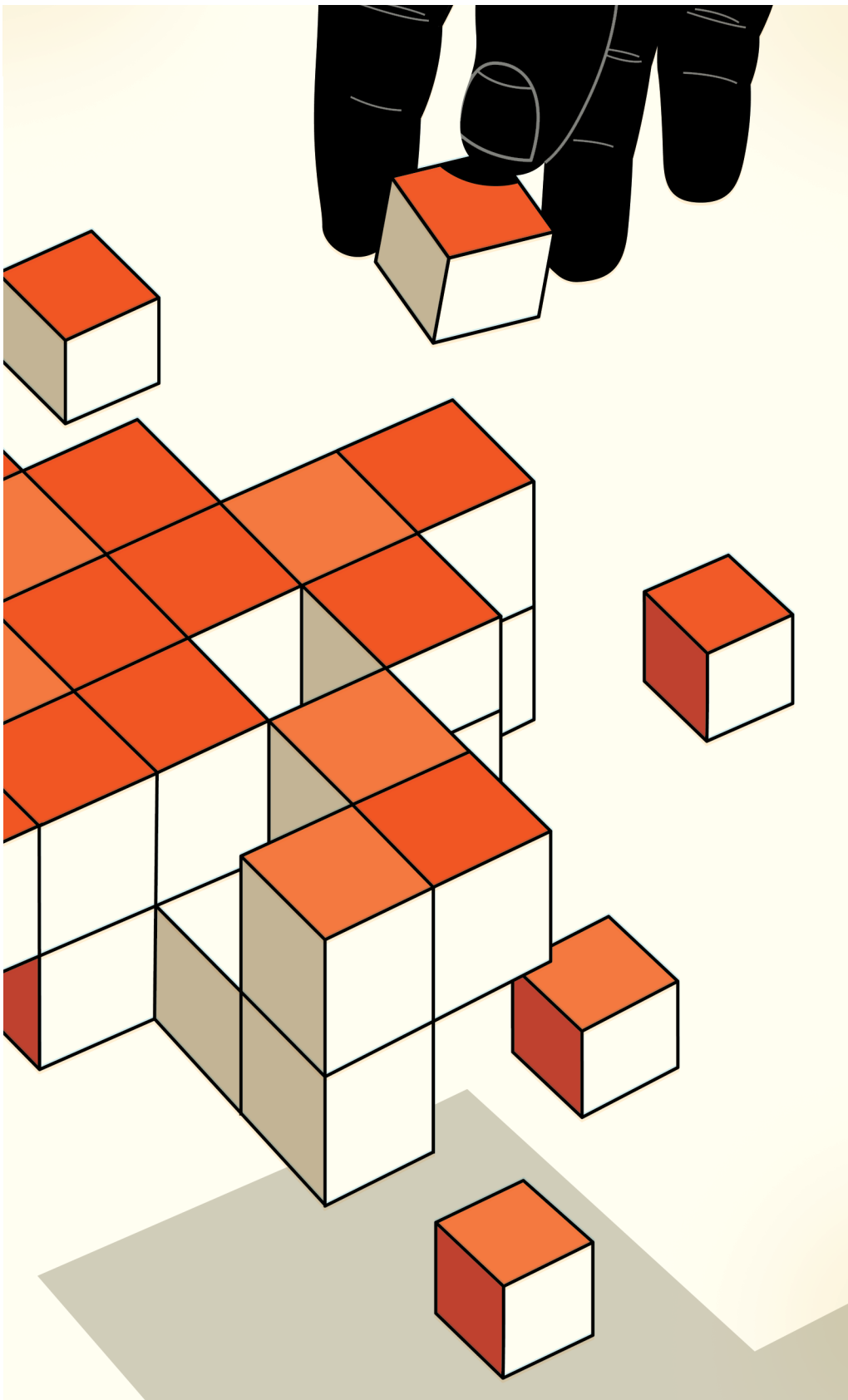
STANFORD MEDICINE

Winter 2016



special report

PRECISION HEALTH

Rethinking mental illness
Will neuroscience lead the way?

With pen in hand
Learning how to say goodbye

Nanotechnology
Beyond the hype

Too early
The quest to stop premature births

Patients like you
Mining the gold in electronic health records

Tom Brokaw interrupted
The broadcaster's battle with cancer

plus

'When Breath Becomes Air'
An excerpt from Paul Kalanithi's searing memoir

Growing drugs
A solution for shortages

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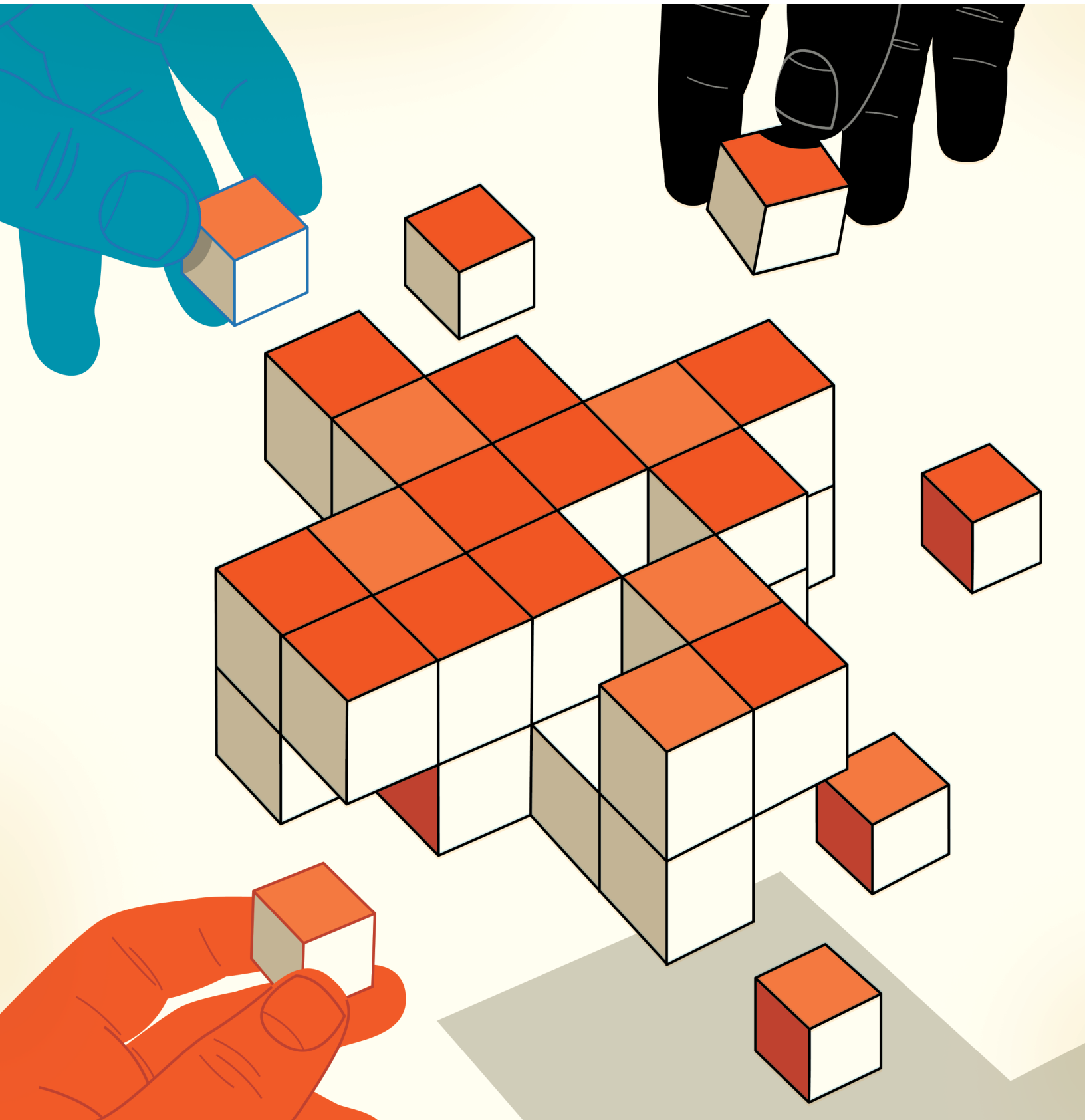


TRACKING PAIN

HOW HEALTH DATA PROVIDED BY PATIENTS ADDS UP TO BETTER CARE

Fifteen years ago, when professor of anesthesiology Sean Mackey, MD, PhD, began working in pain medicine, he found himself hampered by the lack of data available for each patient. "Physicians go through a very laborious, very frustrating, trial-and-error process," he says. That's particularly true when treating chronic pain, where doctors need information on patients' social and emotional well-being, as well as their physical symptoms. • Long-term pain can shift the behavior of the nervous, immune and inflammatory systems in ways that are challenging to predict or track. Loss of physical function can damage a patient's ability to function socially. It's easy for patients to get depressed, anxious and angry. Assessing all of these factors is crucial to recovery, but the data can be overwhelming for patients to provide and for physicians to assimilate. • "I used to pay high school students to scan pen-and-paper patient surveys over the weekend," says Mackey, who holds the Redlich Professorship. "The surveys took 45 minutes for patients to fill out and we couldn't use the information in real time."

JASON HOLLEY

So Mackey and his colleagues created a computer-based system that uses streams of data from many patients to help physicians provide the best care for individuals. "It has utterly changed the way we practice medicine at Stanford," he says.

The system, first used in 2012 in the Stanford Pain Management Center, adapts questionnaires as patients fill them in, skipping irrelevant questions and, as a result, speeding up the process. It also creates graphs displaying the patient's progress in various categories so both the doctor and patient can see it. More recently, the team has begun entering patients' genetic information as well.

The program, called the Collaborative Health Outcomes Information Registry (http://choir.stanford.edu), has since been adopted by other Stanford Medicine clinics and now contains data from about 10,000 people. Physicians can use the data to analyze why some patients improve faster than others and what makes patients vulnerable to complications like depression or addiction to painkillers. The CHOIR team is using it to see which patients are most likely to be dissatisfied with their health-care services, then ensure these patients get more attention.

Stanford's Division of Pain Management and the Center for Clinical Informatics developed CHOIR with support from the National Institutes of Health and the Redlich Pain Endowment. Mackey is sharing the software, which is open-source, nationwide. "The goal is to create a sharing ecosystem of modules," says Mackey. The University of Florida has created a module to integrate CHOIR data into electronic medical records and the Medical College of Wisconsin has contributed one that sends patients reminders using SMS texting. Ming-Chih Kao, MD, PhD, a Stanford clinical assistant professor of anesthesiology and of orthopedics, has developed several modules that together reduce the time physicians spend on the computer and increase time spent with patients.

"The vast majority of challenging medical conditions that we're facing now and into the future are chronic diseases," says Mackey. He says a shift to medical care aided by masses of health information provided by patients may be the most effective way to help those who are chronically ill. CHOIR is a powerful tool to accomplish this, he says.

"This is the future of health care," says Mackey. "What is novel now at Stanford is going to be commonplace in five to 10 years." — LINDZI WESSEL

VOLUME 33 NUMBER 1
WINTER 2016

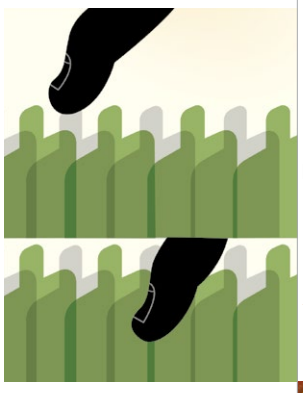
STANFORD MEDICINE

Transforming psychiatry
page 12

SPECIAL REPORT

Precision health

Medical look-alikes
page 32



PLUS

Facing off with chimps
page 3

DEPARTMENTS

COVER: HARRY CAMPBELL

letter from the dean

For as long as people have been caring for the sick,
we have been playing a frantic game of catch-up, working to cure illness after the fact.
Now, for the first time in our history, we are starting to see the possibility to not just win the race against the clock, but to win it before it even begins — to prevent disease before it strikes and cure it decisively if it does. This is the power of precision health.

At Stanford Medicine, we are leading the precision health revolution through a close collaboration that brings together our strengths in fundamental research, biomedical breakthroughs, data science, engineering, business, design, technology, patient care and teaching the next generation of physicians. With a foundation that begins at precision medicine, precision health goes much further by treating people — not just their illnesses — to help them stay healthy. And what unifies these efforts is our culture of relentless creativity and collaboration that has always been the hallmark of Stanford and our home in Silicon Valley. Mariann Byerwalter, interim president and CEO of Stanford Health Care, Chris Dawes, president and CEO of Lucile Packard Children's Hospital/Stanford Children's Health, and I are working together to ensure that the promise of precision health becomes reality for patients.

GLENN MATSUMURA

Stanford Medicine's work on precision health has already delivered solutions for some of medicine's toughest challenges: diagnostics that detect diseases at their earliest, most curable stages; a device that can predict a pediatric asthma attack days before it strikes; new ways to eliminate food allergies; and partnerships with companies such as Apple to help patients not just monitor their health but share that information to improve the health of others.

This is just the beginning. Stanford physicians and researchers are now at work developing new ways to tailor treatments by using the reams of data lying dormant in electronic medical records. When the pathbreaking tool, dubbed the Green Button, is approved for use, it will deliver the power of data, allowing physicians — for the first time — to provide evidence-based medicine faster and with precision.

To the high tech, precision health is also bringing the high touch. Building a culture of health and of disease prevention begins with understanding what is important to our patients, how they feel, what they fear and what they value. The Letter Project — an outreach effort that gives patients more of a voice in how their last days are lived — is one way Stanford physicians are elevating the doctor-patient relationship and focusing on the health of the whole person.

At Stanford, we have a responsibility to see this revolution succeed throughout the world, but it won't be easy. It will require real change — from how the world shares and uses information to how we rationalize the cost of care so innovation becomes truly accessible.

We are closing a chapter in human history. Every day the people of Stanford Medicine are dedicating their lives to writing the next, and we will share this knowledge with the hopes of spreading precision health around the globe.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head & Neck Surgery

upfront

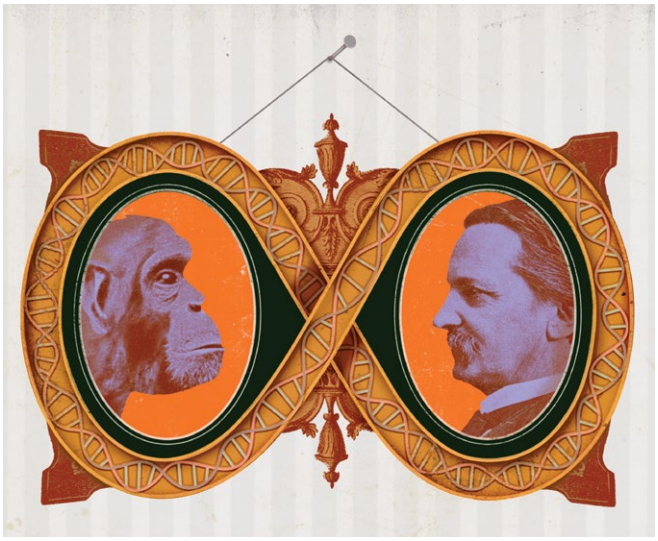
A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Two faced

CHIMPANZEES ARE OUR nearest relatives, genetically speaking. Yet their ears and brows are more prominent, their noses, chins and cheeks less defined and their faces more covered with hair than even the swarthiest human.

Variations in gene expression, rather than dissimilarities among the genes themselves, help explain the differences, according to School of Medicine researchers. Chimps and humans express different levels of proteins known to control facial development, including some involved in jaw and nose length and skin pigmentation.

"We are interested in craniofacial structures, which have undergone a number of adaptations in head shape, eye placement and facial structure that allow us to house larger brains, walk upright and even use our larynx for complex speech," says Joanna Wysocka, PhD, professor of developmental biology and of chemical and systems biology, who shares senior authorship of the study with senior research scientist Tomasz Swigut, PhD. Graduate student Sara Prescott is the lead author of the study, which was published in September in *Cell*.



CHRISTIAN NORTHEAST

The researchers compared areas of DNA known as enhancer regions, which contain chemical tags and proteins bound to the DNA that control the expression of nearby genes, in human and chimpanzee cranial neural crest cells. About 1,000 were more active in one species than the other. Many of those, Wysocka says, "have been previously shown to be important in craniofacial development or associated with normal intrahuman facial variation."

A set of **396** human genes change their activity in response to viral infections, but not bacterial ones. More at http://stan.md/225KQJs.

Here comes the sun

IT'S A COMMON STORY. A few days after birth, a newborn's skin and eyes turn yellow. The diagnosis: jaundice, a build-up of bilirubin in the blood that poses risks of brain damage or death. The treatment: phototherapy under a blue light.

But what if there's no blue lamp or reliable electricity available? Sunlight filtered through commercially available plastic films is just as safe and effective, according to a clinical trial conducted in Lagos, Nigeria, and published in September in *The New England Journal of Medicine*.

"In settings with no access to modern devices, we've shown we can use something that's available all around the planet — sunlight — to treat this dangerous condition," says senior author David Stevenson, MD, a Stanford professor of pediatrics.

DISARM, NOT DESTROY

THE BACTERIUM *Clostridium difficile* wreaks havoc in hospitals — and in patients' guts. It grabs a foothold in those with weakened immune systems, harms their intestines and is hard to get rid of. It kills 15,000 people in the United States each year.

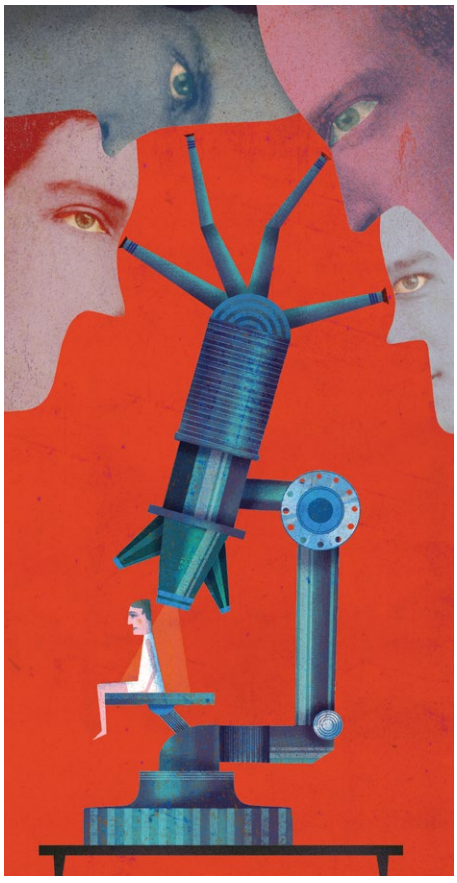
C. difficile infection has traditionally been treated with antibiotics, which unfortunately also wipe out microbes that can resist such pathogens. Infection recurs in a quarter of those treated — and only a quarter of those recover with further antibiotics.

In a series of experiments, researchers at the School of Medicine have demonstrated that the drug ebselen can disable *C. difficile*'s toxins, rather than destroying it entirely. "Unlike antibiotics — which are both the front-line treatment for *C. difficile* infection and, paradoxically, possibly its chief cause — the drug didn't kill the bacteria," says senior author Matthew Bogyo, PhD, professor of pathology and of microbiology and immunology.

The team knew *C. difficile*'s two main toxins were secreted proteins with similar sections of protease activity — proteins that slice up other proteins. They tested 120,000 molecules against the primary toxin. Hundreds shut down the protease activity, but they zeroed in on ebselen because it has already been used safely in clinical trials for other conditions. Subsequent experiments demonstrated that ebselen reduced the clinical symptoms of *C. difficile* infection and blocked persistent gut damage in mice.

The medical mystery tour

AN UNDIAGNOSED ILLNESS, says Euan Ashley, is a particular agony. Families endure odysseys of doctor visit after doctor visit, telling their stories again and again, accumulating debt, exhaustion and an electronic trail of expensive test results. • "Of course, you have the symptoms and signs that any illness has, but just not knowing what it is — not having a name for it, not knowing what the course of it is likely to be, not knowing if you share this with any other people — is a severe form of torment," says Ashley, MRCP, DPhil, a Stanford associate professor of cardiovascular medicine and of genetics. • Ashley is the steering committee co-chair of the National Institutes of Health's Undiagnosed Diseases Network, which aims to harness the expertise of physicians at seven major medical centers to diagnose and build knowledge about rare diseases. The co-principal investigators at Stanford are Paul Fisher, MD, professor of pediatrics, and Jon Bernstein, MD, PhD, assistant professor of pediatric medical genetics. The network builds on an NIH pilot program that was able to diagnose about 25 percent of those evaluated. • Within two years, the UDN expects to treat 250 patients per year. Each will have his or her genome sequenced, and will be accepted from anywhere in the country without regard to ability to pay. "Rare disease touches all sectors of society," says Ashley, "and certainly no one of us is immune."



CHRISTIAN NORTHEAST

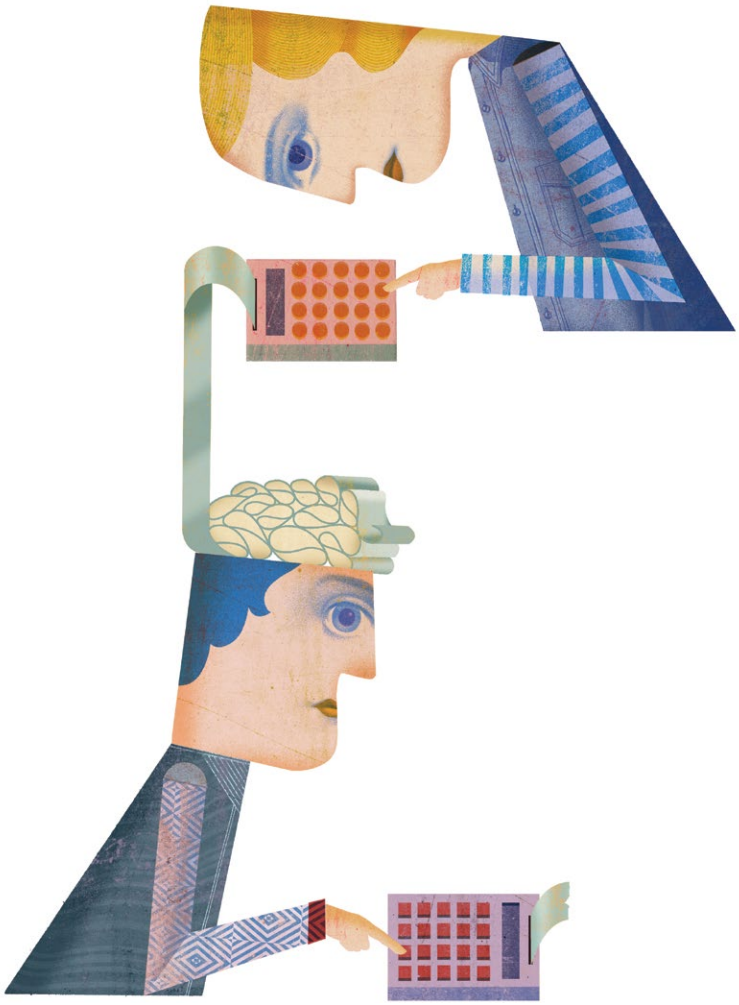
The source

IT'S BEEN a puzzle for a while now. Most tissues have a dedicated population of cells that both self-renew and make new specialized cells. But where was the liver stem cell?

Along the central veins of the organ's lobes, it turns out. Most liver cells are polyploid, meaning they have more than two copies of each chromosome and have trouble dividing normally. These can't do the job of a stem cell. But researchers at the School of Medicine led by professor of developmental biology Roel Nusse, PhD, located a population of cells in mice that acquire stem cell properties from proteins made by the central veins' endothelial cells. The stem cells have the normal two copies of each chromosome. The findings, published in August in *Nature*, could lead to greater understanding of liver disease and better cell cultures for drug testing.

ON THE BRAIN

IN JANUARY, Stanford Health Care opened a new, comprehensive outpatient facility on its Hoover Pavilion campus in Palo Alto for patients with neurological disorders. The Stanford Neuroscience Health Center brings together 21 neuroscience subspecialties to provide integrated patient care and conduct research on new treatments in neurology, neurosurgery and interventional neuroradiology. Among the new building's features: state-of-the-art imaging, a balance and gait lab, a wellness center, an outdoor garden where patients can practice walking on different surfaces and a testing lab for disorders of the autonomic nervous system.



Insulin shocker

BEFORE A PERSON gets Type 1 diabetes, hormone-producing cell clusters within the pancreas become inflamed: Immune cells gang up on the beta cells, which normally pump out insulin, and start to destroy them. By the time the disease's hallmark symptom — chronic hyperglycemia, or high blood sugar — manifests, 90 percent of the beta cells are gone.

A team of researchers from the School of Medicine has arrested that process in mice, using hymecromone, a compound already approved in Europe and Asia to treat gallbladder spasms.

Senior author Paul Bollyky, MD, PhD, assistant professor of infectious diseases, and his colleagues previously found that recently diagnosed Type 1 patients had an overabundance of hyaluronan molecules near their beta cells, whereas long-diagnosed patients did not. Administering hymecromone, which inhibits the body's synthesis of hyaluronan, prevented the onset of hyperglycemia in mice prone to developing Type 1 diabetes; if it was withdrawn, they quickly became diabetic. Bollyky is planning to test the treatment in humans.

Research associate Nadine Nagy, PhD, is the lead author of the study, which was published in October in the *Journal of Clinical Investigation*.

Number sense

Brain characteristics indicated which 8-year-olds would be the best math learners over the following six years.

TAKE A GROUP OF 8-YEAR-OLDS. Give them a set of standardized tests, as well as brain MRI scans. Which one better predicts their math ability at age 14? • The brain scans, say researchers from the School of Medicine. In a longitudinal study of 43 children, the team administered structural and functional MRI scans to measure brain structure and intrinsic functional connection between regions as well as tests to assess IQ, reading, math and working memory. • The children who had greater volume and connectivity of two brain regions, the ventrotemporal occipital cortex and the intra-parietal sulcus, as well as stronger connections between those regions and the prefrontal cortex, had greater gains in mathematical ability. Their test scores at age 8 did not predict their later learning ability in math. • "A long-term goal of this research is to identify children who might benefit most from targeted math intervention at an early age," says senior author Vinod Menon, PhD, professor of psychiatry and behavioral sciences. Postdoctoral scholar Tanya Evans, PhD, is the lead author of the study, published in August in *The Journal of Neuroscience*.

target: HEALTH

Stanford's vision for keeping us well

People like to joke sardonically, "When you have a hammer everything looks like a nail." But the flip side is that when you have a hammer you can build yourself a house on a hill, a fence for your vegetable garden and a bench by the front door, where you can sit and eat a homegrown tomato and look at the view. • A hammer can help create a whole world. From fire to telescopes, technology has always created tools that transform how we see the world and how we live. New tools mean new questions, new answers and new science. If you don't have a telescope, you don't think to ask about Jupiter's moons. And if you don't have new technologies for collecting and analyzing massive amounts of data, you won't think to tackle something as ambitious as precision health — a vision of a world with better health.

BUILDING A BETTER WORLD

At Stanford Medicine, the vision of precision health is to anticipate and prevent disease in the healthy and to precisely diagnose and treat disease in the ill. It's a vision of a future where traditional medicine and population health work hand in hand. And it's a future where the practice of medicine itself becomes grist for the research mill — where data from the sick and the well together inform traditional medicine — and where one-size-fits-all health-care guidelines are refined to fit the

By Jennie Dusheck

ILLUSTRATION BY HARRY CAMPBELL

needs of groups of people and even of individuals.

"The United States spends more of its GDP on health care than any other country in the world," says Lloyd Minor, MD, dean of the Stanford University School of Medicine. "Yet by standard outcome measures such as longevity and infant mortality, the U.S. ranks below many of the most industrialized nations. At Stanford, we're building a future that can change that, optimizing outcomes for both individuals and whole populations. Instead of racing to cure diseases, we can prevent them before they strike. And by focusing on wellness, we can make a dent in health-care costs. At Stanford, we call this vision precision health, where we focus on helping individuals thrive based on the many factors that together make each person unique, including their genetics and their environment."

One example of precision health at Stanford is the Children's Health & Air Pollution Study-San Joaquin Valley program. A collaboration with four public universities and a private consultant, CHAPS simultaneously treats patients and studies their health. The program brings together researchers in immunology, lung biology, developmental biology, population health sciences, health policy and the law. So when people who wheeze come to Stanford for help, they don't just get a nod and an inhaler. Instead, researchers and clinicians collaborate to discover if a patient has asthma or something else and, if it is asthma, what factors have led to its development. Each patient's illness contributes to databases about asthma that will help prevent and treat asthma in others.

Precision health is part of a wider movement to tailor both medical care and prevention. A year ago, President Obama announced his ambitious Precision Medicine Initiative. Obama's initiative will begin by targeting individual genetic strains of cancer. Longer term, the initiative will enroll a million Americans willing to share nearly everything about their health and their daily lives, including information from their genomes, proteins and microbiomes, personal medical records and wearable sensors. New tools from computer science and statistics will manage and analyze the resulting gigantic data sets and help explain why people get ill, how to prevent illness and which treatments work best for whom.

The trick is to find ways to integrate these massive amounts of data into a clear signal doctors and public health experts can use. Making the vision of precision health a reality will require enormous creativity and skill, and Stanford Medicine is home to a nearly perfect combination of such expertise.

"This campus is rich in resources to play in this space," says Stanford cardiologist and chair of medicine Robert Harrington, MD. "We've got great statistics; we've got great informatics; we've got great computer science; we've got great engineering."

Even at this early stage, Stanford Medicine is moving decisively into the field. It has built alliances with tech companies. It has held a series of town hall meetings and lectures over the past year to discuss and frame the future of precision health at Stanford. And it has formed the Precision Health Committee, composed of hospital and school leaders as well as research and clinical faculty, to plan future research and faculty hires. The school also recently founded the Department of Biomedical Data Science, chaired by professor of biomedical data science and of genetics Carlos Bustamante, PhD.

THE MERGING OF MEDICINE AND PUBLIC HEALTH

A major goal of precision health at Stanford is to marry two disciplines that have long held disparate perspectives on health and illness: traditional medicine and public health. Public health primarily keeps people healthy, while medicine primarily treats people after they become sick. And public health helps whole populations, while medicine helps individuals.

Professor of cardiology Euan Ashley, MRCP, DPhil, whose medical research focus is on individual patients, says, "The fundamental concept of precision health is the idea of defining disease better in order to target it more precisely. And how do we define disease better? We do it with new technology. If you look at the history of medicine, we've always defined disease according to the state-of-the-art tools of the time." For many years, cardiologists defined heart disease according to the sounds they could hear through a stethoscope, he says. "But when someone invented the electrocardiogram, we started to define heart disease according to the electrical signals from the heart."

'We call this vision precision health, where we focus on helping individuals thrive based on the many factors that together make a person unique.'

Today, state-of-the-art tools are just as exciting, Ashley says, but now they include things like whole-genome sequencing. "We can now sequence someone's whole genome for less than a thousand dollars," he says. "And we can define diseases in great detail, which lets us target subgroups of patients with specific therapies in areas like cancer or cystic fibrosis."

Throw in more data — such as which proteins a person's cells express and which bacteria make up the microbiome in their gut — and you are well on your way to knowing every-

thing about their health that you need to know to define diseases and identify treatment targets. Or at least that's the enthusiastic view of many researchers.

But there's another point of view from a contingent of researchers equally passionate about the future of health and medicine. Professor of medicine Mark Cullen, MD, says, "I think it's fantastic that we are cracking the genome, but I would like to crack the life-ome." Cullen is an expert in population health sciences, an emerging field that expands beyond public health. It not only draws information from large populations to improve the health of groups but also uses the information to help individual patients and to make basic research discoveries.

Cullen says you can learn more about how long people will live from their ZIP code than from their whole genome. For example, the average life expectancy for a child born in Atwater, California, is 87 years, but just 8 miles down the road in the city of Merced, life expectancy is only 78 years.

In the past, Cullen says, public health and medicine were divided by differences in practice and funding. "Physicians had to integrate everything in the patient's chart with everything they learned in school, and that became the basis for treatment. Physicians and hospitals also received huge reimbursements for taking care of individuals." Meanwhile, public health experts had to prevent illness in millions of people through national vaccination programs or food subsidies. Per-person funding was typically modest. The groups dealt with different data and lived in different economic worlds.

Then came big changes. With the creation of networked electronic medical records, individual doctors suddenly had access to all the details in a patient's record. "And while they were at it," says Cullen, "they could theoretically look at 25 million more records if they were relevant to that one patient." Population health experts' eyes lit up at such volumes of data. "So far," he says, "no one has solved the problem of how to use all that population data at the bedside, but the data are there. And it's a scramble among the smartest people in the best health-care systems to figure out how to do that most effectively."

Next came major changes in health-care economic policies. Medicare, for example, began pegging reimbursements for providers to how all the patients in a system were doing, not just individuals. New rules from Medicare include conditions for which up to 30 percent of the reimbursement will depend on population outcomes, says Cullen. "All of a sudden, hospitals like Stanford had to be able to demonstrate that they were controlling diabetes and getting blood pressure down in everyone, not just in one person."

One model for the melding of medicine and public health is cardiology, which intensively treats cardiovascular disease when people are ill but also prevents disease — with smoking-cessation programs, changes in exercise and diet, and daily aspirin and statins. This two-pronged approach has been so successful that the annual rate of cardiovascular deaths in the United States since the 1960s is down 70 percent.

Precision health aims to achieve similar results in other areas of health. Dean Minor envisions a world where we understand the immune system as well as we understand heart disease. "From four simple tests — total cholesterol level, total triglycerides, LDL and HDL cholesterol — we get a remarkable amount of information about our risk for heart disease," says Minor. Those four tests tell us not only how likely we are to develop heart disease, but to some extent what we can do about it. "At Stanford, we hope to have an immune system profile that's analogous to the lipid profile within five years."

Precision health asks how you apply all the information that's becoming available — about our genetics, physiology, environment and preferences — to the health of smaller groups of people and individuals. "That's what I think we're trying to get at," says Harrington, who chairs the Precision Health Committee at Stanford Medicine, "and that's really different from how we currently practice medicine."

THE GOOD, THE BAD AND THE DATA

Putting precision health into practice depends on gigantic databases queried and managed by experts in computation and informatics. But whether that data comes from genomics, biosensors or electronic medical records *(see sidebar, page 10)*, it presents challenges that Stanford researchers are tackling one by one.

Some of the richest data comes from the accumulation of years of patient records. But a combination of bias and outright errors can make it difficult to extract useful information from electronic medical records. Some mistakes are just mistakes: A medical-coding error can turn asthma into chronic obstructive pulmonary disease.

Fortunately, algorithms can flag inconsistencies that suggest an error. A person with chronic obstructive pulmonary disease, for example, would likely have a history of pneumonia, a record of an antibiotic at some point and probably an X-ray on file. If those associated conditions, tests and treatments aren't there, it's a sign that there's something wrong with the data.

THE TOOL SHOP

A CLOSER LOOK AT THE IMPLEMENTS FOR DOING PRECISION HEALTH

When it's time to prep for surgery, the medical team lays out all the tools, so everything is at hand and it's easy to see if anything is missing. Precision health has its own set of gleaming new tools, including "omic" data, activity and other monitors, and electronic medical records.

Ome sweet ome

THE BODY OPERATES by means of vast arrays of molecules that work together every moment of your life. Decoding how those molecules function is a critical part of improving health care. Professor of genetics Mike Snyder, PhD, and his team recently began studying 14 different "omes" in 100 people, including each participant's complete set of genes, or genome; all of their RNA, or "transcriptome"; all the proteins produced by their cells, or "proteome"; all of their metabolites, or "metabolome"; their immune cells; and five microbiomes, the communities of bacteria living in the gut, the sinuses or other parts of the body.

Among the first to participate in the Stanford omes project are twin astronauts Scott and Mark Kelly. While Scott spends a year in space providing data, Mark will supply all the same data while firmly on the ground. Snyder's team will compare the two sets of data to see how life in space affects health and what problems a traveler to Mars might expect.

Snyder is an old hand at tracking such data: For six years, he has been tracking omic data for just one patient — himself. He's been teased for exploring the "narcissome." But his genome revealed that he was at risk for Type 2 diabetes, and when he discovered that he was in fact developing diabetes, he took steps to reverse it. He's tracked his body's responses in sickness and in health, through mild colds and more serious illness.

Snyder's team is also watching what happens to the microbiome when people change their diet or become infected with a pathogen. "In my case," he says, "I got Lyme disease and we profiled me through that. I took antibiotics, so we're seeing what happens with that."

Truths from trackers

ANOTHER MAJOR SOURCE of precision health data is the plethora of new bio-sensors. Suppose you wear a Fitbit that tells you how many steps you take each day. At the end of the day, it can be a reminder that you never went for that lunchtime walk and maybe you should go after dinner.

If you choose, you could automatically share that information with your doctor, and if she gets a notice that your walking dropped, she might check in with you. Maybe you developed mild hip pain; she has you see a physical therapist and a month later, you are back on track.

Now, suppose a million people share their Fitbit data and health records. Health researchers could have a field day digging through the numbers to find out what happens to people over time if they walk, say, 7,000 steps a day versus 17,000, or what happens if people walk 3,500 steps on weekdays and 20,000 on the weekend. Does that variation change your cholesterol numbers? Does it affect your risk for hip or knee problems?

Devices that monitor our health and daily activities can go well beyond a Fitbit, including thermometers, electrodes that detect changes in skin conductance, chemical sensors that detect changes in our blood or breath, and mechanical sensors that respond to pressure, impact or stretch.

Ideally, say researchers, millions of us will share the data in some form that is anonymous, or "de-identified." When Stanford launched the Apple ResearchKit app MyHeart Counts last year, more than 50,000 people signed up to use their iPhones to monitor and share data about their activity levels, sleep, sense of well-being, diet and overall cardiovascular health.

Mining patient records

SOME OF THE RICHEST DATA comes from patient medical records. Such data includes doctors' notes, X-ray images and MRIs; self-reporting of mood or pain; data from tissue samples and other tests; and records of medical visits and procedures.

Electronic medical records can tell researchers how millions of patients were diagnosed and treated and which approaches worked and which didn't. EMR data is the backbone of patients-like-you programs that propose to identify groups of patients with similar sets of symptoms. *(See story, page 32.)*

Patient records are also a gold mine of answers to specific medical questions. For example, by scouring the medical records of 17,000 prostate cancer patients at two major hospitals, associate professor of medicine Nigam Shah, MD, PhD, demonstrated that prostate cancer patients treated with androgen blockers were at nearly double the risk of later being diagnosed with Alzheimer's disease compared with similar prostate cancer patients who didn't receive androgen blockers.

Omics, activity trackers and medical records are just a few of the tools available in the precision health tool shop. Sophisticated sensors can evaluate your health based on the chemical makeup of your sweat, and algorithms can create order from the data in medical records or reconstruct genomic information. As in any good shop, you can find ever more tools hanging on the walls or tucked away in special drawers.

More insidious, says Nigam Shah, MBBS, PhD, associate professor of medicine, are systemic biases in the data. Medical records serve several purposes, he explains. They help doctors communicate with one another, allow hospitals to get paid, provide documentation in case of a lawsuit and record patient progress. "These uses are not always compatible with each other," Shah says. "Billing is the one that usually dominates. And that can introduce certain biases."

For example, says Shah, suppose a researcher wants to know how many men develop urinary incontinence after prostate cancer surgery. In theory, billing codes would show that. But because doctors get paid the same whether the patient has incontinence or not, most physicians don't take the time to add the code for incontinence. Shah has a clever workaround: "If a patient is incontinent, you bet they will tell their doctor, and the doctor will probably type it out in their note, writing, 'Patient complains of incontinence.' And there are only a few ways to misspell 'incontinence,'" says Shah.

Using EMRs, researchers can also study the practice of medicine itself — for example, looking at what influences physician prescribing practices, how insurance coverage affects patient outcomes, and what factors promote or discourage "upcoding" — practitioners' tendency to code for more expensive procedures or diagnoses.

But even the best data comes with a tangle of questions and problems. One problem is protecting privacy. While identifying information — such as names, addresses and medical record numbers — can be removed, personal genomic information raises special questions because it is as specific as a Social Security number. Regular announcements of successful hacks of customer accounts at Target and Home Depot, and even the personal email account of CIA director John Brennan, suggest we can't completely control who sees our data. Shah and others are exploring ways to corral health and medical data so its power can be exploited only for good.

THE FUTURE OF PRECISION HEALTH

A hammer is a great tool, but sometimes you want a smaller hammer for fine work. Does this patient need aspirin? How much? Is this patient's heart attack a result of a genetic defect, or decades of trans-fat-laden doughnuts?

"The way things are now," Harrington says, "when I'm taking care of patients who've had a heart attack, I give them all aspirin. I don't say, 'Well, are you one of those aspirin non-responders, or are you one of those aspirin hyper-responders?' I just say, 'The evidence says that by treating a population with aspirin we lower the risk of dying by about 25 percent.'" But that's not good enough. "We should have systems in place to guarantee that 100 percent of the people who should get aspirin are getting aspirin," he says. "And if we don't know what we're doing, we should be studying that," he says.

THE PRECISION HEALTH APPROACH can be applied to public health as well. For example, a major way to improve the health of populations is through better nutrition. But how? To find out, Sanjay Basu, MD, PhD, has been studying ways to improve nutrition for vulnerable populations. Basu, an assistant professor of medicine at the Stanford Prevention Research Center, has found that a one-size-fits-all food assistance payment for groceries is just as inappropriate as when physicians give every heart patient the same dose of aspirin.

For example, simply receiving food assistance funds may not be enough. For some people, a van that takes them shopping once a week, and actually gets them to the store, is much more helpful than a food voucher for a market they can't get to. So, whether treating heart attacks or preventing them with better nutrition, it's the precision health approach — looking at what individuals need — that helps people eat better and stay healthy.

Minor sees an opportunity for precision-health thinking to be incorporated into research at all seven of Stanford's schools. Law and business, for example, can inform the development of policies to help populations become healthier, while engineering is helping to develop devices for monitoring health to both prevent and treat disease. Already, says Minor, nearly a third of all faculty at Stanford's School of Engineering are conducting research related to biomedicine, often in partnership with the School of Medicine. One device in development will monitor breathing and heart function of children with asthma while they sleep, delivering an alert as many as 48 hours ahead of a serious asthma attack. Early treatment saves kids from a trip to the emergency room, which is better for the kids, better for their parents and better for already overburdened emergency departments.

"Our vision," says Minor, "is that a doctor can tailor every therapy specifically to what's known about a patient: their genetics, their metabolomics, all their -omics, their imaging, everything about them. At Stanford, we want to live in a world where health-care providers aren't left on their own to somehow aggregate all that information. Instead, information technology helps a doctor to confidently tell the patient, 'You are going to benefit most from doing the following.' We know it will take a sea change in training the doctors of the future, but the benefits will be massive." SM

— Contact Jennie Dusheck at dusheck@stanford.edu

PRECISION

HEALTH

BRAIN WAVES

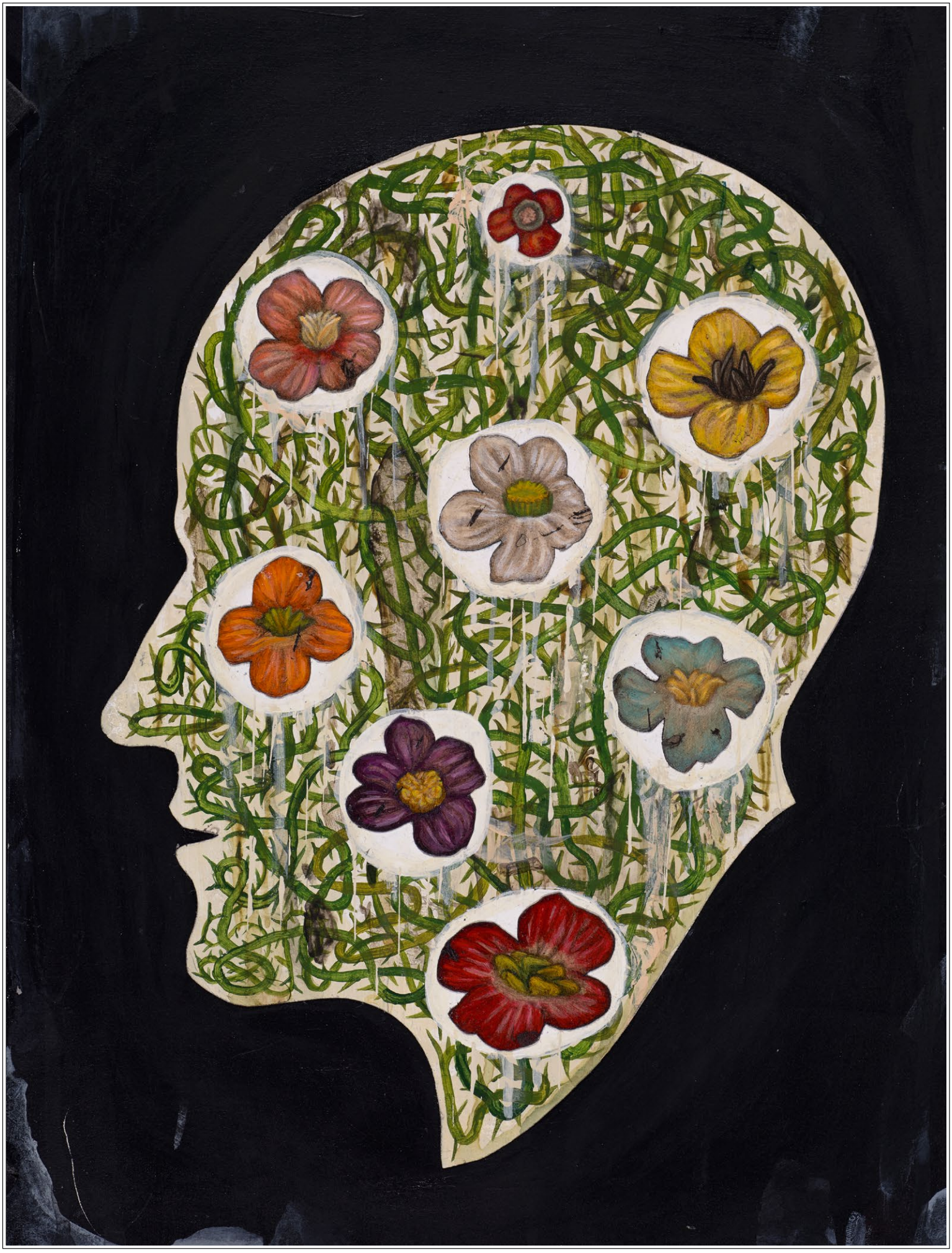
How neuroscience could determine your mental health treatment

The elderly gentleman's screams echoed down the halls of the transitional home for the mentally ill, the voices in his head torturing him. His only relief came when he held a transistor radio, tuned into static, tightly clamped to his ear. • "The voices were not quieted by medication," says Leanne Williams, PhD, a Stanford neuroscientist who vividly remembers her patient from nearly three decades ago, when she was training to become a therapist in Australia. Many of the patients she cared for during those three years in her 20s had been institutionalized for years — some for decades. An older woman who believed she was constantly about to give birth, tortured daily by labor pains. A severely depressed young man whom Williams and her co-worker found one morning hanging lifeless from the back of a bathroom door, the depression finally too much for him to bear. • The experience was frustrating, Williams says. As a therapist, she believed that by understanding the psychology of human behavior she could treat these severely mentally ill patients. But she soon realized she simply didn't have enough tools to understand what was going on inside their brains. Instead, she began to learn from her patients. • "It struck me that the man who heard voices was using the sound frequencies on his radio to modulate his brain activity, yet we were bereft of treatments to do anything similar," she says. "I finished up these work experiences with 100 percent clarity that I needed next to go into research. I wanted to understand brain dynamics and how this understanding could be connected to the real-world experience of mental disorder. From then on, I was on a mission."

By Tracie White

ILLUSTRATION BY JASON HOLLEY

PHOTOGRAPHY BY LESLIE WILLIAMSON



THE PAST QUARTER-CENTURY has seen a wealth of advances in neuroscience, from neuroimaging techniques that make it possible to see inside the live human brain to noninvasive electrical brain stimulation to selective activation of neurons using laser light for research in animals. The popularity of the field has exploded, with membership of the Society for Neuroscientists steadily climbing from its founding in 1969 to 40,000 members today. Yet little if any of this activity has resulted in improvements in clinical care for the mentally ill.

"We haven't yet seen the progress toward improved clinical care that we would have hoped," says Sarah Morris, PhD, acting director of the National Institute of Mental Health's Research Domain Criteria Initiative, a program begun five years ago to accelerate the translation of basic neuroscience research into new models for mental disorder and treatment. This gap, often caricatured as "mindless neuroscience versus brainless psychiatry," must be bridged if modern neuroscience is to bring help to the mentally ill, wrote Thomas Insel, MD, in May 2015 in *Director's Blog*, the blog he produced as director of NIMH.

The disconnect can, in part, be explained by the lack of a working biomedical model of mental illness, many in the field say. The current model of mental health treatment, in use since the days of Freud, is based solely on observation by clinicians and the reporting of symptoms by patients.

The new model combines these traditional methods of diagnosis and treatment with the biological concept of the brain as a network of circuits. The circuit, or network, approach focuses on how the billions of neurons in the brain communicate with one another via electrical signals. It cuts across the current broad diagnostic categories like anxiety or depression, with the hope of creating a new understanding of exactly what mental illness is.

The circuit approach, Williams says, provides a scientific path toward more accurate disease diagnosis and treatment while helping eliminate the stigma associated with mental illness as a personal failing or weakness.

"You boil it down to the superhighways of the brain, which are the routes where most of the neuronal traffic is going for the primary functions of the brain," Williams explains. "Imagine the road system. There are all these little hiking trails, then you've got the big superhighways where most of the traffic occurs. These brain circuits are explaining those main routes." Almost daily, new studies are published mapping these circuits and explaining what they do. Or what they don't, when altered or destroyed.

It's been nearly 30 years since Williams moved on from her career as a therapist and entered the world of brain research. And she's getting restless. Personalized neuroscience, a form of precision health that provides the best treatment for each individual patient, has the potential to change lives now, she maintains.

"I'm shocked so little of this research has bridged this gap," says Williams. She is running a clinical neuroscience study called the Research on Anxiety and Depression, or RAD, project. Funded by NIMH to develop the Research Domain Criteria Initiative approach, hers is one of the first studies to test a step-by-step process that combines neurobiological tests, such as brain scans, with measures of real-world function, such as occupational and social well being, to diagnose and treat patients. She describes it as a "pragmatic" research design that mirrors what would happen in an actual mental health clinic using this approach. By making it comfortable and practical for participants, she has designed a prototype for use in the real world.

'RIGHT NOW IN PSYCHIATRY we don't think about the brain at all when we are making a diagnosis or planning a treatment.'

The trial is an attempt to find an array of biological markers to classify anxiety and depression in new ways. It draws on the new model emerging from neuroscientists and psychiatrists — one that incorporates an examination of the brain as an organ much like a cardiologist examines the heart.

"We take it for granted in other areas of medicine that the organ is relevant," Williams says. "When you go to see the heart doctor with a heart problem, you would expect them to run tests. Right now in psychiatry we don't think about the brain at all when we are making a diagnosis or planning a treatment."

It's time we did, she says.

LEANNE WILLIAMS WANTS TO BRING PERSONALIZED NEUROSCIENCE INTO THE CLINIC.

Noreen Ford, a 59-year-old middle school teacher who lives in Belmont, California, is lying on her back inside a brain scanner — a functional magnetic resonance imaging machine — located in a lab in the university's Main Quad. A mechanical chunk-chunk-chunking noise startles her at irregular intervals. She's suffered mild depression on and off and had panic-like symptoms, but primarily she signed up for the RAD trial because, like many of the other participants, she was interested in "seeing inside my brain."

On a screen in front of her face flashes a series of photographs of smiling and terrified faces. She is supposed to push one of two buttons — one to indicate happy, the other to indicate fearful. This is one of several tests she will take during the hour or so spent inside the machine, each triggering a different brain circuit associated with depression and anxiety.

Williams sometimes seems as much a clinician as a brain scientist: Dressed more formally than the typical researcher, she drops by the lab regularly to check in and offers her lab assistants quiet encouragement. Williams describes the multiple fMRI tests that participants take as akin to "exercise for the brain."

Over the past two years, Ford and about 160 other participants with either anxiety or depression or a combination of the two have participated in RAD. They each spend a day on the Stanford campus for testing. They donate a swab of saliva for a genetic test that can help pinpoint antidepressant effectiveness and the influences of genetic variations on brain circuits, and they take a battery of "brain tests" while inside the fMRI machine for about an hour. After a walk across campus from the lab to the psychiatry building, meant to provide a relaxing break, participants eat lunch and then undergo a traditional symptom-based psychiatric evaluation.

Williams reads and interprets the resulting brain scans, searching for any abnormalities in those circuits. In an optional feedback session, Williams, the patient and the patient's therapist meet together in a comfortable therapy room to discuss how the patient's brain is functioning and possible treatment options, such as drugs, psychotherapy or brain stimulation. All participants also take a follow-up survey 12 weeks after the initial testing. The researchers plan to continue the trial through 2017.

"The results provide a lot more detailed information about what is going on with our clients," says clinical psychologist Nancy Haug, PhD, the research director at the Gronowski Center, a community mental health clinic and a collaborator with the RAD study. "A lot of times, the information confirms what our therapists already know and are already doing; other times it might suggest different treatment alternatives. Often the feedback sessions are very helpful."

Globally, 405 million people experience depression and 274 million experience anxiety disorder. These disorders are the main causes of disability and lost productivity, with an economic cost of about $50 billion per year, according to a study published in a 2013 issue of *The Lancet*.

The current treatment model relies on finding a treatment through a process of elimination.

"There is no objective way of saying which treatment will work best for which patient," Williams says. "Thirty percent of the time it will work. The other 70 percent of the time it fails. It can take a few years of trial and error. What is happening to your brain in the meantime is that it is becoming more and more unwell."

Patients grapple with new side effects each time they try a new drug, or withdrawals each time they change drugs. They jump from drugs to talk therapy to combined

AMIT ETKIN SAYS BRAIN SCANS SHOW PROMISE FOR PSYCHIATRY.

treatments and back again, searching for what works for them. Sometimes they never find it.

To get people better faster, or to get a higher percentage of people better, new drugs are crucial, says Amit Etkin, MD, PhD, assistant professor of psychiatry and behavioral sciences at Stanford Medicine. But the psychiatric drug pipeline has virtually dried up. "There is a huge concern about a lack of new drugs," says Etkin, who is also turning to neuroscience for improvements in mental health care.

RDoC, the NIMH project, has succeeded in increasing the pace of research bridging neuroscience and new clinical models, funding about 30 grants that each average $400,000 per year over four to five years. All of these are still in process, so they have not yet resulted in changes to clinical care.

Some neuroscience-based methods of treatment are close to cracking the clinical door, Etkin says. Brain stimulation methods such as transcranial magnetic stimulation or deep brain stimulation, which activate various brain circuits, have shown promising results as treatment for emotional disorders.

"It's a very active area of research right now," he says. He's also optimistic about the prospect of using brain scans for the early detection of mental illness and getting patients into treatment prior to the onset of symptoms.

"Think of it like a cancer screening test," he says. A routine fMRI scan would be part of a preventive-care treatment plan. "If you wait for symptoms, you've waited too long."

An ongoing national clinical trial called EMBARC is another effort to use the personalized approach. Launched three years ago by psychiatrists at the University of Texas Southwestern Medical Center, the trial — much like RAD and Williams' previous trial, iSPOT-D — is attempting to find biological markers that can better predict how people with depression will respond to medication. Helen Mayberg, MD, a professor of psychiatry at Emory University, made headlines recently with a study that identified a biomarker in the brain that predicts whether a depressed patient will respond better to psychotherapy or antidepressant medication.

Clinical trials are urgently needed to evaluate the efficacy of neuroscience-based treatments in clinical care, Mayberg says. She, like Williams, is an advocate for moving neuroscience research into the clinic now.

"Patients just can't wait for all the scientists to solve all the riddles of the brain," Mayberg says. "Every few months, there's another discovery of another tool to get at another aspect of how the brain is working. The hard part now becomes, how much do you need to know before you can do something practical with it?"

The trajectory of Williams' career has mirrored these developments in neuroscience. After studying behavioral psychology as an undergraduate and working as a clinical therapist for those three years in her 20s, she received a British Council scholarship to study for her PhD in cognitive neuroscience at Oxford University, which she earned in 1996, and began a career as a research scientist.

"I wanted to go to Oxford because of their history of innovative work linking clinical symptoms of mental illness to underlying physiology," Williams says. "This was before the days of brain imaging, and the measures we used included performance on behavioral tasks, physiological recordings and eye-movement recordings."

Understanding the brain as an organ became her new focus, and as technology advanced, functional magnetic resonance imaging became her new research tool.

"The more I wanted to understand what was really going on in the human brain, the more I knew I'd have to understand the neurobiology of the brain," she says. The advent of new imaging tools like positron emission tomography and functional magnetic resonance imaging has been key to advances in modern neuroscience. A PET scan uses radioactive tracers to look for disease in the body. An fMRI measures changes in blood oxygen levels, which can indicate brain activity. In 1999, Williams was recruited to the University of Sydney's psychology school and in 2004 to its medical school, where for 12 years she was the director of the Brain Dynamics Center, which aimed to help create a new neurobiological model of the brain for understanding mental illnesses.

For Williams, the RAD study is a benchmark in her career. Finally, findings from her years of brain research are being tested in clinical care. To design the study, she has drawn on data from the iSPOT-D trial, which included more than 1,000 people with depression and revealed biomarkers — brain circuit patterns and genetic profiles — that appear to predict treatment response. Williams was the lead academic researcher of the industry-sponsored trial from 2008 to 2013.

'THERE IS NO OBJECTIVE way of saying which treatment will work best for which patient. ... It can take a few years of trial and error.'

CONTINUES ON PAGE 42

ahead of time

PREDICTING WHO WILL DELIVER A BABY PREMATURELY

Purnima Gaddam remembers a day in May 2012 when everything seemed to be going just right. Three months pregnant with her first child, she walked home from a long day at work and lay down on the family-room sofa to joyfully contemplate her life. • "We had made all these plans that seemed like they would come to fruition so naturally," Gaddam says. She and her husband, Jishnu Menon, were ready to become parents: Both had jobs they loved, her pregnancy was going smoothly and they were preparing for a kid-friendly house remodel. They were choosing a pediatrician, considering baby names and reading up on cloth vs. disposable diapers. • "I was so happy and so content," Gaddam says. She pauses. "It's a feeling I was never able to recapture." • On July 14, 2012, Gaddam and Menon's eldest son was born just over halfway to his due date, after 22 weeks and five days of what should have been a 40-week pregnancy. He lived only a few hours. • His parents were blindsided. They grieved and they felt deeply frustrated. Gaddam, then 32, was perfectly healthy. She had gone to every prenatal checkup, taken her vitamins and followed her obstetrician's advice. How could such an ideal pregnancy have ended in disaster?

By Erin Digitale

PHOTOGRAPH BY LESLIE WILLIAMSON

PURNIMA GADDAM, WITH HER SON ARCADIUS, AND JISHNU MENON, WITH SEETHA, WERE REFERRED TO HIGH-RISK OBSTETRICS.

IT'S A QUESTION THAT OCCUPIES HUNDREDS OF SCIENTISTS AT STANFORD MEDICINE and across the country. The nation's preterm birth rate began rising in the early 1980s, peaking in 2006, when one in every eight babies arrived at least three weeks early. Nearly half a million families across the country are still affected each year, and although most U.S.-born preemies survive, many have lifelong disabilities. In about half of premature deliveries — including Gaddam's — doctors never learn why the baby came early. And while some early births are necessary to protect the health of the mother or child, in many cases continuing the pregnancy to term would be better.

"Preterm birth remains an intractable problem, and one that is very poorly understood," says David Stevenson, MD, principal investigator of the March of Dimes Prematurity Research Center at Stanford University.

Yet the need to understand it is urgent. Prematurity recently surpassed infectious disease to become the No. 1 cause of death in young children around the world.

"That's the bottom line," Stevenson says. "It is now the main killer of kids through age 5." In the United States, the most common causes of preemies' deaths are extreme immaturity, breathing problems, brain injury, infections and the bowel disease necrotizing enterocolitis. About 40 percent of these deaths occur in the first 12 hours of life; 95 percent happen before the baby is 3 months old. In less-developed countries, where preemies' chance of survival is far worse, they die for lack of basic medical care such as adequate warmth, breastfeeding help for their mothers, low-tech respiratory support and antibiotics. Providing such measures could save three-quarters of these infants, the World Health Organization estimates. But predicting who is likely to have a preterm baby and preventing early labor would be even better.

Stanford's prematurity research center, founded in 2011 with a 10-year, $20 million grant from the March of Dimes, was the first of five such centers now in operation across the country that are working to illuminate the biology of preterm birth. The foundation wants to unite scientists from many disciplines to answer one of the most basic questions about childbirth.

"It's a very simple question," says Joe Leigh Simpson, MD, March of Dimes' senior vice president for research and global programs. "What causes labor? The embarrassing fact is that we don't know."

The human birth process is unusual, rendering animal models of labor mostly useless. In most mammals, a drop in the pregnancy-maintaining hormone progesterone precedes and triggers labor, whereas in humans, whose babies are relatively immature at birth, progesterone levels are at their highest at delivery. But new scientific tools, including several noninvasive techniques emerging at Stanford, are finally giving researchers safe ways to ask what brings human pregnancy to a conclusion. Stevenson and his colleagues hope their discoveries will help predict and prevent preterm deliveries.

On the morning of July 13, 2012, Gaddam felt fine. By afternoon, something was off. • "I'd had a stressful week at work, and I thought it was my body telling me it had had enough," she recalls. Her back ached. She felt vaguely unwell. "I thought, 'I'll rest and I'll be OK.'"

That evening at home, she tried sitting and lying down in different positions, taking a shower, relaxing. Nothing helped.

"Throughout the night, the feeling of not feeling well intensified, but I never had anything that felt like a contraction," she says. "I thought I was just having a hard moment in my pregnancy."

The next morning, Gaddam and Menon went to their local hospital in Mountain View, California, so she could be checked. "I was 4 centimeters dilated," she says. "There was really nothing we could do at that point."

Their baby boy was born that afternoon, arriving two days before what doctors call the threshold of viability, the 23-week pregnancy milestone generally considered the earliest a baby can survive premature birth.

Gaddam and Menon both held their son before he died, as did their parents and Gaddam's brother, all of whom rushed to the hospital.

The loss was so intense it was almost impossible for the bereaved couple to take in.

"When I think back to holding our baby, knowing he was barely alive, it just didn't feel real," Gaddam says. "It felt like it was happening *to* us rather than anything we were participating in."

"It was horrifying but also very hard to believe that it actually happened," Menon says. In the months afterward, they leaned heavily on family and friends for support.

"I didn't force myself to get over it," Menon says. "There's a part of me that doesn't really want to."

Gaddam's thoughts often returned to the most consoling words she heard on the day of her son's birth and death.

"My father said, 'He'll come back.'" Her voice breaks as she recalls her dad's clear faith. "Even though I'm not very religious, it was a really comforting feeling to think that our baby would come back."

But that meant Gaddam and Menon would have to face another pregnancy.

When Stanford's prematurity research center launched in 2011, one early goal was to better understand women's risk factors. • Some were well-known, including pregnancy during the teen years or after age 40, African-American ethnicity, carrying twins or other multiples, certain infections, poverty, stress and lack of prenatal care. Maternal illnesses such as diabetes, high blood pressure and the obstetric complication pre-eclampsia raise prematurity risk, too. But there were others.

Stanford's first new findings appeared in 2014 when a team led by Gary Shaw, DrPH, professor of pediatrics, used a database of nearly 1 million California births to learn that maternal obesity substantially raised the risk of delivery before 28 weeks of pregnancy.

Soon after, researchers from Stanford and the U.S. Department of Veterans Affairs reported a connection between preterm delivery and maternal post-traumatic stress disorder. The researchers studied 16,000 births, including about 1,900 to women who had PTSD diagnosed in the prior year. This group's risk of spontaneous preterm delivery was elevated by 35 percent.

Patients with PTSD do have high rates of other psychiatric conditions and unhealthy behaviors that other studies have associated with preterm delivery, notes the study's senior author, Ciaran Phibbs, PhD, associate professor of pediatrics. "But we found that the effect of PTSD was independent of, and much larger than, these other factors," he says.

In August 2015, a team led by David Relman, MD, professor of medicine and of microbiology and immunology, found another striking relationship, a pattern of vaginal bacteria linked to preterm births. Among the 49 pregnant women in their study, the researchers observed four low-risk patterns of vaginal bacteria, all dominated by lactobacillus, a bacterial genus previously associated with health in women. But a fifth pattern, characterized by more bacterial diversity and different predominant bacteria — such as such as gardnerella and ureaplasma — raised the risk of preterm birth. The longer a woman had the pattern, the greater her chance of delivering early.

The researchers were also intrigued to learn that the high-diversity pattern appeared in nearly all women after they gave birth, and persisted for as long as a year, possibly explaining why closely spaced pregnancies increase prematurity risk.

Encouragingly, the vaginal microbiome may be amenable to treatment during pregnancy. "It's still total speculation," Relman cautions. But he hopes for a future in which the expectant mom's microbiome is tracked the way a park ranger keeps tabs on an ecosystem, "monitoring for invasive species, pruning them away, ensuring the environment gets the right nutrients."

"It's really hard to trust your body again when it's failed in such an immense way," Gaddam says. • After their son's death, she and Menon were referred to high-risk obstetrician Jane Chueh, MD, at Lucile Packard Children's Hospital Stanford. They still wanted a child, and they wanted to know how they might get through another pregnancy.

Chueh explained the treatments that could help reduce the chance of another premature delivery: progesterone supplements starting at 16 weeks of pregnancy, frequent monitoring and a minor surgical procedure called cerclage to temporarily stitch Gaddam's cervix closed midway through gestation. (The cervix, the muscular opening of the uterus, must stay tightly closed until near delivery. Some very premature births may be due to a weak cervix, which doctors try to support with cerclage until near the due date.)

> 'When I think back to HOLDING OUR BABY, KNOWING HE WAS BARELY ALIVE, IT JUST DIDN'T FEEL REAL. IT FELT LIKE IT WAS HAPPENING *TO* US RATHER THAN ANYTHING WE WERE PARTICIPATING IN.'

Gaddam, who manages business development for the global literacy program at the nonprofit Benetech, and Menon, associate general counsel and head of legal at Mozilla, felt somewhat reassured. "Dr. Chueh, from the very beginning, was sure that she could help us have a healthy baby," Menon says. "She would never promise, but her attitude was so amazing. It changes the way you feel about the process, because even getting pregnant again was scary."

But Chueh's well-honed bedside manner masked her vexation over the fact that the techniques for predicting and

CONTINUES ON PAGE 43

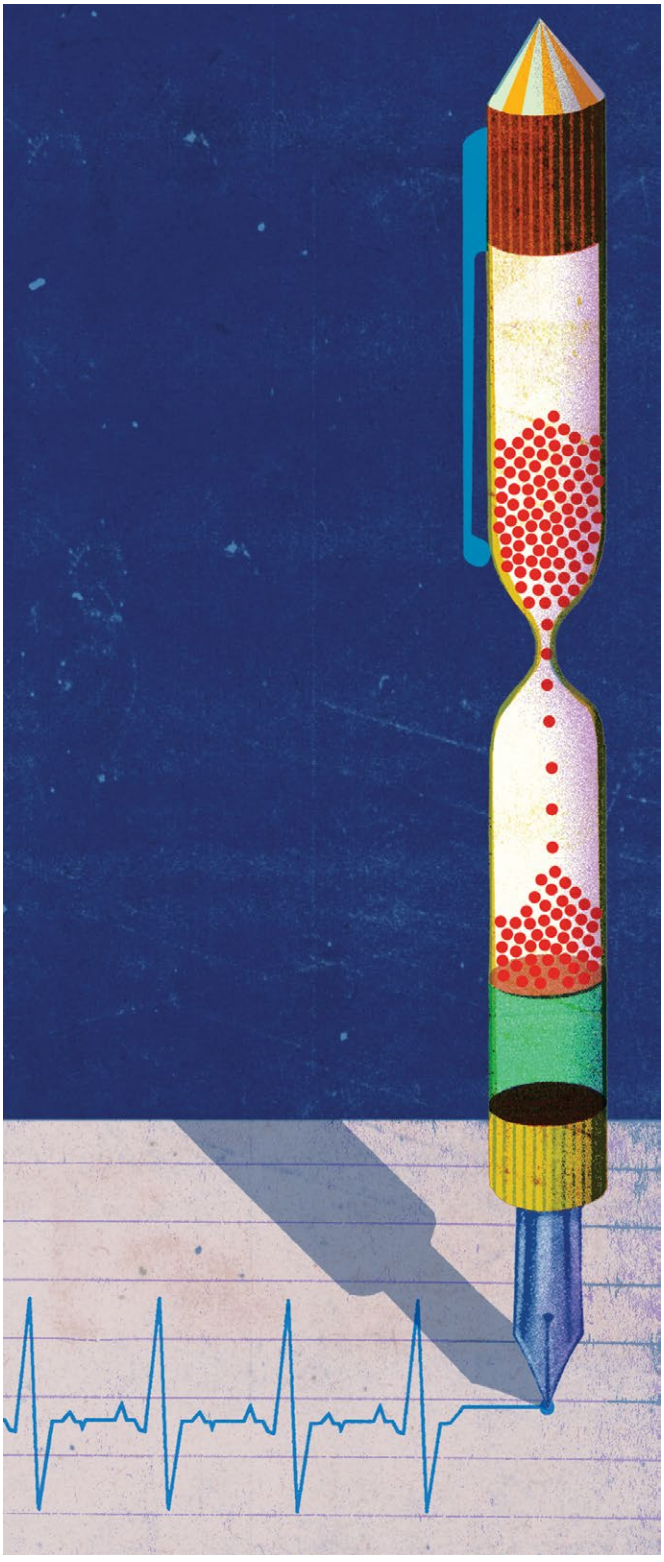
FINAL WISHES

Send them a letter

Stanford palliative care expert V.J. Periyakoil, MD, tells the story of a recent patient in his 60s who was dying of a brain tumor and whose wife was desperate to keep him alive. A gifted cook, the wife had always shown her love for her husband by serving him well-prepared meals. As his tumor progressed, he became confused and developed swallowing difficulties. He became unable to eat, so she asked that he be fitted with a feeding tube that would nourish him and allow her to spend more time with him, even though he had indicated he did not want to be tube-fed. • The tube, inserted in the nose and down the esophagus into the stomach, soon began to cause complications, sucking material from the patient's stomach into his lungs, where it threatened to cause a fatal respiratory infection. The man was uncomfortable and tried to pull it out; the wife designed a beautiful and innovative restraint that left his hands free but prevented him from removing the feeding tube. • Periyakoil gently refused to restrain the dying man and counseled the wife to let clinicians withdraw the tube. The wife ultimately relented, when reminded that her husband was a proud and dignified man who had told Periyakoil he wanted to die gently. He died peacefully that night. • It's a typical end-of-life tale, in which loving, well-intentioned family members opt for ineffective and burdensome treatments, rather than allow loved ones to pass away peacefully, as many patients say they would prefer. • "I tell people that proxy decision-making is one situation where those who love you can hurt you," says Periyakoil, a clinical associate professor of medicine and director of the

By Ruthann Richter

ILLUSTRATION BY CHRISTIAN NORTHEAST



Stanford Palliative Care Education & Training Program.

"They do it out of love and misguided good intent. Because out of love or duty, they may end up doing things that will harm you. We see this all the time. Your doctors won't be able to help you in a situation like this unless you speak your mind and document your wishes."

To help patients do just that, last year Periyakoil launched the Stanford Letter Project, designed to encourage people at all stages of life to express their end-of-life wishes to their physicians and loved ones. The effort gives patients a voice in how their last days are lived — one way that Stanford is elevating the doctor-patient relationship as part of its focus on precision health.

The Letter Project provides individuals with templates in which they can check boxes — for example, "I do not want to be on a breathing machine" — and answer simple questions to create their letters, which they can send to their physicians *(see sidebar, page 25)*.

Periyakoil also encourages individuals to share their letters with family members as an entrée to these difficult conversations.

"The goal here is to empower patients and families to have these conversations within their family, at their own leisure when they are most comfortable," Periyakoil says. "What we find from patients is that one of the barriers is their own family members, because it's such an awkward, uncomfortable topic."

In some cultures, for instance, death is a taboo subject, and people feel that they are invoking death by simply talking about it, she says. Others feel that end-of-life issues are the province of the divine. "For those, it seems presumptuous of humans to go beyond their scope of practice to divine territory," she says.

Every year, some 2.6 million Americans face death, but data suggest that before they pass on, most never have a heart-to-heart talk with their doctors about how they want to finish out their days. The result is untold suffering, as doctors fall back on

aggressive, costly and sometimes harmful treatments that may lead to an end that lacks dignity and comfort, she says.

"Our research has shown that most doctors are uncomfortable conducting end-of-life discussions with their patients," she says. "We need a role reversal in the conversation on dying. Instead of holding their breath and waiting for their doctors to initiate this conversation, patients need to lead this conversation. But most patients do not know how to do this or what to ask for. So we decided we needed to come up with a format that patients and families can use."

THE INITIATIVE DIFFERS from physician-assisted death, which in the United States is available to a small number of terminally ill patients in certain states who have followed a detailed legal process to obtain medication to help them die. The Letter Project, in contrast, focuses on how they want to experience their last days and helps them make the most of the time they have left.

"Physician-assisted suicide is about not living anymore," Periyakoil says, "whereas this, the Letter Project, is about what matters most to each patient. It is not about death, but about life and how people want to live."

In developing the project, Periyakoil says she was motivated in part by the cost of end-of-life care, which consumes a major portion of the nation's health-care budget. Some 20 percent of Medicare dollars are spent in the last year of life, with half of Medicare recipients visiting an emergency department and one in three admitted to an intensive care unit during that final year; one in five have surgery in the last *month* of their lives, studies show. These interventions are not only costly but may interfere with a person's ability to function and enjoy life, and in some cases, may hasten the end, Periyakoil says.

That stands in stark contrast with what polls show people want at the end of their lives: to die gently and comfortably, surrounded by family members. Yet many fail to express their wishes to doctors or family members. In California, only 13 percent of adults have completed an advance directive, a legal document in which people can spell out their end-of-life decisions ahead of time.

And doctors say they are hesitant to broach the topic with their patients. In a study published in April 2015 in *PLOS ONE*, Periyakoil found that more than 99 percent of the 1,040 physicians queried at Stanford Health Care and the Veterans Affairs Palo Alto Health Care System said they were reluctant to start these end-of-life conversations with patients because of cultural, religious, ethnic, language or other barriers.

With this huge communications gap, decisions about end-of-life care typically fall to physicians, whose training and instinct is to keep patients alive no matter what through all-out interventions. Yet 88 percent of physicians would not choose this high-intensity approach for themselves, Periyakoil's research shows.

As physicians, she says, "We are trained, we are rewarded, for doing. We are not trained to communicate, and we are not trained to stand by and support. So everything in our medical genome is geared toward doing more and more. … If you do one more procedure or one more thing, you are keeping them alive longer, because your goal is to save lives."

Moreover, family members who serve as a proxy for incapacitated patients often opt for end-of-life heroics. Periyakoil tells the story of one patient who had suffered a stroke. He later went into respiratory failure, and doctors told his wife he needed an urgent tracheostomy, a tube implanted through the neck into the throat to create an airway. She agreed to the procedure.

"She felt terribly guilty because the decision made him live a life of misery for 10 more years," Periyakoil says. "She told me, 'If I could turn back time and choose again, I would never let the doctor cut open a hole in my husband's throat. After that, he suffered so much. When someone's life is ending, we should let them go through that period as easily as possible.'"

'We are trained, we are rewarded, for doing. We are not trained to communicate, and we are not trained to stand by and support. So everything in our medical genome is geared toward doing more and more.'

In helping families assuage their guilt, David Magnus, PhD, director of the Stanford Center for Biomedical Ethics, says he counsels them to imagine what course their loved one would choose — not to make the judgment for them.

"We frame the conversation by asking, 'What would your loved one say if they were here?' We do it to relieve the burden on the family of making this decision and make them feel like it is their loved one making the decision," he says. Unfortunately, he says, families don't really know what patients want, with studies of paired responses between patients and designated decision-makers showing that the decision-makers "get it right" only two-thirds of the time — all the more reason for individuals to make their desires clear.

HOW IT WORKS

THE LETTER PROJECT is designed to help all adults think about the end-of-life issues they — and their families — may confront in the future. A letter template on the project's website includes a series of questions about what matters most to individuals; their important future milestones, values and preferences for care; and who they want making medical decisions for them when they are unable or unwilling to make decisions for themselves.

For instance, it asks writers to talk about how they handle bad news in the family — whether they are open about issues or want to shield certain family members from troubling information. And it asks them to consider how their family makes medical decisions in general, whether it is a matter of consensus or whether certain individuals hold more sway — information that can be valuable to the patient's medical team. • Letter writers are prompted to specify whether there are certain interventions they would not want at the end of life, such as breathing machines, artificial feeding tubes, dialysis or hospitalization. Patients also can indicate what they *do* want — whether it's to be pain-free, to die at home or at the hospital, to receive their physician's help in dying gently and naturally, and/or to die with the benefit of hospice care. • Letter writers can specify whether they want their stated intentions to be binding or whether they would allow family members to override their wishes. That is distinct from an advance directive, a legal document in which individuals spell out their end-of-life instructions, which designated decision-makers are required to follow under California law, says David Magnus, PhD, director of Stanford's Center for Biomedical Ethics. • "People can say in this letter that if there is a conflict, you must do what I say or do what my loved one says. That is really unique and critically important to address," Magnus says. • Individuals can use the website to email the letter to their physicians or can print it out and mail it to their doctors. Numerous people in the United States have written letters to their doctors in various languages, and a group in the United Kingdom recently began using the Letter Project. The project's director, clinical associate professor of medicine V.J. Periyakoil, MD, also hopes individuals will use the letters as a springboard for conversations with family members about what matters most to them and how they want to spend the last chapter of their lives.

Periyakoil says many people are galvanized to write a letter following the death of a family member, which prompts them to consider their own wishes and preferences.

That was true for Anthony Milki, a 20-year-old Stanford junior, who was motivated to write his letter after his beloved cousin, just 22, died suddenly in 2014 of flu-related complications.

"I think her dying made me get to another level of thinking about it — thinking about what I would want," he says. He understands that families will reach for high-tech interventions at the very end, clinging to the faintest hope of a miracle and fearful of letting go.

"I don't blame families, but it's objectively harmful. I would not want that for myself," he says.

Periyakoil says the Letter Project already has amassed more than 2,000 letters from individuals like Milki who have consented to be included in her research and have their letters shared. Many others across the country also have written letters as other practitioners begin to adopt the model, she says.

She recently won an innovators' award from the American Medical Association, which recognized the project as an "excellent example of a transformational medical practice solution." She says she plans to work with the AMA to help expand use of the letter. She believes the new Medicare policy of reimbursing physicians for time they spend discussing end-of-life decisions with families will spur more people to engage in the process.

"When the system gives you money to do something, it means it's something that the system values," Periyakoil says.

Her goal is to develop a bank of some 20,000 to 25,000 sample letters of people from all ages and backgrounds, as a kind of crowdsourcing of ideas for future letter writers. Individuals can choose to write their letters at any time in their lives, she says, though she encourages them to consider it when they have reached voting age.

"I tell all my patients who are eligible to vote to weigh in on your own fate before you weigh in on the fate of the nation," she says.

Sample letters can be viewed at http://med.stanford.edu/letter.html. The Stanford Letter Project mobile app is available at the iTunes store and at Google Play Store. An app that will convert the letter into a pre-filled advance directive is under development. **SM**

— Contact Ruthann Richter at richter1@stanford.edu

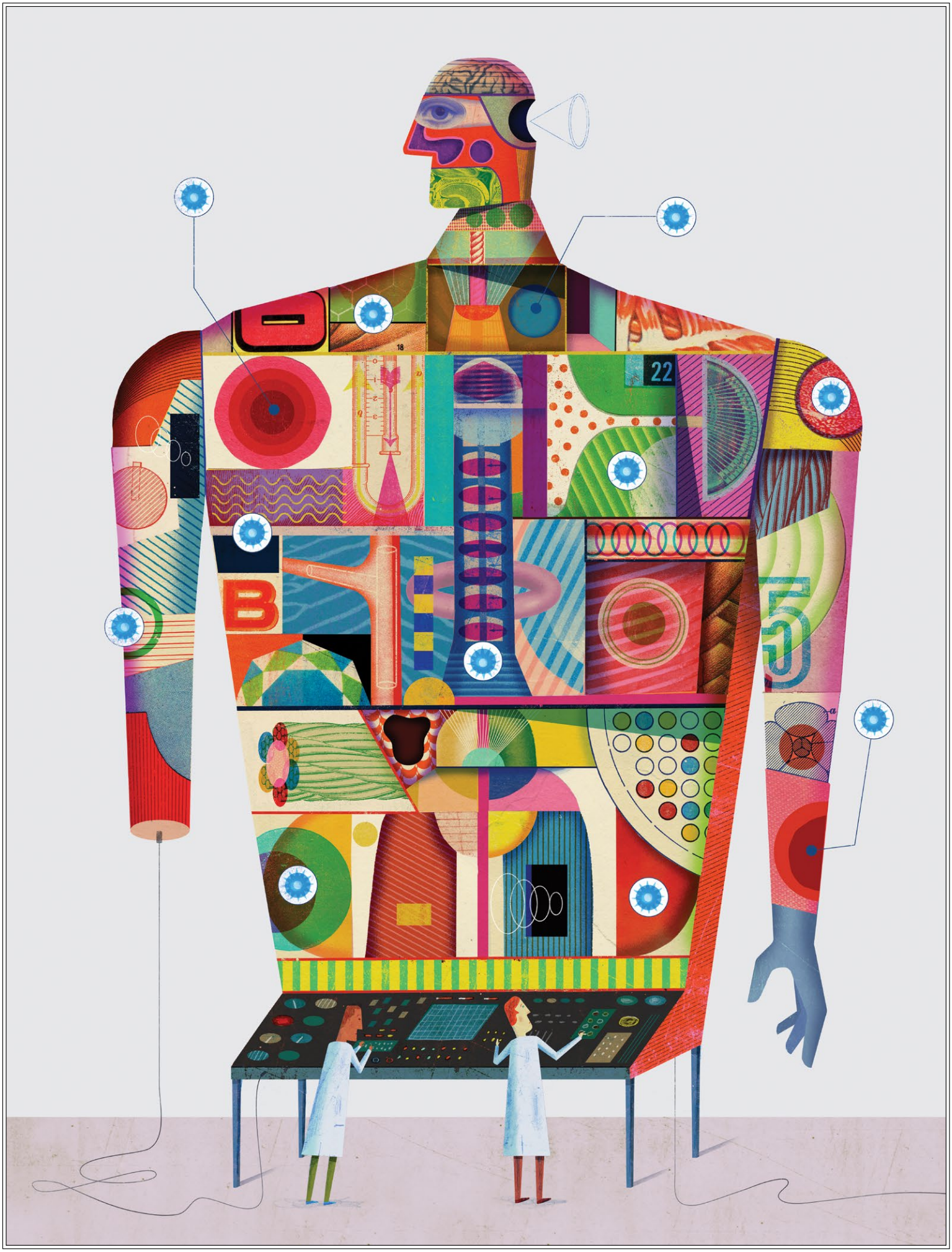
small wonder

HOW NANOTECHNOLOGY COULD DETECT AND TREAT CANCER

The crew of the Proteus has one desperate chance to save a man's life. Shrunk to the size of a large bacterium, the submarine contains a team of scientists and physicians racing to destroy a blood clot in the brain of a Very Important Person. The group journeys through the body, evading giant white blood cells and tiny antibodies while traveling through the heart, the inner ear and the brain to reach and destroy the blockage. • Although events in the film *Fantastic Voyage* were far-fetched when it was released in 1966, they're now being realized every day in labs around the world, particularly in cancer treatment. A growing field called nanotechnology is allowing researchers to manipulate molecules and structures much smaller than a single cell to enhance our ability to see, monitor and destroy cancer cells in the body. • Tens of thousands of patients have already received chemotherapy drugs delivered by nanoparticles called liposomes, and dozens of other approaches are currently in clinical trials. Within the next five to 10 years, our bodies' biggest defenders may be tinier than we could have ever imagined. • "Nanotechnology offers an exquisite sensitivity and precision that is difficult to match with any other technology," says Sam Gambhir, MD, PhD, professor and chair of radiology at the Stanford School of Medicine. "Within the next decade, nanomedicine will change the path of cancer diagnosis and treatment in this country." • The field has some big backers: The National Cancer Institute now spends about $150 million each year on nanotechnology research and training

By Krista Conger

ILLUSTRATION BY CHRISTIAN NORTHEAST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to combat the disease; other institutes and centers at the National Institutes of Health spend an additional $300 million on nanotechnology research for cancer and other disorders. And a national alliance created by the NCI in 2004 to bring together researchers from biology to computer science to chemistry to engineering is now bearing fruit — in the form of dozens of clinical trials — at campuses and companies across the country, including Stanford.

"We can now detect just a few cancer-associated molecules or circulating tumor cells in the body in just a few milliliters of blood or saliva, or map the boundaries of a brain tumor within millimeters to assess its response to therapy or to plan a surgery," says Gambhir. "We've specially designed nanoparticles that can send back a massively amplified, whopping signal when they bind to cancer cells in the colon and we're working on ways to trigger the self-assembly of nanoparticles when they enter a cancer cell. The field has advanced tremendously in the past 10 to 15 years."

Gambhir, the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research, co-directs the NCI-funded Stanford Center for Cancer Nanotechnology and Excellence for Translational Diagnostics with Shan Wang, PhD, a professor of materials science and engineering and of electrical engineering.

The ability to diagnose the very earliest signs of trouble is crucial for efforts to stop disease in its tracks before symptoms or complications arise — which is a key component of what's known as precision health.

As Gambhir explains, "Early diagnosis is absolutely critical, and requires an entirely different type of approach and technology than we've relied on in the past. Without nanomedicine, we wouldn't have a chance of accomplishing our primary goal: to keep our hospitals empty."

Nano schmano — what's the big deal?

SO WHAT'S SO SPECIAL about nanotechnology? As you might guess, it's a matter of scale. A nanometer is one-billionth of a meter. A human hair is about 100,000 nanometers in diameter. An average cell, about 10,000. The Proteus, on its fantastic voyage, was about 1,000 nanometers long, and the antibodies that attacked its passengers were about 10 nanometers in size.

Nanoparticles for medical use are defined as molecules or structures no larger than about 100 nanometers — comparable in size to the tens of thousands of molecules in the body that slip in and out of intact cells and wiggle harmlessly through blood vessel walls and into tissues. Like the Proteus and its crew, they can seek out and interact with individual cells and their contents. But the rules of engagement have

gold standard

nanotechnology's go-to material

ALTHOUGH NANOPARTICLES can be made from just about anything, gold is a popular choice. Yes, gold. It's dense and has other properties that make it easy to visualize with standard imaging techniques, and it's relatively inert, so it doesn't cause many side effects. And even though gold nanoparticles are made from a precious metal, they are relatively inexpensive and simple to produce.

Stanford's Sam Gambhir, MD, PhD, is using gold nanoparticles to seek out and bind to colon cancer cells in the bowel *(see main story)*. He's also used them to locate brain cancer cells in patients by coating them with signaling molecules that can be detected with imaging. But it's possible humankind has been unknowingly using gold as nanomedicine for millennia.

Kattesh Katti, PhD, a professor of radiology and of physics who directs the Cancer Nanotechnology Platform at the University of Missouri, has found that some common plants like tea contain a naturally occurring chemical that not only facilitates the production of gold nanoparticles from ionic gold compounds, but also coats the particles and causes them to target and kill cancer cells. This may be why gold was considered an essential component of ancient medicines. "Perhaps the use of gold nanoparticles today is providing a scientific rationale for what our ancestors did 5,000 years ago," muses Katti.

Now Katti has found a way to supercharge gold nanoparticles to fight cancer by making them radioactive. Although only about 5 to 10 percent of gold nanoparticles in a solution become radioactive with his technique, the benefits appear to be many.

"The idea is to deliver potent radioactivity directly into the cancer cell and selectively destroy it," says Katti. "We have shown that not only is it feasible at the cellular levels, the nanoparticles can combat tumors in small animals."

Katti has tested his technique, first in mice and then in dogs, with prostate tumors. Although the number of animals tested is small, the results appear nothing short of remarkable — the animals are left with no detectable tumor burden.

"Ten or 15 years ago, everything was nano this, nano that," says Gambhir. "It could have been considered a kind of hype. But we are far beyond that now. We've learned that nanotechnology offers something no other technique can: sensitivity, speed, multiplexing and signal amplification — all at a relatively low cost. It's a very exciting time."

changed, as has the possible magnitude of the visitors' effect.

Molecules on the nanometer scale operate in a dusky netherworld where the laws of physics wobble at the edge of a quantum galaxy. Electrons behave strangely on such a tiny stage. As a result, the nanoparticles' essential properties, including their color, melting points, fluorescence, conductivity and chemical reactivity, can vary according to their size.

Nanoscale particles also sport tremendous amounts of surface area as compared with larger particles. A cube of gold with sides 1 centimeter long has a total surface area of 6 square centimeters. But the same volume filled with gold nanospheres with diameters of 1 nanometer has a surface area greater than half a football field.

Researchers like Gambhir and his colleagues have learned how to capitalize on many of these properties in their quests to seek out and destroy cancer cells in the body, or to collect them from a blood sample for further study. By changing the size of the particles, the scientists can "tune" the nanoparticles to behave in specific ways — fluorescing varying colors for imaging purposes, for example, or grabbing onto and then releasing cancer cells for study. Some can be engineered to absorb light energy to power tiny acoustic vibrations that signal the presence of a tumor or to release heat to kill the cells from inside.

Researchers also capitalize on the particles' vast surface area, coating them with antibodies or proteins that home to cancer cells or with signaling molecules that are released by the tens of thousands when a cancer cell is located.

Gambhir believes nanotechnology will be particularly helpful in early diagnosis and treatment. "It's not that our therapies are poor, it's that we apply them too late," he says. "Nanotechnology has the potential to detect and even kill early cancer cells present in the hundreds or thousands versus the billions already present in currently diagnosable tumors."

He and his colleagues envision a day in the not-too-distant future when nanosensors implanted in our bodies, or even in household appliances like the toilet, can alert us to the first signs of trouble — often without our conscious participation. He compares the approach to that of piloting a jet airplane.

"An airplane's engine is constantly monitored, and information is sent to a global portal to diagnose problems in real time. We're missing that in health care today."

But maybe not for long.

'Swallowing the doctor'

THE CONCEPT OF MINIATURE medical minions isn't new. In 1959, noted physicist Richard Feynman, PhD, discussed the possibility of "swallowing the doctor" in a talk at the California Institute of Technology, and British researchers first realized the potential of liposomes for drug delivery in 1961. These spheres can be engineered to contain water-soluble drugs in their interior, while also squirreling away hydrophobic, or insoluble, drugs in their fatty membrane. Careful engineering can result in liposome-based structures that deliver multiple drugs in precise ratios and at high levels without the toxicities that can occur when delivering the medicines orally or through an IV. They accumulate naturally in tumor tissue, or can be targeted to specific cell types by the addition of antibodies or other molecules to their surface.

The technique was first approved by the U.S. Food and Drug Administration in 1995 to deliver the chemotherapy drug doxorubicin to patients with AIDS-related Kaposi's sarcoma. There are now more than a dozen liposomally packaged drugs on the marketplace, and researchers have begun to explore ways to use other types of nanoparticles to deliver not just drugs, but also small RNA molecules to block the expression of specific genes or a payload of radioactivity to kill the cell.

'WITHOUT NANOMEDICINE, we wouldn't have a chance of accomplishing our primary goal: to keep our hospitals empty.'

"From a practical perspective, nano-based techniques aren't the wave of the future. This is the now," says Heather Wakelee, MD, an associate professor of medicine at Stanford who focuses on the treatment of lung cancer patients. "And it's changing how we treat patients in the clinic."

In addition to devising new nanoparticles for use inside the body, the researchers are working on nanosensing technology for use outside the body to identify and characterize tumor cells present at minuscule levels in all manner of bodily fluids — tracking the course of known disease or even pinpointing its inception long before symptoms arise.

Wakelee has worked with center co-director Wang to design a kind of "magnetic sifter" that quickly sorts cancer cells from normal blood based on magnetic nanotags engineered to coat the cells' surface. A key component of the technique is the ability to swiftly release the bound, living cells for further study. Another approach, also launched in Wang's lab, involves a magneto-nanosensor — a silicon-based chip smaller

CONTINUES ON PAGE 44

patient 2/6/40

One of America's most recognizable television news journalists was known inside the halls of the hospital where he was being treated for multiple myeloma as a number: 2/6/40. His birthdate became the stamp of identification throughout his treatment for cancer.

TOM BROKAW has lived a magical professional life: White House correspondent; host of television's longest-running morning news program, *The Today Show*; and anchor of NBC's evening news broadcast when being in the top spot meant editorial heft and authority.

In spite of that jeweled career in TV, Brokaw feels he gained more credibility and trust with the American people through his chronicle of the men and women of World War II in his best-seller *The Greatest Generation*.

In his latest book, *A Lucky Life Interrupted*, Brokaw details his two-year battle with cancer, now in remission. He writes that, of his many fortunes while battling cancer, he had a strong and supportive partner in his wife, Meredith. Also at his side as a medical expert and personal ombudsman was his physician daughter, Jennifer.

Brokaw spoke with executive editor Paul Costello about life and death, mortality and hope, and, yes, luck.

JOE MORSE

COSTELLO: How are you doing?

BROKAW: Gratefully, I am in remission and it's holding. Multiple myeloma is an incurable, but treatable, cancer. I am on a maintenance diet of Revlimid, which is chemotherapy. I have some spine damage. That's a big adjustment, because my back muscles are compensating for the bone damage. But other than that, I am fine. I was pheasant hunting in South Dakota and fly fishing in Montana. I see incremental progress. That's the encouraging thing.

COSTELLO: You've said that cancer was much tougher than you anticipated. Why did you think it might be easy?

BROKAW: I think this is not uncommon. I don't think most patients, once they get over the initial shock and the uninformed fear, have a specific idea of what it is that they may be in for. It is the most vicious opponent that modern medicine runs into. A cancer cell is at war with the body itself.

COSTELLO: What compelled you to lay yourself so bare in the book?

BROKAW: If I have, at this stage in my career, a certain amount of credibility, I almost feel an obligation to share my story. Some of that, frankly, grows out of *The Greatest Generation*. I wrote about that not just for that generation but for their children as well. It seems to have elevated me in the eyes of people beyond anything I did on the air. There's a kind of a trust. I thought, "Maybe I should cash in on that. Maybe I can help people as a journalist and as a patient. Maybe that's a kind of legacy for all that I'm going through."

COSTELLO: Many people have written about cancer in very metaphorical ways. How would you describe cancer?

BROKAW: It's a mysterious force. It's your body turning on you. It never goes away. Even when you're in remission, you're still worried

about it coming back. You know the wheel could turn again in another kind of cancer. You feel a certain sense of betrayal by your own body, which you've always taken for granted. I've worked hard at being healthy and being fit, and then evolution caught up with me and a couple of those 2 trillion cells that are coursing through my body decided to go rogue.

COSTELLO: When you were first diagnosed, what was your reaction?
BROKAW: I was extremely calm. I think that had something to do with my training as a journalist. I've been through a lot of very difficult situations before, seeing a president resign, being in a war zone, being on the air all day on 9/11. Those kinds of things give you a certain amount of conditioning. Then, after that, I had a hard time processing what this meant. I didn't really know what multiple myeloma was.

COSTELLO: Why did you keep your cancer secret?
BROKAW: I knew if it got out it would be all over the Internet because the Internet has this voracious appetite for a recognizable name. I'm quite a private person about my private life and my family life. I could be on some sites that have nothing to do with who I am or what I do, but because they want to fill it up with something they'd say, "Tom Brokaw has cancer, prospects uncertain." I didn't want that universe to become my universe.

COSTELLO: At some point you began seeing the world through the prism of cancer. How did it take over your life?
BROKAW: Part of the issue with cancer is that it's invisible. I had this thing floating around in me attacking my bone marrow. I wasn't frightened by it, but I would wake up in the middle of the night and for a nanosecond I would think, "Everything is fine." Then I'd think, "Oh, my God, I've got cancer and I don't know how we're doing on the treatment of it, if we're making progress or not," because in the early stages you don't know. I didn't get depressed. I had this unbelievably strong support system of my daughter and my wife, who would always look at me and say, "No, you're not going to get on an airplane and go do that, you've got cancer." If my wife thought I was wilting somewhat she'd say, "One day at a time, Tom. One day at a time and we'll be a lot better six months from now."

COSTELLO: Did you ever think you were going to die?
BROKAW: No, I didn't. I really didn't think I was going to die, and I think that's part of the conceit of who I am. [laughs] I can be in a war zone and I think, "That shell's going to hit somebody else. It's not going to hit me." I've been an eternal optimist my entire life.

COSTELLO: Did your treatment give you a new perspective on America's health-care system?
BROKAW: I think the best is the very best in the world. Miracles are performed every day. But I thought a lot about somebody in their mid-40s, early 50s, somewhere in Kansas. Gone to a community college, saved his money, opened a gas station, then a convenience store, then another gas station, a couple of more convenience stores. That's the American Dream realized. Something like this comes along and it shatters that dream, because he or she probably has a self-financed health-care plan that's not nearly as good as mine. Maybe not access to the same kind of expertise that I had. So it's that unevenness that troubles me most of all.

COSTELLO: Is there a time when you say, my old life won't return, but that's OK?
BROKAW: I was 73 when I was diagnosed. Seventy-three years of things going my way and I thought, "Well, I'm in cancer. I'm going to have to deal with it. We're going to get it under control and then I'll have my old life back." Well, I have lot of parts of my old life back, but I don't have it all back. Part of that is aging. I'm two years older than I was then. I'm not as inclined, for obvious reasons, to jump on a plane and go to the Third World, because I am more susceptible to infection now than I was.

COSTELLO: Do you think about mortality more often?
BROKAW: I think it's hard to attribute that just to cancer. It has to do with the fact that I'm now about to be 76. That 76 is pretty much the life expectancy of a white male in America, and I didn't think about that much before. Cancer helped me think about it more carefully.

COSTELLO: So this is a big year in politics — a presidential campaign. Will you be active with NBC News in some way?
BROKAW: Yes. I am not going to be a "boy on the bus." I haven't done that in a long time. But I am going to do essays and I do have a long buildup of institutional and journalistic memory that I can rely on.

COSTELLO: *A Lucky Life Interrupted.* Do you still feel like you're a lucky guy?
BROKAW: Of course. I got this potentially very threatening disease and it turned out I responded extremely well to treatment. So that's a continuation of a lucky streak. I was in a position when I did get diagnosed that I could afford the treatment. I could get access to people who would be helpful to me. I have this fantastic family around me. That all adds up to good luck. I'm a lucky guy. So sure, the good luck continues. **SM**

This interview was condensed and edited by Paul Costello.

WEB EXTRA
Hear the conversation at http://stan.md/1Z6FRUz

On the button

TREATMENTS THAT WORK FOR PEOPLE JUST LIKE YOU

It's hardly a secret among medical practitioners: For most patients, clear treatment guidelines simply don't exist. Take Vera. She is a 55-year-old woman of Vietnamese descent who has asthma. You're her doctor, and you've just learned she also has high blood pressure. Vera's case doesn't fit the data from any clinical trials; there's no medical literature on hypertension medications for middle-aged, asthmatic Vietnamese-American women.

You want to treat her hypertension, but you have no guidelines. Medications that work great in one ethnic group can work dismally in another. Older people metabolize drugs more slowly than young people. Males and females can respond quite differently to the same drug. Among the numerous subjects enrolled in the totality of clinical trials that have been conducted for hypertension, there have been few, if any, asthmatics, because people with multiple conditions are typically screened out. • Vera is sitting in your exam room now. What do you do? • Suppose you could get some guidance simply by pressing a virtual button on a computer screen displaying Vera's electronic medical record? This would trigger a search of millions of other electronic records and, in a matter of minutes, generate a succinct composite summary of the outcomes of 25 or 100 or perhaps 1,000 patients very similar to her — same race, same age, same symptoms, similar lab-test results — who were given various antihypertensive medications. Patients similar to Vera, it turns out, respond particularly well to one particular drug — something you likely wouldn't have guessed on your own. • Vera is a made-up patient, but there are plenty of people who are square pegs in the round hole of clinical-trial results. Scattered throughout millions of electronic medical records, such look-alike cases could point the way to effective treatment options for Vera and others if they could be plucked from the aggregate and formatted for easy interpretation. While some aspects of this approach need to be worked out, such as assuring

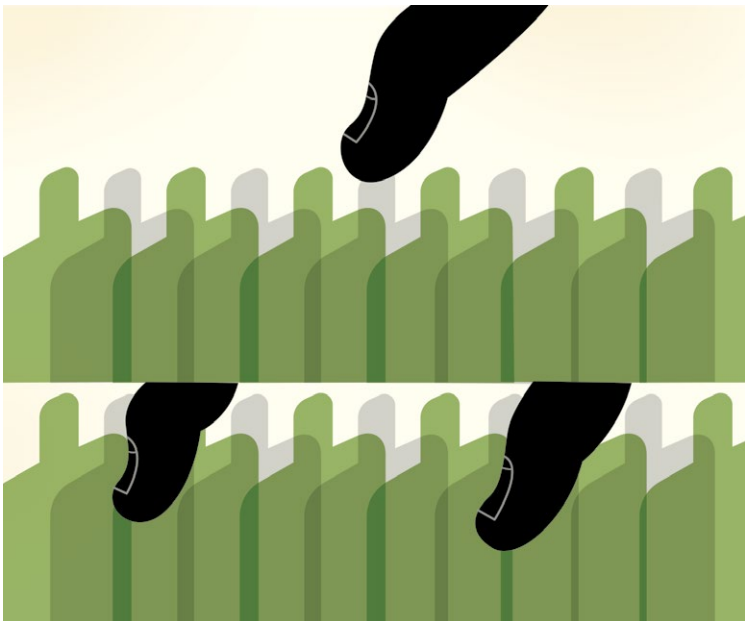
By Bruce Goldman

ILLUSTRATION BY HARRY CAMPBELL

patients their privacy will be protected and making databases compatible between health-care systems, Stanford medical researchers are tackling those problems. The goal is a seamless system that quickly links physicians to the information they need in order to give their patients the best-validated treatments available.

In 2014, three Stanford Medicine faculty members authored an article in a major health policy journal, *Health Affairs*, urging action to make this concept a reality. The solution, which they've dubbed the Green Button, would revolutionize the practice of medicine by tapping the huge volumes of data lying dormant in the EMRs of millions of patients to tailor treatments to individuals.

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



"Every day I encounter patients for whom we just don't have the best scientific evidence on how to treat them," says one of the authors, Christopher Longhurst, MD, who recently stepped down from his position as clinical professor of pediatrics in system medicine and chief medical information officer for Stanford Children's Health. Longhurst is now a professor of biomedical informatics and chief information officer at the University of California-San Diego Health Sciences.

In their article, Longhurst, along with Nigam Shah, MBBS, PhD, assistant professor of biomedical research and assistant director of the Stanford Center for Biomedical Informatics Research, and Robert Harrington, MD, professor and chair of medicine, outlined a vision for drawing medical guidance from day-to-day clinical practice in hospitals and doctors' offices. The idea was to give doctors access to aggregate patient data, right there and then, from a vast collection of EMRs. This near-instant output isn't a substitute for a clinical trial, but it's a lot better than nothing — or than resorting to the physician's own bias-prone memory of one or two previous encounters with similar patients.

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

FROM THE GOLD STANDARD TO THE GREEN BUTTON

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

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

Harrington's specialty, cardiovascular medicine, exemplifies that generalization. "Remarkably, even in the well-studied field of cardiology, only 19 percent of published guidelines are based on randomized controlled trials," he and his co-authors wrote in the 2014 *Health Affairs* paper. Even those trials' findings apply to fewer than one in five of the actual patients with the problems explored in them. Shah concurs. "Clinical trials select only a small, artificial subset of the real population," he says. "A regular, ordinary person who walks into the doctor's office doesn't usually fit."

As a result, "only about 4 percent of the time have you got a clinical-trial-based guideline applicable to the patient fac-

ing you right now," Shah says. The rest of the time, doctors must rely on their own judgment.

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

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

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

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

With advancing technology, the kind of analysis Frankovich performed can be completed in considerably less than an hour today — soon enough for an outpatient finishing an appointment.

Since then, Stanford researchers including Shah have published numerous studies establishing the power of pooling large volumes of data to derive clinically beneficial results — although not yet in real time as would be necessary for implementing the Green Button approach. The Stanford Center for Population Health Sciences, directed by Mark Cullen, MD, professor of medicine, is putting in place a data library housing the records of some 10 million different patients, purchased from another institution.

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

But there are several obstacles to putting the Green Button idea into practice.

SURMOUNTABLE HAZARDS

The stumbling blocks along the road to the Green Button's realization aren't primarily technical — the methodologies are available, and the infrastructure is buildable. But the more idiosyncratic your patient's case is, the larger the initial pool of patient data needs to be. And scaling up presents some challenges.

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

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

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

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

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

Even if the patient-privacy issue turns out to be insurmountable in the short run, there's a workaround, Shah says: Health systems could share with one another descriptions of the kinds of patients they're looking for, rather than request raw patient data. Thus, a health system that received a request for information on female middle-aged patients of Vietnamese descent with asthma and high blood pressure would, in accordance with such an arrangement, automati-

> 'The point is not to outsmart the physician. The point is to tell you the outcomes of the best guesses of 100 of your colleagues. You can choose to interpret or ignore it.'

cally search its own database and share only statistical summaries of what it found, such as the range of outcomes for certain medications given to this cohort.

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

Some smart money is betting these stumbling blocks can be hurdled. Kyron Inc., a Palo Alto-based start-up Shah cofounded in 2013 with technologist Louis Monier, PhD, and Stanford-trained biomedical informaticist Noah Zimmerman, PhD, raised several million dollars and licensed informatics-associated technology from Stanford's Office of Technology Licensing to do just that. Kyron has since merged with Learning Health Inc., another start-up, which now holds licenses on Stanford intellectual property for de-identifying clinical documents, searching patient records and more.

BUILD YOUR OWN RANDOMIZED TRIAL

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

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

But that's not the end of it. The Green Button now shifts gears from merely downloading outcomes of other patients to suggesting what Harrington and others have termed "point-of-care randomization": You give this patient one of the two treatments — call it Treatment A — and the next similar patient who walks through your door (or, more accurately, through any door in your mega-EMR network) gets Treatment B. The similar patient after that one will be prescribed Treatment A, then B, and so on. (Either prescription would be equally ethical because both are within the standard of care.) Keep alternating prescriptions to successive similar patients — while monitoring their responses to minimize the chances of either treatment doing them any harm — and you will have increasingly large cohorts fueling an informed conclusion. A test run of this type of study has already been conducted by a team including Stanford professor of biomedical data science Philip Lavori, PhD, and published in *Clinical Trials* in 2011.

After agreeing to participate in this trial, patients were randomly assigned one of two insulin protocols for diabetes, both equally appropriate according to current medical knowledge. As the trial progressed, EMR software tracked which of the two approaches was associated with the best outcome.

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

Meanwhile, Shah continues to push forward with funding from multiple sources including the National Institutes of Health and, here at Stanford Medicine, the office of the dean's Biomedical Data Science Initiative. Among his front-burner projects: an improved search engine that will be able to deliver a Green Button head count in less than a millisecond.

Big things often take a longer time than you expect to happen, but when they do happen they happen fast. SM

— Contact Bruce Goldman at goldmanb@stanford.edu

BUILDING A BETTER DRUG

Out of the plant, into the lab

In 1962, a botanist named Arthur Barclay hiked into a forest of towering pine and Pacific yew trees in western Washington state to gather bagfuls of bark, leaves and needles. These specimens — a few of the roughly 200 plant samples he collected that year — were key ingredients in a multiyear effort by the National Cancer Institute to search for plant-based sources of anticancer therapies. • Eventually, this program would analyze some 35,000 plant samples, yielding, among other things, a promising new cancer-fighting chemical isolated from Pacific yew bark collected by Barclay and his team. That drug, called taxol, blocked cells from dividing and, in early trials, looked promising for treating a variety of cancers. • "Taxol at that time was a special opportunity. It was the first of its kind for a new way of stopping cell division," says Paul Wender, PhD, a Stanford professor of chemistry. The drug was effective in treating more than 30 percent of women with ovarian cancer, a rate unheard of in the mid-80s. • Wender was one of many researchers who recognized the limitations of using a natural source for the drug — harvesting the bark killed the yew tree — and began trying to synthesize taxol in the lab. He was successful, as were others who developed an even more efficient method used to make the drug today. • Although taxol is now produced without destroying the yew tree, not all drugs derived from plants have an alternate source. More than half the drugs people take today were originally isolated from plants. We are still reliant on those plants, the farmers

By Amy Adams

ILLUSTRATION BY JASON HOLLEY

who grow them and the environment that sustains them for many of our critical drugs.

Concern over this precarious drug sourcing from plants drove Stanford's Christina Smolke, PhD, and Elizabeth Sattely, PhD, to investigate ways of using other organisms to act as factories for the chemicals. In addition to preserving the environment and creating a more stable source of the drug, this alternate method makes it easier to modify the drug to be safer or more effective.

Smolke, an associate professor of bioengineering, recently engineered yeast to produce hydrocodone, a painkiller derived from the opium poppy. Sattely, an assistant professor of chemical engineering, engineered tobacco, a common laboratory plant, to produce the immediate chemical precursor to the cancer drug etoposide, originally isolated from a leafy Himalayan shrub called the mayapple.

The drug-making pathways Smolke and Sattely reproduced are two of only three that have been transferred intact into another plant or yeast. Researchers have partially reconstructed other pathways, meaning that the plant or yeast yields a chemical that can then be transformed into a drug in the lab. Although the successes so far are limited, Smolke says recent advances in technology will make it easier for more drugs to follow.

"I think in 10 or 20 years we will absolutely see more of our medicines produced through this type of biotechnology," Smolke says. "This is the way to get around a lot of the challenges and the headaches that we have faced with trying to extract compounds from natural sources that don't really scale."

When taxol was first found in the bark of Pacific yew trees, desperate patients would sneak into forests to collect the bark.

BOND BY BOND

When taxol was first found in the bark of Pacific yew trees, Wender says, desperate patients would sneak into forests to collect the bark. The process killed trees and destroyed habitat that housed, among other animals, the endangered spotted owl.

Even collected legally, it took the bark of two to 10 mature yew trees, which can take hundreds of years to reach full height, to provide enough taxol to treat a single person. The NCI estimated that keeping up with taxol demand would require harvesting 360,000 mature yew trees per year.

"Its lack of availability was having a huge impact on science and on clinical studies," says Wender. He chaired the National Institutes of Health Taxol Study Section, tasked with balancing the environmental concerns of harvesting the trees against patients' needs for the drug.

"I had a winemaker call me to ask if he should plant yew trees or wine grapes; that's how visible the issue was," he says.

At the time, there were essentially two paths for producing a drug that had been identified in a plant. One was the route Wender took — synthesizing it bond by bond in the lab. This approach isn't always possible for large, complex molecules (which many drugs are), is often slow and may produce yields too low to supply patients.

"In the case of morphine, chemists worked out methods to build that molecule through chemistry," says Smolke. "But the process is very inefficient and, even through decades of research, they've never been able to increase the efficiency to make it competitive to poppy."

If chemistry can't re-create the drug, another option is a hybrid approach in which scientists look for the drug's chemical cousin in other plant species, extract it and use laboratory chemistry to finish the job. That approach, called semi-synthesis, is what's used today to turn a compound found in the needles and twigs of a yew species that is more common than the original source (and can be harvested without damaging the plants) into the taxol taken by patients.

A third option for producing plant-based drugs has recently become more feasible, thanks in part to improvements in genome data, sequencing technology and DNA synthesis. Whereas it was once laborious to sequence and identify genes, many tools now exist to sift through an organism's genetic code to identify bits that are important for any biological process — like making a particular chemical. These advances in technology are in part what inspired the recent creation of the interdisciplinary institute Stanford ChEM-H, of which Sattely, Smolke and Wender are members. ChEM-H intends to leverage chemistry, engineering and medicine to improve human health.

Plants normally produce complex chemicals through the work of protein assembly lines. They start with a chemical from the environment or from within the plant itself. Then proteins called enzymes sequentially nip a bit here and add a bit there until the final chemical — our drug — emerges.

Each of the enzymes in that assembly line is coded for by a gene in the organism's DNA. So, the trick is finding which genes code for the enzymes in the assembly line.

Discovering the enzymes' codes is moving a lot faster now

because of new strategies, says Smolke. "One strategy that we think is particularly powerful is looking at the plant's DNA sequence and using bioinformatics tools to identify regions that code for candidate enzymes." Her team can then put the DNA sequence for that enzyme in yeast to see if the enzyme carries out the expected role.

But there's another hurdle after discovering the relevant enzymes, and that's the matter of getting them to work in a foreign setting. "You are taking enzymes that have evolved to work in a particular organism and then you are asking them to work in a very different organism," Smolke says. For example, the complex origami of how proteins fold into the correct shape occurs differently in plants versus yeast.

In recent years, more information has become available about how plants and yeast differ, and how to modify genes so that the proteins for which they code perform properly in the foreign environment.

In 2013, advances in technology and knowledge paid off when a team of researchers from the company Amyris, UC-Berkeley and the National Research Council of Canada isolated the six genes from sweet wormwood that code for the anti-malaria drug artemisinin — the drug whose discovery earned Chinese scientist Youyou Tu a Nobel Prize in 2015 — and put them into yeast. Today, about one-third of the world's supply of artemisinin is produced by yeast in a lab, rather than extracted from the yellow-flowering herb.

The artemisinin example proved that the cellular machinery from a plant could be coaxed to operate in a completely different organism, but it's a relatively simple six-part system compared with hydrocodone (23 genes) or etoposide (10 genes).

Smolke recently published in *Science* her success in producing hydrocodone, the precursor to morphine and other painkilling drugs, in yeast. The yield is currently small, but she has formed a company focused on scaling up production.

Given the addictive nature of opioids and hydrocodone's close chemical relationship to heroin, Smolke's work raises concerns about providing easier access to illegal as well as legal drugs, a problem that could arise with other legal drugs that have illegal chemical cousins. She says she supports an open, deliberative process that engages scientists, policymakers, regulators and doctors to discuss the concerns about the technology and its benefits, and develop options for governance as it becomes more widespread.

'We don't have to be limited to what nature gives. We can take inspiration from the basic structures, then improve them.'

IMPROVING ON NATURE

Obtaining a more reliable and less expensive source for a drug would be reason enough to pursue this line of research, but there's an added advantage: a chance to refine nature's handiwork.

"When we extract a drug from a plant, we can only use what the plant gives us," says Sattely.

Sattely chose to work with tobacco because it is a relatively common laboratory plant that grows well and is easy to genetically manipulate, and by using a plant she avoids many of the challenges of getting enzymes to work properly in yeast. From here, she may take the extra step of moving the genes into yeast, but she says it might be possible to scale up production in tobacco.

Sattely isn't alone in trying to grow drugs in tobacco, rice, corn or other fast-growing plants. Since the 1990s scientists have realized that plants could be used to grow drugs, called "pharming," but those efforts involved drugs that are the product of a single gene. It's much harder to find multiple genes and get them to work in a coordinated fashion to produce a final product.

Sattely points out that many drugs we take aren't as effective as they could be or have side effects. Once a drug is being produced in a controlled way, it might be possible to introduce a slightly different raw material into the molecular assembly line, which could ultimately produce a better drug.

Or, by mixing and matching genes that make up a variety of different molecular pathways, scientists could create entirely new classes of drugs.

"We don't have to be limited to what nature gives," says Smolke. "We can take inspiration from the basic structures, then improve them to either enhance their therapeutic properties or reduce their negative properties."

For example, could opioids be altered to be as effective without being addictive? Or could an anti-cancer therapy be made less toxic? It's much easier to explore those questions when scientists can tweak the molecular production line.

Wender has already begun chemically modifying taxol, manipulating the drug isolated from yews in such a way that cancer cells are less likely to expel it as they gain resistance.

He and Nelson Teng, MD, PhD, associate professor of obstetrics and gynecology, have shown that the modified drug is effective in animals and in tumor samples from

CONTINUES ON PAGE 45

FROM THE BOOK:
When Breath Becomes Air *by Paul Kalanithi*

to have a child?

Life while facing death

PAUL KALANITHI WAS A CHIEF RESIDENT IN NEUROSURGERY AT STANFORD, WITH ADVANCED DEGREES FROM STANFORD, CAMBRIDGE AND YALE, BUILDING A BRILLIANT CAREER. HE ALSO HAD METASTATIC LUNG CANCER, AND BUT FOR THAT, THE WORLD MIGHT NEVER HAVE KNOWN HE WAS A WRITER. After his diagnosis at age 36, Kalanithi wrote essays for this magazine and for *The New York Times* in which he eloquently contemplated time, relationships, medicine and mortality. "Before I go," published in our spring 2015 issue, garnered millions of readers around the world. Many thanked him, publicly and privately, for his candor and the depth of his insight. Those essays became the basis for Kalanithi's posthumous book, *When Breath Becomes Air*, published in January by Random House with a foreword by author and Stanford professor of medicine Abraham Verghese, MD. In it, Kalanithi talks about how his oncologist repeatedly refused to estimate his remaining life span in years or months, instead exhorting him to focus on what mattered most to him. In the last months of his life, says his wife, Lucy Kalanithi, MD, a Stanford clinical instructor in medicine, he conserved his limited energy for one purpose: to finish the book from which this excerpt is taken.

The bulk of my week was spent not in cognitive therapy but in physical therapy. I had sent nearly every one of my patients to physical therapy. And now I found myself shocked at how difficult it was. As a doctor, you have a sense of what it's like to be sick, but until you've gone through it yourself, you don't really know. It's like falling in love or having a kid. You don't appreciate the mounds of paperwork that come along with it, or the little things. When you get an IV placed, for example, you can actually taste the salt when they start infusing it. They tell me that this happens to everybody, but even after 11 years in medicine, I had never known.

In physical therapy, I was not even lifting weights yet, just lifting my legs. This was exhausting and humiliating. My brain was fine, but I did not feel like myself. My body was frail and weak — the person who could run half marathons was a distant memory — and that, too, shapes your identity. Racking back pain can mold an identity; fatigue and nausea can, as well. Karen, my PT, asked me what my goals were. I picked two: riding my bike and going for a run. In the face of weakness, determination set in. Day after day I kept at it, and every tiny increase in strength broadened the possible worlds, the possible versions of me. I started adding reps, weights and minutes to my workouts, pushing myself to the point of vomiting. After two months, I

PHOTOGRAPH BY GREGG SEGAL

could sit for 30 minutes without tiring. I could start going to dinner with friends again.

One afternoon, Lucy and I drove down to Cañada Road, our favorite biking spot. (Usually we would bike there, pride forces me to add, but the hills were still too formidable for my lightweight frame.) I managed 6 wobbly miles. It was a far cry from the breezy, 30-mile rides of the previous summer, but at least I could balance on two wheels.

Was this a victory or a defeat?

I began to look forward to my meetings with Emma [the oncologist]. In her office, I felt like myself, like a self. Outside her office, I no longer knew who I was. Because I wasn't working, I didn't feel like myself, a neurosurgeon, a scientist — a young man, relatively speaking, with a bright future spread before him. Debilitated, at home, I feared I wasn't much of a husband for Lucy. I had passed from the subject to the direct object of every sentence of my life. In 14th-century philosophy, the word patient simply meant "the object of an action," and I felt like one. As a doctor, I was an agent, a cause; as a patient, I was merely something to which things happened. But in Emma's office, Lucy and I could joke, trade doctor lingo, talk freely about our hopes and dreams, try to assemble a plan to move forward. Two months in, Emma remained vague about any prognostication, and every statistic I cited she rebuffed with a reminder to focus on my values. Though I felt dissatisfied, at least I felt like somebody, a person, rather than a thing exemplifying the second law of thermodynamics (all order tends toward entropy, decay, etc.).

NEUROSURGEON PAUL KALANITHI WROTE *WHEN BREATH BECOMES AIR* IN THE FINAL YEAR OF HIS LIFE.

Flush in the face of mortality, many decisions became compressed, urgent and unreceding. Foremost among them for us: Should Lucy and I have a child? Even if our marriage had been strained toward the end of my residency, we had always remained very much in love. Our relationship was still deep in meaning, a shared and evolving vocabulary about what mattered. If human relationality formed the bedrock of meaning, it seemed to us that rearing children added another dimension to that meaning. It had been something we'd always wanted, and we were both impelled by the instinct to do it still, to add another chair to our family's table.

Both of us yearning to be parents, we each thought of the other. Lucy hoped I had years left, but understanding my prognosis, she felt that the choice — whether to spend my remaining time as a father — should be mine.

"What are you most afraid or sad about?" she asked me one night as we were lying in bed.

"Leaving you," I told her.

I knew a child would bring joy to the whole family, and I couldn't bear to picture Lucy husbandless and childless after I died, but I was adamant that the decision ultimately be hers: she would likely have to raise the child on her own, and to care for both of us as my illness progressed.

"Will having a newborn distract from the time we have together?" she asked. "Don't you think saying goodbye to your child will make your death more painful?"

"Wouldn't it be great if it did?" I said. Lucy and I both felt that life wasn't about avoiding suffering.

Years ago, it had occurred to me that Darwin and Nietzsche agreed on one thing: the defining characteristic of the organism is striving. Describing life otherwise was like painting a tiger without stripes. After so many years of living with death, I'd come to understand that the easiest death wasn't necessarily the best. We talked it over. Our families gave their blessing. We decided to have a child. We would carry on living, instead of dying. **SM**

WEB EXTRA
A conversation with Lucy Kalanithi:
http://stan.md/1SfXLUM

CONTINUED FROM PAGE 17

For example, her report, published in the journal *Neuropsychopharmacology*, indicated that participants whose fMRIs showed low reactivity in the amygdala — a small structure in the brain that plays a key role in processing emotions — would respond better to the SSRI class of antidepressants like Prozac and Zoloft than to SNRIs like Cymbalta or Effexor.

It was this trial that initially brought Williams to Palo Alto. She came to Stanford, which was one of the study's 12 sites, in 2011 as a visiting professor. In early 2013 she joined the faculty as a professor of psychiatry and behavioral sciences with a joint appointment at the Palo Alto Veterans Affairs Health Care System. Shortly thereafter, she was awarded the RDoC grant and began recruiting for the RAD trial.

The RAD study envisions a future in which a physician with an anxious or depressed patient would order various neurobiological tests, such as an fMRI brain scan, to help make a more precise diagnosis and to guide treatment choice. Currently, the diagnostic categories are extremely broad, Williams says. Patients with anxiety or depression could have widely varying symptoms, and the cause could be very different, yet the first-line treatment is often the same. The model she is developing breaks down these broad diagnostic categories into "types" based on brain circuit dysfunctions. Matching each type of depression or anxiety with the best evidence-based treatment is the ultimate goal.

In the study, researchers scan six of the large-scale neural circuits that most neuroscientists agree are associated with anxiety and depression. These circuits are evoked during different tasks like the one Ford underwent in the fMRI machine. The intrinsic architecture of these circuits is also scanned when the patient is at rest inside the machine.

The six brain circuits are mapped out for each of the participants, then compared with how the circuits should look in a healthy brain. Any deviations — faulty connections that are generating too little or too much communication between brain regions — are used to diagnose a specific brain-based type of anxiety or depression.

For example, the "threat" circuit, which follows a circular path of neuronal activity from the amygdala to several other parts of the brain and back to the amygdala, is involved with how we react to threat or loss. Terrifying facial expressions, like those in Ford's fMRI brain test, trigger this circuit. A breakdown in the "threat" circuit can result in a type of depression Williams refers to as the "negativity bias."

> 'THINKING OF MENTAL ILLNESS IN THESE TYPES OF BRAIN TERMS SEEMED MORE REASONABLE THAN THE CONCEPT OF MENTAL ILLNESS BEING SOMEONE'S FAULT OR A LACK OF TRYING HARD ENOUGH.'

"In depression, you will see some people get stuck in one of those circuits for negative emotion," she says. "They'll say they feel bad, that everything feels bad. Trying to concentrate and switch to a different mode — a different circuit — can be really hard, almost impossible." In this case, a clinician should pick a treatment that will help get the patient unstuck. There is evidence certain antidepressants work well for this because the action of the medication matches the function of the circuit, she says.

"We are trying to link all this science to the real world," Williams says. "We talk to participants about their symptoms, their work experiences, their quality of life, how they cope, how they regulate their emotions. All the things that could be pertinent to how your brain functioning relates to your experiencing the world."

As a neuroscientist conducting clinical research, Williams says it has been important to build strong partnerships with clinicians. Since she is no longer a therapist, she needs this pipeline for study recruitment, but she also believes communication with patients and therapists is essential if she wants to know how best to translate her research into clinical care.

"I always think, how can we translate this back to the patient?" she says.

"I talked to one software engineer who was finding it hard to concentrate at work," she says. "He was needing to take a nap in the afternoon."

Using mappings of the engineer's brain circuits, Williams explained how his "default mode" circuit was in overdrive even when he was at rest, which put him into a state of rumination about his negative thoughts. This disruption meant the man, who was depressed, had problems engaging his "cognitive control" circuit and dampening down the ruminative thoughts in order to focus. Instead, his brain was stuck in overdrive, making it difficult to concentrate at work.

When she talks to participants stuck in this state of rumination and dysregulated circuits, she asks:

"When you wake up in the morning is your brain immediately overwhelmed? Are you like 'Oh my God, I've got this to do, that to do, and I can't see a way through'?

"When I give the feedback, I tell them to try things that will help shift them out of that state of overdrive. I think of analogies from heart health where the best current

evidence suggests combining new interventions, drugs and lifestyle changes. As a lifestyle change, try really fast walking, or listening to music, something that will get your brain into a different kind of rhythm because you can't ruminate while walking really fast or while dancing, for example."

The software engineer told her that he enjoyed Latin dancing, so she recommended he try that as a way to break out of rumination and over-firing of his default mode circuit. A complementary option was transcranial magnetic simulation, which can help regulate the default mode circuit and the way it interacts with the cognitive control circuit.

"So that's the concept of the personalized approach," she says. "Thinking of mental illness in these types of brain terms seemed more reasonable than the concept of mental illness being someone's fault or a lack of trying hard enough."

While it's not yet clear how to deploy these individualized treatments on a broad scale, Williams says, she believes it's time to try.

"I don't understand why we can't do it now. It's not unsafe. We are still giving the same treatments. It's hard to see a bad outcome. Why not try it?" **SM**

— Contact Tracie White at traciew@stanford.edu

FEATURE

Ahead of time

CONTINUED FROM PAGE 21

preventing preterm labor have not improved in decades. Similarly, when women come to the hospital in premature labor, doctors' tools are rudimentary: drugs that only sometimes, temporarily, stop contractions — maybe buying enough time for a few doses of other medications that temper the effects of prematurity on the baby's brain and lungs.

Gaddam thought a lot about the possibility of a second tragedy. "It was really hard, knowing it was likely that my body wouldn't be able to sustain a pregnancy to term, to be aware that it was my responsibility to gauge what was happening internally and communicate it to the medical team," she says. "I felt like I had no idea what was happening in the first pregnancy, and it was hard for me to believe that I would be able to tell if something happened again."

Asked about her wish list for preventing prematurity, Chueh is succinct: She wants tools that reduce the guesswork for expectant moms and their doctors. "It would be really nice to have a test we could use in the first part of pregnancy to identify people at risk for prematurity," she says. "And we would love to have an etiology, something we could treat."

Several scientists are trying to understand the exact molecular path connecting risk factors such as maternal obesity or PTSD to early contractions of the uterus. Their working hypothesis: While myriad genetic and environmental factors play into prematurity risk, one major biologic mechanism must translate these into a delivery trigger. Mounting evidence suggests inflammation is key.

"Think of pregnancy as a state of immune tolerance that suppresses inflammation," says Martin Angst, MD, professor of anesthesiology, perioperative and pain medicine. As long as the mother's immune system accepts the immunologically foreign fetus, the pregnancy continues. "But at some point, her body is no longer immune-tolerant; instead it's now more in a pro-inflammatory state."

Inflammation is the immune system's and body's way of getting rid of potentially harmful material. It's also associated with obesity, stress, infections and diabetes — a litany of prematurity risk factors.

Angst and his collaborators published a study comparing immune cells from the blood of mothers who had preterm deliveries against similar cells from mothers who had full-term pregnancies. The researchers used a relatively new technique, called cytometry by time-of-flight mass spectrometry, to test the inflammatory response of specific immune cell subsets. The technique lets scientists take a simultaneous look at all immune cell subsets represented in blood. They wanted to see if, under lab conditions, immune cells taken from women who had had a preterm birth were more sensitive to an inflammation trigger.

Indeed, immune cells called monocytes from women who had given birth prematurely responded differently when the researchers induced inflammation in the lab. In particular, certain components of the toll-like receptor 4 pathway, which acts like the stone that starts the avalanche of the inflammatory response, were more readily activated in these mothers' monocytes.

"There is a change in the immune disposition of these people and we can see it," Stevenson says. A future in which at-risk women receive targeted immunotherapy to block the pathways involved in preterm birth now seems possible, he adds. "We can probably understand not just the biomarkers of preterm birth but also the associated changes in gene expression — it's a really interesting story."

Stevenson is alluding to work by another Stanford researcher, Stephen Quake, PhD, professor of bioengineering and of applied physics, whose team has developed a technique to track RNA in the maternal blood that may function as a "molecular stethoscope" to detect the signature of impending prematurity. RNA, the message genes send as they act, is released in tiny amounts by dying cells. Quake's team now has the ability to read these signals not just from the mom's cells but also from the fetal cells that make their way into the mother's blood. They can detect physiological changes in the tissues and organs of both the mother and the baby, and hope to use this information to measure genetic

programs of distress that they think will accompany premature delivery.

"It gives you this unparalleled window into the whole process of pregnancy, from the point of view of the pregnancy and also of the mom," Quake says. "There is exquisite specificity to what you're measuring."

RNA, microbial, immune and other biomarkers will soon, the researchers hope, give obstetricians the specific predictive and preventive tools they now lack. "The goal is to try to find a simple blood test to alert us to which women are at risk so they can be appropriately cared for," Quake says. "Hopefully that will give them a safer and more comfortable pregnancy, both physically and psychologically."

Purnima Gaddam had two pregnancies after her premature son's death. They were neither physically nor psychologically comfortable, but they did have happy outcomes. Gaddam and Menon's second son, Arcadius, was born in August 2013, about four weeks early, and is now a healthy 2-year-old. His little sister, Seetha, arrived in August 2015, only 2½ weeks before her due date; Gaddam felt signs of labor a few weeks earlier, but quickly went to the hospital, where medications stopped her contractions.

Now that they are past the difficult wait through Gaddam's pregnancies, the couple is enjoying their children. Menon relishes the new perspective they've brought him: "As an adult, you've seen, say, a car over and over," he says. Arcadius, however, thinks cars are exciting, and his excitement is infectious. "Even the most basic things become great again in a new way."

Gaddam, an avid reader, jokes that Arcadius managed to start a book club before she did: At his small day care, he makes the other children sit and look at books with him, becoming upset if they lose interest too quickly. "There's one other baby who always follows him around, and while he turns pages and babbles on, she will stay," she says, laughing. "He has one really devoted attendee."

In a more serious vein, she reflects on how the death of her first child changed her outlook. "When you've been lucky enough to have things happen the way you hoped, you feel agency and control — that if you work hard you can get what you're working for," she says. "But when something like this happens, it makes you realize that nothing is ever promised."

After her loss, a different, bittersweet promise was realized: her father's belief that her son would return. "We did have a son," she says. "We always have felt he was coming back to us." **SM**

— Contact Erin Digitale at digitale@stanford.edu

FEATURE

Small wonder

CONTINUED FROM PAGE 29

than a dime that can detect and quantify magnetic nanotags on cancer cells or cancer-associated DNA or protein molecules based on changes in the chip's external magnetic field.

This approach is being tested in clinical trials by MagArray, a company based in Milpitas, California, for its ability to detect multiple lung and prostate cancer biomarkers in patients' blood. Like other nanotechnology, it is exquisitely sensitive.

"This technology can detect molecules present at levels orders of magnitude lower than the detection limit of current optical-based techniques like fluorescence microscopy or enzyme-linked immunosorbent assay," says Wang. "It's also possible to test a single sample for the presence of many different proteins or nucleic acids simultaneously in a technique known as multiplexing. This will be very useful not just for early diagnosis, but also to monitor an individual patient's response to therapy."

These techniques may allow researchers to not just count the circulating tumor cells in a patient, but also to sequence the cells' genomes or assess the levels of expression of cancer-associated proteins on their surfaces. Wakelee is also working with colleagues to develop ways to capture and sequence tumor DNA that circulates freely in the blood of cancer patients.

"We're looking for specific gene mutations that could change therapy," she explains. "In this way, we're moving away from invasive biopsies for our patients and toward a simple blood draw to learn more about an individual's specific cancer."

Gambhir is working to design gold and silica nanoparticles for use inside the body to detect colon cancer. The particles, which would be swallowed as pills, coat pockets of tumor cells that would normally be invisible during a colonoscopy, and can be visualized with a special endoscope designed by the team. The technique is under review by the FDA.

"These nanoparticles give highly amplified signals that just light up the bowel when bound to cancer cells," says Gambhir.

How to monitor invisible particles

REGULATORY CHALLENGES exist, of course, particularly for techniques that deliver nanoparticles directly into the body. The very ability of nanoparticles to slip into tissues and cells raises the specter of danger, particularly if the particles could become airborne or accidentally introduced into people other than the patient. The FDA and the National Institute of Environmental Health and Safety are exploring ways to ensure safety.

A critical component of nanomedicine, of course, is the ability to get the engineered particles to their destination. Although they can be targeted to a tumor via cancer-protein-specific antibodies on their surface, many of today's studies capitalize on the fact that the blood vessels that feed a rapidly growing tumor are often leaky. As a result, nanoparticles of all stripes naturally seep out of the blood vessels and accumulate in tumor tissue.

"The FDA doesn't yet have a clear approval process for nanoparticles intended

for use inside the body," says Gambhir. "One problem is that nanoparticles are never all exactly the same size. The manufacturing process delivers particles that might be 80 or 94 or 100 nanometers in size. This and other sources of heterogeneity means that it's harder to get the approval from the FDA, which values homogeneity."

Jianghong Rao, PhD, an associate professor of radiology at Stanford, is trying another approach that might be more palatable to the FDA: nanoparticles that self-assemble after they are introduced into the body as small molecules. The assembly process is triggered by the presence within a cell of a protein involved in a cancer-associated cellular death pathway. The small molecules that act as starting material for this approach are uniform in size and composition and might be more easily approved by the FDA, the researchers believe.

Gambhir compares the FDA's current struggle to the challenges it experienced when PET imaging was on the rise in the mid-1990s. Although the agency was at first concerned about the long-term effects of the radioactive tracers injected into patients, it now has an entire arm dedicated to assessing and approving new PET reagents, which can now happen relatively quickly.

The need for new cancer treatments and the urgency for early diagnosis of particularly lethal forms, coupled with the national effort to advance nanotechnology to treat the disease, will likely mean that cancer care will soon look very different. But, as in the quest of the Proteus' diverse crew, progress will take a concerted effort from several disciplines.

"Cancer is a very difficult disease to treat, and it's also difficult to diagnose early," says Piotr Grodzinski, PhD, who directs the NCI's nanotechnology for cancer programs. "The alliance was created to bring together engineers and materials scientists, for example, with biologists and oncologists to understand, first, how nanoparticles interact with biological systems and, second, how they interact with cancer cells and what they can do to the tumor."

"Stanford, in the heart of Silicon Valley, is a unique place for this kind of technology to develop," says Gambhir. "The collaborative atmosphere brings together people to solve specific problems in cancer diagnosis and detection."

The crew on the Proteus managed to band together to save the Very Important Person — in the nick of time, of course — escaping through a tear duct after destroying the blood clot in his brain just before ballooning back to normal size. Nanomedicine for future patients will likely be less fraught with urgency, but the outcome will be more important. After all, the next VIP could be you. **SM**

— Contact Krista Conger at kristac@stanford.edu

FEATURE

Building a better drug

CONTINUED FROM PAGE 39

women whose ovarian cancer has developed resistance to taxol. They plan to test the modified drug in women with ovarian cancer soon. These kinds of improvements on nature could be much simpler when a plant, rather than a chemist in the lab, is doing the work.

Teng helped carry out some of the earliest trials of taxol, producing the extraordinary results that drove desperate patients into the woods to harvest their own yew bark. He calls the work by Smolke and Sattely game changing.

"A lot of time, intuitively, we don't think we can change life," Teng says. "But it turns out that it's not quite true; we can actually change yeast or plants at the genetic level such that their machinery can make molecules of almost any design."

Teng says a grateful patient once gave him a package of taxol tea, made from the bark of Pacific yew trees. He never drank it, he says, because although it might contain beneficial compounds like taxol, it might also contain any number of other chemicals that are detrimental to human biology. Why risk it?

Advancing chemical engineering techniques could change that balance — biological organisms might be coaxed to produce chemicals with the effects we need without the effects we don't. **SM**

— Contact Amy Adams at amyadams@stanford.edu

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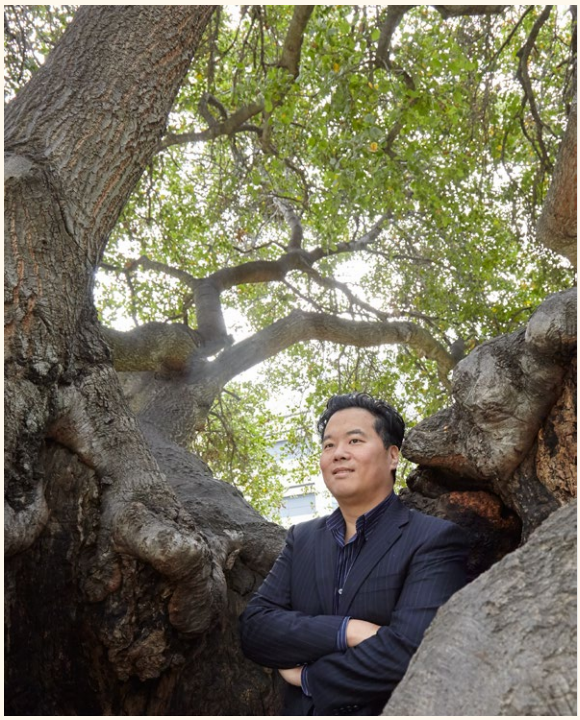
OUNCES OF PREVENTION

A PHYSICIAN'S PERSONALIZED QUEST FOR BETTER HEALTH

It was meant as a joke, but it stung. Larry Chu, MD, had just stood up in front of the room at the closing dinner of the first Medicine X conference, a fast-paced, multi-day program on emerging technology in medicine for which he is the executive director. He remarked that he hadn't eaten anything all day. A senior faculty member said, "Really, Larry? Because it looks like you could afford to skip a meal." • "I was speechless," says Chu, an associate professor of anesthesiology whose weight has fluctuated between 200 and 275 pounds over the past 12 years. "Now I can say, 'Go look at my blog. Look at those days I ate 500 calories a day and didn't lose any weight.'" • Chu's blog, Precision: me (precisionme.org), chronicles the first 90 days of his effort to lose weight and reverse prediabetes. On it, he tracks his weight, lab values, medications, food, exercise, and symptoms like hunger and headaches. • "Obesity and weight loss are a very strong case for precision health. We know that one single approach will not work for everyone," he says. Chu and his weight-loss physician, Rami Bailony, MD, of Enara Health, knew Chu had gotten stuck at certain weights in the past, unable to lose any more. His exercise regimen was solid; he'd been working out with a personal trainer for a decade. And he'd had periodic success with low-carb diets — they curbed his appetite — but he couldn't cease them without regaining weight. Bailony and Chu thought that Chu's high insulin levels were contributing to his weight gain, and that a very-low-calorie diet would lower them while providing balanced macronutrients. If it didn't work, they'd use what they'd learned to try something else.



Larry Chu and his physician used his health data to develop a personalized weight-loss plan. In 90 days, he lost 48 pounds and reversed prediabetes.

Chu believes this type of physician-patient partnership will become increasingly common. "Precision: me is in many ways a demonstration project of how people can participate in precision health care," he says. "Imagine what we could learn if people shared their data the way I'm sharing the data, and we could then pool that data. We'd have a much more detailed and powerful view of obesity."

As fond as he is of data — and this is a man who has strapped a continuous glucose monitor to his leg and named it "Dexy" — Chu also emphasizes the value of storytelling: "Stories add context to the data." Precision: me includes podcasts in which he and Bailony discuss misconceptions about obesity — fat people are lazy, make bad choices, just need to take better care of themselves — as well as the judgment and guilt Chu has felt over the years. "I'm really glad we have the website and the blog to show people: This is my world," he says during the "Frustration" podcast. "I ate 800 calories a day for 10 days and I didn't lose any weight."

Ultimately, Chu did shed 48 pounds over the 90-day experiment. By Day 60, his hemoglobin A1C — a three-month average of blood sugar — had almost normalized and his triglycerides, a type of fat in the blood associated with insulin resistance and heart disease, had plummeted. In one puzzling result, however, his low-density lipoprotein, or "bad cholesterol," increased. Perhaps sharing the data online, Bailony says, "will allow someone to pipe in and say, 'Hey, I know why.'"

Although the blog project is finished, the personalized approach is not. "As I come off the very-low-calorie diet, Dexy will be even more useful," Chu says. Based on how much his glucose spikes within an hour of eating, he is developing a "personal glycemic index" of foods.

"We don't know his long-term story," Bailony says. "Hopefully, he'll decide to share that." — KATHY ZONANA

LESLIE WILLIAMSON

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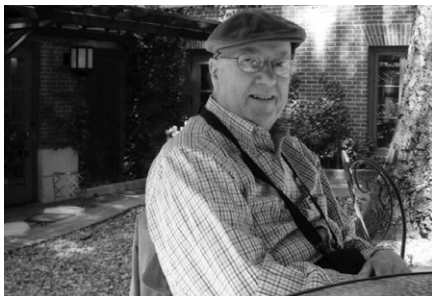
Father of the magazine

SPYROS ANDREOPOULOS WAS A GIANT IN THE PUBLIC-INFORMATION WORLD

***Stanford Medicine* magazine's founder, Spyros Andreopoulos,** a champion of openness in university communications, led Stanford's medical center news and public affairs office for 30 years. He died at 86 on Nov. 20, 2015, at a nursing home in Menlo Park, close to his residence on the Stanford campus.

"In my experience, Spyros was one of the most competent, most helpful and most completely honest people in the public-information world," says longtime *San Francisco Chronicle* science reporter David Perlman. "You could always count on him to give you a straight answer and be totally forthcoming on matters of medical center policy. He was one of the very best in the business."



Born in Athens, Greece, on Feb. 12, 1929, Andreopoulos learned English in German-occupied Salonica as a teenager and served as a communications liaison in Greece's air force during the Korean War. After the war, Andreopoulos returned to Greece and worked for the United States Information Agency, helping produce films about the Marshall Plan. This led him to Kansas State University in 1953, where he learned about agriculture for a film series on modern farming methods. Though the project was canceled, he stayed in the United States to study journalism. He went on to work at the *Wichita Beacon* newspaper, and then as assistant director of information services at the Menninger Foundation in Topeka, Kansas.

In 1963 he came to Stanford, where he served as spokesman for the medical school and Stanford Hospital, director of the medical center's news office, adviser to the organizations' leaders, and editor of *Stanford M.D.* magazine and its successor, *Stanford Medicine*. He was also a prolific writer and editor. He won national awards for books he edited on health-care policy, published the article "Gene Cloning by Press Conference" in *The New England of Journal of Medicine*, penned dozens of newspaper op-eds and even published a novel, *Heart Beat*.

When Andreopoulos retired, then-dean David Korn, MD, had a commemorative scroll prepared for him. Framed in the house where Andreopoulos lived for decades, it reads: "A respected and loyal friend of Stanford, a man of the highest principles, you served as the conscience of the Medical Center, working with uncommon skill and probity to translate and disseminate scientific research, striving always to discern and communicate the truth. We salute your long and distinguished career."

— ROSANNE SPECTOR

COURTESY OF CHRISTIANE ANDREOPOULOS