By Tracie White

Gary Saxon has a nice nose. A gray beard covers his chin, and bushy eyebrows shade his eyes, but nothing hides his nose. It holds a position of prominence, sticking right out there in the middle of its owner’s slightly grizzled face, like noses do. It’s well-sculpted and well-proportioned — with a slightly turned-up tip that complements Saxon’s positive perspective on life. And best of all, it works.

Saxon is lucky. A year ago, all he had been a bloody hole where his nose used to be.

“I was beat up. I’ll admit,” said Saxon, sitting between jam-packed rows of LPs at his record shop in Redwood City. “I had no nose. But my spirit was still there. I figured, well, I’m still alive, so now what?”

Part science, part architecture, part art, the surgical reconstruction of a missing nose is a most “compelling surgery,” said Sam Most, MD, a facial plastic surgeon who has rebuilt nearly 1,000 severely damaged or destroyed noses over the past 15 years as chief of the Division of Facial Plastic and Reconstructive Surgery at the School of Medicine. For many of those noses, including Saxon’s, the key to reconstruction was the use of an age-old surgical technique commonly called the “forehead flap.”

Venerable technique

The forehead flap — so named for the unsightly flap of forehead skin left plastered over a patient’s nose for weeks following surgery — happened, by chance, to be the first surgical procedure Most ever witnessed. He observed it while a first-year medical student at Stanford, quietly standing at the back of the operating room. More than two decades later, a master craftsman of the technique himself, he has also published his own research to help improve upon it. He remains somewhat amazed that the success of these complex nose reconstruction surgeries still depends upon a technique that’s probably older than Christianity or even the Roman Empire.

“I think it is just fascinating that we can take the skin from the forehead and create this outer-lining shape of the nose and make it turn into the shape of a nose,” said Most, a professor of otolaryngology-head and neck surgery. Without the forehead flap, the reconstruction of a missing nose — perhaps the most challenging of facial reconstruction surgeries — would fail.

Most is quick to recount the historical significance of the forehead flap technique, which originated in India, probably before the birth of Christ, but wasn’t widely known to Western medicine until 1794, with the publication of a letter to the editor in The Gentleman’s Magazine.

Gary Saxon, who owns a record store in Redwood City, lost most of his nose in a medical procedure to remove skin cancer. It was rebuilt by a Stanford surgeon.

Wearable device detects, analyzes real-time changes in sweat composition

By Jennie Dusheck

A team of researchers has combined two separate technologies to create a health-monitoring device that is noninvasive, doesn’t interfere with strenuous outdoor activities and can continuously track a user’s health at the molecular level.

The two-part system of flexible sensors and a flexible circuit board sticks to the skin and then detects and analyzes a profile of chemicals in sweat.

The device is described in a paper published online Jan. 27 in Nature.

The project, led by senior author Ali Javid, PhD, professor of electrical engineering and computer sciences at the University of California-Berkeley, is a collaboration with researchers at the Stanford School of Medicine.

“This wearable device provides more information than any other wearable sensors. It provides insight about an individual’s physiological state at molecular levels,” said Sam Emaminejad, PhD, a joint postdoctoral scholar at Stanford and at UC-Berkeley, who is the co-lead author with UC-Berkeley postdoctoral scholar Wei Gao, PhD.

Other noninvasive sweat biosensors either monitor only a single molecule at a time or lack signal processing that can adjust for temperature effects or interactions among different molecules. The new device, tested on a team of sweaty volunteers, is a fully-integrated "perspiration analysis system" that binds to the skin and measures certain sweat metabolites and electrolytes, and can calibrate its readings based on skin temperature. In the future, this kind of wearable biosensor could be able to alert athletes and patients to fatigue, dehydration, overheating and other health problems.

Emaminejad said that when he first came to Stanford several years ago, he wanted to earn a doctorate in electrical engineering and to work with renowned scientist Ron Davis, PhD, professor of biochemistry and of genetics and director of the Stanford Genome Technology Center. Over a 30-year career, Davis has been the originator, with others, of a series of disruptive technologies, such as a way to map RNA, a technique for splicing fragments of DNA together, the first DNA microarray for profiling the expression of genes and a method for mapping genes.

See SWEAT, page 5

Many malpractice claims linked to small number of physicians, study finds

By Beth Duff-Brown

A substantial share of all malpractice claims in the United States is attributable to a small number of physicians, according to a study led by researchers at Stanford University and the University of Melbourne.

The team found that just 1 percent of practicing physicians accounted for 32 percent of paid malpractice claims over a decade. The study also found that claim-prone physicians had a number of distinctive characteristics.

“The fact that these frequent flyers looked quite different from their colleagues helped us identify groups of physicians at higher risk for claims,” said main author Andrew Max, PhD, a professor of medicine and of health policy studies at Stanford. "Our research, which is based on 11 years of practice, shows that doctors can judge how likely they are to be sued.”

See MALPRACTICE, page 6

The percentage of physicians involved in a claim over a decade is known as their “malpractice exposure.” The study found that 0.01 percent of all physicians — fewer than one in a thousand — accounted for 32.2 percent of claims.

The study found that the physicians involved in the claims were more likely to be male, older, white, from a large or urban practice, and to practice specialty medicine.

Emoticons were commonly used in tweets from these claim-prone doctors, according to the researchers.

See MALPRACTICE, page 6
Herbert Abrams, pioneering radiologist, anti-nuke activist, dies at 95

By Elaine Ray

Renowned radiologist Herbert Le- noy Abrams, MD, who co-founded the Nobel Prize-winning organization International Physicians for the Prevention of Nuclear War, died Jan. 20 at his Palo Alto home. He was 95.

Abrams was a professor emeritus of radiology at the Stanford University School of Medicine, a senior fellow at Stanford’s Freeman Spogli Institute for International Studies and an affiliated faculty member at the Center for International Security and Cooperation.

Abrams’ illustrious, multi-faceted ca- reer embraced what he called the “four dimensions of bio-medicine” — patient care, research, teaching and advocacy.

“For as long as I have known him, I could only describe Herb Abrams as a class act,” said Sanjiv Sam Gambhir, MD, PhD, professor and chair of radiol- ogy at Stanford. “It is upon the shoulders of giants such as Herb that we our- selves stand today at the cutting edge of radiology.”

Former U.S. Secretary of Defense and CISAC colleague William Perry praised Abrams for his “wisdom and carefully chosen words” in his advocacy for better control of nuclear weapons.

“The forces maintaining nuclear weapons and creating the danger that we might use them are very powerful and very hard to stop,” and Herb and the In- ternational Physicians for the Prevention of Nuclear War were an early voice of sanity in this field,” Perry said.

Visionary pioneer in radiology

Born in 1920 in New York to im- migrant parents, Abrams declined to go into the family hardware business. He graduated from Cornell University in 1941 and earned a medical degree from Long Island College of Medicine in 1946.

According to his family, Abrams had planned to become a psychiatrist until he was captivated by radiological imag- ing, which provided the road map for virtually all surgical and many medical therapies.

Abrams, his wife, Marilyn, and daugh- ter, Nancy, moved to the West Coast in 1948. Their son, John, was born a year later. Abrams completed his residency in radiology in New York in 1952 and joined the faculty as an assistant professor in the department in 1954.

While Abrams rose to become direc- tor of diagnostic radiology at Stanford, he and Marilyn raised their children in the Bay Area during what his children say he often called the “golden years” — rich with deep friendships, youthful exuberance, guitar-playing, family ad- ventures and professional success.

Abrams was an internationally known authority on cardiovascular radiology and wrote more than 190 articles and seven books on cardiovascular disease and health policy. For many years he served as editor-in-chief of Postgraduate Radiology, and he was founding editor-in-chief of the journal Cardiovascular and Interventional Radiology.

In 1961 he published Angiography, the first comprehensive volume on the sub- ject, which now is in its fourth edition (edited by Stanley Baum) under the title Abrams’ Angiography: Vascular and Inter- ventional Radiology.

“Under his guidance, Stanford pio- neered in the fields of coronary artery imaging and the diagnosis of adult and congenital heart diseases, as well as vas- cular diseases, such as renal artery nar- rowing as a cause of hypertension,” said Lewis Wexler, MD, professor emeritus of radiology at Stanford, who was a resident under Abrams.

“For many years, I referred to him as ‘Dr. Abrams,’ even though he requested a less formal address,” Wexler added. “I think I waited until I was a full profes- sor before I called him ‘Herb.’ His wife and a number of his old friends from San Francisco called him ‘Hoppy,’ an endear- ment that aptly describes his energy, ex- citement and ability to jump effortlessly from discussing radiology [to discussing] health policy, politics, religion, art and music.”

Herbert Abrams co-founded International Physicians for the Prevention of Nuclear War. He said that for physicians, nuclear weapons and nuclear war were “the central health issue of the 20th century.”

“He was a very determined man. I could only describe Herb Abrams as an anti-nuclear activist,” Perry said.

Abrams had a vision that began during “still growing up” at that time and that building.” He added that radiology was “one of his career as an anti-nuclear activist.

On his 95th birthday Abrams played four-generation tennis with his son, grandson and great-grandson on Mar- tha’s Vineyard, where his family spent summers for 45 years. Until the last months of his life, he played doubles three times a week.

In addition to Marilyn, to whom he was married for 73 years and their daughter Nancy (Richard Elbirtt), of Lincoln, Massachusetts, and son John (Christine) of West Tisbury, Massachusetts, Abrams is survived by three grandchildren and three great-grandchildren.

Memorial donations in memory of Abrams may be made to Physicians for Social Responsibility, 1111 14th St. NW, Suite 700, Washington, DC, 20005, or by visiting the organization’s website at www.PSR.org.

A service to celebrate his life will be held on the Stanford campus on March 19; details will be announced.

Steven Seltzer, MD, chair of radiol- ogy at Brigham and Women’s Hospital, who holds the the same professorship Abrams previously held, remembers his longtime mentor as a visionary who helped broaden the scope of radiology as a discipline.

“When Seltzer arrived at Brigham and Women’s in 1976 to do his radiology residency in what was then a very small department, he recalled being, ‘incred- ibly impressed with the professional growth opportunities and the values and quality of the program that Abrams was building.’ He added that radiology was “still growing up” at that time and that Abrams had a vision that began during his years at Stanford and developed dur- ing his years in Boston.

“Herb was a very determined man. I fully bought into that vision. I thought he was a good person to have as a mentor and a role model, because I also aspired to live in a world that had similar char- acteristics that Herb had dreamed of,” Seltzer said.

Anti-nuclear advocacy

Toward the end of the Boston years, in the early 1980s, Abrams developed a keen interest in the effects of ionizing radiation and nuclear weapons and the problems of accidental or inadvertent nuclear war, which led to the next phase of his career as an activist.

“He leveraged his training in radiol- ogy to become one of the leading experts on the health ef- fects of low-dose radiation,” said David Kohn, MD, professor of medicine at Stan- ford and current co-director of CISAC.

“It’s a problem that doesn’t get as much attention as the immediate effects of a nuclear blast, but the long-term conse- quences of low-dose radiation was something that Herb … helped promote as a serious issue, worthy of attention and study,” Relman added.

Abrams discussed the threats posed by radiation in a story published in the spring 1986 issue of Stanford Medicine magazine. He said that, for physicians, nuclear weapons and nuclear war were “the central health issue of the 20th century.”

CISAC was founding vice president of In- ternational Physicians for the Prevention of Nuclear War, which won the Nobel Peace Prize in 1985, just five years after the organization was established. He also served for many years on the national board of directors and as national co- chair of Physicians for Social Responsi- bility, a U.S. affiliate of IPPNW.

“His contributions were huge,” said Scott Sagor, PhD, professor of political science at Stanford. Sagor added that under Abrams’ leadership the IPPNW “did yomam’s work to try to educate the public and world leaders about the con- sequences of nuclear war at a time when many including some Reagan ad- ministration, were minimizing the con- sequences of nuclear weapons use.”

Abrams returned to Stanford in 1985 as a professor of radiology, but spent most of his time in research at CISAC, working to link various disciplines and philosophies in the political, interna- tional and academic arenas to create a better understanding of international se- curity during the nuclear age.

In the 1990s Abrams began to focus on presidential disability and its poten- tial impact on decision making.

In 1992, he published The President Has Been Shot: Disability, Confusion and the 25th Amendment, which brought to- gether important issues at the intersec- tion of medicine, politics and humanism.

A vibrant family life

Always at the core of Abrams’ life was bringing together his family to travel, to ski, to play tennis and to celebrate birth- days and holidays.

On his 95th birthday Abrams played four-generation tennis with his son, grandson and great-grandson on Mar- tha’s Vineyard, where his family spent summers for 45 years. Until the last months of his life, he played doubles three times a week.

In addition to Marilyn, to whom he was married for 73 years and their daughter Nancy (Richard Elbirtt), of Lincoln, Massachusetts, and son John (Christine) of West Tisbury, Massachusetts, Abrams is survived by three grandchildren and three great-grandchildren.

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Writers Steve Fyffe and Susan Ipaktchian contributed to this report.

February 8, 2016 INSIDE STANFORD MEDICINE
Oleg Jardetzky, visionay in magnetic resonance imaging, dies at 86

By Rosanne Spector

Oleg Jardetzky, PhD, a pioneer in the use of nuclear magnetic resonance to understand the structure and dynamics of proteins, died Jan. 10 at his Stanford home after a period of decline of several months. He was 86.

Jardetzky, a professor emeritus of molecular pharmacology at the School of Medicine, founded and served as director of Stanford’s Magnetic Resonance Laboratory, one of the world’s first and premier facilities dedicated to using nuclear magnetic resonance for biological research.

He and his students identified the field of protein NMR spectroscopy,” said Stanford Opella, PhD, a former graduate student and now a professor of chemistry and biochemistry. “Oleg played a role in this as a true pioneer. Many of his innovations are still being used in the field.

In short, he was way ahead of his time in research.”

By the late 1940s, nuclear magnetic resonance was a phenomenon discovered some 20 years prior by physicist Felix Bloch and physicist and chemist Edward Purcell at Caltech. The technique was developed to measure nuclear spin and electron magnetic properties. Jardetzky was the first to use the phenomenon to analyze chemicals, but it wasn’t until the mid-1950s and 1960s that Jardetzky and a few others with a biological bent applied the technology to biochemical molecules, like proteins.

Burning the midnight oil

Over his more than 40 years of research, Jardetzky became an internationally known authority on applying the technology to biology. He served terms as leader of the American Society for Magnetic Resonance and co-organized and edited more than 250 scientific articles, was named a fellow of the American Association for the Advancement of Science in 1977 and also was a co-founder of the International Union of Nuclear Science and Technology in 1959.

In 1969 he joined the Stanford faculty as a professor in the Department of Pharmacology (renamed the Department of Chemical and Structural Biology in 2006). “He loved the academic freedom to explore scientific questions independently,” said one of his sons, Theodore (Ted) Jardetzky, PhD, a professor of structural biology at Stanford. Oleg founded the Stanford Magnetic Resonance Laboratory and directed it from 1972 to 1997. At Stanford, he trained and inspired students to push the boundaries of science, and many went on to leadership roles in the field.

“Oleg was a very forceful person, and he used that to motivate the group and tackle new areas for the first time,” said Opella. “He certainly prepared his students and postdocs for academic life and what was needed to succeed.”

Oleg Jardetzky

Jardetzky spent the following year at Caltech as a National Research Council Fellow, working with Nobel laureate F. Albert Davis, PhD, studying the structure of water. He burned the midnight oil to pursue his own research: nuclear magnetic resonance studies on amino acids and proteins, using a chemistry professor’s NMR machine from 10 at night until 2 in the morning.

In 1957, Jardetzky joined the Harvard Medical School faculty and founded the first NMR laboratory dedicated to biological research. He worked there for 10 years, establishing the foundation for future research in this field.

“Forcesful presence”

“We came in with the idea of possibly using it [NMR] for determination of protein structures, which proved to be absolutely impossible at the time,” said Jardetzky in a March 2015 interview for the Stanford Historical Society. “The resolution was not good enough. At that time, you could just study the structure of amino acids in small peptides and nucleotides and the interactions between them. You could look at the spectrum of a protein — but it was a big mess.”

He married his second wife, Norma Gene Wade, in 1964, and in 1967 they moved to New Jersey so he could work for Merck, Sharp and Dohme Laboratories, first as a director of the biophysical department, then as vice president of the research division.

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“Oleg was a very forceful person, and he used that to motivate the group and tackle new areas for the first time,” said Opella. “He certainly prepared his students and postdocs for academic life and what was needed to succeed.”

Ribbonucleases and the tryptophan repressor

In 1975, he married Erika Ahlensberg, PhD, who had been a close friend in Austria. Together, they enjoyed visiting friends and family there, traveling the world and having guests at their home.

By Ruthann Richter

Stanford Medicine and Intermountain Healthcare to collaborate

Stanford Medicine and Intermountain Healthcare, two health care system based in Utah, have formed a new collaboration to support innovative projects in research, patient care and medical education, it was announced Jan. 27.

As a first part of the effort, Intermountain will commit $2.5 million as matching grant to Stanford Medicine to support clinical research projects, particularly in the fields of genomics and proteomics, as well as novel methods to improve health care delivery and clinician training. With its total of $3.25 million, this will provide $1.25 million to match the grant to bring total research funds to $2.5 million. In addition, Intermountain will commit another $1.25 million for operational expenses and additional projects, for a total $3.75 million investment by the two institutions across five years.

The collaboration is integrated with Stanford Medicine’s broader mission to improve patient care and training for the future.

“We will work with colleagues at Stanford to more rapidly assess new treatment modalities and move these into the care of our patients,” said Charles Cleeland, MD, president and CEO of Intermountain Healthcare.

Researchers at Stanford and Intermountain are already working together on several projects, including research in cancer genomics, clinical and translational research in neurofibromatosis and clinical genomics, and studies in applied clinical informatics.

In addition, Intermountain has been identified as a pilot site for a Stanford project on “ambulatory care ICUs,” a new form of outpatient care to prevent costly and dangerous health crises among patients with severe, chronic illnesses. The project is led by Arnold Milstein, MD, director of Stanford’s Clinical Excellence Research Program, who also serves on the board of Intermountain.

Clinician-researchers at the two institutions are also sharing work on other medical conditions, exploring expanded use of clinical pathways, which are science-based guidelines that help reduce errors and improve patient outcomes. Intermountain, a longtime pioneer in educating health care providers in clinical pathways and clinical methodologies, has collaborated in establishing a similar program at Stanford.

The recent experience of Intermountain, which has been open to site exchanges, which in residents and fellows will do rotations at collaborating institutions, and sharing approaches to reduce blood utilization, was
Un-medical care: Child life program helps children handle stresses

By Erin Digita
e

It was a young girl with epilepsy who made Susan Kinnebrew certain she'd chosen the right career.

The girl was scheduled to undergo surgery for her seizure disorder. She was scared. To get through the procedure, she wanted something beyond the expert minimizations of her brain surgeon, anesthesiologist and operating room nurses. She wanted to bring her favorite doll.

Kinnebrew was just starting her career at a Florida hospital as a child life specialist, an expert in helping children and their families handle the stresses of illness and the hospital environment. She understood the importance of that security object.

She and the other caregivers made a plan: Kinnebrew and the doll would accompany the girl into the operating room, where the doll could stay on the girl's bed until she was anesthetized. Kinnebrew would then take the doll and make sure it was back on the girl's bed before she awoke.

"Going to the OR with her, I knew this was for her," Kinnebrew said. She saw how much the doll's presence — and her own — eased the child's fear.

She eventually had a total of four surgeries, and even at the last one, at age 18, she said, 'I need you with me.'

Supportive role

Today, Kinnebrew directs Child and Family Life Services at Lucile Packard Children's Hospital Stanford, where she took over the director's role in November 2014.

"We set out to find hidden layers of susceptibility in the regulatory regions of these genes," said Bejerano. "Not every disease will be associated with an abnormal cardiac death; and we represent infants and children of young men who had mutations in regions controlling genes associated with cardiac output; and a person with high blood pressure had mutations in regions controlling circulating sodium levels in the blood.

"The beauty of having whole genomes available for study is that you can then ask completely agnostic questions," said Gill Bejerano, PhD, an associate professor of developmental biology, of pediatrics and of computer science at Stanford. "We set out to find hidden layers of susceptibility in the regulatory regions of these genes. We were very pleased that our analysis gave such clear and significant associations between the mutations and medical histories."

Bejerano, a genomics who is a member of the Stanford Artificial Intelligence Lab, Child Health Research Institute, Neurosciences Institute, Cancer Institute and Bio-X, is the senior author of a paper describing the research, which was published Feb. 4 in PLOS Computational Biology. The first author is Harendra Guturu, PhD, a former Stanford graduate student who is now a research associate in pediatrics at the university.

Importance of regulatory regions

The researchers focused their analyses on a relatively small proportion of each person's genome — the sequences of regulatory regions that have been faithfully conserved among many species over millions of years of evolution. Proteins called transcription factors bind to regulatory regions to control when, where and how genes are expressed. Some regulatory regions have evolved to generate species-specific differences — for example, mutating in a way that affects the expression of a gene involved in foot anatomy in humans — while other regions have stayed mostly the same for millennia.

"In these cases, evolution has given a clear signal that these regions are important to key biological pathways, and it's important for them to stick around," said Bejerano. "All of us have some natural variation in our genome, accumulated through bethched DNA replication, chemical mutation and simple errors that arise when each cell tries to successfully copy 3 billion nucleotides prior to each cell division. When these errors occur in our germ or egg cells, they are passed on to our children and perhaps grandchildren. These variations, called polymorphisms, are usually, but not always, harmless."

Gill Bejerano

Great work

Guturu looked for what are called single nucleotide polymorphisms, or SNPs, in the DNA of five people who have made their genomes and information about their own or their family's medical history publicly available for use by researchers worldwide. SNPs are places along a chromosome where the DNA sequence varies from a composite human DNA reference sequence to another.

Rather than search through the whole genome, Guturu focused on SNPs in the conserved regions of regulatory regions. Even within these regions, each person had many SNPs. So Guturu used a software program, Predicting Regulatory Information of Single Motifs, developed in the Bejerano lab, to predict which nucleotide changes were likely to disrupt the conserved binding of a transcription factor.

Guturu then turned to so-called Genomic Regions Enrichment of Annotations Tool to determine whether the disrupted binding sites were likely to perturb the expression of groups of genes that together control a particular biological function. GREAT, which was also developed in the Bejerano lab, classifies genes by the unique functions of thousands of different groups of genes. For any set of genomic regions a user inputs, GREAT determines the most common set or sets of nearby genes.

Using this approach to study the genomes of the five individuals, Guturu, Bejerano and their colleagues found that one of the individuals who had a familial history of sudden cardiac death had a surprising accumulation of variants associated with "abnormal cardiac output"; another with hypertension had variants likely to affect genes involved in circulating fluid levels; and a third with seizures and ADHD affecting parasympathetic nervous system development. In all five cases, GREAT reported results that jibed with what was known about that individual's self-reported medical history, and that were rarely seen in the more than 1,000 other genomes used as controls.

Exciting avenue for study

The researchers would like to create a web portal that would allow others to easily conduct similar studies. However, they concede that, for some diseases, the results may not be so clear-cut.

"We are the sum of billions of transcription-factor binding events in thousands of cell types throughout our bodies," said Bejerano. "Not every disease will be amenable to this type of analysis. But this study shows that, even with a noncoding genome, can be very benevolent when you ask the right questions. And it may help us begin to combine our knowledge about variation that occurs naturally in the genome. It's a very exciting avenue for study."

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

Other Stanford co-authors of the paper are graduate student Sandeep Chinchali and former graduate student Shoa Clarke, MD, PhD.

The research was supported by the National Institutes of Health, the National Science Foundation, the Howard Hughes Medical Institute, a Stanford graduate fellowship and the King Abdullah University of Science and Technology.

Bejerano and Guturu have filed a patent application on the algorithm used in this study.

Stanford's Department of Developmental Biology also supported the work.
Sweat
continued from page 1
that led to the Human Genome Project. His work has repeatedly changed the face of biomedical research and earned him membership in the National Academy of Sciences.

“[For personalized medicine],” said Davis, “we need other techniques to immobilize the patient; during a procedure, child life specialists can also help make it easier for a child to hold still or cooperate. For example, Kinnebrew vividly remembers using guided imagery — verbal cues that enable the listener to use their imagination to relax — so that she could help her own toddler cope with getting stitches for a minor injury. While the sutures were going in, she ran through the plot of her favorite movie, Toy Story, distracting him so successfully that the medical team did not need other techniques to immobilize the patient.”

Research demonstrates that all these efforts make a difference for hospitalized kids and their families. Child life programs have been shown to reduce children’s postoperative pain, lower parents’ anxiety about their kids’ hospital stays and decrease the emotional distress children feel about being at the hospital.

“The most personal you can do is to be the voice that is helping a child get through a hard time,” said Kinnebrew. “That’s what makes the field of child life so powerful and effective.”

Designing the device
After earning a PhD in electrical engineering at Stanford, Emaminejad became a postdoctoral scholar jointly at Stanford and UC-Berkeley. The result of the collaboration between researchers at the two universities is an array of sensors and circuits that can detect the chemical constituents of sweat in real time. The research team tested the device on a group of men and women who pedaled indoors on stationary bikes or ran outdoors.

The prototype device consists of two parts: a set of five sensors and a flexible circuit board for signal processing and wireless transmission of data. Sticking to the skin is a flexible plastic bandage with sensors that can measure skin temperature and four constituents of sweat: sodium ions, potassium ions, lactate and glucose.

The soft, flexible sensor bandage feeds data from the skin’s sweat to the second part of the device, a wireless circuit board of interconnected chips, called a flexible printed circuit board, which comes to a wristband or headband.

The circuit board’s job is to amplify, filter, calibrate and transmit the signal. After processing the information from the sensors, the circuit board beams it to a nearby smartphone or other device for storage and further analysis. The flexible sensor array that binds to the skin is disposable and might last a few days at most, while the less-flexible printed circuit board is reusable.

Complementary technologies
Neither the sensor nor the circuit board could have done the job by itself. “Each technology has strengths and weaknesses,” said Javey. “If you were just using silicon integrated circuits, you would not have been able to do this.” The team integrated circuits that are too small and too rigid to come in good contact with the skin. It’s just not realistic to use them for the sensing part.

On the other hand, a flexible integrated sensor array can be printed onto a large surface area that conforms to the body. It makes a great sensor but isn’t able to do great for doing computation, signal processing or transmission, said Javey. Together, the two technologies complement one another and create a lightweight biosensor.

The Nature paper describes how the flexible sensors detect the presence of different molecules and ions based on their electrical signals, said Emaminejad. “The more glucose or lactate in your sweat, the more electrical current is generated on the sensor’s surface. And the more sodium and potassium, the larger the voltage.”

“Both the current and the voltage generated are themselves affected by temperature,” Gao said. When your skin temperature goes up, the generated signal from the sensor appears larger, making it look like you are releasing more glucose in your sweat than you actually are. It is important to measure both temperature and molecules at the same time to calibrate the device.

The device could open up new fields of research. “With continuous, real-time monitoring of populations of people,” said Davis, “we’ll be able to mine the collected data for patterns that can guide clinically oriented investigations and deliver personalized medicine.”

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 sick.

Emaminejad said the device will enable researchers to do sweat science experiments that couldn’t be done before. “I think we will learn a lot about sweat itself and what its composition is telling us about our health,” he said. Another Stanford-affiliated co-author of the paper is PhD student Samyuktha Chakravarthi.

This research was supported by the National Institutes of Health, the Berkeley Sensor & Actuator Center and the U.S. Department of Energy. Stanford’s departments of Electrical Engineering, of Biochemistry and of Genetics also supported the work. 

Dr. Susan Kinnebrew, who directs Child and Family Life Services at Packard Children’s, meets with members of her staff.

Susan Kinnebrew, who directs Child and Family Life Services at Packard Children’s Hospital, helps children handle stress, have fun at Lucile Packard Children’s Hospital Stanford

Sweat can be used to diagnose certain conditions. To detect drug use and to optimize athletic performance. But the resulting data aren’t real-time or continuous. It’s like watching 10 seconds of a football game and trying to guess how the game went.
Nose
continued from page 1
of London. The letter provided the first account in English literature of the procedure.

Rewards for noses
At the time, the British East India Company ruled parts of India. A sultan, working with 21st-century surgical tools who had his nose and one of his hands cut off as punishment for delivering supplies to British troops. It happened 12 months later, after he joined the Bombay Army of the East India Company:

First, a piece of wax was sculpted to the shape of his nose, then flattened out to create a nose template. Next, this template was laid on the forehead and outlined. An incision was made along the outline, and the skin was peeled away, while remaining attached at a point near the top of the nose. The flap was then twisted to keep the outward skin facing on top, pulled down over the face and molded around the area of the nose. For several weeks, the flap remained attached by a bridge of skin on the forehead to maintain a blood supply. After blood vessels from the nose began to nourish the flap, the ugly connection to the forehead was cut, and a normal-look-
ing nose emerged. This same type of procedure remains the most popular method of nose reconstruction today.

More than 200 years later, Most, working with 21st-century surgical tools at his disposal, used nearly the exact same procedure to rebuild Saxon’s nose — with a few additions. Saxon, like the bullock driver, had most of his nose removed, but in his case it was due to a serious cancer. It was the role of a dermatological surgeon trying to root out an in-
vasive case of squamous cell carcinoma.

Skin cancer
Skin cancer has replaced bounty hunting as the most common cause of major nose deformities that require forehead flap procedure reconstruction, Most said.

“Unfortunately we are seeing skin cancers in younger and younger pa-
tients,” Most said. “We get patients in their late 30s, early 40s who need total nasal reconstruction.”

The 72-year-old Saxon said his own nose story began more than 40 years ago, when he was 30 years old.

“When I was 30 years old, a dog bit off the tip of his nose,” Saxon said. “It was a mama Dalmatian who’d just had pups. I bent down to pat her and boom, boom, snap.” Three nips later, the tip of his nose was gone.

“It healed up, but I had a sore on the tip of the nose for years that kept fester-
ing and coming back for decades,” he said. Finally, four years ago, he had it biopsied, and it came back positive for cancer. The dermatologist scheduled him for a surgical procedure called Mohs, which is a way of precisely removing the cancerous tissue. The patient sits in the waiting room while the tissue that’s been removed is examined for cancer to determine whether all of the dis-
ased cells have been cut out. If not, the patient returns to the operating room for addi-
tional tissue removal.

“I had no nose left”

“I was there for nine hours and probably 20 growers. By that point, I had no nose left. I was stunned.” In addition, he learned that he was still not well, that even a cancer patient’s body was traveling to his brain, and he’d need rad-
iation therapy to treat it.

Most performed the nose reconstruc-
tion surgery the very next day, before Saxon even had time to miss the presence. “When he arrived, there was a very extensive hole all the way to the base of the lip,” Most said. “They had chopped off most all of the nose.” Before the flap procedure could be performed, Most had to rebuild the missing cartilage with cartilage taken from Saxon’s ear.

“When you reconstruct a nose, you have to worry about nasal function and create the nasal skeleton both to make it look right and so that it doesn’t collapse, so the person can still breathe,” Most said.

To recreate the aesthetic compo-
nent of the nose, the surgeon attempts to recreate the nose in subunits, dividing it into sections where the natural shadow lines of a nose should fall. The nose is re-
built with the intention of hiding the scars or stitches along these shadow lines.

“For Mr. Saxon, his entire cartilage framework of the septum in the front of the nose and the cartilage that formed the tip of the nose were gone,” Most said.

“The cartilage structure of the septum and the tip had to be rebuilt in order to give him a tip again, to make it look like a natural-looking nose.”

Creating the template
After the primary reconstruction, the forehead flap was cut out and brought down to form the nose.

Most used a piece of sterile pad dressing to create a template of the nose. He drew an inked outline around the nose defect, placed the template on top to create an inked negative and then placed that on Saxon’s forehead. The flap was in-
cised along this inked on line, the skin peeled away, turned over and placed over the area of the nose, where tiny stitches molded it into place.

“It’s not pretty,” Most said, describing what it looks like to wear a forehead flap over your face for the typical three- to four-week period.

“People have a horrible time with it. They walk around with this giant bridge of skin sticking down. It’s scary looking. They can’t go to work.”

In an effort to decrease the length of time, Most has published two studies in medical jour-
als showing evidence that new imag-
ing techniques can allow surgeons to see exactly when the nose’s blood vessels are supplying the skin graft.

“Someday there is — there is no real evidence out there that you have to wait three to four weeks or longer before you can cut that umbilical cord,” Most said. By using laser-assisted angiography, the surgeon can actually see, rather than guess, when the new vessels are supplying blood to the graft.

A natural-looking nose
For Saxon, the new technology didn’t reduce the amount of time he lived with the attached flap. The damage to his nose was too extensive. For more than a month, he walked around with the flap while undergoing radiation therapy for his remaining cancer. After the umbilical cord was cut, he was free to go. He didn’t have to wait three to four weeks for his swelling to go down and for a natural-
looking nose to emerge.

“We kept the flap for about six weeks,” Saxon said. “I went to work. I wasn’t going to hide out.” When you are a small business owner, that’s just the way it is, he said. You have to work; you can’t stay home.

It hasn’t been easy, and he’s still at risk for a return of the cancer. But he said he’s extremely grateful for his new nose.

“My nose looks really different to me, but other people don’t notice,” he said. For the six-month recovery period, the nerve regeneration made his new nose itch like crazy, and he would feel sharp pains rip through it. But his new nose is a nice nose. He’s finished radiation therapy, and he doesn’t have to worry about nasal function and breathing, he’s finished radiation therapy, and he’s not going to hide out.”

“I’m satisfied, and I’m grateful,” he said, scratching his new nose as naturally as could be.

Malpractice
continued from page 1
Malpractice claims
“Malpractice claims have almost tripled in the past 10 years,” the authors noted. “As compared with the risk of recur-
cence of internal medicine physicians, the risk of recurr-
ce was approximately double among neurosurgeons, orthopedic surgeons, surgeons, and obstetrician-gynecologists.”

The lowest risks of recurrence occurred among psychiatrists, psychologists, and toxicologists. Male physicians had a 40 percent higher risk of recurrence than female physicians, and the risk of recurrence for physicians younger than 35 was about one-third the risk among their older colleagues, the study found.

“If it turns out to be feasible to predict accurately which physicians are going to become frequent flyers, that is something liability insurers and hospitals would be interested in,” Studdert said.

“But institutions will then face a choice,” he added. “One option is to kick out the high-risk clinicians, es-
suring that they can’t work where they are. But our hope is that the knowledge would be used in a more constructive way, to target measures like peer counsel-
ing, mentoring, and enhanced supervision. These are interventions that have real potential both to protect patients and reduce litigation risks.”

Stanford’s Department of Medicine helped to sup-
port the work.
Spectrum awards more than $1 million in pilot grants to 30 projects

By Kris Newby

Thirty biomedical projects at Stanford have received a total of $1.1 million in research funding through the Spectrum pilot grant program.

Spectrum, the Stanford Center for Clinical and Translational Research and Education, is focused on accelerating the translation of medical research from bench to bedside. Its pilot grants are awarded to investigators with bold ideas that address health-care problems through novel approaches and multidisciplinary teams.

Medical technologies
- "Automated real-time monitoring of differentiated stem cells for quality assurance in regenerative medicine," Berta Piovesan, MD, professor of obstetrics and gynecology; and Thomas Baet, PhD, executive director of the Stanford Biomedical Innovation Network.
- "Passive home monitor for early detection of asthma exacerbations in children," David Cornfield, MD, professor of pediatrics.
- "Targeted topical therapy to treat inflammation bowel disease using a novel thermostimulating delivery platform," Siddharth Sinha, MD, instructor of medicine; Aida Hacebrin, MD, MSc, assistant professor of medicine; "A low-cost, rapid, point-of-care nucleic-acid-based diagnostic test," Stephen Quirk, PhD, and Anthony Oto, MD, PhD, professor of dermatology.

Population health sciences
- "Assessment of novel outcomes in the Women's Health Initiative using Medicare claims: An exploration of a new administrative and clinical trial data linkage opportunity at Stanford," Jacqueline Baras Shreibati, MD, cardiology fellow; and Anthony Oto, MD, PhD, professor of dermatology.
- "Post-traumatic stress disorder, deployment fatigue, and associated mental health and behavioral health outcomes following deployment in Iraq and Afghanistan," Bertozzi, PhD, professor of chemistry; and Mark Hlatky, MD, professor of medicine; and Mark Hlatky, MD, professor of medicine; and Jason Andrews, MD, assistant professor of radiology and of medicine; and Marcella Alsan, MD, PhD, assistant professor of medicine.

Predictives and diagnostics
- "Prospective validation of a three-gene set for diagnosis of tuberculous and population-based populations," Sussman, MD, neurosurgery resident; and Atman Shah, MD, assistant professor of health research and policy.
- "Improving early HIV detection with an unsupervised data mining approach: Analyzing images and reports to improve decision-making," Carolyn Bertozzi, PhD, professor of chemistry; and Mark Pandori, PhD, associate clinical professor of laboratory medicine at UC-San Francisco.
- "Point-of-care diagnostics for resource-poor settings," Mamu Prakash, PhD, assistant professor of bioengineering; and Saad Bhamla, PhD, bioengineering.
- "Sentry AH: Harnessing machine learning for the early detection and diagnosis of melanoma," Roberto Novoa, MD, clinical assistant professor of dermatology and of pathology; and Sebastian Thrun, PhD, professor of computer science.

Stanford Learning Health Care Innovation Challenge
- "Accuracy of weekly self-reporting of health-care utilization, infections and antibiotic use among pregnant women and their infants," Julie Parsonnet, MD, professor of medicine and of health research; and Jon Kronisch, PhD, professor of communication.
- "Electronic patient portal-enabled clinical decision support to improve health maintenance: A randomized evaluation," Lance Downing, MD, fellow in clinical informatics; and Paul Heidenreich, MD, professor of medicine.
- "Creation and use of decision aids fueled by patient-reported outcomes: Building the bridge between doctor and patient for improved shared decision-making," Cindy Mitchell, MD, assistant professor of surgery; and Kate Boudorf, MD, MPH, associate professor of health research and policy.
- "Data-driven mammography decision support for analyzing imaging-based patient outcomes in breast cancer diagnosis," Daniel Rubin, MD, assistant professor of radiology and of medicine; and Marcella Alsan, MD, PhD, assistant professor of medicine.
- "Community first-responder training for medical emergencies: Empowering Bay Area high school students," Henry Curtis, MD, clinical instructor of emergency medicine.
- "Creation of a management tool for identifying and treating asthma exacerbations in children," Lance Downing, MD, fellow in clinical informatics; and Paul Heidenreich, MD, professor of medicine.
- "Creation of a management tool for identifying and treating asthma exacerbations in children," Lance Downing, MD, fellow in clinical informatics; and Paul Heidenreich, MD, professor of medicine.
- "Low cost accelerometers for profiling early mobilization progress following spinal surgery," Allen Ho, MD, neurosurgery resident; Arjun Pundharkar, MD, neurosurgery resident; Eugene Susman, MD, neurosurgery resident; and Atman Shah, MD, clinical assistant professor of neurosurgery.
- "A population-wide analysis of emergency department length of stay for patients with asthma exacerbations in the interfacility transfer for severe psychiatric illness," Suzanne Lippert, MD, MS, clinical assistant professor of emergency medicine; and Nancy Wen Wang, MD, professor of emergency medicine.

The Stanford Cancer Institute is sponsoring its second annual symposium to highlight the work of young cancer investigators.

Graduate students, postdoctoral fellows, and early-career researchers will convene from 12:30-6 p.m., Feb. 23 at the Li Ka Shing Center for Learning and Knowledge. Participation in the symposium, which will also give oral presentations on their research projects. The topics span the breadth of cancer research, including basic, translational, clinical and population-based research. The deadline for abstract submission has passed.

The Stanford Cancer Institute coordinates and supports all aspects of cancer-related research and treatment conducted or provided through Stanford Medicine.
Researchers develop fast and accurate cystic fibrosis test

By Erin Digitale

Researchers at the School of Medicine have developed a fast, inexpensive and highly accurate test to screen newborns for cystic fibrosis. The new method determines virtually all mutations in the CF gene, preventing missed diagnoses that delay babies' ability to begin receiving essential treatment.

A paper describing the new test was published online Feb. 1 in The Journal of Molecular Diagnostics. Cystic fibrosis, which causes mucus to build up in the lungs, pancreas and other organs, is the most common fatal genetic disease affecting 30,000 people. To develop the disease, a child must inherit two mutated copies of the CF gene, one from each parent.

Newborns in every U.S. state have been screened for CF since 2010, but the current tests have limitations.

"The assays in use are time-consuming and don't test the entire cystic fibrosis gene," said the study's senior author, Curt Scharfe, MD. "They don't tell the whole story." Scharfe was a senior scientist at the Stanford Genome Technology Center when the study was conducted and is now associate professor of genetics at the Yale School of Medicine.

"Cystic fibrosis newborn screening has shown us that early diagnosis really matters," said Iris Schrijver, MD, a co-author of the study and professor of pathology at Stanford. Schrijver directs the Stanford Molecular Pathology Laboratory, which has a contract with California for the state's newborn CF testing.

Early diagnosis, medical attention

Prior studies have shown that newborn screening and prompt medical follow-up reduce symptoms of CF such as lung infections, airway inflammation, digestive problems and growth delays. "When the disease is caught early, physicians can prevent some of its complications, and keep the patient alive longer," Schrijver said. Although classic CF still limits patients' lives span, many of those who receive good care live now into or beyond their 40s.

In the current test, babies' blood is first screened for immunoreactive trypsinogen, an enzyme that is elevated in the lungs of people with cystic fibrosis. If this test is positive, the infant's entire CF gene is sequenced. Since the majority of infants with high trypsinogen will not develop CF, most U.S. states follow up with genetic screening to detect mutations in the CF gene. California, which has the most comprehensive screening process, tests for 40 CF-causing mutations common in the state. (More than 2,000 mutations in the CF gene are known, though many are rare). If one of the common mutations is identified, the infant's entire CF gene is sequenced to try to confirm whether the baby has a second, less common CF mutation.

"The process takes up to two weeks and can miss infants who carry two rare CF mutations, particularly in nonwhite populations," Scharfe said. "Unfortunately, these CF changes scientists have limited knowledge.

DNA from dried blood spots

The Stanford-developed gene-sequencing portion of the assay determines the genetic profile of each newborn in one step, at a lower cost and in about half the time now required. Stanford University is exploring the possibility of filing a patent for the technique.

"To enable these improvements, the team developed a new way to extract and make many copies of DNA about 1 nanogram — from the dried blood spots that are collected on cards for babies for newborn screening. "These samples are a very limited and precious resource," Scharfe said. The entire CF gene then undergoes high-throughput sequencing. This is the first time scientists have found a way to reliably use dried blood spots for this type of sequencing of CF, which typically requires much more DNA.

"In our new assay, we are reading every letter in the book of the CF gene," Schrijver said. "Whatever mutations pop up, the technique should be able to identify. It's a very flexible approach."

In the new test for the newborn, the molecular pathology lab needs to train its staff on the new procedure and run thorough validation studies as part of regulatory and quality requirements to show that the reliability of the test in a research setting will be maintained in the larger-scale clinical laboratory. California newborn screening officials will then have the opportunity to decide whether they want the new test to replace the current method. Schrijver expects the process will take less than a year. "Regardless of how the state decides, the new technique can be widely adopted in different settings," she said, noting that the technique could also be used for carrier and diagnostic testing and to screen for other genetic diseases, not just CF.

"Ultimately, we would like to develop a broader assay to include the most common and most troublesome newborn conditions, and be able to do the screening much faster, more comprehensively and much more cheaply," Scharfe said.

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. The lead authors of the paper are Martina Leferova, MD, PhD, a former molecular genetic pathology fellow at Stanford; Peidong Shen, PhD, research associate; and Justin Odegard, MD, PhD, instructor in pathology. Other Stanford-affiliated co-authors are Eula Fung, MS; Toovy Chiang, PhD; and Ronald Davis, PhD, professor of biochemistry and of genetics.

Researchers at the University of Texas and the California Department of Public Health also contributed to the paper. The research was funded by a grant from the National Institutes of Health.

Stanford's Department of Pathology also supported the work.