

S T A N F O R D  
M E D I C I N E

Spring 2014

special report

MYSTERIES OF  
THE HEART  
YIELDING TO RESEARCH

Stem cells

The future of cardiac treatments

Dick Cheney

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Untangling the heart

A birth defect repaired

Portable heart gadgets

A new wave of monitoring devices

The high-cholesterol  
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Hidden and deadly

Dear Dr. Shumway

A boy, two frogs and an airmail letter

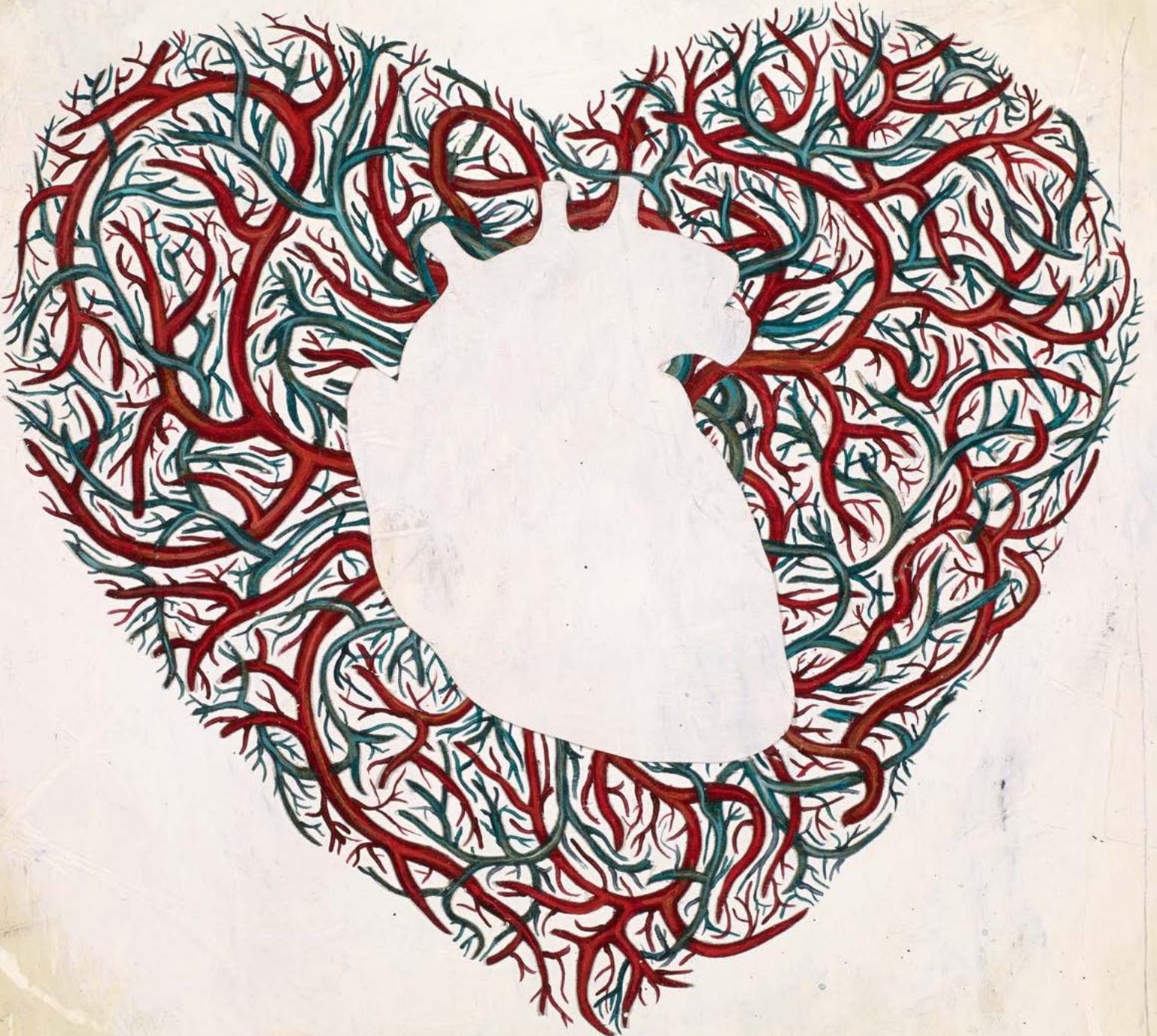
plus

Big data's boon to  
medicine



S T A N F O R D  
M E D I C I N E

Spring 2014



# TWICE CHARMED

## STOCKHOLM FAIRY TALE

2013 was a very good year for Stanford Medicine, with two faculty members winning Nobel prizes. Thomas Südhof, MD, professor of molecular and cellular physiology, was awarded the Nobel Prize in Physiology or Medicine on Oct. 7. Two days later, Michael Levitt, PhD, professor of structural biology, won the Nobel Prize in Chemistry. • They accepted these most desired of awards in December at the Stockholm Concert Hall in Sweden. • Südhof got the call that he had won the prize while driving in Spain to a symposium. "I cannot tell you how much I enjoy what I do," Südhof said when he got the news. "I have always considered it an enormous privilege to be a scientist."

He shared the \$1.2 million prize with James Rothman, PhD, a former Stanford professor of biochemistry, and Randy Schekman, PhD, who earned his doctorate at Stanford under the late Arthur Kornberg, MD, another laureate. Rothman is a professor at Yale, and Schekman, a professor at UC-Berkeley. They were awarded the prize "for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells."



### POMP IT UP

At the 2013 Nobel ceremony, the laureates receive their diplomas and medals on the Stockholm Concert Hall stage.

Stanford's Michael Levitt stands at front left, Stanford's Thomas Südhof steps forward.

These vesicles are essentially bubbles that deliver materials from inside cells to outside. They do this by carrying substances inside them, moving to the edge of the cell, fusing with the cell's outer membrane and then spilling their contents overboard.

Südhof's research focuses on how this happens in neurons. He purified key protein constituents sticking out of the surfaces of neurotransmitter-containing vesicles, protruding from nearby cell membranes, or bridging them. Then he elucidated how the interactions among these proteins contribute to membrane fusion. As a result, signal transmission between neurons is today one of the best-understood phenomena in neuroscience.

Levitt's award, which he shared with Martin Karplus, PhD, of Harvard and the University of Strasbourg in France, and Arieh Warshel, PhD, of USC, is "for the development of multiscale models for complex chemical systems." They dramatically advanced the field of structural biology by developing computer algorithms to build models of complex biological molecules — protein, DNA and RNA — that are responsible for life at its fundamental level. Delineating the precise molecular structures of biological molecules is a necessary first step in understanding how they work and in designing drugs to alter their function.

Levitt's research set the stage for most subsequent work in the rapidly growing field. It also led to methods for making non-human antibodies more similar to humans', which was key to developing anticancer therapies such as Avastin — one of the world's most prescribed cancer drugs.

"Like everyone else, one is surprised," Levitt said of receiving the early morning call from Sweden. "Now I just hope to get through the day and make sure that, in the end, my life doesn't change very much. Because I really have a wonderful life." — ROSANNE SPECTOR

Additional writing and reporting by Krista Conger and Bruce Goldman

For complete coverage, see <http://stan.md/Mn9RxN>

S T A N F O R D  
M E D I C I N E

SPECIAL REPORT

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YIELDING TO RESEARCH



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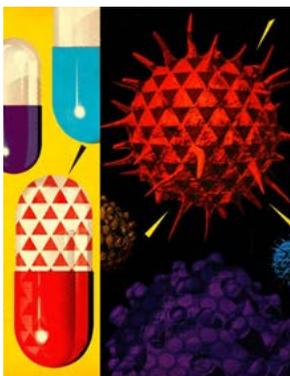
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# letter from the dean

**It was a cool evening in Palo Alto on Jan. 6, 1968, when Stanford University School of Medicine professor Norman Shumway removed the failing heart of steelworker Mike Kasperak and replaced it with the heart of the late Virginia White.**

Dr. Shumway didn't like the limelight, but as he and his team performed the first successful human heart transplant in the United States, journalists climbed the walls of Stanford Hospital to try to catch a glimpse of the historic operation.

It was the kind of pioneering breakthrough that could happen only at Stanford Medicine. Drawn to the most difficult problems, we are known for developing the paradigms that shape the future. And we achieve these breakthroughs by integrating our clinical, research and educational missions. Dr. Shumway was an extraordinary surgeon, but he was also a prodigious researcher and an exceptional teacher and mentor. He was a consummate academic physician.



Years of laboratory work had prepared Dr. Shumway and his team for that first heart transplant. And after that first trial in humans, he went back to the lab to improve the procedure — developing new techniques for overcoming immune rejection, predicting organ rejection and preserving donor hearts — when many other centers had abandoned it because early results were so dismal. His vision and perseverance have paid dividends for the thousands whose lives have been prolonged by this now-standard operation.

One of Dr. Shumway's trainees is Dr. William Brody, president of the Salk Institute and a Stanford University trustee. Dr. Brody says that he and his colleagues used to joke that Norman Shumway was “the world's greatest first assistant” for the trust he put in his trainees, believing that “how” is more important than “who.” Dr. Shumway's patients had astounding results. His trainees went on to become national leaders of cardiac surgery.

Since that famous operation nearly 50 years ago, Stanford's cardiac surgeons have continued to innovate — taking discoveries from the lab to the operating room and bringing new ideas from the operating room back to the lab. Our long list of firsts includes the world's first combined adult human heart-lung transplant, by Dr. Bruce Reitz, and the world's first surgical implantation of a ventricular assist device as a bridge to transplantation, by Dr. Philip Oyer.

And our achievements are not limited to adults. Our outstanding pediatric cardiac surgery program has made Lucile Packard Children's Hospital Stanford an international referral site for complex and challenging open-heart surgeries. The “unifocalization” procedure developed by Dr. Frank Hanley repairs a complex and life-threatening congenital heart defect with a single surgery. In the lab, Dr. Hanley and his colleagues are actively involved in exploring new approaches for surgical repair of pediatric heart defects and disease. In the operating room, they are passing down these innovations to the next generation of heart surgeons.

Today, Stanford's Department of Cardiothoracic Surgery is under the leadership of another consummate academic physician. On Jan. 1, renowned heart surgeon Dr. Joseph Woo began his tenure as chair, carrying on the legacy begun by Norman Shumway. At once a distinguished investigator, an expert surgeon and a respected mentor, Dr. Woo is an innovator who embodies the academic mission of Stanford Medicine. I cannot wait to see what the department will achieve with his leadership.

Sincerely,  
LLOYD B. MINOR, MD  
Carl and Elizabeth Naumann Dean of the School of Medicine  
Professor of Otolaryngology-Head & Neck Surgery

GLENN MATSUMURA

# upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

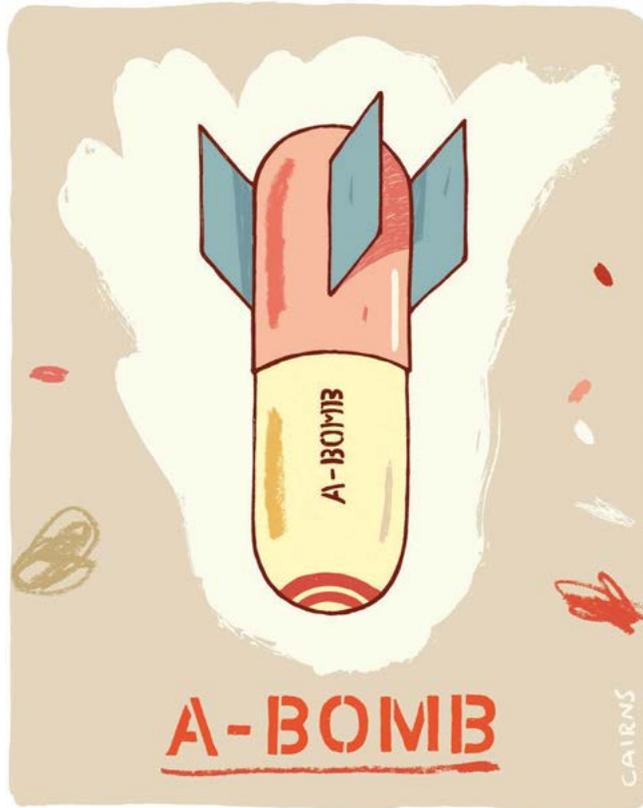
## Gutted

A NEW STUDY by researchers at the School of Medicine could help pinpoint ways to counter the effects of the antibiotics-driven depletion of friendly, gut-dwelling bacteria.

We have difficulty living without the thousands of distinct bacterial strains that inhabit our gut, says Justin Sonnenburg, PhD, assistant professor of microbiology and immunology and the senior author of the *Nature* study. They make vitamins, provide critical training to our immune systems and even guide our tissues' development. Antibiotics decimate this gut-microbe ecosystem, which may take a month or more to regain its numbers and appears to suffer the permanent loss of some constituent bacterial strains.

It is thought that our commensal, or friendly, bacteria serve as a kind of lawn that, in commandeering the rich fertilizer that courses through our gut, outcompetes the less-well-behaved pathogenic "weeds." It has also been suggested that our commensal bugs secrete pathogen-killing factors. Another theory holds that the disruption of our inner microbial ecosystem somehow impairs our immune responsiveness.

"Our work specifically supports the suggestion that our resident microbes hold pathogens at bay by competing



for nutrients," Sonnenburg says. "Antibiotics open the door for pathogens to take hold." In the first 24 hours after administration of oral antibiotics, a spike in carbohydrate availability takes place in the gut, the study shows. This nutrient surplus, combined with the reduction of friendly bacteria due to antibiotics, permits potentially deadly pathogens to get a toehold.

Sonnenburg says he thinks researchers may be able to find drugs or probiotics that, co-administered with antibiotics, could inhibit the carbohydrate spike.

— BRUCE GOLDMAN

## Bleach of promise

IT'S LIKE A MINI SPA. • Mice enjoying frequent dips in a lukewarm, dilute bleach solution emerge not only fluffy and squeaky clean, but also (after two weeks of daily treatment) with thicker, more-elastic skin on their bellies.

Dermatologist Thomas Leung, MD, PhD, has learned that the simple treatment impedes processes that age and damage skin cells by blocking the activity of a protein called NF-kB. The finding, published in the *Journal of Clinical Investigation*, suggests similar baths might help human patients repair damage from radiation therapy or excess sun exposure.

— KRISTA CONGER

# \$20

is the cost of a student-designed brace to treat clubfoot in developing countries. Video at <http://stan.md/1mhLvm9>.

## Caribbean genes

SLAVERY, colonization and immigration. The Caribbean has been a busy place for the past several hundred (and thousands) of years. Geneticists Andres Moreno-Estrada, MD, PhD, and Carlos Bustamante, PhD, recently dove into this melting pot in an attempt to discern exactly how much of human history remains stored in the modern-day genes.

The answer?

More than you might think.

The researchers compared genetic variants in 251 people of Caribbean descent with those in more than 3,000 non-Caribbeans. Using a new way of analyzing DNA to infer genetic ancestry at a fine geographic scale, they identified an influx of European genes within a generation of Columbus'

arrival, as well as two geographically distinct pulses of African immigration corresponding to the transatlantic slave trade.

Their study in *PLOS Genetics* explains why populations sometimes classified by medical researchers as a single group instead display marked differences among populations in susceptibility to diseases or responses to therapeutic drugs.

"If we don't understand the origin of our genetic variants," says Moreno-Estrada, "we won't be able to design personalized, or even population-level, medicine."

— KRISTA CONGER

## LIVER LODE

IN A FEAT OF MODERN-DAY ALCHEMY with huge potential for regenerative medicine, Gary Peltz, MD, PhD, and his colleagues have developed a fast, efficient way to turn cells extracted from routine liposuction into liver cells.

Using mice's bodies as a living laboratory, the scientists converted adipose (fat) stem cells they'd harvested from human liposuction extracts into liver-like cells that flourished. Similar methods of creating liver cells exist, but they rely on other types of stem cells and require introducing foreign and potentially carcinogenic genes.

All aspects of the new fat-to-liver technique are adaptable for human use, says Peltz, who is a professor of anesthesia. The new process takes nine days from start to finish — fast enough to regenerate liver tissue in acute liver poisoning victims, who would otherwise die within a few weeks, barring liver transplantation. — BRUCE GOLDMAN

## In the nose

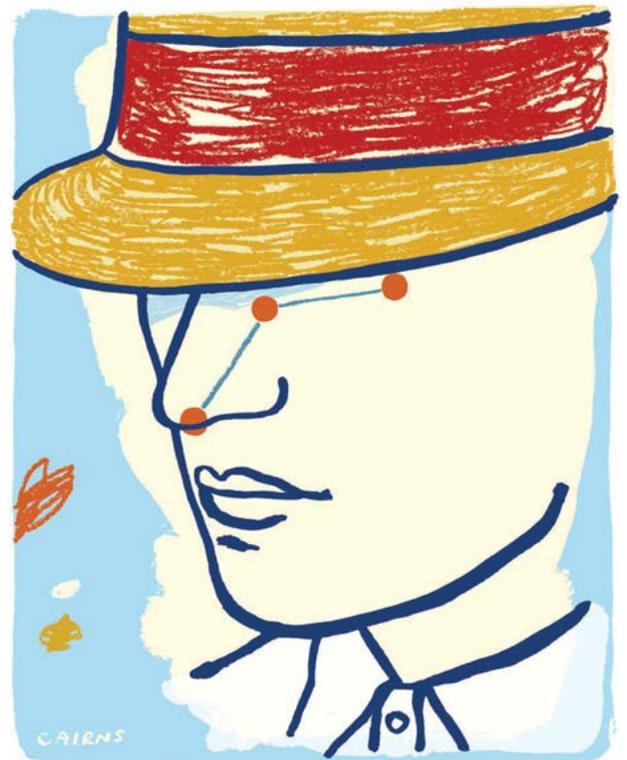
DAVID RELMAN, MD, professor of medicine and of microbiology and immunology, and his colleagues have revealed that formerly overlooked sites deep inside the nose can be reservoirs for *Staphylococcus aureus*, a major bacterial cause of disease. • About one-third of us persistently, and another third occasionally, carry *S. aureus* on our skin and in our noses. The vast majority of the time the microbe does little or no harm. But a wound, a medical incision or catheter placement can let *S. aureus* get into the bloodstream, potentially causing serious and even life-threatening problems such as sepsis, pneumonia or infection of heart valves. Not so good if you're in, say, an ICU.

Rigorous regimens for ridding people's skin and noses of *S. aureus* exist, but typically the bug bounces back before long. The new study in *Cell Host & Microbe* may explain why.

Using special instruments to guide tiny swabs to three precise locations within 12 healthy subjects' noses, Relman's team found that if *S. aureus* was present at the outermost site — where most attempts to rid the nose of the bug are focused — it was probably present at the other two, harder-to-reach sites.

An implication: Treating only the most easily accessible site won't banish the bugs. It's reminiscent of the proverbial drunk looking for his car keys under the lamppost, because it's easier to see there.

— BRUCE GOLDMAN



# Ladykillers

WOMEN, IF YOU'VE EVER THOUGHT the men in your life were trying to kill you, you could be right. That is, if you're a roundworm. • For a few years, it's been known that the mere presence of males of certain species of flies and worms can shorten the life span of their female or, in the case of some roundworms, hermaphroditic counterparts by as much as a third. But it hasn't been clear why. Some researchers theorize that the physical stress of mating causes early death.

Stanford geneticist Anne Brunet, PhD, suggests something more than sex is to blame — specifically, that the males are carrying out a calculated plan at the molecular level to off the baby-makers after they've done their jobs.

This "male-induced demise" could conserve precious resources for a male's offspring or decrease the supply of mates for other males.

Brunet's research, published in *Science Express*, shows that males secrete signaling molecules that initiate the killing process across distances. But as tempting as it is to extend the findings to mammals and — dare we say it? — humans, this strategy would likely backfire in situations where mothers are needed to rear the young.

"In worms, once the male has mated and eggs are produced, the mother can be discarded," Brunet says. "She is not needed to care for the baby worms. Why should she be allowed to stay around and eat?" — KRISTA CONGER

## DOWN INSIGHT

IS DOWN SYNDROME a stem-cell-associated disease? Recent research published in *Nature* by cancer biologist and stem cell expert Michael Clarke, MD, suggests that it could be — at least in part.

He and Craig Garner, PhD, the co-director of Stanford's Center for Research and Treatment of Down Syndrome, found that mouse and human stem cells from throughout the body struggle to grow and self-renew when they have an extra copy of chromosome 21 (the triplication of this chromosome is the cause of the condition). But blocking the expression of just one gene, called *Usp16*, on the chromosome helps the cells function more normally.

The findings suggest answers to many long-standing mysteries about the condition, including why people with Down syndrome appear to age faster and often exhibit early Alzheimer's disease. It could be because their stem cell pools are exhausted too quickly during development. Blocking this expression might alleviate some of the cognitive difficulties associated with the condition.

"There appear to be defects in the stem cells in all the tissues that we tested, including the brain," says Clarke. "We believe *Usp16* overexpression is a major contributor to the neurological deficits seen in Down syndrome." — KRISTA CONGER



# 25%

is the portion of ultrarunners who reported having allergies in a study of their health characteristics. More at <http://stan.md/1mhB8Pv>.

## It's all in the translation

A STANFORD CENTER focused on accelerating the translation of medical research from bench to bedside will receive \$45.3 million over four and a half years from the National Institutes of Health.

The Stanford Center for Clinical and Translational Research and Education, also known as Spectrum, is among 15 institutions to receive Clinical and Translational Science Awards from the NIH. Spectrum earned the top peer-review score on its proposal for the new funding.

"The award is a strong vote of confidence for our work in translational discovery," says Lloyd Minor, MD, dean of the School of Medicine.

Spectrum's director, Harry Greenberg, MD, says the funding helps address one of the nation's biggest challenges: providing better, safer and less costly health care for all.

—KRIS NEWBY

**F R E S H**  
**S T A R T S**  
**F O R**  
**H E A R T S**

CARDIOVASCULAR  
MEDICINE  
LOOKS TO STEM CELLS  
FOR ANSWERS

Six-year-old Sierra Bingham had the flu. But the rural Oregon girl didn't bounce back from the illness like most children do. "She just kept vomiting and looking worse and worse," recalls her father, Jason, of that spring in 2006. "After about two weeks, she woke up and her face was swollen." • Sierra's step-grandmother, a nurse, suggested a chest X-ray to rule out a problem with Sierra's heart, and her parents called their primary care physician that day. They were not overly concerned. Jason and Stacy had two other children, and Stacy — also a nurse — was pregnant with their fourth. They were familiar with sick kids. But the X-ray at the hospital in Baker City netted them an immediate referral to a pediatric cardiologist in Boise to investigate some troubling findings. • "I was sitting in the hospital waiting for the results of Sierra's X-ray, and I overheard a doctor in the hall on the phone to the intensive care unit," says Jason. "I was thinking 'Wow, that kid he's describing is really very sick.' And then I realized he was talking about Sierra." By that night, she was on a ventilator in the intensive care unit. • Sierra was diagnosed with a condition called dilated cardiomyopathy, in which the heart muscle weakens and begins to fail. Although some genetic mutations are known to be associated with the condition, the cause is often unknown. It affects about one child in every 100,000 in this country,

**By Krista Conger**

ILLUSTRATIONS BY JASON HOLLEY  
PHOTOGRAPHY BY BRIAN SMALE



and 40 percent of those with symptoms like Sierra's either die or undergo a heart transplant within two years of diagnosis.

Sierra was already desperately ill.

For about two months, doctors in Boise tried to help Sierra as an outpatient by giving her intravenous medication to help her heart pump better. But after the third trip to the hospital, they decided enough was enough. Stacy and Sierra were airlifted to Lucile Packard Children's Hospital Stanford. Sierra was placed on the heart transplant list shortly thereafter.

"Our world changed in an instant," says Jason. "You just don't assume your kid has a crazy heart disease. The odds of that happening were so slim. It was crazy."

In 2006, the options for children like Sierra were limited to medications meant to help the heart beat more efficiently and reduce its workload. Children whose hearts became too weakened to support life could be tethered to machines to pump their blood during the weeks and months they waited for a new organ — but even that lifesaving technology was rudimentary for someone of Sierra's age and size.

Sierra was lucky. She received a donor heart on Aug. 3, 2006, just before she was slated to go on mechanical support. Her heart transplant saved her life.

In many ways, she's now a typical teen. But she still returns regularly to Packard Children's Hospital so doctors can monitor her heart function and treat her for organ rejection. Meanwhile, the Bingham family has become well-known at the hospital — in part because their journey with heart disease hasn't ended with Sierra.

For a child or adult newly diagnosed with dilated cardiomyopathy today, treatment remains largely the same as it was for Sierra. Watchful waiting coupled with medication is still standard, although options for mechanical support for children have since become widely available and have saved many lives.

But many experts believe better options are coming: They expect research on stem cells to bring about a revolution in care for heart disease patients. These unusual cells, with the ability to turn into many other kinds of cells, could be used to repair damaged hearts and eventually, perhaps, make entirely new organs. And researchers like cardiologist Joseph Wu, MD, PhD, director of the Stanford Cardiovascular Institute, envision a day when stem cells are used not just to treat heart disease, but to quickly identify which medications are most promising for individual patients, or to pinpoint others that are likely to result in cardiac toxicity.

It's not a pipe dream. The California Institute for Regenerative Medicine has doled out over \$120 million to hasten potential therapies into clinical trials — including \$20 million to Wu and Deepak Srivastava, MD, director of cardio-

vascular and stem cell research at the Gladstone Institutes in San Francisco. And in January 2014, big pharma stepped up with a \$12.5 million investment from Johnson & Johnson in Los Angeles-based Capricor Therapeutics Inc. to investigate whether cardiac stem cells can repair heart attack damage.

Interest in the therapeutic use of stem cells in cardiac medicine isn't limited to California, either. Research groups across the country and around the world are working feverishly to explore how best to use the versatile cells, and patients themselves have reported improvements after some preliminary treatments. In 2011, the National Institutes of Health launched the Center for Regenerative Medicine to speed promising stem-cell-based treatments for a variety of diseases to the clinic by tackling technical hurdles and providing access to well-characterized stem cell lines for study.

At the same time, regulatory agencies like the FDA are working to adapt to a new era in medicine that relies on stem cells, either from human embryos or created from adult cells. Standards — what type of stem cells, how they are used and on whom — will be necessary to codify treatment recommendations and move the field forward. But speed is essential.

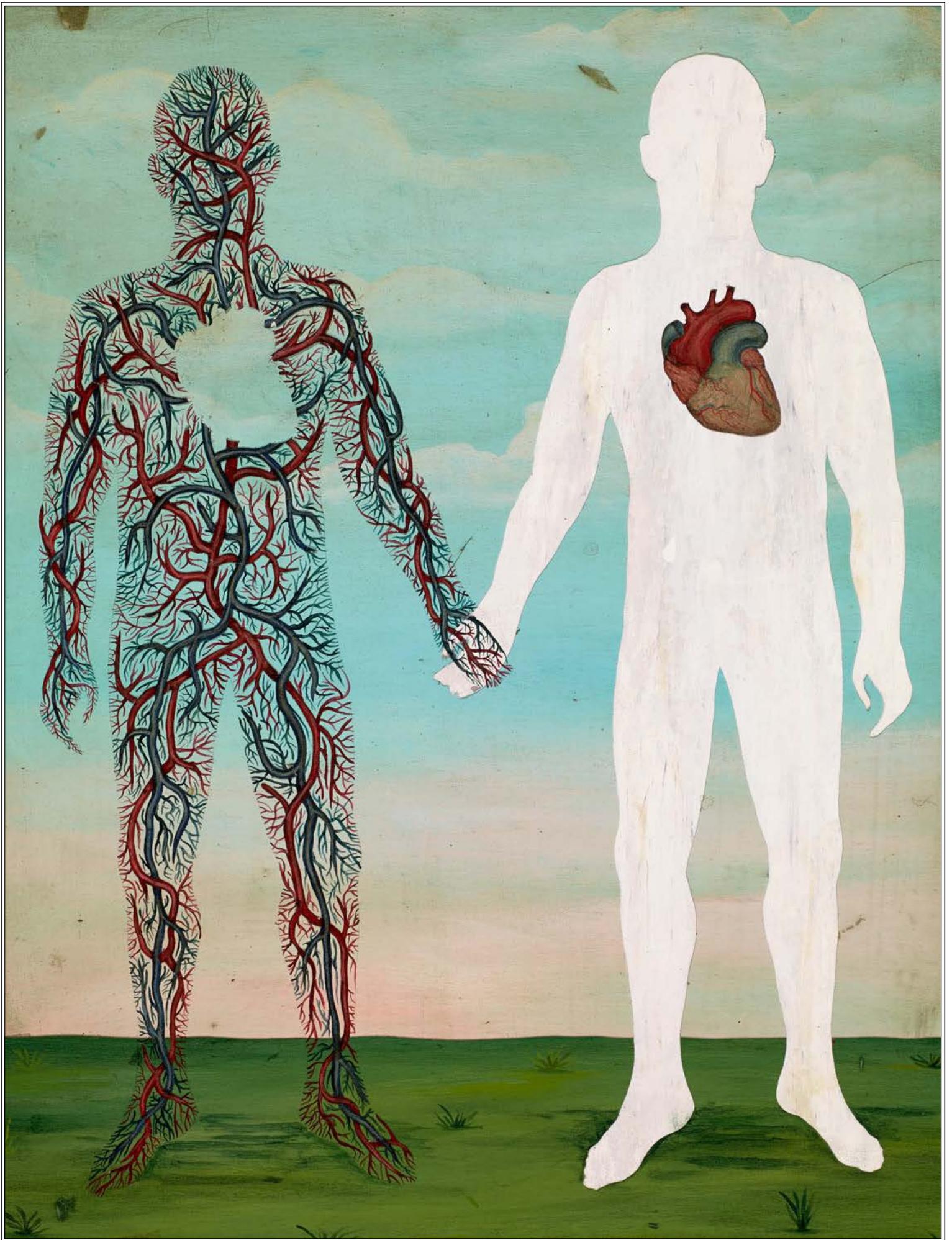
"Heart disease remains the No. 1 cause of death for men and women in this country," says Gladstone's Srivastava. "One half of people with end-stage heart failure will be dead within two years. People are waiting for these treatments, and they are dying while waiting."

Nobody knows this better than the Bingham family. On May 17, 2012, then-7-year-old Lindsey woke up with a swollen face. "I can't put into words the pit I felt in my stomach that morning," says Jason. "Within days we were right back in that hell." A visit to the emergency room in Baker City confirmed their worst fears. Lindsey had severe dilated cardiomyopathy. On May 21, Lindsey was airlifted to Packard Children's Hospital, accompanied by her mom.

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The human heart begins beating about 21 days after conception. But most of the heavy developmental lifting is done before then.

The organ forms from a hollow tube made from a type of embryonic tissue called mesoderm. The mesodermal cells give rise to cardiac precursor cells; once formed, the tube loops around itself to the right, and sections along the loop begin to bulge outward to form the atria and ventricles, which are then each bisected by a wall of tissue to form the left and right halves of the heart.



# HEART CENTRAL

## THE STANFORD CARDIOVASCULAR INSTITUTE

A PROTEIN CHEMIST testing her theory that mitochondria, our cells' tiny powerhouses, control whether heart tissue lives or dies after a heart attack. A physician assessing a lifestyle-change program for new moms vulnerable to post-pregnancy heart disease. A research group developing a low-cost, rapid diagnostic test that can detect genetic mutations underlying heritable heart diseases.

These are examples of the projects being pursued by the 500 researchers and students in the Stanford Cardiovascular Institute. What unites all of them is their common goal: transforming cardiac health care.

As the hub of all heart-related research at Stanford, the institute brings together scientists from a dozen disciplines dedicated to improving health care of the heart. From developing stem cell therapies that heal damaged tissue to delving into rare disorders, their research helps physicians better detect, treat and prevent heart disease. Directed by cardiologist and stem cell researcher Joseph Wu, MD, PhD, the institute provides the funding, support and other resources needed to coordinate research activities and fuel collaboration. The latest additions to the institute include two core labs: one for biomarker and imaging studies, and the other for designing ways to deliver drugs and biomaterials.

The institute supports interdisciplinary research projects through annual seed grants ranging from \$20,000 to \$100,000. Since its launch in 2006, the grants have funded 49 projects for a total of \$2.5 million. Funded projects include clinical trials and fundamental studies that probe the mechanisms of heart disease. One such project, for example, brings together a vascular surgeon, a particle physicist and a mechanical engineering professor who are using X-ray scattering technology to study how fatty buildup in blood vessels forms and worsens, leading to blood clots — and ultimately heart attacks or stroke.

The institute also aims to provide top-notch education through its training programs for undergraduates and post-doctoral scholars, continuing medical education for practitioners, and summer programs for high school students.

— RANJINI RAGHUNATH



When completed, the heart's four chambers pump blood through the body in a kind of figure-eight pattern: With the heart at the center, blood circulates first from the right ventricle to the lungs and routes back through the heart for an extra push from the left ventricle before traveling through the rest of the body and returning again to the heart. The atria serve as a staging area for the blood before it enters each ventricle.

It's the left ventricle that weakened, for whatever reason, for Sierra and Lindsey. To compensate, their hearts began beating faster, and the ventricle slowly enlarged until the girls were in complete heart failure.

When Lindsey came to Packard Children's, doctors suggested genetic testing to try to find a cause of the family's seemingly inherited condition. They turned to the Stanford Center for Inherited Cardiovascular Disease, directed by cardiologist Euan Ashley, MD, PhD. Mutations in more than 50 genes have been linked to dilated cardiomyopathy; researchers wanted to investigate each one. So far there's been no obvious culprit to blame for the girls' condition, and Jason and Stacy have no sign of cardiomyopathy. The Binghamms are desperate to find a reason or a cause, even perhaps an environmental component.

"We want to know that this is not something that we did to our kids," says Jason. "We've had our water tested, we threw out all our furniture and had our carpets cleaned. I don't know if I hope it's genetic, but I'd do almost anything for an answer." The stakes were high. The Binghamms now had five children, and a sickening familiarity with the heart transplant process.

The heart is comprised  
of four main types of cells:  
cardiomyocytes,  
endothelial cells, fibroblasts and  
vascular smooth muscle cells.

Of these, cardiomyocytes are responsible for contracting in a coordinated manner to pump the blood. They're the ones researchers would most like to be able to use to replace damaged or malfunctioning tissue. But the jury is still out as to the ideal starting material to repair damaged hearts, and approaches may vary according to a patient's specific problem.

Until about 10 years ago it was believed that the heart and brain experienced little, if any, regeneration during a person's life: You die with the same cells you had as an infant (unless you're unfortunate enough to suffer a heart attack, which can kill up to 25 percent of heart muscle cells by starving them of oxygen).

More recent research has shown, however, that cell turnover does occur slowly — about 1 percent of cells are replaced



#### UPS AND DOWNS

Life can be good despite unexplained heart disease: Gage, Sierra and Lindsey Bingham (from left).

each year. It's not clear, however, which cells give rise to these new ones. Possibilities include existing cardiomyocytes or as-yet-unidentified cardiac precursor cells that hide out in the heart until called into action by aging or damage.

"We're learning that nature has devised a system that is much more sophisticated than we had imagined," says Stanford's Wu. "When you think about it, we are all composed of stem cells that sustain us through our lifetimes; without them we would all die from premature aging. Now the question is 'What stem cells are involved, and how much renewal capacity do they actually have? Can we make them potent enough or activate them for therapeutic applications?'"

With one child in California and four to juggle at home in Oregon, Jason, an accountant and cattle rancher,

found himself traveling back and forth during the first month of Lindsey's hospitalization in the cardiovascular intensive

care unit while Stacy stayed with Lindsey. While Packard doctors, including the director of its pediatric heart failure program, David Rosenthal, MD, and pediatric cardiologist and former director of Packard Children's heart center Daniel Bernstein, MD, worked to support Lindsey's failing heart with intravenous medication and oxygen, relatives and friends stepped up to care for the other Bingham kids. In mid-June, Jason, Stacy and their other three children underwent yet another round of precautionary testing to look for potential heart problems.

"We really weren't surprised, at that point, to learn that Gage, our 3-year-old son, had a slight enlargement," says Jason, noting physical similarities between Gage, Sierra and Lindsey. But the physicians assured him Gage's problems were slight. The other two children, 10-year-old Megan and 5-year-old Hunter, had some issues, but no immediate red flags.

Unfortunately, stem cell medicine was not advanced enough to help Lindsey. But researchers like Wu and Srivastava are hopeful that will change within five to 10 years. Their grant from the California's stem cell institute funds

research into using human embryonic stem cells to generate cells like cardiomyocytes to help failing hearts. With the right coaching (in the form of added proteins and special growing conditions) these stem cells, isolated from human embryos, can become any cell in the body, including cardiomyocytes. These homemade heart cells beat spontaneously in a lab dish, and have been shown to integrate and electrically couple with existing cells when injected into the hearts of guinea pigs.

With support from the CIRM grant, Wu and Srivastava are extending these studies to larger animals and plan to file an Investigational New Drug application with the FDA — a necessary step before a product-based treatment can be tested in humans — within the next four years.

Another possible route to therapy is to use a patient's own cells, collected from skin or other tissue. These cells can be induced to become pluripotent, or embryonic-stem-cell-like, by adding just a few proteins that are normally not present in adult cells. Induced pluripotent stem, or iPS, cells can in turn be nudged to become cardiomyocytes for potential therapeutic uses or to diagnose cardiac problems in specific patients.

Wu's research has shown that these iPS cells generated from people with inherited cardiomyopathy can give rise to cardiomyocytes that beat differently than those derived from iPS cells from people with healthy hearts. These patient- and disease-specific iPS-cell-derived heart cells also respond differently to various drugs prescribed to patients with heart conditions. Wu has received \$1.4 million from CIRM to collect tissue samples from up to 800 patients like Sierra and Lindsey with idiopathic dilated cardiomyopathy (as well as 200 healthy subjects). The iPS cells from the patients' tissue will be used to create cardiomyocytes to learn more about the disease process in each individual and to test specific drugs.

"This will be the personalized medicine of the future," says Wu. "Instead of giving a drug to 5,000 patients as part of a clinical trial, we can test the drug in the laboratory on iPS-derived beating heart cells from patients — a kind of clinical trial in a dish. And, if you have heart disease, we'll be able to test potential drug therapies on your cells rather than using you as a guinea pig as we try to figure out what works best."

Many researchers agree that in the near term the use of

#### THE PARENTS

Stacy (below) and Jason Bingham (opposite).





iPS-derived cells for drug screening and disease modeling will provide a more immediate benefit to patients than the use of cells as therapies. In fact, cardiologist Bernstein recently spent a year on sabbatical in Wu's lab working on the iPS cell project. But as yet, the use of iPS cells to select medications for individual patients is not routine. Instead, Gage was placed on three different medications, and his parents monitored his heart rate and blood pressure daily as physicians worked to find the correct combinations and dosages for their youngest child.

Meanwhile, Lindsey was worsening. On June 29, Jason, then in Oregon, got the call to come to California immediately. Lindsey's heart urgently needed mechanical support.

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**Jason got to Packard Children's Hospital on June 30, just before Lindsey was to receive an external heart pump called the Berlin Heart.**

This time he brought Gage along. Gage had been acting strangely in Oregon the previous day and his heart rate had seemed abnormally low — only about 40 beats per minute.

Jason thought that, in the stress over Lindsey he might have recorded it incorrectly.

In 2004, the hospital was one of the first institutions to use the Berlin Heart in children in the United States. The pump can prolong a patient's life during the wait for a suitable transplant organ and allows young patients more mobility than would have been possible with older, much larger machines. But it's still a temporary fix.

During the surgery, two thick tubes were inserted through Lindsey's abdomen and up into her heart. Blood cycled out of her heart into the pump, which then gave it the extra push Lindsey's damaged ventricles were unable to muster. The operation is now routine at Packard, but it means a nearly irreversible step toward transplantation.

While waiting, Jason asked Lindsey's nurse to take a quick listen to Gage's heart.

"What happened next was completely unbelievable," says Jason. "Gage was admitted and he and Lindsey, who had just come out of surgery, ended up side by side in the cardiovascular intensive care unit. They had the crash cart, the defibrillator paddles and more doctors around Gage than around her."

Gage was in complete heart block, a condition in which electrical impulses from a patch of pacemaker cells on the



Hunter Bingham

wall of the right atrium, called the sinoatrial node, fail to propagate correctly across the heart to the ventricles. As a result, the ventricles must trigger their own ungainly, sluggish contraction.

“For six years, Sierra had been *the one*,” says Jason. “She was the child we were always concerned about. To learn we had a second child with the same problem, we thought we were going to have a mental breakdown. And now a third? At the same time? It was blowing our minds.”

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### Although researchers are pinning a lot of hopes on possible therapies using embryonic or induced pluripotent stem cells,

there are still many hurdles to be overcome. Because the cells are pluripotent, it is possible for them to become any tissue in the body. This is both a blessing and a curse.

“Effective cell therapies will likely require tens of millions of cells,” says Wu. “If we inject cardiomyocytes made from pluripotent cells into a patient’s heart, we have to be sure these contain no other cell types.” Other concerns include the fact that cells derived from embryonic stem cells could spark an immune reaction in the recipient that could lead to rejection, and the need to learn how, when and exactly where to deliver the cells to patients.

In August 2012, researchers from the FDA’s Center for Biologics Evaluation and Research outlined in a paper published in *Science Translational Medicine* some of the challenges and approaches to working with cell-based therapies such as stem cells. Hurdles include the fact that cells used for therapy are living entities that respond dynamically to their environment, both before and after transplantation. This makes it

difficult to establish benchmarks for standardization when preparing the cells, particularly if they are isolated anew each time from individual patients. (Should an investigator aim for a certain cell number? Or a certain length of time the cells are grown in the laboratory? How can the cells’ purity be maintained during the period they are outside the body?) Furthermore, unlike a drug that degrades and is excreted in a (mostly) predictable manner, transplanted cells may migrate or differentiate into various other cell types in ways that could be difficult to predict or track.

Despite these challenges, there are currently dozens of cellular therapy clinical trials at Stanford and elsewhere for cardiomyopathy, angina and heart attack. Some of these trials use a specialized, and well-characterized, subpopulation of adult stem cells from the bone marrow called CD34-positive cells that are known to give rise to the endothelial cells that line the interior of blood vessels.

A 2012 review by the nonprofit Cochrane Collaboration of the outcomes using adult bone marrow stem cells in more than 1,700 patients with heart attacks in 33 clinical trials concluded that this type of treatment can confer “moderate benefit” to at least some patients, although it’s not clear whether the cells help by delivering more blood to the heart or by generating new muscle tissue.

The trial run by Capricor and supported by CIRM and Johnson & Johnson takes another approach. They’re using cardiac tissue samples obtained through biopsy to generate patient-specific, stem-cell-rich bodies called cardiospheres. A preliminary study of the technique (conducted at Cedars-Sinai in Los Angeles) studied the effect on 17 patients who had suffered recent heart attacks. After six months, the researchers reported those patients treated with cardiospheres experienced a significant reduction in scar tissue and an increase in functional muscle



Megan Bingham

mass in the organ, although the organ's pumping ability appeared unchanged.

The next portion of the trial is expected to enroll up to 274 people who have had heart attacks within the previous 12 months. In this trial, investigators will be using prepared, well-characterized cardiospheres from donors, rather than isolating heart tissue and preparing cardiospheres from each participant. Doing so will allow them to treat patients more quickly, and the use of a standardized product will eliminate some experimental variables and help accurately assess the effect of the intervention.

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With Lindsey and Gage  
both in the CVICU, stem cells of  
any type were far from Jason and Stacy  
Bingham's minds on June 30, 2012.

While Lindsey recovered from her Berlin Heart surgery, doctors surgically implanted an internal pacemaker to help Gage's heart maintain a healthy, normal rhythm. Then the family settled into a room at the Ronald McDonald House at Stanford to wait for Lindsey's transplant. This time, the vigil was longer than it was for Sierra.

Heart transplants may be the only answer for kids with dilated cardiomyopathy, but they're difficult to come by. According to the National Heart, Lung and Blood Institute, about 3,000 people are on the heart transplant list in this country on any given day, but only about 2,000 to 2,500 organs become available each year. For older people whose heart damage was caused by heart attack, there aren't many options.

"We've done a great job with therapeutic interventions at the front end," says Sean Wu (no relation to Joseph Wu), MD, PhD, assistant professor of cardiovascular medicine at the Stanford Cardiovascular Institute, "and this has saved many lives. But we have little to offer to people who have survived their heart attacks but have lost a lot of their cardiac tissue function. These people have a mean survival of only about three years."

Sean Wu's lab is working on a technique in which iPS cells are injected into developing mouse embryos genetically incapable of forming their own working hearts. The researchers have been able to generate entire working organs in these animals with iPS cells. The hope is that one day researchers will be able to grow patient-specific organs-to-order in large animals like pigs simply by using iPS cells created from skin or blood samples.

"This may sound like science fiction," says Sean Wu, "but

maybe, considering the speed of progress in the field, it's not as far-fetched as it seems." Noted stem cell researcher Hiromitsu Nakauchi, MD, PhD, recently recruited to the Stanford Institute for Stem Cell Biology and Regenerative Medicine, has been conducting similar studies with positive results.

Growing a new heart from a patient's own cells is likely to be time-consuming and expensive. But in theory it should solve any problems with rejection because the heart would be an exact match to the patient. Rejection is not rare, and often not inconsequential. Sierra has been struggling with a type of antibody-mediated rejection of her donated heart since about 2011; doctors are treating it with regular intravenous infusions of immunoglobulin that helps remove antibodies attacking the heart.

Most organ transplants have a limited life span, be it five years or 25. Depending on the age of the recipient, future transplants may be necessary. Sierra's experience had taught the Bingham family that life after transplant is still challenging — Sierra must take multiple daily medications to suppress her immune system and prevent or slow rejection. But they also knew that a transplant was Lindsey's only hope.

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On the evening of Feb. 12, 2013,  
after more than seven months  
in the hospital  
— with occasional quick forays

to the outdoor fountain or hospital cafeteria — Lindsey and her family received the news they had been waiting for. A matching heart was available for Lindsey.

They celebrated while they waited throughout the night and the next day for the surgery to begin (paperwork, matching of other organs, removal and transportation of the donated heart can take many hours).

And then, just hours before Lindsey's transplant, the unthinkable happened. A routine checkup for Sierra landed her in the CVICU for dangerously high pressures in her donated heart. Once again, Jason and Stacy found themselves shuttling between two children just doors apart from each other, saving their breakdowns for the hallway.

On Feb. 14, Valentine's Day, Lindsey got her new heart.

Simultaneously, down the hall, Sierra's doctors brainstormed ways to try to protect her transplant.

"Seven years ago, I would never have imagined being in this situation," says Stacy. "We worried about normal kid stuff, like whether they're liked by their friends at school. Not how long their hearts were going to last."

C O N T I N U E S O N P A G E 4 7

Midway through the story of his heart troubles, Scott Radabaugh hesitates, gently placing a hand on his chest. He feels a twinge there, he says with a frown. He leans in a bit over the table in the San Ramon, Calif., café and tells me the questions flooding his mind: Could it just be a sore muscle from his workout? Or a sensitivity to the wires supporting his sternum, a remnant of his quadruple bypass surgery? Or is it a more ominous sign? • At 6 feet tall with a weightlifter's physique and a ruddy complexion, Radabaugh appears to be the epitome of a healthy man. But he has what he calls a "sleeping giant" of a disease, a gene that makes him prone to soaring blood levels of low-density lipoprotein, known as LDL — the so-called bad cholesterol. At age 46, he's already had two major surgeries to clear arteries blocking blood flow to his brain and his heart, and he is on the lookout for signs that he will need a third. • "I'm on hyper alert," says the human resources manager and single father of three from Danville, Calif. "Once I have chest pains it may be time.... What's scary is that I don't go anywhere without nitroglycerin or aspirin [to help defuse a blood clot or heart attack].

## H I D I N G

## I N

## P L A I N

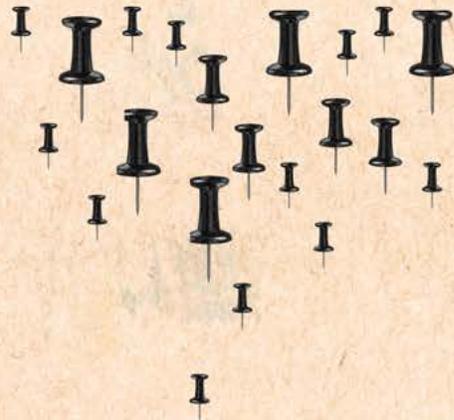
## S I G H T

### A H I G H - C H O L E S T E R O L G E N E

I think about my own mortality many times a day." • His condition, known as familial hypercholesterolemia, or FH, is a genetic disease in which individuals are born with high levels of LDL that build up in the arteries and can ultimately choke off blood flow to the heart if not treated. Radabaugh hadn't heard of FH until a few years ago, though it's highly prevalent in the United States. It's thought to affect more than 600,000 adults and children — or one in 500 — and is far more common than other widely known genetic diseases, such as cystic fibrosis or breast cancer among women with a mutation in the BRCA1 gene. • Cardiologist Joshua Knowles, MD, PhD, an FH expert at Stanford, says FH is a condition that has been seriously neglected in this country — under-reported, under-treated and under-researched. Sadly, he says, many people don't learn about it until they have a heart attack. • "It's an invisible disease," says Knowles, an instructor in medicine. "If you don't have your cholesterol checked and get treatment, you're a ticking time bomb until something happens." • Though cholesterol is essential to body function, genetic changes can affect how people clear it from the blood. People with FH lack receptor proteins on the surfaces of their cells that help regulate the amount of circulating

**By Ruthann Richter**

ILLUSTRATION BY LINCOLN AGNEW



LDL. Without functioning receptors, the cells can't latch on to the harmful protein, and that allows it to flood the bloodstream and accumulate in the artery walls. High-density lipoprotein, or HDL, on the other hand, is considered the "good" cholesterol because it helps remove these dangerous deposits.

**F**H IS OFTEN THE CAUSE of premature heart attacks in young people, including athletes who seemingly out of the blue drop dead on the field. (Among the best known is Darryl Kile, pitcher for the St. Louis Cardinals, who died of a heart attack in 2002 at age 33, shortly before a big game in Chicago. Kile's father died of a heart attack at age 44.) The disease is an underlying cause for some 24,000 heart attacks each year among people under age 60 in the United States, Knowles says. It often affects multiple family members, as children have a 50 percent chance of inheriting it from their parents. In rare instances, children inherit two copies of the gene — one from each parent — making them unusually vulnerable, at risk for heart attack in childhood.

Because it's an asymptomatic disease, it often goes unnoticed by patients and their caregivers, says cardiologist Robert Harrington, MD, professor and chair of medicine at Stanford. "When you are a busy pediatrician or primary care provider, you don't really see the disease. And until patients have a problem, they don't complain about their high cholesterol," Harrington says. Cholesterol is a major risk factor for heart disease, though it's not the only contributor, as diet, exercise, smoking, blood pressure and stress all may play a role.

Knowles and his colleagues follow some 60 FH patients at Stanford Hospital & Clinics, diligently tracking their cholesterol numbers. A faculty member in his 40s, he is reserved and thoughtful, saying his aim is to get patients to a place where their risk of a major heart event is low. Radabaugh first visited

him as a patient in early 2013 at Stanford's Familial Hypercholesterolemia Clinic for a second opinion on whether he'd need another bypass operation. "He was comforting. He took a lot of the fear away," Radabaugh says of Knowles. Before then, he says, he had no clear sense of what his risks were. "He's given me some assurances that I don't have issues in the short term and could go years without another bypass. But of course nobody can say for sure."

Radabaugh says that because of his family history, he long suspected he was prone to high cholesterol. As a child, he remembers his mother coming home from the doctor, upset to learn that her cholesterol was out of range. By age 52, she had suffered a blockage in an artery that was propped open by a stent, followed eight years later by a double bypass. Radabaugh watched as she emerged from the painful procedure, determined that he would do everything possible to avoid bypass surgery for himself.

A Texas native, he was 27 when he got his first human resources job in Houston in 1995 and decided he should be checked out. When his cholesterol results came back, his doctor was alarmed, as his LDL level was high, nearly 300 mg/dl. The American Heart Association defines LDL levels

of below 100 mg/dl as ideal; people with FH commonly have levels of 200 to 400. He was prescribed cholesterol-lowering statin drugs — the mainstay of FH treatment — and advised to watch his intake of fat.

He is still very much the Texan, arriving for our meeting in black cowboy boots, black Wrangler jeans and a work shirt with pockets. Radabaugh works out regularly, and it shows. He also played football and baseball in high school and lifted weights while in college at Texas A&M, he says, all of which made him feel he was doing the right thing for his health.

"I fell into the mistaken belief that if I ate a low-fat diet and exercised — and doctors reinforced this — I



**SCOTT RADABAUGH**

**Heart disease taught him to cherish life and family.**

COLIN CLARK

**'I FELL INTO THE MISTAKEN BELIEF THAT  
if I ate a low-fat diet and exercised — and doctors reinforced this — I could reduce  
my risk to that of the general population.'**

could reduce my risk to that of the general population,” says Radabaugh, who maintains a strict dietary and exercise routine. “They were missing that one important piece: that if it’s genetic it begins the day you are born.”

**O**NE DAY IN 2010, while he was pedaling on the elliptical machine at the gym, he felt a burning sensation in his chest. He stepped off the machine, and the pain subsided. But he was terrified, he says, as he stood in the crowded facility in San Ramon, Calif.

He dialed his primary care physician, who scheduled him for a stress test at 7 a.m. the next day at John Muir Medical Center in Walnut Creek, Calif. He failed miserably, barely able to sustain three minutes on the treadmill before his legs started to burn, as his heart wasn’t delivering enough oxygen to his extremities. That test was followed by an angiogram, an X-ray of the arteries, which showed blockages in four major vessels, including one directly leading to the heart. He was stunned to hear that he needed immediate bypass surgery — that “brutal” procedure (in which the sternum is split in half and later stapled together) that he’d tried so hard to avoid.

“My surgeon said, ‘You were really lucky. You would have had a heart attack in two to three weeks, and where the blockage was located it would have been fatal,’” he says. “You hear about these guys at the gym who work out and they’re in great shape and they drop dead. That would have been me.”

He was just 43. Radabaugh had assumed he was one of the many people with garden-variety high cholesterol. He did not realize then that he was an FH carrier and had been building up stores of cholesterol since birth.

“If you’re a normal person, you begin worrying about heart disease when you’re in your 60s or 70s,” Knowles says, “but if you’re an FH patient, the heart attacks start happening in your 30s and 40s.” Men with FH have a 50 percent risk of heart attack by age 40, while women have a 30 percent risk by the time they are 60.

As Radabaugh now says, “I may be 46, but I have the cardiovascular system of a 76-year-old.”

Because of his family history, his doctor suggested he have his three children tested as well, though they were just 5, 8 and 12 at the time. So in April 2011 — on the first anniversary of his bypass surgery — Radabaugh took them on a

family outing to the lipid clinic at UCSF. Astonishingly, all three children proved to have high LDL numbers and were prescribed statins. For the first time Radabaugh heard the term, familial hypercholesterolemia. There was some relief in knowing the source of his problems, he says. “At least I had a name for this monster I was fighting. I felt empowered.” He resolved to become an advocate, educating others about the condition and encouraging them to go for testing.

“If you have any possibility of high cholesterol or family history, get yourself and your family members checked,” he tells people. “Once you have the knowledge, you can do something. If you don’t, the hand of God may reach down and grab you at any moment.”

FH may not be widely recognized today, but it has lurked in the background for decades. Its scientific roots go back to 1938, when a Norwegian scientist linked high cholesterol with the odd, yellowish swellings or bumps that appeared on patients’ limbs and around their eyes. Known as xanthomas or in the case of the eyes, arcus, these are often a hallmark of the condition: cholesterol-laden deposits that pillow under the skin and may pop up on the elbows, hands, feet, Achilles tendons or other body parts.

**I**N THE 1970s, scientists began to explain some of the underlying biology of the disease. At that time, Michael Brown, MD, and Joseph Goldstein, MD, at the University of Texas Southwestern Medical Center, discovered that cells have surface receptors that regulate how much LDL circulates in the bloodstream. The cause of FH was a shortage, or complete absence, of these receptors, they learned. The finding earned them the Nobel Prize in 1985.

The following year, Thomas Südhof, MD, who was working then in their lab, succeeded in cloning the gene for the LDL receptor — one of the genes that when mutated is responsible for FH. The discoveries laid the groundwork for the development in the late 1980s of the first statin drugs to lower cholesterol, revolutionizing cardiovascular medicine and leading to what Südhof, who is now a Stanford professor of molecular and cellular physiology and winner of a 2013 Nobel Prize, calls “one of the major medical advances of mankind.”

Since identifying the first LDL receptor gene, known as

LDLR, scientists have pinpointed two other, less common genes important for FH. When a person with FH is tested, 60 to 80 percent of the time a disease-causing mutation in one of these genes shows up, says Knowles. All told, at least 1,500 mutations are known that affect LDLR, while just a few affect the other two genes.

Genetic testing for FH in Europe has been found to be cost-effective, as it saves the cost of major procedures, tests and hospitalizations. But in the United States, this testing is uncommon because it's expensive — \$800 to \$1,300 — and not typically covered by insurance, Knowles says. Because the condition is so prevalent and treatable, the U.S. Centers for Disease Control and Prevention has made screening for the disease a top priority, encouraging first-degree relatives of people with FH to be screened, though not necessarily to get a genetic test.

Some European countries with national health-care systems also have launched campaigns to identify and treat patients with the disease. In the Netherlands, for instance, a government-led effort has identified 71 percent of patients thought to have FH, based on an estimated prevalence of one in 500 in the general population. A similar campaign in Norway has pinpointed 43 percent of affected individuals, while in the United States, that number is less than 1 percent, according to a recent *European Heart Journal* study.

**K**NOWLES HAS BEEN WORKING with the 2-year-old FH Foundation, a nonprofit patient advocacy group, to help change that. As the foundation's chief medical officer, a voluntary position, he spearheaded its September 2013 launch of a national online registry to gather information about affected individuals and their family members. The goal is to help document the number of patients, learn about their history, their treatment, their participation in clinical trials and how the disease is impacting their lives, all in the interest of improving patient care and developing new therapies. The registry is a collaboration with the Duke Clinical Research Institute, which Harrington directed before he came to Stanford in 2012.

Harrington says the database is unusual in that it is driven by patients, who anonymously supply their own information. "It's a next step in terms of empowering patients," he says. "It will allow the FH Foundation and the academic community to provide valuable insights into the disease."

The first person to sign up for the registry was Radabaugh, who met Knowles through the foundation. More than 100 people are now in the registry, which is accessed through the

foundation's website: <http://thefhfoundation.org/>.

Cardiologist Euan Ashley, MD, PhD, says the registry offers a rare opportunity. "Here you have a very straightforward and relatively benign intervention — cholesterol testing and treatment — that can be done very early on and save lives. That is very unusual for any genetic disease. So it's a great opportunity — if you can find people with the disease," says Ashley, associate professor of medicine and director of the Center for Inherited Cardiovascular Disease at Stanford.

Knowles is seeking other ways to identify FH patients and funnel them into treatment. He recently completed a study in which he and his colleagues reviewed the electronic medical records for all Stanford Hospital patients who have had cholesterol testing in the last 10 years, tagging those with "very suspicious" LDL levels. He was able to identify some 150 patients, whose health-care providers were then notified. About 10 patients have since come in to Stanford for follow-up, though others may have seen caregivers elsewhere, he says.

He is now seeking funding to apply that same model in other health-care systems, such as the massive Veterans Affairs Health Care System, with the hopes of identifying a broader swath of individuals with FH.

"I think it's an area where electronic medical records could be very valuable," says Michael McConnell, MD, a professor of medicine and co-director of the Preventive Cardiology Clinic at Stanford. "We want to be careful and not alarm patients, but there is a public benefit not only to the patient but also to the family members who may not have been screened."

Ashley also is working with the American Heart Association on guidelines to encourage information sharing among insurance companies. The goal is to identify family members who may be dispersed across the country, covered by different health plans, and unaware that FH is a common family trait.

"It's much cheaper for them to pay for a simple test than to pay for the heart attack, the heart bypass and the coronary care unit," he says. "And it's much better for the patient."

**T**HE AMERICAN ACADEMY OF PEDIATRICS also recommends that all children between the ages of 9 and 11 get a cholesterol panel, but the guideline is not widely implemented, Knowles says. Some pediatricians may not be aware of the guidelines or are reluctant to draw blood in a child, while others may not want to do cholesterol testing unless they are prepared to give the child medication. But Knowles says at the very least, a child found to have high cholesterol could benefit from diet and lifestyle changes, while knowing the child's cholesterol status could help identify other

**'HERE YOU HAVE A VERY STRAIGHTFORWARD  
and relatively benign intervention — cholesterol testing and treatment — that can be done  
very early on and save lives. That is very unusual for any genetic disease.'**

family members at risk. “If you did that and screened a lot of kids at an early age, you’d pick up a lot of the FH cases,” he says.

Once patients are identified, they must follow a particularly aggressive drug regimen, typically based on the use of a high-potency statin. The statin drugs work by inhibiting an enzyme that is key to the liver’s production of cholesterol. Major studies from the Netherlands and Great Britain have shown that taking statins and controlling cholesterol are highly effective in reducing mortality among FH patients to levels similar to the general population, Knowles notes.

The goal for FH patients is to bring their LDL down at least 50 percent and ideally even lower (perhaps as low as 70 mg/dl) to compensate for the body’s long-term cholesterol exposure, Knowles says. But fewer than 20 percent of patients actually reach healthy cholesterol levels because doctors, often unaware of a patient’s FH status, may not pursue aggressive treatment, while patients don’t always take their pills. The drugs also may carry side effects, with up to 10 to 20 percent of patients experiencing problems such as muscle aches, which limit their use.

“Compliance is a challenge for everyone,” says Mary Ann Champagne, RN, a Stanford nurse who has worked with FH patients for 20 years. “It’s a silent and asymptomatic disease and people don’t see or feel an immediate benefit from taking their prescribed medication.”

Statins have been the dominant treatment for decades and are among the country’s most widely prescribed drugs, with Lipitor (atorvastatin), the leading statin, commanding a market of \$7.2 billion in 2010, according to the pharmaceutical research firm IMS Health. Most statins, including atorvastatin, are now generic and, as a result, inexpensive.

But more recently, drug development has focused on an entirely new class of compounds that could have huge implications for treatment, Harrington says. These drugs target PCSK9, an enzyme that makes it difficult for the body to clear cholesterol. Early-stage trials have shown that when the enzyme is blocked, LDL levels drop to unprecedented levels. Several companies are sponsoring large-scale clinical trials with variants of the drug to assess their impact on heart disease. Results are expected in the next year or two.

Radabaugh clings to the promise of these potent new medications. Though he is diligent in taking his pills — he

and his children down their “vitamins” daily — he still struggles to bring his LDL into a low range, he says.

**M**UCH OF HIS LIFE these days revolves around management of the disease and his preoccupation with what the future will bring. In late 2012, a CT scan of his carotid arteries, which carry oxygen and blood through the neck into the brain, showed that the artery on his left side was 90 percent blocked, putting him at serious risk of stroke. He underwent a procedure known as carotid endarterectomy, in which surgeons opened up the vessel to clear the deposits. The procedure left him with a 3-inch scar on his neck and a slight swelling there that gives him a throaty voice at times.

Then in the spring of 2013, he learned that two of his bypass grafts had failed; this is not entirely uncommon, as about half of bypass grafts fail within 10 years because the substitute vessels, typically veins taken from the leg, aren’t equipped to deal with high arterial pressure. So Radabaugh faces the prospect of another procedure. A second bypass operation could be complex because doctors would have to steal arteries from another part of his body, likely his arms. They are hoping to postpone the procedure for as long as possible.

And so Radabaugh waits, as the prospect of a major heart event hovers in the background.

“I’m waiting for chest pains and another bypass or, God forbid, I could have a massive heart attack,” he says.

In the meantime, he harks back to an experience in the hospital’s intensive care unit when he was awaiting his bypass procedure. A woman in the next room suffered a fatal heart attack that marshaled the entire staff and left family members swooning in grief. Watching the incident unfold, he says, gave him an entirely new perspective, as he could savor the joy of his own survival.

“I’ve had the chance to stand on the cliff with my toes on the edge, but thank God I didn’t fall in. So it’s given me a good perspective. I realize now it’s only our relationships in life that matter.”

He has learned to cherish what he has. “Every day I appreciate the time with my kids and my life,” he says. “I don’t wait to tell them how I feel about them. My life is focused on what is important.” **SM**

*Contact Ruthann Richter at richter1@stanford.edu*

MYSTERIES OF THE HEART:

Yielding to research

# A CHANGE OF HEART

## A CONVERSATION WITH DICK CHENEY

Dick Cheney's first heart attack occurred when he was 37, a young man running for the U.S. House of Representatives in Wyoming. His most recent — a fifth — happened in 2010. By then, the former vice president had taken advantage of everything technology and medicine had to offer a man with chronic heart problems: stents, defibrillators, an extended-battery-powered heart pump and quadruple coronary bypass. He was at what he believed was the end of the road.



Illustration by TINA BERNING

Facing end-stage heart failure, he received a left ventricular assist device, or LVAD, in the summer of 2010 that saved his life. But for Cheney, the device wasn't enough. He realized that a transplant was the only option that would set aside decades of heart ailments and give him a gift by then he thought was impossible: longevity. Twenty months later, when he was 71, a late-night phone call informed him a donor had been found. Life for Cheney would begin anew.

Nearly two years after his transplant, Cheney and his cardiologist, Jonathan Reiner, MD, have written a book about his history of heart ailments, *Heart: An American Medical Odyssey*. Paul Costello, executive editor of *Stanford Medicine*, spoke to Cheney about life after near death.

**COSTELLO:** You've written a book that serves up intimate details about your health over 35 years of heart disease. Why did you decide to tell your story?

**CHENEY:** While I was living on a heart pump, the left ventricular assist device, awaiting transplant, I got a call one day from someone at the Cleveland Clinic who said they were getting ready to have a conference on innovation in cardiology. They had suppliers and doctors coming in to speak but they needed a patient. I had virtually everything done to me that you could do to a heart patient since my first heart attack in 1978, so I agreed. That started the wheels rolling.

I also get questions all the time and letters from people about various aspects of my case. Some have a loved one awaiting a transplant or getting ready to undergo the LVAD procedure. Nearly one in four Americans has some kind of heart problem. This told us there's a story to be told that was useful and that would also tell the success that we've experienced in medical innovations under our existing health-care system.

**COSTELLO:** What did you hope to accomplish?

**CHENEY:** We didn't write it for political reasons. It was a combination of being able to tell a story and the fact that during 35 years of

install the LVAD. I had a very tough recovery coming out of that. Five weeks in the ICU. I contracted pneumonia. I was heavily sedated on a respirator for part of that time. I was one sick puppy.

I was confident early on that I wanted to go for a transplant if I could get one. It offered the hope of a return to a normal life and the prospect of taking 35 years of coronary heart disease and putting them behind me. In my mind, it wasn't a close call.

**COSTELLO:** You were at death's door in 2010. But you write that you were at peace facing death. Why weren't you more fearful?

**CHENEY:** The fifth heart attack was in February, and by June I reached the point where I was obviously in end-stage heart failure. All I wanted to do was to get out of bed in the morning, sit down in my chair and sleep some more. I'd lost most of my physical abilities to do anything.

I had my first heart attack at 37 years old, when you think you're going to live forever. Over time, with chronic heart issues, I concluded that sooner or later, I was going to run out of technology and new innovations in the area of heart medicine.

That's how my dad had died. That's how my maternal grandfather had died. I fully expected there would come a time when, indeed, that would be representing the end of my days. I thought about it. I was at peace. It wasn't painful. It wasn't surprising or frightening. I had lived a wonderful and remarkable life. I had a tremendous family. Everything a man could ask for. Now my time had come. I wanted to talk with my family about final arrangements. It was a very hard conversation for them, much more so than it was for me, but I felt I needed to express my views. I was at peace. That was the only way I could think of to describe it. It was not frightening, unpleasant or disturbing. It was my time.

**COSTELLO:** Now you're living without a threat of imminent death. Can you even describe how that feels?

**CHENEY:** A day doesn't go by that you don't think about the fact

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**'IT OFFERED THE HOPE OF A RETURN TO  
a normal life and the prospect of taking 35 years of coronary heart disease and  
putting them behind me. In my mind, it wasn't a close call.'**

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heart ailments, I've held some pretty important jobs. I've been able to live a full and active life while dealing with heart disease as we went through it.

**COSTELLO:** When you made the decision to proceed with surgery if a heart became available, what factors carried the day?

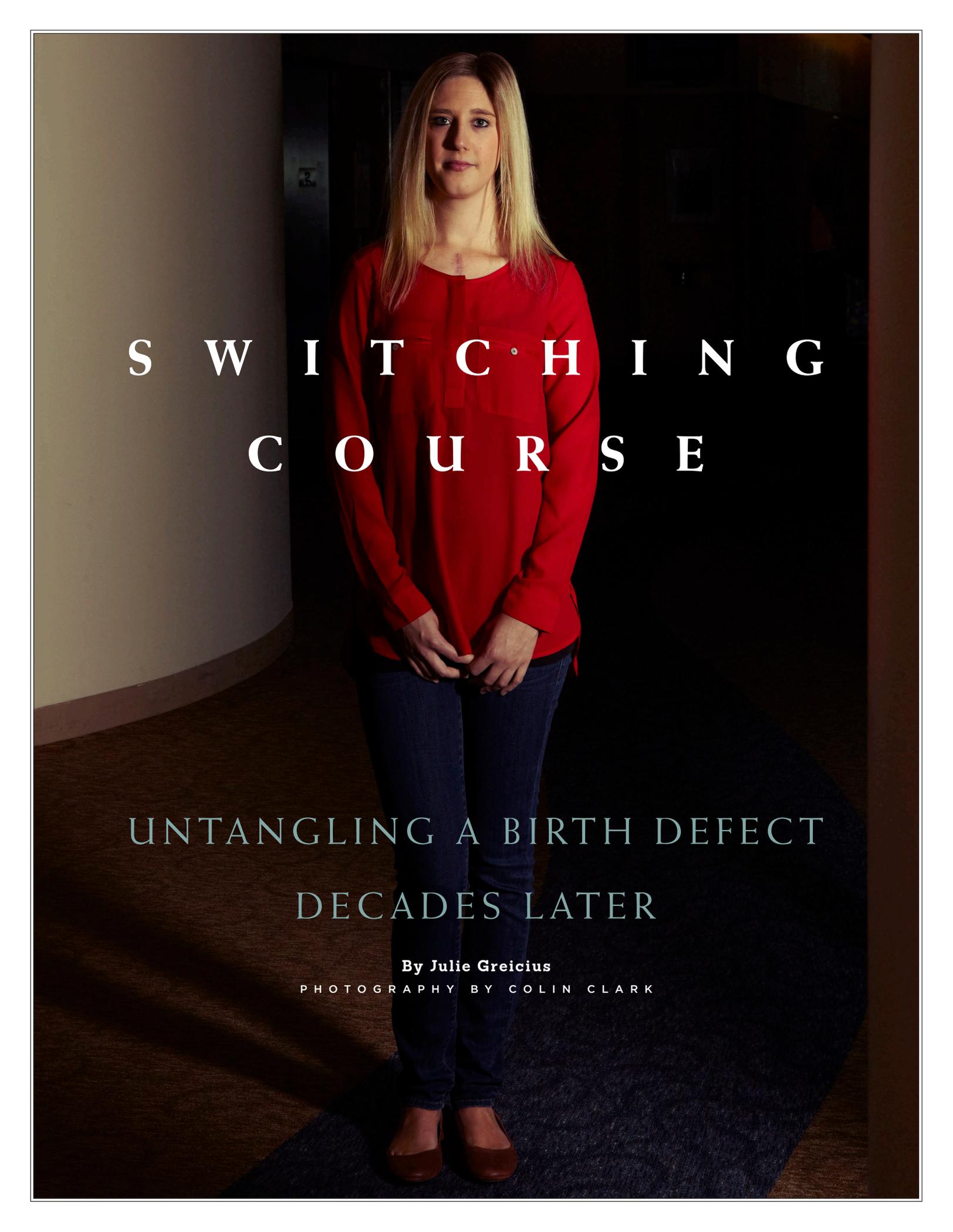
**CHENEY:** The main consideration was longevity. We got into the LVAD because I was at the end of my line. I'd had five heart attacks and an incident of sudden cardiac arrest, and by early July of 2010, I was near death. My ejection fraction was down somewhere around 10 percent. My heart was no longer able to provide an adequate supply of blood to my liver and my kidneys. We reached the point where the only way to deal with that crisis was an all-night surgery to

that you've been a beneficiary of a miracle that's a result, I always remember, of a donor. I wake up every morning with a smile on my face, grateful for another day that I never expected to see.

**COSTELLO:** When you consider the conversations you had with your physicians over the years about your heart issues, is there any one conversation that stands out?

**CHENEY:** It was 1978. I was 37 years old and running for Congress, my first campaign for elective office. I had a heart attack. It was a mild one. As I was recovering in Cheyenne, Wyo., I asked my doctor, Rick Davis, if this meant I would have to give up my campaign. He replied, "Aw heck Dick, hard work never killed anybody." That's what

C O N T I N U E S O N P A G E 4 7



S W I T C H I N G  
C O U R S E

UNTANGLING A BIRTH DEFECT  
DECADES LATER

By Julie Greicius

PHOTOGRAPHY BY COLIN CLARK

When people ask 24-year-old Brooke Stone about her chest scar, she gives them the simplest answer she can:

**"I tell them I was born with my heart attached backwards."**

As a newborn in 1988, Brooke was diagnosed with a congenital heart defect known as dextro-transposition of the great arteries, and underwent a complex surgery to correct her blood flow. • Stone's doctors knew that this surgery would probably not be her last. Of the 40,000 children in the United States born with congenital heart disease each year, 50 percent will require at least one major surgery, according to the Children's Heart Foundation. Of those, almost all will require regular follow-up care, with many needing one or more additional surgeries because of later-life complications. Those whose lives are saved by early surgical intervention will never be entirely free of the risks of their condition. • The challenge today is to ensure that post-surgical patients survive long enough to benefit from advances in care that are evolving as patients age. Surviving means receiving ongoing monitoring and care — which only about half of adolescent and adult patients currently receive — allowing doctors to intervene before patients suffer irreversible cardiac damage. • Some lifesaving advances take decades to achieve. The second procedure that saved Stone's life evolved over more than half a century, the result of work by five surgeons from five different countries — Sweden, Canada, Brazil, Australia and the United States. •

"We waited 24 years for this surgery," says Stone's dad.

"Twenty-four years."

LEFT: BROOKE STONE

After her third heart surgery, she's finally "living to live."

## 'I WAS UPSET.

I mean, I was living a normal life. I was in college. I was fine. I could not understand why they wanted to take a perfectly fine person and do this.'

Because the heart is so complex, its defects are diverse, with more than 40 different types. Transposition of the great arteries alone has several variations, of which dextro- (or "complete") is just one. In dTGA, the two main arteries that come out of the heart — the pulmonary artery and aorta — are connected to the wrong chambers of the heart. As a result, blood fails to circulate properly: Instead of circulating from the heart to the lungs, where it gathers oxygen, back to the heart and then out to the rest of the body, it flows in two closed loops. In a heart with dTGA, blood from the lungs flows back to the lungs and blood from the body flows back to the body without ever getting the oxygen it needs.

"Transposition of the great arteries was almost 100 percent fatal before the late 1950s," says Frank Hanley, MD, director of the Children's Heart Center at Lucile Packard Children's Hospital and a professor of cardiothoracic surgery at Stanford. Hanley has been repairing the hearts of infants born with TGA for decades. But, over the years, repair for TGA has evolved dramatically. Patients like Stone, whose lives were saved by an earlier surgical method developed in the late '50s, may find themselves aging out of that childhood surgery and facing heart failure anew.

**S**TONE'S FIRST SURGERY — a Senning procedure, named after Åke Senning, the Swedish surgeon who developed it in 1957 — was the most trusted repair available for TGA at the time. It would be years before surgeons would become technologically advanced enough to reliably switch the misplaced arteries to their anatomically correct position. Instead, the Senning procedure was an "atrial switch," which opened a space in the wall between the heart's two upper chambers (the right and left atria) and redirected the blood flow using a baffle — a panel constructed out of heart tissue — to guide blood correctly through the transposed arteries and allow oxygenation. "Instead of righting the wrong," says Hanley, "they added these two wrongs to make a right."

Sitting with her in a bright café eating lunch, it's hard to imagine the radiant, healthy adult Brooke Stone as a 4-pound, 10-ounce newborn with skin tinted blue from her lack of oxygen. But for her parents, Barb and George Stone of Paso Robles, Calif., those memories are vivid.

Right after Brooke's first surgery at University of California-San Francisco, doctors told Barb that Brooke would not survive adolescence without additional surgery. So when Brooke was still a baby, Barb began decades of international detective work, calling hospitals and universities, searching for breakthroughs and doctors who could help her daughter. Each time, she was led back to one of the doctors who, as a young surgical fellow, had assisted in Brooke's first surgery: Frank Hanley.

By then, Hanley was practicing at Packard Children's heart center and developing his own lifesaving interventions for congenital heart disease. In the Adult Congenital Heart Program at Stanford, Hanley, a slender, silver-haired man who favors a tweed jacket over his scrubs when he's not in surgery, also treats many adults — some even in their sixth and seventh decade of life. Some patients have had a problem similar to Brooke's: a failing right ventricle resulting from an early-childhood Senning procedure — or from a similar atrial-switch named after the Canadian surgeon, William Mustard, who refined it in 1964.

The early Senning and Mustard repairs saved the lives of countless children who did well through their 20s, 30s and sometimes 40s before anyone realized there was a problem: The right ventricle, part of the heart muscle that normally pumps blood at low pressure to the lungs, was never designed to pump at the higher pressure needed to push blood through the whole body. After decades of bearing this burden, the right ventricle could eventually fail. Young adults like Brooke suddenly found themselves with an entirely new, life-threatening heart problem.

"Doctors had three choices for solving this problem," explains Hanley. "The first was to manage these patients with medications — not a complete cure. The second was heart transplant — an imperfect solution because of limited donors and the potential for organ rejection." The third, rarest, approach was potentially the most beneficial: undo the original repair and move the originally transposed arteries back to their correct positions.

Switching the arteries back to their correct positions was first successfully performed in newborns by Brazilian surgeon Adib Jatene, MD, in the late 1970s. It proved more challenging in adults.

In a normal heart, the left ventricle does the heavy lifting, pumping blood through the whole body. But for patients

with TGA who had the Senning or Mustard procedure as infants, the left ventricle becomes like a strong man who's been sitting on a couch his whole life, gently pumping blood at low pressure to the lungs. The left ventricle needs training to get back in shape to pump at a pressure strong enough to move blood through the whole body as it was designed to do. "The heart muscle is just like the muscles in your arms and legs," explains Hanley. "If you tell people who've never worked out to go to the gym and bench-press 200 pounds, they probably can't do it. But if you train them for a year, maybe they can. It's the same with the heart muscle."

In the late 1980s, Hanley was the first to follow Australian surgeon Roger Mee, MD, in training a patient's left ventricle by placing a band around the pulmonary artery. By tightening the band at intervals over the course of 12 to 18 months, the left ventricle would have to work harder to push blood through this smaller opening, increasing its ability to pump at higher pressure. The heart would then be ready to have its old Senning or Mustard repair undone and an arterial-switch performed to fully correct the heart.

"Like a lot of new things," says Hanley, "there was a flurry of interest and a whole bunch of cutting-edge institutions jumped on board to try it. A lot of those patients didn't do well, and many surgeons were discouraged by the bad results. So they abandoned it." But not Hanley. He looked closer. "The idea that everyone who needed the procedure could just be slam-dunked into the arterial switch was wrong," he says. "We focused on setting rigid criteria for accepting people into the program, and setting up a five-point report card after left-ventricle training to ensure that we were selecting appropriate patients who would have good outcomes."

Today, Hanley is the only U.S. surgeon still doing the procedure. His careful process, which involves lifelong monitoring and management by a cardiologist — and eventually by Hanley himself — as well as patient selection and rigorous evaluation, is key to his approach. Now, when he carries out these surgeries, the outcome is successful more than 90 percent of the time, proving that the procedure is a viable and even advantageous alternative to transplant.

*"My whole life I knew that I had to have something," says Brooke.*

*"There was always this inevitable something." Knowing does make it easier. Many patients with congenital heart disease mistakenly believe that if they're feeling fine, then their heart must be doing well. And if they believe they're doing well, then they don't visit the doctor.*

"You go on throughout your whole life feeling normal," says Brooke. "It almost felt like getting diagnosed with something new." But, as she discovered, the heart of a person with congenital heart disease may be weakening and experiencing potentially lethal, abnormal rhythms, known as arrhythmias, without any outward signs or symptoms. During the summer of 2012, when her arrhythmia was first discovered, she says, "I felt the best I've ever felt in my whole life."

Luckily, Brooke had been carefully monitored — a critical aspect of care for anyone with congenital heart disease. Each year, Barb made an appointment with the family's local cardiologist, John Owens, MD, for a complete study of Brooke's heart function. As the years passed, and Brooke felt healthy and more independent, it became ever harder to justify annual checkups.

"I was upset," says Brooke. "I mean, I was living a normal life. I was in college. I was fine. I could not understand why they wanted to take a perfectly fine person and do this."

The desire to lead a "normal" life can be a slippery slope. "For Brooke's sake," says Barb, "we always treated her as a normal child. She couldn't go to the mountains and she couldn't do sports, and she couldn't do a lot of things. But nobody knew, unless they looked at her scar and asked. I thought it was important for her to be treated normally by all of her peers. We began to think that way, too, because that's what happens. And then when a doctor says, 'We've got to go in,' you think: You've got to be kidding. Look at her!"

Yet, Brooke's parents knew monitoring was vital to her survival. Each year, in addition to the necessary echocardiograms, catheterizations and MRIs, her cardiologist sent her home with a 24-hour monitoring device that would record Brooke's heart activity as she went about her day.

"It was the fanny pack," says Brooke's father, referring to the belt-case that held the 24-hour Holter monitor. "The fanny pack gave it away." The monitor recorded the life-threatening heart rhythms that were going on as Brooke slept.

So it is with many congenital heart disease patients: Catching the failing heart with monitoring is the often-ignored solution to early intervention and survival. "Catching it at the right time saved my life," says Brooke.

In Brooke's case — and with similar patients managed by Hanley — a carefully monitored left-ventricular outflow-track obstruction had narrowed the space in her pulmonary artery and increased pressure from the inside, just as Hanley's band-tightening procedure would have done from the outside. The result was that Brooke's left ventricle was already strong enough to pump blood to the body, making Brooke — and patients like

C O N T I N U E S O N P A G E 4 8

## DEAR DR. SHUMWAY

## A BOY, TWO FROGS AND AN AIRMAIL LETTER

T

he envelope was addressed in pencil, postmarked March 25, 1968, with 2 cents postage due, and was simply addressed: “Dr. Norman Shumway, Stanford, California.” For 45 years, it lay in the archives of Stanford medical center’s communications office, one document among thousands that intern Jerome Macalma was charged with scanning in the summer of 2013. • The enclosed letter got right to the point: “Dear Dr. Shumway, I am 11 years old and I admire your work.” Two months earlier, Shumway and his team had performed the first successful human heart transplant in the United States, and the pioneering surgeons were celebrated worldwide. • The 11-year-old went on to say that he “and his 18-man surgical team” were planning to perform a transplant six weeks hence, and he would be most grateful if Dr. Shumway would impart a bit of advice. The letter was signed, “Robert J. A. Wise, 1st Surgeon.” Below his John Hancock-sized signature were the signatures of the “2nd, 3rd and 4th” surgeons on his team. • These many years later, those of us in the office who read the letter were instantly charmed. Here was a kid who’d clearly been served a couple extra helpings of chutzpah, and we were dying to discover where his audacity had taken him. We had to track him down. • So Macalma turned to Facebook: Using the names of the four “surgeons,” he zeroed in on the correct Robert Wise. We were ecstatic. We emailed him the letter, and asked if he’d be willing to talk with us. He was. In fact, he said he “was flabbergasted to discover that anyone actually had a record of the letter.” • We called the following afternoon. “Of course, I remember writing the letter!” he laughed. “I haven’t opened the attachment yet, but I’ll do it right now.” Enthralled, we listened as he worked his way through the letter, and the 56-year-old fondly re-connected with his 11-year-old self. His memories poured out, and our mystery began to dissolve away. • His interest in medicine went back to age 4 when his grandparents lived with his family. Their poor health required frequent vis-

By **M.A. Malone**

its from the family physician. He was a gentle, patient man and Wise was his shadow, “rounding” with him as he did his exams.

For this youngster from Middle Village, N.Y., medicine was mother’s milk. While most kids opened a newspaper to find the funnies and check the box scores, Wise scoured the papers for medically related articles. Instead of a tree house or fort, he built a lab in a corner of his basement where he did his chemistry experiments, surrounded by animal specimens in jars, and Frank Netter anatomical drawings on the walls. He devoured medical books and journals, but had little taste for schoolbooks and homework. His obsession with medicine was legendary. “I was something of a kooky celebrity at school,” he remembered with pride.

At age 16, he began volunteering in the emergency department at LaGuardia Hospital in Queens, N.Y. He developed X-rays, set up suture trays, took vitals and tagged along with the doctors. “That was my wheelhouse,” he said. “That’s exactly where I wanted to be.” He practically lived there during the summer, working 16 to 18 hours at a stretch. By age 18, he was certified as an emergency medical technician. He worked his way through college and medical school, and eventually became a — what else — physician in emergency medicine, with a clinical interest in cardiovascular emergencies.

So, now we knew that this letter to Shumway wasn’t just an 11-year-old’s slice of pie in the sky — Wise really had become a bona fide doctor. But we still wanted to hear about that transplant, and we wondered if Shumway had ever written back. Unfortunately, he hadn’t. But Wise had also sent letters to Christiaan Barnard, MD, and Adrian Kantrowitz, MD, two other transplant pioneers. Within a week, he received a long, encouraging letter from Kantrowitz. “I remember standing in the living room in complete disbelief

that someone had actually responded!”

As for that scheduled transplant, word travelled fast in the ‘hood, and it was quickly SRO in the operating theater, a.k.a., the Wises’ garage. The two patients were prepped and positioned on the table. The scalpels, hemostats and sutures were at the ready. They’d been donated by “2nd Surgeon” T. Bower, MD, the father of one of Wise’s friends, and an ardent supporter of his medical zeal. He also donated a bottle of ethyl chloride, which they used in combination with hypothermia to anesthetize the patients. “We filled a Planters Peanuts can with the ethyl chloride,” Wise explained, then put the patients — two backyard bullfrogs — “into the can and shut the lid to induce anesthesia, after which the frogs were kept on ice-filled trays.”

Plastic insulation from fine-gauge copper wiring was used to connect the frogs’ circulatory systems. They split the insulation, removed the wire, then sterilized it in alcohol. “We laid the vessels next to each other, then slipped them into the insulators and tied them off with sutures.” Using blue and red, they color-coded them to the arterial and venous connections. Gloved and gowned, the team of five worked its way through the procedure. “It wasn’t so much a heart transplant,” Wise recalled. “It was more like a heart-swap.”

Without a doubt, this is a story with a happy ending. The airmail letter launched a mystery that turned into a terrific tale; the boy really did grow up to be a doctor. And the two frogs? They made their mark in the annals of neighborhood history, but, alas, they croaked on the table. **SM**

Robert J. Wise  
80-16 Conley Ct  
Middle Village,  
New York  
Feb. 24, 1968

Dr. Norman Shumway  
Palo Alto, California

Dear Dr. Shumway,

I am 11 years old and I admire your work as a matter of fact I plan to become a doctor myself. On April 6, 1968 an 18 man surgical team including 2 M.D.s a Hospital head nurse and myself plan to perform a heart transplant on a minor scale, Frogs to be exact. This will not be the only operation we will do we plan many operations over the summer months. The reason I write is to ask you if you have some advice for me, if you do I should like very much to have it.

over

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**SO NOW WE KNEW THAT THIS LETTER  
to Shumway wasn't just an 11-year-old's slice of pie in the sky — Wise really had  
become a bona fide doctor.**

# THE HEART GADGETEERS

HERE THEY COME

S

upposing Stanford were to name a chief heart gadgeteer, it might be Michael McConnell, MD, a cardiologist with degrees from MIT in electrical engineering and bioengineering. McConnell, tall and fit with laser-blue eyes, isn't wearing a physician's white coat on the day he escorts two young Silicon Valley fitness app developers out of his office. Dressed in black from head to foot, he is among a new breed of physician-engineers, fluent in both medicine and technology. • This year, in addition to caring for heart patients, McConnell is trying to figure out how to integrate a new wave of heart- and fitness-monitoring devices into the medical system. • Traditional heart-monitoring equipment lives in hospitals. The equipment is utilitarian, safe and ugly, hooked up to wires, electrodes and monitors. A new generation of portable heart gadgets has the potential to leapfrog these old approaches. Looking more like fashion accessories than medical equipment, these gadgets leverage advances in smartphones, sensors and digital video, and, in many cases, perform their functions better and faster than the old equipment — for a fraction of the price. • Yet the medical establishment isn't quite ready for them. So the heart gadgeteers are working overtime to address the regulatory hurdles, funding issues and institutional inertia keeping these devices out of mainstream medical use.

## THE INTEGRATOR

"I knew I wanted to study the heart before I knew I wanted to go to medical school," says McConnell. "It represents the best of engineering — fluids, electrical and mechanical — all in one organ."

In his roles as director of cardiovascular health innovation and co-director of the preventive cardiology clinic, he tries to figure out how to get more of his heart patients to use wearable fitness devices, to encourage them to exercise more and eat right.

"Eighty percent of heart disease, particularly coronary artery disease, is preventable through diet and exercise," he says.

By **Kris Newby**

ILLUSTRATION BY LINCOLN AGNEW

“The problem is that the current system only reimburses physicians *after* someone has heart problems.”

Today the U.S. health-care system largely operates on a fee-per-service model, in which health-care providers receive payments for each service, test or procedure performed. This structure encourages physicians to order more tests and treatments than may be necessary because there is no penalty, only additional profit, in adding extra charges. Government-run, single-payer health programs, on the other hand, compensate physicians with fixed annual salaries and all-in-one fees based on a patient’s health problem. This financially motivates providers to order services more wisely, coordinate care between specialists and look for ways to prevent expensive health problems down the road.

The U.S. structure is slowly evolving for the better with changes launched under the 2010 Patient Protection and Affordable Care Act. The new law offers carrots and sticks to motivate health-care providers to become more efficient, less fragmented and more accountable. There are incentives for cost reductions, disease prevention and quality improvement, including bonuses for hospitals that show improved outcomes for heart failure, pneumonia and surgery. And there are billions in government grants for funding comparative-effectiveness research, studies that identify which treatment options are the most effective for any given condition.

McConnell is using these and private funds to gather evidence on the effectiveness of these new devices.

“We want to prevent patients from having heart attacks by making them more cognizant of the effects of diet and exercise on their heart.”

As a start, McConnell and his colleagues are pilot testing a number of off-the-shelf, wearable fitness monitors — Nike, Fitbit, Jawbone and Lark, to name a few.

He’s already witnessed dramatic results when patients with strong personal motivations to improve their health are given tools to help them reach their goals. For example, when one of his patients with worsening diabetes was given

parenting responsibility for a grandchild, he started using a pedometer to track his progress in trying to walk at least 10,000 steps a day.

“The patient’s weight, blood sugar and blood pressure all came down, and he was able to go off medications,” said McConnell. “A dramatic result to be sure, but regular physical activity is a critical factor for health and longevity.”

McConnell and his cardiology colleagues are also in the planning stages of integrating data feeds from consumer health tools and prescription heart devices into a unified, heart-health web-based dashboard. The first phase of this initiative will focus on patients who’ve had heart attacks, allowing them and their physicians to track recovery, activity, diet and medication adherence through smartphone-based tools

and a website that links patient and physician. (Recent studies show that heart patients are bad at taking their prescribed pills: After hospitalization for a serious cardiac event, one in three patients stop taking at least one of their heart-related medications after a month, according to Michael Ho, MD, at the Denver VA Medical Center.)

In addition to helping heart attack patients, Stanford Hospital and Stanford University are giving employees at risk of developing diabetes tools to encourage them to exercise more and eat healthier foods. Using an online program created by Omada Health, these patients get coaching and social support as well as wearable fitness moni-

tors and scales with wireless Internet connections that help them track diet, weight and exercise goals.

The hospital also has hired a former Jawbone information technology expert to link this data from wearable devices and mobile apps into the patients’ electronic medical records.

Some insurers are following suit. Aetna, one of the largest health insurance providers in the United States, recently launched CarePass, a program that offers customers a free iPhone app and access to a website that integrates patient medical records with data from fitness-monitoring devices from Fitbit, Jawbone and Withings. United Health Care has a similar program, called OptimizeMe. While these insurers



don't pay for the wearable devices, Fitbit and Jawbone offer volume discounts to corporations.

#### THE INNOVATOR

When a medical gadget crosses the line from personal health monitoring to diagnosing medical conditions in the United States, it must be approved by the Food and Drug Administration and can be prescribed only by physicians. For heart devices, the additional time and expenses required for clinical testing, regulatory approval processes, insurance reimbursement approvals and physician acceptance can significantly slow the movement of newer, better technologies into the medical system.

One expert on these processes is Uday Kumar, MD, an entrepreneur-in-residence in the San Francisco office of Third Rock Ventures. Kumar, a cardiac electrophysiologist by training, typically dresses in the de facto uniform of Silicon Valley entrepreneurs: open-collared shirts and jeans. He has founded or co-founded four medical and information technology companies and is a consulting associate professor of bioengineering and the fellowship director of Stanford's Global Biodesign Program, which trains technology innovators to address medical needs in developing regions.

In 2006, while a Stanford Biodesign fellow himself, Kumar co-invented a radically improved heart device, the Zio Patch, a translucent, silver, wearable sensor that detects intermittent, irregular heartbeats, called arrhythmias. This device and information service, marketed through iRhythm Technologies Inc., which Kumar founded, is a good case study on the difficulties startups face in getting their inventions into the hands of physicians. (Disclosure: Stanford University has financial ties to this company.)

The old standard for detecting arrhythmias, designed 60 years ago, is the Holter monitor, a boxy device worn around the neck or on a belt, with electrode wires that have to be positioned in multiple locations across the chest. Unlike the Zio Patch, the Holter device typically records only a day or two of heartbeats. It is uncomfortable to sleep in and it can't get wet.

Zio Patch users, on the other hand, adhere a 2-by-5-inch sensor on the chest over the heart, where it continuously records all heart activity for up to 14 days. Users tap a button on the device to flag when they feel symptoms, so that the specific heartbeat activity at that time is highlighted on the physician's report. After the monitoring period, patients mail the patch back to iRhythm's data center. The heart data is analyzed and a report is prepared for electronic review by a physician.

Evidence says that patients who use the Zio Patch find it

easier to wear over long periods of time, so it is more likely to record an arrhythmia and lead to an early, lifesaving intervention, such as a pacemaker. It can be prescribed by primary care physicians, so it could save on the cost of referrals to specialists. And it speeds the time to diagnosis and treatment, potentially reducing the expenses of hospitalization and surgery. These results were published in a study led by prominent Scripps Health cardiologist Eric Topol, MD, published online Jan. 3, 2013, in the *American Journal of Medicine*.

Despite the fact that the Zio Patch was cleared by the FDA in 2009, and patients and physicians prefer it to the Holter monitor, adoption has hit some snags because not all regional Medicare and Medicaid programs reimburse it fully. This affects people with private insurance as well, as many private insurers are slow to reimburse for a new device unless it's also fully covered by Medicare.

**G**ETTING ON THESE REIMBURSEMENT lists and being compensated fairly for creating paradigm-busting devices is difficult. Rather than having free-market, supply-and-demand forces determine the retail price of new devices, prices are set annually by a committee from the Centers for Medicare and Medicaid Services. The quickest route for a device to get on the government list is to be assigned an established reimbursement code used by older devices, and sometimes the company can apply for a new technology "add-on" reimbursement that will help cover the additional value and cost of the new device. Or a company can apply for a temporary code for the initial deployment of the device or service.

Either way the manufacturer must gather further evidence to prove that its device or service provides additional features and benefits. But, often by the time this evidence is gathered, the submission windows have closed and the manufacturer has to wait another year to go before the coding and price-setting review committees. In the meantime, insurance claims are denied because of "insufficient evidence of clinical improvement."

Herein lies a Catch-22 of launching new heart gadgets: Care providers rarely prescribe devices that aren't on the reimbursement lists, and cash-strapped startups often have trouble financing the large, evidence-gathering studies required to gain acceptance by the FDA, insurers and physicians. Because of this, the mortality rate of new device companies is high.

"Between the requirements of FDA regulation and reimbursement, the U.S. seems to be doing its best to starve the innovation ecosystem in medtech," says Paul Yock, MD, director of the Stanford Biodesign Program. "We are being as



### FOLLOW YOUR HEART

**Uday Kumar co-invented the Zio Patch to improve detection of irregular heartbeat rhythms.**

adaptive as we can in this new environment, but we are facing the most challenging set of conditions we have experienced for many decades.”

Despite this, Kumar is hopeful: “If the problem being addressed is important and the idea truly has merit and is beneficial to patients, providers and the health-care systems as a whole, companies can make it through, even though it may be slow going at first and require a company to raise significant capital to get through this.”

### THE PERSUADER

Marie Guion-Johnson, CEO of AUM Cardiovascular, is on the money trail. She needs to raise a second round of capital by the end of the year to finish the clinical trials required to get her new heart device through the FDA-approval process.

This device, called the CADence, detects blocked arteries from the surface of the chest. The device, a sleek, palm-sized unit that looks a bit like an air hockey paddle, is placed at several locations on a person’s chest, where it digitally records signals of blood flowing through arteries. Proprietary software identifies the noisy signals of blood turbulence associated with arterial blockages, then generates a report to help physicians with diagnosis and treatment plans.

Guion-Johnson, a bioengineering PhD, adjunct professor of biomedical engineering at the University of Minnesota and former Stanford Biodesign fellow, founded her company in 2009 for personal reasons — she wanted to create a heart device that could’ve saved her first husband’s life. At age 41, he died unexpectedly of a blockage in the left anterior descending coronary artery, nicknamed “the widow maker” for its frequent involvement in sudden cardiac deaths.

Her early research into using acoustics for detecting coronary artery disease took her all over the world during a stressful time of her life.

“In 2004 I moved to Turin, Italy, to study coronary hemo-

dynamics with a professor at the Politecnico di Torino,” says Guion-Johnson. “The people around me thought I had lost my mind. I didn’t know Italian, my son was 2 years old and my daughter was a first grader. I was a single mom without a clothes dryer or a car in a foreign country. At the time I thought I’d never make it but here I am.”

Because no similar devices exist to detect obstructive artery disease the FDA considers the CADence novel, and this makes its road to approval for use and insurance reimbursement more complex, time-consuming and expensive.

After FDA approval, she says her next big hurdle will be physician acceptance. And she believes that one of the quickest ways to get doctors to try a new class of device is to gather safety and efficacy data in a clinical trial, then have her participating cardiologists publish the results in high-profile medical journals. A trial is under way.

“You can see the obvious benefits [of CADence],” says Robert Wilson, MD, a cardiology professor at the University of Minnesota and the former chair of the CADence clinical trial. “There is absolutely no risk, and the cost is substantially less than a heart stress test, both to the health-care system and to the patient.”

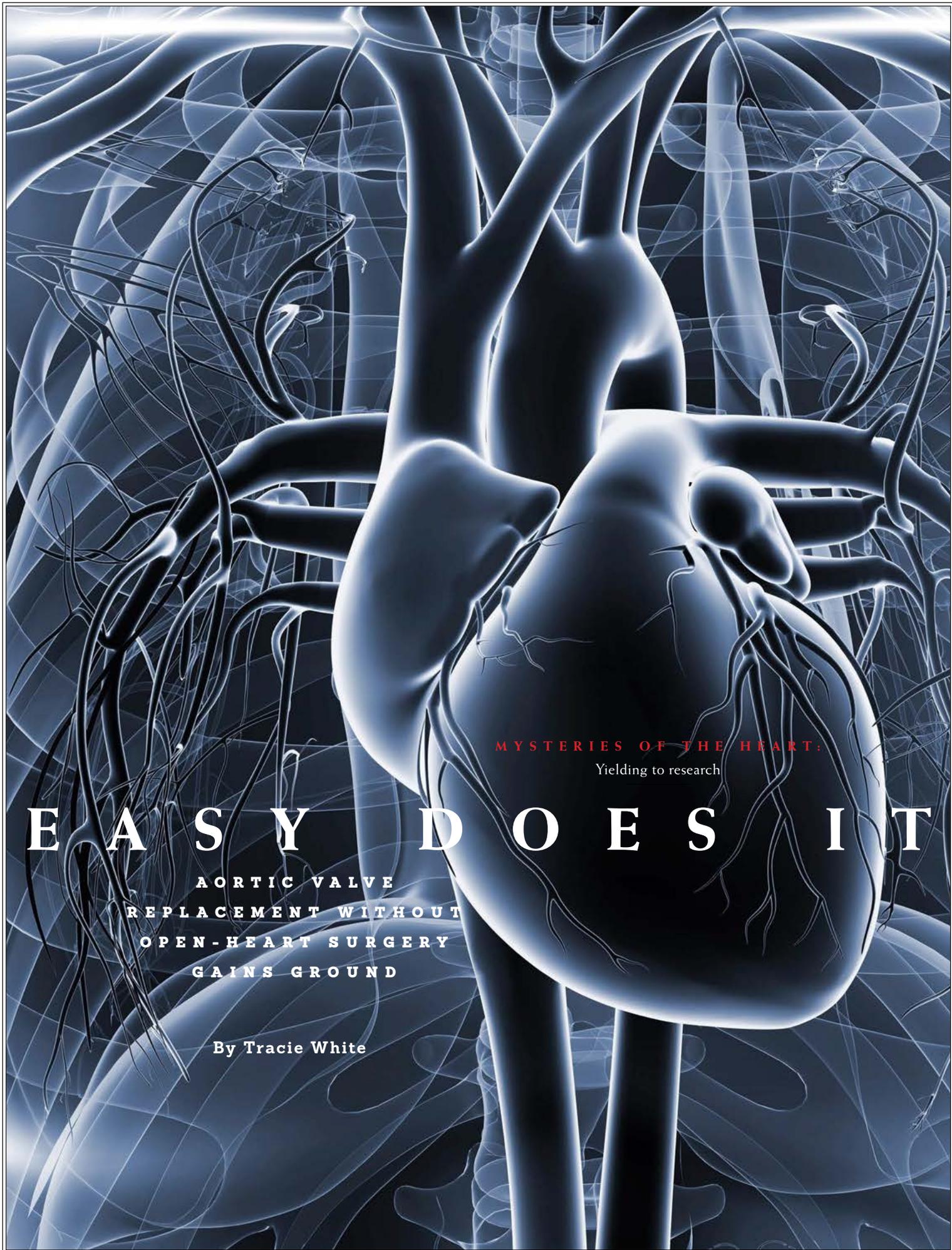
Sometime during the fourth quarter of this year, the company will analyze the results of the CADence FDA “pivotal clinical trial,” which is being run at 13 research institutions, including the Mayo Clinic, University of Minnesota and UCLA Medical Center. Guion-Johnson is hoping that these results will show that her device, which is expected to cost around \$120 a test, will reduce the need for expensive nuclear heart tests, where patients are injected with radioactive tracer and their heart is photographed with special cameras. A nuclear stress test can cost \$900 or more.

C O N T I N U E S O N P A G E 4 8



### LISTENING IN

**Marie Guion-Johnson created the CADence to identify blocked arteries inexpensively and without risk to patients.**



MYSTERIES OF THE HEART:  
Yielding to research

# EASY DOES IT

AORTIC VALVE  
REPLACEMENT WITHOUT  
OPEN-HEART SURGERY  
GAINS GROUND

By Tracie White

When Maryann Casey  
battled breast cancer  
more than  
30 years ago,  
her doctors warned  
that the radiation  
therapy  
could damage her heart.  
Still, she was  
caught off guard when,  
after an  
echocardiogram  
in 2012, she  
**was diagnosed  
with severe  
aortic stenosis,  
a potentially  
fatal heart-valve  
disease.**

“They were telling me I could drop dead,” says Casey, 62, who lives in San Jose with her husband and 20-year-old daughter. Her local doctors said the key valve that carries blood out of the heart into the aorta had severely narrowed, obstructing blood flow and dangerously stressing her heart. “They said, you need to have open-heart surgery immediately.” It felt like lightning had struck twice, she says.

Despite that frightening warning Casey, who retired after 24 years as a security manager in Silicon Valley, soon learned that open-heart surgery wasn’t her only option. After the shock of receiving her second diagnosis of a potentially fatal disease, she quickly made an appointment with her oncologist, the same Stanford physician who she credits with saving her life and who continues to give her yearly physical examinations and mammograms.

“I was told by my oncologist I would probably never heal correctly after open-heart surgery,” Casey says. “He knew about this new treatment at Stan-

ford and recommended I go talk to the heart doctors there.”

Casey was lucky. Her Stanford oncologist, Frank Stockdale, MD, PhD, the Maureen Lyles D’Amrogio Professor of Medicine Emeritus, was well-informed about treatment options for aortic stenosis, a calcification of the heart valve. This new nonsurgical approach to valve replacement involves placing an artificial heart valve, made of cow tissue supported by a stainless steel mesh frame, inside the damaged valve. Referred to as “transcatheter aortic valve replacement” or TAVR, the procedure is designed for patients with severe, symptomatic aortic stenosis who have health conditions that make the preferred treatment, open-heart surgery, very high risk.

“The odds were that she would not heal well,” says Stockdale. Casey’s fast-growing, inflammatory form of breast cancer had required especially high doses of radiation, which he suspected caused additional long-term damage to the skin and muscles of her chest and to the heart muscle.

**A**BOUT 300,000 AMERICAN PATIENTS suffer from deterioration of the valve, which forces the heart to work harder to pump blood, often leading to heart failure and sudden death. Each year, about 50,000 of these patients undergo open-heart surgery to replace the valve, which involves cutting through the breastbone, stopping the heart, removing the old valve and sewing a new one into place. Thousands of other patients are turned away, deemed too old or ill to survive the operation, or because they have so many other serious medical problems.

Enter TAVR, a procedure that many in the field refer to as a game changer. In the first year after FDA approval in late 2011, about 7,000 U.S. patients

with severe aortic stenosis were treated with transcatheter valve replacement. Doctors are grateful for this new alternative, but they warn that the obvious appeal of a less invasive procedure should not be the overriding factor in choosing a treatment plan for severe aortic stenosis.

“This has been an incredible advance for patients who wouldn’t have had options in the past,” says Stanford heart surgeon Michael Fischbein, MD, PhD, assistant professor and residency program director in cardiothoracic surgery. “But this device isn’t for everyone. It’s important to consider the risks and benefits in each individual patient. There are downsides.”

TAVR has emerged from the trend over the past three decades toward less invasive heart treatments — catheter-based procedures instead of open-chest surgery. The artificial tissue valve is a feat of engineering able to fold up into a fraction of its functional size. To get it inside the heart, it’s compressed and placed in the tip of a thin catheter, about as wide as a pen. This gets inserted into a blood vessel, usually an artery in the leg, then threaded up through the aorta and down into the heart. At the site of the diseased valve, the artificial valve is released from the delivery catheter and expanded with a balloon. This pushes open the damaged valve and lodges the bioprosthetic one within its cavity where it immediately starts opening and closing, allowing blood to leave the heart and preventing it from leaking back in.

The U.S. Food and Drug Administration first approved a TAVR valve in 2011, allowing it to be used for patients who were deemed too sick to be candidates for open-heart surgery. In 2012, the FDA added an approval for TAVR for patients who, like Casey, are considered at high risk of complications or

death from open-heart surgery. Both approvals were based on the results from the PARTNER 1 clinical trial, which was sponsored by the company that makes these bioprosthetic heart valves, Edwards Lifesciences Corp., based in Irvine, Calif. In the fall of 2015, the results of the PARTNER 2 clinical trial are due out, and they could once again move that line. This new randomized trial is testing the use of the minimally invasive technique in patients with severe stenosis at moderate risk for open-heart surgical aortic valve replacement.

Until this year, the Sapien valve produced by Edwards Lifesciences had been the only transcatheter aortic valve with FDA approval. Each of these valves costs about \$33,000, but with competition the price is expected to drop. In January the FDA granted approval to a second device for use in extreme-risk patients — Medtronic's CoreValve system — and other companies are expected to jump in within the next few years with their own valves.

#### THE DECISION

Casey is far from the average TAVR patient. She's much younger and healthier. Most patients are in their 80s or older. Typical TAVR candidates are much more weakened by the valve narrowing, which impedes the delivery of blood to the body and stresses the heart. Casey hadn't even yet realized that the swelling in her ankles and the "fuzziness" or light-headed feeling she experienced were results of her weakened heart. She was still exercising regularly on a treadmill right up until her diagnosis, when her doctors told her it was too dangerous to continue.

At the recommendation of her much-loved oncologist Stockdale, she went to the Stanford Transcatheter Heart Valve Clinic where she was seen

by William Fearon, MD, associate professor of medicine and director of interventional cardiology, and by Fischbein. Her doctors categorized Casey as high risk for open-heart surgery because of the radiation therapy she underwent in her 30s. The radiation, which probably caused the damage to her heart valve, also impaired the ability of the muscles and skin of her chest to heal. Unlike open-heart surgery, TAVR would not require a sternotomy, an incision in the center of the chest, which meant an easier recovery. And because the heart continues to beat throughout the procedure, no heart-lung machine would be required.

"I was scared about the skin healing, having my chest broken open, the lengthy recovery," Casey says. "My doctors showed me the valve. I took a picture of it. I thought this might be a better way to go."

Stanford Hospital is one of only a handful of hospitals in Northern California to offer the transcatheter procedure; the team here has performed more than 300 since October 2008 as part of clinical trials and now under commercial use guidelines. Each new patient with aortic stenosis who comes to Stanford and is a potential candidate for TAVR, like Casey, undergoes consultations with both a cardiologist and a cardiac surgeon as part of a team approach to determine which treatment is best — TAVR, surgical aortic valve replacement, which would require open surgery or, in certain cases, medications alone. This team approach is not new to the world of heart disease management, but it has been forgotten for decades, heart doctors say. Treatments such as inserting stents through catheters are done by the cardiologists and open operations are performed by cardiovascular surgeons. Usually the two specialties operate in separate worlds.

Typically the heart team would recommend open-heart surgery for patients with aortic stenosis who, like Casey, are in their 60s.

"Most of the patients we treat are in their 80s or 90s," says Fearon. "But occasionally we treat younger patients, like Maryann, because they have a condition that makes traditional aortic valve replacement surgery too risky."

Weighing the pros and cons between the two procedures for each individual patient is essential, the physicians say. According to the PARTNER 1 trial, the risk of stroke is higher with the TAVR procedure, as is vascular bleeding at the site of catheterization. Recovery time is clearly shorter after TAVR, but the valve's longevity remains an important unknown.

The two types of valves used for open-heart surgery have known life spans. Mechanical valves are expected to last the life of the patient. Valves made of animal tissue are estimated to last 10 to 15 years or more if the patient is over 80. Currently there are only preliminary data showing that TAVR valves may last at least five years, without any signs of early degeneration. This adds to the risk, particularly for younger patients, that another replacement valve will be needed.

"We decide which is the right valve for each patient based on the research we have so far," says Fischbein, who, along with Fearon and D. Craig Miller, MD, the Doelger Professor of Cardiovascular Surgery, and Alan Yeung, MD, the Li Ka Shing Professor of Medicine and chief of cardiovascular medicine, has been involved with the clinical trials used to test TAVR.

"This is another option, an incredible option, for those too high-risk for surgery," Fischbein says. "Now this opens the door for them."

CONTINUES ON PAGE 49

The medical world has begun quarrying its new natural resource: big data.

**Produced over the past decades, stored in rapidly multiplying and expanding databases,**

this information consists of great agglomerations of digital medical records, DNA sequences from clinical trial participants, disease registry entries, gene activation patterns during sickness and health, and more.

• "Large data sets well beyond what people can analyze on their own are being generated in just about every field of biology," says Mark Guyer, PhD, deputy director of the National Human Genome Research Institute. • Guyer says the future of biomedical research depends on large-scale data analysis. The federal government gave the data mining field a boost when it launched the Big Data Initiative in 2012, committing more than \$200 million to mine data and develop tools to analyze it. • Stanford is encouraging progress by hosting the Big Data in Bio-Medicine Conference with Oxford University. This year it takes place at Stanford May 21-23.

For a look at what some of the world's most innovative medical data miners have been up to, read on.

# DIGGING DOWN

**BIG DATA'S  
BOON  
TO  
MEDICINE**

**G R E A T**

**M E D I C A L**

**M I N E S**

**THE HEALING  
POWER  
OF PATIENT RECORDS**

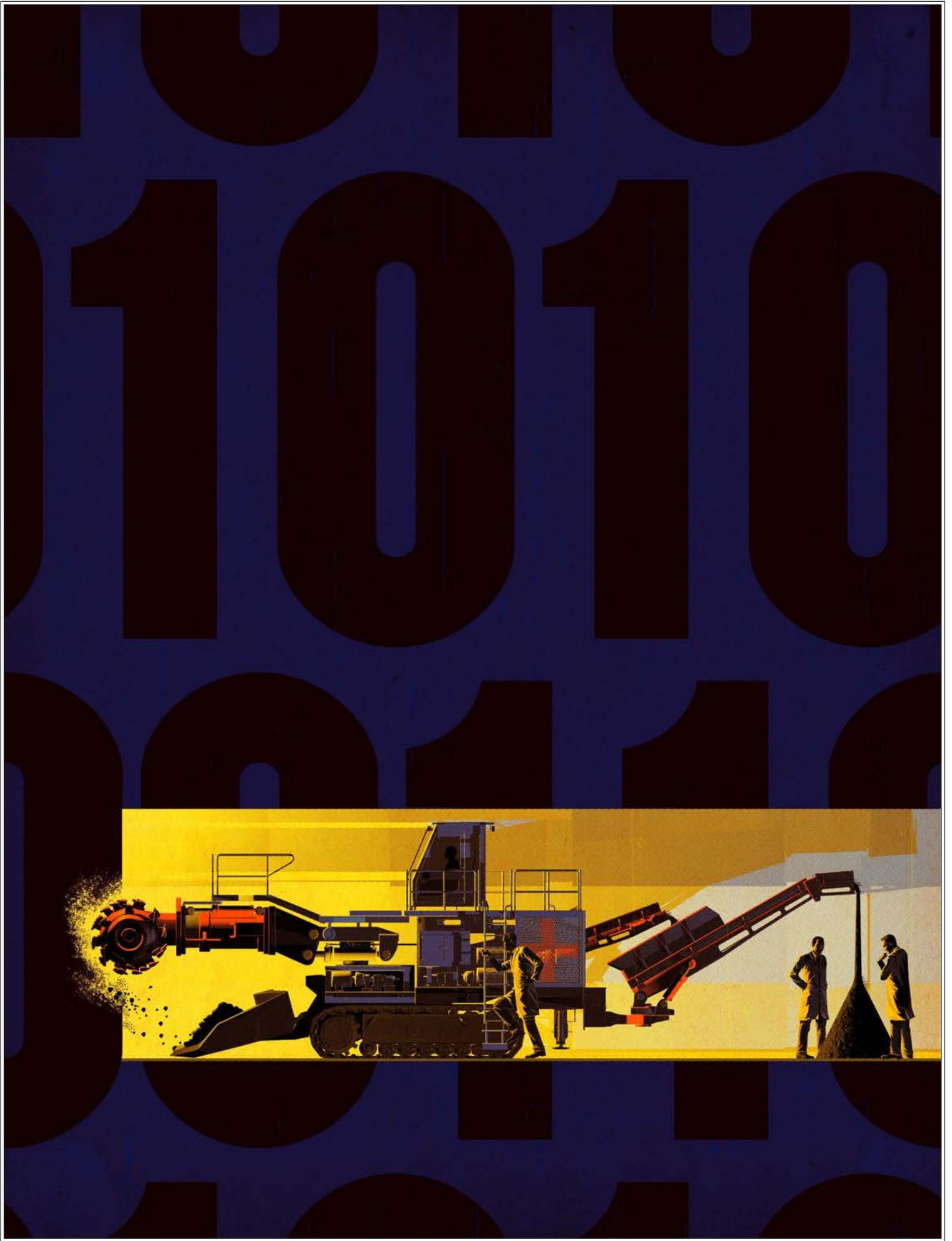
Nigam Shah has never peered into a child's eyes, watching for the dusty haze of chronic inflammation that — if found too late — can lead to blindness.

**But by designing computer programs that sift through millions of electronic health records, Shah, MBBS, PhD, has helped pediatricians save youngsters' sight.**

Children with the most common form of arthritis, juvenile idiopathic arthritis, not only have inflamed joints, but up to 30 percent of them also get eye inflammation, or uveitis. Uveitis doesn't always cause symptoms — and kids don't always tell anyone if they do — so these young patients need to be checked by an ophthalmologist every three to six months. Yet even with reminders, busy

**By Elizabeth Devitt**

ILLUSTRATION BY TAVIS COBURN



schedules can crowd out follow-up appointments and doctors may miss their chance to treat the earlier stages of uveitis.

So Shah, an assistant professor of medicine, and his team at Stanford's Center for Biomedical Informatics Research joined forces with rheumatologist Jennifer Frankovich, MD, a clinical assistant professor of pediatrics at Stanford, to take a closer look at a group of young arthritis patients to search for risk factors that might provide early warning cues. They applied automated methods and a customized algorithm to search 1.2 million electronic health records specifically prepared for research use at Stanford. Through this effort, they discovered that if some of these children also had allergies, their odds of developing uveitis were two-and-a-half times higher than those of other youngsters with this condition. This new information may help medical teams identify which patients are in critical need of keeping up with their eye exams.

A growing cadre of database miners are creating algorithms to wrest more knowledge from data piling up in virtual warehouses — gene sequences, protein structures, archived medical images and electronic medical records, to name some of the types of information they're digging through. Sorting through this biomedical "big data" has become a specialty practice in its own right, with consulting companies vying to analyze medical information for the benefit of industry or — as is the case with a company launched by Shah — patients. The results of this type of research are changing the way doctors and hospitals deliver medical care.

"People are beginning to realize data mining is more than just genomics," says Shah. "And when people hear that data mining can keep a kid from going blind, they want to know more."

#### **A NEW APPROACH TO RESEARCH**

Nowadays, the recommended practice for doctors is to base treatment decisions on the results of clinical trials; software like the popular UpToDate decision aid has made that information easily accessible online (for a fee). Shah's long-term vision has doctors tapping into biomedical big data for information to guide their treatment decisions just as easily.

With the right algorithm, says Shah's colleague and collaborator Russ Altman, MD, PhD, professor of bioengineer-

ing, of genetics and of medicine, sifting through electronic health records can become a learning system for one doctor, a group of doctors in one clinical practice, an entire hospital, a network of hospitals or a nationwide health-care system. "There are two big buckets of applications for data mining," says Shah. "Those that drive the practice of medicine and those that drive science." The answers that can be teased out of the data depend on the question you ask.



As to the practice of medicine, he envisions a world in which care is customized to individual patients. Shah and two partners recently founded a company called Kyron to provide a search engine for physicians looking for clinical evidence in real time — to explore the best medical-care options for the person in their exam room right at that moment.

"Instead of pulling up a paper that provides a summary of someone else's research, doctors will be able to ask questions based on their own patient," Shah says. For example, if a physician sees a patient with a history of heart attacks and seizures, a computer algorithm could search millions of records to find people of the same age and ethnicity, and with similar conditions, to determine whether a new prescription would conflict with the anti-seizure medication or worsen the underlying heart disease. The customized answer could include how many patients were found with similar medical issues, how strongly their query was associated with those other patients, and — most important — whether the associations between the questions and answers would make any difference in the health of the patient. Right now, Shah says, creating those computer programs is a brute force enterprise: "It's like the early days of the Web at Yahoo where someone was manually categorizing Web pages."

With the help of Louis Monier, the former chief technical officer of the Internet search engine AltaVista, and Noah Zimmerman, PhD, a Stanford biomedical informatics alum, Shah hopes Kyron can offer doctors a new way to practice medicine before the end of 2014. If the company is suc-

cessful, analyzing medical records from routine care to generate medical insights could become as simple as a Web search.

In research, letting computers do the legwork can save major amounts of time and money. Traditionally it takes about seven years from the time a researcher applies for a National Institutes of Health grant to the publication of study results. But with access to huge databases, studies can be done in weeks — at far less cost. For instance, when the Ohio-based MetroHealth health-care provider joined forces with a health-care analytics company, it spent only three months and about \$25,000 to get the same results as a multimillion-dollar Norwegian study that took 13 years to follow 26,714 people and discover that men were at an increased risk of blood clots if they were tall and obese.

The learning-based system also affords researchers an opportunity to uncover “natural experiments,” says Shah. These are experiments that can’t easily be done because it would be hard to recruit a group of people with a specific list of treatments or medical procedures. For example, Shah and his colleagues used EHRs to investigate cilostazol, a drug prescribed for people who suffer from blood vessel blockage in their legs. Although the label states the drug shouldn’t be used in patients with congestive heart failure, some clinicians still feel that their patients would benefit from it. By mining the EHRs in Stanford’s database, they were able to show that using cilostazol caused no additional deaths in these high-risk patients.

“You can’t do a randomized clinical trial for everything,” says Shah, referring to the gold standard of medical knowledge: dividing patients with similar traits and treatment needs into groups, then testing the treatment options against a placebo, without anyone knowing which treatment they received. Although he’s quick to point out that data mining isn’t meant to replace clinical trials, Shah notes the computer “trials” may represent “real” patients better than the trials that enroll people who meet very specific criteria.

Altman usually spends his research time studying pharmacogenomics, harnessing the speed of computers to search da-

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INFORMATION?’**

tabases for tiny variations among people’s genes that can be linked to responses to drugs. “But mining electronic medical records is a natural outgrowth of that work,” he says. “What better way to find these different drug effects than to utilize EHRs which have much more diverse sources of information?”

At Stanford, researchers benefit from access to STRIDE, a comprehensive database of Stanford patient records, spearheaded by Henry Lowe, MD, an associate professor of medicine and former director of the Stanford Center for Clinical Informatics. He designed the database to provide researchers access to clinical data

without compromising patient privacy. At the last accounting, STRIDE contained information from 2 million medical records of patients from the Lucile Packard Children’s Hospital and Stanford Hospital & Clinics, including 25 million clinical documents, 1.3 million surgical pathology reports, 16 million pharmacy orders and 157 million laboratory test results.

Stanford researchers use STRIDE for almost 400 consultations a year, says Lowe. Most often, they explore the data as a “first step” to see how many patients might match what they are looking for in a study: age, gender, ethnicity, prescriptions, health problems and medical procedures. “STRIDE is a big enabler,” says Lowe. Without a way to aggregate that patient information and then de-identify the material to protect patient privacy it would be “a mind-numbing process” to search millions of records for the widely divergent sources of patient information — doctors’ notes, prescription orders or reports from medical procedures — that might be needed for a study, he says.

#### **BEYOND STANFORD**

The scientists at Stanford aren’t the only ones trying to milk more information from millions of patient records pooling in hospitals around the world.

In 2013, the University of Oxford, in the United Kingdom, announced the launch of its Big Data Institute. Described by Oxford vice chancellor Andrew Hamilton as an opportunity

to “transform the way we treat patients and understand disease in the coming decades,” researchers at the new institute plan to analyze large patient data sets — which include electronic health records collected through the National Health System — to uncover more effective medical treatments.

In the European Union, a handful of initiatives, such as EURECA and the European Medical Information Framework, are linking EHRs with other databases to deepen their mining resources. The National Center for Hematology in Moscow uses EHRs from more than 3 million patients to more efficiently recruit patients for clinical trials.

**C**loser to home, scientists in eMERGE, a consortium of nine research groups spread across almost a dozen states and clinical sites, can search DNA databases linked to all their EHRs. For example, researchers at the Vanderbilt University School of Medicine in Nashville, Tenn., a network member, searched eMERGE databases to study the DNA of 6,300 people with abnormally low levels of the thyroid hormones. As a result, the scientists found a previously unknown association with a tiny change in one gene, locating a new risk factor for this common thyroid disorder — all by using information already there, says Joshua Denny, MD, an associate professor of biomedical informatics and medicine at Vanderbilt. “It might take more than a year to find all those people for a clinical trial, and then we would have to do the genotyping,” says Denny. “I see EHR mining as cheaper, faster and better.”

It’s also a handy way to get research results quickly corroborated by other scientists. When Altman mined the Food and Drug Administration database of adverse drug reactions and found that the combination of a common blood pressure drug and a particular antidepressant could cause blood sugar spikes, his next step was

to see if that finding held true when he searched for that effect in Stanford patient records: It did. Then he simply emailed a colleague at Vanderbilt and asked him to run a similar search through his EHRs. At the same time, Altman sent that request to another researcher at Harvard. “The time from the first email to a submitted paper was 46 days,” says Denny. He couldn’t even estimate how many months — or years — it would take to run the same study as a regular clinical trial.

The Kaiser Permanente Medical Group relies on its 14-million-patient database and half a million DNA sequenced samples to improve patient care and efficiency, says Robert Pearl, MD, the executive director and CEO, who also lectures at the Stanford Graduate School of Business on strategic change in the health-care industry. “Right now, mining big data allows us to ask clinical research questions such as: Which hospitalized patients are likely to get much worse, so I can get them into ICU sooner? In the future, our clinicians will be able to query the database with patient info and then find out what happened with the last 1,000 patients with that condition. Today that ability resides at the research level,” says Pearl.

Public health organizations are also using electronic health data in many ways, including automated reporting of notifiable diseases such as tuberculosis, keeping tabs on influenza outbreaks, and assessing the safety of medical products. The FDA’s Mini-Sentinel program runs surveillance through a distributed data network that includes electronic health data from more than 120 million people to monitor the safety of medical products on the market. “Electronic health information has enormous potential to improve a whole range of patient activities,” says Richard Platt, MD, principal investigator for the FDA program and chair of the Harvard Medical School’s Department of Population Medicine.

In December 2013, the Patient-Centered Outcomes Research Institute, known as PCORI, announced \$93.5 million in funding for the U.S. National Patient-Centered Clinical Research Network, which has the goal of speeding up comparisons of the effectiveness of

**‘THE TIME FROM THE FIRST EMAIL TO A SUBMITTED PAPER WAS 46 DAYS.’ IT WOULD HAVE TAKEN MONTHS — OR YEARS — TO RUN THE SAME STUDY AS A REGULAR CLINICAL TRIAL.**

medical treatments. “Electronic health information will be a critical component of this network and the potential return on this investment is very large,” says Platt, a director of the network’s coordinating center.

#### WORKING OUT THE KINKS

Lynn Etheredge, a consultant with the Rapid Learning Project at George Washington University in Washington, DC, says the biggest stumbling block for mining EHRs is the lack of standardization in the information that is collected and stored. “We could have an extraordinary system of national registries and database networks for all illnesses that have the critical pieces needed for clinical research, but our EHRs don’t yet deliver on this potential,” he says. Currently every institution is building its own system and few of them “talk” directly to each other. (A recent paper by Stanford’s Lowe and colleagues in the *Journal of the American Medical Informatics Association* described a method to transform clinical data into a sort of universal currency to help algorithms analyze multiple clinical data sets.)

Another caveat is that EHR systems are built for individual patient care. As a result, substantial effort may be needed to make the data useful for addressing questions that require combining information from many systems, says Platt. The FDA invests millions of dollars a year in working with its data-generating partners, such as the 18 organizations that comprise the Mini-Sentinel project, to assure consistency, quality and completeness of data across health-care organizations — but even so, the available data is insufficient to answer some research questions. For instance, says Platt, information in health-care records is often lacking or imprecise about important risk factors, such as smoking or exposures to over-the-counter medications.

The other obvious concern in setting up searches through millions of patients’ medical records is privacy. In fact, wouldn’t the patient privacy law, known as HIPAA, preclude use of patient data in this way? Not necessarily. Although the law restricts unauthorized sharing of personal health information, it allows such sharing if it would benefit the public’s health.

While health-care providers take every precaution to eliminate information that could identify individual patients before researchers get access to the data, it’s hard to

ignore the threat posed to privacy when researchers examine broad swaths of patient information. With a written request, patients can opt out of including their medical information in Stanford’s research database built from their records. But Altman notes that some patients are more than willing to give up a little privacy in return for improved medical care, pointing to the growth of websites such as PatientsLikeMe where more than 200,000 people have shared intimate details about their disease symptoms with the hope of learning better ways to manage their illnesses. “The kind of privacy that we used to know is an illusion in this day and age,” says Shah. “What’s critical is security — you don’t want unauthorized access to people’s medical information. So we need to have a discussion about what is an acceptable risk of privacy loss.”

As EHR use gets mainstreamed into health care, the reams of medical information generated will attract more data miners and companies like Kyron that could profit from patient information in the process of improving their health care. “Who owns that data?” is a very important and relevant question to ask, says Shah. Right now, he says people willingly trust their data to Facebook and Google and the like, who mine it to make money (mostly by showing ads). “I don’t have all the answers,” Shah says. “But if there is money to be made then ultimately obtaining consent in some form is necessary.”

Steve Goodman, MD, PhD, professor of medicine at Stanford and the vice chair of PCORI’s methodology committee, says the benefits will likely outweigh the risks. Plenty of people appear to agree. In a 2012 survey conducted by *Consumer Reports*, nine in 10 responded positively to the statement: “My health data should be used to help improve the care of future patients who might have the same or similar conditions.”

“A system like this has the amazing ability to support physicians and give on-the-fly summaries of patients,” says Altman. “If you’re an internal medicine specialist like me, you’ll most likely follow 2,000 to 3,000 patients really well over the course of your career. Maybe you’d see another 10,000 to 20,000 patients on top of that. Imagine if you could augment that experience to 1 million patients. That’s what data mining can do — and we’re only scratching the surface.” **SM**

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**M I X**

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## SEEKING UNEXPECTED TREATMENTS IN BIOMEDICAL DATABASES

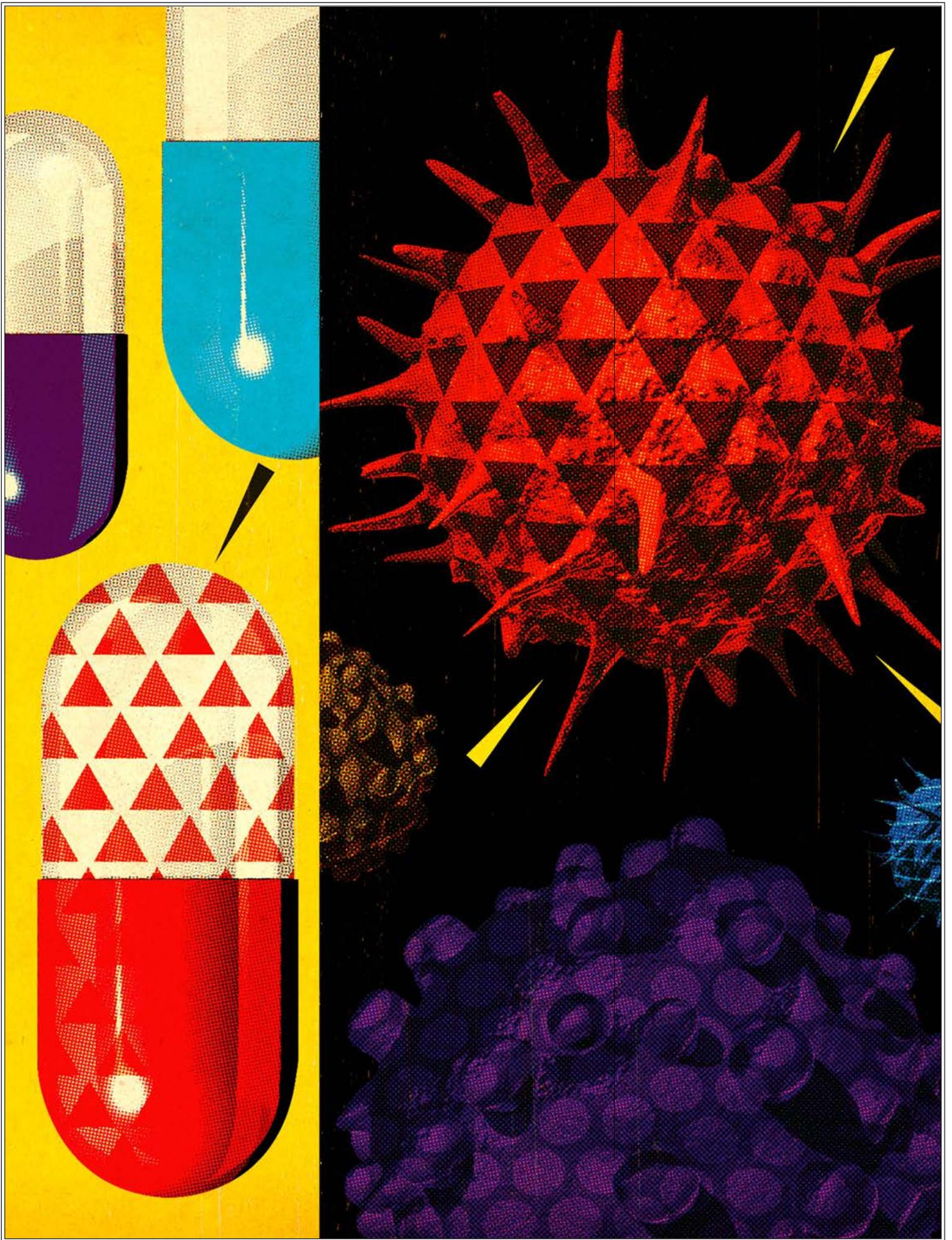
Researchers have found a new way to draw on the world's  
wealth of biological data:

**They're digging through it to find new uses for old drugs — a strategy  
called drug repositioning.**

This approach, they say, could cut down the time from treatment concept to drug approval: Instead of an average of 15 years, it could take just a few. • While pure serendipity or painstaking molecular analyses have guided repositioning in the past, associate professor of pediatrics Atul Butte, MD, PhD, and colleagues have recently matched four drugs to new uses by analyzing biological information amassed in public databases — a biomedical big data approach. • Since 1997, atorvastatin, better known as Lipitor, has lowered cholesterol levels in millions of patients by blocking an enzyme in their livers. Now Butte and his team have shown that atorvastatin can also jam the signals that cause a patient's immune system to reject a transplanted organ. • In addition, they've found an antidepressant and an antiulcer drug that combat two kinds of lung cancer, and an antiepileptic therapy that might treat Crohn's disease, a type of inflammatory condition of the gastrointestinal tract. • Now Butte's expanding the search for treatments by digging into an even larger trove of molecules: those that passed clinical trial safety tests but failed efficacy tests. While the FDA has approved around 5,000 drugs for use in patients,

**By Molly Sharlach**

ILLUSTRATION BY TAVIS COBURN



Butte estimates that there are many more molecules that are known to be safe but have not been proven effective to treat their intended condition.

Two public databases in particular have made computational drug repositioning possible for Butte and his team: the Gene Expression Omnibus and the Drug Connectivity Map. Hosted by the National Institutes of Health, the GEO is a repository of clinical and laboratory experiments from around the world that allows researchers to discern patterns of genes turned on or off by different diseases. The Broad Institute of Harvard and MIT curate the Drug Connectivity Map, a collection of experiments testing the effects of 1,300 distinct drug molecules on gene activity in human cells. Both of these databases continue to gain and release data at an exponential rate.

With the assistance of a computer algorithm Butte's team developed, they have mined data from both sources and matched disease patterns with drug patterns. To find a potential treatment for a given condition, they searched for a drug that would reverse the changes in gene activity caused by the disease. For instance, genes involved in calcium signaling showed high activity levels in some cancer cells, and data from the Drug Connectivity Map revealed candidate drugs that could counteract this effect. The researchers' computational approach to repositioning enabled them to simultaneously identify many such patterns.

Though millions of data points give bioinformaticists confidence in their predictions, computers still can't do biology. Cells are complex collections of machines, and only tests using the actual compounds can discern the true effects of throwing a wrench into the works.

**A**MONG THE FIRST of these discoveries to be tested in patients is a compound that might treat small cell lung cancer, which is responsible for 12 to 15 percent of lung cancers in the United States. This cancer has a high mortality rate; chemotherapy can improve survival, but no current treatment cures it. In the search for an existing drug to fight small cell lung cancer, Nadine Jahchan, PhD, a postdoctoral scholar working with associate professor Julien Sage, PhD, ran six drugs identified as promising by Butte's algorithm through a triathlon of experiments.

Jahchan and her team first compared the drugs' ability to kill cancer cells in petri dishes. Three of these were further tested on human small cell lung tumors transplanted into mice. Finally, imipramine, an antidepressant, and promethazine, a drug commonly used to alleviate motion sickness and allergies, went head to head in a contest to treat lung tumors in mutant mice. Imipramine emerged as the victor.

Less than two years since the initial computer prediction, assistant professor of oncology Joel Neal, MD, PhD, is running a clinical trial of desipramine, a closely related molecule, on 10 patients with small cell lung cancer and other high-grade neuroendocrine cancers to look for hints of efficacy. He's proceeding with the utmost caution, as tricyclic antidepressants "have potent side effects, including sleepiness and even fatal heart arrhythmias in modest overdoses."

Drug repurposing is not a new tactic for pharmaceutical companies, which have long sought to extend returns on their tremendous investments in research. In a classic example, thalidomide began as a morning sickness remedy, but was discontinued in the 1960s because it caused severe birth defects. More recently, thalidomide gained approval as a treatment for leprosy and myeloma. Now, rather than relying on isolated incidents, the industry is recognizing the commercial value of systematically predicting new drug applications.

In 2008, Butte and his wife, Gini Deshpande, PhD, founded NuMedii, a startup that partners with pharmaceutical companies to find fresh therapeutic uses for drugs. To pinpoint viable treatments among those suggested by the computer algorithm, NuMedii evaluates both clinical and commercial factors. "We go through this translational process before we test any of the indications so that we identify the best pair of drug and disease," says Deshpande.

Public repositories of data from clinical trials, including failed ones, could be the next bioinformatics treasure trove, says Butte. For example, in a failed trial, a drug may have successfully treated a quarter of the patients. Mining the trial's data could reveal that all these patients had a particular genetic profile or medical condition. This finding could guide the development of a novel precision medicine. Butte is the new principal investigator of ImmPort, one of the first NIH-funded repositories for the public dissemination of raw clinical trials data, which will enable such studies.

Currently, it takes five to 10 years for a new treatment to move from clinical trials to widespread implementation. Butte envisions an automated system that will make recommendations to physicians based on amassed trial results. "If there are three trials, or 10 trials, all saying the same thing, our electronic health-care system of the future could directly see that data and carefully change medical practice with the physicians working at our hospital," says Butte. A notification sent to a doctor in the morning could bring more effective treatment to a patient by afternoon. "Why are we waiting so long for this to change medicine?" **SM**

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**FEATURE**

Fresh starts for hearts

CONTINUED FROM PAGE 15

Sierra needed a port to simplify the regular intravenous treatments needed to combat her rejection. She was also put on an additional, third, immunosuppressant and released to the Ronald McDonald House. Meanwhile, Lindsey recovered from her transplant.

On Feb. 28, after 264 days in the hospital, Lindsey was also discharged, and on May 30, the family headed home to eastern Oregon. The girls play volleyball and basketball with their siblings. They swim and they jump on the trampoline. They have a dog they named Axelrod after one of their favorite Packard doctors, pediatric cardiologist David Axelrod, MD. By many measures, their lives are normal.

But their time at Lucile Packard Children's Hospital Stanford continues. Megan and Hunter get annual checkups for cardiac problems. Lindsey is assessed for organ rejection about once every two months, and Gage's pacemaker is adjusted every three months. Sierra comes in once a month for a 14-hour treatment to remove the antibodies her body makes against her donated organ and to monitor blood pressure inside her heart. And, although there have been some tantalizing hints, the root cause of their condition remains unknown.

The efforts of the physicians at Packard Children's and untold clinical advances in transplantation, technology and immunology unquestionably saved the lives of three of the five Bingham children. But there's still more that can be done. In November, researchers from cardiologist Joseph Wu's laboratory collected blood samples from each of the seven family members to begin the process of making iPSC cells to try to identify the molecular basis of the children's weakened hearts — a process that could take years to complete.

"It could be any of several causes," says Joseph Wu. "Maybe it's a problem with the cellular channels that propagate the signal to contract, or maybe it's a problem with the muscle components themselves. We won't know until we have their heart cells beating in a laboratory dish and can examine them more closely." Although identifying a molecular cause of the disorder won't immediately help Sierra or Lindsey, who now have donated hearts, it's possible that it may make it easier for clinicians to find the right medicine to help Gage's heart last as long as possible.

"My goal, as the founder of the Stanford pediatric heart transplant program," says cardiologist Bernstein of these efforts, "is to put us out of business."

Researchers from the Stanford Center

for Inherited Cardiovascular Disease haven't given up either. Ashley, who is Jason and Stacy's cardiologist, also co-directs the newly launched clinical genomics service for patients at Stanford Hospital and Packard with mystery conditions or inherited cancer, cardiovascular or neurological diseases.

"The Bingham families like them are why we set up the Center for Inherited Cardiovascular Disease at Stanford," says Ashley. "We gather many experts together in one room and plan the best approach. In this case, we completed regular sequencing of a smaller number of targeted genes including those of the mitochondria (the 'powerhouse' of the heart cells) then moved to sequence the genomes of the most affected children. The first pass did not uncover a smoking gun, but we have just launched our newest analysis tools and have them aimed squarely at this target. We remain hopeful."

Finding a genetic cause would be a relief, but it also extends the long arm of the disease. Should Sierra, Lindsey or Gage have children, it's possible they will pass along their defective genes.

"I will worry about this for the rest of my life," says Jason. "I'll worry about my kids, and then I'll worry about my grandkids and my great-grandchildren."

But there's hope. Although it remains to be seen whether advances in regenerative medicine occur quickly enough to help Gage avoid a transplant, they are at least likely to render a better medical outlook for Jason and Stacy's grandchildren.

Ideally, they'll be diagnosed quickly through genome sequencing at or shortly after birth, and the optimal medication and dosage will be determined for each through the use of matched, iPSC-derived cells. If necessary, stem cells will be used to strengthen their weakening left ventricles. If transplantation becomes necessary, organs could be grown specifically for them to ameliorate the chances of rejection.

But in the meantime, the Bingham family wait.

"The fact is, I still have two kids with transplants, and one who is likely going to need one," says Stacy. "If the researchers can find a cause for this, or if they could help Gage, that would be wonderful. But I don't feel like we have the time to sit around and worry. We have five kids, and life just goes on." **SM**

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**FEATURE**

A change of heart

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I wanted to hear. I can tell now, by going back and looking at medical records from

that period of time, that Rick and another doctor who also treated me had reservations about my going forward with a campaign. Neither of them believed that telling me to get out was the right thing to do because I was so committed to the campaign and because it meant so much to me. So, while privately they clearly had some reservations, what I took away from those conversations was Rick's advice: "Hard work never killed anybody." I sort of lived that way through my career. There was never a moment when I wasn't eager to get back to work. A crisis would arise. We'd deal with it and then I'd move on. The mindset I came away with was that I wasn't a patient or a victim.

**COSTELLO:** You wrote that the dramatic reduction of the incidence of heart disease over the past 40 years is a national treasure and deserves to be protected. Can you expand on that? What needs to be done to protect it and what might stand in the way?

**CHENEY:** The first thing that comes to mind is that, as efforts are made to try to reform our health-care system, you don't want to do something stupid or that has unanticipated consequences. For example, the idea of a device tax, which is part of Obamacare. Putting a tax on the first dollar of revenue on the folks who come up with those innovations and implementing them is a really bad idea. Why would you want to slap a medical device tax on those devices that not only in heart care, but in other areas, save lives?

**COSTELLO:** Is the protection of NIH funding critical too?

**CHENEY:** Well, I think that ought to be a priority. If you want to have the best health-care system that's effective, you've got to have the necessary investment in research. NIH is part of that process.

**COSTELLO:** What are you doing to take care of your new heart?

**CHENEY:** One, I don't eat raw seafood. When you suppress your immune system, one of the big no-no's is oysters on the half shell or sushi. I used to enjoy all those foods but that's not a hard sacrifice.

I ride a recumbent bike about 30 minutes a day. I live a normal, active life. I love to fish and hunt. I am getting plenty of exercise and doing those things I've always loved doing. I have to wear a hat every time I go outside because you're more vulnerable to skin cancer when your immune system has been suppressed.

**COSTELLO:** Aren't you amazed that four years ago you were at death's door and now you're able to live life?

**CHENEY:** Exactly. It's the gift of life itself.

**COSTELLO:** You dedicate your book to your family and your donor. I wonder, have you ever considered, what if you have the heart of a liberal Democrat?

**CHENEY:** [laughs] Well, I don't worry about it. People speculate, "Did it change you? Do you have different values and attitudes?" Not that I'm aware of. I operate on the basis that it's my new heart. I don't spend a lot of time thinking about where the heart came from. What kind of life did they live? Who were they? From my own standpoint, it's a great gift from a donor and the donor's family but now it's my heart. It's that mindset that I think works best for me. **SM**

*This interview was condensed and edited by Paul Costello.*

**WEB EXTRA HEAR THE INTERVIEW AT**  
<http://stan.md/1flrbYr>

## FEATURE

Switching course

CONTINUED FROM PAGE 27

her — an ideal candidate for the arterial switch procedure, with no left-ventricle training required. She would, however, need an additional procedure the following year to replace her left ventricular outflow track. This procedure, also performed by Hanley, finally put Brooke's heart in nearest-to-normal condition — the result she and her family had sought for so many years.

To date, Hanley has managed 36 patients with failing atrial-switch — a number rivaled only by retired surgeon Roger Mee. For 21 of those patients, Hanley completed the atrial-switch takedown and arterial-switch operation, with an overall survival rate of 81 percent. But the overall success rate doesn't reflect his increasingly positive results: Over the past 15 years, as the criteria for selection and the procedure have evolved, the survival rate is much higher, with the last unsuccessful procedure performed in 1999. Twelve new patients are undergoing pulmonary artery banding. Early in the development of this procedure, two patients died of right ventricle failure before training was complete. Hanley notes that today these two patients would not qualify for the surgery because their hearts had decompensated to an extent that the procedure, he now knows, would be unsafe. These early cases helped guide Hanley to the further-refined, safer criteria he uses today.

Hanley estimates that thousands of adults who had Mustard or Senning repairs in childhood may now need interventions of

some kind, though many may not know it.

"During that 25-year period from 1959 to the early '80s, atrial-switch repair was the only solution available to these patients," Hanley explains. "This means there are thousands of people alive now with atrial switches in whom this right ventricular failure risk is lurking."

As the most common birth defect, congenital heart disease kills twice as many kids as all childhood cancers combined. Those who survive depend on their parents to stay ahead of the disease. And yet, "many parents of children with congenital heart disease don't recognize that their kids need lifelong cardiac care," says Susan Fernandes, program director of the adult congenital heart program at Stanford, and lead author of a 2011 study on the topic. "It is estimated that more than 50 percent of adults with congenital heart disease are not receiving specialized, adult congenital cardiac care or are lost to follow-up, most falling out of appropriate care before mid-adolescence."

Those who are monitored are often followed by a primary care doctor who may not know about the potential complications of their condition. This unseen risk points to the larger problem of how to provide the best monitoring and care of survivors of congenital heart surgery.

"There's a big push among those who care for congenital heart patients in this country to organize adult survivors of congenital heart surgery and bring them into clinics where they can be treated effectively," says Hanley. Lucile Packard Children's Hospital Stanford is one of those, with its multidisciplinary adult congenital heart program. This program is a major priority for the institution. Stanford recently recruited George Lui, MD, clinical assistant professor of cardiovascular medicine, as medical director of the program.

The push for more organized care can't happen soon enough. With resources and clinic directories for patients across the country, the Adult Congenital Heart Association is a leader in this effort.

"It's a real big timing thing," says Barb. "And there are so many kids who are left until it's too late." Staying on top of the disease gave Brooke treatment choices she may not have otherwise had and allowed her to plan ahead.

Hanley told Brooke she would need surgery within three to five months. She could pick the date, which allowed her to graduate college and enjoy her summer.

Her eight-hour surgery took place at Packard Children's on Sept. 27, 2012. Expecting a three-week stay, she recovered in nine days and was released.

"She came out of the hospital and smiled," says Barb. "She looked up at the blue sky and she started crying. That was a moment I will never forget, because I could see the feeling in her, like, 'I am alive.'"

Today, Brooke is living in Aptos, Calif., with her dog, Maddy, and taking some time to relax and appreciate life. She takes every opportunity to get the word out to young adults living with a congenital heart defect about the importance of appropriate care, giving a talk at the Lucile Packard Foundation for Children's Health last September.

She's also doing supervised interval workouts six days a week. And she's taken up the hula hoop. "It feels great to be using my body to its full potential," says Brooke.

"I'm looking forward to running," she says, "and just being able to not have any limitations — living to live instead of living to survive."

For her parents, getting used to the promise of Brooke's healing heart is an adjustment. "I still take each day at a time," says Barb. "As of right now, it's just hard to believe this is real. It's the most amazing thing. We're so grateful." **SM**

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## FEATURE

The heart gadgeteers

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"This disruptive technology has the potential to save thousands of lives a year," says Guion-Johnson. "Getting this idea to market has been more difficult than I ever imagined, but I know it'll be worth it."

### THE BRIDGE BUILDERS

Back at his office inside Stanford Hospital, McConnell sits at a desk that offers a visual reminder of the chasm between the dream and the reality of new heart gadgets. On one side of his desk is the "big picture" — a colorful architectural rendering of a planned heart-gadget information center. Styled after Apple's genius bar, it includes demonstration units of heart- and fitness-monitoring devices, posters and experts to help educate consumers on the latest offerings.

On the other side of his desk are tall stacks of old-fashioned patient folders. McConnell points to one stack in the corner of his office. "Those are some Zio Patch reports waiting to be reviewed," he says. Though Zio Patch reports are electronically available, in the short term, the hospital still uses the old Holter-era process of printing readouts on paper, primarily so that it's easier to work with the community physicians who lack access to electronic medical records or prefer paper reports.

This illustrates an important point

brought up by both McConnell and Kumar — whatever new heart devices come along, someone has to make it easy to integrate them into health-care providers' electronic medical record systems and physicians' daily work flow. Bridging this divide means device developers also have to become systems integrators and software developers.

Early in the development of Zio Patch, Kumar realized that iRhythm had to become more than a device company.

"We had to provide a complete solution that enabled the use of the Zio Patch," he says. "So that meant spending a few years and significant resources building a sophisticated algorithm to analyze the heartbeats. We also had to create a completely new way of presenting all of this data in a report, so it could be usable by all types of physicians, from super-specialists to generalists. And then we had to provide all of the back-end logistics regarding processing devices and reports. In the end, I like to think of iRhythm as an information technology company enabled by a novel device supported by a service." The company's total solution costs about four times more than a Holter monitor per patient, but collects seven to 14 times more heart data. The hope, says Kumar, is that the Zio Patch will result in cost savings to the medical system over time. So far it has been prescribed to more than 150,000 patients.

**The heart gadgeteers are a special breed. Part visionary and part bulldog,** they know that medical device development is not a get-rich-quick business. It's a passion that drives them to get up every morning for years, and, one by one, knock off the 10,000 steps required to get an innovative new medical device into the hands of physicians and patients.

There's a lot at stake as the nation struggles to improve overall health while reducing medical costs. But by moving these heart devices into the mainstream, the gadgeteers know they can significantly reduce the physical, financial and emotional impacts of cardiovascular disease, the leading cause of death in the United States. **SM**

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## FEATURE

Easy does it

CONTINUED FROM PAGE 36

### THE PROCEDURE

On Oct. 16, 2012, Casey became one of the more than 120 patients that year at Stanford to undergo the TAVR procedure. The first catheter-based aortic valve transplant was in 2002 in France. It has been approved for

use for the past six years in 40 other countries including most of Europe, with a total of 45,000 procedures conducted worldwide.

In the United States, institutions such as Stanford, the Cleveland Clinic, Columbia University and the University of Pennsylvania have been leaders in introducing the new procedure and determining its effectiveness through the clinical trials.

Careful patient selection is key to the successful use of the procedure, says Miller, and that sometimes means not recommending TAVR for a patient who is too old or too sick with other illnesses to benefit from the device.

"That's a very sobering point," says surgeon Miller. For patients who are too old or ill, undergoing the procedure may not increase their quality of life or life expectancy; Miller says that the boundary line between TAVR "utility and futility" is still being defined. For younger, relatively healthy patients like Casey, the unknown longevity of the valve is a major concern.

The TAVR procedure is performed by a team that includes an interventional cardiologist, cardiothoracic surgeon, echocardiographer and cardiac anesthesiologist. The procedure takes about 45 minutes. Once inserted, the new valve immediately starts working.

"Unlike most open-heart operations, the heart is beating throughout the TAVR procedure," says interventional cardiologist Fearon. "During the actual valve deployment, we use a temporary pacemaker to briefly speed the heart up so that it cannot contract effectively and dislodge the valve."

Recovery from the TAVR procedure is on average about a three- to-five day hospital stay compared to an average seven-day stay for open-heart surgery.

Casey, again, not your average TAVR patient, recovered more rapidly.

She checked into Stanford the night before the procedure on Oct. 15 and checked out on Oct. 17. Stockdale came to visit her in the hospital, where she was up and walking before she checked out. Now, instead of having a 6-inch scar down her chest, she is scar-free. She recovered at home after about two weeks and started exercising, back on the treadmill, after a month. Throughout the entire procedure and recovery period, she never felt any pain in her chest.

"I took a high dose of Tylenol, that was it," Casey says. "I never even filled the pain pill prescription. I was in and out of the hospital in 46 hours."

Casey is concerned about how long the valve will last before she needs another replacement, but she's confident this was the right decision for her. She's got more energy

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now and exercises three to four times a week, either walking outside or on her treadmill for 30 minutes. She's on her feet constantly, cooking, cleaning, caring for her family.

"I got the call saying I had breast cancer, I'll never forget, on New Year's Eve," Casey says, remembering back. "I had a good cry." But both times she received those potentially fatal diagnoses, she never really believed she was going to die. "I guess I've beaten the odds a second time." **SM**

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# SEARCH, RATE, COMMENT

## BEHIND BIOMEDICAL PUBLISHING'S NEW FORUM FOR COMMENTING ON JOURNAL ARTICLES

What would you do if you saw an error in a medical journal article? • If you're biostatistician Rob Tibshirani, PhD, you'd try to correct it. And then, because there's no easy way to do that, you'd get frustrated and think, "Wouldn't it be nice if there were a website where you could let people know about mistakes in journal articles?"

Tibshirani, a Stanford professor of statistics and of health research and policy, had this thought most recently after noticing what seemed to be a serious drawback with a new method, published in *Science*, for analyzing large data sets. So he asked Pat Brown, PhD, professor of biochemistry, what he thought: Was a website for commenting on journal articles feasible? Brown was a good person to ask. He co-founded Public Library of Science, an open-access publishing venture, in 2000 and started one of the first open-access journals, *PLOS Biology*.

"Pat told me *PLOS* had tried it, but didn't have enough traffic to make it work," Tibshirani says. "He suggested we try it at a place with a lot of traffic: PubMed." PubMed, the massive literature index run by the National Institutes of Health's National Center for Biotechnology Information, is one of the Internet's busiest biomedical websites, with millions of users a day.

Over Skype, Tibshirani and Brown pitched the idea to David Lipman, MD, the NCBI's director. Lipman, in fact, had been thinking about doing something like this for nearly a decade. "But I was concerned how we could manage it, and until recently I didn't think it would get the support of NIH leadership," he says.

Now he thought it was worth a try. So Tibshirani became the community organizer, recruiting 300 people to discuss the ground rules and test an early version of the site, and Lipman proposed it to the leaders of the NIH. The result is PubMed Commons, which opened to a wide audience in the fall of 2013. The site, <http://www.ncbi.nlm.nih.gov/pubmedcommons/>, allows all authors of articles indexed in PubMed to make comments on any article indexed there. The comments, which numbered roughly 600 as of January, can be read by anyone with an Internet connection.

It's a step forward for what's been termed "post-publication peer review," which many scientists argue will speed scientific progress. The development team hopes it will become not only a place for criticism but for discussion — for questions about techniques, for suggestions and for praise.

In some ways, it's surprising that the NIH leaders have let comments go forward, Tibshirani says. He knew there was concern that comments could have financial ramifications, be used to attack competitors or harm the reputation of NIH-funded research.

To keep commenters responsible and to make any potential conflicts of interest transparent, no anonymous comments are allowed, and commenting is restricted to the scientific community, at least during the pilot period.

During Tibshirani's discussions with researchers as the site was being developed, he found that 10 to 20 percent of them worried about its repercussions, or just didn't see the point. "They say you could trash someone's reputation," Tibshirani says.

But is that so bad?

"My thought is if someone publishes something really wrong, maybe their reputation shouldn't be trashed but it should be at least tarnished. Should the facts not come up? I think yes, they should. It's in everyone's interest."

— ROSANNE SPECTOR



**Rob Tibshirani** helped launch a commenting system on PubMed, one of the world's largest indexes of scientific literature.



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## Seizure song

A STETHOSCOPE FOR THE BRAIN

**A few years ago on a whim**, neurologist Josef Parvizi, MD, PhD, and composer Chris Chafe, DMA, began investigating whether it would be possible to turn the electrical activity recorded from an epilepsy patient's brain into music. Now, the two Stanford faculty members believe their work could lead to the development of a powerful clinical tool. • Their prototype, which they have called a "brain stethoscope," records the brain's electrical activity through a band of electrodes on the patient's scalp, then converts the signals to music by assigning a "voice" to each electrode. As the brain fires, the electrodes produce different notes, creating a musical representation of the brain activity. In patients with a seizure disorder, the device can be used literally as a stethoscope to check if the brain is having seizure activity. (This is useful because sometimes seizures have no obvious symptoms.) • Before the seizure begins, the peeps and pops from each electrode almost fall into a clear rhythm. In the moments leading up to the seizure event, though, the notes become progressively frequent and disorganized. Then, after the complete chaos during the full seizure, the music calms as the neurons trail off, with single electrodes peeping every so often, like the final few kernels popping in a bag of popcorn. After such furious activity, the brain sounds fatigued. The work by Parvizi, an associate professor of neurology, and Chafe, a professor of music, was supported by a seed grant from Stanford's Bio-X Interdisciplinary Initiatives Program.



**Professor Chris Chafe (left) and undergraduate Michael Iorga discuss brain activity patterns seen in this graphic representation of a seizure.**

Now the pair are in the final stages of developing a noninvasive, electrode-laden headset that anyone could put on. They hope to take this brain stethoscope setup into clinical trials to test how effectively physicians and epilepsy patients can interpret the precursor sounds to a seizure.

Parvizi and Chafe also have hopes for the device as a neurofeedback tool for everyone. They think people managing anxiety or chronic pain might find comfort in listening to how their coping mechanisms can bring relative peace to their brain activity. "We've really just stuck our finger in there," Chafe says. "We know that the music is fascinating and that we can hear important dynamics, but there are still wonderful revelations to be made." — BJORN CAREY

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