INSIDE STANFORD MEDICINE

Volume 7, No. 19 ■ October 26, 2015 ■ Published by the Office of Communication & Public Affairs

Speakers at two separate events addressed precision health.

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Green Button: The promise of personalizing treatment guidelines for patients in real time

By Bruce Goldman

It's hardly a secret among medical practitioners: For most patients, clear treatment guidelines simply don't exist.

Take Vera. She is a 55-year-old woman of Vietnamese descent who has asthma. You're her doctor, and you've just learned that she also has high blood pressure. Vera's case doesn't fit the data from any clinical trials; there's no medical literature on hypertension medications for middle-aged, asthmatic Vietnamese-American women. You want to treat her hypertension, but you have no guidelines. Vera is sitting in your exam room now. What do you do?

Suppose you could get some guidance simply by pressing a virtual button on a computer screen displaying Vera's electronic medical record? This would trigger a search of millions of other electronic records and, in a matter of minutes, generate a succinct composite summary of the outcomes of 25 or 100 or perhaps 1,000 patients very similar to her — same race, same height, same age, same symptoms, lookalike lab-test results — who were given various antihypertensive medications. Patients similar to Vera, it turns out, respond particularly well to one drug type — something you would have been hard put to guess on your own.

ALEXWHITE / SHUTTERSTOCK

Pretend patient

Vera is a made-up patient, but there are plenty of people with conditions that are just as complicated. Scattered throughout millions of electronic medical records, such lookalike cases could point the way to effective treatments options for Vera and others if these could be plucked from the aggregate and formatted for easy interpretation. While some aspects of this approach, such as assuring patients that their privacy will be protected and making databases compatible across health-care systems, need to be worked out, Stanford medical researchers want to tackle those problems. The goal is a seamless system that quickly links physicians to the information they need in order to give their patients the best-validated treatments available.

A pediatrician, a cardiologist and a biomedical informaticist at the School of Medicine have come up with an idea that could revolutionize the practice of medicine. Their brainchild, which they've dubbed the Green Button, will do that by tapping the huge volumes of data lying dormant in the EMRs of millions of patients.

The Green Button approach leverages the increasingly routine use of these records and the fast-paced progress taking place in computation and data transmission. It could enable a real-time solution to a big problem: the inadequacy of results from clinical trials — the foundation upon which treatment guidelines are built — for the vast majority of patients. Clinical trials are experiments in which new medications and procedures are tested on people. In order to achieve understandable results, investigators tend to select participants for trials who are a lot alike in terms of age, sex, ethnicity, medical conditions and treatment history. Yet the average patient walking into a doctor's office seldom resembles a patient included in those trials.

'Just press the Green Button'

"Every day I encounter patients for whom we just don't have the best scientific evidence on how to treat them," said Christopher Longhurst, MD, clinical professor of pediatrics in systems medicine and chief medical information officer for Stanford Children's Health.

In a 2014 *Health Affairs* article, Longhurst along with Nigam Shah, MBBS, PhD, assistant professor of biomedical research and assistant director of the Stanford Center for Biomedical Research, and Robert Harrington, MD, professor and chair of medicine, outlined a vision for drawing medical guidance from day-to-day medical practice in hospitals and doctors' offices. They called it the Green Button. The idea was to give doctors access to aggregate patient data, right there and then, from a vast

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Sleep deprivation affects stem cells, reducing transplant efficiency in mice

By Krista Conger

Drowsy mice make poor stem cell donors, according to a new study by researchers at the School of Medicine.

Asya Rolls

A sleep deficit of just four hours affects by as much as 50 percent the ability of stem cells of the blood and immune system to migrate to the proper spots in the bone marrow of recipient mice and churn out the cell types necessary to reconstitute a damaged immune system, the researchers found.

Although the research was done in laboratory mice, the findings have possible implications for human stem cell transplants. Tens of

See SLEEPY, page 7

Why a 61-year-old underwent heart surgery at Lucile Packard Children's Hospital Stanford

By Erin Digitale

At 61 years old, Sang Hee Yoon seems an unlikely patient for a children's hospital.

Yet earlier this year, the San Jose, California, man was wheeled into an operating room at Lucile Packard Children's Hospital Stanford as one member of a fast-growing group of adults whose congenital heart defects require the expertise of pediatric heart surgeons.

When Yoon was born, few babies with severe congenital heart disease survived childhood. Today, after a half-century of improvements in the ability to repair such defects, more than 1 million U.S. adults are living with congenital heart disease, and their ranks are growing by 20,000 per year. The triumph of their long survival brings new challenges for them and their doctors.

"Patients come back at 40 or 50 years old, telling us, 'My doctor said I was cured,'" said George Lui, MD, medical director of the Adult Congenital Heart Program at Stanford, a collaboration between the Heart Center at Lucile Packard Children's Hospital and Stanford Health Care. Some patients' childhood surgical repairs were initially judged so successful that they never expected to return to a cardiologist, said Lui, who is also clinical assistant professor of

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NORBERT VON DER GROEBEN

Sang Hee Yoon (center) received care through the Adult Congenital Heart Program at Stanford. Also pictured are his wife, Min Wha Yoon, and (from left) doctors George Lui, Daniel Murphy and Katsuhide Maeda.

Precursor cells identified that could help grow heart arteries

By Christopher Vaughan

Researchers at Stanford have discovered which type of cell develops into the muscular lining of arteries that feed the heart.

The finding, in mice, as well as the discovery of the molecular signals that govern this transformation, may ultimately lead to human therapies to regrow healthy coronary arteries, the researchers said.

Scientists previously showed that portions of the coronary artery develop from cells on the surface of the heart called epicardial cells. However, the direct progenitors to coronary artery smooth muscle cells, the important component that encases the artery and gives it strength, were not identified.

Through a series of sophisticated techniques, the researchers solved the mystery: They determined that smooth muscle cells in cardiac arteries grew out of a kind of cell called a cardiac pericyte. Perhaps more important, scientists also identified a molecule called notch3 as the signal that governs the conversion of pericytes to cardiovascular smooth muscle cells.

A paper describing the work was published Oct. 19 in *eLife*.

"What is important about this study is that a precise stem cell technology was used to visualize coronary progenitors among the millions of other cells in the developing heart," said Irving Weissman, MD, the Virginia and D. K. Ludwig Professor in Clinical Investigation in Cancer Research and the director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, who is a co-author of the paper. "This was the key to discovering that pericytes turn into smooth muscle cells in response to increased blood flow."

Collateral blood vessel formation

Scientists have known very little about how collateral blood vessels form to reroute blood flow around blocked coronary arteries or how to stimulate their development to treat coronary artery disease, said Katharina Sophia Volz, PhD, the lead author of the paper and a researcher at the stem cell institute. Volz pointed out that injured hearts can regenerate tiny blood vessels, but cannot form larger arteries that have the layer of smooth muscle cells required to provide significant blood flow to healing tissues. "Providing the right molecular signals to turn pericytes into smooth muscles cells may promote a transition from tiny blood vessels to true arteries," she said.

Kristy Red-Horse, PhD, assistant professor of biology and the paper's senior author, said she believes that "if we discover the molecular signals that form coronary blood vessels in mouse embryos, we could test their ability to stimulate new vessels in adult mice and potentially use this knowledge to one day repair injured adult human hearts."

Red-Horse said this process could potentially be replicated in adult mice and then adult humans through the use of these molecular signals. "Since adult human hearts are filled will small capillary blood vessels that are also covered in pericytes, we believe that these can be coaxed to reignite their developmental program and create new coronary arteries," she said. "Now that we are beginning to really understand the coronary artery developmental program, we have begun studies to reactivate that program in injured hearts and hope to someday use these same methods to help treat coronary artery disease."

Other Stanford-affiliated co-authors are postdoctoral scholars Daniel Riordan, PhD, and Aruna Poduri, PhD; and graduate students Andrew Jacobs, Heidi Chen, Andrew McKay, Natalie Kofler and Jan Kitajewski.

Support for the research was provided by the National Institutes of Health, the California Institute for Regenerative Medicine, the Virginia and D.K. Ludwig Fund for Cancer Research and the Searle Scholars Program. ISM

Christopher Vaughan is the communications manager for the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Cardiovascular Institute awards $200,000 in seed grants

The Stanford Cardiovascular Institute has awarded seed grants to eight research projects led by faculty members and young investigators to help improve both diagnosis and treatment of cardiovascular disease.

The recipients were chosen from 43 applications. They share a total of $200,000 in grants from the institute and the Stanford Child Health Research Institute, which funded two of the projects.

The projects were funded for their potential to create new, fundamental knowledge and to translate cardiovascular research from the laboratory to the patient. Following are the grant recipients and their projects:

ANITRA ROMFH, MD, clinical assistant professor of pediatric cardiology, and **MANISH BUTTE**, MD, PhD, assistant professor of pediatric immunology, for "T-cell deficiencies in adult congenital heart disease."

RONALD DALMAN, MD, the Dr. Walter C. Chidester Professor of Surgery and professor of vascular surgery, for "Regulation of abdominal aortic aneurysm pathogenesis by hypoxia-inducible factors."

DAVID CAMARILLO, PhD, assistant professor of bioengineering, and **PAUL WANG**, MD, professor of cardiovascular medicine, for "Autonomous ablation treatment of cardiac arrhythmia using robotic catheters."

KENNETH MAHAFFEY, MD, professor of cardiovascular medicine; **FRANCOIS HADDAD**, MD, clinical assistant professor of cardiovascular medicine; **HOLDEN MAECKER**, PhD, associate professor of microbiology and immunology; and **MARK DAVIS**, PhD, the Burt and Marion Avery Family Professor and professor of microbiology and immunology, for "Defining the role of immune biomarkers in non-ST elevation myocardial infarction: Analysis from TRACER trial biorepository."

EVGENIOS NEOFYTOU, MD, an instructor at the cardiovascular institute, and **DAVID STEVENS**, PhD, professor emeritus of medicine, for "Modeling chronic chagasic cardiomyopathy disease mechanisms using human induced pluripotent stem cells."

PHILIP TSAO, PhD, professor of cardiovascular medicine, for "MicroRNA regulation of blood-brain barrier function and hypoperfusion-induced cerebrovascular disease."

SANJAY MALHOTRA, PhD, associate professor of radiation oncology, and **SAYED NAZISH**, MD, PhD, instructor of cardiovascular medicine, for "Stem-cell-based mechanistic study of FDA-approved drugs for repurposing of their drug actions."

JOSEPH WOO, MD, the Norman E. Shumway Professorship in Cardiovascular Surgery and professor of cardiothoracic surgery, and **AMANDA STEELE**, a PhD student, for "A pilot study for an engineered HGF fragment for the treatment of myocardial infarction in a preclinical ovine model." ISM

Cardiovascular Institute to hold symposium on Oct. 27

Envisioning a future in medicine that ensures all varieties of heart damage can be repaired will be the focus of the 2015 Stanford Cardiovascular Research Symposium.

The annual event, which is free and open to the public, will be held from 8:20 a.m. to 6:30 p.m. Oct. 27 at the Li Ka Shing Center for Learning and Knowledge.

The symposium will feature 15 speakers from Stanford and outside the university. Topics covered will range from outcomes research to editing genomes to building new technologies for repairing damage to the cardiovascular system.

Speakers will include Nobel laureate Brian Kobilka, MD, professor molecular and cellular physiology at Stanford, and Lloyd Minor, MD, dean of the Stanford School of Medicine.

A total of 61 research posters will be presented from multiple disciplines, including surgery, pediatrics, vascular medicine and genetics. The symposium includes breakfast, lunch and a reception scheduled to begin at 4:30 p.m. To register, visit http://med.stanford.edu/cvi/support-our-research/2015-cv-research-at-stanford.html. ISM

Laurence Baker tapped to head Department of Health Research and Policy

By Jennie Dusheck

Laurence Baker, PhD, was appointed chair of the Department of Health Research and Policy, effective Oct. 1

A leading health economist, Baker has served as the department's chief of health services research since 2001. He is also a fellow at Stanford's Center for Health Policy/Center for Primary Care and Outcomes Research, a senior fellow of the Stanford Institute for Economic Policy Research and a research associate of the National Bureau of Economic Research in Cambridge, Massachusetts.

Baker replaces Phil Lavori, PhD, who departed to become vice chair of the School of Medicine's new Department of Biomedical Data Science.

"Laurence is a natural and excellent choice for the HRP chair position, well-respected, trusted and admired by his peers," said Lloyd Minor, MD, dean of the School of Medicine. "As one of the top health economic experts in the world with a strong policy focus, Laurence will bring the unique perspective, energy and thoughtful guidance needed during this time of change for the department."

Laurence Baker

Baker's current research focuses on how changes in health-care delivery systems influence the cost and quality of care, with a particular focus on the growth of large, multi-specialty and hospital-affiliated medical practices.

"It's an exciting time for HRP," Baker said. "My key goal is to make sure we are well-positioned to take advantage of emerging new data and techniques and to be involved in exciting opportunities like the population-health and big-data initiatives. As we pursue these goals, we'll be looking for ways to strengthen and build our faculty and our educational programs, and take advantage of opportunities to collaborate with colleagues at the School of Medicine and around the university."

Lavori, the departing chair, said, "Baker is trusted, admired and respected by all his colleagues in HRP. His colleagues in health economics consider him to be one of the top experts in the world, and under his leadership the HSR division has grown in strength. He has a keen eye for talent and a magnetic reputation, and will be able to lead the faculty in building the strength of HRP."

Over 10 years, Lavori recruited talented faculty, trained a cohort of physician scientists and made significant contributions to the Stanford Cancer Institute and Stanford's Center for Population Health Sciences.

"I've learned a lot from Phil and have really appreciated his steady and thoughtful leadership of HRP and his insightful approaches to seeking excellence at a time when lots of things have been changing," Baker added. Lavori also launched two PhD programs: one in epidemiology and clinical research, and the other in health services research.

"Phil built a strong foundation for HRP's continued growth and preeminence, and I thank him for his years of service," Minor said. ISM

INSIDE STANFORD MEDICINE

Inside Stanford Medicine is published monthly in July and December and semi-monthly the rest of the year.

is produced by
Office of Communication & Public Affairs
Stanford University
School of Medicine
3172 Porter Drive
Palo Alto, CA 94304
Mail code 5471
(650) 723-6911
http://med.stanford.edu/news/

Paul Costello
Chief communications officer
Susan Ipaktchian
Director of print & Web communications
John Sanford
Editor
Robin Weiss
Graphic designer

Send letters, comments and story ideas to John Sanford at 723-8309 or at jsanford@stanford.edu. Please also contact him to receive an e-mail version of *Inside Stanford Medicine*.

STANFORD MEDICINE

Researchers suss out brain tumors with a new PET tracer

By Krista Conger

Locating a tumor hiding in a thicket of brain cells can be a tricky proposition. But doing so accurately is critical to removing the cancer via surgery, or for monitoring its response to therapy.

Now researchers at the School of Medicine have devised a new way to cause brain tumor tissue to stand out clearly during a type of imaging scan called positron emission tomography.

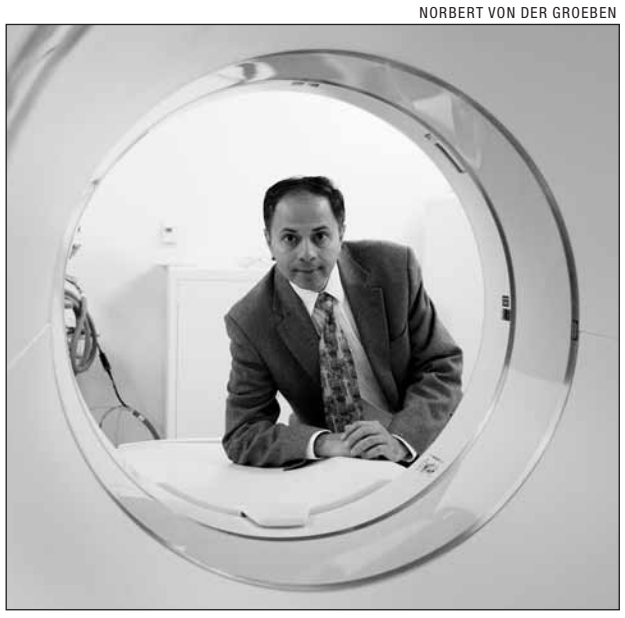
They capitalized on the fact that rapidly dividing cancer cells require vast molecular stockpiles to create new cells. To meet this need, cancer cells express higher-than-normal levels of a protein called pyruvate kinase M2, or PKM2.

"Tumor cells do all kinds of things to survive and prosper in the body," said Sanjiv Gambhir, MD, PhD, professor of radiology and director of the Molecular Imaging Program at Stanford. "One of the key things they modify is a master switch that controls cell metabolism and allows the cell to make more of the building blocks necessary for cell division. But until now we've had no way to assess the presence or activity levels of the PKM2 protein involved in that switch."

Gambhir, who holds the Virginia and D.K. Ludwig Professorship for Clinical Investigation in Cancer Research, is the senior author of a paper describing the research. Former postdoctoral scholar Timothy Witney, PhD, and instructor of radiology Michelle James, PhD, share lead authorship of the paper, which was published Oct. 21 in *Science Translational Medicine*.

They developed a molecular tracer to track PKM2 activity that can tell researchers exactly where in the brain the cancer cells are hiding. Although the tracer has only been tested in mice to date, the researchers believe it could also give important, and speedy, information about how a tumor is responding to therapy. "This is the first time we can noninvasively interrogate the biochemistry of a tumor with respect to this master switch PKM2," said Gambhir. "If we treat a tumor with a drug, we now see whether the cancer cells' metabolic properties are changing. So we could know very quickly, possibly within a few days, whether the therapeutic approach is working. If it's not effective, we won't have to waste a month or more waiting to see if the tumor itself is shrinking."

NORBERT VON DER GROEBEN



Sanjiv Gambhir and his colleagues have devised a new way to cause brain tumor tissue to stand out clearly during a type of imaging scan called positron emission tomography.

FDA approval expected

Gambhir and his colleagues expect the new tracer, called [11C]DASA-23, to be approved by the Food and Drug Administration for use in humans within about a year or so.

All cells in the body face a kind of catch-22 as they metabolize energy sources like glucose. They can either convert the energy into special storage molecules called ATP, or use it to generate cellular building blocks like amino acids. Pyruvate kinase is a key regulator of this process. When present as a complex of two pyruvate kinase molecules, called a dimer, it favors the accumulation of amino acids; when four molecules bind together, the cell generates more ATP.

The researchers knew that cancer cells tend to have higher levels of the dimer. They also knew that members of a family of molecules called DASA bind to the dimer. They labeled one family member, DASA-23, with a radioactive carbon molecule, and they used PET scans to watch in laboratory mice as the labeled molecule sought out and bound to human glioblastoma cells implanted in the brains of the mice. Using the technique, the brain cancer cells stood out clearly against a background of normal, noncancerous cells.

"This new molecule, or tracer, works particularly well in the brain because normal brain cells have very low levels of PKM2 dimers," said Gambhir. "It's possible, though, that this tracer could also be used in cancers in other tissues like the prostate, or to even learn more about how normal tissues adjust their metabolism during development or in response to varied environmental conditions."

Other Stanford-affiliated co-authors are research associates Bin Shen, PhD, Edwin Chang, PhD, Aileen Hoehne, PhD, and Gayatri Gowrishankar, PhD; postdoctoral scholar Christoph Pohling, PhD; former research assistant Natasha Arksey; former postdoctoral scholar Adam Shuhendler, PhD; research assistant Jun-Hyung Park, PhD; high school student Deepika Bodapati; visiting student Judith Weber; associate professor of radiology Jianghong Rao, PhD; and assistant professor of radiology Frederick Chin, PhD.

The research was supported by the Ben and Catherine Ivy Foundation, the National Institutes of Health and the Canary Foundation. ISM

National Academy of Medicine elects 3 new members from medical school

By Lindzi Wessel

Three members of the School of Medicine faculty have been elected members of the National Academy of Medicine, formerly known as the Institute of Medicine.

Glenn Chertow, MD, MPH; Amato Giaccia, PhD; and Robert Harrington, MD, are now among the academy's 1,826 members and 137 international members.

Chertow is the Norman S. Coplon/Satellite Healthcare Professor in Medicine and chief of the Division of Nephrology. He maintains an active clinical practice, and his research interests include clinical epidemiology, health-services research, decision sciences and clinical trials in acute and chronic kidney disease. He was elected to the Association of American Physicians in May. He has authored or co-authored more than 400 peer-reviewed manuscripts and mentored numerous junior faculty and trainees.

Giaccia, the Jack, Lulu, and Sam Willson Professor, is the associate director for basic science in the Stanford Cancer Institute and associate director for research in the Department of Radiation Oncology. He also directs the Division of Radiation and Cancer Biology and the Cancer Biology Interdisciplinary Graduate Program. He is a recipient of the American Cancer Society Junior Faculty Research Award, the Michael Fry Award from the Radiation Research Society and a 2013 gold medal from the American Society for Radiation Oncology.

Harrington joined Stanford as the chair of the Department of Medicine in 2012 after serving as the director of the Duke Clinical Research Institute. He is the Arthur L. Bloomfield Professor in Medicine and a member of the Stanford Cardiovascular Institute. Harrington's research focuses on cardiovascular disease, including mechanisms, treatments and clinical trial methodologies. He has authored or co-authored more than 400 peer-reviewed manuscripts, reviews, book chapters and editorials.

Established in 1970, the National Academy of Medicine is recognized as a national resource for independent, scientifically informed analysis and recommendations on health issues. The academy has almost 2,000 active members selected on the basis of their professional accomplishments and volunteer services. ISM

Glen Chertow

Amato Giaccia

Robert Harrington

Anne Crowe, assistant director of Center for Biomedical Ethics, dies

By Kathy Zonana

Anne Glenister Crowe, assistant director of the Stanford Center for Biomedical Ethics, died of cancer Oct. 2 at her home in Sunnyvale, California. She was 48.

As the center's chief administrator, Crowe oversaw finance, grant administration, human resources and facilities. In 2014, she received the School of Medicine's Spirit Award, given to staff members who demonstrate outstanding performance, dedication and positive attitude on the job. In an interview about the award, she referred to her job as "the perfect combination of a really interesting and diverse set of duties in a forward-thinking, scientific environment, working with brilliant people."

Anne Crowe

Before coming to Stanford in 2007, Crowe held a similar position in the engineering department at UC-Berkeley. She earned a bachelor's degree from UC-Santa Barbara and an MBA from the University of San Francisco.

"Anne Crowe loved working for Stanford," said David Magnus, the center's director and the Thomas A. Raffin Professor in Medicine and Biomedical Ethics. "She was completely dedicated to serving the mission of the medical center in any way she could. Her commitment and unwavering support for faculty and staff, and her willingness to tackle any challenge, no matter how great or small, made her a beloved figure."

"She was the center of our family," said her sister-in-law, Julia Glenister. "She was the only sister, and nearly the youngest." Crowe was the chief planner of holiday gatherings, and also the champion of family heritage. "She loved the fact that she was a Glenister — there are very few in the United States," Glenister said. "She went to a Glenister family reunion in England of about 100 people, and was very proud of that."

Crowe also toured Australia, where her parents were from, and traveled throughout Europe and the Caribbean. "She was our big globetrotter," Glenister said. In June, Crowe was quite ill and had made the decision to enter hospice care. But first, she and her husband, Roderic Crowe, traveled to Tahiti, staying in a hotel at the end of a pier. "It was one of her bucket-list destinations," she said.

In addition to her husband, Crowe is survived by her mother, Jill Glenister; her father, John Glenister; her stepmother, Lisa Glenister; and her brothers, Peter, Chris, Rodney, David, Mark and Brian Glenister.

A service for Crowe was held Oct. 16 in Memorial Church on the Stanford University campus. ISM

Chinese, American experts explore big data, health technology at symposium

By Jennie Dusheck

In a recent cartoon in *The New Yorker*, a bureaucrat across a desk remarks to a man in a chair, "You can't list your iPhone as your primary-care physician." But maybe someday our smartphones will in fact be the guardians of our health, said Euan Ashley, MD, in a wide-ranging discussion of precision health and mobile health devices Oct. 15.

Ashley, an associate professor of cardiovascular medicine and of genetics at Stanford, spoke at the ninth Sino-U.S. Symposium on Medicine in the 21st Century, which was held at the Li Ka Shing Center for Learning and Knowledge. The two-day event brought together 335 health researchers from China and the United States to foster collaboration and friendship, and to share their knowledge of precision health, mobile health devices, population health, genomics and cancer.

"Health care is the opportunity of our time," Lloyd Minor, MD, dean of the School of Medicine, said in opening remarks at the symposium. "We have the opportunity to harness the power of genomic data and electronic medical records, and to deliver better care, more personalized care for acute illness and, perhaps even more importantly, to predict and prevent disease before it even occurs — thereby moving the focus of medicine from sick care firmly toward health care."

Ashley showed *The New Yorker* cartoon as he concluded his talk, remarking, "We're almost but not quite at the point where you can list your iPhone as your primary care physician. I think lots of my patients would like to do that because of the convenience, and I think we can use the phone in their pocket to do a lot more than just be a portal to the Internet."

Many people already carry one or more devices that track their activity, sleep and heart rate, Ashley noted. "With the next generation of wearable sensors, we can detect heart arrhythmias," he said. "Imagine if we could pick up atrial fibrillation before someone had a stroke. Imagine if they had a wearable sensor on, and we could get to them with a blood thinner before they actually have the stroke."

A future with cloud-based monitoring?

Alan Yeung, MD, the Li Ka Shing Professor in Cardiology and professor of cardiovascular medicine at Stanford, described a similar vision. In China, clinics are so crowded that people line up in the morning to get a lottery number to be seen, he said. Yet, 1.3 billion people there own a smartphone that can potentially help monitor health. Globally, he said, 4.8 billion people own a cellphone.

"We could score someone's risk of a heart attack and, depending on their risk factors, give them medications that would lower their risk," said Yeung. "The idea at the end if the day is instead of one patient coming to a clinic, health-care providers come to a small clean room to monitor tens of thousands of patients and see who is in trouble."

Cloud computing that monitors people's heart rate, heart rhythm, blood pressure and glucose levels, for example, could alert health-care providers when heart attack risk factors started to shoot up for a particular person. "We could schedule a quick call and find out what's up," said Yeung, "and then change whatever the problem is before they become entrenched in their habits."

Jerry Yang, co-founder of Yahoo, board member for the Chinese Internet portal Alibaba and technology investor through AME Cloud Ventures, spoke about some of the many ways to collect personal data. He described sensors that can monitor an individual's sleep patterns, temperature, blood pressure and heart rate; home devices that can do a full urine or blood test; wearable sensors that monitor not just activity, but also posture, how much you stand or sit, core movements and even gait.

"As we see more sensors in our environment, we should think about what the implications of all those sensors are," Yang said.

Some of those implications are about privacy and security. Others have to do with standardizing devices to make sure they are generating accurate data.

Gap between collecting, using data

Data scientist Yixue Li, director of the Shanghai Center for Bioinformation Technology, said another challenge is the gap between our ability to collect data and our ability to deploy it in a way that helps physicians and patients. Li distinguished between the kind of data generated by Alibaba or Google and that which comes from living entities, such as human beings. He said biological data is far more heterogeneous than data from the Internet and contains intricate causal relationships that makes analysis challenging.

Yeung also pointed out that while the Internet is rife with gamelike apps that promise to motivate people to eat better, walk more and become healthier, none are scientifically validated. And there's very little accurate data on how much physical activity helps. Most data comes from what people remember, or think they remember, he said. "Everyone thinks they did a lot of exercise last Monday, but in reality you were sitting in front of your computer answering email," he said. Wearable sensors could tell us more precisely just how much exercise actually helps whom. **ISM**

NORBERT VON DER GROEBEN

From left, Jieming Qu, Euan Ashley, Guoyuan Yang and Taha Kass-Hout participate in a panel discussion on precision health Oct. 15 at the Sino-U.S. Symposium on Medicine in the 21st Century, which was held at the Li Ka Shing Center for Learning and Knowledge.

From bedside to patient: An Ebola survivor's odyssey

By Ruthann Richter

Ian Crozier, MD, is a walking laboratory for Ebola and a living testament to the damaging, long-term consequences of the disease, which are still very poorly understood.

As a volunteer physician with the World Health Organization in Sierra Leone, he worked furiously last fall to save patients in the heat of the Ebola crisis in West Africa. Then on Sept. 9, 2014, he became one of those patients himself and was airlifted to Emory University Hospital in Atlanta, where his vital organs rapidly began shutting down.

During an Oct. 21 appearance at Stanford, Crozier recounted his astonishing recovery, during which he rebounded from a torturous period of being hooked to a ventilator and a kidney dialysis machine, experiencing abnormal heart rhythms, and developing severe encephalopathy that left him delirious and then unconscious for weeks, ultimately suffering several hemorrhagic strokes.

"If I you had told me on day one that I would develop multisystem organ failure and asked me to predict my chances of survival, I would have said my chances were zero," he told more than 100 faculty, students and staff in a standing-room only talk at the School of Medicine. "They [the Emory caregivers] really changed the game…. I really think they were walking on the moon, but in a different kind of space suit."

He was among the sickest of patients to survive the disease and continues to suffer from a variety of disturbing consequences, including eye problems, hearing loss with tinnitus, short-term memory loss, seizures and sleep dysregulation, he said. He wryly cautioned his audience that he was approaching his "hour of narcolepsy" as he started his late- afternoon talk.

Crozier's talk was sponsored by the Stanford Center for Innovation in Global Health, Stanford Immunology and the Stanford Medical Scientist Training Program.

It coincided with a plethora of recent news reports on the long-term consequences suffered by many Ebola survivors. The epidemic has killed more than 11,300 people and has not reached its end; in just the last few weeks, three new cases were reported.

Virus reservoirs, relapses

In the Oct. 14 issue of *The New England Journal of Medicine*, a team of researchers found that male survivors of Ebola may carry a reservoir of the virus in their semen for as long as nine months. Another report in the same issue of the journal cited the first molecular evidence of a case of a Liberian woman who contracted Ebola through sexual transmission.

Moreover, earlier in October, a Scottish nurse who was declared cured of Ebola 10 months ago suffered a relapse and remains in "serious but stable" condition at the Royal Free Hospital in London, according to news reports.

"This virus is teaching us in this last tenth of this last mile, as it stutters along, that we have a lot to learn," Crozier said. In the last 18 months, he said, clinicians in the field have begun to learn a lot more about the "survivor's predicament."

Crozier's medical odyssey began Sept. 7, 2014, when he developed fever, headache and intense fatigue. He had come to Sierra Leone from Uganda, where he had been concentrating on developing the clinical skills of African doctors caring for HIV and tuberculosis patients at the Infectious Disease Institute in Kampala. He was among Sierra Leone's early physician volunteers, working in the country's only Ebola treatment unit where, at peak, the team helped care for overwhelming numbers of Ebola patients and those suspected of having it. He saw many patients and some colleagues die from the virus. Then, he suddenly found himself among the sick, on an air ambulance back to the United States. To this day, he does not know how he became infected.

At Emory, he developed severe diarrhea, losing 8 to 9 liters of fluids a day. His lungs began to fail, followed by his kidneys. He developed delirium, high fever and encephalopathy. He went through a prolonged period of unresponsiveness, with later MRI scans showing evidence that he suffered several large hemorrhagic strokes, he said.

"It must be odd to hear me talking about my own case … in what may seem a detached manner," Crozier told the audience. "This **See EBOLA, page 5**

in the limelight

Faculty panel considers promises, challenges of precision health at town hall

By Jennie Dusheck

NORBERT VON DER GROEBEN

Lloyd Minor (far left) moderates a panel discussion on precision health featuring Mark Cullen, Mary Hawn and Mike Snyder on Oct. 12.

A population-health scientist, a surgeon and a geneticist discussed how clinicians could take advantage of large health data sets and advances in genomics during a panel discussion at an Oct. 12 Stanford Medicine Town Hall.

Moderated by Lloyd Minor, MD, dean of the School of Medicine, the discussion focused on the future of precision health — health care whose goal is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

The town hall took place at the Li Ka Shing Center for Learning and Knowledge and was hosted by the dean; Amir Dan Rubin, president and CEO of Stanford Health Care; and Christopher Dawes, president and CEO of Stanford Children's Health.

Panelist Mark Cullen, MD, professor of medicine and director of the Center for Population Health Sciences, said how and when clinicians are able to harness big data sets will depend on advances in computer engineering and data analytics. Cullen noted that the ability to collect and store information from individual human genomes, from electronic medical records and from portable health and activity trackers, such as Fitbits, is exploding. "It's an extraordinary wealth of data about individuals, which can be rolled up and looked at across large populations," he said. The challenge, he added, will be managing and analyzing that data so it can be brought to clinicians and patients.

Knowing your "omes"

Panelist Mike Snyder, PhD, professor and chair of genetics and director the Center for Genomics and Personalized Medicine, noted how cheap genomic sequencing has become. A person can get their whole genome sequenced for $1,400, he said. "The sequencing is no longer the barrier. It's the cost of interpreting the results, which can run to $15,000. Sequencing is so cheap now you can bring it into the clinic. We see genomics having a huge impact in the area of cancer and rare diseases in kids. But how do we bring this to healthy persons?" One solution, he said, is to look not just at genomics, but also at proteomics, metabolomics, microbiomes and all the other "omics" that capture what we know about human biology.

Snyder gave the following example: A woman has no history of breast cancer in her family, but she carries the BRCA gene variant, which is known to dramatically increase the risk of breast cancer and ovarian cancer. She is still healthy, but now that she knows her genetic information, she can take steps to reduce that risk. Knowing which gene variants a person carries is like an "orange alert," he said.

We don't yet have those massive data sets from genomics, electronic medical records and wearable devices, but the panelists agreed that the data is just around the corner. The big question is how to use modern analytics to present that data to clinicians at the bedside in a format they can actually use to help individual patients in real time. EMR data was designed to facilitate the transfer of information among different health-care providers, not as a research database, Cullen said. Finding ways to deploy EMR data in the clinic will depend on sophisticated analytics.

"We can see what risks the patient is bringing to the table and mitigate those risks."

Mitigating risks

Mary Hawn, MD, professor and chair of surgery, discussed how precision health could help surgeons better understand their patients' risk factors for surgery and mitigate those risks. "We know we aren't going to get the same outcome from surgery for every single patient," she said. Health-care providers have to know individual patients and what their individual risks might be. At the same time, providers need to be able to communicate that information to patients and their families, so they can make decisions that feel right to them. Ideally, Hawn said, "We can see what risks the patient is bringing to the table and mitigate those risks."

"We surgeons have been humbled by biology. We think we can do a great operation, but in the end, the biology wins," Hawn said. "So, knowing that upfront, we can have a much more frank conversation with a patient about how invasive, how radical an operation to have if we can't beat biology."

Looking into the future, Cullen said that because studies of comparative effectiveness (comparing the relative effectiveness of competing medical interventions) are strong at Stanford, it's a fruitful avenue of research. "If we do that well, we'll align with national policies," he added.

"Sometimes things take longer to happen than you think they should. Then they happen faster than you thought they could," Minor said in concluding remarks, paraphrasing a famous quote by the economist Rudiger Dornbusch. "I think our challenge and our opportunity is to move from the category of things taking longer to happen than we think they should and into the category of making them happen faster than we thought they could." ISM

Ebola

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RACHEL LESLIE

Ian Crozier, who was a physician volunteer in West Africa, recounts his story of surviving the Ebola virus and the complications that ensued.

was not theoretical. I'm standing here, and I'm alive, and yet I've described some of the worst disease we've seen with Ebola."

Several indicators of fatal outcome in this and prior outbreaks were at play in his case. Relatively speaking, he was, at age 44, "old" to survive Ebola, had a very high blood viral load, and developed multisystem organ failure. He credits his survival in large part to the game-changing critical care and life support provided at his Emory bedside, as well as to eventual strong cellular immune responses that may have been sculpted by his particular genetic background. He also received some experimental treatment unavailable to patients in West Africa, including a plasma transfusion from an Ebola survivor — a British nurse who had been a colleague — as well as the experimental drug TKM-Ebola, though he said neither the presence of benefit nor the absence of harm from either could be clearly shown.

"I probably would have died in a week had I not been evacuated," he said. "On one hand, I'm alive and incredibly grateful to the WHO, to the U.S. State Department and, of course, to a remarkable Emory team. At the same time, I'm alive and am haunted in some ways by the fact that so many of our patients, including some colleagues and friends, did not have access to the same care."

Residual symptoms

As he began to rebound, Crozier had to relearn how to walk and talk again. He had lost 30 pounds on his 6-foot-5 frame, and during his talk showed a photo of himself bent over a walker. On Oct. 19, 2014, he was discharged from Emory.

Like other survivors, he had residual after effects, pain (including severe joint and muscle aches), as well as problems sleeping. Two or three weeks after discharge, he suddenly lost the hearing in his left ear, and has also developed a high-pitched ringing in his ears that persists today.

Two months after discharge, he developed left eye pain and blurred vision. Last December, his doctors at the Emory Eye Center sampled the fluid inside the eye and found billions of copies of the virus teeming there.

"This was a shocking realization," he said. His vision rapidly deteriorated and he lost pressure in the eye, which began to soften and lose its architecture.

Within a few weeks, he went blind in the eye. "As I looked out at the world, all I could see was a dense obstruction, like a bramble hedge thicket. I couldn't see what was right in front of me," he said. One day, he woke up and found that his once-blue eye had turned green.

He was treated with steroids and an experimental oral antiviral (favipiravir), and then went home for New Year's, convinced he was going blind in that eye. A few days later, he developed headache and fevers, and had to be readmitted to the Emory hospital. During this hospitalization, amid these fevers, he noticed that some of his vision had begun to improve.

While his vision is not completely back to normal, much of it has returned. The eye is an area of the body, like the brain and the testes, that is "immune-privileged," meaning the immune system is partially segregated from the eye and immune responses are essentially "dialed-down" in the ocular environment.

He speculates that this immune privilege may have eventually collapsed, allowing his already-primed immune system to fight off the virus that had "hijacked" that privileged space. Determining what role the antiviral agent or the steroid injection played in the eye's recovery is really impossible in a single patient's case, he added.

"I walked out of the Emory unit as an Ebola survivor — quite remarkably — and I'm still trying to understand what enabled that walking out, and whether we can learn something from that that can be multiplied many times over at African bedsides," Crozier said. ISM

Button

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collection of EMRs. This near-instant output isn't a substitute for a clinical trial, but it's a lot better than nothing — or than resorting to the physician's own bias-prone memory of one or two previous encounters with similar patients.

"You don't have to type anything in," said Shah. "Just press the Green Button."

From gold standard to Green Button

The randomized clinical trial is considered the gold standard of medical research. In a randomized clinical trial, a number of participants are randomly assigned to one of two — or sometimes more — groups. One group gets the drug or the procedure being tested; the other is given a placebo or undergoes a sham procedure. Ideally, the study is blinded — patients don't know which option they're getting — or even better, double-blinded — the investigators and their assistants don't know, either. Once the trial's active phase ends, rigorous statistical analysis determines whether the hypothesis, spelled out in advance of the trial, was fulfilled.

"It goes without saying that you should use randomized trial evidence when it's available," said Harrington, who also holds the Arthur L. Bloomfield Professorship of Medicine. "But a lot of times, it's not."

Shah concurred. "Clinical trials select only a small, artificial subset of the real population," he said. "A regular, ordinary person who walks into the doctor's office doesn't usually fit."

He continued: "Clinical trials are designed to prove one thing, and you're testing it on people with just one thing: Type 2 diabetes, eczema, whatever. But most real-life people don't have just one thing. They have three or four or five things."

As a result, "only about 4 percent of the time have you got a clinical-trial-based guideline applicable to the patient facing you right now," Shah said. The rest of the time, doctors must rely on their own judgment.

Yet even though there may not be clinical-trial evidence to guide a doctor's choice of treatment options for a particular patient, "tons of applicable evidence" are locked away in health systems' EMRs, Shah said. The inspiration for the 2014 *Health Affairs* paper in which he, Longhurst and Harrington elaborated their Green Button concept was a real-life, real-time data search conducted by Jennifer Frankovich, MD, now a clinical assistant professor of pediatric rheumatology at Stanford. A 13-year-old girl with lupus had been admitted to Lucile Packard Children's Hospital Stanford with severe kidney and pancreatic inflammation. She was considered at risk for blood clots. While anticoagulants could counteract clotting, they would also increase her risk of bleeding from some procedures likely to be used during her hospital stay. There were no clear clinical-trial-based guidelines on whether to give the girl anticoagulants, and different clinicians had different thoughts about what was advisable.

But owing to a research project she was involved in, Frankovich had access to a Stanford database containing the EMRs of pediatric lupus patients admitted between 2004 and 2009. So she was able to perform an on-the-spot analysis of the outcomes of 98 kids who'd been in situations similar to the one confronting her patient. Within four hours, it was clear to Frankovich that kidney and pancreatic complications put kids with lupus at much higher risk of clotting.

Frankovich and her teammates decided to give the girl anticoagulants right away. The young patient suffered no clotting or other adverse events. Frankovich was the lead author of a 2011 article in *The New England Journal of Medicine* describing the story, of which Longhurst was a co-author.

That serendipitous result, said Longhurst, led to a follow-on question: "How can we go about doing this in a purposeful way on a continuing, case-by-case basis?"

With advancing technology, the kind of analysis Frankovich performed can be completed in considerably less than an hour today — soon enough for an outpatient finishing an appointment. But there are several obstacles to achieving this goal.

Stumbling blocks

The stumbling blocks along the road to the Green Button's realization aren't primarily technical — the methodologies are available, and the infrastructure is buildable. But the more idiosyncratic your patient's case is, the larger the initial pool of patient data needs to be. And achieving the scale necessary for generating enough records of lookalike patients to provide meaningful results presents some challenges.

As Shah put it: "What if you press the Green Button and nothing happens?" If you can't access enough records of similar patients to begin with, you're out of luck.

Assembling that huge data pool gets easier if numerous institutions can be coaxed into contributing to it. The numbers are certainly there: Stanford Health Care alone has close to 2 million patient EMRs. Kaiser Permanente, which has been using EMRs for a decade or more, has 9 million, and the University of California health system has 14 million. The U.S. Department of Veterans Affairs has 20 to 25 years' worth of longitudinal data on many millions of veterans.

Chris Longhurst

The key lies in integrating these disparate databases to yield valuable, personalized medical insights.

But sharing data across institutions is no simple matter. "Any hospital CEO today would kick you out of the office if you propose data-sharing," Shah said. "That's rational on their part. Sharing data puts you at risk of leaks, and compromised patient privacy can mean big financial and public-relations pitfalls."

Federal law guards patients' privacy, but it doesn't make the data in their medical records totally off limits. For instance, as Longhurst points out, the law specifically allows the use of patient data for improving quality of care.

Yet even if the patient-privacy issue turns out to be insurmountable in the short run, there's a workaround, Shah said: Health systems could share with one another descriptions of the kinds of patients they're looking for, rather than request raw patient data. Thus, a health system that got a request for information on patients of Vietnamese descent with asthma and high blood pressure would, in accordance with such an arrangement, automatically search its own database and share only statistical summaries of what it found, such as the range of outcomes for certain medications given to this cohort.

Meanwhile, there is progress. Stanford researchers including Shah and Longhurst have published numerous studies establishing the power of pooling large volumes of data to derive clinically beneficial results. The Stanford Center for Population Health Sciences, directed by Mark Cullen, MD, professor of medicine, is putting in place a data library housing the records of some 10 million different patients, purchased from another institution.

These developments are keyed to efforts around precision health, Stanford Medicine's push to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill. Precision health aims to give researchers and physicians better tools for predicting individual risks for specific diseases, developing approaches to early detection and prevention, and helping clinicians make real-time decisions about the best way to care for patients.

Asked whether the Green Button idea could meet resistance from medical practitioners who object to taking orders from an algorithm, Shah said, "The point is not to outsmart the physician. The point is to tell you the outcomes of the best guesses of 100 of your colleagues. You can choose to interpret or ignore it."

Some smart money is betting that these stumbling blocks can be hurdled.

Nigam Shah

Kyron Inc., a Palo Alto-based start-up Shah co-founded in 2013 with technologist Louis Monier, PhD, and Stanford-trained biomedical informaticist Noah Zimmerman, PhD, has raised several million dollars and has licensed informatics-associated technology from Stanford's Office of Technology Licensing to do just that.

Build your own randomized trial

"Virtually 100 percent of the 3,000 kids who get diagnosed with cancer every year in the U.S. are in clinical trials," said Longhurst. "How many adults with cancer are in clinical trials? Maybe 2 or 3 percent — we can't possibly afford to put 100 percent of adults into trials. So the other 97 percent may be getting treated, but the health-care system isn't learning anything from their outcomes." For his part, cardiologist Harrington noted that fewer than 10 percent of heart-attack patients are actually enrolled in a clinical trial.

The Green Button approach may be able not only to substitute for randomized trials, but to generate them. Suppose you're a doctor, and a patient walks into your office. You take the patient's history, perform a workup, update the patient's EMR accordingly and hit the Green Button. But, it turns out, there's not enough data on similar patients to provide decent information on which of two treatment options is best for this patient.

But that's not the end of it. The Green Button now shifts gears from merely downloading outcomes of other patients to what Harrington has termed "point-of-care randomization": You give this patient one of the two treatments, and the next patient who walks in the door and is similar to this one gets the other treatment. Keep alternating prescriptions to successive similar patients — while monitoring their responses to minimize the chances of either treatment doing them any harm — and you will have increasingly large cohorts fueling an informed conclusion.

"Applied this way, the Green Button will let clinicians learn more from the patients they're caring for each time they see one of them," said Shah. "Every patient becomes part of a scientific experiment." **ISM**

NORBERT VON DER GROEBEN

Robert Harrington co-authored a 2014 article in *Health Affairs* that outlined a vision for drawing medical guidance from a vast number of electronic medical records.

DOUG PECK

New wheels

Adolescent medicine specialist Seth Ammerman, MD, stands in front of Lucile Packard Children's Hospital Stanford's new Teen Health Van, which made its official debut Oct. 20 at a ribbon-cutting ceremony in East Palo Alto. The van is where Ammerman now runs his free, mobile clinic serving homeless and uninsured Bay Area youth. (The previous van had been in operation since Ammerman founded the program in 1996.) Supported by grants and equipment from the Children's Health Fund and Samsung, as well as other donor gifts, the new van's two exam rooms are equipped with technology for video chats between patients and specialists at other locations, and Samsung tablets loaded with interactive health information to help doctors explain patients' diagnoses and medications. "I am very excited about our new mobile medical unit," says Ammerman, a clinical professor of pediatrics at the School of Medicine. "This will allow us to continue to provide outstanding comprehensive primary care to underserved youth."

Heart

continued from page 1

cardiovascular medicine and of pediatrics at the School of Medicine. In other cases, the first surgery was so unusual and risky that the surgeon discouraged the patient from undergoing further operations.

But most adults with repaired congenital heart defects are not cured, doctors have learned. As their discipline has matured, cardiologists have honed their understanding of how to help patients like Yoon navigate the risks of living with lingering heart problems, as well as learned how congenital defects interact with cardiovascular problems people acquire with age.

The doctors draw on knowledge from both pediatric and adult cardiology to diagnose the current condition of patients' hearts and provide lifestyle counseling, medical management and interventional and surgical treatments. They also work to help adolescents with congenital heart defects make a smooth transition from pediatric to adult care.

Surgery for tetralogy of Fallot

Yoon was diagnosed at age 21 in his native South Korea, when a test showed tetralogy of Fallot, a heart and blood-vessel defect characterized by poor blood flow to the lungs. The diagnosis explained his years of intense headaches, chest tightness, blue lips and nail beds, and severe shortness of breath. As a child and teenager, he could not walk more than a few feet without having to stop and squat to catch his breath. His body wasn't getting enough oxygen. He also struggled with depression, feeling that he was too ill to lead a normal life.

"I couldn't dream of marriage because with that condition you are not supposed to marry," Yoon said, speaking through an interpreter about his memories of the time before his diagnosis.

Yoon's November 1975 surgery was one of the first performed for tetralogy of Fallot in South Korea. His surgeon was unsure how well the repair would work, warning that Yoon would still have a heart murmur from a malfunctioning valve. But Yoon recovered strongly from the surgery and felt much better. He married, became a pastor, and he and his wife had four children. In 1999, the family moved to California.

Then, in 2002, Yoon was trimming trees at home in San Jose when he felt dizzy and faint. Some of his earlier symptoms had never completely vanished — he had lingering chest pain and trouble breathing at high altitudes. However, at checkups with cardiologist Daniel Murphy, MD, at Stanford's adult congenital heart clinic, Yoon was initially reassured to learn his heart was in relatively good shape.

But eventually, things changed. Earlier this year, an MRI scan revealed that the right side of his heart had enlarged, a precursor to heart failure. As is common in adults with congenital heart disease, the malfunctioning valve was taking a toll. Blood was backwashing into his heart and making it work harder.

"I feel such gratitude that now I can enjoy my new life."

"Mr. Yoon's right ventricle, the heart chamber that pumps blood to the lungs, had gotten bigger and bigger," said Katsuhide Maeda, MD, pediatric cardiothoracic surgeon at Packard Children's, who is also part of Stanford's adult congenital heart disease team. "It was almost double its normal size."

'The boat is sinking'

Murphy and Maeda recommended a new heart valve, which would require open-heart surgery. The prospect made Yoon nervous, but the doctors reassured him that such procedures had become safer since his first operation in Korea decades ago, and cautioned that, without the valve, his heart would continue to weaken.

"Dr. Murphy's explanation of his condition was perfect," said Yoon's wife, Min Wha Yoon. "He said, 'The boat is sinking and water is coming inside the boat. If you have strong muscles, you can pour out water strongly, but if you do not have much strength, you can't.'"

"If you wait too long, the heart doesn't recover," said Murphy, who is also professor of pediatrics at the School of Medicine. "We really try to protect the heart muscle by replacing the valve."

That advice made up the Yoons' minds. "After that explanation we decided: This is the time to have surgery again," Min Wha Yoon said.

The surgery, on May 13, took about four hours. "We put in a bio-prosthetic valve made of pig tissue," said Maeda, who is also clinical assistant professor of cardiothoracic surgery at the School of Medicine. "It's a pretty standard procedure and it went very, very smoothly." Sang Hee Yoon was definitely the only 61-year-old receiving surgery at the children's hospital that day.

After he woke from the operation, he was surprised to find that the lingering pain he had endured for decades was gone. As he recovered, he said he felt healthier than he had at any other point in his life.

"Breathing is much, much easier than before," he said. His generalized body aches and chest tightness are completely gone, too. His children and his 10 grandkids are delighted in the changes. "They are so happy about my condition," he said. "Not only family members but everybody I know is saying, 'You look so healthy!'"

The Yoons have already visited Kings Canyon National Park, a destination they chose for its mountainous scenery. "I feel such gratitude that now I can enjoy my new life," Yoon said.

He'll still need checkups, but Yoon is in better shape than many adults with congenital heart disease, half of whom are estimated not to be receiving any specialized care. Instead of facing their uncertain fate, his surgery has moved him into the category of healthy individuals the Adult Congenital Heart Program aims to create.

"We don't want them to be heart patients; we want them to be people who come here to get their hearts checked," Murphy said. "It's about giving people healthier, happy lives by offering a lifetime of high-quality care." **ISM**

Sleepy

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thousands of these procedures, often referred to as bone marrow transplants but more properly called hematopoietic stem cell transplants, are performed each year to rescue patients with immune system disorders or cancers.

"Considering how little attention we typically pay to sleep in the hospital setting, this finding is troubling," said Asya Rolls, PhD, a former postdoctoral scholar at Stanford. "We go to all this trouble to find a matching donor, but this research suggests that if the donor is not well-rested it can impact the outcome of the transplantation. However, it's heartening to think that this is not an insurmountable obstacle; a short period of recovery sleep before transplant can restore the donor's cells' ability to function normally."

Rolls, who is now an assistant professor at the Israel Institute of Technology, shares lead authorship of the study, which was published Oct. 14 in *Nature Communications,* with Stanford postdoctoral scholar Wendy Pang, PhD, and Ingrid Ibarra, PhD, the assistant director of the Stanford Cardiovascular Institute. Luis de Lecea, PhD, a professor of psychiatry and behavioral sciences, and Irving Weissman, MD, director of the Stanford Institute of Stem Cell Biology and Regenerative Medicine, share senior authorship.

Rested mice yield more effective stem cells

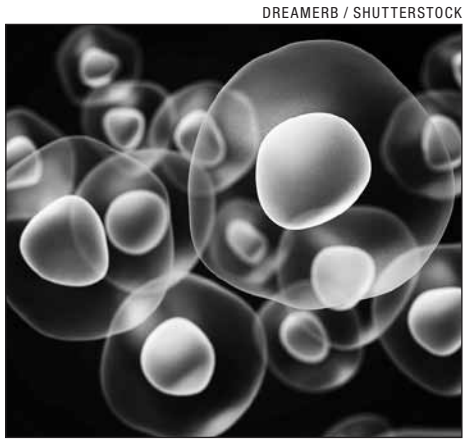
Rolls studied laboratory mice that had been gently handled for four hours to prevent them from sleeping while their comrades dozed. She and her colleagues then collected stem cells from the bone marrow of drowsy and of well-rested mice and injected them into 12 mice that had received what would normally be a lethal dose of radiation. (The recipient mice also received an injection of their own bone marrow cells collected prior to radiation to make it possible to quantify the relative abilities of the donated stem cells to engraft successfully.)

The researchers then assessed the prevalence of a kind of immune cell called a myeloid cell, which were derived from the donated stem cells in the blood of the recipient mice, at eight and 16 weeks after transplantation. They found that, although stem cells obtained from well-rested donors gave rise to about 26 percent of the myeloid cells in the animal over time, stem cells from sleepy donors gave rise to only about 12 percent of the recipients' myeloid cells.

Rolls and her colleagues compared the ability of fluorescently labeled stem cells from sleepy and from rested mice to migrate properly from the recipients' blood into the bone marrow. After 12 hours, 3.3 percent of stem cells from spritely mice were found in the bone marrow, versus only 1.7 percent of stem cells from sleepy mice.

Further testing in the laboratory dish showed that hematopoietic stem cells of the sleep-deprived mice responded less strongly than those of their rested peers to naturally occurring chemical signals that trigger cellular migration. They also expressed lower levels of an RNA message that controls the expression of a family of proteins called SOC, known to inhibit the migration of hematopoietic stem cells.

DREAMERB / SHUTTERSTOCK



Tens of thousands of hematopoietic stem cell transplants are performed each year to rescue patients with immune system disorders or cancers.

CYGNOIR

In sleep-deprived mice, just two hours of ZZZs restored the ability of the animals' stem cells to function normally in the researchers' transplantation tests. Above, mice unaffiliated with the study.

When tired mice catch up on sleep

Although the effect of sleep deprivation was stark in this study, Rolls and her colleagues found that it could be reversed by letting the drowsy mice catch up on their ZZZs. Even just two hours of recovery sleep restored the ability of the animals' stem cells to function normally in the transplantation tests.

"Everyone has these stem cells, and they continuously replenish our blood and immune system," said Rolls. "We still don't know how sleep deprivation affects us all, not just bone marrow donors. The fact that recovery sleep is so helpful only emphasizes how important it is to pay attention to sleep."

Other Stanford-affiliated authors are former senior research assistant Damien Colas, PhD; postdoctoral scholar Patricia Bonnavion, PhD; and H.C. Heller, PhD, professor of biology.

The research was supported by the National Institutes of Health, the California Institute for Regenerative Medicine, the European Molecular Biology Organization, the Ludwig Institute, a Rothschild fellowship and the Klarman Family Foundation.

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

Who's hungry? You can't tell by looking, pediatricians say

By Joan Semeria

KAREN ANDE

KAREN ANDE

These photos were featured in the exhibition *Who's Hungry? You Can't Tell by Looking*, an exhibition, spearheaded by the American Academy of Pediatrics of California and created by San Francisco-based documentary photographer Karen Ande.

When Lisa Chamberlain, MD, began seeing patients in East Palo Alto more than 10 years ago, she never thought one of her top concerns would be whether they had enough food to eat.

It was during the 2010 recession that Chamberlain, a pediatrician with Stanford Children's Health, learned from families at the Ravenswood Family Health Center that 50 to 60 percent of them were struggling to pay rent and buy food.

"We are trained to ask these questions because it's not always obvious that families aren't eating adequately. Most of the kids look normal and healthy," said Chamberlain, an associate professor of pediatrics at the School of Medicine.

Some children are even obese because low-income families tend to shop and eat at places that don't have many healthy options, she said. They may be hungry or experiencing "food insecurity," meaning their families don't always have the means to buy food.

"There are some children who have real hunger, but more commonly we see children who live in families where there is a lot of stress around making ends meet," she said.

Food for the needy

After seeing many families in need, Chamberlain decided to start a hunger program with her colleague Janine Bruce, MPH, director of the pediatric advocacy program at the School of Medicine. Begun as a collaboration in 2012 with the Ravenswood City School District and Revolution Foods Inc., the project has grown to include the YMCA of Silicon Valley, Second Harvest Food Bank and the San Mateo County Library System, working together as the East Palo Alto Food Security Collaborative.

The collaborative has provided more than 33,000 meals to families and children since it started. The program is funded by Lucile Packard Children's Hospital Stanford and the School of Medicine, among others.

Chamberlain, medical director of the pediatric advocacy program, also works with Bruce to mobilize pediatric residents, medical students and undergraduates to address community needs through education, service and research.

Raising awareness

That advocacy has taken Chamberlain to Sacramento, where she works closely with state Sen. Richard Pan, MD, to raise awareness about children's healthcare needs. This year, they attracted the attention of state legislators with the installation of a photo exhibition, titled *Who's Hungry? You Can't Tell by Looking,* in the state capitol. The exhibition, spearheaded by the American Academy of Pediatrics of California and created by San Francisco-based documentary photographer Karen Ande, was designed to illustrate the problem of child hunger in Northern California, where one in four children lacks adequate food and may suffer the ache of hunger. With permission from their parents, Ande took photos of 20 children at a health fair in the Tenderloin district in San Francisco. The children then were screened to determine which were from families with food insecurities.

> **"It was impossible to tell which 10 of the 20 children in the photos had food insecurity."**

"It was impossible to tell which 10 of the 20 children in the photos had food insecurity," Chamberlain said. "They didn't look any different. These families live in and among us, and we are unaware of their struggle. That's why pediatricians have a key opportunity, and even a responsibility, to break the cycle by asking questions, because it's really the only way to find out if there is a problem. And then we need to do something about it."

Although the situation has improved somewhat with the economic recovery of the last few years, Chamberlain said, increased rents have created a noticeable uptick in families needing help. So she, Bruce and their community partners continue to address the issue and raise public awareness.

"We need more public and private partnerships to think about solutions to these problems," she said. "There is a lot of innovation and wealth around us, and I think if we come together, we can eradicate hunger and food insecurity for our neighbors. I welcome anyone who wants to work with us and alongside our many dedicated and inspirational community partners."

For more information about this program, visit http://pedsadvocacy.stanford.edu. ISM

Joan Semeria is a freelance writer.

OF NOTE

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

KATHERINE BURKE, MM, MSc, was appointed deputy director of the Center for Innovation in Global Health, where she'll lead efforts to grow interdisciplinary global health initiatives across the university and oversee administrative operations of the center. Her interests include building research, training and health leadership capacity in low-resource settings, and online education as a tool for training health workers in Africa. Prior to joining Stanford, Burke served as a senior fellow in global health sciences at the UC-San Francisco.

LAURA DUNN, MD, was appointed professor of psychiatry and behavioral sciences, effective Sept. 1. Dunn will serve as the director of the Geriatric Psychiatry Fellowship Training Program and director of the Geriatric Psychiatry Outpatient Clinic. Her research has focused on informed consent, decision-making capacity, and ethical aspects of research and treatment of people with psychiatric and cognitive disorders. She has also conducted research in psycho-oncology, including work on characterizing trajectories of depressive and anxiety symptoms in cancer patients and their family caregivers.

SERGIU PASCA, MD, assistant professor of psychiatry and behavioral sciences, received a Biobehavioral Research Award for Innovative New Scientists from the National Institute for Mental Health. Pasca will receive more than $1.6 million over five years to support his research on developing the next generation of personalized, 3-D neural cultures for capturing the pathogenesis of neurodevelopmental disorders, such as schizophrenia and autism. The BRAINS award is given to outstanding scientists in the early stages of their careers to support them in launching innovative approaches for understanding, diagnosing, treating or preventing mental disorders.

RICHARD POPP, MD, professor emeritus of medicine, received the European Society of Cardiology Gold Medal at a ceremony Aug. 29 in London in recognition of his achievements in the field of cardiology. Popp is the founder of the Stanford Echocardiography Lab. He made significant contributions to two-dimensional and three-dimensional echocardiography, Doppler ultrasound, color flow imaging, trans-esophageal echocardiography, contrast echocardiography and intravascular ultrasonic imaging.

NANCY WANG, MD, was appointed professor of emergency medicine, effective June 1. Wang serves as associate director of the pediatric emergency medicine program. She teaches general emergency medicine physicians how to better care for children both in the United States and in underserved areas internationally. Her research focuses on understanding disparities in access to emergency care and the resulting outcomes for children; screening for social needs of populations presenting to the emergency department; and developing ED-focused interventions with community partners.

LEANNE WILLIAMS, PhD, professor of psychiatry and behavioral sciences, has been awarded a three-year, $2.5 million grant from the National Institutes of Health to study variations in brain circuitry with the aim of better understanding how to tailor behavioral treatments for depression and depression coexisting with obesity. Williams shares the grant with Jun Ma, MD, PhD, professor of health policy and administration at the University of Illinois-Chicago. Ma and Williams are co-principal investigators of the study.

MATTHEW LOVETT-BARRON, PhD, a postdoctoral scholar in bioengineering, has received the Donald B. Lindsley Prize in Behavioral Neuroscience, supported by the Grass Foundation, from the Society for Neuroscience. Lovett-Barron received the $2,500 prize for his doctoral thesis at Columbia University, where he combined a variety of techniques to observe and control distinct circuit elements in the mouse hippocampus, a structure essential for learning and memory. His research revealed a circuit mechanism that allows mammals to associate specific environments with fearful events. ISM

Katherine Burke

Laura Dunn

Sergiu Pasca

Richard Popp

Leanne Williams

Matthew Lovett-Barron