

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

Fall 2012

special report

MONEY CRUNCH

Medicine's funding pool
is drying up

The paper chase

Scrambling for research dollars

Band of rebels

Health care's new visionaries

Melinda Gates

'My life's work'

Inside their minds

Why donors give

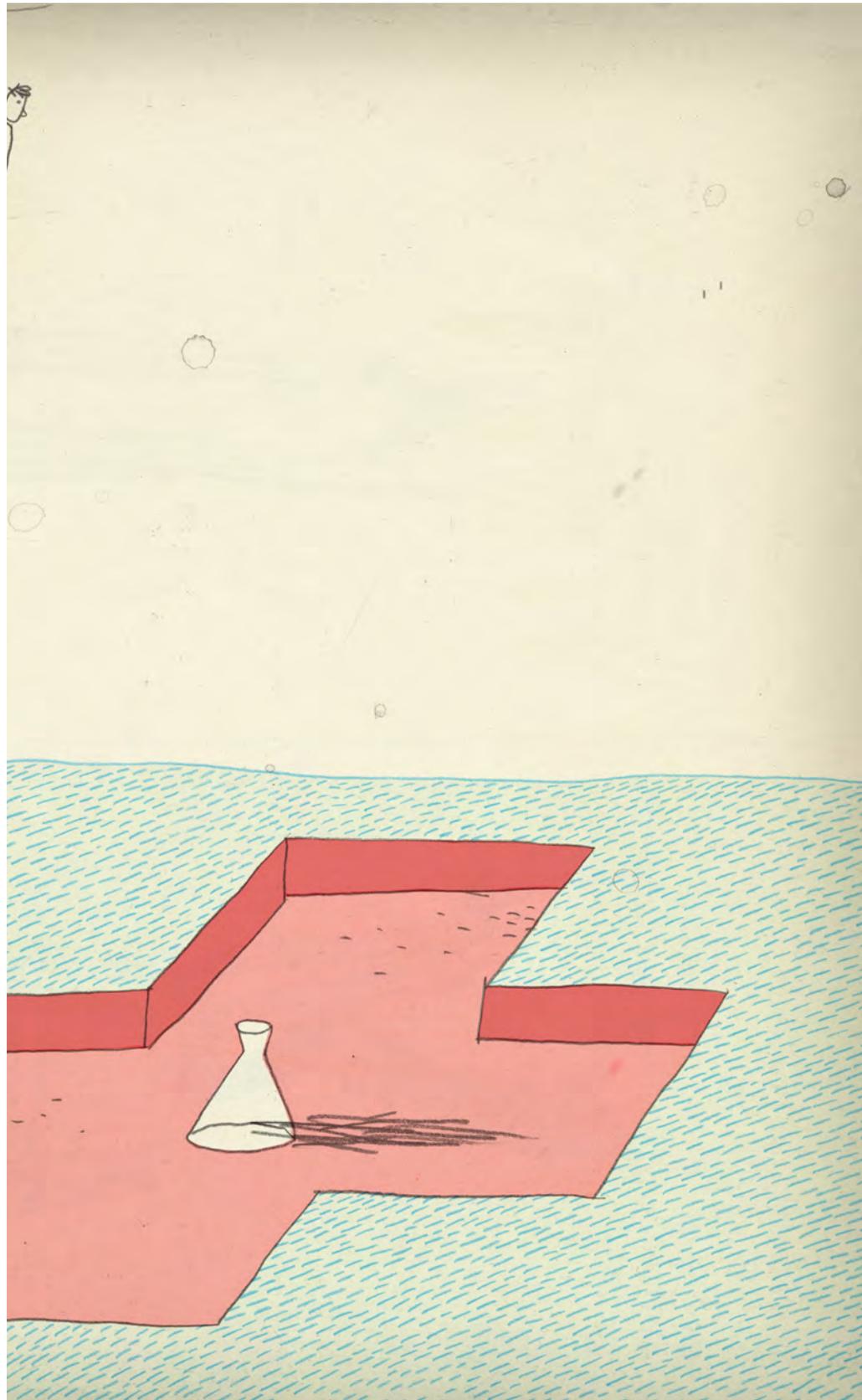
Overscreening?

Medical testing controversy
rages on

plus

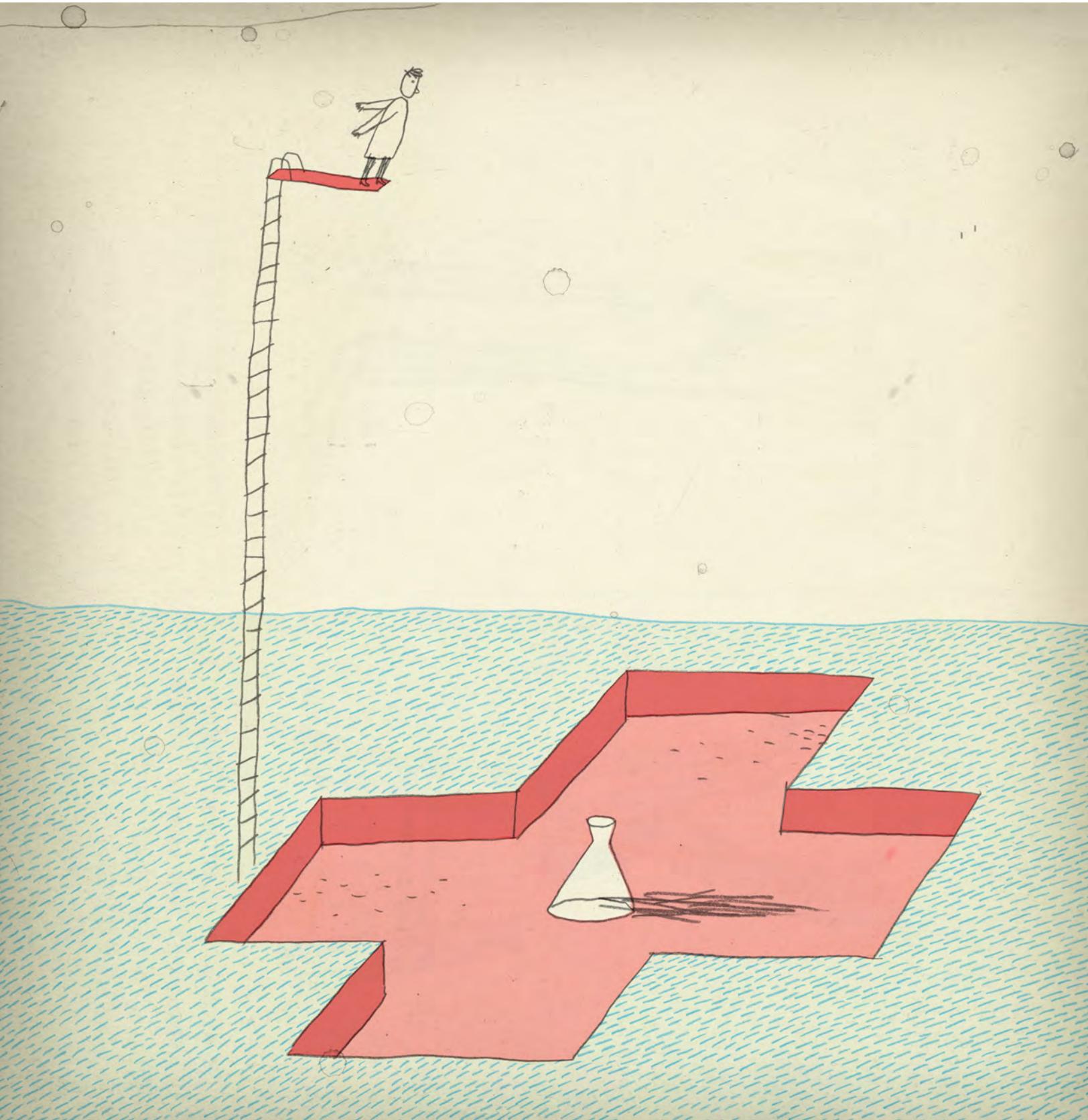
Philip Pizzo

His remarkable run as dean



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

Fall 2012



HEAL SIMPLE

HOW TO COORDINATE COMPLEX CARE

A new and relatively small clinic at Stanford Hospital & Clinics could play an outsized role in influencing care for chronically ill patients. • The Stanford Coordinated Care Clinic opened in the spring to university and medical center employees who struggle with one or more complex, chronic conditions. It aims to help such patients lead healthy lives and get regular medical support. • For people with multiple chronic conditions, getting good overall care is often complicated by insufficient, or non-existent, communication among their many doctors. The result is a lack of agreed-upon goals for health improvement, little or no coordination of care and no accountability.

Not only is this bad for patients' overall health, it's also bad for their pocketbooks and their insurers' bottom lines. When no one closely monitors and manages such patients — or properly educates them about how to deal with their diseases — they tend to land more frequently in emergency rooms and

intensive care units, racking up lots of hospital bills. More than 75 percent of health-care costs are due to chronic conditions, according to the U.S. Centers for Disease Control and Prevention.

The new clinic, directed by the husband-and-wife team of Alan Glaseroff, MD, and Ann Lindsay, MD, serves as a home base for such patients — a kind of health-care command central — where they can turn for 24/7 help. Its clinicians will even visit patients at home. The staff, which includes a nurse, a social worker, a physical therapist and patient-care coordinators, monitors patients' medical regimens and progress toward health goals; coordinates with specialists to make sure they understand the patients' needs and preferences; and gives patients the tools and knowledge to manage their diseases.

"Patients are the most important determinant of their own health outcomes," Glaseroff says. "Their own behavior is at least four times as important as the care they receive. It makes sense to make them a member of the care team rather than an object of its services."

Providing aggressive primary care to the sickest patients to reduce their use of hospital services has been done before elsewhere. But these efforts have focused on specific populations, such as a single company's workers or a city's most vulnerable residents. Glaseroff and Lindsay want to figure out how to replicate this kind of care across a broader demographic.

They will report what they learn from running the clinic to the Pacific Business Group on Health, a coalition of 50 large businesses that is leading a \$19.1 million program to improve care coordination for 30,000 Medicare and dual-eligible Medicare-Medicaid beneficiaries in California and Arizona with multiple chronic conditions. The program is funded by the Center for Medicare & Medicaid Innovation.

The couple also will report on their experience with Priority Care, a similar program led by Glaseroff in Humboldt County.

"We're trying to develop a framework that could be used anywhere," Glaseroff says.

At present, the clinic cares for about 65 patients, and that number is growing. It plans to expand its services to non-Stanford employees in the future.

"It can be hard to face a chronic condition alone," Lindsay says. "We will help patients take control of their life and health." — JOHN SANFORD



Ann Lindsay and Alan Glaseroff run Stanford's clinic for people with multiple chronic health conditions — a clinic they hope will influence others.

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

SPECIAL REPORT

Medicine's money crunch



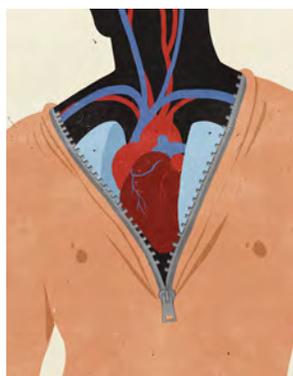
The chase for
research grants
page 8

- 6 **Bottom line**
MEDICINE'S FUNDING POOL IS DRYING UP
- 8 **The competition** *By Rosanne Spector*
ON THE HUNT FOR RESEARCH DOLLARS
- 14 **Against the odds** *By Kris Newby*
A BAND OF REBELS FIGHTS TO SAVE HEALTH CARE
- 21 **Giving well** *By Tracie White*
PHILANTHROPISTS ROLL UP THEIR SLEEVES
- 26 **Melinda Gates on family matters**
A CONVERSATION ABOUT CONTRACEPTION
- 28 **Testing testing** *By Ruthann Richter*
WHY SOME CANCER SCREENINGS STIR SUCH CONTROVERSY

PLUS

- 34 **Marathon man** *By Susan Ipaktchian*
PHILIP PIZZO NEARS THE END OF HIS REMARKABLE RUN AS DEAN

The screening fix
page 28



Why painkillers
numb only some
page 4



DEPARTMENTS

- Letter from the dean 2
- Upfront 3
- Backstory 42

letter from the dean

When I agreed to join the Stanford community as the dean in December 2000, the medical school, medical center and university were in a very different time and place.

Financial challenges and deep-seated questions about the future of the school and its major teaching hospitals were topics of considerable discussion and concern. Despite those questions, the resilience, vision and creativity, as well as the passion for innovation and reinvention by our faculty, students and staff, quickly took us forward. Their combined efforts account for the excellence of Stanford Medicine as we know it today — an institution that values the incredible contributions of our alumni and that seeks to create opportunities for current and future students and trainees.

Institutional culture and values can make a major difference during periods of constraint or limited resources. Great institutions tend to rise above daunting challenges by finding new directions and solutions, and by supporting the creative energies of their communities. In the end, the individuals who comprise an institution, and who define its fabric and focus, are its most precious resource.

Having spent my pre-Stanford career in East Coast institutions, which tend to be defined by their history and tradition, it was exciting to become part of a community that preferred to look toward the future. This spirit of innovation has defined the culture of Silicon Valley, usually by asking seemingly unimaginable questions, and of not fearing failure.

Today Stanford Medicine is poised for new challenges and opportunities. Many of these are external forces: the depressed national economy, and the resulting constraint in research funding from public and private sources; the impact of rapidly evolving technology on virtually every one of our missions, from teaching and learning to the delivery of medical care; and the changes unfolding in our health-care system. But I hope the most exciting forces for change will come from the creativity and innovations of our faculty, students and staff responding to these external challenges in ways that also help define Stanford Medicine as a leader at the intersections of science and medicine, compassion and humanity.

Because this is my last letter to Stanford Medicine as dean, I want to thank our entire community for allowing me to be part of this extraordinary institution and for the pleasure of working with so many of you to pursue opportunities and shared ventures. It has been a privilege. I have every confidence that new heights will be achieved under the leadership of Dr. Lloyd Minor, who becomes dean on Dec. 1. It is an honor to pass the torch (or the wand, depending on one's metaphor) to Dr. Minor, and for me to take a place among the crowd cheering for the future of Stanford Medicine.



Sincerely,
Philip A. Pizzo, MD
Dean

Stanford University School of Medicine
Carl and Elizabeth Naumann
Professor, Pediatrics, Microbiology
and Immunology

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD UNIVERSITY MEDICAL CENTER

Alzheimer's risk

THE MOST COMMON genetic risk factor for Alzheimer's disease disrupts brain function in healthy, older women but has little impact on brain function in healthy, older men. The findings, revealed in a study published June 13 in the *Journal of Neuroscience*, may help explain why more women than men develop this disease, says the study's senior author, Michael Greicius, MD.

For every three women with Alzheimer's, only about two men have the neurodegenerative disorder, says Greicius, an assistant professor of neurology and neurological sciences and medical director of the Stanford Center for Memory Disorders.

Women with the gene variant, known to be a potent Alzheimer's risk factor, show brain changes characteristic of the neurodegenerative disorder that can be observed before any outward symptoms manifest.

Both men and women who inherit two copies (one from each parent) of this gene variant, known as ApoE4, are at extremely high risk for Alzheimer's, a syndrome afflicting about 5 million people in the United States and nearly 30 million worldwide. But the double-barreled ApoE4 combination



is uncommon, whereas about 15 percent of people carry a single copy of this version of the gene.

Greicius' team demonstrated for the first time the existence of a gender distinction among outwardly healthy, older people who carry at least one copy of the ApoE4 variant. In this group, women but not men exhibit two telltale characteristics that have been linked to Alzheimer's disease: a signature change in their brain activity, and elevated levels of a protein called tau in their cerebrospinal fluid.

Identifying the prominent interaction between ApoE4 and gender opens a host of new experimental avenues that will allow Greicius' team and the field generally to better understand how ApoE4 increases risk for Alzheimer's, he says. — BRUCE GOLDMAN

Rare window

Life with a rare disease can be isolating, but a new film shows how patient-advocacy groups can provide a support network and spur researchers to look for cures.

Rare — directed by Maren Grainger-Monsen, MD, director of the Stanford Program in Bioethics, and Nicole Newnham, a filmmaker and writer in the program — focuses on Donna Appell and her daughter, Ashley, who has Hermansky-Pudlak Syndrome (HPS), a rare genetic disorder, often leads to albinism. Other symptoms can include blindness, bleeding problems, colitis and pulmonary fibrosis.

The film follows the Appells spreading the word about the Hermansky-Pudlak Syndrome Network and seeking enough patients for a drug trial. "It shows why the efforts of patient-advocacy groups really matter," Grainger-Monsen says.

— Susan Ipaktchian

250 million people worldwide have rare diseases. For information about ordering and viewing the film *Rare*, visit <http://www.rarefilm.org>.

New digs for kids

Pediatricians at children's hospitals increasingly treat the sickest of sick kids, with chronic illnesses, cancer, organ failure and congenital defects that would have been fatal just a few years back. To keep pace with the growing numbers and needs of these patients, and the needs of Northern California's expectant mothers, Lucile Packard Children's Hospital is growing, too.

On Sept. 6, Packard Children's broke ground for an expansion to add 521,000 square feet and 104 beds to its 21-year-old pediatric and obstetric care hospital.

The \$1.2 billion expansion, which opens in December 2016, is located at Quarry and Welch roads adjacent to Packard Children's original 257-bed hospital. The construction site, now abuzz with jackhammers, bulldozers and cranes, will become a high-tech, environmentally friendly hospital surrounded by 3.5 acres of peaceful gardens and green space.

— ERIN DIGITALE



Ow in the family

OPIATES ARE THE MAINSTAY MEDICATION for easing pain, but because of side effects they don't work well for everyone. Now a Stanford study shows that susceptibility to the worst of these side effects runs in families.

"One of the most hated side effects of these opiates, nausea, is strongly inherited," says Martin Angst, MD, professor of anesthesia, who was a leader of the study published in the July issue of *Anesthesiology*. Slowed breathing, one of the most dangerous side effects, also was inherited, as was dislike for the drug, says Angst, director of the Stanford Human Pain Research Laboratory.

Researchers recruited 121 pairs of twins for the randomized, double-blinded and placebo-controlled study of opiates, a class of drugs that includes morphine, methadone and oxycodone. Heritability accounted for 30 percent of the variability for slowed breathing, 59 percent of the variability for nausea and 36 percent for drug disliking — which the researchers also tied to decreased likelihood for addiction.

"Our findings strongly encourage the use of downstream molecular genetics to identify patients who are more likely or less likely to benefit from these drugs — to help make decisions on how aggressive you want to be with treatment, how carefully you monitor patients and whether certain patients are suitable candidates for prolonged treatment." — TRACIE WHITE

TOTALLY RAD

"It took us three years and 750 tries to make it work, but we finally did it," says postdoctoral researcher Jerome Bonnet, PhD, who helped engineer a genetic equivalent of a binary digit — a "bit" in data parlance.

Bonnet and two co-authors published a paper June 5 in the *Proceedings of the National Academy of Sciences* describing how they used genetic engineering techniques to repeatedly encode, store and erase digital data within the DNA of *Escherichia coli* bacteria.

They've named their biotech data storage recombinase-mediated DNA inversion, or RAD, after the enzymatic processes used to cut, flip and recombine DNA within the cell.

They used RAD to modify a section of DNA that controls how *E. coli* fluoresce under ultraviolet light. The microbes glow red or green depending on the section's orientation. Using RAD, the engineers can flip the section back and forth.

To create the system, the team

had to balance the dynamics of two opposing proteins, integrase and excisionase, within the microbes. "Previous work had shown how to flip the genetic sequence irreversibly in one direction through the expression of a single enzyme," Bonnet says, "but we needed to reliably flip the sequence back and forth."

"The problem is that the proteins do their own thing. If both are active at the same time, or concentrated in the wrong amounts, you get a mess," adds co-author Pakpoom Subsoontorn. After years of tinkering and testing, they got the balance right. The next goal is to go from the single bit to eight bits — or a "byte" — of programmable genetic data storage.

"I'm not even really concerned with the ways genetic data storage might be useful down the road, only in creating more scalable and reliable biological bits as soon as possible," says assistant professor Drew Endy, PhD, the paper's senior author. "Then we'll put them in the hands of other scientists to show the world how they might be used."

— ANDREW MYERS

COMMUNITY GOOD

Government-funded community health centers, which serve low-income and uninsured patients, provide better care than do private practices. That's the surprising conclusion of a study published in the August *American Journal of Preventive Medicine* by professor of medicine Randall Stafford, MD, PhD.

Stafford and researchers at UC-San Francisco examined records of 73,074 health-center visits to private practices and to Federally Qualified Health Centers and other government-supported organizations where low-income and uninsured people get care. Community health center physicians performed as well as their private-practice colleagues in 13 of 18 measures of care and better in five of those measures.

That's good news in light of the Affordable Care Act, which depends on community health centers to serve more patients. "If community health centers are going to be taking up some of the new demand, we can be confident that they're giving relatively good care," Stafford says. — MANDY ERICKSON



Cochlear kids

DOCTORS ROUTINELY GIVE cochlear implants to deaf children as young as 1 year old. But what if children show signs of mental retardation and might never learn to talk? Does it make sense to implant "bionic ears" then?

Doctors usually don't, but they should seriously consider it, says associate professor of otolaryngology John Oghalai, MD, who with colleagues studied the records of 60 developmentally delayed and 144 cognitively normal children who received cochlear implants.

The researchers found the implants could substantially benefit children's intellectual development, even if they don't learn to talk, he says.

The combination of deafness and developmental delay is increasingly common as more children survive extremely premature birth, which often results in both conditions, as well as many other impediments.

"If you can fix one of the sensory problems, it might help to mitigate the effects of the other disabilities," they say. The research appeared in August in *Otology & Neurotology*. — ERIN DIGITALE

Lasker for Spudich

Stanford biochemist James Spudich, PhD, received the 2012 Albert Lasker Basic Medical Research Award for his investigations of the molecular motors that drive our skeletal muscle contractions and heartbeats, enable our cells to divide, and power patrolling immune cells through our tissues.

The prize, widely considered the American equivalent of the Nobel, carries an honorarium of \$250,000, which Spudich, the Douglass M. and Nola Leishman Professor of Cardiovascular Disease, will share with two other researchers.

Molecular motors reside inside every cell in our bodies. These motors use the chemical energy of ATP — the small, ubiquitous molecule that serves as the body's energy currency — to produce forward motion. Much as a car's engine burns gasoline, these motors "burn" ATP by splitting it in two, liberating chemical energy that is then coupled to mechanical movement.

Clinical trials testing drugs based on Spudich's understanding of how muscles contract offer hope for people prone to heart failure, amyotrophic lateral sclerosis and perhaps even the frailties of old age. "It would be great if a small-molecule drug that bound to skeletal-muscle myosin could strengthen muscles with minimal side effects and let you get out of a chair, or walk down the street," he says. — BRUCE GOLDMAN

At age **6**
JAMES SPUDICH acquired his first in a series of progressively more advanced chemistry sets, foreshadowing his scientific ambition. By his teens his prowess had progressed to the point where he succeeded in triggering a three-engine fire alarm.



BOTTOM LINE

MEDICINE'S FUNDING POOL IS DRYING UP

If you don't have your health, you don't have anything.

Unfortunately, in the United States protecting this most precious asset is breaking the proverbial bank.

This is not news.

In fact, decades have rolled by while the nation's health-care bill has ballooned.

MOST OF US TRY NOT TO THINK ABOUT THE FACTS, BUT WE IGNORE THEM AT OUR PERIL. A FEW STUNNERS:

- **U.S. health-care spending neared \$2.6 trillion in 2010**, which is 17.9 percent of the nation's gross domestic product. This translates to \$8,402 per person.
- **More than 75 percent of U.S. health-care spending is due to chronic conditions**, which are expected to become even more prevalent as the baby boomer generation ages. In 2000, 125 million people suffered from chronic conditions; by 2020, that number is projected to reach 157 million.
- **Competition for biomedical research funding has become cutthroat.** At the National Institutes of Health, the world's biggest funder, requests for dollars rose from 3.6 times the supply in 1998 to 6.5 times the supply in 2011. Driving this dynamic is a huge increase in applicants: from about 19,000 in 1998 to approximately 32,000 in 2011.
- **Meanwhile, the U.S. economy is stagnant**, which means it's unlikely the government will pick up much more of the tab for health-care costs. It also means there's little chance that funding for biomedical research will return to the rapid growth it enjoyed in decades past. When adjusted for inflation, NIH funding is back to where it was a decade ago. And not surprisingly, the United States, long the world's leader in biomedical research, faces challengers. The Chinese government's spending on medical research, for example, increased 67.3 percent between 2009 and 2010.

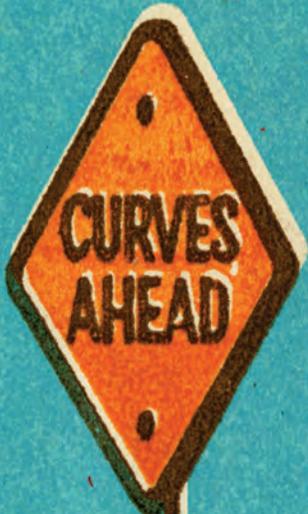
What's behind the crisis? How can we dig ourselves out of this predicament?

Stanford Medicine's special report on medicine's money crunch offers some answers and poses more questions.

ILLUSTRATION BY BRIAN REA



2691
621

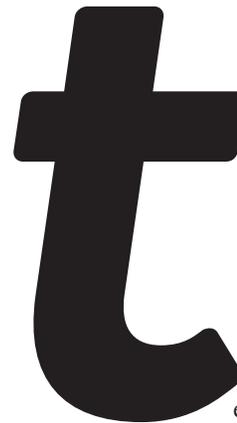


Taxals



the competition

ON THE HUNT FOR RESEARCH DOLLARS



ears welled up in Christopher Gardner's eyes. Sitting in an airport terminal on a summer afternoon in 2011 awaiting a connecting flight, he had just read the email from the National Institutes of Health, and the news was good. Yes, good. Gardner, a mid-career professor at Stanford, had gotten a high score on his grant application, in the top 10th percentile, high enough to likely qualify to receive funding for a study he'd been trying to get off the ground for years — an investigation into why certain weight-loss diets work for some people but not others. • *The thought, "It's still not a sure thing," flickered through his mind.* There was yet another review to clear. But it looked like the hundreds of hours spent writing and rewriting the proposal had paid off. • *Gardner says he got into science because of a zeal to search for truth.* He still has that zeal. But these days, of necessity, he's on a search for funding. Gardner's case is in no way unique. His ultimate goal is an R01 research project grant from the NIH, an independent research grant with up to five years of funding, the goal of nearly every medical researcher whose career depends on winning grants (the vast majority). Gardner had previously won NIH grants, but he had begun to wonder if he'd ever get another. Not only would it help fund his research, salary and the upkeep and growth of the medical school itself, but it's a stamp of approval for his research program. • *What's involved?* In an R01 grant proposal, a researcher has 12 pages to detail the project's aims, background, preliminary data and research plan. But most of the effort isn't the writing; it's coming up with the idea for the project in the first place, then generating the preliminary evidence and rationale that it might really work. • *Over the past decade, getting an NIH grant has grown increasingly difficult, and not just for Gardner.* This is not surprising. It's what happens when Congress halts the more than a half-century of prodigious growth in the NIH grants budget, and the number of proposals for those funds rockets upward. The result: Last year, the percentage of successful proposals was the lowest ever: 18 percent. NIH's review groups of primarily peer scientists selected those from 49,592 submissions — also an all-time record, and up 8 percent from the year before.

By Rosanne Spector

ILLUSTRATION BY GARY TAXALI

W

HAT DOES A STANFORD MEDICAL SCHOOL PROFESSOR DO ALL DAY? UNLESS YOU WORK AT A MEDICAL SCHOOL YOURSELF, YOU'LL PROBABLY BE SURPRISED BY THE ANSWER. Professors engage in a variety of activities, of course. Nearly all do some teaching. Many provide health care. At research-intensive medical schools like Stanford, many devote most of their time to scientific investigation — designing experiments and analyzing data. But what nearly all faculty members whose specialty is research do for hours every day — not just at Stanford but at every U.S. medical school — is chase money.

The chase can be exhilarating, but it can also be exhausting. And after a decade of constriction in NIH funding, many people within medical research, even the institute's leaders, think the U.S. system for fostering medical discovery is close to breaking.

That system is fueled largely by federal grants from the NIH, which made its first grants in 1947 and steadily increased its grant funding for decades. Then in 1998, Congress upped the pace, leading to a doubling of the budget in just five years. The budget reached \$27.3 billion in 2003.

Not surprisingly, this ever-increasing grant supply has led medical schools to hire more faculty who in turn win more grants, which allows their schools to build yet more research facilities. Graduate students and postdoctoral fellows, also often supported by federal grants, conduct the research for relatively low pay in the spirit of apprenticeship, hoping one day to lead a lab of their own. This system has made the United States the world's leading source of biomedical discovery.

It was great while it lasted. After the biggest, fastest increase in the NIH's history — the spurt ending in 2003 that's become known as “the doubling” — the grant budget hit a wall. Aside from the short boost of stimulus funding from the 2009 American Recovery and Reinvestment Act, grant funding has risen only minimally, and when inflation is accounted for, it has fallen.

“It's an undoubling,” says Sally Rockey, PhD, director of

the NIH extramural grants program. “Our buying power is back to about the year 2000.

“We still have excellent research going on. But you can imagine if we go on without increased investment we will be in the crisis stage,” says Rockey.

“The long-term consequences of these declining investments in research are enormous and tragic, especially given the extraordinary opportunities that abound,” says Philip Pizzo, MD, dean of Stanford's School of Medicine. “Even for the most seasoned and successfully NIH-funded faculty, concerns about the future are serious and highly worrisome. In addition to the amount of time spent in writing grants and exploring new funding sources, the ability to propose the most creative and innovative research becomes a question mark when study groups and research councils focus more on what's achievable than what can be imagined.”

Biochemistry professor Suzanne Pfeffer, PhD, past president of the American Society for Biochemistry and Molecular Biology, says at Stanford, the high quality of research provides some cushion, “but across the country people are closing labs, retiring early. This is a crisis.”

Of course, medical leaders and researchers can be expected to decry a reduction in a flow of funds on which they've grown dependent. But the implications go beyond the ivory tower. While the United States is curtailing funding, other nations are boosting funding for scientific and medical research for the long-term good of their economic growth. This trend is most evident in Asia, where several nations have made medical research a priority. China's government spending on medical research increased 67.3 percent between 2009 and 2010 to reach \$567 million. India's increased 15 percent to \$135 million. South Korea's government spent \$1.05 billion in 2009, a 23.6 percent increase from the year before.

The widespread assumption is that U.S. federal spending for medical research will stay flat, or maybe continue to drop. “Nobody in their wildest dreams would expect to see anything like the growth we've had in the past,” says Ann Bonham, PhD, chief scientific officer at the Association of American Medical Colleges. “Institutions across the nation

‘Our buying power is

BACK TO ABOUT THE YEAR 2000. WE STILL HAVE EXCELLENT RESEARCH GOING ON. BUT YOU CAN IMAGINE IF WE GO ON WITHOUT INCREASED INVESTMENT WE WILL BE IN THE CRISIS STAGE.’

are coming to grips with the new normal.”

On the level of an individual medical researcher like Gardner, a failure to win federal research grants signals that he's not making the grade, not only in his own eyes but also in those who decide whether he'll be reappointed.

Stanford medical faculty members are hired into one of three categories: university-tenure line faculty are expected to achieve excellence in research, medical-center line faculty are expected to devote most of their time to patient care and clinically related research, and non-tenure line faculty focus either on teaching or, as in Gardner's case, research. All three lines include some teaching. Faculty at most medical schools fall into similar categories.

“In the university-tenure line, it would be a very rare faculty who gets promoted without any grant funding,” says Stanford medical school's senior associate dean for research, Harry Greenberg, MD. “That's because you generally need funding to do most kinds of medical research, and you get the funds because your peers think highly of what you propose to do.”

Non-tenure line faculty specializing in research like Gardner are uncommon at Stanford — there are only 56 in this role — but they are even more dependent on grants or contracts for funding. If for more than two years they fail to secure sponsorship that covers 80 percent or more of their salary, they are at risk of losing their job.

As biomedical leaders and faculty in research trenches don't expect the federal grant budget to grow much if at all, they're looking for other solutions.



GARDNER'S EXPERIENCES SECURING NIH GRANTS ARE PAR FOR THE COURSE FOR A MEMBER OF THE STANFORD MEDICAL FACULTY WHOSE PRIMARY WORK IS RESEARCH and who began a career in the last few decades. In short, the experiences have gone from challenging to maddening.

“It used to be that you would think about funding all the time, but you wouldn't talk about it, at least not about failing to get it or losing it. It was embarrassing,” says Gardner, an associate professor in the Department of Medicine's Stanford Prevention Research Center. “Now people are open. You say you didn't get funding and they'll say, ‘I know, me too. It's brutal.’”

When Gardner wrote his first NIH grant application, it was during the five-year doubling and he had a relatively easy time of it. In 1998, he proposed a study of the effects of chemicals in soybeans known as isoflavones on prostate, breast and bone as part of a massive joint proposal with other researchers. The joint proposal didn't get funded but the

next year he submitted just his part and obtained his first R01 grant, \$1.25 million over five years.

Gardner was on a roll. In 2002, he got an R01 grant to compare the effects of garlic on cholesterol levels, with total five-year funding of about \$1.5 million. (The only time he got an R01 proposal funded on the first-round submission.) Then in 2003, he won a grant to do his first weight-loss diet study. Landing that one, which led to the most important study of his career so far — a comparison of four popular diets, ranging from low- to high-carbohydrate intake — was not so easy.

Gardner first proposed the weight-loss study in 1999 before he joined the Stanford faculty. He takes a certain masochistic pleasure in tracing it from its beginnings. “This will be fun,” he says, launching into the history.

It started on a whim when he had a short-term faculty position at UC-Davis and competed for a \$50,000 internal grant to compare several diets' effectiveness. He didn't get it. But a colleague suggested he make it much bigger and submit it to the U.S. Department of Agriculture. “So I spent a bunch of time and made it into a \$3 million grant,” says Gardner. “They didn't even read it.” That was because Gardner made a beginner's mistake: He hadn't realized the funding was capped at \$1 million. So he resubmitted the grant the following year, rewriting it to fit within the funding limit. He didn't get it. That was the third try.

Hired back to Stanford in 2001 (he was a postdoc and a research associate from 1993 to 1999), Gardner called the NIH program officer for advice. “Could I submit this massive thing? Or should I drop it?” The program officer suggested that since Gardner had no track record in weight-loss studies he submit it as a smaller, less expensive project — a pilot study. After many hours of discussion, research and rewriting, Gardner sent in the scaled-down proposal, but it was rejected too.

It was only after additional revisions, and a resubmission in 2003 (the fifth overall try since 1999) that he got the grant. Not only that, but a few months after he started the pilot study he learned to his delight that he had been awarded an additional \$1.5 million for the study — he was the recipient of a portion of the \$5 million court judgment against dietary supplement-maker Metabolife. He used the additional funds to expand the study, a clinical trial of diets. He published the results of what he called the “A TO Z weight-loss study,” in 2007 in the *Journal of the American Medical Association*, one of medicine's top journals. The trial, which made him famous in nutrition circles, compared the results of a year of the Atkins diet (extremely low carbohydrate), Zone (low-carbohydrate, high protein), Ornish (very low fat) or USDA/Food Pyramid LEARN (high carbohydrate/moderate-low fat) for 311 overweight women. What he found was that none of the diets worked well for all followers, but on average, those on the Atkins diet ended up with a

'Donors do not give

US MONEY TO TURN THE LIGHTS ON, REPAIR THE ROOF,
PREPARE FINANCIAL STATEMENTS, IMPROVE THE WIRELESS
INFRASTRUCTURE OR PAY FOR AN UGLY SEISMIC RETROFIT...
NO ONE'S GOING TO GIVE US MONEY FOR THAT.'

modest advantage in both weight loss and metabolic health.

It was a finding that flew in the face of accepted nutrition tenets, and raised a lot of new questions. For Gardner, the biggest was why each of the diets worked great for some people but not for others. "It's an obvious question — there was huge variability *within* each of the diet groups, much more so than *between* any of the diets." He submitted proposals to NIH to investigate this question, refining the approach after each rejection. Initially he proposed testing whether someone's insulin status — insulin resistance vs. insulin sensitivity — explained an important amount of the within-diet variability. These weren't funded. Now on the seventh try, a proposal to test whether a genetic signature can predict which diet will work best for different individuals finally made it into the top 10th percentile. Each NIH granting body sets a payline — a percentile rank up to which nearly all R01 applications can be funded, and Gardner's proposal had passed that test.

The proposal had just one more gauntlet to run. It had to pass muster with the body's advisory council — a group of scientists, patient advocates and community representatives that makes recommendations based not only on scientific merit but funding priorities. But with obesity a major public health problem, he thought it had a good shot.

AS GARDNER AND OTHER FACULTY APPLY FOR GRANTS, STANFORD MEDICAL SCHOOL'S SENIOR ASSOCIATE DEAN FOR FINANCE AND ADMINISTRATION, MARCIA COHEN, MONITORS THE HEALTH OF THE SCHOOL'S FINANCES. Clinical activities and research grants and contracts are the largest sources of revenues at Stanford, as at most medical schools. Then come various other smaller sources, including tuition, the parent institution (the state if the school is public, or the university if it's private) and philanthropy. Stanford medical school's revenues have been on an even keel — for the most part. The big question mark is the grant funding, which accounts for 38 percent of the medical school's

budget. "This year our research revenues are 5 percent lower than last year because the majority of our grants from the federal stimulus program ended. With the possibility of more NIH budget cuts in January, I am worried," says Cohen.

While Stanford University's fundraising success and its approximately \$17 billion endowment provide a degree of security few universities enjoy, those dollars won't solve the potential problems at the medical school.

"We can be rich and still feel very constrained, because in medical school finances we have a lot of restricted funds," says Cohen. "Donors are passionate and interested in giving you money for specific research. They don't just say, 'It's for the general support of the medical school.' Donors do not give us money to turn the lights on, repair the roof, prepare financial statements, improve the wireless infrastructure or pay for an ugly seismic retrofit to make sure the building doesn't collapse. No one's going to give us money for that. It's still tricky for us to balance our operating expenses."

Hence, the reliance on federal funds to help cover overhead costs. With every federal grant, a research institution receives not only the funds budgeted specifically for the proposed project but an additional percentage that goes to the institution for overhead. Every few years, research institutions negotiate this percentage, called the indirect cost rate, with the federal government. The government establishes the rate after examining the costs for facilities and administration incurred since the last assessment. Stanford's current rate, 57 percent, is a bit lower than those at many comparable institutions: Harvard Medical School's is 69 percent, Yale's is 66 percent, Johns Hopkins' is 62 percent. Neighboring UC-San Francisco's is nearly identical to Stanford's at 56.5 percent.

What this means for Stanford is that for every \$1 million the researcher gets for the direct costs of the project, the university can receive up to \$570,000 for the indirect costs. Non-NIH funding sources rarely pay full indirect costs.

"If we don't have a growing research base, or if it doesn't at least stay flat, then the school doesn't have as much money to pay for the infrastructure costs that we need to house and manage all the research we do," says Cohen.

As for solutions? NIH is typically the source of 70 to 75 percent of Stanford medical school's grants, but Cohen is seeing a trend among faculty to apply for funding from other federal sources, in particular the Department of Defense, Department of Energy and USAID, as well as State of California grants and contracts, including awards from the California Institute for Regenerative Medicine.

The medical school's Research Management Group also provides an exhaustive collection of funding opportunities on its website, ranging from a \$100,000 innovation grant from Alex's Lemonade Stand Foundation ("fighting childhood cancer one cup at a time") to a \$2.5 million clinical trial award from the Department of Defense to test treatments for combat injuries. Beyond this, the school's institutes and some of the departments have staff that match faculty to prospective grants and then help prepare and submit the proposals. One of Cohen's quandaries is how much to increase the staff in these positions beyond the current handful, if at all.

Ultimately, however, unless the federal grants boom again — and no one interviewed for this article was counting on that, or even expecting it — medical research must find other sources of support or risk atrophy.

G

ARDNER HAS A NEW PASSION.

"I WANT TO BUILD AN INTERDEPARTMENTAL PROGRAM AROUND FOOD SYSTEMS, partly because I think this will be the wave of the future for improving diets in the country, but also partly because of my frustration with getting funds through traditional routes," he says. He's not giving up on federal grants but he's also seeking philanthropy. He believes such a program could become a magnet for individuals willing and able to fund research the NIH won't. In part to build a case for a program, in 2010 he began hosting the Stanford Food Summit, an annual interdisciplinary conference on food. He's also raising his profile by speaking at conferences and workshops beyond the walls of academia. He's already had some success, securing two grants totaling \$75,000. He's using these funds to support studies designed to improve the quality of hospital food, to assess the feasibility of increasing the amount of produce distributed through food banks, and to see whether a farm-themed summer camp can improve preferences for vegetables among low-income children.

With food a national obsession, and Gardner an enthusiastic fundraiser, his hopes for philanthropic support seem justified. But researchers like Pfeffer, who study more arcane topics, like the basic molecular workings of cells, probably don't have alternatives.

That's troubling because basic research enlarges our under-

standing of health and disease and opens new routes for developing treatments and cures. It's the kind of work the United States excels at. But it's expensive to run a lab, and it requires a great deal of university infrastructure to support it — in terms of technical support staff and research space. For these indirect costs, the nation's medical schools have relied on federal grants.

"Universities have set up a business model dependent on grants with indirect costs," says Pfeffer. "If you say, 'Well, we have to cut indirect costs,' we'll have to think of different ways of how to operate." And she holds out hope for philanthropy as well. "What will really help Stanford is endowments. I think that's how Stanford is going to survive," she says.

I

N THE HERE AND NOW, THOUGH,

THE NIH STILL OFFERS A TREMENDOUS AMOUNT OF RESEARCH FUNDING AND INVESTIGATORS EXPEND TREMENDOUS ENERGY TRYING TO OBTAIN SOME OF IT. • Gardner estimates he has spent hundreds of hours each year writing and rewriting proposals. In addition to applications for grants to fund his own research, he led the writing of a massive \$6 million proposal for more than 50 Stanford investigators to create an interdisciplinary nutrition/obesity research center. The proposal was 500 pages long. He submitted it in 2009, and when it failed to get funded he and his colleagues revised and resubmitted it in 2011. Still no dice. "I easily spent pretty much full time two months on each one. Obviously pretty frustrating to put in all that time and get no funding out of it."

As for the seventh iteration of the weight-loss study follow-up, he really wants to do it. "This is the logical follow-up for the last decade of weight-loss diet studies," says Gardner. "For decades people said low fat was best, but the obesity epidemic didn't end. So people said, 'No no, you got it wrong, it should be low carb,' but they didn't have any evidence. Until recently the conclusion was forget both and just focus on calories. What I'm saying is it's still a reasonable question, but just stop randomizing the average person. Look for predictors of different responses to the same diet. Use insulin-resistance status or genetic information to guide which diet to recommend. I think this is where the field is going."

On Sept. 13, 2012, Gardner got his happy ending: notice of award for the project, "Do Genotype Patterns Predict Weight Loss Success for Low Carb vs. Low Fat Diets?" The award, for \$3.3 million over five years, comes with full indirect costs. **SM**

Contact Rosanne Spector manishbma@stanford.edu



against the odds

A
BAND
OF
REBELS
FIGHTS
TO
SAVE
HEALTH
CARE

by *Kris Newby*
photography by *jamie kripke*

AT LEFT:
MANALI PATEL

MANALI PATEL, MD, HAD DARK CIRCLES UNDER HER EYES AFTER A ROUGH WEEK BATTLING TUMORS AT THE STANFORD CANCER INSTITUTE. PATEL, 33, DOE-EYED AND 99 POUNDS SOAKING WET, LOOKED MORE LIKE A COLLEGE FRESHMAN THAN AN ONCOLOGY FELLOW SIX YEARS OUT OF MEDICAL SCHOOL. • Lately, she had seen a lot of bad endings. Several patients who wanted to die at home said their last goodbyes from a hospital bed, tethered to machines with tubes and wires. Another patient was referred to the hospital without knowing why. It was Patel's job to deliver the grim news: He had incurable lung cancer and only a few months to live. • Then, as she hung up her white coat for the day, she received the worst call of her life — her mother had breast cancer. • This began Patel's journey down the patient side of cancer treatment, away from the traditional career path of a working doctor. She joined a small, idealistic band of physicians, engineers and management scientists with an ambitious goal — to battle the waste and perverse financial incentives in America's increasingly unaffordable medical system. • Her mother's call also brought a personal urgency to a nagging problem that is easy to ignore while working 80-hour weeks and managing the treatments of 100 or so cancer patients a month: Few oncologists have the time to talk to cancer patients anymore. • Less than a third of oncologists have end-of-life discussions with terminal cancer patients. As a result, cancer patients are left out of the decisions that determine how and where they spend their last days. Recent studies show that when cancer

patients understand the big picture — treatment side effects, survival odds and pain-relief options — they live longer and enjoy a better quality of life.

Listening to her mother's voice over a bad cell phone connection 3,000 miles away, Patel realized that her mother was about to be rushed off to chemotherapy.

"Wait. We need to talk first," said Patel, as she started to formulate her plans to try to bring compassion and affordability back into cancer care, for mother and country.

PATEL GREW UP WITH HER PARENTS AND TWO SIBLINGS IN SHELBY, N.C., THE RURAL APPALACHIAN TOWN WHERE *THE HUNGER GAMES* WAS FILMED. Her parents, who emigrated from India in 1973, worked hard to give their three children a good education in a community of primarily cotton farmers and textile workers. Patel's mother held two jobs and her father ran his own textile design company. They bought only books, never toys, for the children. And ultimately, all three were accepted into a competitive science high school near Duke University and the University of North Carolina's medical school.

Around town, Patel's mother is known as "Mrs. Patel with the long hair," because of the long, dark braid that comes down to her knees. Though Patel and her mother look very much alike — petite with caramel-colored skin — their cultural backgrounds are very different.

"My daughter is the protector of the family, aggressive and outspoken," says Mrs. Patel, who asked that her first name not be used.

Patel's mother, whose marriage was arranged by aunts and uncles in Gujarat, India, was raised to follow elders' and doctors' orders without question.

When Mrs. Patel's local physician first diagnosed her with cancer, he immediately sent her to a local oncologist for chemotherapy. "Once my doctor said the word 'cancer' I started crying and heard nothing," says Mrs. Patel. "I thought it was the end of the world."

Patel, the daughter-oncologist, was upset that her mother hadn't gotten a second opinion. She told her mother to put everything on hold until she could talk to a breast cancer specialist at Stanford. And, for the first time, she experienced "the cancer talk" from the other side of a physician's desk.

"This Stanford breast cancer specialist, who had never met me, called me back at 10 p.m. that same day," says Patel. "He spent an hour on the phone with me, reassuring me, telling me what I needed to know about my mother's cancer and teaching me how to be her caregiver."

Patel flew her mother out to meet with the Stanford specialist, who then spent two hours with her mother discussing

her condition and wishes. The deciding factor in her mother's treatment plan came at the very end of the meeting: "My mother said she didn't want chemotherapy because she didn't want her hair to fall out," says Patel. "Back in India, her family had a tradition of never cutting hair. None of her American children had realized that this was so important to her."

Instead of chemotherapy, Patel's mother was given six weeks of daily radiation, followed by a five-year course of a non-chemo drug that doesn't cause hair loss.

"Going through this with my mother made me a better doctor. And it made me realize that these cancer discussions take time," says Patel.

Though she worried about whether her mother had made the right choice, she realized the importance of letting this be her mother's well-informed decision, not hers.

As she finished her oncology training, she decided to take action on what she had learned. So she hit "pause" on that \$380,000 median oncologist's salary, buying a house and starting a family. Instead, she joined the Clinical Excellence Research Center at the Stanford School of Medicine.

LEAP OF FAITH

THE CERC IS LED BY ARNOLD MILSTEIN, MD, THE CENTER'S DIRECTOR AND A PROFESSOR OF MEDICINE. The 2-year-old center's mission is to find more affordable ways to deliver better medical care to the sickest of our population who consume the bulk of the country's health-care spending.

The CERC team takes aim at the unintentional wastefulness of the U.S. medical system, which is by far the most expensive in the world, yet is ranked 37th in quality of care. In Milstein's opinion — forged after 25 years as a health-care advisor to Fortune 100 companies, three White House administrations and Congress — there is no quick fix. Our country needs to safely improve the value of its health-care

As she finished her oncology training, she decided to take action on what she had learned. So she hit 'pause' on that \$380,000 median oncologist's salary, buying a house and starting a family.



THE CLINICAL EXCELLENCE RESEARCH CENTER'S FELLOWS AND TERRY PLATCHEK, FELLOWSHIP DIRECTOR.

From left: Sarah Adler, Graham Abra, Manali Patel, Platchek, David Moore and Sundeep Singh.

system by at least 2.5 percent per year, every year, in order to align health spending with national income growth. Anything less means more uninsured people, higher taxes and, eventually, fiscal Armageddon.

Milstein, a soft-spoken Midwesterner with a fondness for corduroy jackets, is building a pipeline for creating and testing innovative health-care delivery methods.

“To anchor our process, we recruit very smart postdoctoral and master’s-level research fellows with a history of fresh thinking and successful doing,” says Milstein. “We expose them to successful health-care innovators, pair them with Stanford faculty and Silicon Valley mentors to formulate better health-care models, then recruit health-care organizations and insurers to test the effectiveness of their concepts.”

Over the years, Milstein has won a number of epic battles in health-care redesign. He co-founded the Leapfrog Group, which defined hospital patient safety goals that became the de facto standard across the nation. He was the force behind Congress’ decision to stop paying hospitals for the cost of treating preventable patient complications. He launched an outpatient care delivery model for medically frail patients, called the “ambulatory-care ICU,” which

improved health and lowered annual per-patient spending by more than 15 percent. And he’s the founding medical director of the Pacific Business Group on Health, the nation’s largest regional health-care improvement coalition of large employers, whose members include Chevron, Safeway, Walmart, Boeing, HP, Cisco, Facebook, CalPERS and Stanford University.

For the fellows’ first year, Milstein targeted four of the most debilitating and expensive medical conditions in the U.S. system — chronic kidney disease, morbid obesity, colon cancer and poor-prognosis cancer, which was Patel’s area of focus.

Though the fellows have diverse backgrounds, all have had personal experiences that have motivated them to join this small group of reformers.

For example, Graham Abra, MD, a nephrology fellow, was curious about why some medical institutions provide better patient care than others, and whether innovative approaches could make health care more affordable. Psychologist Sarah Adler, PsyD, became interested in obesity after researching the mental health underpinnings that may contribute to overeating. Sundeep Singh, MD, a gastroenterology fellow with a bachelor’s degree in industrial and systems engineer-

ing, sought to develop systems-based solutions to health-care delivery. Kimberly Stone, MD, a surgery resident, wanted to see if making low-cost bariatric surgery more widely available might extend life for morbidly obese patients. And David Moore, PhD, an industrial engineer and consultant, became interested in the redesign of health services after working on a system to improve efficiency in surgical suites.

Abra, who worked on the chronic kidney disease and cancer care models, spoke about his first impressions: “It was pretty risky signing up for a new type of fellowship program. There’s this professor with the crazy idea that better health care can cost much less. But he was giving us a chance to fix the medical system at a higher level. So I joined.” And he adds with a smile, “It was a leap of faith.”

VALLEY OF DESPAIR

THE TEAM GOT TO WORK IN AUGUST 2011 WITH A MONTH-LONG “INNOVATION BOOTCAMP.” It started with almost 50 briefings by eminent health-care economists, biostatisticians, futurists, clinical specialists, faculty, information technology experts, human factors gurus and behavioral scientists. They also met with leaders from efficient health systems, such as the Permanente Medical Group in California, ThedaCare in Wisconsin, Intermountain Healthcare in Utah, and government-run health systems in British Columbia and Sweden.

“I was star-struck, and I even felt a little guilty about how many top national experts met with the six of us,” says Patel.

Optimism was high among the fellows as they began their clinical research and observations. To help structure their search for solutions, the center adapted the Stanford Biodesign Program innovation methodology, which has spawned more than 300 patents and 26 medical technology companies. This training teaches inventors to identify the most pressing unmet needs within a medical system, so that the resulting solutions improve clinical outcomes and save money. The team spent two months immersed in clinical settings, observing patients, families and physicians. They interviewed care delivery innovators in the United States, Canada, Sweden and other countries. And they gathered new ideas from scientific literature and medical experts.

Fast forward two months: It was almost 11 p.m., and the fellows were in a conference room cluttered with marker-scratched white boards, fast food carnage and stacks of studies. The fellows had fallen into the “valley of despair,” the ugly, chaotic middle of the innovation design process.

“We were all so exhausted and suffering from information overload,” says Patel. “That was the low point. We couldn’t imagine how we were going to make sense of everything we’d learned.”

That was where the Biodesign process helped — as well as its credo: “Given enough time, sugar and caffeine, you *will* invent something.”

At this stage of the project, the fellows had a list of about 200 unmet needs (a.k.a. problems to fix) for each target condition. The needs were entered into a database and ranked by characteristics such as importance to patients and clinicians, and potential cost savings. This helped the team narrow the best ideas to those that addressed the most critical “needs clusters.” Then, during the late winter and spring, Patel and the other fellows began assembling their care models, folding in feedback from faculty and mentors.

When Milstein reviewed the first round of care models, he was worried. He felt that some of the fellows had fallen prey to “anchoring bias,” the human tendency to fixate too early on one piece of information when making decisions.

“That’s where David Moore, our operations researcher, really helped the team,” says Milstein. “He created the economic and analytical framework for each of the care models, and in the case of Patel’s plan, the biggest cost-benefit in cancer care came from an unexpected line item — rapid symptom relief.”

TALK IS CHEAP

THE SIDE EFFECTS OF CANCER TREATMENTS — PAIN, SEIZURES, DEBILITATING HEADACHES AND NAUSEA — CAN EASILY OVERWHELM PATIENTS AT NIGHT OR DURING WEEKENDS, WHEN ONCOLOGISTS ARE DIFFICULT TO REACH. Suffering patients often end up in crowded emergency rooms, waiting hours for relief. Sometimes they’re hospitalized overnight, waiting until the oncologists arrive the next morning, accruing thousands of dollars in unnecessary medical bills.

Patel’s model provides patients with 24-hour telephone access to nurses trained in cancer care. They guide patients’

‘We were all so exhausted and suffering from information overload. That was the low point. We couldn’t imagine how we were going to make sense of everything we’d learned.’

use of symptom-control medications, pre-positioned at home or delivered within hours.

“Quick symptom relief is not only more humane, but it literally saves thousands of dollars per year for these cancer patients,” says Patel.

Another component of her care model is providing patients with more convenient local access to chemotherapy infusions, giving patients with low-risk treatments the option of receiving the drugs at home, via home health nurses, or at nearby infusion centers, such as those operated by Walgreens across the country. These treatments would be monitored by experienced nurses and pharmacists, and remotely guided by expert oncologists. Patel discovered that this approach is already working well for the Nebraska Veterans Administration hospital.

Perhaps the most important aspect of her model is earlier cancer patient counseling, institutionalizing shared decision-making well before a patient is on the brink of death and emotions overwhelm the decision-making skills of patients, their families and clinicians.

According to a recent study, end-of-life discussions typically take place only 33 days before death. With Patel’s new cancer care model, patients would be thoroughly briefed on the survival odds and side effects before being rushed off to surgery or chemotherapy. Many months before the family is gathered around a loved one’s deathbed, a person’s final wishes — resuscitation, feeding tubes, assisted breathing and whether a person wants to die at home — would be well-informed and documented.

“Eighty percent of all cancer patients express a desire to die at home, yet only 10 percent do,” says Patel. “These conversations, which typically take two hours in the beginning and require many follow-on conversations, are too hard, time-consuming and draining for a busy oncologist to do well.”

These conversations would automatically occur whenever the probability of death is 30 percent or more within three years, based on oncology survival tables.

After months of scenario building and faculty critiques, the team’s care models crystallized for each of the four conditions, and three-year health spending reductions were projected.

Based on a conservative financial model, Patel estimated that her team’s new care model would lower the \$123,000 annual per-capita health spending of poor prognosis cancer patients by 30 percent — even after paying for its new services.

The problem? Clinics, hospitals and insurers have to be convinced that paying for these additional services on the front end will pay off on the back end. And this was Patel’s challenge as the academic year came to a close — to find partners willing to test her plan, so she could gather and publish evidence on effectiveness.



ARNOLD MILSTEIN

The center’s leader and advisor to government and industry.

Finally, after 10 months Milstein and the other faculty decided that the fellows’ care models were ready for their first public airing.

THE PITCH

IT WAS JUNE, SIX DAYS BEFORE THE SUPREME COURT ANNOUNCED ITS RULING ON WHETHER THE AFFORDABLE CARE ACT WOULD STAND. Patel and her colleagues were about to present their new care models to about 100 health benefit plan leaders of the Pacific Business Group on Health at its annual strategy retreat. The meeting was in a conference center, once a turn-of-the-century mansion, now landlocked in a sea of San Jose tract homes. The conference room walls were papered in easel notes from the previous day, filled with ideas on how to provide the best possible medical care to their employees in the face of escalating health-care costs.

Milstein introduced the Stanford fellows and summarized the writing on the wall: “The only way we’re going to bring per-capita health-care spending in line with revenue growth is to create a continuous flow of more efficient ways of delivering health care. Today, our research fellows will illustrate the first wave of Stanford-designed care models, and we ask that you to consider testing our ideas.”

Patel was second up in the presentation, a little nervous and

barely tall enough to be seen behind the podium. She stated the problem in her target area: Cancer is the second-leading cause of death in the United States, with costs estimated to be \$173 billion by 2020. These rising costs are unsustainable.

And what do many poor-prognosis cancer patients get for all the money spent? “Horrible treatment,” she said, citing a statistic that silenced the room: Seventy-three percent of terminal cancer patients *never* have an end-of-life discussion with their oncologists. “Many patients are rushed off to chemotherapy without understanding the big picture. And when predictable treatment side effects happen at night and on weekends, patients who are unable to reach their oncologist end up in misery in emergency rooms and hospitals. Later in their illness, many die painfully in intensive-care facilities that bankrupt their families emotionally — and sometimes financially.”

During her presentation, Patel’s eyes became dark pools that threatened to overflow. A few people in the audience wept silently, perhaps remembering loved ones who had similarly suffered.

“Overall, these added services improve the quality of life of patients, giving them what they need and want without delay,” she added after describing her model. “And best of all, we lower health insurance costs ... simply by *doing the right thing.*”

Afterward, leaders from Disney, Tesla, Boeing and Safeway asked Milstein and the fellows for more details on implementing their models.

The following week, however, some of Patel’s conference calls to health-care providers and insurers didn’t go as well.

At a large clinic in the Midwest, the medical director said to Patel, “Our cancer center is one of the few areas where we’re profitable. Thanks just the same, but we’ll pass.”

A representative from a large national private health insurer said, “We can’t afford to alienate any more of our oncologists by lowering their income.”

Another health-care insurer in Seattle referred to her proposal, only half-jokingly, as a “death panel,” using the Tea Party’s misnomer for the counseling sessions on end-of-life cancer care and hospice that were to be reimbursed under the Affordable Care Act. This provision, which was misinterpreted as government committees encouraging seniors to forgo treatments to save money, was pulled from the act before it passed.

By the end of the second week of presentations, Patel was deflated. Her care model was dead last in attracting test sites, and she began to realize that a major flaw in her plan was that it threatened the livelihood of the plan’s most important participants — oncologists.

The near-term savings from her care model would come off the bottom-line revenues of oncology practices and cancer centers. Unlike other medical specialties, private-practice

oncologists earn most of their money through selling drugs — 65 percent of total revenues come from drug sales and another 21 percent from fees associated with drug infusions, imaging and radiation services, according to the National Oncology Practice Benchmark 2011 Report published in the *Journal of Oncology Practice*.

This report goes on to show that only 8 percent of a typical private-practice oncologist’s earnings, strictly speaking, comes from “patient time,” the revenues earned through conversations about cancer, treatments, side effects, outcomes and end-of-life issues.

“Current incentives are often misaligned to reward doing the most aggressive and expensive actions, as long as patients are satisfied, because this leads to the highest return to the practice,” says Thomas J. Smith, director of palliative care at Johns Hopkins, in a 2010 article in *Oncologist*. “Some consequences include U.S. cancer treatment costs that are twice that of any other nation with no or minimal differences in survival, late referrals (if at all) to hospice, and 14 to 20 percent of patients receiving chemotherapy within 14 days of their death, when it is highly likely to harm and cause complications.”

Private-practice oncologists, on the other hand, argue that they are losing money because Medicare reimbursement rules don’t cover overhead costs for drug administration, inventory and bad debt. They understandably want to fight the erosion of their revenue base, which has fallen 33.5 percent in the last six years. But as the Affordable Care Act seeks to wean the medical system away from the fee-per-service structure, Patel hopes her model can be the bridge from the old compensation model to a new one, based on shared savings from more humane and effective treatments.

After the first two weeks of sales pitches, Milstein organized an expert panel to critique the fellows’ presentations, prepping them for more presentations over the summer. Milstein was joined by Rob Rebitzer, a CERC consultant and a former partner in Accenture’s health-care consulting group. Together, they offered advice on speaking more simply and slowly, “like Mr. Rogers,” to certain groups. And they suggested clarifying that the substantial savings from each new care model would be shared by employers, physicians and patients within large health insurance groups.

For Patel’s plan, they recommended that criticism of oncology compensation structures be replaced with ideas on oncology profit-sharing incentives. And overall, Patel should stress the win-win aspects of her model — better care that saves the system money.

At the end of the session Milstein spoke from the heart to his fellows: “I know it’s difficult to offer advice to a room full of senior health-care professionals who are all older than you,

C O N T I N U E S O N P A G E 4 1

GIVING WELL

PHILANTHROPISTS ROLL UP THEIR SLEEVES

The explosion of wealth in Silicon Valley has brought about a new type of philanthropist, an entrepreneur who not only donates money but draws up a business plan for how that money will be used. This hands-on movement has morphed into a national trend, with more philanthropists not only advocating for their causes but lending their executive expertise as a side benefit.

• “It’s a change in public philosophy,” says Leslie Lenkowsky, professor of philanthropic studies and public affairs at Indiana University. “Instead of saying, ‘Government should do that,’ philanthropists are more than ever stepping in. Instead of letting the U.N. handle malaria, Bill Gates set up his own foundation. • “The epicenter of philanthropic giving in America has shifted from New York to Silicon Valley,” he says. “A lot of people have gotten very wealthy who want to give something back and who want to do it in their active years when they can be involved.” • The roots of what’s been dubbed intentional giving could be said to be as old as U.S. philanthropy itself. Modern-day philanthropy emerged at the end of the 19th century, when an unprecedented number of Americans — including John Rockefeller and Henry Ford — became rich enough to have a role in shaping community and national affairs, says University of Virginia history professor Olivier Zunz, author of *Philanthropy in America*. • Andrew Carnegie, in his 1889 essay *The Gospel of Wealth*, gave birth to the idea that the rich should, instead of “leaving their wealth to their families, administer it as a public trust during life.” • “Instead of giving charitable donations to, say, sailors’ widows in Salem, giving became something much more broad ‘to the benefit of mankind,’” Zunz says. • Philanthropists have made enormous social changes in the United States, from Carnegie’s support for science research and higher education to today’s efforts by Bill and Melinda Gates to find solutions to the spread of disease worldwide, says Zunz. • Not surprisingly, many of Stanford University Medical Center’s major financial supporters are deeply involved in solving health

By Tracie White

ILLUSTRATIONS BY JOE CIARDIELLO

care's challenges, with many contributing not only funds but years of hands-on volunteer work. Read on for some of their stories about how and why they give.

Ask John Levin, WHO HAS DONATED MILLIONS TO STANFORD UNIVERSITY and volunteered his time in numerous capacities for more than 30 years, where his passion for public service comes from, and he pauses. Levin, 64, the co-founder and chairman of the San Francisco law firm Folger Levin, who seems rarely lost for words, spends a few extra moments searching for just the right ones.

"I suppose it goes back to my childhood," he says quietly.

"My mother contracted polio when I was an infant. She was in an iron lung in the hospital for years. When I would visit her I just remember her head poking out from the iron lung. She always had a smile on her face. That's all I could see of her. I was a kid. I didn't understand the terror that she was going through trapped in an iron lung for years."

Levin goes on to tell the story of his mother's dedication to public service despite seemingly overwhelming obstacles. How she left the hospital a quadriplegic attached to a portable respirator. How she started reading to blind college students in their Los Angeles home and how that motivated her to return to college, eventually becoming a staff therapist at a suicide prevention center answering hotline calls from home. She realized that even as a quadriplegic she could find meaning in

life by being involved and useful in helping others.

"I've no doubt my mother's story had a great influence over my life," he says.

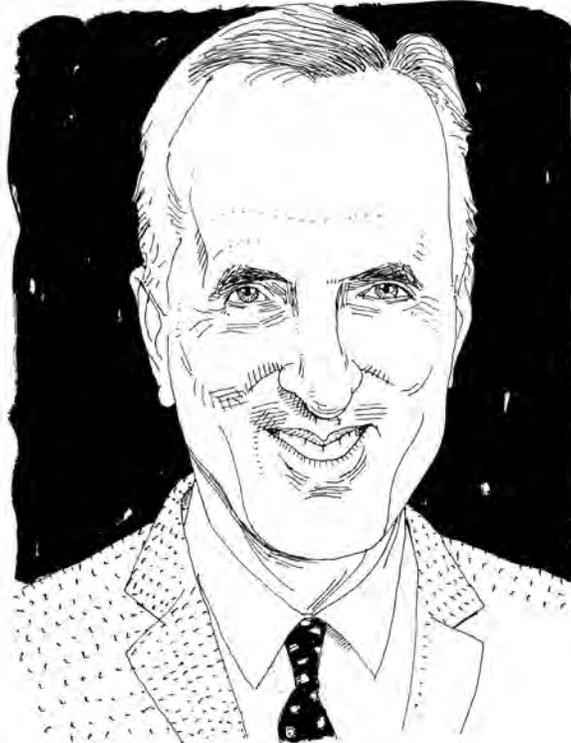
Levin and his wife, Terry, are both Stanford alumni and longtime Stanford volunteers. (The couple's twin 25-year-old daughters are Stanford alumni too.) John has served on the university's and Stanford Hospital's board of trustees for decades. He's been active in fundraising at the law school and as a mentor to law students. Together he and his wife donated \$3.75 million to establish the John and Terry Levin

Center for Public Service and Public Interest Law at the law school in 2007 — the center's mission is to make public service a pervasive part of every law student's experience.

"The whole notion of law as a profession is the fact that it's primarily about service to others," says Levin, who received his law degree from Stanford in 1973.

The Levin family's most recent donation of \$10 million to help build the new Stanford Hospital and John's participation in the hospital's fundraising campaign perhaps most clearly reflect the influence of his mother as a role model, her struggle with polio and her passion for public service.

"Back to my infancy, I understood the impact and power of medicine to make a difference in people's lives," Levin says. "It's a universally important subject. There are a few issues that are of paramount importance to the country and the world, chief among them education and medicine.



STANFORD MEDICAL CENTER'S CAMPAIGN

The Campaign for Stanford Medicine, a \$1 billion initiative to advance research and teaching at the Stanford University School of Medicine and enable the building of the new Stanford Hospital, has reached more than \$600 million in commitments through Aug. 31.

Stanford University President John Hennessy announced the campaign in May.

Among the recent pledges to the campaign are \$10 million commitments to the new hospital from Jill and John Freidenrich, Terry and John Levin, and a third anonymous donor. The Younger Family has pledged an additional \$5 million to Stanford Hospital & Clinics and the School of Medicine, adding to a previous pledge of \$5 million.

'IT'S OBVIOUSLY A VERY SCARY, VERY FRIGHTENING

THING. MY WIFE'S CANCER CLEARLY WAS A MOTIVATING
FACTOR FOR BOTH OF US.'

I believe philanthropy and engagement should be coupled. The more you get involved, the more effective you can be in making a difference."

NEARLY A DOZEN YEARS AGO, **John Freidenrich**, a longtime supporter of the university and the medical center, attended one of the yearly retreats held by the medical school's dean, Philip Pizzo, MD, in the Monterey area. That year, the retreat focused on the topic of "translational medicine" — the efforts to put research from the science lab to use in clinical care.

"I offered to give the dean a ride home," says Freidenrich, 75, a lawyer turned venture capitalist and investor, and an alumnus of both Stanford University and the law school. "Along the way, I told him, 'Phil, that was a great program, but if you don't do something about it, it's just going to go up into thin air. By next year no one will remember it.'

"Don't ever ride in a car with Phil," he jokes. "It was a very expensive ride."

John and his wife, Jill, who met as Stanford undergrads, live in Atherton, Calif., and have been married for 49 years. They have two children and six grandchildren. John's early work as a lawyer led to the founding of Ware and Freidenrich, catering to the business, legal and financing needs of start-up companies. The firm, now part of the global law giant DLA Piper, and John's later career in venture capital and investment management, paralleled the rise of Silicon Valley.

The Freidenriches have been committed donors to the university for decades. John has chaired the university's board

of trustees and countless committees. The couple's support of the arts at Stanford is reflected in the Freidenrich Family Gallery at the Cantor Art Center. Jill, a breast cancer survivor, founded Breast Cancer Connections, a Palo Alto support network for people with breast cancer. They've funded Stanford scholarships and in 2009 created the Freidenrich Support Foundation, organized exclusively for charitable, scientific and educational purposes at Stanford.

But there was more to come.

"Several years later, Phil came back to me after that car ride and said that the School of Medicine had been working on this idea and wanted to create a program for translational medicine, including a building dedicated to this research."

The building and program would become the Jill and John Freidenrich Center for Translational Research at Stanford University, designed to be the hub for the school's work in translational medicine. It officially opens this fall.

The Freidenriches donated \$25 million to the School of Medicine to boost its work in translational research in cancer and other diseases.

"It's one thing to do research. But if you really want to help people who are ill, you

want to develop the best therapies and then conduct clinical trials. We have to find more ways to go from the bench to clinical trials to patients."

But one of the strongest motivating factors for this donation was Jill's battle with breast cancer. "It's obviously a very scary, very frightening thing," he says. "My wife's cancer clearly was a motivating factor for both of us. Stanford has



world-class researchers and clinicians, so I don't think there's any place better suited to carry out this work."

Denise O'Leary HAS GIVEN BOTH TIME AND MONEY TO STANFORD UNIVERSITY for so long it has become a way of life. A Stanford graduate, who met her husband, also a Stanford alum, while they were both getting their MBAs at Harvard University, her history of giving began when she returned to Silicon Valley.

"I came back to the West Coast and started working in the venture capital world," O'Leary says. "I wanted to see if I could get involved doing some volunteer work at Stanford, something more issue-related than just working on my reunions."

While working, first as an associate, then a general partner, for Menlo Ventures, O'Leary started her first volunteer stint at the university as a member of the Subcommittee on Investment Responsibility during the 1980s, when university investments in South Africa during the anti-apartheid movement sparked campus protests and political debate. From there, she became an alumni-elected member of the board of trustees and was assigned to its medical center committee. A few years later, she became an active hospital volunteer and never really quit.

O'Leary now has 31 years' combined service on the boards of both Stanford Hospital & Clinics and Lucile Packard Children's Hospital.

"In my venture world, I did a lot of health-care investing so naturally I was interested in both hospitals. That, com-

bined with my work on the board of trustees, led me to join both hospital boards." About 15 years ago, she quit full-time work in venture capital to spend more time with her children, a son and a daughter, but continued volunteering at Stanford.

"I really fell in love with Stanford Medicine," O'Leary says. "What our faculty do there is so transformative. You don't do 31 years of volunteer work unless you really love it. It's become like a third child."

During her years on the hospital boards helping with fundraising efforts, she's become something of an expert on medical philanthropy — donors' motivations and the trends

in philanthropic giving. She also has firsthand experience as a medical philanthropist herself. Her family has endowed a professorship at the university, given to Stanford athletics and other funds on campus, and pledged \$1 million to the Stanford Hospital Campaign. Her husband, Kent Thiry, is chief executive officer of DaVita Inc., a kidney dialysis company, which moved its headquarters from California to Denver in 2009. O'Leary has continued her work at Stanford from Colorado, traveling west many times a year.

Medical philanthropists, she says, tend to be passionate givers. They are often moved to give to say "thank you" for

medical care that saved their own lives or the lives of loved ones. Others give because they've lost loved ones due to a lack of medical advances.

"Some donors have been touched by a medical crisis and there was no answer," O'Leary says. "They get very passionate with donating to research."



'YOU DON'T

DO 31 YEARS OF VOLUNTEER WORK

UNLESS YOU REALLY LOVE IT.

IT'S BECOME LIKE A THIRD CHILD.'

Over the years, she has also seen a growing desire among donors for accountability as to how their donations are used. Along with this has come more hands-on giving, with donors volunteering their time and their skills.

“The days of writing a \$10 million check and not really caring exactly how it’s used are pretty much gone,” she says. “Given our role in Silicon Valley, there’s this excitement around the whole ‘venture philanthropy’ movement. People talk a lot more about ‘intentional philanthropy.’ Donors are more involved.”

Venture philanthropy applies the concepts of venture capital finance to achieve philanthropic goals — focusing on getting measurable results; on giving financial, intellectual and human capital; and on a willingness to try new approaches.

All of these trends are welcomed at Stanford, situated in the midst of Silicon Valley, says O’Leary. The medical center is a natural draw for medical philanthropists in the valley, searching for a meaningful way to give, she says. “The power of a place like Stanford is our ‘bench to bedside’ ability,” she says, referring to the ability to transfer success in the laboratory into improved care at the hospital. “And health care is an enormous motivator. All other things in life pale in comparison to health.”

FOR **Christopher Redlich**, A 1972 STANFORD GRADUATE, GIVING TO THE MEDICAL CENTER began with a concerted effort to choose an area that both interested him and could help change the world. Five years ago, as he approached his retirement years, he began planning for a meaningful way to give. He’d made his fortune as chair of Marine Terminals Corp., which has interests in ports, marine terminals, stevedoring, warehousing, industrial maintenance, leasing, insurance underwriting and software development. Certainly nothing to do with medicine.

But medicine had made his list of philanthropic interests, along with education, the environment and government reform.

“I retired in 2007 and was talking to people. I was doing my own research, looking around,” he says. He chatted informally with Mariann Byrwalter, chair of Stanford Hospital’s board and a friend of his wife’s who lived in their Hillsborough, Calif., neighborhood.

“It was sort of a curious thing,” he says. “We would meet as I was taking my walk and she was coming up from golf, and we’d stop and talk about it for a while and then she’d go on her way and I’d go on my way. And then finally one time she said, ‘Now Chris, are you really interested in this thing?’”

Redlich, 62, began volunteering as a member of the board, a position where he could learn about Stanford Hospital and the people involved with it. “I was very impressed with the professionalism and collegiality of the board and was given the honor to join as a full board member shortly thereafter.” Eventually he saw that Stanford’s medical center could become a major change agent, and he decided to donate \$50 million to help launch the center’s current fundraising campaign and the construction of Stanford’s new hospital.

“I see the hospital as the first step in a long chain of steps that need to take place that will hopefully make a significant contribution to the health of this country, both from a medical and fiscal standpoint,” he says.

“Hospital facilities are part of the attraction to top talent,” he says. “By putting this hospital in this location, in this university, we will be able to attract the best people, we’ll be able to provide the best medical services, and we’ll be able to adjust and adapt as medicine changes throughout time. We’ll be able to provide an example to the world.”

But the choice to give to the hospital was not purely intellectual. Personal experience was also a strong motivation. Redlich watched as a number of his relatives died in hospitals, and he began to note the mistakes made in their care along the way. His own visit to an emergency room for an

infected toe helped him spot what he describes as the inherent weaknesses in the medical system.

“Good customer experience creates better business opportunities,” says Redlich. “What you don’t do is waste huge amounts of people’s time, make them wait for weeks for appointments, send them from specialist to specialist, leave them waiting for hours in the waiting room.”

What you do, he says, is get involved and help fix the problems.

“The question becomes, how do you make things better?” **SM**

Contact Tracie White at traciew@stanford.edu



Melinda Gates on family matters

A CONVERSATION ABOUT CONTRACEPTION

It's hard not to gush about Melinda Gates and her philanthropic verve. The world's fourth-most powerful woman, according to *Forbes* magazine, has stepped into the exceedingly sharp-edged world of family planning in a substantial way. In July, the Bill & Melinda Gates Foundation co-hosted the London Summit on Family Planning with the U.K. Department for International Development.

There, participants from developing countries, international agencies, foundations and the private sector made new financial commitments amounting to \$2.6 billion, exceeding the summit's goal. The event galvanized political commitments and raised the financial resources to deliver contraceptives to an additional 120 million women in the developing world by 2020, which is estimated to cost \$4.3 billion in cash and developing country resources. The Gates Foundation will have invested over \$1 billion into voluntary family planning services by 2020. • To be sure, it's a philanthropic endeavor that's not without pushback. A Roman Catholic, her church's doctrine is clear that contraception is a sin. Yet Melinda Gates is resolute and at peace with her decision. She believes that giving women access to contraceptives is critical for them to be able to provide a better future for their children, and that in the long term, this has the potential to improve the health, productivity and economic opportunities of families in some of the world's poorest countries. Paul Costello, executive editor of *Stanford Medicine*, posed some questions to Gates about this initiative and to find out why family planning looms so large in both her heart and her mind.



PAUL COSTELLO: You've made a huge financial commitment to family planning and are raising even more. How will this money be used?

MELINDA GATES: The commitments will seek to address the policy, financing, demand and delivery barriers to women accessing contraceptive information, services and supplies. By 2020, these efforts will result in 200,000 fewer women dying

in pregnancy and childbirth, more than 110 million fewer unintended pregnancies, over 50 million fewer abortions and nearly 3 million fewer babies dying in their first year of life.

COSTELLO: For someone who hasn't often stepped into the glare of the public spotlight, you've certainly chosen an issue filled with controversy. How did you reach this decision?

GATES: I have been given the privilege to travel extensively in developing countries, to learn what life is like for women and girls. Today, more than 200 million women and girls in developing countries who don't want to get pregnant lack access to contraceptives. I wrestled with my feelings when it came to speaking out about this issue but the more I learned, the more I felt compelled to do something about it, and it became a very clear decision for me. I have made the issue of family planning my priority because these women tell me that having the power to decide when to

have a child is a key to achieving their goals in life. They want to be able to feed their children, take them to the doctor when they're sick and send them to school so they can fulfill their potential. I don't see any controversy in helping women determine their own future.

COSTELLO: You must have heard unforgettable stories from these women.

GATES: Last year, I met with a mother's group in a slum outside Nairobi. The women were taking turns explaining why they use birth control. Finally, a woman named Marianne summed up the whole conversation in a phrase I'll never forget. She said, "I want to bring every good thing to one child before I have another." That's universal. We all want to bring every good thing to our children. What is not universal is our ability to provide every good thing to our children.

COSTELLO: I've heard you call access to contraception a social justice issue. Why social justice?

GATES: As I travel and talk with women in developing countries, what's universally clear is that when a woman can decide if and when to have children, she's healthier, her children are healthier, her family is more successful and her community benefits. Empowering a couple to lead the life they want and decide whether and when to have a child can create opportunities for transformational improvements in their family's health and prosperity. Our foundation exists to help parents in the world's poorest countries give their children the opportunity for that better future.

COSTELLO: There's a huge hole in R&D on birth control medications and devices. Is this an area where the Gates Foundation might make financial investments?

GATES: Longer-term, more innovative research and development work needs to be done to create new contraceptives that meet more of women's needs. It has been many years since the R&D community developed new contraceptives for women, but I believe there is momentum behind this priority.

For example, Pfizer is testing a convenient, single-dose, injectable contraceptive that makes it easier for health workers to administer in



women's homes. Eventually, women might even be able to administer it themselves.

The secret to these innovations is not secret at all — it is thinking about what a woman needs from the outset. That frame of mind yields an endless supply of potentially powerful solutions that can be tested and continually improved. Bill and I are committed to bringing the best of those solutions to women everywhere.

COSTELLO: Of all the critical issues from which you could choose, why do you want family planning to be your lifetime's work?

GATES: I know that having access to contraceptives was very important in giving me the power to lead the life I wanted. When I talk to women in poor countries, they tell me contraceptives would do the same for them. Their ability to decide if and when to have a child enables them to create new opportunities in their communities and a better future for their children. But hundreds of millions of women don't have access to these lifesaving,

life-changing contraceptives, and I believe I can use my voice to help change that. It will take many years and the commitment of countless partners on the ground in countries around the world, but I believe together we can help to provide all families the opportunity to lead healthy and productive lives. That is why I am making this my life's work. **SM**

Melinda Gates
MEETS WITH MOTHERS AROUND
THE WORLD. OPPOSITE PAGE: IN UTTAR
PRADESH, INDIA; ABOVE: AT A
MOTHER'S GROUP IN NAIROBI'S KOROGOCHO
SLUM; BELOW: AT A NUTRITION CENTER
IN DHAKA, BANGLADESH.



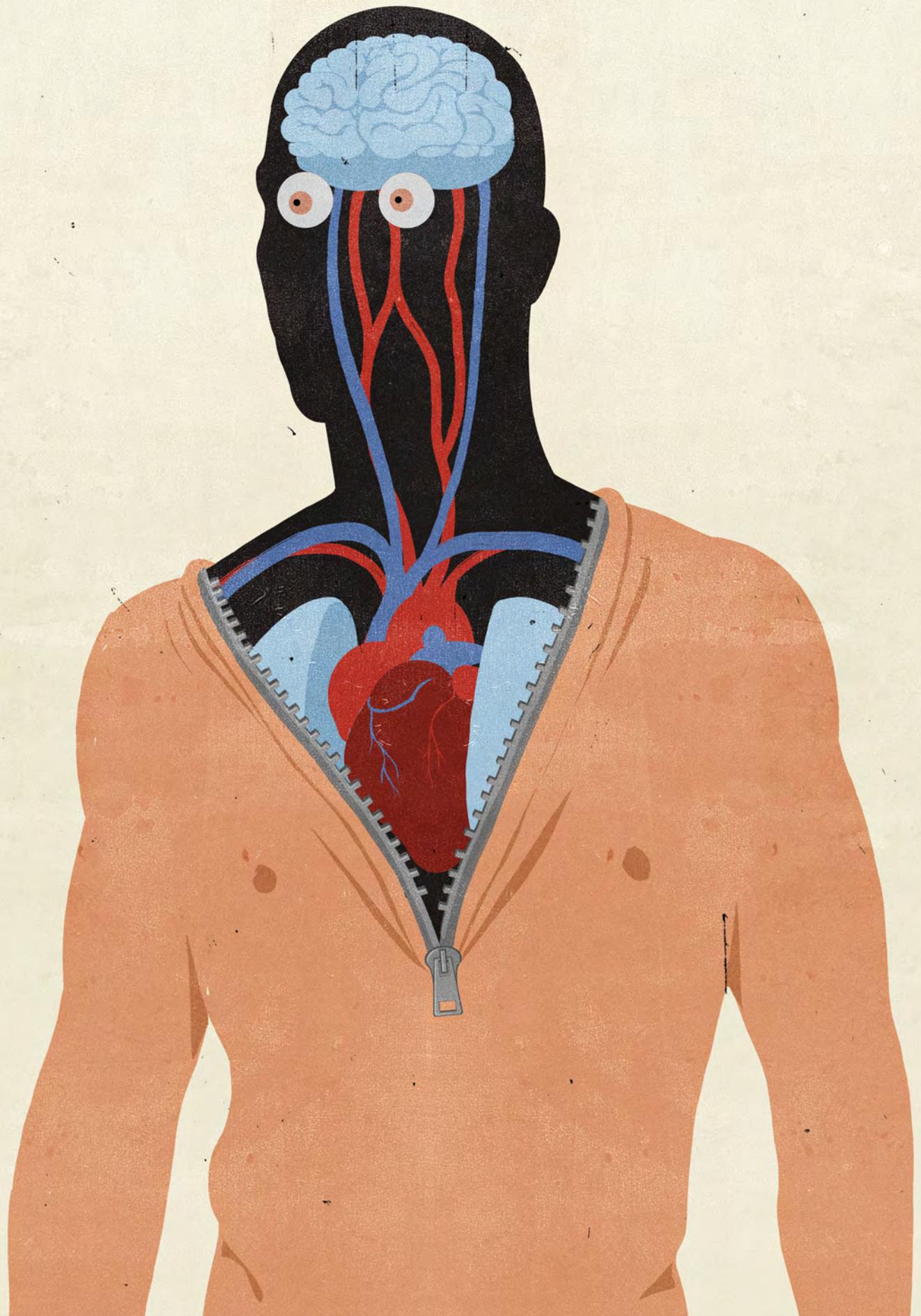
testing testing

WHY THE COSTS
AND BENEFITS
OF SOME
CANCER SCREENINGS
STIR SUCH
CONTROVERSY

OTIS BRAWLEY, MD, IS ADMITTEDLY A SKEPTIC OF THE MEDICAL SYSTEM. An African-American, he was raised among people who had a deep distrust of doctors and hospitals, believing they could cause as much harm as good. • And that is how Brawley has come to view screening for prostate cancer with the long-established blood test. He believes it causes as much — if not more — harm as good. It's an issue on which he has become a crusader. • Brawley, the medical director of the American Cancer Society, opposes routine, widespread screening using the prostate-specific antigen test, or PSA, as a way to detect prostate cancer in healthy men. He argues that men have been misled into believing that prostate cancer screening saves lives, when science has never definitively shown that to be the case. Rather, he believes large-scale PSA screening has resulted in great suffer-

By Ruthann Richter

ILLUSTRATION BY SHOUT



ing from needless and potentially damaging treatments, with uncertain benefits.

Brawley is among the many health-care leaders calling attention to the problem of overscreening — not just for prostate cancer, but for conditions from breast cancer to heart disease — which adds billions of dollars to health-care costs annually. Screenings and the medical procedures that may result, such as biopsies following a high PSA reading, feed the U.S. medical spending juggernaut. The Institute of Medicine reported in September that \$750 billion is wasted by the U.S. health-care system each year. Unneeded care amounts to \$210 billion of that total.

Nonetheless, the PSA screening controversy, which has persisted for more than a decade, shows how dilemmas in medical practice can impede change.

OVERDOSING ON SCREENING?

Millions of men in the United States now take the PSA test, which measures the level of a protein produced by the prostate gland that can be an indicator of prostate cancer — the second-leading cause of cancer death for U.S. men. This year, it will take the lives of 28,000, estimates the American Cancer Society. A man's lifetime risk of dying of prostate cancer is 2.8 percent among Caucasians and 3.5 percent among African-Americans. The cancer society had recommended in 1993 that men receive a PSA blood test annually starting at age 50 — age 40 for African-Americans and others at higher risk — though it backed off in 1997, saying men should talk with their doctors first about the benefits and drawbacks of the test and make an informed decision before being screened.

A big limitation of the PSA test is that it is imprecise, unable to effectively distinguish between slow-growing, harmless cancers, which are most common, and more aggressive, deadly ones. And high levels sometimes don't indicate cancer at all, but instead more benign conditions such as an enlarged or inflamed prostate.

A high PSA result often leads men down a path to surgery, radiation or hormone therapy which may — or may not — be of benefit and which can have lifelong complications, including impotence, incontinence and problems of bowel control. Unfortunately, no better method for detecting potential prostate cancer exists. It has become entrenched in the medical care system, with many vested interests involved, including doctors, hospitals and pharmaceutical firms.

“Prostate cancer is a poster child for the problem of overdiagnosis,” says H. Gilbert Welch, MD, MPH, with the Dartmouth Institute for Health Policy and Clinical Practice and author of *Overdiagnosed: Making People Sick in the Pursuit of Health*.

“We have done it for 20 years because some people thought it might save lives,” says Brawley, professor of oncology and epidemiology at Emory University. “But we told people — we in medicine — that it saves lives and you should get it. My own American Cancer Society recommended every man over 50 get prostate cancer screening — every black man over 40 — back in 1993 without adequate scientific data. Everybody is so brainwashed into thinking that prostate screening is the right thing to do,” adds Brawley, who has been both praised and vilified for his views on the highly divisive issue. (To be clear, however, he and other critics of the test endorse its use to track the growth of cancer once it has been identified.)

In a May article in the *British Medical Journal*, health journalist Ray Moynihan, a senior research fellow at Bond University in Australia, and two co-authors identified prostate cancer as one of a dozen commonly overdiagnosed conditions. The others included breast cancer, asthma, osteoporosis and attention deficit disorder, according to the researchers, who said medicine's ability to heal the sick is becoming overshadowed by its capacity to harm the healthy.

“Screening programmes are detecting early cancers that will never cause symptoms or death, sensitive diagnostic technologies identify ‘abnormalities’ so tiny that they will remain benign, while widening disease definitions mean people at ever lower risks receive medical labels and lifelong treatments that will fail to benefit many of them,” the researchers write.

Next fall, the Dartmouth institute is hosting an international conference on the wider problem of overdiagnosis, partnering with Bond University, *BMJ* and *Consumer Reports*.

The costs to the system are enormous. In one study, published this April in the *Journal of the American Medical Association*, Donald Berwick, MD, former chief of the U.S. Centers for Medicare and Medicaid, and colleague Andrew Hackbarth of the Rand Corp. estimated that between \$158 billion and \$226 billion was wasted in 2011 in the United States on care that can't help patients, including some end-of-life care and surgical treatment when simple monitoring of a condition would have sufficed.

Americans have embraced the concept of medical screening in the belief that more knowledge is better, says internist Randall Stafford, MD, PhD, a professor of medicine at the Stanford Prevention Research Center who studies the adoption of disease prevention practices. But sometimes that knowledge sends patients down a path to more testing and more treatments, which are not only costly, but harmful.

“While some screening tests have limited utility, patients often expect that a full evaluation will include them, includ-

ing an EKG, urinalysis or blood count,” says Stafford. “We now recognize that there is tremendous overuse of those diagnostic tests.”

The problem is that the tests not only cost money, but also can lead to more unneeded health-care activities. “An EKG that is suspicious for coronary artery disease leads to a stress test, which leads to a catheterization, which in turn leads to a bypass surgery, all of which might not have been necessary,” says Stafford. “These tests are not specific. That is, a suspicious test result may not always represent actual disease.”

while hormone therapy may lead to erectile dysfunction, breast enlargement and hot flashes, according to the report, published in May 2012 in the *Annals of Internal Medicine*.

“Based on this work, the task force concludes that many men are harmed as a result of prostate cancer screening and few, if any, benefit,” concludes the task force on its website.

The recommendation provoked outrage in the urology community, with the American Academy of Urology calling it “inappropriate and irresponsible.” The group notes prostate cancer mortality has significantly declined in the

Americans

have embraced

the concept of medical screening in the belief
that more knowledge is better.

Cancer screening is particularly controversial. In 2009, the U.S. Preventive Services Task Force set off a firestorm when it recommended women start getting routine mammograms at age 50, rather than 40, and switch from annual checks to every other year. The organization, which reviews the scientific justification for clinical preventive services, found evidence lacking for earlier and more frequent screenings.

When the decision came out during the national debate over President Obama’s health-care reform legislation, opponents decried it as health-care rationing. Many physicians’ groups also denounced it, as did some breast cancer research and treatment advocacy groups. Congress went on to undermine the recommendation by writing a requirement into the health-care reform law for insurers to cover mammograms for women ages 40 to 49 despite the task force’s conclusion.

Then this spring, the task force added further fuel to the debate when it gave the PSA test a “D” rating and recommended against it for the general population. In its report, the panel noted that a large percentage of men who are screened opt for treatment, with various ill effects.

Among 1,000 men screened, as many as five will die within a month of prostate cancer surgery and between 10 and 70 will have serious complications, the panel reported. At least 20 to 30 percent of men undergoing radiation therapy or surgery will have long-term side effects, including urinary incontinence, erectile dysfunction and bowel dysfunction,

United States, which it believes is largely due to the advent of widespread PSA screening. In June, the American Medical Association voted to officially express concern over the task force’s recommendations on both mammography and PSA testing.

“In the United States, death rates from prostate cancer have decreased by 40 percent, and the percentage of men who present with metastases has decreased by 80 percent,” says Northwestern University urologist William Catalona, MD, a screening advocate whose early studies helped validate use of the test. “So we are detecting prostate cancer earlier and detecting it in a curable stage more often. Screening has fallen victim of its own success. Now we have people saying we are detecting it too early and treating it too often.”

THE TEST’S HISTORY OF CONTROVERSY

The PSA, the “poster child” for overdiagnosis, first came into vogue following a 1987 report in the *New England Journal of Medicine* by Stanford’s Thomas Stamey, MD, now an emeritus professor of urology, which suggested it could be useful as a marker in the blood for the disease. Men rushed in, eager to know their status, leading to an immediate spike in prostate cancer diagnoses. These men would go on to have their prostates biopsied, with doctors sampling tissue through a needle from a dozen spots in the gland, which is about the size of a golf ball. Biopsies are not only uncomfortable, but

can cause bleeding, infection and, in 1 percent of cases, hospitalization.

In those days, if a bit of biopsied tissue came back positive, the patient would usually go on to have the entire organ removed, and possibly radiation therapy. Because the prostate is deep in the pelvis, surrounded by other organs and hard to access, it is difficult for surgeons to avoid damaging nerves that control vital functions, such as ejaculation and urination.

By 2004, Stamey himself began to question the test, saying it was turning up far too many cases of small, low-grade tumors that were unlikely to spread and cause any harm, yet were subjecting men to unwarranted treatment. His paper that year in the *Journal of Urology* highlighted a major flaw in the test — its inability to distinguish between slow-growing tumors that may never be troublesome and the more aggressive, potentially deadly ones. His conclusion, that the test was of limited value, caused a furor among urologists.

Two major studies have been completed since then, yet neither has been sufficient to settle the controversy.

A large U.S. study, known as the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, enrolled men at 10 centers around the country over six years. The results, pub-

er or not to screen depends on how an individual patient feels about the possible harms and benefits.

UNCOUPLE SCREENING AND TREATMENT

James Brooks, MD, a professor of urology at Stanford and prostate cancer expert, says a moratorium on testing, as recommended by the task force, is akin to “throwing the baby out with the bathwater.” He still believes the PSA is useful, recommending annual tests for men ages 50 to 75.

“Elevated PSA is a marker of risk, much as high blood pressure is a marker of risk for death from heart disease,” says Brooks, chief of urologic oncology at Stanford Hospital & Clinics.

He says the task force ignored the fact that death rates and the incidence of metastatic disease have significantly declined, with studies suggesting the decline is related to screening and treatment of localized disease and less so to improved treatments of advanced disease, as some critics argue.

He also believes the task force erred in directly linking screening to treatment. If, for instance, a man has a high PSA, he can go on to have a biopsy, and that may show that he has low-grade disease, in which case the cancer would just

‘People are
scared because they hear the word, “cancer.”

Doctors are scared because they hear the word “cancer.”

Together this prompts treatment.’

lished in January in the *Journal of the National Cancer Institute*, showed no difference in mortality among men in the screening group versus controls. Unfortunately, many men in the control group could not restrain themselves from being tested, so the results were considered contaminated.

A separate study, published in 2009 in the *New England Journal of Medicine* and involving 162,000 men in seven European countries, showed a 20 percent relative reduction in mortality among men receiving the test, though the authors noted that screening is associated with as much as a 50 percent risk of overdiagnosis. The study is often cited by patient advocates and others favoring PSA screening as clear evidence of the value of the test. In August, Dutch researchers published a follow-up to the European study, saying wheth-

be monitored, not treated.

“We have learned that low-grade cancers can be watched safely. Because of that I uncouple screening and treatment. Men with low-risk cancer are watched, and men with aggressive cancer are treated,” he says. “There are two randomized trials that show that operating on men with intermediate and high-risk cancers, rather than doing nothing, improves their life expectancy and decreases their chance of developing metastatic prostate cancer. Those are the patients to whom we offer treatment.”

At the core of the problem with PSA screening is the fear inflamed by a diagnosis of cancer. “People are scared because they hear the word ‘cancer.’ Doctors are scared because they hear the word ‘cancer.’ Together this prompts treatment. It

does not help that there are monetary incentives that drive those decisions,” says Brooks.

Brawley, who recently authored the book *How We Do Harm: A Doctor Breaks Ranks about Being Sick in America*, says he is particularly concerned about free mass screenings at county fairs, shopping malls, churches and other public venues that are sponsored by special interests seeking to attract new patients but that don't provide men the opportunity to make informed decisions. (One past sponsor has been Kimberly Clark, the maker of Depend diapers for adults, he notes.)

“There's a lot of publicity out there — some of it by people who want to make money by recruiting patients — that oversimplifies the issue by saying that prostate cancer screening clearly saves lives. The truth is if you are concerned about prostate cancer, understand there are proven risks and possible benefits.... Every man needs to decide for himself,” says Brawley.

LIVING WITH UNCERTAINTY

Often the first reaction among men is to have the cancer removed until they learn about the serious side effects surgery can cause, Brooks says. Once he describes them, he says, many become open to the idea of active surveillance, in which they are monitored with periodic PSA tests, biopsies and physical exams.

“In 1997, virtually all of our patients who were diagnosed, even if the tumor was small and low-grade, got an operation,” he says. “Now, one-third of those patients are in active surveillance.”

Bill, a 70-year-old Oakland, Calif., resident, is one such patient. Since 2002, he had been getting annual PSA tests, and while the numbers bounced around, they showed a gradual upward trend. So in 2008, at the suggestion of a Berkeley, Calif., urologist, he had a prostate biopsy, which detected something suspicious. The urologist then launched into a discussion of his various treatment options. “My mind said that if I had some kind of cancer, I want to take care of this. This was based on ignorance,” says Bill, who asked that his last name not be used to protect his privacy.

He went home and talked to his wife and then began asking more questions of his urologist. “We started talking about side effects — impotence and incontinence, that sort of thing. I kind of felt I was getting different stories at different times.”

He decided to get a second opinion and came to Stanford, where he learned that he actually had very little, very low-grade cancer and was a good candidate for active sur-

veillance. Brooks has continued to measure his PSA levels quarterly and do a biopsy every 18 months. Bill's PSA has been trending down.

“On the whole, I'm glad I'm getting the PSAs, and I'm glad I didn't rush into treatment because there are lots of side effects from the treatment,” he says. “The cancer is small and doesn't cause me any problems. Treatment would probably cause more problems than having the cancer. So I'm really feeling good about the decision.”

THE NEW ATTITUDE

While the PSA test remains widely used, medical associations, including the American College of Physicians and the American College of Preventive Medicine, have begun to advise caution, saying men need to have a detailed conversation with their doctors before proceeding with the test and possible follow-up treatment. Even the conservative American Academy of Urology, in its 2009 Best Practice statement, recommends that men be informed of the risks of screening and of the option of active surveillance for newly diagnosed patients; the organization is currently revising its guidelines to reflect the state of the science.

Which begs the question, what *is* the state of the science? One unfortunate aspect of the debate over the PSA test is that valuable time has been lost, when scientists could have been looking for other alternatives, Brawley says.

“The urologic industry has been so fixated that they've delayed finding something better than PSA. So what's a man to do since we've been so foolish,” he asks.

In fact, efforts are now under way to find a better option, with researchers using genomics, new imaging techniques and other strategies to develop more reliable indicators of the disease. Brooks is involved in several of these studies, including one in which 700 men are under active surveillance, undergoing periodic testing in an effort to develop a marker that can distinguish aggressive tumors from non-aggressive ones.

In another study, he is collaborating with Sanjiv Sam Gambhir, MD, PhD, professor and chair of radiology at Stanford, in using nanotechnology to measure proteins in the blood that may be better indicators of the disease than PSA. And at least two Bay Area companies have alternatives in clinical studies that aim to single out those cancers most likely to progress and require treatment.

“There are certainly plenty of men who are getting treated who don't need to be,” says Brooks. “So we have to move the ball down the field. We just need better tests.” **SM**

*Contact Ruthann Richter at
richter1@stanford.edu*



M A R A T H O N

M A R A T H O N

THEY SAY LIFE IS A MARATHON, NOT A SPRINT.
THAT'S LITERALLY THE CASE FOR PHILIP PIZZO, MD.

For most of the past 30 years, Pizzo has run 50 to 70 miles a week and entered two or three marathons (including the Boston Marathon) each year. That level of commitment on its own is commendable, but is even more remarkable considering his job — leading one of the top medical schools in the country. • Distance running holds a particular appeal for those like Pizzo who want to determine their own destiny. How fast and how far they go is determined by how well they've prepared. And the training takes time and discipline. They're the only ones tracking their times, their distances and their progress. • Runners get a high from seeing just how much they can push themselves. And they often speak of how the solitude of running replenishes their ability to deal with other aspects of their lives. • Pizzo began running when he was 30 in part to lessen the affects of the asthma he developed as a child. But running became more than just a way to improve his health. "It gives me a sense of stamina and the ability to do my day job because I know that I've been through so many different physical challenges that I can probably sustain myself through some of the emotional and mental ones," he says. • While the mentality of distance running remains firmly embedded in Pizzo's approach to life, right now he's focused on the art of passing the baton. As he prepares to step down after 12 years as dean of the School of Medicine, Pizzo seeks to make a smooth handoff to his successor, Lloyd Minor, MD, who will take over on Dec. 1. • He's passing on the leadership of a school that that has experienced a rebirth of sorts in the past decade, with new organizational structures that have strengthened the collaborations between basic scientists and clinicians. Morale has improved, the faculty has become more diverse and the biggest building boom since the school moved to the Stanford campus in 1959 is well under way. • While this will be another finish line for Pizzo, he's already scouting for the next course and new challenges. "This is definitely not a path toward retirement," he says. "It's a path toward transition and renewal."

By Susan Ipaktchian

ILLUSTRATION BY GREGORY MANCHESS

On the personal side, that means more time with his wife, children and his grandchildren, who refer to him as “Indy,” after the intrepid Indiana Jones character. Professionally, he’s looking forward to plunging more deeply into clinical and academic endeavors. And physical renewal is on the menu as well. Since April, he’s been rehabbing his back to counter the effects of less-than-ideal posture and inattention to “core training” over the years. “I’m in a musculoskeletal repair situation,” he says ruefully, but quickly adds that once he’s recovered, he’d like to train for a 50- to 100-mile ultramarathon.

“People question my sanity, but you have to have a goal, right?” he says.

THE TRAINING

Pizzo was born in New York City in December 1944 to working-class parents who immigrated from Sicily. Finances were tight for the family of four (he has a younger brother, Michael). “I lived through the eyes of discoverers, inventors and heroes whom I encountered through reading books,” he recalls.

As a teen he was already drawn to science, and conducted experiments down the street in his aunt’s garage after his mother deemed them “too messy” for the family’s home; they involved mice purchased from the local pet store.

Pizzo earned scholarships that enabled him to attend Fordham University and became the first person in his family to graduate from college. Then it was on to the University of Rochester for medical school. While working toward his medical degree, he married Peggy Daly in 1967, who went on to a distinguished career in early childhood education and public policy. (She is a senior scholar in Stanford’s School of Education.)

Contemplating his future in medicine, he knew he wanted it to encompass patient care as well as research. “I’ve always been the kind of person who put one’s heart and soul into asking, ‘What’s the big question? What’s the big problem?’”

When he graduated in 1970, he served his residency in pediatrics at Children’s Hospital in Boston where he began to focus on infectious diseases and cancer. While there, he read a paper tracking fevers in adult cancer patients, and decided that similar work was needed to understand how fevers affected children with cancer. “This led to a review of 1,000 charts in the record room at 4:30 each morning, and the first

report of 100 cases of fevers of unknown origin in children published in *Pediatrics*,” recalls Fred Lovejoy, MD, who was chief resident at the time and is now a professor of pediatrics at Harvard. “This resulted in a lead authorship for Pizzo, with his chief resident — me — buried in the middle,” Lovejoy adds with a laugh.

Pizzo’s clinical research examined a wide range of issues involving infection and fevers in children whose immune systems were compromised by cancer, and helped identify the best ways to treat the infections.

After completing his residency, he went on to a fellowship in pediatric oncology at the National Cancer Institute where he continued both his clinical work and his research. Working with children facing cancer diagnoses helped Pizzo hone the communication skills that have persisted throughout his career. “As a pediatric oncologist, I had to learn very clearly the art of listening and of being honest, and of being able to share news and information with mothers and fathers and families in a way that always bore integrity and honesty,” he says. “You learn never to walk away and leave the words unsaid that need to be said, and to say them with a sense of compassion and sensitivity.”

When his fellowship ended, Pizzo got a full-time position at the NCI, first as an investigator in pediatric oncology, then heading the pediatric infectious-disease section. It was during this time that the AIDS epidemic began to unfold.

“At that time, the NCI focused on cancer,” says David Poplack, MD, director of the Texas Children’s Cancer Center and a professor at the Baylor College of Medicine. The pair had served their residencies together in Boston and then worked at the NCI. In 1989, Pizzo and Poplack published what has become the definitive book on cancer in children, *Principles and Practice of Pediatric Oncology*, now in its sixth edition.

“Phil realized we were one of the few centers that had a scientific focus that could and should focus on HIV,” Poplack says. “He influenced the NIH leaders to take on the care of pediatric HIV cases, and the new retrovirals to treat HIV were developed in that setting. His absolute devotion to treating HIV disease in children and finding answers was incredible to witness.”

Caring for patients, carrying out clinical research, authoring books and papers, mentoring trainees. It was a heavy

REFLECTIONS ON THE DEAN

‘HE BELIEVES STRONGLY IN
THE WORTH AND VALUE OF FELLOW HUMAN BEINGS. HE IS TOTALLY DEDICATED TO
CHILDREN. TO SEE HIM INTERACT WITH PATIENTS AND THEIR
FAMILIES IS TO SEE A TRULY WONDERFUL PERSON. HE WEARS HIS HEART ON
HIS SLEEVE — IT’S RIGHT OUT THERE FOR ALL TO SEE.’

— DAVID POPLACK, MD, DIRECTOR OF THE TEXAS CHILDREN’S CANCER CENTER AND
PROFESSOR AT THE BAYLOR COLLEGE OF MEDICINE

'PHIL PIZZO HAS BEEN A REMARKABLE DEAN OF THE SCHOOL OF MEDICINE, MOST NOTABLY FOR HIS SUPPORT OF BASIC RESEARCH, AND FOR BEING THE SPARK PLUG FOR SCIENTIFIC DISCOVERY AND TECHNOLOGY DEVELOPMENT AND THEIR IMPACT ON TRANSLATIONAL MEDICINE.'

— LUCY SHAPIRO, PHD, DIRECTOR OF STANFORD'S BECKMAN CENTER FOR MOLECULAR AND GENETIC MEDICINE

workload, but colleagues say Pizzo did it with charm, grace and a deep well of empathy. "I used to try to keep up with him, but I finally said to hell with it," says Poplack. "People consider me a workaholic, but I don't even rate at the lowest level of the Pizzo scale."

STRETCHING

Pizzo describes himself as "a product of the 1960s." He saw his role going beyond clinical practice, teaching and research. "I'm one of those people who really thought that you could change the world, make it a better place, through one's commitment, zeal and activities," he says. While at NIH, Pizzo also learned how to be an effective advocate as he reached out to lawmakers, regulatory agencies and influential figures to raise funds and promote awareness.

"When President Reagan came to NIH and visited our ward, Phil took him on rounds and was holding a baby who had HIV. He said, 'Here, Mr. President, why don't you hold him,' and literally handed the baby to Reagan," Poplack recalls. At the time, many in the public viewed those with the disease as pariahs, and AIDS activists were criticizing Reagan for failing to forcefully address the growing epidemic. Poplack says he nervously watched, afraid Reagan would refuse to hold the baby Pizzo was proffering. "And just the opposite happened — Reagan embraced the child. The next day, there was a photo of Reagan with the baby in *The New York Times*. I think it did more to de-stigmatize the disease than any other photo."

Pizzo's advocacy eventually extended to developing the Best Pharmaceuticals for Children Act, enacted in 2002, to promote clinical trials for children. He also raised funds for and established the Children's Inn, which houses the families of children being treated at the NCI, and Camp Fantastic, a weeklong camping experience for children who have completed their cancer treatments. The camp just celebrated its 30th anniversary.

He also met Elizabeth Glaser, who contracted HIV through a blood transfusion and unknowingly passed on the disease to two of her children. Glaser formed the Elizabeth Glaser Pediatric AIDS Foundation in 1988 to help spur research and funding for the disease; Pizzo was one of the first members of the foundation's health advisory board, and later a member of its board of directors.

And despite the many demands on his time, Pizzo willingly

offered his help to other physicians with perplexing cases. One young doctor who sought him out was Charles Prober, MD, who had recently started a pediatric infectious disease position in Toronto. When he had patients who had infections complicated by cancer, he remembered reading Pizzo's papers and called the NCI to seek his advice. "He got back to me extraordinarily quickly and personally," says Prober, now a professor of pediatrics at Stanford. "He took such an interest and really wanted to help me find the best answers to my questions. That personality trait — of being so responsive to queries from anybody at quite literally any time — has always been a part of his life."

By 1996, Pizzo had been at the NCI for 23 years, serving for 15 of them as chief of pediatrics. He had collaborated with physicians and researchers throughout the world, and helped contribute to the significant gains in treating cancer and infectious diseases in children. But he wanted to spend more time training and mentoring the future leaders of pediatrics, and so in 1996 he went to Harvard where he chaired the Department of Pediatrics.

And then one of his long-distance mentorships helped steer him across the country.

THE STARTING LINE

In 2000, a search committee was looking for a new dean at the Stanford School of Medicine. Though Stanford has always enjoyed a strong reputation as a research-intensive medical school, spirits were low on the campus. Stanford and UC-San Francisco had attempted a merger of their clinical enterprises that ultimately proved unsuccessful, and the costs from the failed effort had been heavy. Additionally, the school was facing potential sanctions from the Liaison Committee for Medical Education, which accredits all U.S. medical schools, for its inadequate classroom and library facilities.

Prober, who wasn't a member of the search committee but often played golf with University President John Hennessy, PhD, mentioned that Pizzo would be a good candidate. (Prober adds that he and colleague Ann Arvin, MD, professor of pediatrics and the university's vice provost for research, still jokingly argue over which of them was the first to suggest Pizzo's name to the committee.)

Pizzo says that when he was approached about the Stanford deanship, he saw the possibility of helping to train medical leaders in fields beyond pediatrics. And he also saw a tantalizing challenge.

“Stanford was an institution that was rich in heritage, extraordinary in terms of its intellectual capital, but was also trying to recalibrate where the medical center was going,” he says. “That is what always drives my personal passion. It’s about trying to craft a future agenda, project it, think about it and then try to move toward it.

“I also realized that this was a world — Palo Alto, Silicon Valley, Stanford — that didn’t have ‘can’t be done,’ in its lexicon. That aspiration of taking on the challenges and not letting ‘no’ get in the way is, to me, the driving force of this institution.”

He accepted the job, and likes to point out that he began serving as dean on April 2, 2001; he didn’t want to start on April Fool’s Day.

One of Pizzo’s first actions as dean gave a clear sense of his leadership style. In the preceding years, school officials had been working on plans for a new education building that would address the Liaison Committee for Medical Education’s concerns about classrooms and library facilities, and had a deadline of 2001 for implementing the plan. But as Pizzo took stock of the effort, it became clear that few were happy with the way the plans were shaping up. Nonetheless, they felt they needed to proceed to satisfy the LCME.

Pizzo put the brakes on the plan, asking for a new analysis and an approach that would truly serve the future needs of Stanford’s medical students. He convinced the LCME to give Stanford more time. “Many people in his situation would have said, ‘Oh, well, we are moving in a direction that’s needed and so let me hop on that train and see where it goes,’” says Prober. “But that is not his style. He carefully re-analyzed everything, thought about the optimal direction for the facility and set about raising the money and building it.” The resulting building, the Li Ka Shing Center for Learning and Knowledge, opened in 2010. In addition to state-of-the-art classrooms and training technology, it houses the dean’s offices and serves as the school’s official front door.

Pizzo was also aware that his background in clinical research made the school’s basic scientists uneasy. “When he came, there was a certain suspicion that perhaps he would not be very supportive of basic science,” says Nobel laureate Paul Berg, PhD, professor emeritus of biochemistry. “But now I don’t think there’s anybody who doubts for a moment his commitment to and support of the basic sciences.”

But the biggest need Pizzo wanted to address was morale and reducing the fragmentation that he saw. In addition to the low spirits in the wake of the de-merger with UCSF, Pizzo sensed that many faculty didn’t feel much kinship with the larger community at the School of Medicine. He wanted to encourage greater connections between basic and clinical scientists, between staff and administrators, between the school and the two hospitals, and between the medical center and the university.

One of his first steps was to organize a retreat at which the full spectrum of the medical center and university were represented. He has often recounted how, at the first year’s gathering, the basic scientists clustered on one side of the room while the clinicians were on the other. But as the weekend progressed, relations thawed. “People began saying to each other, ‘I think I see now what your role is better than I did before. I think I see why basic science is so important to the future of clinical care,’” he says. “They began to galvanize as a community, and the school became something that people wanted to be part of, that they wanted to contribute to.”

Pizzo used the discussions and work from that meeting to draft a master plan for the medical school, a document titled “Translating Discoveries,” and held a series of town hall meetings to get input from the broader school community. Several of the recommendations were already being put into action by the time the second annual retreat rolled around. This time, Pizzo says, there was much greater interaction among the participants.

This deliberate outreach is one of the hallmarks of his leadership style. “I’m pretty clear about saying, ‘These are the things I think we should take on and challenge,’ and then learning from the responses of others who critique it and help to reshape it. It’s a top-down, ground-up fusion style,” Pizzo says. “I’ve viewed my role as being a steward — hopefully more in the background than foreground — in trying to move or stimulate or catalyze ways of going forward, which others would then carry on.”

That forward progress covered all fronts. In research, Pizzo created the school’s Institutes of Medicine — five organizations that span a variety of departments and disciplines in order to move discoveries from the bench to the bedside, and link the school’s researchers to their counterparts in clinical programs at Stanford Hospital & Clinics and Lucile Packard Children’s Hospital.

REFLECTIONS ON THE DEAN

‘I’M A STRONG ADMIRER

OF PHIL’S. OVER A PERIOD OF TIME,

YOU JUST FALL IN LOVE WITH THE GUY. HIS TENURE HERE HAS BEEN THE MOST

PRODUCTIVE AND TRANSFORMATIVE TIME

IN THE HISTORY OF THE MEDICAL SCHOOL ON THE STANFORD CAMPUS.’

— PAUL BERG, PHD, NOBEL LAUREATE AND PROFESSOR EMERITUS OF BIOCHEMISTRY

‘VISIONARY. DETERMINED. FOCUSED.

LOVES A CHALLENGE. THESE ARE A FEW
WORDS THAT COME TO MIND WHEN I THINK OF PHIL PIZZO.’

— JOHN HENNESSY, PRESIDENT OF STANFORD UNIVERSITY

Pizzo also worked closely with the CEOs at the two hospitals to dramatically increase the number of physicians and physician-scientists on the faculty, while also focusing on the quality and service of the medical care being delivered. One of his highest priorities has been making sure that the quality of the medical center’s patient care matches the school’s long-standing record of excellence in research.

Ann Weinacker, MD, who has been chief of staff at Stanford Hospital & Clinics since 2011, can attest to Pizzo’s concern for patients. She recalls that in December 2008 she went to Pizzo to find out how to better serve the medical school. He had just finished writing an issue of his twice-monthly newsletter, and one topic he addressed was making sure that physicians saw their patients as human beings, not simply as an illness or injury to be treated, that patients didn’t get “lost” in the complex academic medical environment, and that they knew who their doctors were. Weinacker and Pizzo brainstormed about how to ensure compassionate care. Weinacker began meeting with three other medical service directors to devise strategies for “treating patients as we would want to be treated, seeing them as people who are often vulnerable, but always deserving of being empowered to make decisions about their own care.”

That effort has since grown and been embraced by hospital leaders, Weinacker says. “Dr. Pizzo’s been 1,000 percent behind this whole thing — making sure that patients are treated not just appropriately in medical terms, but also appropriately as individuals, as people who deserve the best we have to offer,” she says.

On the education front, he played a leading role in revising the curriculum for medical students to further solidify Stanford’s goal of creating the next generation of leaders in academic medicine. In addition to better integrating classroom learning with clinical training, the new curriculum required medical students to complete a scholarly concentration in which they select a specific aspect of medicine for multiyear study. And to ensure that the students will be excellent clinicians as well as top-notch researchers, the school implemented the Educators-4-Care program to provide students with ongoing training in the doctor-patient relationship throughout their time at Stanford.

Pizzo also aggressively advanced the effort to improve diversity at the school, creating the Office of Diversity and Leadership and appointing Hannah Valentine, MD, to implement programs to attract and retain a professoriate that re-

flects the nation’s diversity. For instance, Stanford previously lagged behind the national averages and its peer institutions in the number of women faculty at all ranks. Today, Stanford is well ahead of its counterparts and the national averages.

He also implemented programs to ensure that the integrity of the medical school and its employees remained above reproach. This included prohibiting faculty members from accepting industry gifts of any size, including drug samples, and from participating in speakers’ bureaus in which they are paid to deliver company-prepared presentations on drugs, devices or other commercial products. The school also declined to accept support from pharmaceutical or device companies for specific programs in continuing medical education.

The industry-interaction policies didn’t sit well with many faculty members, but Pizzo was adamant. “I want to be able to honor the public trust,” he said in 2008 when the CME policy was announced.

There were also a few actions that represented his personal concerns about health and safety. He spurred a policy that prohibits smoking throughout the medical center, and readers of his newsletter often saw his admonitions for bike riders to wear helmets.

“He’s a grandma,” Berg quips. “He’s got to take care of everybody.”

And that caretaking extends to the personal level. Without fail, those who know Pizzo remark on his genuine interest in the people he meets and works with. He remembers details about their lives and their families, and is the first to offer help.

Berg cites an incident involving a colleague who was briefly hospitalized in San Francisco after an accident. When Berg became concerned that the colleague was being discharged too quickly and might need further attention, he called Pizzo for advice. “In 15 minutes, Phil called back and he had already talked to our trauma center so that they could follow up [with the patient], and he explained how these kinds of cases are typically treated,” Berg says. “I know he was just getting ready to go into a long conference call, and yet he got right back to me. He really cares about people; it’s extremely sincere.”

SETTING THE PACE

As the demands of running a medical schools are many, it would’ve been understandable for Pizzo to step away from any type of clinical duties. Yet he has continued to be involved in weekly teaching rounds with medical students, and takes a

week or two each year to spend time in Packard Children's Hospital, treating children with infectious diseases. "It's a way of reaffirming my role as a care provider," Pizzo says. "During the time that I've been at Stanford as dean, it's been a way of communicating to colleagues that I am able and willing to do some of the same difficult work that they're doing."

He also made the deliberate decision to steer clear of board positions with pharmaceutical or biotechnology companies, preferring to avoid anything that might cast suspicion on his integrity or the school's.

"Phil is an extremely moral person, and morals and ethics go together," Berg says. "I think if anything would really upset him, it would be somebody who violates an ethical or moral principle."

Pizzo's years as dean also coincided with the controversy over stem cell research. He expressed concern when then-President George W. Bush imposed severe limits on federal funding for embryonic stem cell research, and began looking for alternate ways of continuing the work. That, in part, led to the creation of the first of Stanford's five institutes, the Stanford Institute for Stem Cell Biology and Regenerative Medicine. When California voters approved Proposition 71 in 2004 to provide \$3 billion for stem cell research, Pizzo was the first person named to the oversight committee for the state's new stem cell agency.

The state's support for stem cell research also figured into the overall plans for replacing the school's aging facilities. The classrooms and laboratories first built when the medical school moved to the Palo Alto campus in 1959 weren't adequate for today's research and technologies. As Pizzo and his team worked on the new educational facilities, they also developed plans for other research buildings that would allow for the kind of interdisciplinary collaboration envisioned by the school's institutes. The first of these facilities, the Lorry I. Lokey Stem Cell Research Building, opened in 2010.

THE RESULTS

Looking back on the past 12 years, the physical changes to the medical school campus — the new buildings — are the easiest to see. And there is a long list of other accomplishments. The number of faculty at the medical school has risen to 872 (from 710 at the time Pizzo arrived), and more than 600 of them have been hired during his watch. Additionally, the school has gone from the \$245 million in sponsored research in 2001 to the \$498 million the school earned in fiscal year 2011. Under his leadership, the school also secured approximately \$1.6 billion in philanthropic support. And the school and the two hospitals continue to work strategically to provide excellent service and look for ways to enhance value while reducing health-care costs.

But Pizzo measures his success by a single yardstick — greater cohesiveness among the faculty, staff and students.

"If the members of our community feel prouder to be here, and be members of the Stanford community, today, compared with a decade ago, that is a wonderful and exhilarating accomplishment," he says. "I'd like to think of them as years of catalytic and fusal change. A time when the community rallied around the sense of mission — translating discoveries, building on new knowledge, fostering the creation of new approaches to education and to clinical care and its delivery. A time of really saying, How could we — as Stanford Medicine, as small as we are in the sphere of this nation's medical enterprise — be a role model for change? How could we be a place that others will look at and say, 'They've really done something important there. They've gotten it right?'"

That kind of atmospheric change is hard to measure, but those inside and outside the medical school attest to its reality.

"I think there's been a real culture change in how people view their role in the medical school," says Berg. "A feeling of being part of the medical school rather than being biochemists or developmental biologists is firmly

entrenched. He really has created a sense of the School of Medicine being a principal focus."

Hennessy, the university's president, says Pizzo "anticipated research directions and reorganized the school's research programs — transforming the medical school and raising the profile of Stanford Medicine. We celebrated the medical school's 100th anniversary four years ago, and thanks to Phil's leadership, Stanford Medicine is well-positioned for another century of pioneering discoveries."

"When Phil Pizzo took over as dean, the morale in the School of Medicine, particularly in the clinical departments, was at an all-time low in the wake of the unsuccessful merger with UCSF," says Provost John Etchemendy, PhD. "Through sheer force of will, Phil managed to right the ship and steer it in a new, more positive direction. He now leaves the school in the best shape it's ever been — academically, clinically and physically — poised for even greater achievements to come. That is his legacy, and a remarkable one it is."

SECOND WIND

In the last few years, Pizzo began thinking more about the next phase of his life. His daughters — Cara, a pediatrician at the Palo Alto Medical Foundation, and Tracy, a program manager at Google — live nearby and have families of their own, and he relishes being a grandfather. Not quite ready to be called Grandpa, he asked his grandchildren to call him "Indy" after the movie character that first enthralled him 31 years ago. In fact, Pizzo displayed the character's trademark fedora and whip on a wall in his National Cancer Institute office for years until someone took the whip. What appeals to him about Indiana Jones is "the opportunity for adventure, for outlandish — if sometimes heroic — acts that are at the edge of appropriateness, that dig into the past and maybe, in a way, transform a little bit of the future," he says. "I also identify with a fear of snakes."

Pizzo sees life as a series of cycles, and the belief that he was heading toward a new cycle began to crystallize as he pre-

sided over meetings in 2010 where a policy was being developed to help senior faculty with transitional career planning. "I looked around the room and realized that at 66, I was the senior member of the group and that if I was going to model this, I needed to engage with this on a personal level," he says.

Ever the mentor, Pizzo says he also wanted to make sure his choices for the next stage of his life made it clear "that it's OK to make a transition to something other than the next acquisition of power and stature and leadership. That it's OK to say that you want to find a balance between your personal and your professional life. To me, it's important to signal that becoming a senior member of a community is not a prescription for obsolescence. It's an

opportunity for recalibration."

He is already scouting out a new course. On Dec. 1, he will begin a 12- to 18-month sabbatical in which he will reconnect with his academic and clinical roots in pediatric cancer and infectious diseases. He also plans projects both with Stanford's Center on Longevity and the new Clinical Excellence Research Center, which aims to find ways to lower health-care costs while improving patient outcomes. He plans to do some writing as well as that possible ultramarathon once his back is fully healed. "And I might even indulge a long-held dream of learning to play the cello," he says.

When he says "renewal, not retirement," he clearly means it. **SM**

Contact Susan Ipaktchian at susani@stanford.edu

FEATURE

Against the odds

CONTINUED FROM PAGE 20

but think back on all the knowledge that you've gained over the last year. And remember, you represent *hope* to these people."

IN THE WAITING ROOM

BY THE END OF JULY — AFTER DOZENS OF PRESENTATIONS ON HER ADVANCED-CANCER-CARE MODEL, PATEL GOT GOOD AND BAD NEWS.

The good news was that five groups expressed interest in piloting her program. One large hospital in California agreed to test most of her new care model. A large employer agreed to offer financial incentives to fully implement her care model with a health system serving a large number of its employees. Three others were leaning toward implementation but had not given the final go-ahead.

The bad news: Patel's mother came back to Stanford for a follow-up appointment with her oncologist to make sure her breast cancer hadn't recurred. The mammogram showed no tumors, but the bone scan showed an anomaly, and now Patel and her mother were going through the tor-

tuous process of waiting for results.

"My mother is my best friend," says Patel. "I talk to her about everything. Except my worries about her cancer."

Watching the compassionate handling of her mother's case by the veteran Stanford breast cancer specialist forever changed Patel's view of how physicians should talk to cancer patients and their families. It impressed her with the need for a calm, experienced, neutral coach to talk a patient through the life-changing experience of a cancer diagnosis. She realized that there are thousands of factors, seen and unseen, involved in cancer treatment decisions. And that an informed patient — with the support of friends, family, counselors and oncologists — needs to be at the center of those decisions. Now she wants to share what she's learned with others.

Mrs. Patel recently spoke about how proud she is of her daughter: "Four years after my cancer, I'm still here. I thank my daughter for that. I can't wait to see how she will make a difference in helping other cancer patients."

As Patel sat in the waiting room with her mother, she mentally ran through worst-case scenarios of other cases she's seen, and she worried. But

Executive Editor:

PAUL COSTELLO

Editor:

ROSANNE SPECTOR

Art/Design Direction:

DAVID ARMARIO DESIGN

Director of Print and Web Communication:

SUSAN IPAKTCHIAN

Staff Writers:

KRISTA CONGER

ERIN DIGITALE

BRUCE GOLDMAN

MAX MCCLURE

ANDREW MYERS

KRIS NEWBY

RUTHANN RICHTER

JOHN SANFORD

TRACIE WHITE

Copy Editor:

MANDY ERICKSON

Circulation Manager:

JULIE ELWARD

Stanford Medicine is published three times a year by the Stanford University School of Medicine Office of Communication & Public Affairs as part of an ongoing program of public information and education.

© 2012 by Stanford University Board of Trustees. Letters to the editor, subscriptions, address changes and correspondence for permission to copy or reprint should be addressed to Stanford Medicine, Stanford University School of Medicine, 555 Middlefield Road, Building 110, Menlo Park, CA 94025. We can be reached by phone at (650) 736-0297, by fax at (650) 723-7172 and by e-mail at medmag@stanford.edu.

To read the online version of *Stanford Medicine* and to get more news about Stanford University School of Medicine visit <http://med.stanford.edu>.

For information from the Stanford Medical Alumni Association visit <http://med.stanford.edu/alumni/>.

she understood that her mother needed to be able to make these decisions on her own.

Then Patel was handed her mother's bone scan report. She looked it over and breathed a sigh of relief. It was clear. And at that moment, she took off her white coat and tried to simply be a supportive daughter. **SM**

Contact Kris Newby at krisn@stanford.edu

PG

TEAMING WITH PARENTS OF KIDS WITH AUTISM

Pediatric psychiatrist Antonio Hardan, MD, who studies and treats children with autism, is driven in his work by a sense of awe — for his patients' parents. • Children with autism have language and social interaction deficits, and perform repetitive or stereotyped behaviors. Sixty to 70 percent also display what their doctors call irritability. "We're not talking about mild things: This is throwing, kicking, hitting, the child needing to be restrained," says Hardan, an associate professor of psychiatry and behavioral sciences at Stanford and director of the Autism and Developmental Disabilities Clinic at Lucile Packard Children's Hospital. • Over and over, Hardan has seen moms and dads react with grace and love to behaviors that would tax even the most patient of souls. He has watched parents make huge sacrifices of time, energy and

money to get their children the help they need. "It's life-changing, seeing what these families go through," he says.

What he sees motivates Hardan to cast a wide net in searching for new autism treatments. It was a parent's idea, for instance, that instigated a recent Stanford pilot trial testing the efficacy of a dietary supplement — the antioxidant N-acetylcysteine, or NAC — for autism symptoms.

"NAC is being used by community practitioners who focus on alternative, non-traditional therapies," Hardan says. "But there is no strong scientific evidence to support its use. Somebody needs to look at it."

So, with funding donated by another parent, Hardan's team carried out a small study involving 31 children. The results were encouraging: NAC lowered irritability and reduced children's repetitive behaviors. Though Hardan is cautious about the results, stressing that they need to be replicated in larger trials before NAC is recommended for autism, he also sees potential advantages to NAC treatment.

Currently, doctors prescribe second-generation antipsychotics to treat irritability and other "side" features of autism like mood swings and aggression. These drugs cause serious side effects, including weight gain, involuntary motor movements and metabolic syndrome, which increases diabetes risk. By contrast, NAC's side effects are generally mild, with gastrointestinal problems such as constipation, nausea, diarrhea and decreased appetite the most common.

In the study, the results of which were published June 1 in *Biological Psychiatry*, children with autism received either a placebo or NAC for 12 weeks — 900 mg daily for four weeks, then twice daily for four weeks and finally three times daily for the last four weeks. NAC treatment decreased irritability scores from 13.1 to 7.2 on the ABERANT Behavior Checklist, a widely used clinical scale for assessing irritability. The change is not as large as that seen in children taking antipsychotics. "But this is still a potentially valuable tool to have before jumping on these big guns," Hardan says. In addition, children taking NAC showed a decrease in repetitive and stereotyped behaviors, which lack effective treatment.

Hardan's team is now seeking NIH funds to re-examine NAC in a large, multicenter trial. A crucial piece of their application is the pilot data that came from a parent's idea — and Hardan's willingness to try it. Without that combination, the research would never have gotten off the ground. — ERIN DIGITALE



Antonio Hardan tested a nutritional supplement as an autism treatment and found signs it works.

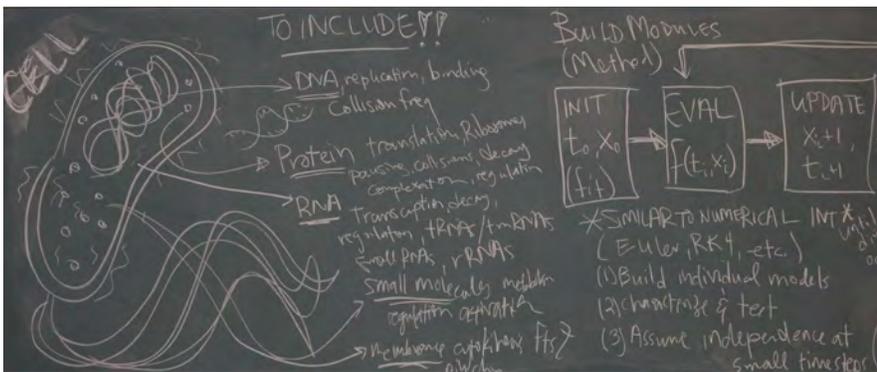
Stanford University School of Medicine
Office of Communication & Public Affairs
555 Middlefield Road, Building 110
Menlo Park, CA 94025

Change Service Requested

Virtual life

THE FIRST FULLY SIMULATED ORGANISM

Mycoplasma genitalium is not an ambitious organism. Historically, the tiny bacterium has been content to quietly parasitize the human urethra. But having a genome an eighth the size of *E. coli*'s affords you certain privileges — such as being the first living thing to be completely reproduced, down to the last molecular interaction, in a computer. • The man behind the virtual microbe, assistant professor of bioengineering Markus Covert, PhD, isn't particularly interested in *M. genitalium*. He's concerned with biologists' ability to fully understand the reams of data it's producing. Faced with the interactions of hundreds or thousands of genes, how do you know what experiments to perform next?



"No one person can wrap their mind around every fact," Covert says. Even the computational model of *M. genitalium* required over 1,900 parameters from more than 900 research papers. "So you make a computational model and use that to drive your experimental program."

The Covert lab built its digital parasite by modeling individual biological processes — protein synthesis, cell division, etc. — as separate "modules," each governed by its own algorithm. These modules then exchanged data after every cycle, making for

a unified whole that very closely matched *M. genitalium*'s real-world behavior.

The team has already used the modeled cell, which it described in a paper published July 20 in *Cell*, to address questions about the bacterium's biology that have been too complex to approach with standard laboratory experiments.

"If you use a model to guide your experiments, you're going to discover things faster. We've shown that time and time again," says Covert.

But the researchers' ultimate goal is something bigger: a biological version of computer-aided design, or CAD. The technology that allows engineers to mock up a new airplane fuselage on a desktop computer could allow bioengineers to rationally design entirely new micro-organisms.

According to co-author and Stanford graduate student Jonathan Karr, the only thing that's keeping CAD out of the life sciences for now is the lack of more modeled organisms. "This is potentially the new Human Genome Project."

— MAX MCCLURE

TO SUBSCRIBE
TO STANFORD MEDICINE
e-mail medmag@stanford.edu
or call (650) 736-0297.