Kenneth Mahaffey

People with diabetes and kidney disease are at extremely high risk for kidney failure or 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 drug or placebo every day. Two-thirds of patients in the group received canagliflozin, and one-third received placebo. The study’s primary results were published in the New England Journal of Medicine last year.

The study’s results were presented in a press release by the American Heart Association, the American Diabetes Association and the International Society of Nephrology.

"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."

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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.

“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-division 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 how changes in the genetic and epigenetic 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 interactions 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 a highly collaborative and integrative team and to derive insights from complex data sets,” Plevritis said. “Right now, we’re at the center of a tremendous revolution in which 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.”

NIH awards $12 million grant renewal for flu vaccine research

By Bruce Goldman

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

“The grant is a milestone in efforts to understand the human immune system, an area that has been sorely neglected because it 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 breakthrough 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 of 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.”

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 and will make significant and valuable contributions in this area.”

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

Ruth Lathi

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Michael Snyder

Anita Kishore

Michael Snyder

Carolyn Rodriguez

Nicholas Giori

Ruth Lathi

Kyle Loh

Andrei Iagaru

Bo Wang

Carolyn Rodriguez

Michael Snyder

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