

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

Fall 2016

special report

DIAGNOSTICS

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of zeroing in

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Eight new ways to see inside

When no one knows

Chasing down rare diseases

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plus

Ebola

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Something for the pain

An excerpt from
Drug Dealer, MD



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

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TB CRUSH

VIDEO GAMERS HELP DEVELOP A BETTER TEST FOR TUBERCULOSIS

Purvesh Khatri, PhD, had a better test for active tuberculosis. TB is hard to diagnose accurately, but Khatri and his team had discovered that the ratio of three particular RNA molecules from a blood sample could show if a person had the disease. One thing was missing, however: a cheap way to deploy the test in some of the most remote locations in the world.

While at the Big Data in Biomedicine conference at Stanford last year, Khatri came upon a surprising solution. Sitting next to him was Rhiju Das, PhD, who told him about a research team ideally suited for the project: 100,000 registered players of Eterna, a video game Das launched five years ago to design useful biomolecules.

The two Stanford professors hatched a new challenge for the players: to design a single RNA molecule, dubbed OpenTB, that could calculate the ratio among the three RNA molecules. The two recruited assistant professor of genetics Will Greenleaf, PhD, who had just invented a technology that could test hundreds of thousands of player-designed molecules.

If the players succeed, they'll help save millions of lives. TB infects a third of the world's people and kills about 1.5 million each year. Yet there's no easy-to-use blood test that can detect active infection and

identify who could benefit from antibiotics. OpenTB would be the indicator molecule needed to create an assay as simple as a home pregnancy test.

Unlike two-stranded DNA, RNA is single-stranded, floppy and spontaneously folds into myriad shapes. Over the years, Eterna players have become expert in designing complex RNA molecules, says Das, an associate professor of biochemistry.

Six months into the new game, the results are encouraging, says Das. "We have promising leads, in several cases from brand-new players who started playing Eterna after hearing about the OpenTB challenge," he says.



In the video game Eterna, players design RNA molecules to solve medical problems.

Although OpenTB would be one RNA molecule, it would have three parts, each of which would bind to one of the TB-related RNA molecules.

The OpenTB molecule must also assume different shapes depending on the proportions of the three kinds of RNA. "If I have a lot of RNA molecules A and B around," says Das, "OpenTB will fold into shape 1. But if there's a lot of C around, OpenTB will fold into shape 2."

For OpenTB to work, shape 1 also must be able to bind to a fluorescent tag, while shape 2 must not bind to the tag. So individual molecules with shape 1 would emit light and those with shape 2 would not.

By measuring the brightness, says Das, you can calculate what proportion of Eterna molecules have folded into shape 1, revealing the proportion of RNAs A and B relative to C. If the light is above a certain threshold of brightness, you know the patient has active tuberculosis.

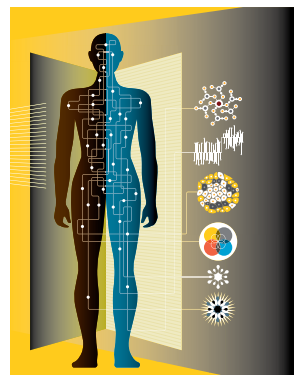
"I love this idea because it changes the biological research paradigm," says Khatri, an assistant professor of medicine. Khatri came up with the idea for the TB test after analyzing gene expression data from more than 1,000 blood samples, all from publicly available data sets. If OpenTB is successful, says Khatri, "it would allow us to say, 'We can use publicly available data — ultimately provided by patients themselves — to find a diagnostic signature of one of the biggest killers of mankind. And then we can engage the public to design molecules that can help deploy that test using a video game platform.'" — JENNIE DUSHECK

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

SPECIAL REPORT

Diagnostics

THE POWER AND LIMITS OF ZEROING IN



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Diagnostics transformed the practice of medicine in the 20th century as blood tests, imaging, endoscopy and biopsies offered physicians an insider's view of a patient's signs and symptoms.

Now diagnostics are poised to help lead another revolution in medical care toward the more predictive and preventive care of precision health.

Already diagnostics are being used to predict disease. Through genetic testing, individuals can learn of their risk for certain genetically linked conditions while they are still asymptomatic. With a diagnostic blood test, a woman can learn whether she has the BRCA gene mutation, for example, thus helping to predict her risk of developing breast cancer and allowing her to make an informed choice about whether to take prophylactic measures to reduce that risk.

But most disease is not the result of faulty genes. It is determined by social and environmental factors as well as the health choices that we make on a daily basis — whether to exercise, smoke or eat vegetables. The future of diagnostics is to help us better understand what makes us healthy as well as unhealthy, and to empower us with knowledge about how our behaviors can mean the difference between wellness and disease.

Encouraging health-promoting choices is not an easy task — I once heard a Silicon Valley investor say he would never invest in a company that was trying to change human behavior, no matter how promising — but I believe it can be done.

Stanford Medicine research has already demonstrated how. Abby King has spent her career studying how to encourage health-related behavior change, particularly among older adults and those living in disadvantaged communities. Again and again, she has found that motivationally targeted mobile apps significantly increase physical activity. Analytical approaches, which include personalized goal setting and self-monitoring, are effective, and so are social approaches, which include social comparisons, norms and support.

The demand for these kinds of diagnostic and motivational tools is growing. More than 50,000 people so far have signed up to use MyHeart Counts, a mobile health app developed by Stanford Medicine faculty that runs on Apple's ResearchKit platform. Through MyHeart Counts, participants can monitor their daily activities and risk factors for cardiovascular disease and then share this data with researchers. Though most people visit their doctor only a few times a year, their phone is almost always at hand. With MyHeart Counts, they can get continual feedback about their behaviors and how to improve those behaviors in a way that promotes heart health.

I believe this is the future of health care. In its various forms, digital technology has fundamentally and irreversibly changed the way we think and act. Now it's time we harness technology to impact behavior in a health context. The diagnostics of the 21st century are helping people become partners in managing their own health as well as consumers who are as focused on improving their well being as they are on defeating disease. In sum, that's the precision health revolution.

Sincerely,

Lloyd Minor, MD

Carl and Elizabeth Naumann Dean of the School of Medicine

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Taking steps

SIX MONTHS AFTER A STROKE, DOCTORS DON'T EXPECT IMPROVEMENT in a patient's recovery, says Stanford professor and chair of neurosurgery Gary Steinberg, MD, PhD. But in a recent phase-1 clinical trial, Steinberg and his colleagues demonstrated that injecting modified stem cells into the brains of chronic stroke patients improved their motor function — even though their strokes had occurred six months to three years previously.

The researchers took mesenchymal stem cells — the precursors to muscle, bone, fat and tendon — from the bone marrow of two adult donors and modified them to increase their ability to restore neurologic function. They then injected them into the brains of 18 patients, with an average age of 61, whose strokes had severely affected their muscle function.

Although the transplanted cells do not appear to survive very long in the brain, patients showed significant improvement



in their motor function within a month's time, and sustained those improvements a year after surgery. Steinberg says it's likely the mesenchymal cells secrete factors that stimulate lasting regeneration or reactivation of nearby brain tissue.

"This wasn't just, 'They couldn't move their thumb, and now they can,'" he says. "Patients who were in wheelchairs are walking now. We thought those brain circuits were dead. And we've learned that they're not."

Steinberg is the lead and senior author of the study, which was published in the July issue of *Stroke*.

Comprehensive cancer care

THE STANFORD CANCER INSTITUTE HAS been designated a Comprehensive Cancer Center by the National Cancer Institute, a part of the National Institutes of Health. The designation, the NCI's highest, recognizes the institute's strength in laboratory and population-science research, clinical care, and community outreach and education.

The institute is a partnership between Stanford Medicine and the Cancer Prevention Institute of California. It has nearly 400 members, a multidisciplinary group of scientists and physicians, and is directed by professor of medicine Beverly Mitchell, MD.

In a study of Britons, natural selection has upped the prevalence of 551 'tallness' genes. More at <http://stan.md/2ej3PIh>.

Pain relief

Researchers have identified a novel compound that, in mice, provides the same painkilling power as the most potent prescription opioids without suppressing respiration — and thus without causing overdoses. It may also be less addictive than opioids.

"This promising drug candidate was identified through an intensively cross-disciplinary, cross-continental combination of computer-based drug screening, medicinal chemistry, intuition and extensive preclinical testing," says Brian Kobilka, MD, a Stanford professor of molecular and cellular physiology. Kobilka is a senior author of the article describing the work in the Sept. 8 issue of *Nature*.

When an opioid such as morphine binds to the mu opioid receptor, a cell-surface protein found throughout the brain and spinal cord, it triggers both pain relief and respiratory

suppression. The trick was to find a drug that triggers only the pain relief — and that doesn't bind to any additional opioid receptors.

The researchers analyzed the mu opioid receptor's binding pocket, then computationally screened a database of 3 million compounds. After simulations and testing, just one candidate emerged. With a chemical tweak, it fit the receptor like a hand in a glove.

The study, driven by Stanford Distinguished Fellow Aashish Manglik, MD, PhD, was a collaboration with scientists at Stanford, the University of California-San Francisco, the University of North Carolina and the Friedrich Alexander University in Erlangen, Germany.

INNOVATION HUB

CURE, PREVENT OR MANAGE ALL DISEASES by the end of the century. That's the central goal of the science arm of the Chan Zuckerberg Initiative, created by Facebook founder Mark Zuckerberg and his wife, Priscilla Chan, MD. Their first scientific investment: the \$600 million Biohub, bringing together scientists and engineers from Stanford, the University of California-San Francisco and the University of California-Berkeley to engage in large-scale collaborations, build new biotechnology tools and support researchers.

"The Biohub will be the sinew that ties together these three institutions in the Bay Area like never before," says Stephen Quake, PhD, Stanford professor of bioengineering and of applied physics, who will co-lead the Biohub with Joseph DeRisi, PhD, professor and chair of biochemistry and biophysics at UCSF. It will be headquartered in San Francisco's Mission Bay with an outpost at Stanford.

Resident Biohub scientists will work on two overarching projects: the Cell Atlas, a comprehensive catalog of all the biologically significant characteristics of every cell type in the body, and the Infectious Disease Project, which is devoted to tackling microbial diseases, including emerging biothreats and pandemics.

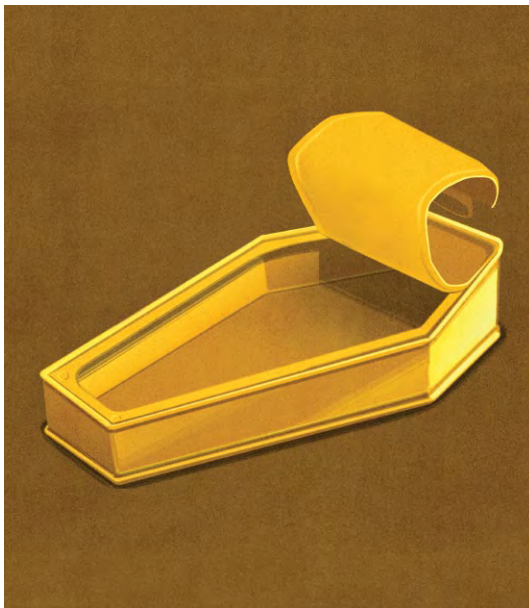
In the can

CONCERNS ABOUT BISPHENOL A aren't just for plastic bottles anymore. A study published in the October issue of *Environmental Research* shows that eating some canned foods increases exposure to BPA, a hormone disrupter linked to diabetes, cardiovascular disease and other health problems.

BPA is used in the resins that coat the inside of food cans and jar lids. In a study of 6,372 participants, researchers found that the more canned food they consumed, the higher their urinary BPA concentrations. Canned soup was the most pernicious, followed by canned pasta, vegetables and fruit. "I could eat three cans of peaches and you could eat one can of cream-of-mushroom soup and have a greater exposure to BPA," says lead author

Jennifer Hartle, PhD, a former postdoctoral scholar at Stanford who is now an assistant professor of health science and recreation at San José State University.

Although the problem is clear, the solution is less so. "Many food and beverage companies are moving away from the use of BPA," Hartle says. "However, we do not know if synthetic BPA replacements are safe either."



Unblinded

AFTER PATIENTS DEVELOP CATARACTS, THE LEADING CAUSE OF BLINDNESS, vision can often be restored through surgery. But little can be done to restore vision in patients with glaucoma, the second-leading cause of blindness, or other forms of optic-nerve damage.

Researchers led by Andrew Huberman, PhD, associate professor of neurobiology, have restored partial vision for the first time in mice whose optic-nerve cables were completely severed. They coaxed the cables, which convey visual information from the eye to the brain, to regenerate, retrace their former routes and re-establish connections with the appropriate parts of the brain.

Information is transmitted from the eye to the brain via the retinal ganglion cells, whose long, wirelike axons travel down the optic nerve and then fan out to more than two dozen areas of the brain. Like most axons in the mammalian central nervous system, retinal axons do not regenerate, so damage means permanent vision loss. One reason: a set of molecular interactions called the mTOR pathway, which enhances axons' growth, winds down after early development.

When the researchers biochemically activated the mTOR pathway in mice, exposed them to constant visual stimulation in the form of a moving black-and-white grid and covered their undamaged eye to encourage them to use their damaged eye, substantial numbers of axons regrew and migrated to their appropriate destinations in the brain. The mice were able to use that eye to discern an expanding dark circle — analogous to an approaching bird of prey — but not for tasks that required finer visual discrimination.

Huberman is the senior author and Jung-Hwan Albert Lim, a graduate student at the University of California-San Diego, is the lead author of the study, which was published in the August issue of *Nature Neuroscience*.

FORGET IT

THERE HAS BEEN GOOD NEWS AND BAD NEWS about hormone therapy for post-menopausal women. Now, there's equivocal news. • A recent study led by a Stanford Medicine researcher and published online in July in *Neurology* has shown that hormone therapy has no appreciable effect on a woman's cognitive skills, regardless of whether she begins treatment shortly after menopause or a decade-plus later.

"Our results suggest that healthy women at all stages after menopause should not take estrogen to improve memory," says the study's senior and lead author, Victor Henderson, MD, professor of health research and policy and of neurology and neurological sciences. "At the same time, they don't need to be overly concerned about negative effects of estrogen on memory."



Doctors mum on genital cutting

Female genital cutting is illegal in Egypt, but physicians are not discouraging the practice, according to a recent study. "Based on the women we interviewed, the doctors are not coming out and saying, 'You really don't need to do this,'" says lead author Sepideh Modrek, PhD, who was a Stanford instructor of medicine when the work was conducted.

One-third of the mothers interviewed said they were uncertain about genital cutting or were worried about the risks to their daughters — which include infection, hemorrhage and death — so they sought out doctors for advice. "They have heard mixed messages," says Modrek, "and are looking to the doctor for the final decision." The study was published online in August in *International Perspectives on Sexual and Reproductive Health*.

One-third of mothers said they were uncertain about genital cutting or worried about the risks to their daughters.

DIAGNOSTICS

The power and limits of zeroing in



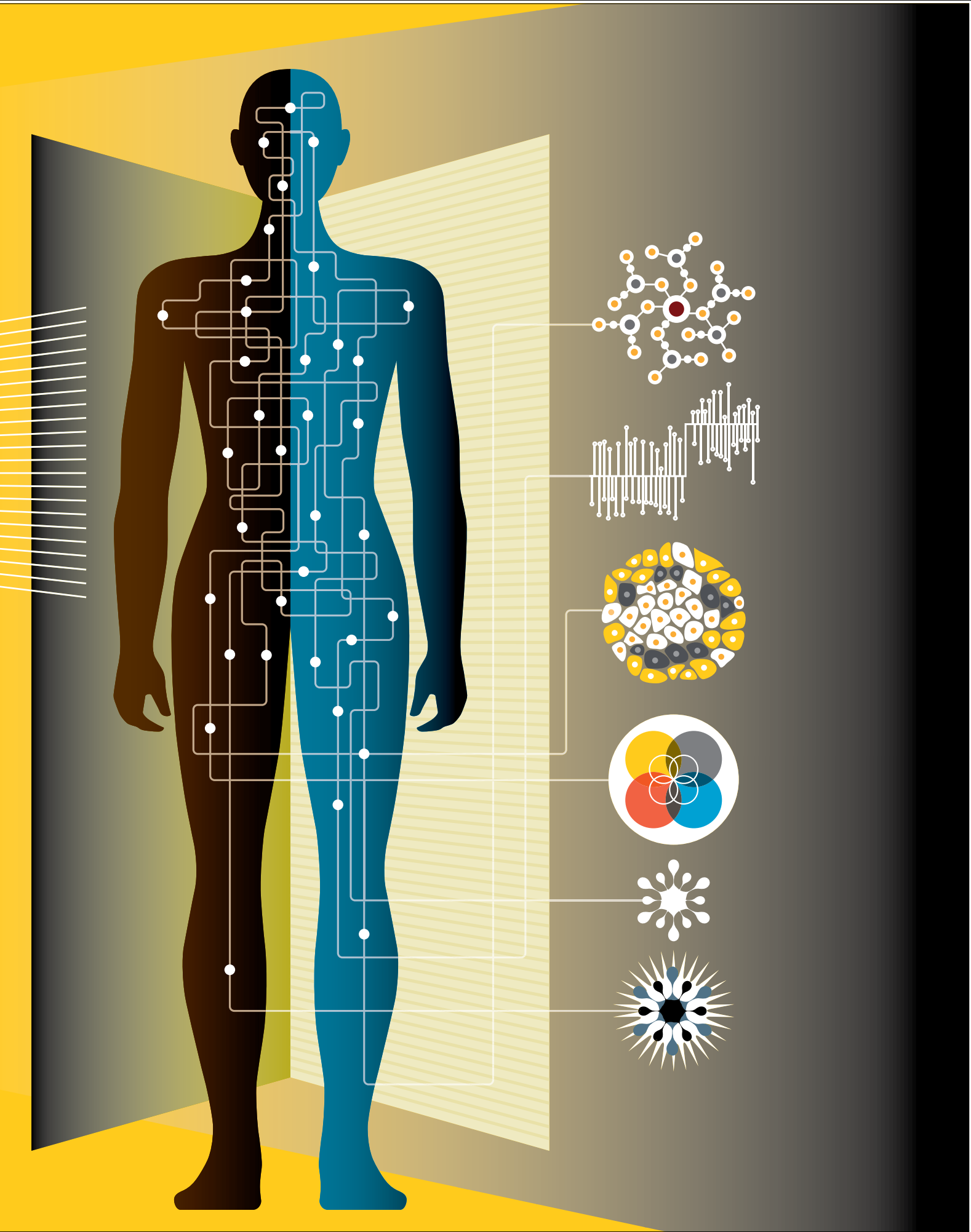
DIAGNOSE THIS

A HEALTH-CARE REVOLUTION IN THE MAKING

Imagine it's the future. Imagine your future self rolling out of bed in the morning and heading for the bathroom. Your smart toilet is an older model and you are thinking of getting a new one. • Sure, the old toilet can do a basic urinalysis, picking up indicators of incipient diabetes or infection. And it can alert you to blood in your stool, a potential sign of colon cancer, just as quickly as you can flush and squint at the readout. Your special test-strip toilet tissue — *"Accurate yet Soft!"* — gives you a green thumbs-up on 30 different daily diagnostics. And the toilet reports that your gut microbiome is up to snuff.

BY JENNIE DUSHECK

ILLUSTRATION BY PAUL WEARING



But your model doesn't test for any of the dozen healthful new gut bacteria discovered among African San hunter-gatherers.

You took the San+™ probiotic capsules; have the microbes colonized your gut yet?

What really has you lusting for a new toilet, though, is the lack of data-share options for your old toilet. Honestly, your doctor and one emergency contact? That's it? Who's going to help you make sense of all this information? What about GloMM, the global health record data bank founded in 2021 that stores and shares all your mobile and other health data? What about your two dating sites? A lot of potential partners expect to know how healthy you are. Not to mention SocialWell, which will match the government's \$3,000 rebate if you get a new smart toilet before the end of the year.

Back in the present, we are talking with Sanjiv Sam Gambhir, MD, PhD, who's working to translate such a scenario — or one a little like it — into reality. Gambhir, chair of Stanford's Radiology Department and director of the Canary Center at Stanford for Cancer Early Detection, envisions a future where we nearly continuously monitor our health. The resulting data might tell each of us or our health-care team, right away, if something is amiss. Are we developing tiny aggressive tumors? A slight tremor suggestive of the onset of a neurodegenerative disease? Or organ-damaging high blood pressure?

Current diagnostics, says Gambhir, are so intermittent, it's like trying to watch a movie but seeing it only every 20 to 30 minutes for a few seconds each time until near the end of the movie when you get to watch it for a few minutes. Inevitably, we'll miss critical parts of the story.

In general, diagnostics have been underappreciated. According to a 2015 National Academy of Medicine report, "The delivery of health care has proceeded for decades with a blind spot: Diagnostic errors — inaccurate or delayed diagnoses — persist throughout all settings of care and continue to harm an unacceptable number of patients." Gambhir is one of the few who recognize how systemic the problem is, how colossal the challenge, and who want to change things.

'THE FUTURE IS ALL ABOUT BEING ABLE TO INTERCEPT DISEASES EARLY AND, IDEALLY, PREVENT THEM. IF WE CAN ACTUALLY DO SOMETHING ABOUT A DISEASE SUCH AS AN AGGRESSIVE CANCER, THEN IT IS WORTH MONITORING FOR IT.'

The underpinnings of a greater emphasis on diagnostics will be devices that can monitor health at all times. Radiology lecturer Seung-min Park, PhD, who works in the Gambhir lab, is helping to lay the foundation for Gambhir's diagnostic vision. If you want to continuously monitor the body, says Park, you can't do that with anything like surgery, blood draws or X-ray imaging. No one would put up with that.

It is clear, Park says, that the perfect sources of diagnostic information are the molecular contents of sweat, saliva, urine and feces, naturally excreted every day and packed with information. Researchers around the world have realized that these substances can provide clues to our health.

Park is engineering a smart-toilet prototype that can collect urine for testing several times a day. To get the project started, he's using an off-the-shelf commercial test strip that measures 10 factors such as acidity, which can tell you about your risk of kidney stones, and glucose, an indicator of diabetes.

The Gambhir lab is also working on a smart bra designed to continuously image breast tissue. The bra uses a combination of infrared light and sound to image and detect minuscule breast tumors, so they can be removed long before they metastasize. Like the smart toilet, the smart bra is still under development. For now, the lab's engineers are scratching their heads over challenges like how to analyze the nonstop flow of data and where to place the battery.

Cardiologists are already making the vision of continuous monitoring a reality. Information from pacemakers and other devices implanted in the heart can be transmitted automatically through ultralow radio frequencies so that patients can be monitored for signs of crisis.

For example, when an infant was born with a deadly heart arrhythmia, her doctors at Lucile Packard Children's Hospital Stanford implanted a pacemaker and defibrillator in her heart that could report back to her doctors if the defibrillator was activated. At 7 months, the defibrillator began to go off. Although the baby looked fine to her parents, she was in serious trouble. The hospital told the parents to bring the baby in right away, and within a few weeks a heart transplant saved her life.

Gambhir's vision

DIAGNOSTICS HAVE MOVED far beyond old-fashioned X-rays for broken bones. We already live in a world where, if we wanted, we could monitor our health around the clock with a variety of ingenious devices that can potentially help foretell illness.

Wearable and implantable devices can deliver rivers of information that can both help health-care systems

track the health of individuals and help researchers study the effectiveness of treatments or preventive health programs in whole populations. Some people won't want to be monitored all the time, Gambhir acknowledges, but he thinks that for many the desire for the benefits will outweigh their concerns about privacy.

Gambhir compares the future of diagnostic medicine to the approach used to keep the engines of commercial jets spinning smoothly and safely. "Most people have taken a flight on a commercial jet," he says. "You may not know it, but the jet engines on that plane are almost continuously monitored by an engine-health portal that sits at General Electric or Rolls-Royce. Every 30 seconds, each engine on the airplane sends information down to the engine-health portal. Hundreds of sensors built into that jet engine are letting the health portal know if there's a problem with the engine — even in flight. If there's a problem, adjustments to the engine can be made, without the pilots even knowing, still in flight." For more serious problems, a plane can be forced to land. Just as importantly, jet engine engineers have learned when not to intervene and just continue to monitor — to avoid false alarms.

"There is no real equivalent in health care," says Gambhir. "There isn't a continuous monitoring of your health. The future is all about being able to intercept diseases early and, ideally, prevent them. If we can actually do something about a disease such as an aggressive cancer, then it is worth monitoring for it."

Yet when research dollars are doled out, diagnostic tools are often treated as an afterthought, Gambhir says. People don't think of diagnostics as saving lives, but treatment depends heavily on accurate diagnosis — and biomedical research even more so. Expenditures on the field of diagnostics research are not tracked separately, but he estimates that no more than 7 percent of total biomedical research dollars go to diagnostics, with the rest going to discovering ever more treatments.

Gambhir would love to see that ratio reversed, he says, so that the "anticipating and preventing disease" part of Stanford's precision health approach takes priority over endless new treatments.

But he concedes he'd be happy with a 50:50 funding split between diagnostics and therapeutics and anticipates such a transition in the coming years. It makes much more sense, he argues, to put resources into preventing disease or at least diagnosing disease early — when, in many cases, it's easier to treat — than doing nothing until people are quite ill.

But the way biomedical research is funded and the way

medicine is practiced are still structured around treatment, not diagnosis. So a diagnostics-first approach would mean major changes.

The structure of medicine

KATHRYN MCDONALD, the executive director of Stanford's Center for Health Policy and the Center for Primary Care and Outcomes Research, concurs with Gambhir that diagnostics are severely understudied, given how important they are. "Our health-care system is organized around what happens once you already know what's wrong, as opposed to figuring out what's wrong," McDonald says.

In 2015, the National Academy of Medicine reported that at least 5 percent of U.S. outpatients experience a diagnostic error, 6 to 17 percent of adverse events in hospitals result from diagnostic errors, and diagnostic errors contribute to 10 percent of all patient deaths.

Yet, despite the importance of diagnostics, they receive minimal funding, says McDonald, who serves on the National Academy of Medicine's Committee on Diagnostic Errors in Health Care. "If you look at the dollars associated with diagnostic testing, it just pales in comparison to dollars spent on pharmaceuticals. And there's a parallel in the research world."

One reason is that diagnostics is primarily a cognitive activity, McDonald says. It's your doctor sitting and thinking, reading, thinking some more, calling a colleague and talking until they figure out what's wrong with you. And there's almost no support for thinking and talking, she says. Physicians and others are compensated for treating patients and, to a lesser extent, for seeing patients, but not for thinking about them.

We need to look for ways to reward that cognitive work and teamwork, says McDonald.

False positives, false negatives and false reassurance

ALTHOUGH DIAGNOSIS may happen through thinking and communicating, diagnostic tests themselves, and how physicians think about them, are susceptible to error. Tests are notorious for generating false positives and false negatives, and the more rare the condition, the easier it is to be misled by such false information.

In the case of a test for blood in the urine, a false positive would indicate there was blood when there wasn't actually blood there. Likewise, a false negative would

C O N T I N U E S O N P A G E 4 6

DIAGNOSTICS

The power and limits of zeroing in

HEARING THINGS

PATIENTS WERE BOTHERED BY THE SOUNDS

OF THEIR EYEBALLS,

THEIR DIGESTIVE SYSTEMS,

THEIR BLOOD. ONE LOOK

IN THEIR EYES,

AND A SURGEON-SCIENTIST

KNEW WHY

In the spring of 1995,
a patient
with a bizarre set of
symptoms entered the office
of Lloyd Minor, MD,
an expert on inner-ear disorders at Johns Hopkins.

THE 50-YEAR-OLD GENTLEMAN TOLD MINOR THAT WHEN HE SANG IN THE SHOWER, THE ITEMS IN THE SHOWER — THE SHAMPOO BOTTLE, THE LOOFAH, THE SHOWER HEAD — began to move about. And it was always in a specific pattern, as if the items were following one another around the face of a clock. • The patient told the doctor that he had also noticed that if he hummed a similar tone or heard certain loud noises while looking in the mirror, he saw his eyes move in response. • “And in fact he said, ‘Look, I can show you,’” says Minor, now dean of the Stanford University School of Medicine, “if you just give me something so I can put a loud noise in my right ear.” • So Minor asked the patient to hum the particular tone. He recorded a tone of a similar frequency on a Dictaphone, played the sound in the patient’s right ear and looked into his eyes. Just as the patient had said, his eyes moved. Minor also noticed that they moved in a specific pattern. • “It wasn’t a random eye movement,” Minor says. The eyeballs, he says, move in three dimensions — vertical, horizontal and torsional (rotation about the line of sight, when described from the patient’s frame of reference) — and as he watched this patient, he paid attention to all three. The patient’s eyes moved upward and counterclockwise. The pattern never varied, and was tightly linked to the sound.

By Tracie White

PHOTOGRAPHY BY TIMOTHY ARCHIBALD



LLOYD MINOR FELL IN LOVE
WITH THE VESTIBULAR SYSTEM
IN AN UNDERGRADUATE
BIOENGINEERING COURSE.

That's essentially all it took for Minor to solve the mystery. Upon seeing the direction of the eye movement in response to this particular sound, he suspected that the source of the problem was a hole in the superior semicircular canal — one of the three tiny canals hidden deep within the inner ear. These canals serve as part of the vestibular system, a set of inner-ear structures that provides input to the brain on motion, equilibrium and spatial orientation. When just a few weeks later a second patient came to see him with similar symptoms and similar eye movements, Minor was convinced he was right.

"Both of them had very, very large eye movements evoked by sound following a similar set pattern," Minor says. "It's partly by chance that these two patients both had very prominent eye movements that were very easy to see."

He had discovered a disorder that he named superior canal dehiscence syndrome — and went on to develop a surgery to treat it.

Minor was far from the only physician to see patients with bizarre sets of symptoms involving hearing,

vision and perceptions of motion. At about the same time Minor was examining the eyeballs of his first patient at Johns Hopkins, a French horn player in Germany was telling his doctors that his voice echoed like a kazoo in his brain, that eating anything crunchy sounded like a gun going off. And an audiologist in Atlanta told her doctors that she could hear a loud scratching sound whenever her eyeballs moved. Both would eventually make their way, years later, into Minor's office.

Symptoms described by these patients ranged from relatively mundane (though unpleasant) nausea and dizziness to superhero-like abilities to hear the inner workings of their own bodies — their pulse, their chewing, their digestive systems. They got misdiagnosed, underwent unnecessary surgeries, fell into depression, withdrew from the world.

"Doctors had no answers," says the audiologist, Cindy Hirsch, AuD. "I had an eye specialist tell me this was a psychiatric case because I could hear my eyes move."

"There was this whole bucket of patients, and

we really didn't understand what was wrong with them," says Robert Jackler, MD, chair of otolaryngology at Stanford. "A lot of physicians thought they sounded mentally ill; they had such peculiar complaints. No one could figure out what was wrong."

Minor first began studying the vestibular system in a bioengineering course

as an undergraduate at Brown University. Immediately, he was hooked. He was fascinated by the mathematical symmetry involved; he loved the elegant way the system worked to maintain the senses of motion and balance.

"The course used mathematical and engineering models to understand physiological systems," Minor says. "And the professor used the balance system, and the eye movements associated with it, as an example of how you could not only describe the way the system worked, but you could learn mechanistically about how the brain was working."

Like many scientists, Minor really likes to figure out how things work — the more complex the better. And the vestibular system is complex. Take what Minor refers to as "vestibular illusions." Why, when you step onto an escalator that isn't moving, does your brain tell your body that it is? Or why, when you're sitting on a stationary train and the train next to you starts to move, does it feel like you're moving even though you know you're not? Unlike most of us, Minor knows exactly how complicated the answers to these questions can be.

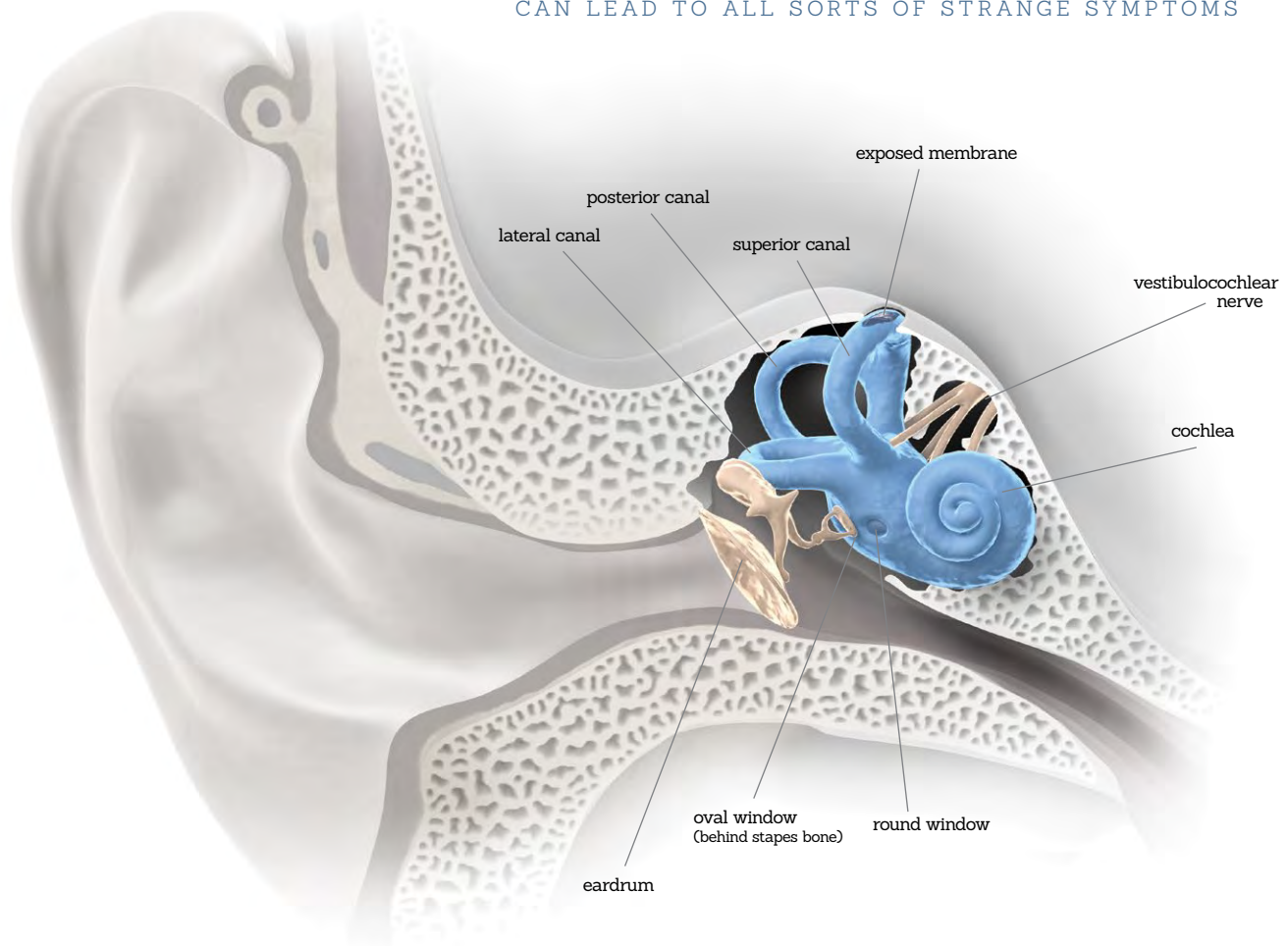
"It was during that undergraduate course that I read the papers of the person who later became my mentor," Minor says. That person was Jay Goldberg, PhD, now a professor emeritus of pharmacological and physiological sciences at the University of Chicago, who wrote a seminal series of scientific papers in the 1970s that captured the imagination of the young Minor. Goldberg had described for the first time the dynamics governing the responses of sensory neurons carrying information from the vestibular receptors in the inner ear to the brainstem, setting the stage for future studies in the field of vestibular neurophysiology.

Minor later wrote to Goldberg, and then traveled to Chicago to meet with him. They stayed in touch throughout Minor's medical school years.

**'DOCTORS
HAD NO
ANSWERS.
I HAD AN EYE
SPECIALIST
TELL ME THIS
WAS A
PSYCHIATRIC
CASE BECAUSE
I COULD
HEAR MY
EYES MOVE.'**

WHAT GOES WRONG

A HOLE IN THE BONE OF THE SUPERIOR CANAL
CAN LEAD TO ALL SORTS OF STRANGE SYMPTOMS



The inner ear includes the vestibular (balance) system and the cochlea, a hearing structure. Normally, it is a closed capsule with only two openings: the oval and round windows, two membranes that vibrate in opposite directions to move fluid through the cochlea, enabling it to translate sound waves into nerve impulses. But if there is an opening in the bone that should cover the superior canal of the vestibular system, the exposed membrane serves as a third mobile window into the inner ear. Sound may enter or leave through the new window, resulting in hearing problems: If it enters, it can amplify bone-conducted sounds from the body; if it leaves, it may diminish air-conducted sounds from the environment. And sounds or pressure changes in the affected ear may activate the fluid in the superior canal, causing vestibular symptoms such as eye movements, the perception that stationary objects are moving, vertigo and nausea.

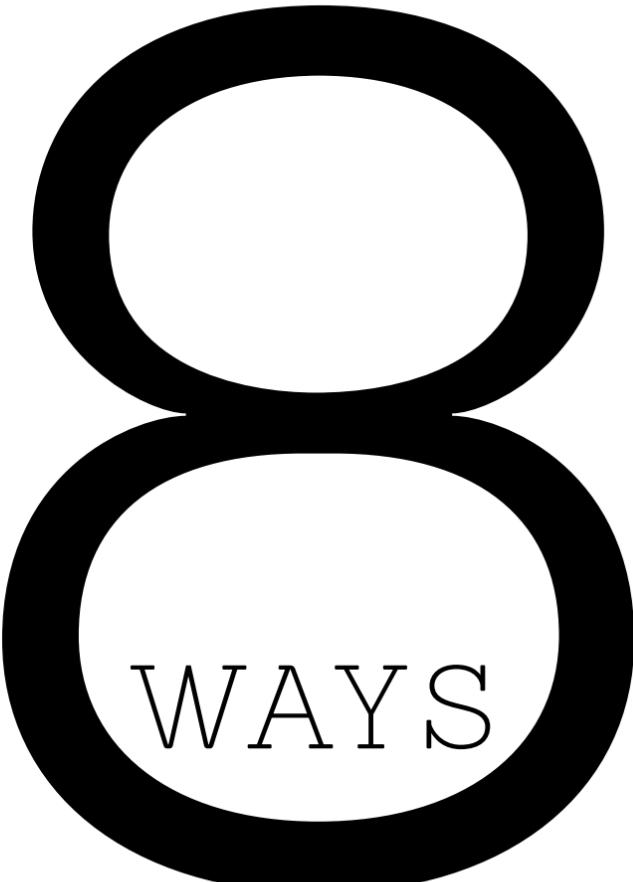
“We made plans that I would come to work with him after I graduated from medical school.”

In between his surgical residency and a residency in otolaryngology, Minor spent four years working in Goldberg’s lab, conducting experiments in animal models that further explored vestibular neurophysiology. By the mid-1990s,

as both a surgeon and an expert on the science of the vestibular system, Minor was unusually well-equipped to solve the mystery of the patients who could hear their eyeballs scratching as they moved back and forth.

The vestibular system controls how we move through the

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



WAYS

TO
LOOK
INSIDE

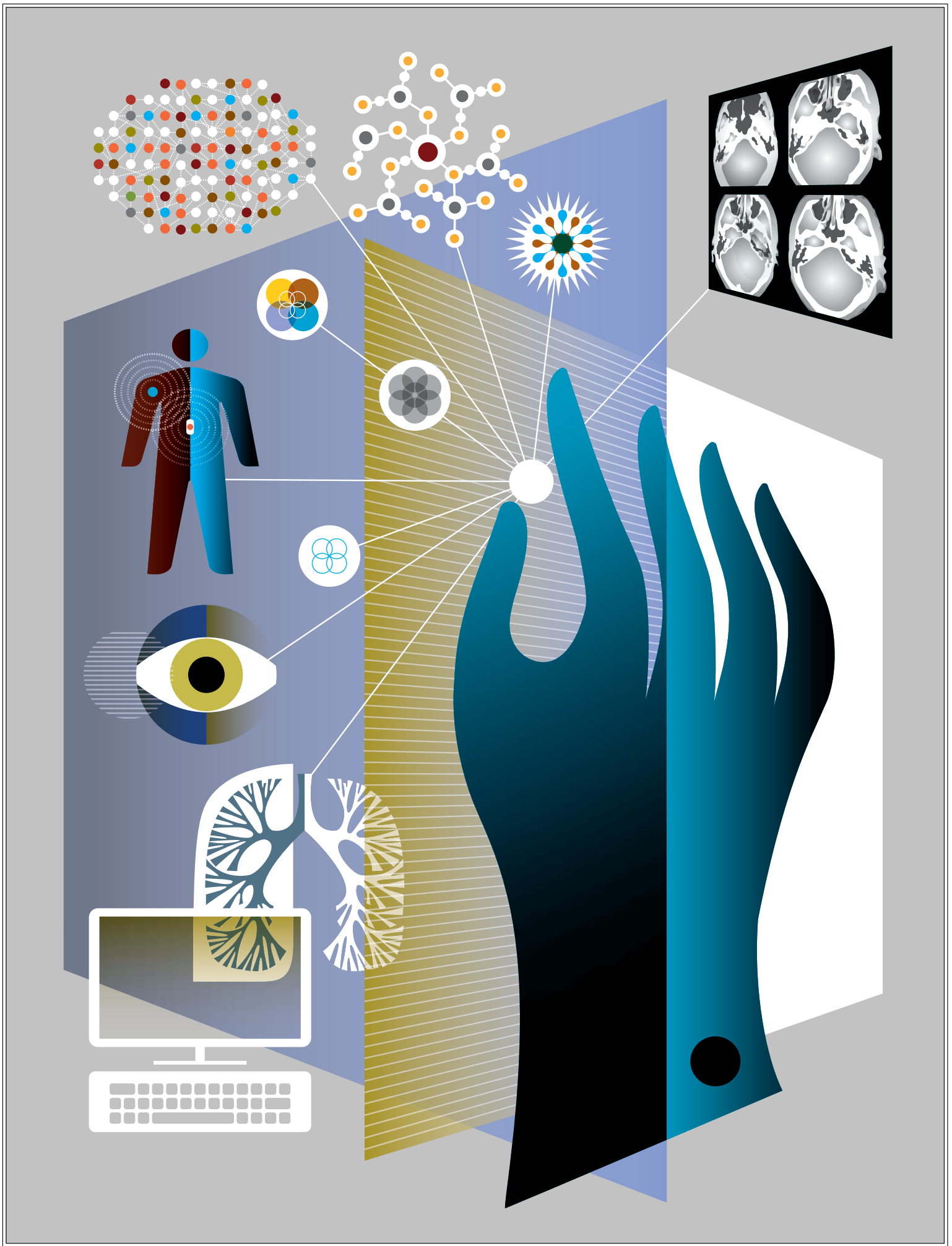
**A SAMPLER
OF DIAGNOSTICS
EMERGING FROM
STANFORD**

BY KATHY ZONANA

ILLUSTRATIONS BY PAUL WEARING

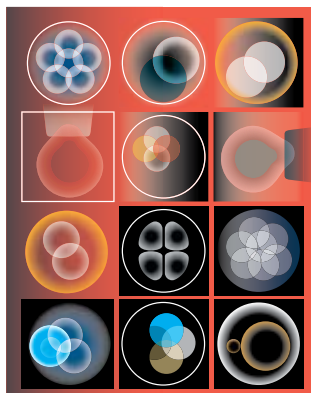
"PLEASE DON'T CONFUSE YOUR GOOGLE SEARCH WITH MY MEDICAL DEGREE," READS ONE NOVELTY COFFEE MUG. BUT WHAT IF INTERNET SEARCHES, IN THE AGGREGATE, COULD LEAD TO IMPROVED DIAGNOSES? Take Eric Horvitz's work. Horvitz, MD, PhD, is a technical fellow at Microsoft Research, where he serves as the managing director of the company's main research lab. When he and his colleagues look at search logs, they don't see hypochondriacs. They see people who are individually investigating their symptoms, and collectively telegraphing their syndromes. For example, months before a person is diagnosed with pancreatic cancer, he might search for "back pain." A little later, "weird weight loss." And then "itchiness" and "dark urine." If his search engine has been taught to notice the pattern, it might one day provide an alert to make an appointment with someone who has, yes, a medical degree.

Harnessing the power of big data is just one of the approaches researchers are using today to develop new diagnostic tools. Another trend is to democratize diagnosis by creating inexpensive, easy-to-use devices that can be deployed in the farthest reaches of the globe, or the nearest corner of your living room. And scientists are prototyping gadgets that were once the province of science fiction, including a machine that detects a dozen diseases with one drop of blood. Here are eight innovative ways to figure out what's going on inside of us.



Goldilocks' embryo

WHEN DAVID CAMARILLO, PHD, was a graduate student in mechanical engineering at Stanford in 2007, he collaborated briefly with Barry Behr, PhD, on using imaging technol-



ogy to select the best in vitro-fertilized embryos to transfer into a patient. Something Behr said stuck with him: Some embryos are squishier than others.

"It's like a Goldilocks 'just right' type of thing," says Behr, a professor of obstetrics and gynecology. When injecting sperm into an egg, embryologists might think, "This is too easy — there's no resistance," he says. "Or this is like chewing gum — I can't break the membrane." Both extremes seemed suboptimal, but there was no way to quantify them. "Scientifically, 'too hard' or 'too soft' is not adequate," Behr says.

percent more likely to result in live births. Clinical trials in humans are underway, and the researchers plan to start a company to put their findings into the marketplace.

"I think it could change how we do IVF," says Behr. The trend in infertility treatment is already to implant a single embryo, but this could increase the likelihood that that embryo will develop into a healthy baby. It could allow doctors to set expectations for patients whose embryos are unlikely to be viable. And it could enable embryologists to fertilize fewer eggs in the first place, thereby reducing the number of couples who must grapple with the ethical question of what to do with embryos they don't plan to use.

"Most of what we think we're measuring is the egg," says Yanez. The researchers are confirming that their method of assessing squishiness works as well for eggs as it does for embryos. If it does, it will benefit egg-freezing patients as well as IVF patients.

"There is no egg viability test, and we feel that if we can establish our correlation between the viscoelastic

'THE LONG-TERM FUTURE WILL BE IDENTIFYING A GOOD EGG

AND A GOOD SPERM
AND MAKING A GOOD EMBRYO.'

So when Camarillo returned to Stanford in 2012 as an assistant professor of bioengineering, he and Behr decided to scientifically assess squishiness. Or, more precisely, to determine whether an embryo's viscosity and elasticity signified something about its viability. "Let's just try taking a pipette and sucking on the embryo a little bit to see how much it deforms," Camarillo proposed.

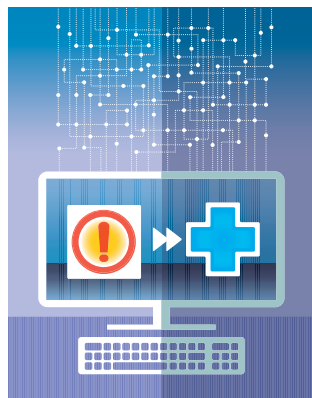
That method, called micropipette aspiration, is quick, minimally invasive and commonly used to assess cell viscoelasticity. "We compare it to a gentle squeeze — we call it the embryo hug," says Livia Zarnescu Yanez, who earned her PhD this year in Camarillo's lab and is the lead author of a paper published in February in *Nature Communications* describing the work.

The researchers found that both mouse and human embryos within a certain range of viscoelasticity — not too hard and not too soft — are more likely to form healthy blastocysts, the ball of cells that begins to form about five days after fertilization. They could predict with 90 percent accuracy which embryos would do so. And when they implanted the mouse embryos into mice, those classified as viable were 50

properties and the egg's ability to be fertilized, it's going to have far greater value," Behr says. "The long-term future will be identifying a good egg and a good sperm and making a good embryo."

The searchers

ERIC HORVITZ WAS TALKING ON the phone with his childhood friend Ron when Ron mentioned he had been feeling oddly itchy lately. Horvitz, MD, PhD, probed a little about



other symptoms, then suggested his friend see a doctor. Ron was diagnosed with pancreatic cancer within a month, and died within a year.

"He was relaying non-specific symptoms to me," Horvitz says. "Pancreatic and lung cancers are devastating because by the time the diagnosis is made, it is often too

late.” Horvitz wondered if the patients were leaving clues earlier. And he knew just where to look: their web searches.

Horvitz and his Microsoft colleagues identified anonymous users whose search queries provided strong evidence of a recent diagnosis of pancreatic cancer. They then went back several months in the search logs and found that many of those users had searched for symptoms such as back pain, abdominal pain, itching, weight loss, light-colored or floating bowel movements, slightly yellow eyes or skin, and dark yellow urine.

“Separately these might not worry someone enough to see a doctor,” says Horvitz, “but is there a temporal fingerprint that would be informative to a machine-learning algorithm with thousands of terabytes of data?” It turns out there is: By examining the patterns of symptoms in a recent feasibility study, the researchers were able to predict up to 15 percent of those whose searches would subsequently indicate that they’d been diagnosed with pancreatic cancer, while maintaining a low false-positive rate. They are now working on a method to verify and extend their findings by asking recently diagnosed patients for permission to correlate their search logs with their electronic health records.

Horvitz has collaborated with Stanford researchers Russ Altman, MD, PhD, professor of bioengineering, of genetics and of medicine (the two are longtime friends from their days as Stanford graduate students), and Nigam Shah, MD, PhD, associate professor of medicine and of biomedical data science, to analyze search logs for adverse effects of medications. For example, in 2011, Altman’s lab demonstrated that two commonly prescribed drugs taken in combination, the antidepressant paroxetine (Paxil) and the statin pravastatin (Pravachol), can cause hyperglycemia. The researchers then went back into the search logs for 2010 and found that users were telegraphing this finding: People who conducted searches for both drugs over the course of the year were more likely to search for “diabetes words” — 50 plain-spoken phrases like “fatigue” or “peeing a lot” — than people who searched for only one of the drugs.

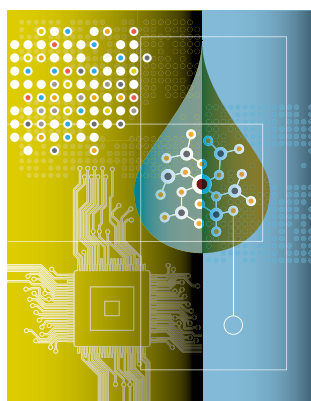
Horvitz and Altman emphasize that the goal isn’t for your search engine to diagnose you or alert you to algorithmically detected drug interactions. But it might nudge you to go to the doctor, or serve as a complement to the Food and Drug Administration’s adverse event reporting system.

The use of search-log data for medical research garners two main criticisms, Altman says: the denominator problem (“You don’t know how many people are taking the drug and doing fine, or taking the drug at all”) and the numerator problem (“We know not everyone reports their side ef-

fects”). Nevertheless, he says, there are insights to be gained. People are candid online — Horvitz calls it “whispering to your search engine” — and the data is voluminous and essentially free. Plus, Altman adds, there are ways to control for biases in the data. “An intelligent person analyzing it could make inferences,” he says. “It’s also possible you could be dead wrong.”

Magnetic attraction

WHEN SHAN WANG, PHD, joined Stanford’s Department of Materials Science and Engineering in 1993, the magnetism expert didn’t expect to develop diagnostic devices. “I wanted to do data storage,” he says. “I still have a little bit



of research going on on spintronics.” But the pull of detecting human disease has proven stronger. “There are so many unmet needs in medicine,” he says. “There are too many to work on. We have to pick and choose carefully.”

The one he chose was to detect and quantify cancer biomarkers — the proteins, nucleic acids and cells associated with cancer progression. “Cancer is the area that is lagging behind heart-disease diagnosis,” Wang says. “We feel it’s the high-impact area in which we can make a difference.”

Wang and his colleagues developed the magneto-nanosensor, a device that detects cancer proteins with sensitivity hundreds of times greater than the current commercial method, the enzyme-linked immunosorbent assay, or ELISA.

The miniature magneto-nanosensor chip, less than half the size of a dime, has either 64 or 80 “capture antibodies” on it. They can all be antibodies that bind to the same biomarker, or they can be intentionally varied so that the array of sensors measures more than one biomarker at the same time. A sample is added — a drop of whole blood, plasma, serum, urine or saliva — followed by a second batch of antibodies tagged with magnetic nanoparticles. These antibodies also bind to the biomarkers in the sample, creating a sandwich structure. Finally, the device measures the stray magnetic field produced by the nanotags and determines how much of each biomarker is present.

“We want to attack all cancer; that’s our mission,” Wang says. He has co-founded a company, MagArray, to bring the

technology to market. Once it is certified as a clinical laboratory, the company will begin by offering testing services for prostate and lung cancer.

The magneto-nanosensor can also be used to detect diseases beyond cancer, and may someday be deployed in medical clinics and even in patients' homes. "I'm very drawn to point-of-care testing," Wang says. "With essentially one finger prick, you can detect multiple diseases, multiple biomarkers. We are actually talking about what Theranos wanted to do."

Wang's lab has joined forces with the digital-health company CloudDX to enter the Qualcomm Tricorder XPrize competition. The competition promises \$10 million to the entrant who creates a device that best measures 13 health conditions and five vital signs, much like the tricorder Dr. McCoy used to diagnose patients on *Star Trek*. CloudDX's prototype incorporates the core technology of the magneto-nanosensor; Wang's lab contributed the cartridge where the sample is inserted. It is one of seven finalists for the prize, which will be awarded in early 2017.

"I feel like I'm in the best field right now," Wang says. "It's tough to get funding and to get things to work well — there are lots of challenges — but in terms of promise, it's exhilarating."

Iron works

PEDIATRIC CANCER PATIENTS make an awful lot of visits to radiology, undergoing scans to track the progress of their treatment and to look for recurrences and metastases. "The



current standard of care for a lot of our cancer patients is PET/CT," or positron emission tomography/computed tomography, "and that is associated with a lot of radiation exposure," says Heike Daldrup-Link, MD, associate professor of radiology. "One CT scan wouldn't be a problem, but our oncology patients get a lot of these scans before, during and after treatment, and then potentially for the rest of their life."

Some research suggests the accumulated radiation exposure from multiple CT scans could lead to secondary cancers later in life. "Secondary cancers usually develop after decades," Daldrup-Link says. "So a 70-year-old may not encounter their secondary cancer, but a young patient would."

Daldrup-Link has developed a technique to scan the whole body of pediatric cancer patients with magnetic resonance imaging, which is radiation-free. To do this, she injects a novel contrast agent — iron nanoparticles, known as ferumoxytol — into the patient's bloodstream. Ferumoxytol is typically used for the treatment of anemia.

"We can beautifully see all the blood vessels everywhere," says Daldrup-Link, looking at a scan from an MRI with ferumoxytol. "Our surgeons can nicely relate tumor deposits to the vessels. I think we really get a soft-tissue contrast that is not otherwise available."

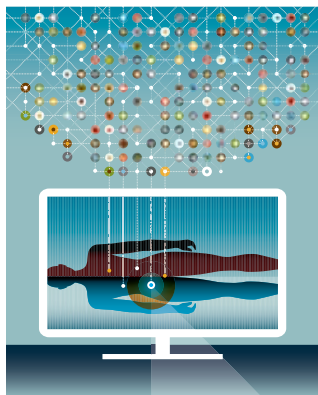
Daldrup-Link has shown that combining this MRI technique with PET reduces radiation exposure by 77 percent compared with PET/CT. She and a nationwide network of colleagues are now evaluating different tumor types to see which patients should be scanned with PET/CT, PET/MRI or MRI only. In addition to minimizing radiation exposure, Daldrup-Link strives to ensure patients have to climb into only one machine each time they are scanned. "For our young patients, it's huge to have just one scan instead of two or three," she says. "We believe PET/MRI can provide that."

Ferumoxytol also has advantages over gadolinium chelates, the traditional MRI contrast agents. Ferumoxytol remains visible in the blood vessels for at least 24 hours, whereas gadolinium peaks quickly, making it challenging to scan both the primary tumor and the entire body of sometimes wiggly patients. Also, recent studies show gadolinium may deposit in the brain. Hearing that their child will receive an iron supplement instead, Daldrup-Link says, comes as welcome news to worried parents. "Gadolinium is a heavy metal, so it's not very natural to our body, whereas an iron product is basically a concentrated steak, or a ton of strawberries." There is a risk that some patients may be allergic to iron compounds such as ferumoxytol, so Daldrup-Link follows an FDA protocol to monitor patients closely for signs of allergic reactions and treat them if they occur.

Iron nanoparticles may have other applications, as well. In tumors, they are taken up by immune cells called macrophages, which may enable radiologists to track the success of cancer immunotherapy treatment. In mice, "we do see the retention of our iron nanoparticles is reduced in those that have been treated with therapies that deplete cancer-promoting immune cells," Daldrup-Link says. The nanoparticles may even help fight cancer: In a surprise finding in another mouse study, they activated cancer-fighting macrophages to destroy tumor cells.

Follow the crowd

JOSEPH LIAO IS LOOKING AT a video on his computer. “It’s a papillary tumor — it looks like a broccoli — but then you kind of slice it like a loaf of bread,” says Liao, MD, associate



professor of urology at Stanford, gesturing as the video proceeds to display cross-sections of the tumor.

Liao was the first urologist to use confocal laser endomicroscopy, in which a fiber-optic probe is inserted into a standard endoscope, to create these “optical biopsies.” Surgeons can use optical biopsies

to assess tumors in real time, without waiting for pathologists. “Even if we get it back in an hour, that’s actually too late,” Liao says. “The case is done by then.”

Techniques like this are particularly promising for bladder cancer, which is the most expensive cancer to treat on a per-patient basis because of the lifelong surveillance required. “One of the challenges of bladder cancer is that it has a very high recurrence rate, and that may stem in part from the cancer biology itself, but also it’s the way that we cut these things out,” Liao says. “The better we can see, the better we can cut them out. The better we can cut them out, the lower the likelihood it’s going to recur.”

Using CLE for bladder cancer is in its infancy, and Liao has turned to some unconventional sources to help him determine how best to train others in the technique. First, he and his colleagues determined which features of the optical images indicated high-grade disease, low-grade disease or a benign condition and developed a training module. Then, they had novice observers — from urologists to pathologists to researchers with doctorates in nonmedical fields — undergo the training and assess 32 images. Overall, the observers demonstrated moderate agreement in cancer diagnosis and grading, comparable to pathologists in other studies. Plus, there was a twist: “The engineers did the best,” Liao says. “They know nothing about clinical medicine, but if you want

them to do pattern recognition, they’re very good at it.”

Liao and his colleagues then refined their training module and presented it to a group of crowdsourced workers: 602 people willing to watch videos of optical biopsies for 50 cents each through Amazon’s Mechanical Turk platform. “They were able to correctly diagnose cancer in 11 out of 12 cases,” says Liao. “What was cool was that they generated this much information in less than 10 hours.” In the previous study of novice observers, gathering the data had taken months.

The use of crowdsourcing to identify cancer has piqued much curiosity. “Is the idea piping images in real time while you’re in the operating room and asking the crowd to help you decide?” Liao asks. “No. That’s not the point. We’re not trying to ask a medically naive crowd to help us diagnose cancer.” The point is to learn how people come to discern the valuable information in the images — what they master easily and what they don’t — and improve training accordingly. And the methodology is by no means limited to the CLE technique, Liao says. “The bigger question is how we can use crowdsourcing more effectively as an educational tool, as a mechanism for review, training and recertification.”

Eye spy

WHEN DAVID MYUNG, MD, PHD, was a first-year ophthalmology resident at Stanford in 2012, he frequently found himself in the emergency room in the middle of the night, wishing



he could just send a picture of the eye in front of him to his supervisors. “I would see a traumatic eye injury and want to be able to share an image of it with my senior resident or my attending, but instead could only describe it over the phone in words,” says Myung, now a member of the ophthalmology faculty at the Veterans

Affairs Palo Alto Health Care System and co-director of the Ophthalmic Innovation Program at the Byers Eye Institute

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at Stanford. He tried using the camera on his iPhone, but it didn't have the right optics or lighting. "There was no way to take a good photo of the front or the back of the eye."

Meanwhile, assistant professor of ophthalmology Robert Chang, MD, had been experimenting with ways to document findings in the clinic by attaching an iPhone to a slit lamp, which uses a narrow beam of light and high-quality magnifying lenses to examine the inside of the eye. With the advent of the iPhone 4S, Chang and Myung were coming to the same conclusion: The camera now took photos of sufficient resolution to make some medical decisions. The two teamed up to develop an inexpensive, pocket-size smartphone adapter that bypassed the slit lamp, harnessing the power of the iPhone camera and standard retinal-exam lenses that practitioners already own.

They began by scrounging for parts. "I started tinkering in my living room while my kids were running around," says Myung, a former medical device engineer. "The first functioning prototype had a piece of Lego, parts from Amazon, some electrical tape and a small LED flashlight."

Chang pitched the project at the 2013 StartX Med Innovation Challenge weekend hackathon, where he recruited mechanical engineering graduate student Alexandre Jais to the project. Jais not only provided expertise; he also had a 3D printer in his dorm room, which enabled the team to rapidly refine prototypes. With seed funding from two School of Medicine programs, they developed an adjustable adapter with its own custom light source, so it could be attached to the ever-evolving sizes and shapes of smartphones "like a selfie stick," Myung says.

The device is now sold by DigiSight Technologies as the Paxos Scope, under a license from Stanford. (Myung is a design consultant to DigiSight.) To ensure patient privacy, an app transmits encrypted images through a cloud-based platform.

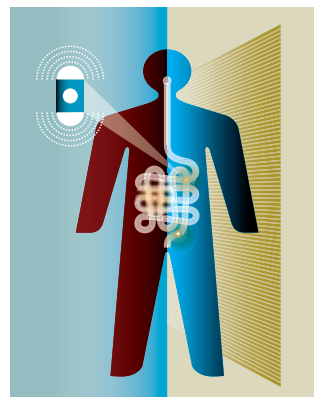
The researchers envision the device being used outside of eye clinics to determine whether referrals to ophthalmologists are warranted. Chang recently led a feasibility study in Hyderabad, India, which demonstrated that technicians could easily learn to capture high-quality eye images with the device. A study led by professor of ophthalmology Mark Blumenkranz, MD, showed that the device captures photos comparable to in-office ophthalmic exams for diabetic eye screening.

The researchers are particularly excited about the device's potential value in remote areas of the world. The ASCRS Foundation has donated 12 Paxos units through the Himalayan Cataract Project to the Tilganga Eye Centre in Kathmandu, Nepal. "In the past, ophthalmic technicians at outlying clinics hundreds of miles from Tilganga have had to decide when to refer patients,"

says Myung. "It's a full day's ride through mountainous terrain, and the trip involves paying for a bus, taking time out of work and leaving family just to be seen briefly in the tertiary eye clinic." Now, the technicians can transmit Paxos Scope photos to Tilganga, where physicians can advise them on which patients need to be seen right away — and which can wait.

Better pill to swallow

LET'S SAY YOU WANT TO KNOW what's going on inside the small intestine — maybe assess it for cancer or bleeding. A gastrointestinal endoscopy won't get down far enough, and a



colonoscopy won't get up high enough. You could use video capsule endoscopy, in which the patient swallows a pill cam, but it has only a 170-degree field of view, and takes photos just of the tissue on the surface. You could miss a tumor that way.

Stanford researchers are designing an ultrasound pill cam that would solve these problems. It would provide a 360-degree view of patients' innards, to a depth of 5 centimeters, enabling physicians to detect and stage cancers of the small intestine. If it could be convinced to dwell in the stomach for an hour, it also might be able to detect pancreatic cancer and pancreatitis.

"Optical pill cams don't know where they are," says Butrus Khuri-Yakub, PhD, professor of electrical engineering, who is leading the effort in collaboration with several Stanford colleagues, including professors of radiology Brooke Jeffrey, MD, and Eric Olcott, MD, and assistant professor of electrical engineering Amin Arbabian, PhD. "This sees the organs outside. It can presumably know where it is. Eventually, one can imagine modalities to put propulsion in it to control the location, transit and speed of transit."

The device uses a capacitive micromachined ultrasonic transducer, a miniaturized type of ultrasound developed in Khuri-Yakub's lab, adapted to wrap around a capsule that contains an integrated circuit, a transmitter, an antenna and two small batteries. It will capture data from its eight-hour journey through the gut at a rate of four frames per second, transmitting it to an external receiver worn on the waist. (The other option was to extract the pill after it was excreted, "but we don't want to get involved in this," says Gerard Touma, one of three graduate students in Khuri-Yakub's lab working on the project, along with Farah Memon and Junyi Wang. "We just want to

'THE FIRST FUNCTIONING PROTOTYPE HAD A PIECE OF LEGO, PARTS FROM AMAZON, SOME ELECTRICAL TAPE AND A SMALL LED FLASHLIGHT.'

stick to wirelessly transmitting it outside the body.”)

There are many steps before the device is ready for market — a process Khuri-Yakub estimates could take five years. After the prototype is complete, it will undergo simulations in the lab, then proceed to bench-top testing. “We’ll go to the butcher shop and buy an intestine and put a pill in it,” he says. Assuming all goes well, the researchers would proceed to animal and human testing and pursue FDA approval. Khuri-Yakub is optimistic about the latter, pointing out that this device uses components similar to approved pill cams and that ultrasound is already being used endoscopically.

“There are a lot of challenges,” Khuri-Yakub says. “It’s a major accomplishment to build a whole ultrasound system on a chip 6 millimeters by 6 millimeters. But they are not unsurmountable challenges. Hopefully we will knock them over one by one.”

Pathologists’ prognosticator

LUNG CANCER IS ONE of the most prevalent and deadly cancers worldwide, but pathologists looking at slides of tumor tissue under a microscope can’t effectively predict



how long individual patients will live. Nor is it easy for pathologists to distinguish between the two most common types of lung cancer, which has implications for patients’ treatment.

Enter the computer.

Using a machine-learning algorithm, Stanford researchers led by Michael Snyder, PhD, professor and chair of genetics, have developed a software program that can distinguish between adenocarcinoma and squamous cell carcinoma, and predict how long patients will live, with up to 85 percent accuracy.

The researchers fed data from more than 2,000 patients into the program: their slide images, the grade and stage of their tumors as determined by pathologists, and how long they lived after diagnosis. They trained the program to ex-

amine almost 10,000 characteristics of lung-tumor tissue — far more than a human eye can detect. The machine-learning algorithm then identified 240 of those characteristics that best differentiated adenocarcinoma from squamous cell carcinoma, 60 characteristics that predicted how long an adenocarcinoma patient would survive after diagnosis and 15 that predicted how long a squamous cell carcinoma patient would survive. The researchers validated their findings on data from a separate group of patients.

“It’s nice to have automated processing do this rather than have the subjectivity that pervades medicine,” Snyder says. Two pathologists assessing the same lung-cancer slide agree about 60 percent of the time. But even if they agreed more frequently, their analysis wouldn’t reveal how long a patient might live. For example, more than half of stage-1 adenocarcinoma patients die within five years of diagnosis, but 15 percent of them live more than 10 years. Having a better sense of patients’ prognosis, which the software provides, “will affect how aggressively you treat cancers,” Snyder says.

The machine-learning approach should work well for any organ tumor. “Moving into other cancers is a no-brainer,” Snyder says. The researchers will tackle ovarian cancer next, “because it is pretty deadly.”

Snyder sees the software as an important aid, but not a replacement, for human pathologists. “My own view is that it should be used every time, right off the bat,” he says. “Pathologists will still review images, but it reduces the chances of a mistake. It’s easier to confirm what the machine has done than to do it de novo.” Plus, he says, it’s cost-effective: “In the long run, it should save a lot of money. Machines are faster than people, and pathologists cost a lot more.”

Snyder would like to see automated evaluation of tumor slides deployed in the clinic within two years — most likely via companies that sell microscopes, which are interested in building the software into their platform. Combining this technique with other advances in understanding tumors at the molecular level, such as biochemical, genomic, transcriptomic and proteomic assays, will provide a “more comprehensive view of cancer,” he says. “I think that will be the future.” **SM**

— Contact Kathy Zonana at kathy@stanford.edu

LISTEN

THE STETHOSCOPE AT 200

UP

JOHN KUGLER, MD, GENTLY PLACES THE STETHOSCOPE ON THE UPPER CHEST OF THE ELDERLY, WHITE-HAIRED WOMAN WHO IS SLEEPING PEACEFULLY WHILE PROPPED UP IN BED, her head cocked to one side as a dialysis machine clicks away in the background. He spends a few seconds listening to her heart and lungs, which have a crackling sound — a sign of possible fluid in the lungs or another respiratory problem. Her breath sounds are faint.

He then reaches into his black nylon bag for his other ever-present medical tool, a portable ultrasound machine the size of a smartphone. He gingerly lifts the patient's light-green gown so as not to disturb the dialysis wires, and after massaging some gel on her belly, he applies the ultrasound probe to view her lungs on the small screen.

BY RUTHANN RICHTER PHOTOGRAPH BY MAX AGUILERA-HELLWEG



"She still has a pretty big effusion there," he tells the medical student, pointing to a spot on the screen where he sees a collection of fluid. "It's going to take some time for that fluid to be absorbed."

The ultrasound can also reveal some signs of infection or inflammation, things he can't discern by listening with the stethoscope.

"So we learn more by using the ultrasound. It's not a magic wand, but it's useful," says Kugler, a clinical assistant professor of medicine at Stanford.

The stethoscope — that time-honored symbol of the medical profession — is still the first line of diagnostic inquiry for most clinicians, but it is losing ground to imaging technologies that can yield more precise and expansive information about a patient's condition. And as its stature fades, so is the fine art of listening to the inner workings of the body.

Does the 200-year-old instrument have a place in medicine's future? It depends on whom you ask.

A 200-year history

SINCE THE TIME OF HIPPOCRATES, PHYSICIANS HAVE RELIED on sound to diagnose physical ailments: To listen to the heart beat they simply put their ear to the patient's chest. The modern-day stethoscope first came to life in 1816 when René Laennec, a reportedly shy French physician, encountered a plump young woman with an apparently diseased heart. As the story goes, he was too embarrassed to lay his ear to her ample chest, so, inspired by seeing children in a Paris park scratch at one end of a piece of wood while listening at the other, he rolled up a piece of paper into a tube. When he placed the crude device against the woman's chest, he was delighted to hear distinct heart sounds, better than any he had heard before. He soon switched to wood, designing his first, foot-long prototype in pine, with a funnel-shaped piece at the end for listening. By examining patients on autopsy, he began to correlate the sounds he heard with specific problems in the heart and lungs.

Laennec christened the device the stethoscope — Greek for looking (scope) into the chest (steth). The initial model underwent various changes, including the introduction of other materials, such as ivory, silver and brass, but the biggest advancement occurred in the 1850s with the introduction of the binaural stethoscope, with flexible rubber tubes used for listening with both ears, which dramatically reduced external noise and improved quality of sound. That basic design is

not all that different from the stethoscopes doctors dangle around their necks today, says pediatric cardiologist Daniel Bernstein, MD.

The refinement of the device ushered in the golden era of auscultation, the listening art that became an essential part of the physical exam. The stethoscope remains quite simple in design, consisting of the chestpiece, which is placed against the patient's chest, and two tubes that carry the sound from the chestpiece to each ear. One side of the chestpiece is the diaphragm, a plastic disc, while the other side is a bell, a hollow cup. When either side is placed on the chest, the body's sounds cause it to vibrate, creating acoustic pressure waves that are carried through the tubes to the listener's ears. The bell picks up low-frequency sounds, while the diaphragm picks up sounds of a higher frequency.

The stethoscope came to be commonly used for detecting heart and lung problems — like the whoosh of a heart valve that is not closing properly or the crackling sound of pneumonia. It also became valuable for detecting abnormalities in the digestive and vascular systems, such as the gurgling that may accompany an obstructed bowel.

Longtime practitioners like Bernstein recall the days of the master diagnosticians in his field of pediatric cardiology, who could discern multiple aspects of the quality of a murmur and use it to identify not only a specific cardiac anomaly but the severity of that anomaly simply by listening to the heart, refined skills that he fears are fast disappearing.

"When I was a student, you walked around the wards with your attending physician and everybody listened," says Bernstein, the Alfred Woodley Salter and Mabel Smith Salter Endowed Professor in Pediatrics. "You had 10 white coats in a room, and everybody took their turn to listen to the patient. That way everyone learned. Now there are 10 clinicians with computers on wheels, and few examine the patient. So I think those skills are at risk of being lost."

Concerned about the decline of basic bedside skills, Abraham Verghese, MD, a professor of medicine at Stanford, created the Stanford 25 — a set of 25 essential exam skills — nearly 10 years ago to help reinforce the practice and the importance of the physical exam in diagnosis, including auscultation. In addition to regular sessions for trainees, he brings clinicians to Stanford from around the country as part

of a movement to keep alive the culture of bedside medicine.

"I would emphasize that there is a ritual to the doctor-patient encounter. Patients undress and

WEB EXTRA

Stethoscope skills
in action
<http://stan.md/2dBE5vW>

'WHEN I WAS A STUDENT, YOU WALKED AROUND THE WARDS

WITH YOUR ATTENDING PHYSICIAN AND EVERYBODY LISTENED.
I THINK THOSE SKILLS ARE AT RISK OF BEING LOST.'

allow you to touch them, which in any other context would be viewed as an assault. So they give you this great privilege,” Verghese says. “There is a craft to this, and if you don’t do it with skill, patients pick up on that.”

He says the stethoscope is a key element of this ritual and can provide a “piece of the puzzle” for diagnostic purposes. “The stethoscope allows me to very quickly discern some information, and the ultrasound allows me to refine that. So they are additive. What’s important is that you use these instruments and use the exam well.”

The technology challenge

THE STEADY EROSION OF PHYSICAL EXAM SKILLS BEGAN in the 1970s with the advent of new imaging technologies, such as MRI, CT and particularly ultrasound, a painless, radiation-free tool that uses sound waves to create a moving visual of the internal organs. Clinicians now could directly view the anatomy beneath the surface with great precision. While the early ultrasound machines were bulky devices that had to be wheeled into a room, they have progressed to handheld versions with greatly improved visual clarity, produced at increasingly reduced cost.

Many physicians now routinely carry these pocket-sized devices on their rounds, while larger, portable ultrasounds, resembling a computer laptop, have become standard fare in hospital intensive care units and emergency rooms.

In the past, while clinicians might have spent 15 minutes using a stethoscope to discern the quality of a heart murmur, they may do a quick listen, then order an echocardiogram, an ultrasound of the heart, says pulmonologist and critical care specialist Ann Weinacker, MD.

“You don’t have to spend 15 minutes or so trying to figure out what you think you hear and putting patients through various maneuvers,” says Weinacker, a professor of medicine. “You can just put an ultrasound on their chest and find out. And there are measurements you can get with an ultrasound that you can’t get with a physical exam — or not very easily.”

For instance, she says nowadays it’s possible to do an ultrasound of the lungs, something not commonly practiced just five years ago. Among other things, the test can show the severity of a collapsed lung — something that may not always be discernible by listening alone. It can also show the extent of fluid around the internal organs — a possible sign of heart failure or other problem — and be used day after day to measure fluid changes without exposing patients to ionizing radiation, as an X-ray or CT scan would.

“The truth is if you use technology well, you can get a lot more information,” says Weinacker, who routinely uses it in the intensive care unit to assess a patient’s status.

Jagat Narula, MD, PhD, professor and chair of cardiovascular medicine at Icahn School of Medicine at Mount Sinai, is among those who believe the stethoscope has become a “vintage accoutrement,” rightfully supplanted by swiftly advancing imaging technology.

“It has outlived its time,” says Narula. “Now I can clearly look into the chest, and not only the chest, the whole body. ... You have a much superior thing in your hand,” he says of the ultrasound. “Why would you not use it? The stethoscope is obsolete. We should write an obituary for it.”

Just listen

YET THE STETHOSCOPE CONTINUES TO INSPIRE DEVOTEES in part because it sometimes works better than anything else, at least in their hands — and ears. Certain problems that would not be detected by ultrasound can be discerned by listening, such as the wheezing of a patient with asthma or with chronic obstructive pulmonary disease, Kugler says. Listening also may point the clinician down a path to diagnosis, providing guidance, for instance, on where to direct the ultrasound probe to confirm a suspected problem.

Bernstein says clinicians can overlook serious conditions in young patients if they fail to do a thorough clinical exam,

C O N T I N U E S O N P A G E 49





DIAGNOSTICS

The power and limits of zeroing in

‘AND YET, YOU TRY’

A FATHER'S QUEST TO SAVE HIS SON

A speedboat cut across Lake Tahoe on a sunny day in October 2012.

With two of his closest friends at his side, 14-year-old Milan Gambhir rode an inflated raft tethered to the back of the boat. The boys bounded over each wave, laughing as the water splashed back over them. “Half the fun was falling off into the cool water,” Milan’s friend Christopher “Kiki” Fann remembers. But the boat was going so fast that when Milan lost his grip on the raft’s handle, his head hit the water hard. “He just went flying,” Fann says. Instead of cushioning Milan’s landing, the water hit him like a wall.

“When he got back in the boat we were asking him questions, trying to tell if he was OK or not,” says Fann. “He had trouble with some of them, which was disconcerting, because a guy who was as smart and bright as he was suddenly couldn’t say the alphabet backwards.” Also on the boat

BY JULIE GREICIUS

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

SAM AND ARUNA GAMBHIR'S ONLY CHILD, MILAN, DIED AT 16 OF GLIOBLASTOMA MULTIFORME — THE DEADLY BRAIN TUMOR HIS FATHER, A SPECIALIST IN EARLY CANCER DETECTION, HAD BEEN INVESTIGATING IN HIS LAB.

was Fann's mother, a physician, who determined that Milan had a slight concussion. She drove him to the local emergency room. There, doctors suggested a CT scan — a method of imaging that combines multiple X-rays to produce a single three-dimensional image of the inside of the body. She telephoned Milan's parents at home in Portola Valley to get their permission for the scan.

Milan's father, Sanjiv Gambhir, MD, PhD, who goes by the name Sam, is also a physician, an expert in diagnostic imaging who chairs the Stanford Department of Radiology and also directs Stanford's Molecular Imaging Program. He and Milan's mother, Aruna Gambhir, CEO of a small San Francisco biotechnology startup, agreed that the scan was necessary to make sure their only child didn't have a hidden brain bleed or skull injury. "Let's play it safe," Sam Gambhir recalls thinking.

Milan's CT scan was clear. His father and Milan's aunt, Sangeeta Gambhir, MD, a radiologist in San Francisco, scrutinized the image later and saw that not only was there no injury or bleed, there were no problems of any kind. Milan's brain looked healthy.

in the band room with me and our friend Jose," says Fann. "He'd show us chords, notes, riffs and stuff." On weekends Milan would have friends over for video games, pool parties and some Airsoft rifle target practice, which left a speckling of telltale pockmarks on the metal rim of the chimney far above the pool.

The preceding summer, Milan had worked alongside his father in the Canary Center at Stanford for Early Cancer Detection, where Sam Gambhir is the director. In 2011, Gambhir had received a five-year, \$10 million grant from the Ben and Catherine Ivy Foundation to use molecular imaging to improve the detection and management of one of the deadliest brain tumors, glioblastoma multiforme. "Milan was learning about basic techniques in keeping a lab notebook, how chemical solutions are made, that sort of thing," says Sam Gambhir. Laboratory regulations prevented Milan from working with any cell specimens, but he was still excited to be there.

Milan's experience in his father's lab helped pave the way, midway through his freshman year, for a position in the re-

HE AND ARUNA, SIDE BY SIDE WITH MILAN,

TOOK IN THE NEWS AND DID THEIR BEST TO REMAIN CALM.

'I ACTUALLY DON'T KNOW HOW THEY DID IT.'

Shreyas Vasanawala

But beneath Milan's apparent vitality was a vulnerability he'd carried since conception, one so microscopic that a CT scan could not detect it. Perhaps radiation from the CT scan itself set in motion cellular changes that were the beginning of something much worse than a concussion. A tumor was developing in Milan's brain, one so aggressive that even his father — a renowned expert in early cancer detection — could neither anticipate nor defeat it. Nine months later, the CT scan Milan had in Tahoe had become a time stamp, marking the last confirmed date his brain was seemingly healthy.

BACK AT HOME, MILAN CONTINUED IMMERSING HIMSELF IN HIS freshman year at Bellarmine Preparatory School in San Jose. He participated in speech and debate, jazz band and twice-a-week hapkido martial art classes, where he was on track to earn his black belt. Already a piano player and percussionist, Milan had taught himself to play guitar in middle school from YouTube tutorials, becoming skilled enough to teach other kids. "Each day at lunch and break time he'd jam

search lab of Adam de la Zerda, PhD, assistant professor of structural biology and of electrical engineering at Stanford.

De la Zerda accepts only about one in a hundred high school students who apply to work in his lab. "Most of them want the recommendation letter for college, and their parents are pushing them," he explains. "But once they get to the lab they couldn't care less about research. They hate it. They'd much rather spend their time outside playing soccer." Milan was happy to do both.

His first assignment was a statistical simulation of how photons proliferate in the human body. "Now, in order to do a really good job there, you need to know calculus, which of course being a 14-year-old kid he did not know at the time," de la Zerda would say later. "So there I found myself explaining to him what integrals and double integrals are. Then Milan looks at me and asks, 'But wait — we live in a three-dimensional space, so we probably would want to know how many photons we have in a full volume.' So I asked him, 'How would you calculate it?' And there he was; he jumped at my whiteboard and started writing triple integrals on it, as though it just came to him intuitively."

Milan worked on the project for about five months. When summer came, he started driving to work with his father and working full time in de la Zerda's lab. In mid-July 2013, Milan came to de la Zerda with a new idea.

Milan explained: His mother had recovered from two instances of breast cancer — the first when Milan was a year old and she was 37, then again 10 years later — and her father, Milan's grandfather, had died from esophageal cancer in his 50s. As a cancer survivor, Aruna was advised to return for frequent check-ups. To make life easier for survivors like his mom, Milan wanted to develop a comfortable, low-cost ultrasonic wristband device that could diagnose a recurrence of cancer through microbubbles that would attach to circulating tumor cells in the bloodstream.

He took de la Zerda through his plan: "He was talking about using antibodies to detect circulating tumor cells. He was going to use this small ultrasound device, and had been looking at several companies that sell them. He was convinced there was one that could be miniaturized. He had a really good plan."

"Milan was always up early, excited about going to work," Aruna Gambhir says. "I never had to wake him." But just two days after he'd told de la Zerda about his idea, and only a few days before his 15th birthday, Aruna had trouble getting him up. "It was very unusual," she says. Later that morning, walking through the parking lot with his father, he dropped his mug. His father didn't think much of it — people drop things all the time — until later that evening. Aruna was home with Milan, eating dinner and watching television, when Milan suddenly started talking gibberish. "I said, 'Stop it, Milan,'" Aruna recalls. "But he kept going, and spilled his milk. A minute or two later, when it stopped, I asked him what was going on."

"I couldn't control it," Milan told her. "I don't know what's going on."

Milan's parents drove him to the Stanford Health Care emergency department. On the way in, Sam Gambhir called his colleague Shreyas Vasanawala, MD, PhD, associate professor of pediatric radiology, who met them there.

"There was a concern that he might be having a stroke," Vasanawala says. "We started with a CT scan, which showed that Milan had some bleeding in his brain. From that, Sam already knew there was a serious situation. The next step

was to try to get a better understanding of what might be causing the bleeding. For that, we did an MRI."

"It was probably 3 in the morning when we got the diagnosis," Aruna says. "Sanjiv saw the scan as it was coming out."

Doctors confirmed what Milan's father could already see: Milan had a brain tumor measuring about 2½ inches. Worse, the tumor was likely a glioblastoma multiforme, the very tumor Sam Gambhir had been investigating in his lab. Gambhir knew GBM all too well. A type of glioma tumor, arising from the brain's glia cells, GBM is one of the most aggressive cancers, commonly taking the lives of patients just 14 months after diagnosis. Fewer than 5 percent survive for more than

five years. For Gambhir, the coincidence was brutal.

He and Aruna, side by side with Milan, took in the news and did their best to remain calm. "I actually don't know how they did it," says Vasanawala. "They must have wanted to do that for Milan, too. And even Milan, over the entire course of things, was an exceptionally composed and mature person. I still don't understand how somebody that young could be so aware and mature."

"It was good that I didn't know what lay ahead. I was clueless," Aruna says. "My beautiful son. The worst thing he ever had in his life before then was a cold. One time he had the flu, maybe a knee scrape but nothing beyond these tiny little things. Nothing at all. I said, it has to be an infection or something. It cannot be this. Not the worst-case scenario."



MILAN GAMBHIR DOVE INTO HIS WORK IN ADAM DE LA ZERDA'S LAB, INCLUDING PLAYING SPORTS AT A LAB PICNIC IN JULY 2013. "HE WAS FULL-ON, FULL THROTTLE," SAYS HIS MOTHER, ARUNA. "THAT'S THE KIND OF KID HE WAS."

Aruna pinned her hopes on her husband. “We have Sanjiv here, and he can get us access to everything,” she remembers thinking. “We’re going to be fine. ‘Don’t worry, Milan. Everything’s going to be OK.’ But Sanjiv knew. That was the problem, that he knew. Sanjiv was the one who needed to be sedated.”

Sam Gambhir's role as a specialist at Stanford Medicine, his work on GBM and his access to a worldwide network of medical experts were all sources of hope for his family. Yet that hope eluded Gambhir himself.

“From the very beginning, based on what I knew about this particular disease, I knew the chances of beating it were so small, especially because by the time Milan’s GBM was caught it was already quite spread,” recalls Gambhir. “It is more frustrating and anxiety-provoking when you know what the outcomes of patients with GBM are. And you feel helpless to do anything. And yet, you try.”

Immediately, he began communicating with colleagues at Stanford and beyond. One of his first calls was to Parag Mallick, PhD, assistant professor of radiology at Stanford and director of a lab within the Canary Center that focuses on precision diagnostics. Mallick had been personally recruited to the Canary Center in 2011 by Gambhir, who trusted his expertise in the study of therapeutic response, and in predicting which drug is likely to work on which patient.

Mallick was home when he received Gambhir's call. "He started off very rational," Mallick recalls. "He said, 'I hope I'm not bothering you.' I said, 'No, what's up?'"

Gambhir relayed the details of Milan's diagnosis, and was soon speaking through tears. "He was trying to figure out what we had to do from day one to make sure that we gave

Milan the best chance, and asking if I could help."

“We have to save him,” Gambhir said.

“He knew that molecular analysis would be important,” says Mallick, referring to the process of profiling the tumor’s DNA, RNA and protein. “So he wanted

to know what we could do, what we should do. He also recognized that he wasn't in a state to drive the process himself — he was, understandably, hugely emotional and needed to focus on being with his family. At the same time, he knew the surgery would be happening soon, and that the resected tumor tissue needed to be handled in a way that could be scientifically and clinically actionable — that it must be saved, and saved in the right way. Because you only have one shot. If you don't collect it right and store it right, there is no hope for precision medicine."

Precision medicine — care tailored to a patient's unique molecular profile — is the vanguard of cancer treatment. Specific molecular markers of an individual's tumor cells can be used to identify the most beneficial therapeutic approaches. To obtain a reliable genome se-

quence of Milan's DNA, to develop testable cell models and to enroll Milan in clinical trials all depended on his tumor tissue being carefully resected and handled properly. "There was a lot of frenzied planning prior to the surgery," says Mallick. "All in just a few days."

Another concern was removing as much of Milan's tumor as possible without harming his brain. "Even though you do surgery," says Sam Gambhir, "there's just no way to catch the cells that have already spread to other parts of the brain. And you know those will be the ones that will eventually come back and lead to death."



EVEN DURING TREATMENT, MILAN ENTERED HIS
CONCEPT FOR AN ULTRASONIC WRISTBAND THAT DETECTS
CANCER RECURRENCE IN SCIENCE COMPETITIONS.
AFTER A NEW TUMOR WAS FOUND IN HIS BRAIN, FRIENDS
BOUGHT AND SIGNED A GUITAR FOR HIM.

THE MORNING AFTER HIS SON'S DIAGNOSIS, SAM GAMBHIR, who still hadn't slept, stopped by to see Milan's oncologist, Paul Fisher, MD, chief of the division of child neurology. "He came into my office and just cried for about half an hour," Fisher says. Fisher, who has two decades of experience treating patients with brain cancers including glioblastoma, could offer little hope. Even the most advanced treatments ultimately fail against GBM. "Sam was taken aback by this chasm between the scientific — the basic-science world — and the clinical world, what we're able to do for patients. I think it was the first time in his life that science disappointed him. You commit your life and work to science, and then, it's almost like religion: How could you fail me now?"

But Gambhir was still determined to do whatever he could. "Sam obviously wanted progress for Milan's sake," Fisher says, "but he also knew that any progress that helped his son would also be for the greater good."

Milan spent a few days in the hospital following his diagnosis, and was then given clearance to celebrate his 15th birthday at home. "A bunch of his friends came over," says Aruna Gambhir. "Everyone knew something was wrong and he was going to have a surgery the following Monday. But at least we had him home for the weekend."

Surgeon Michael Edwards, MD, professor of pediatric neurosurgery at Lucile Packard Children's Hospital Stanford, led the surgery on July 22 to remove Milan's frontal lobe mass, sending the resected tissue to neuropathology

Monje and her team sent Milan's de-identified cultures to about 30 research labs around the world, as well as several labs right on the Stanford campus. "His cells are now in every country that does high-impact research on pediatric high-grade gliomas," she says. "In Canada, Spain, England, China, all over the world."

Three days after Milan's surgery, Sam Gambhir emailed James Ford, MD, professor of oncology and of genetics and director of the Stanford Clinical Cancer Genetics Program. He asked Ford about the likelihood of genetic or hereditary conditions playing a role in his son's glioblastoma diagnosis. "We talked about his wife's history of breast cancer," Ford says. "Her father also had cancer, and now her son had contracted glioblastoma at a young age. I suggested we start by testing for Li-Fraumeni syndrome."

Li-Fraumeni syndrome — named for Frederick Pei Li and Joseph F. Fraumeni Jr., the American physicians who first identified it in 1969 — is a rare, inherited condition that dramatically increases the risk of many types of cancer. Since 1969, approximately 500 families worldwide have been reported to have the condition, though its actual prevalence is unknown. In his discussion with Gambhir, Ford heard the indicators that tipped him off: a family with multiple generations of cancer diagnoses, including childhood brain cancer and breast cancer in a young woman.

Most patients with Li-Fraumeni are more susceptible to cancers because of a mutation in what Ford calls the most important gene in all cancers: the gene for tumor protein 53,

'I THINK IT WAS THE FIRST TIME IN HIS LIFE THAT

SCIENCE DISAPPOINTED HIM. YOU COMMIT YOUR LIFE AND WORK TO SCIENCE, AND THEN, IT'S ALMOST LIKE RELIGION: HOW COULD YOU FAIL ME NOW?'

Paul Fisher

where sections could be made to release for research. From there, Milan's cancer cells were personally handled by Michelle Monje, MD, PhD, an assistant professor of neurology at Stanford who was the first to culture brainstem glioma cells from a deadly childhood tumor called diffuse intrinsic pontine glioma. Monje carefully cultured Milan's cancer cells so they could be grown, de-identified, and distributed worldwide for research.

"These types of cell cultures are rare," says Monje. "Few labs successfully make these cultures, and even fewer distribute them widely for use. Yet they're very important for understanding the fundamental biology of these tumors and developing more effective therapies."

or p53. When it's functioning properly, p53 is indispensable, playing several roles, including supervising our cells' growth and DNA replication and, when DNA is damaged, activating repair proteins. If the cell fails to repair, p53 can either halt the cell's growth or initiate its death. DNA damage is commonly caused by things like overexposure to sunlight or other forms of radiation, smoking, toxins in food or pesticides, or simply from aging and normal metabolism, but if that damage doesn't develop into cancer, it's because p53 is on the job.

Most patients with Li-Fraumeni syndrome have inherited a mutation in the p53 gene that prevents it from performing its lifesaving role in routine DNA repair. As a result, cells

with damaged DNA grow freely, resulting in additional genetic mutations and allowing a variety of cancers to proliferate, particularly sarcomas and cancers of the breast, brain and adrenal glands. These account for about 80 percent of all cancers in patients with Li-Fraumeni, many of which are treatable when caught early. Lifetime cancer risk for men with the syndrome is up to 85 percent, and nearly 100 percent for women, largely due to the increased likelihood of breast cancer.

"It's very different than, for example, inherited BRCA1 or 2 gene mutations that increase a woman's risk for breast and ovarian cancer," says Ford. "Those are bad enough, but at least you know what tissues to focus screening on. In Li-Fraumeni syndrome, you're at risk for cancer anywhere in the body."

Most people haven't heard of Li-Fraumeni syndrome, because so few people are diagnosed with it. "At Stanford, our genetic counselors and our clinic saw over 1,500 patients last year for genetic counseling and genetic testing for cancer families," Ford explains. "Of those, maybe 10 were considered for Li-Fraumeni." Even this, he says, is a big increase from five to 10 years ago: "With more comprehensive genetic testing, we're finding these families more often."

About a week after his glioblastoma diagnosis, and after genetic counseling, Milan was tested for Li-Fraumeni syndrome. A few weeks later, so was his mother. Both tested positive for the inherited p53 mutation.

The Li-Fraumeni diagnosis helped Aruna Gambhir understand her family medical history. "I could say, 'Oh, I see. That's what's been wrong,'" she recalls. "With my dad dying, and then me getting it, and then Milan getting sick, there was some reason for it. But there was no relief. Milan got the worst of the worst cancer he could have gotten."

their chances of cancer. We will never know for sure."

For those who know they have Li-Fraumeni syndrome, regular monitoring is crucial to detect cancer early and at a potentially curable stage. But because of patients' heightened vulnerability to radiation exposure, the method of diagnostic monitoring is just as important as the frequency. Ford and his team use only annual whole-body MRI scans. Magnetic resonance imaging uses strong magnetic fields and radio waves to create images, making it a safer option than CT scans and X-rays.

"If you know the risk, and know which cancers you're at risk for, and at what age, often you can detect them early enough where you can deal with them and often cure them," says Ford. And that is the painful irony of Milan's diagnosis, he adds, "because of course Sam's entire career is focused on this, and that's what the Canary Center is dedicated to."

SAM GAMBHIR'S LAB AND OTHER LABS IN THE CANARY CENTER at Stanford are making advances in early detection of a variety of cancers, from blood-based "in vitro" diagnostics that sample blood, urine, stool, saliva, tears or breath to newly identified biomarkers — molecules that are early, telltale signs of illness — as well as devices that can spot them.

"We've been developing newer imaging techniques like photoacoustics where light goes into your body, interacts with the tumor and then produces sound that we can detect. Light in, sound out," Gambhir says. "And radio-frequency acoustics, where we send radio-frequency waves in, they interact with the tumor, and send sound out." Stanford physicians performed the world's first prostate cancer imaging with photoacoustics in 2015. And the Gambhir lab is preparing to test devices that conduct imaging while people are go-

'WITH MY DAD DYING, AND THEN ME GETTING IT, AND THEN

MILAN GETTING SICK, THERE WAS SOME REASON FOR IT. BUT THERE WAS NO RELIEF. MILAN GOT THE WORST OF THE WORST CANCER HE COULD HAVE GOTTEN.'

Aruna Gambhir

The deeper diagnosis of Li-Fraumeni also helped Milan's parents understand how their son could be diagnosed with an advanced brain tumor just nine months after having had a clear CT scan. "It's possible that he developed this tumor from the CT scan radiation," says Sam Gambhir. "When you carry this p53 mutation, you are much more susceptible to radiation. In a normal person, a CT scan wouldn't be a big deal. But in someone with this mutation, it likely increases

ing about their regular lives: a "smart bra" that continuously images breast tissue and a "smart toilet" that looks for molecules in stool and urine that could be biomarkers of colorectal cancer or prostate cancer.

"We think the best populations to test these on first are high-risk for the disease, and Li-Fraumeni is one of those," says Gambhir. "Also patients who already have the disease, in whom we're looking for recurrence." These methods show

promise for early detection of a variety of cancers, but glioblastoma multiforme is not one of them. “It’s more difficult because it’s a rare tumor, so it’s harder to get blood samples from patients. But also because of the blood-brain barrier. Things that are being shed by the tumor in the brain aren’t necessarily available in the blood or urine. So it’s important to understand that glioblastoma is likely one of the last tumors we would try to do early detection for. It’s just not a tractable problem right now.”

Ford emphasizes the importance of counseling Li-Fraumeni patients and families on the stress of living with their heightened cancer risk, as well as helping growing families understand their reproductive options. When one parent has Li-Fraumeni syndrome, choosing to adopt children is one way to avoid the 50 percent possibility of passing the gene on to their child. Other families opt for in vitro fertilization so they can select embryos that do not contain the mutation. When genetic test results confirm Li-Fraumeni in the midst of a pregnancy, some parents choose to terminate.

“It raises all kinds of interesting paradoxes about what you do with genetic mutations like this that aren’t lethal at the time you’re born, but carry a bad prognosis,” says Sam Gambhir. “Some family members have lived almost to the age of 60. It’s very uncertain. If we had known this diagnosis before Milan was born, would we have chosen to abort? If so, he would have never existed, and then we would never have had the 16 years we did have with him. Even having those 16 years is better than having no years.”

Since the day of Milan’s diagnosis, Sam Gambhir had been “madly searching, literally working around the clock trying to find something that could slow down this tumor,” he says.

“Sam was emotionally overwhelmed for a while,” recalls Mallick. “He was still effective and reaching out across the globe to get answers, but you definitely felt this sense of helplessness and desperation — something you never feel from

Sam.” But then, one day, he just snapped out of it. “I remember him saying to me something along the lines of, ‘I feel more awake, aware, plugged in and on top of things than I have ever in my career.’ And so there was this radical transformation where he went from being in shock and dismay to taking charge. It was remarkable, seeing him click back over into problem-solving scientist mode.”

Gambhir’s widespread search led him to explore some unorthodox therapeutics. At a medical conference a few months after Milan’s diagnosis, Gambhir noticed a poster identifying a natural plant extract as a potential anti-cancer agent. The plant, called ashwaganda, had been known for thousands of years in Ayurveda medicine — a natural healing system originating in India about 5,000 years ago — to have some unusual properties against many diseases. “I said, well, this is a long shot, but why don’t we test it?” Gambhir says.

After his surgery, Milan had radiation therapy for about seven weeks, which was necessary to keep his tumor in check, even though it might also cause further cell damage. “He had braces,” says Aruna Gambhir, “and

had to go to the orthodontist to get them removed so that they could do the radiation therapy.” For analysis of Milan’s image findings and guidance on his therapy, Sam Gambhir relied on his colleagues Sarah Donaldson, MD, professor of radiation oncology, and professors of radiology Nancy Fischbein, MD, and Tarik Massoud, MD, PhD.

Milan was well enough to return to school for his sophomore year, and the family did its best to return to a sense of normalcy. Even before he went back to school, Milan was determined to keep up with the activities he’d started before he got sick. “Not only did he continue working in the lab,” says Aruna, “but he was doing an accelerated precalculus class so that he would qualify to take advanced-placement calculus when he went back to school in the fall as a sophomore. We told him to



MILAN'S TUMOR CELLS ARE USED IN GLIOBLASTOMA RESEARCH ALL OVER THE WORLD. HIS FATHER'S LAB WILL OVERSEE THE DEVELOPMENT OF THE CANCER-DETECTION DEVICE HE CONCEIVED.

CONTINUES ON PAGE 50

GOOD SPORT

Travis Tygart knows there's no simple way
to stop doping in sports.

He's run the
U.S. Anti-Doping Agency for more
than a decade and was on the front lines during
the cycling doping scandal that
ensnarled mega-abuser Lance Armstrong.

Cleaning up sports, Tygart emphasizes, is a long-term fight that demands the will to effect cultural change.

Perhaps a scientific breakthrough in testing would alter the landscape, but it's the everyday slog on behalf of clean athletes that fuels Tygart's passion and the mission of USADA.

Russia's state-sponsored doping that led to the banning of more than 100 athletes from the 2016 Summer Olympics in Rio is the most recent news to cause one to ponder: Is the goal of clean sports even possible? Executive editor Paul Costello got Tygart's take on what's next in the struggle to level the playing field.

COSTELLO: What are the major lessons learned from the Rio Olympics about global anti-doping efforts?

TYGART: Obviously, the state- and sport-run doping system in Russia was exposed. I think the covering up of positive tests for athletes and sending those athletes to major international competitions opened the eyes of a lot of people to the lengths that some will go in order to win. That it was exposed shows the tremendous advancement in the effort to clean up sports. I don't think we would have gotten to the point of exposing a government-run, sport-run system that's been in place for decades but for major steps that have been made in the anti-doping fight over the last 10 to 15 years.

COSTELLO: One former anti-doping official said, "Anti-doping is all about trust. Trusting your competitors and trusting the drug testers." What happens when that trust is eroded? How do athletes regain that trust?

TYGART: Listen. It is about trust. Athletes have to trust that those in the position of authority to protect their rights are doing everything they can — obviously within the law, within the rules — to ensure that their rights are protected. It's the greatest injustice in sport when athletes or teams who are playing by the rules get robbed of their accomplishments, their successes or their victories because someone cheats them. We're here to fight as hard as we possibly can. And the answer for athletes is not to throw in the towel and join the cheaters. The answer is also not to quit the sport. The answer is to double down on their efforts to win the right way, to be outspoken about the need for all countries to be held to the highest standards, and really demand that sport authorities and leaders are held to account that cheating doesn't happen.

COSTELLO: What are the ramifications of cheating?

TYGART: Doping just inherently undermines the very value of sport. If it becomes a win-at-all-costs, stop-at-nothing endeavor, then it loses its value and all the good that flows from that — hard work, teamwork, dedication to a common goal and how to be tenacious in accomplishing that goal. Those are the very things that make people successful in relationships, as well as in careers and in life.

COSTELLO: Do you understand the mind of a doper?

TYGART: Well, we hear all the pressures that they're under, and different influences they face, whether it's coaches, or supplement marketing, or team pressure, or the pressure to maintain a family and to provide for themselves.

DIAGNOSTICS

The power and limits of zeroing in



COSTELLO: Why is it so difficult to clean up sports?

TYGART: The will. I think we have to decide: Is this a fight we're willing to win for clean athletes? Are we willing to let clean athletes truly compete clean? Sport frequently wants just the best entertainment as long as there's no bad news, even if it's an unfair event. Human nature is such that people are always going to look for some advantage if they think they can get away with it, and the benefits of getting away with it are sometimes so high. The culture of sports is much better today than it was during the cycling cheating. We've just got to ensure that progress continues to be made and hopefully one day we truly return the playing field to clean athletes.

COSTELLO: As far as diagnostics and testing, have there been significant leaps forward?

TYGART: I wouldn't limit it just to testing, because testing is just one aspect of the overall program. The testing, the investigations and the results management process have advanced significantly since 2000. You have to look at pre-2000 to really get a sense of the progress that has been made. In 1999, you had myriad rules and regulations. There was no uniform list, so athletes in different sports were subject to testing for certain substances that others in different sports weren't subjected to. Some countries had policies; others had no policies. It was just a mess. Some called it the wild, wild West. Since then,

the world has come together. Close to 400 sports have signed the World Anti-Doping Code, which unifies and harmonizes anti-doping policies across all countries that compete in the Olympics. A uniform list, uniform sanctions, uniform collection process — all of those are material to having an effective program.

COSTELLO: What's a realistic goal as far as eliminating doping?

TYGART: One athlete getting robbed of their dream is an injustice. We have to fight as if we are going to win this for all clean athletes.

COSTELLO: You know there are some who believe that the anti-doping effort has failed on many counts. They feel it's time to drop the rules and legalize doping.

TYGART: If you get rid of the rules it's not going to be a level playing field. Certain people just by their natural physiological reaction to the drugs respond in different ways. If the drugs work and the athlete responds to them, these are game-changing responses. If you have a body that can maximize the use of drugs like EPO, you'll win or be at the front end of the competition. You will also have an arms race. There would have to be set therapeutic-use allowances, and competitive athletes would just go above that if they thought more of the drug would do them some good. You would have to draw the line somewhere, because some athletes are going to push themselves to the brink of death. We saw that in cycling in the late '90s: a rash of young cyclists who were dying of cardiac arrest because they were using too much EPO. Perhaps most importantly, human competition is what we want out

of sport. True athletic competition, as we know it and value it. I'm the father of three young kids who play sports. I'd like to see them get and learn life lessons through sports. If we allow doping at the elite level, it's just a matter of time before every kid in this country is having to seriously contemplate — to get a scholarship or make the varsity team or even make the junior varsity team or the eighth-grade soccer team — which of these drugs am I going to inject in myself?

COSTELLO: I guess you're saying, where does it stop?

TYGART: Yeah. It just trickles down all the way. There is no stopping point. **SM**

This interview was condensed and edited by Paul Costello.

WEB EXTRAS

CME Partnership

USADA and Stanford Medicine have teamed up to provide HealthPro Advantage: Anti-Doping Education, a free online continuing medical education course for physicians who treat athletes. It is available at <http://stan.md/2fdyRdb>

Podcast

Hear the conversation between Paul Costello and Travis Tygart at <http://stan.md/2cNi7GM>

BREAKING



AFTER KIM AND ZACH NYE'S SON, COLTON, BACK RIGHT, WAS BORN WITH THE SAME SEIZURE DISORDER AS HIS SISTER TESSA, LEFT, WITH UNAFFECTED SIBLINGS LILY, RIGHT, AND MAGGIE, FRONT, DOCTORS WERE ABLE TO PINPOINT THE GENETIC CAUSE.



THE CODE

INSIDE THE SEARCH FOR A DIAGNOSIS

DIAGNOSTICS

The power and limits of zeroing in

When Colton Nye was born in August 2013, his parents saw his arrival as “our cherry on top.”

Kim and Zach Nye had hoped for a large family and were excited to welcome a baby brother for their three daughters. But there was one shadow on their anticipation: They worried Colton might be born with the same severe form of epilepsy as his oldest sister, Tessa.

During Kim’s pregnancy with Colton, the family tried to take reassurance in the fact that extensive testing had not uncovered a genetic cause for Tessa’s seizures. Besides, their two middle daughters were perfectly well. Colton would probably be fine.

“I remember my obstetrician delivering Colton and saying, ‘This is a *healthy* baby boy! Congratulations!’” says Kim. “We went back to our room, and it felt like, ‘Life is perfect!’ Then everything just crumbled.”

When he was about 12 hours old, Colton began turning blue around the mouth and struggling to nurse. The same thing had happened the day Tessa was born. Doctors soon confirmed that Colton was having seizures.

Kim and Zach felt pangs of fear as they remembered how scary Tessa’s early years had been. Her epilepsy was so bad that she had 40 to 50 ambulance trips before the age of 3. She had physical and developmental delays, and didn’t walk until she was almost 5, when doctors finally hit on a combination of medications that prevented her worst seizures. Before that, she sometimes required a medically

BY ERIN DIGITALE

PHOTOGRAPHY

BY TIMOTHY ARCHIBALD

induced coma to quell them.

“My child was nearly dying in our arms on a regular basis and nobody could make it stop or tell us why it was happening,” Kim says. “It felt like there had to be an answer.”

With two complete sets of genetic data to compare — Tessa’s and Colton’s — the family’s doctors at Lucile Packard Children’s Hospital Stanford soon collaborated with colleagues elsewhere to identify a single-gene mutation that causes both children’s seizures. And yet the Nyes couldn’t help but wonder why they hadn’t gotten an answer earlier. Tessa had been evaluated by dozens of physicians around the country and had even seen an expert team at the National Institutes of Health without turning up a culprit gene. Did finding a single genetic error have to be so harrowing?

Needle, meet haystack

Although Tessa was only 9 when her baby brother arrived, the two children began their lives in different eras of genetic medicine. Tessa’s December 2003 birth came just a few months after the completion of the Human Genome Project, the first sequence of all 3 billion base pairs of human DNA. Getting that first reference-quality copy of the genome took 12 years and cost more than \$500 million. By 2013, when Colton was born, individual whole-exome sequences that catalog all the protein-coding parts of the DNA cost around \$9,000, took two to four months, and were beginning to be used to help patients and to discover new genetic diseases. Today it’s even easier and cheaper to sequence one human genome, and our ability to interpret what we find is growing fast: Each year, a cause is found for about 250 previously unexplained monogenic diseases, those linked to single-gene errors.



GILL BEJERANO DEVELOPS COMPUTATIONAL TOOLS THAT HELP IDENTIFY GENETIC CULPRITS. “THE GENOME IS ULTIMATELY A PROGRAMMING LANGUAGE,” HE SAYS.

Yet diagnosing single-gene diseases remains a chancy and surprisingly low-tech process, requiring 20 to 40 hours of manual analysis per patient by expert geneticists after gene sequencing is complete. Even with all that work, 75 percent of patients aren’t diagnosed the first time their DNA is analyzed, revealing how much we still don’t know about the human genetic code. Experts say we’re facing two big problems: We need automated ways to mine genetic data and identify deleterious genetic changes that are already known to science, and we need better ways to find unknown gene-disease connections. Researchers are making progress on both fronts.

“At some level, the monogenic diseases are really simple because there’s a single point of failure in the code,” says Gill Bejerano, PhD, associate professor of developmental biology, of computer science and of pediatrics at Stanford. “If we had access to every gene sequence and a bit of medical information for everyone in the world, we would be able to flush all of them out; the genome would just scream, ‘Look here, figure it out!’”

From a computational point of view, finding a one-gene error is much simpler than determining all the ways genes can influence each other, be modified by regulating molecules or interact with the environment to cause disease. Monogenic diseases can stem from a change as small as a single-letter error in the genetic code, where one nucleic acid in the DNA is swapped for another. The reason it’s so time-consuming to understand these changes is that there are so many of them. Each of us has about 10,000 single-letter errors in the protein-coding parts of our genes. Common errors — those seen frequently in healthy people — are unlikely to cause rare diseases, but even after winnowing them out, there are about 300 genetic changes left per patient for experts to evaluate in their search for the true answer.

With gene and health data from enough people, Bejerano believes the right mathematical algorithms could shake all

the truths out. “I wish we had millions of human genome sequences today,” he says.

Today, however, we’re mostly still stuck with manual analysis. Geneticists scour patients’ data for rare mutations known to cause disease, and for plausible suspects. When possible, children’s genes are also compared with their parents’ sequences, which can give extra clues. The process works best for kids whose diagnoses have already been discovered in someone else.

When it comes to identifying a new disease, successful diagnosis often hinges on serendipitous links between patients, whether they’re siblings like Tessa and Colton or strangers who find each other another way. In some cases, families of children with the same mutation have found each other on the internet and asked their doctors to confirm that the kids share the same symptoms and genetic changes.

The Undiagnosed Diseases Network

One early milestone in diagnosing rare, one-gene diseases came in May 2008, when a small team at the National Institutes of Health in Bethesda, Maryland, launched the NIH Undiagnosed Diseases Program. In its first six years, 3,100 children and adults with undiagnosed medical conditions applied to be evaluated by the program, and 750 were accepted; one of them was Tessa Nye. Unfortunately, her analysis didn’t provide her family an answer.

can offer whole-genome sequencing and other diagnostic tests that aren’t yet widely available or covered by insurance. (Once the UDN accepts a patient, the NIH covers the cost of his or her evaluation.) Stanford’s human immune monitoring core, for example, is beginning to yield information about previously unknown autoimmune and antibody-based diseases that can’t be detected by looking at the genes. Stanford researchers have developed ways to characterize the activity of certain categories of immune cells — as well as profiling patients’ cytokines and antibodies — to give strong clues about such diagnoses.

“These are investigational diagnostics that are not quite ready for prime time yet but are nonetheless very powerful,” says Ashley, who is an associate professor of medicine, of genetics and of biomedical data science. Once these tests are more widely used, he thinks they’ll help find answers for a sizeable share of the patients who aren’t diagnosed using genetic techniques.

Perhaps more importantly, the network provides an organized way for physicians all over the country to compare patients’ symptoms and genetic abnormalities. Since the network formed in 2014, a few dozen patients across the country have been diagnosed. UDN investigators have also discovered two new genetic diseases, described in recent publications in *Human Molecular Genetics* and *The American Journal of Human Genetics*.

The UDN’s work is taking place in an environment of broader efforts at Stanford to understand genetic problems

‘IF WE HAD ACCESS TO EVERY GENE SEQUENCE

AND A BIT OF MEDICAL INFORMATION FOR EVERYONE IN THE WORLD, THE GENOME WOULD JUST SCREAM, “LOOK HERE, FIGURE IT OUT!”

Gill Bejerano

But overall, the program was a big success: The NIH estimates that 25 to 50 percent of the patients its team saw by mid-2014 were eventually diagnosed. And the number of people applying for evaluation kept growing.

In July 2014, Stanford was named as one of six additional clinical sites chosen for a national Undiagnosed Diseases Network, with Euan Ashley, MD, PhD, at the helm of the Stanford site.

“We’re working with patients who really have done everything they can,” Ashley says. “They’ve consulted so many different doctors, traipsed around the country, been on the internet every night for years and haven’t been able to find an answer.”

As part of the Undiagnosed Diseases Network, Stanford

and use the new findings to help patients. In a few cases, new genetic tools have begun to help some Stanford patients who aren’t enrolled in the UDN, and dozens of Stanford researchers continue to make advances in the laboratory, too.

For instance, Michael Snyder, MD, professor of genetics, is conducting research to understand the influence of gene mutations occurring outside the sequences that code directly for protein.

“We have a number of mutations outside our genes, in control sequences of DNA, and so far we’re very poor at identifying and understanding those,” Snyder says. “It’s an invisible part of our genetic picture but we think it counts for quite a bit.”

Remedying the near misses

Genetic testing faces a big challenge: figuring out the best way to harness the growing data deluge. “With each passing month, more of the world’s genetic diversity is represented in scientific databases, and each time more information is there, it’s easier to interpret the next thing you see,” says Jon Bernstein, MD, a clinical geneticist at Packard Children’s. That’s useful for new patients, but may not help children who have previously been told that their doctors can’t find a genetic diagnosis.

In July, Bernstein and Bejerano published a report in *Genetics in Medicine* about matching previously undiagnosed patients with new knowledge. The scientists tested whether computational tools that compare patients’ lists of mutated genes with current gene databases could yield diagnoses. They studied 40 people who had not received genetic diagnoses after their first round of analysis, and found that four could be diagnosed with recently discovered diseases. One patient, an 18-year-old from Stockton, California, named Shayla Haddock, was found to have a disease first described in the scientific literature in August 2012, only two weeks after her family had been told that her doctors could not identify a diagnosis. The researchers, whose tools have since solved dozens of other cases, want to end these near misses.

“Our study demonstrates that reanalysis of patients’ gene-testing results is useful because there’s a steady rate of discovery,” says Bernstein, who is also an associate professor of pediatrics at the School of Medicine.

“But there is no way we’ll have enough manpower to continue to do all the analysis manually,” says Bejerano, the study’s senior author, noting that several million Americans may have some form of rare genetic disease. And typically, patients have not been offered reanalysis; it’s too labor-intensive.

Bejerano led the computer

scientists who devised the automated approach used in the new research. “The genome is ultimately a programming language,” Bejerano says. “We would like to use machine learning and other approaches to build computer systems that leave as little work as possible for the human expert. When it comes to people’s lives, there is no substitute for a human expert, but we think we can take the process 80 to 90 percent of the way by computer and provide a huge time savings to relieve the human bottleneck.”

The learning machine

Bejerano’s team has recently gone a step further, developing a more granular way to evaluate single-letter mistakes in the genetic code. The program they built, called M-CAP and described in an Oct. 24 paper in *Nature Genetics*, uses a machine-learning algorithm to classify tiny genetic variants according to whether they are likely to cause disease. It’s freely available online for noncommercial purposes to geneticists around the world.

“Our challenge was to try to make the shortest list we could of all the variants that look particularly nasty, not just rare and potentially functional,” Bejerano says. M-CAP chops the list of variants that need to be evaluated by hand from around 300 per person to about 120, and Bejerano’s team expects it will become even more specific as more disease-causing variants are discovered.

“If you take a pool of all the nastiest mutations in our genome, tens of thousands of changes implicated in causing severe early childhood disease, and compare them to all the variants in healthy people’s genomes, they look very different,” he says.

M-CAP is not the first program to sort patients’ gene mutations, but it is much more accurate than its predecessors, failing only 5 percent of the time to include the genetic mutation that is “the answer” on the list of mutations that researchers



BRENDA PORTER HAS WORKED WITH THE NYE FAMILY TO GET THE WORD OUT ABOUT CITRATE TRANSPORTER DISORDERS. “EPILEPSY IS SO MANY DIFFERENT DISEASES,” SHE SAYS.

'TESSA AND COLTON ARE NOT OK

IN THAT THEY'RE NOT HEALTHY, BUT OUR LIFE IS OK. WE HAVE
FOUR REALLY HAPPY CHILDREN.'

Kim Nye

should analyze. Bejerano can't conceal his enthusiasm about the new method — one of its predecessors misclassifies 40 percent of disease-causing mutations as benign. "That's what we're replacing. Dude, it's the 21st century!"

Why diagnose?

After the uncertainty of waiting for a diagnosis, families who learn that their child has a rare genetic condition may be left with mixed feelings about the final result. "Every single person whose disease we identify is incredibly grateful and relieved to find the problem," says Snyder. "But then they wonder, 'How does that help us?' Understanding the underlying defect doesn't necessarily lead to a therapy."

Sometimes success is obvious. One child recently evaluated by Stanford's UDN was found to have Marfan syndrome, a connective-tissue disorder, which was combined in her case with a second, much rarer genetic disease that made it hard to recognize. People with undiagnosed Marfan can suffer rupture of the aorta; now that her diagnosis is known, cardiac monitoring may save her life.

Sometimes, even when doctors can't do anything about a patient's condition, identifying an errant gene can bring a family peace of mind. For Shayla Haddock, whose 2012 attempt at genetic diagnosis was an agonizingly near miss, knowing her gene mutation doesn't change her physicians' approach to her symptoms — which include deafness, developmental delays, epilepsy, short stature and unusual facial features. But her family has learned that she has a *de novo* gene mutation, meaning it arose spontaneously in her and isn't shared with either parent. Her mom, Cheryl Siloti, says the news ended years of worry about whether Shayla's symptoms might have somehow been prevented. And her siblings, who have begun to have their own children, now know they don't carry the mutation, either.

And sometimes after a diagnosis, families find themselves on the vanguard of rare-disease research. That's what has happened to the Nye family, whose physicians now are starting to understand how Tessa's and Colton's nerve cells malfunction. The cells lack a transport protein that moves citrate, an intermediate molecule in sugar metabolism, from one part

of the cell to another. The resulting seizures can't necessarily be treated in the same way as seizures with other origins.

"Epilepsy is so many different diseases," says Brenda Porter, MD, Tessa and Colton's pediatric neurologist at Packard Children's. "We used to lump patients together and treat them based on their seizure type, but I think that's naïve. We need to move beyond that and think about the pathophysiology of each kind of epilepsy. We can really be more precise."

How to get there is still an open question. For now, both children are receiving anticonvulsants plus a diuretic, a combination that Tessa's doctors hit on through years of trial and error. Colton started this treatment when he was just a few hours old, and it's saved him from the devastating emergencies of Tessa's early years. Although he still has occasional seizures, he's now 3 and has never ridden in an ambulance. "Colton's life has been so different from Tessa's experience that we consider it a success story," Kim says.

And though both kids have some developmental delays, and Tessa still has dozens of small seizures per day, Kim and Zach have figured out how to handle all of it. "Tessa and Colton are not OK in that they're not healthy, but our life is OK," Kim says. "We have four really happy children."

Tessa loves her siblings, likes books and puzzles, and has a group of close friends she's known since kindergarten. "She's a really nice person to be around, and she's definitely in this world," Kim says. Colton is doing well in physical, occupational and speech therapy, although Kim schedules his therapies for the morning hours "because when his sisters are on the scene, he just wants to play."

Against the background hum of their family life, Kim has also plunged into advocating for epilepsy research. The kids' genetic sequencing was done at Baylor University, where geneticist Matthew Bainbridge performed a manual analysis of both children's genomes to identify the culprit. For confirmation, he needed at least one unrelated child with the same mutation and similar symptoms; he identified a boy in Texas. While Bainbridge was writing a manuscript about the three children, an independent team in France published a similar report of more families with the same type of epilepsy.

"I think this will remain a rare disease, but it reassured us

C O N T I N U E S O N P A G E 51



FEVER

PITCH

WHEN SCIENCE COLLIDES WITH POLITICS

BY NANCY SNYDERMAN

Two years ago, Ebola jumped from the jungle into West African cities and ultimately the United States. As a physician-journalist for ABC and NBC News, I had covered tough stories around the globe — from epidemics to wars and refugee camps. But nothing prepared me for the drama and sociopolitical fallout from Ebola. We had all been watching the devastation from this epidemic play out from a distance in print and on television. With each compelling story, Ebola became increasingly tragic and exotic, yet it was safely oh-so-far away.

And then Thomas Eric Duncan brought everything home. The Liberian man who arrived in Dallas on Sept. 20, 2014, was infected with Ebola, and within hours of his hospitalization, a nation was on edge. For all the upheaval that was to follow, it is important to look back and remember that he remains the *only* person to have died of this disease in the United States. Two health-care workers who cared for him became infected but survived, and none of Duncan's family members contracted the disease. Yet Ebola held America hostage.

The arrival of Ebola on U.S. shores set up a collision of science, politics and public trust unlike anything we had ever witnessed in public health. People exhibited great distrust and, ultimately, disregard of the government and institutions like the Centers for Disease Control. Health officials struggled to calm people and keep the message on track: that Ebola is spread through direct contact with bodily fluids, that only symptomatic patients are contagious and that the virus would be contained in a country with the medical and public-health infrastructure of the United States. But every day, with the help of a ravenous 24-hour news cycle, the truth got derailed. The fear that Ebola would sweep across the United States, however improbable, was palpable.

Duncan's family was appropriately quarantined in their apartment because they had been in contact with him after he developed a fever, vomiting and diarrhea. No one entered or left the premises. Soon, however, the word "quarantine" would be used loosely and sloppily, adding a new layer of confusion.

My NBC News team and I left for Liberia on Sept. 26, one day after Duncan was seen in a Dallas ER and sent home febrile with antibiotics. He returned three days later, critically ill, and was hospitalized. While Dallas would soon become the center of attention for most Americans, I believed the real story was still in Liberia. I thought if I could explain what was happening at the epicenter of the epidemic, we could quell people's fears at home. I was wrong; soon my team and I would become part of the story and complicate the narrative even more.

While in Liberia, we hired a young American journalist, Ashoka Mukpo, who had spent a lot of time in Monrovia, the capital city. He was on the team for less than a day when he developed a fever. After malaria was ruled out, Ebola was confirmed and within days he was on a chartered flight to the University of Nebraska Medical Center. My team stayed in Liberia and we continued to report for several days before it was time for us to come home. For all the devastation I wit-

nessed on the streets of Monrovia, where every day people lived in constant fear of contracting Ebola or losing a loved one, I was blind to the persistent fright in the United States.

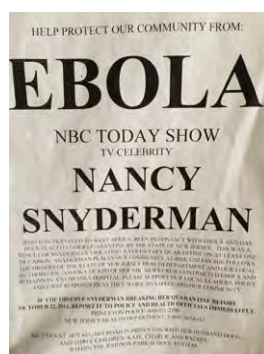
The cardinal rule in Liberia was to touch no one — no exceptions. We took our temperatures four times a day and reported them to one another. We all kept our distance — 4 to 6 feet was the norm and that was true of my interactions with Ashoka. While working with us, his temperature was normal, which meant he was not contagious. His fever didn't develop until hours after leaving one evening; after that, all contact was via phone or text. But once the word was out that a "member of an NBC News team has Ebola," the media firestorm began. There were tweets calling for us to be detained in Liberia.

I was warned by my colleagues that rhetoric on the homefront was increasingly angry and fearful, with some voices clamoring that allowing sick people, or even healthy journalists, back into the United States could put people at risk. But I knew the science told another story. And I had seen our country face infectious diseases before — influenza, polio and HIV/AIDS. Each time we emerged stronger, smarter and more thoughtful. We became better doctors and scientists and more compassionate citizens. But those epidemics had one thing in common. They occurred before social media was an entity.

The staff at Nebraska Medicine knew that accepting an Ebola patient would set up a scenario that would need to be handled like nothing they had experienced before. The medical team had been practicing for 10 years to contain such a deadly infectious disease, and the doctors knew that messaging would be as important as the quality of the medical care. So while Dallas was bleaching sidewalks, this medical community in

America's heartland addressed the public immediately. Daily press conferences served to teach and allay fears and invited the community to trust their doctors and institutions and be proud about the work that was being done. The doctors said, "We built our bio-containment center for this kind of emergency. We want you to know that the public is not at risk. We will be speaking with you every day." They kept their word.

Life in Omaha remained calm and normal. The doctors and nurses who spent days with the infected patients took showers after their shifts, changed back into their street clothes and went into their communities — grocery shopping, attending school plays and having dinner with their



AFTER NANCY SNYDERMAN TRAVELED TO LIBERIA TO REPORT ON THE EBOLA EPIDEMIC, THE STATE OF NEW JERSEY CONFINED HER TO HER HOME, AND COMMUNITY MEMBERS PUT UP "WANTED" POSTERS.

THE DEALER IS IN

HOW PHYSICIANS
ARE FUELING THE OPIOID
EPIDEMIC

When Anna Lembke, MD, began working as a psychiatrist in the late 1990s, she told the clinic's intake coordinators not to send her any patients with addiction to drugs or alcohol.

She did not, at the time, view addiction as a real mental illness, and hence turned such patients away.

What she soon discovered was that she had no one left to treat. Studies show that 50 percent to 75 percent of patients with mood and anxiety disorders are also struggling with addiction to alcohol and drugs. Lembke also discovered that some of her patients were addicted to the very drugs she was prescribing. • Lembke realized that in order to help her patients and not harm them, she was going to have to learn how to target and treat addiction — in particular, prescription drug misuse. Her realization happened to coincide with a dramatic increase in prescription opioid misuse across the country. In the United States today, over 16,000 people die each year as a result of prescription opioid overdose. • In her new book, *Drug Dealer, MD* (Johns Hopkins University Press, November 2016), Lembke weaves case studies with cultural anthropology, public policy and neuroscience to examine the unseen forces driving the epidemic. She concludes that the prescription drug epidemic is a symptom of a faltering health-care system, and calls for reforming health-care delivery for all patients, not just those addicted to prescription drugs. • The following excerpt from *Drug Dealer, MD*, tells the story of a young woman who became addicted to prescription opioids as a teenager, while under the care of her physicians.

AN EXCERPT FROM *DRUG DEALER, MD*.

BY ANNA LEMBKE

ILLUSTRATION BY FRANCESCO BONGIORNI

MY PATIENT MACY BECAME AN OPIOID REFUGEE. I FIRST MET HER IN THE PAIN CLINIC WHERE I WAS ASKED TO ASSESS WHETHER OR NOT SHE HAD BECOME ADDICTED TO PRESCRIPTION PAINKILLERS, and more importantly, what might be done for her if she had. When she first saw me, she was in her early 20s. I was just one stop in a very long road of doctors. As I came to know her, I realized that her story started with the story of her father, Mike. He was her primary caregiver when she became ill in her mid-teens.

Mike grew up poor in the 1980s in the drug-ridden neighborhood of East Oakland, which transitioned in a single generation from a mixed ethnic middle-class neighborhood to a predominantly poor black one, notorious for gang drug warfare. Mike was the youngest of five children, and every member of his family, except Mike and his oldest sister, was addicted to something.

As soon as Mike was old enough, he got out of East Oakland and started a family of his own. He was determined to give his kids a better life, as far away from drugs as possible. He and his young wife moved to a townhouse in Fremont, a middle-class community south of Oakland. They had two daughters: first Katherine, and then, seven years later, Macy came along. Their life was complete.

When Macy was a junior in high school, she began experiencing unbearable leg pain. Mike, to whom she had always been especially close, wasn't sure what to make of it and assumed it was growing pains, so did nothing. But a month later, Macy collapsed while playing volleyball at school and was rushed to the nearby emergency room. The doctors performed a number of tests and couldn't find anything wrong with her. Despite the absence of any pathology, they gave her intravenous morphine to treat the pain and sent her home. Two weeks later Macy was back in the emergency room with the same pain. More tests revealed an unusual mass on her diaphragm and on her ovary. The doctors worried it was cancer, and they switched from intravenous morphine to intravenous Dilaudid, and she was admitted for surgery to remove

the tumors. As it turned out, the mass on her ovary was a teratoma, a benign growth of no consequence. The mass on her diaphragm was a bit of lung tissue, also benign, the resection of which was more involved and required yet another hospitalization and more surgery. The doctors hoped the removal of the masses would eliminate Macy's pain, although a relationship between the masses and her pain had never been clearly established. In the meantime, she was given intravenous morphine, Dilaudid and hydrocodone, all potent opioids with addictive potential, during and after each surgery. Altogether, Macy was hospitalized for two months, October and November of 2010, and barely remembers any of it because she was so altered by prescription painkillers.

At no point in the course of Macy's medical procedures was

the risk of opioid addiction discussed. Nor was Macy's family history of addiction considered relevant. When Macy's various surgeries were complete, her doctors declared that she should be pain-free. Despite having received heavy doses of opioids daily in the hospital for two consecutive months, Macy was sent home without a single pill. For the next six weeks, she experienced excruciating opioid withdrawal — nausea, vomiting, fever, chills — as well as unbearable muscle and bone pain throughout her body, even worse than the original leg pain.

In the grips of opioid withdrawal, Macy would lie on the floor screaming and crying out. Her parents, unsure

what else to do, took her back to the local emergency room every few days, where she was given the opioids her body craved and promptly discharged again. Sometimes the doctors would readmit her to the hospital and give her intravenous morphine to control her pain, then discharge her again without opioids, follow-up or any semblance of a treatment plan. Between 2012 and 2014, Macy's parents took her back and forth to the emergency room in an endless cycle of despair and frustration. The doctors never seemed able to tell them what was wrong with Macy, or how to help her, except for writing more opioid prescriptions.

Then, in 2014, on one of the emergency room visits, the



doctor came out of the room and said to Mike with barely veiled hostility, "Is your kid on drugs?" He was implying street drugs like heroin, not the pain-killers Macy's doctors were prescribing, although chemically speaking there is almost no difference between the two. Would his reaction have been the same if Macy were white instead of black?

"No," said Mike, without a moment's hesitation. "How do you know?" challenged the doctor.

"I know because I know my daughter, and because we're with her all the time, and because she's not hanging out with other people doing drugs."

"Your daughter is a drug addict," the doctor said. "Don't come back here for pain medicine again."

Mike said nothing. He was without words. He gathered Macy up in his arms and drove her home. When he got her there, she lay on the floor, moaning and crying out.

"Give her some pain pills," he said to his wife and daughter Katherine, who were looking on helplessly.

"They're all gone," said his wife, a pleading look in her eyes. "Dammit," Mike shouted. He wanted to shut his eyes and make it all go away. Then he made a decision.

"That's it," he said, grabbing his car keys. "If those doctors won't help her, I will." Without another word, he left the house and got in his car. He headed back to the old neighborhood, silent tears streaming down his cheeks. He still had some old friends who sold drugs. He would find them and buy some Percocet, or some heroin if he had to. That would stop Macy's pain.

As Mike was driving, a memory from his childhood intruded on his thoughts. He was crouched at the base of the chimney in his childhood home, tracing the outline of the inner brickwork with his chubby fingers, looking for the hole between bricks where the

mortar had long ago crumbled away. He felt the divot and shoved his fingers inside, hoping for the crinkle of plastic. He found it. He pinched his fingers to get a hold of the bag and slowly pulled it out.

"Mommy, Mommy," Mike called, "I found one!"

He ran to the kitchen holding the plastic bag in front of him, the little blue and red pills bouncing around inside of it.

His mother was cleaning the kitchen, tired after working one of the many jobs she had over the years — house-cleaning, cooking at a local diner, working the line at the Del Monte Cannery, forklift driving. Mike was her fifth child, with a different father than the rest, her child of that no-good drunk she sent away the day Mikey was born, knowing in her heart he wasn't going to be the father her son needed. She dried her hands on her apron and folded the little boy in her arms.

"You found one, so you get a dollar from me," she told him, "just like I promised."

She reached inside her purse and handed him a dollar bill.

"Now you listen to me," she said, kneeling down and looking him in the eye, "I don't want you ever doing those drugs like your brother and sister. It's no good, no good."

"I won't Mama," he said, "I promise. I don't ever want to make you cry."

As if waking from a dream, Mike took the next exit off the freeway, turned the car around, and drove home again. When he got home, he bundled the still crying Macy back into his car and took her to a different hospital emergency room. After hours of waiting, the doctor finally came. Mike turned to him and said, "This is my daughter Macy, and she has terrible pain all over her body which no one can understand. She is also addicted to pain pills, and

doctors made her that way, so don't turn your back on her. Don't judge her. Help her."

This new doctor, perhaps humbled by Mike's desperate admission, took Macy in and admitted her to the hospital, using the occasion to get her a treatment plan that included assessment and treatment for addiction, which had never previously been suggested or offered and which is how she eventually ended up with me.

Once in addiction treatment, Macy's problems did not magically disappear, but with time, patience, courage and effort, Macy made her way slowly to a better place, with decreased pain, improved function, a job and plans for the future, which Macy also deserves. **SM**

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FEATURE

Diagnose this

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essentially be a miss; the test result would say there is no blood when in fact there is.

False positives can generate a lot of anxiety for patients and waste health-care dollars for everyone. But besides the problem of false positives and negatives, McDonald also points out that continuous monitoring could be prone to false reassurance. If you are using a smart toilet or smart bra, she says, you might decide you don't need a regular lab test. But the device could stop working, and you might not know it.

The integration piece

Collecting information about ourselves is only a piece of what gets us to better patient care, says Leslie Saxon,

MD, professor of clinical medicine at the University of Southern California. Saxon heads the USC Center for Body Computing, a major center for the development of diagnostics.

Diagnostics could be information from wearable devices, says Saxon, a member of the small cadre of researchers interested in what diagnostics can contribute to the future of medicine. “But diagnostics is also what patients are telling me, or what their mother or sister are telling me: ‘He hasn’t gotten out of bed for three days. He’s depressed.’” Diagnostics, she says, have to be integrated with everything we know about patients.

For example, information from devices for monitoring heart activity have to be considered in the context of what else we know — whether a patient is taking her prescriptions or how she is using the monitor.

And diagnostics and biomarkers are just a piece of the puzzle, she says. The bigger challenge may be handling that information — processing it, integrating it and sharing it — in a way that helps both patients and researchers.

Not so fast

Peter Schmidt, PhD, senior vice president and chief mission officer at the National Parkinson Foundation, casts a gimlet eye on what he views as overenthusiasm for biomarkers and diagnostics.

It’s not that he’s against diagnosing people who are ill. But for a variety of reasons, not all diseases are good targets for continuous monitoring, he says. Cancer, for example, is an appropriate target for continuous monitoring because it’s typically easy to treat when caught early, difficult or impossible to treat when caught later. But neurodegenerative diseases such as Parkinson’s disease are difficult to treat at all, let alone cure, so knowing you have it before you even feel sick could

be a negative.

“A human is not a jet engine and we deal with problems in our own way,” Schmidt says. He questions the wisdom and ethics of diagnosing people with illnesses when they feel fine and when intervention won’t clearly do them any good.

Imagine, he says, that you are 70 years old and have been feeling fine, but a test has just revealed that you have Parkinson’s disease. “You aren’t actually aware of any symptoms, and then you die a year or two later from a heart attack. Having been told you have Parkinson’s disease would have helped you not at all.

“Parkinson’s disease can be completely managed for a year or two after diagnosis,” Schmidt adds. “During that two-year period, Parkinson’s disease is mostly a disease of fear, where people will think, ‘Eventually this disease is going to overcome the effects of the medications, and it is already doing something bad to my brain.’ That’s a scary thing.”

Manifold challenges

Diagnostics encompass far more than just figuring out what is wrong with one patient. If medicine moves toward a more preventive model, that will require better diagnostics. Such a future requires support for research on diagnosis and structural support for timely and accurate diagnosis, says McDonald.

“And,” she says, “the research is not just about training physicians to do a better job. It’s about how the delivery system is supporting them in doing that, how the payment system is supporting them in doing that, how the legal system is supporting them in doing that.”

The number of people looking at how the entire health-care system can support diagnostics is, for now, a “small tribe” of people, says McDonald. “This problem matters. It needs attention, and no one is funding the research to

build a knowledge base to help you write your article,” she says with a smile.

As Gambhir emphasizes, the changes, if they come, could take decades, and the challenges are manifold. At one level, he says, the challenge is in understanding both our biology and the output from all these new devices well enough to know what to do with the information. The biology of early disease is not necessarily the same as that of late disease. Another major challenge, says Saxon, is handling and processing and sharing that information in a way that helps patients. And, as McDonald says, “The current health-care system is shaped more for treatment than for diagnosis, more for action than for thinking.”

The smart toilet of the future won’t be a stand-alone device, but part of an integrated network of information about you and billions of other people, in a system — of devices, servers, institutions and individuals — that actively prioritizes diagnosis, communication and prevention. Instead of flushing millions of petabytes of data into the sewers each day, we’ll wrest from it the seeds of a healthier future. **SM**

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FEATURE

Hearing things

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world. It works with our senses to give the brain information about where we are in space, whether we are moving, and the direction and rate of our movements. It keeps us from stumbling when we get out of bed in the middle of the night; it maintains balance and spatial orientation and keeps us from falling.

The sensory information about motion, equilibrium and spatial orientation is provided by the vestibular

apparatus, which in each ear includes the utricle, saccule, and those three semicircular canals, bones so small that together they can fit on the surface of a dime. The utricle and the saccule, two sacs located just below the semicircular canals, contain small stones and viscous fluid that enable hair cells to detect linear motion and orientation relative to gravity. The saccule and utricle detect vertical linear motion, like when you drop in an elevator, and horizontal linear movement, such as zooming forward in a car. The fluid-filled semicircular canals detect rotational movement and inform the brain about angular head movements.

Each of the canals lies along a different plane, perpendicular to one another, and sends messages to the balance center in the brain for head rotation in its plane. When the head rotates in a direction sensed by a particular canal, the fluid within it lags behind because of inertia and exerts pressure against a specialized structure — the canal's sensory receptor. The receptor then sends nerve impulses to the brain about movement from the specific canal that is stimulated.

One of the most important functions of the vestibular system is to keep the eyes focused on objects of interest during head movements, like when you're driving down a bumpy road. Rotatory motion upward and downward is where the superior semicircular canal comes in. As Minor knew from studying late-19th-century experiments on the vestibular system in pigeons, pressure on the superior semicircular canal causes the eyes to move in the plane of that canal. It was this motion that Minor saw when he watched his two patients' eyes move in response to sound, and suspected that it must be the superior canal that was damaged.

"The specific pattern of the eye movements, that was a smoking gun pointing to the superior semicircular canal being

the source of the problem," Minor says. Normally, the inner ear is a closed capsule with only two openings — the oval and round windows of the cochlea. Having a hole in one of the canals — a third opening — can lead to a number of auditory and vestibular disturbances. Among the most dramatic: Sounds from inside the body can enter directly into the inner ear through bone conduction.

"Some of the sounds that are already in our body, our pulse, our neck creaking, our own voice, those get into the inner ear through that hole much more readily than normal, so people report these crazy symptoms like hearing their eyes move, hearing their blood," says John Carey, MD, one of Minor's colleagues at Johns Hopkins who assisted in the later surgeries and research. "It may be too loud or distorted because they are hearing their voice come through their bones directly into their ear. Their voices sound loud, uncomfortable, distorted. Many patients resort to whispering."

TO TEST HIS THEORY, MINOR AND COLLEAGUES COLLABORATED with a neuroradiologist to develop a more sensitive version of a CT scan to search for a tiny hole in the canal.

Within months, they were able to scan the gentleman who liked to sing in the shower. Sure enough, there was a hole in his right superior semicircular canal.

Finally, an answer.

"In addition to being sent to a psychiatrist and told that he was imagining these things, which he clearly wasn't, the patient was concerned that maybe he had multiple sclerosis or a neurological disease," says Minor. "For him it was just a real frustration. Once we figured out what it was, he felt reassured and did not feel he needed the problem to be corrected. He just stopped singing in the shower."

About two-thirds of patients with

the syndrome choose to live with it; others have symptoms that are just too disabling, Minor says. They want a cure badly.

His second patient, also at Johns Hopkins, fit into this category. Like the first patient, she had sound-induced wobbling vision known as oscillopsia, but she also had disequilibrium.

Minor and his colleagues at Johns Hopkins developed an operation to correct the disorder. The surgery entails making an incision above the ear and then gently elevating the temporal lobe of the brain to reveal the superior canal, using fascia and bone to plug the canal hole, securing the opening in the skull with titanium plates and sewing the scalp back up. Other surgical approaches to correct the disorder have also been developed in the intervening 20 years.

In 1996, he operated on his second patient and her symptoms immediately disappeared. In 1998, Minor and colleagues at Johns Hopkins published their first paper on the disorder, in the *Archives of Otolaryngology Head and Neck Surgery*, describing eight patients with the syndrome. A series of additional publications followed.

"We showed that there were specific hearing abnormalities associated with the syndrome," Minor says. "We also showed that there were other vestibular abnormalities that could be evaluated by clinical tests. We established that the surgery was selective in its effects on the superior canal. That the sound-induced eye movements went away. That the hearing often returned to its normal range. Most of the severe symptoms were gone. Patients were much better than before. In making these discoveries, we also extended our understanding of vestibular physiology. Our work on this syndrome has been a wonderful synthesis of bench to bedside and back to bench."

Exactly how many people suffer from this syndrome remains unclear, Minor says. At Johns Hopkins, surgeons have performed about 240 procedures, and they are often done at Stanford as well. What is known: Many patients are diagnosing themselves online. Both the audiologist from Atlanta and the horn player from Germany found out about Minor's research and discoveries online, then contacted him at Johns Hopkins by email. Minor eventually operated on both. Some have suggested the disorder be renamed Minor's syndrome.

For the horn player, surgery ended 22 years of suffering. He was able to return to his music. Hirsch, the audiologist, had endured the syndrome for seven years.

"My symptoms kept getting worse," she says. "I stopped attending weddings, bar mitzvahs and my children's sporting events. I became a social recluse. In November 2004, I went searching for answers online, found Dr. Minor and emailed him. He called me that night at 5 p.m. on a Friday. I was overwhelmed and honored to hear directly from him."

On Feb. 10, 2006, at Johns Hopkins, she became the 34th patient with superior canal dehiscence syndrome to have canal-plugging surgery. After waking up from surgery, the surgeons asked if she was OK. She motioned with her hand for them to wait, then closed her eyes and moved them back and forth. There was no sound. Her eyeballs had been silenced. **SM**

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FEATURE

Listen up

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including listening carefully with a stethoscope. For example, he has en-

countered children with coarctation, or a narrowing of the aorta, a congenital problem that can stress the heart and compromise the cardiovascular system. "I've seen 18-year-olds with coarctation where the diagnosis has been overlooked because nobody did a good physical exam," he says.

And there are instances, he says, where the results of an echocardiogram may be inconclusive or conflict with something on the physical exam. Once, while examining a patient in a pediatric cardiology outreach clinic in San Luis Obispo, he noted a whooshing sound over the left side of the patient's chest. The initial echocardiogram did not show any abnormality, but with this discrepancy between the clinical findings and the ultrasound, Bernstein and the ultrasound technician persisted, and were able to find a tiny but potentially life-threatening tear in the wall of the aorta. The patient was transported to Lucile Packard Children's Hospital Stanford, where his aorta was successfully repaired. "Had we relied only on the initial ultrasound, this could have been a disaster," Bernstein says.

For the basic care of newborns, the stethoscope is essential, says William Benitz, MD, the Philip Sunshine M.D. Professor of Neonatology. It's needed for checking a baby's heart rate or listening to the heart and lungs for possible signs of a major anomaly, such as a diaphragmatic hernia, an abnormal opening of the diaphragm.

"In a matter of a few minutes, you can move from not knowing very much about a baby that is not behaving very well to having a specific diagnosis, and it's all based on a stethoscope," Benitz says. "So I don't think we're on the verge of replacing physicians with machines just yet. But I do worry we're not training our young people to trust their exam skills and ask the right questions and trust their intuition. They have

so much more to learn than we did 30 years ago. We just have to strike some kind of balance."

Skills set

Some younger physicians acknowledge they don't rely on the stethoscope the way their older counterparts do.

"A lot of people know there will be an imaging or ultrasound exam that they are going to do anyway and because we are less likely to make critical decisions without having the information from imaging, inevitably clinical skills will not be as robust as they were years ago, when that was all you had," says Andrew Chang, MD, co-chief resident in internal medicine at Stanford. Nonetheless, trainees and younger practitioners still value the stethoscope as a diagnostic tool, he says.

"Even if individuals say young doctors aren't as attuned to the sounds that come through their stethoscopes — and I do think there is less of an emphasis on this and we aren't as well-trained in this — I still feel it's something we heavily rely on," says Andre Kumar, MD, co-chief resident in internal medicine, who says he would feel "naked" without his stethoscope.

Both he and Chang are interested in global health and have found themselves in places like Uganda, Bangladesh and Nepal, where resources were limited, ultrasound a luxury and stethoscopes absolutely essential for diagnosis. These situations exposed the importance of basic skills, they say.

"There were so many times when I felt woefully unprepared to diagnose what was wrong with my patients, sometimes as a direct consequence of my physical-exam skills," Kumar says.

But one needn't stray far from Palo Alto to encounter situations where a low-tech approach to diagnosis is extremely valuable, as in a middle-of-the-night emergency when imaging isn't

available, or in a clinic where the cost of a scan may be out of reach for patients, says Lars Osterberg, MD, MPH, associate professor of medicine.

“A great example is the Cardinal Free Clinics. For a while, we didn’t have chest X-rays, and I would diagnose pneumonia without X-rays, which could cost the patient \$100,” Osterberg says. “We forget that we are in a privileged society that has access to all these things. That’s not always the case. Just down the street or across the highway people can’t afford certain things. If we did an ultrasound or an X-ray on everyone, it would add up.”

The cost of a cardiac ultrasound varies widely, with Medicare reimbursing between \$153 and \$698, depending on the type of test, according to published data. And while the cost of ultrasound machines has been steadily declining in recent years, a stand-alone or portable device may cost as much as \$100,000. Clinicians typically don’t charge patients when they use a handheld ultrasound during exam, but the device itself can cost at least \$8,500. By contrast, “a really decent \$50 stethoscope can go a long way,” Osterberg says.

Looking to the future

Most important, some clinicians argue, is the role of the stethoscope as an enduring symbol of the physician and as the center of the ritual encounter between physician and patient.

The stethoscope “puts you close to the patient,” says cardiologist Eddie Atwood, MD, a professor of medicine who has been practicing for more than 40 years. “You’re leaning in. You’re touching the patient. But psychologically, and more important to me, it makes you think about your patient. You spend more time with the patient. By virtue of putting this on, you are right in the patient’s space and thinking about him while you’re working.

... That may never go away. This is an element that maybe shouldn’t go away.”

To recognize the stethoscope’s signature role in medical practice, medical schools like Stanford pay homage to it every year in a ceremony in which each incoming medical student receives his or her first listening device.

“Maybe in the future, instead of the stethoscope ceremony, you will get an ultrasound probe,” says S.V. Mahadevan, MD, associate professor and chair of emergency medicine. “We may see the evolution as that being a symbol of our profession.”

But for now, the stethoscope retains its stature. “This stethoscope represents the physician-patient connection,” Lloyd Minor, MD, dean of the School of Medicine, told the 93 incoming medical students during the Aug. 26 ceremony. “When you wear this, you commit to the physician-patient relationship above everything else.” **SM**

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FEATURE

‘And yet, you try’

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take a few months off or reduce his load, because he was in all honors and AP classes. But the only thing he would drop was speech and debate, which was hard for him to give up. He was full-on, full throttle. That’s the kind of kid he was.”

“Most people, if they were as sick as Milan, would take a break, go to the beach, relax,” says de la Zerda. “How many people would say they want to push even harder to focus even more on their work? Milan never let go. He had the utmost dedication and passion you can imagine.”

“I think how he saw it,” says Fann, “was that it was this physical thing he had to overcome, and that he could do it with

hard work like he had always done.”

From October 2013 through May 2014, while undergoing several courses of chemotherapy and cancer vaccines, Milan presented his diagnostic device concept at five different science competitions. He was named a regional finalist at the Siemens Competition, a grand prize winner at the 2014 Synopsys Silicon Valley Science and Technology Championship and a Fourth Grand Award winner in Medicine and Health Sciences at the Intel International Science and Engineering Fair in May. To the first competition, he wore a hat to cover the areas where his hair had not yet grown back. “Milan never let anybody in the competitions know about his situation,” says Aruna. “He wanted to win purely by his own merit.”

Aruna Gambhir also had to attend to her own health. After her recurrence of breast cancer when she was 47, doctors had advised her to eventually undergo, a complete hysterectomy — surgical removal of the uterus and cervix — based on the increased risk of uterine cancer in women with certain types of breast cancer. “At that point I thought, let me just wait on that,” she says. “I wasn’t ready.” But her Li-Fraumeni diagnosis introduced a new urgency, and Aruna had the preventive hysterectomy in the summer of 2014. “I didn’t want something to happen where I couldn’t support Milan,” she says. “I just had to get it over with so I could get home and focus on him.”

That summer, Milan continued to work in de la Zerda’s lab, celebrated his 16th birthday and earned his driver’s license. On Sept. 1, 2014, he drove himself to his first day of his junior year at Bellarmine. “I guess he is not that sweet baby who held on to my hand before the start of preschool,” his mother wrote on the CaringBridge web journal that she used to keep friends and family updated about his life. “Milan is cher-

ishing his independence.”

“We didn’t really talk about how sick he was, or how he felt about it,” Fann says. “We spent a lot of time driving his car around, playing music, just trying to be normal.”

Just a couple of months later, in November 2014, an MRI scan revealed a new tumor at the base of Milan’s skull. “When we got the news of the recurrence, he went into his room for a few minutes,” Aruna Gambhir says. “Then he came out and said he was ready to fight.” Milan had a second surgery to remove the new tumor, followed by radiation treatments that lasted until January 2015. In February he went to Gainesville, Florida, for six weeks to undergo an experimental stem cell transplant designed to manipulate his cells to mobilize his immune system. “It was a clinical trial of one,” says Aruna Gambhir.

His friends all pitched in to buy Milan a white electric guitar, which they signed with messages of hope and affection. Jose Hernandez, the friend Milan and Kiki Fann had played guitar with in middle school, rode his skateboard more than 9 miles from his home in East Palo Alto to sign the guitar and help present it to Milan. “He was the best teacher I ever had,” Hernandez told Aruna Gambhir.

After a year and a half of study, Sam Gambhir and his team confirmed that a molecule in the ashwaganda plant known as Withaferin A was indeed an active ingredient with significant anti-brain-tumor effects. Best of all, since the drug was a natural agent, it would require neither FDA approval nor a prescription to administer to patients. The results were published as the cover story in the January 2016 issue of the *Journal of Neuro-Oncology*.

For Milan, the results came too late. “We saw that it was working in the last few weeks before he died,” Gambhir says. “But I had worries that it might

cause some unexpected toxicity.” Milan was too ill to undertake a new treatment, even a natural extract. “His death was extremely hard, because he lost his hearing, then he lost his vision, then he lost his ability to speak, his ability to move, and he was in home hospice for several months.” On May 2, 2015, 21 months after his tumor was diagnosed, Milan died. He was 16 years old.

Milan’s laptop still sits on his desk in the home office he shared with his mother. Its cover bears the cardinal “S” for Stanford, where he had always hoped to enroll as a freshman this fall. Instead, a memorial for him was held on May 13, 2015, in Stanford’s Memorial Church. The grand Romanesque Revival sanctuary, which seats 1,200, was nearly full. Two family friends performed “Tears in Heaven,” by Eric Clapton, on the guitar, and a recording of one of Milan and Kiki Fann’s jam sessions was played. Carolyn Carhart Quezada, the mother of one of Milan’s closest friends since preschool, remembered Milan building his own lemonade stand out of PVC pipe, and later helping her son build a computer. She called him “a friend of a lifetime.”

“I keep hearing that he’s gone,” says Fann, “but I just feel like he’s still here and still helps me through things. I think, if Milan were here, how he’d encourage me to do things differently. And that’s made me try things I might not have tried, like speaking out in speeches and classes. And I’m still playing guitar, working on an album this year, and planning to major in music at college.”

Milan lives on not only through the memories of his family and friends, but through his scientific legacy. Today, as glioblastoma research progresses in labs around the world, his living cells, coded in anonymity, are part of it. And a few days after Milan’s death, the Wearable Ultrasonic Device for the Early Detection of

Tumor Recurrence he had developed with de la Zerda was granted its patent. Sam Gambhir’s lab will oversee the process of bringing a device to fruition, which is expected to take several years. Lab members are also preparing the related research paper, which Milan kept working on until the final stages of his illness, for publication. “We’re hoping it will come out sometime soon,” says de la Zerda. “And when it does, I have all expectations that it will draw a lot of attention.”

For Sam and Aruna Gambhir, grief is woven into the fabric of their lives now. “The worst has already happened,” Aruna says. “We can’t change it.” Though Aruna must continue to monitor her own cancer vulnerability, finding the motivation to do so is, for the moment, difficult. “I don’t want to go in there,” she says, referring to the cancer clinic. “I’m not sure when I’ll want to.”

“I have a tough time walking through Lucile Packard Children’s Hospital now,” Sam Gambhir says. But the experience also deepened his empathy for other parents. “I think I was always empathetic toward illness,” he says, “but not as empathetic as I am now, knowing what it’s like to have a sick child.” Around the time Milan had his second surgery, “I remember seeing a parent in the hospital with a small baby who had a brain tumor,” Gambhir says. “It was so good to be able to try to talk to them and comfort them. It also made me appreciate how lucky we were that Milan made it to 16 years.” **SM**

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FEATURE

Breaking the code

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that this was a real thing,” Kim Nye says. Once the mutation was known,

she wrote a Wikipedia entry about citrate transporter disorders. Nye linked it to a website she set up (with help on the content from Porter) that allowed people to contact her, a strategy that other parents have also used to find families affected by their child's rare disease.

"We started hearing from families around the world," Kim says. "The first response was from a parent in Michigan who said, 'I have two children with severe epilepsy, and our exome sequence said *no pathological mutations*, but your gene was in an area of interest that the kids shared.'" Those children have Tessa and Colton's disease. Soon other families wrote, too, from places as far-flung as Iceland, the Netherlands and Brazil. So far, 16 families have joined their network. The families recently answered a detailed questionnaire about their children's epilepsy that Kim helped to develop, and Porter and her colleagues published the results in *Molecular Medicine* in May. The Nyes have launched a foundation to raise money for the work, with Porter at the helm of its scientific advisory board, and Kim has helped read applications for grants they are awarding to researchers.

"The Nyes are unusual because they fundamentally want to find a cure and are willing to go outside their comfort zone to help," Porter says. "It's so hard, but they're doing a great job."

"I did not see this as my life," Kim says. "It surprises me but we're doing it because there's real purpose behind it. There are probably lots of families with one affected child, and they deserve a diagnosis. Having spent 10 years trying to figure this out for Tessa, I know how frustrating and heartbreaking it is. It's a terrible feeling."

An important next step for the research, and one that's possible only

with the genetic information now in hand, is for scientists to create cell and animal models of the citrate transporter defect so that possible new treatments can be tested.

"We've been plunking dozens of drugs in our children to see what works," Nye says. "Let's make the *guinea pigs* be the guinea pigs."

Reflecting on the mix of challenges that knowledge of Tessa and Colton's diagnosis has brought, Porter says, "It's so exciting to actually be able to tell why they have this." Yet she knows there is uphill work ahead to find an effective treatment.

"People have this mentality that getting a diagnosis is the goal, that it gives closure," Kim says. "What's really eye-opening is that it's not. It's actually the beginning of the journey." **SM**

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FEATURE

Fever pitch

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children. Instead of fear and shunning, these brave health-care workers were met with love and support. Science, impeccable communication and compassion prevented politics and bad policy from hijacking the work at hand. To this day, people in Omaha speak of the pride they have for the role their city played in treating the Ebola patients.

Back on the East Coast the language was anything but tempered. While Ashoka remained in Omaha, I was home in New Jersey, housing two of my NBC colleagues. Our bosses had warned us that the rhetoric around Ebola was escalating in the United States but I was not taking their concerns to heart. Ebola may be a flamboyant virus and an attention getter but I knew it wouldn't sweep

across the country.

We arrived home to public health chaos. The New York State Department of Health disagreed with the New York City Department of Health, which differed from the New Jersey Health Department. And no state body wanted to follow the CDC guidelines. Each of us had been interviewed by a CDC official in Monrovia, cleared for travel and given a risk score of zero. To me, the CDC guidelines were the most important: to monitor our temperatures twice a day, report in with our local health official, and avoid large gatherings like churches and grocery stores. We need not be confined. That made sense to me. But states are not required to follow federal guidelines, and common sense was not ruling the day.

Several days after being home, I was seen in my car and a woman anonymously dialed 911. That call triggered the New Jersey State Police who reported the event to Gov. Chris Christie. With all the mistakes that had been made in handling Duncan in Texas, I believe that Christie wanted to set a different example. And what better way to address Ebola than to crack down and say, "Not in my state."

At 10 p.m. on a Friday my team and I were served with papers confining us to my house. The word "quarantine" was used but not in a scientific way. While the three of us were confined to the premises, other people were allowed to come and go — which made no sense. Quarantines are not porous. The fallout was insane. Because my 89-year-old mother had been in my house — she brought us groceries — Princeton's senior center would not give her a flu shot. "Wanted" posters were placed on public kiosks with my children's names and our address, urging people to keep an eye on us. It was ugly and frightening. Even the town

council, while agreeing that the posters were offensive and dangerous, declared that they were protected by the First Amendment.

A few weeks later, on Oct. 24, Gov. Christie detained Kaci Hickox, a nurse returning from working with Ebola patients in Sierra Leone, and held her in a tent at Newark Airport, despite the fact that she was afebrile and posed no threat to the public. Her clothes were taken from her and she was given hospital scrubs; her bathroom was a port-a-potty. It was not a very flattering view of the hospital capabilities in New Jersey. But the message was strong. "Not in my backyard. I don't need the CDC's advice. This is how we are handling it."

Today, Ebola is a distant memory and Zika is the medical headline of the day. Ebola exploded, liquefying bodies and destroying countless lives, and just as suddenly retreated into the African bush. But it will be back. Viruses, once they make themselves known, do not go away.

Which brings us to Zika and the reality that this virus has come to American shores to stay. As with Ebola in the early days, we watched from afar and wondered what would happen. But while Ebola burst on the U.S. scene, Zika trickled. That trickle allowed the CDC to get ahead of the messaging, and television network reporting was measured. In real time we all tracked the movement of mosquitoes to Brazil and Puerto Rico and finally Miami.

And this time we have a vector as an enemy. We can hate mosquitoes, fear them and not each other. A virus in an insect is somehow less terrifying than a virus in a person who has traveled from afar. Zika is not flamboyant. It has no movies or popular books to help conjure up images of bodies liquefying. It caused a flurry of handwringing around the Rio Olym-

pics, but the Games went on and there were no reported cases of infection. Now winter is upon us, and we can hope that mosquitoes in North America will die their usual seasonal deaths. And so it goes.

But have we really learned anything about the dangerous interference of politics with medicine? While President Obama and National Institute of Allergy and Infectious Diseases director Dr. Tony Fauci implored Congress to release funds for Zika vaccine research, Congress instead left for summer break, putting clinical trials of a vaccine and hopes of fast-tracking it in peril. A line in the bill allowing Zika funding to be used in Planned Parenthood clinics along with other community health centers was enough to stall the allocation of funds. Congress finally approved Zika funding of \$1.1 billion in late September.

We are becoming a scientifically illiterate nation, and rising populism fuels distrust of our nation's scientists and revered institutions. Politicians add to the mess by denying evolution, vaccine safety and climate change. Our failure to address Ebola and Zika with a sound scientific discourse hurts us far beyond these two outbreaks. It does nothing to quell the anti-science, anti-immunization zeitgeist, which puts our vaccination programs at further risk and chips away at our public health system.

Viruses don't care about walls, or bad politics, or frightening rhetoric. The next viral outbreak that Americans have never heard about is just around the corner. We can't afford to let good science, public safety and global health be hijacked by politics. The public has a right to accurate information, rather than fear-mongering. Physicians who serve in Congress need to be better leaders, and the press has a responsibility to push for truth and follow the

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



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science. Science is not linear, and the scientific process can be messy — just like democracy. And that makes our collective responsibility all the more important. **SM**

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NO LIMIT?

CHALLENGING THE VIEW OF SICKLE CELL TRAIT

If you inherit a sickle cell gene variant from each of your parents, the result is sickle cell disease, which in its most severe form leads to bouts of intense pain and can drastically shorten your life. But what if you carry just one copy of the sickle cell variant — as is the case for 1 in 13 African-Americans? • Earlier studies had suggested that this status, known as sickle cell trait, could have dire consequences, including higher mortality from a condition called exertional rhabdomyolysis, which has been known to felled football players, often when they are practicing too hard in the hot sun without drinking enough water. ER, which occurs when molecules from the breakdown of muscles end up in the kidneys, is also a risk for soldiers on active duty.

But Stanford associate professor of medicine Lianne Kurina, PhD, questioned these studies. When she reviewed the literature, she saw it was dominated by reports about individual patients. She also saw that in one influential study — from a large population — the actual sickle cell trait status of every individual was not known.

In search of a more definitive answer, Kurina and her colleagues conducted the first-ever longitudinal cohort study of sickle cell trait in African-American soldiers of all ages. The result: no increase in mortality for soldiers with sickle cell trait, provided they follow standard safety precautions, including gradual increases in exercise and adequate water and rest breaks.

For the study, the researchers reviewed the health records of 47,944 African-American soldiers who served on active duty between 2011 and 2014 and for whom sickle cell status was known. The researchers got the health records from the Stanford Military Data Repository data set, which was created by Kurina and D. Alan Nelson, PhD, a postdoctoral scholar and former Army medical officer.

The repository includes all digitally recorded health encounters at military medical facilities or civilian institutions, general health information, and official records of physical performance and mortality of all active-duty U.S. Army soldiers. To protect privacy, the data in the repository are de-identified.

The researchers found that the risk of exertional rhabdomyolysis was only 54 percent higher among African-American soldiers with sickle cell trait than among those without it. A 54 percent increase might sound like a lot, but it's far less than the 300 percent increase caused by some ordinary prescription drugs. And smoking, obesity and increasing age each incurs a heightened risk of ER that is about the same as sickle cell trait's, the study showed.

"The most important thing to come out of this study is the really reassuring news that under conditions of universal precautions against dehydration and overheating, we don't see an elevation in the risk of mortality in people with sickle cell trait," says Kurina.

The assumption that sickle cell trait increases health hazards has led to mandated screening by organizations such as the Air Force, the Navy and the NCAA. But the American Society of Hematology and other organizations have argued that screening programs raise questions about job discrimination.

The study's results call into question the need to screen service members with sickle cell trait, especially with better safety precautions during intense exertion, Kurina says.

Kurina, Nelson and their team published the study in August in *The New England Journal of Medicine*.

— JENNIE DUSHECK



People with two copies of the sickle cell gene variant have sickle-shaped red blood cells, which can stick to vessel walls and cause severe health problems. A recent study of those with only one copy of the gene showed that they are at much less risk of death from overexertion than previously thought.

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State of mind

WHAT HAPPENS DURING HYPNOSIS

You are getting sleepy, very sleepy ... but why? • "Hypnosis is the oldest Western form of psychotherapy, but it's been tarred with the brush of dangling watches and purple capes," says David Spiegel, MD, professor and associate chair of psychiatry and behavioral sciences. "In fact, it's a very powerful means of changing the way we use our minds to control perception and our bodies." • Spiegel is the senior author of a new study, published online in July in *Cerebral Cortex*, showing which areas of the brain have altered activity during hypnosis. The researchers used functional magnetic resonance imaging to observe the brains of 57 subjects — 36 who were highly hypnotizable and 21 who were quite the contrary. They saw three changes in the highly hypnotizable group while those subjects were under guided hypnosis, but not while they were at rest or recalling a memory.

First, they saw a decrease in activity in an area called the dorsal anterior cingulate, part of the brain's salience network. "In hypnosis, you're so absorbed that you're not worrying about anything else," Spiegel says.

Second, they saw an increase in connections between two other areas of the brain — the dorsolateral prefrontal cortex and the insula. Spiegel describes this as a brain-body connection that helps the brain process and control what's going on in the body.



Last, the researchers observed reduced connections between the dorsolateral prefrontal cortex and the default mode network, which includes the medial prefrontal and posterior cingulate cortex. This likely represents a disconnect between people's actions and their awareness of their actions, Spiegel says — which may allow them to engage in activities suggested by a clinician, or that they suggest to themselves, without being self-conscious about doing so.

In highly hypnotizable individuals, hypnosis has been shown to reduce pain, treat addiction, and ease anxiety, phobias or post-traumatic stress disorder. The new findings might help scientists develop treatments for the rest of the population — those who aren't naturally as susceptible to hypnosis.

"We're certainly interested in the idea that you can change people's ability to be hypnotized by stimulating specific areas of the brain," Spiegel says.

— SARAH C.P. WILLIAMS

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