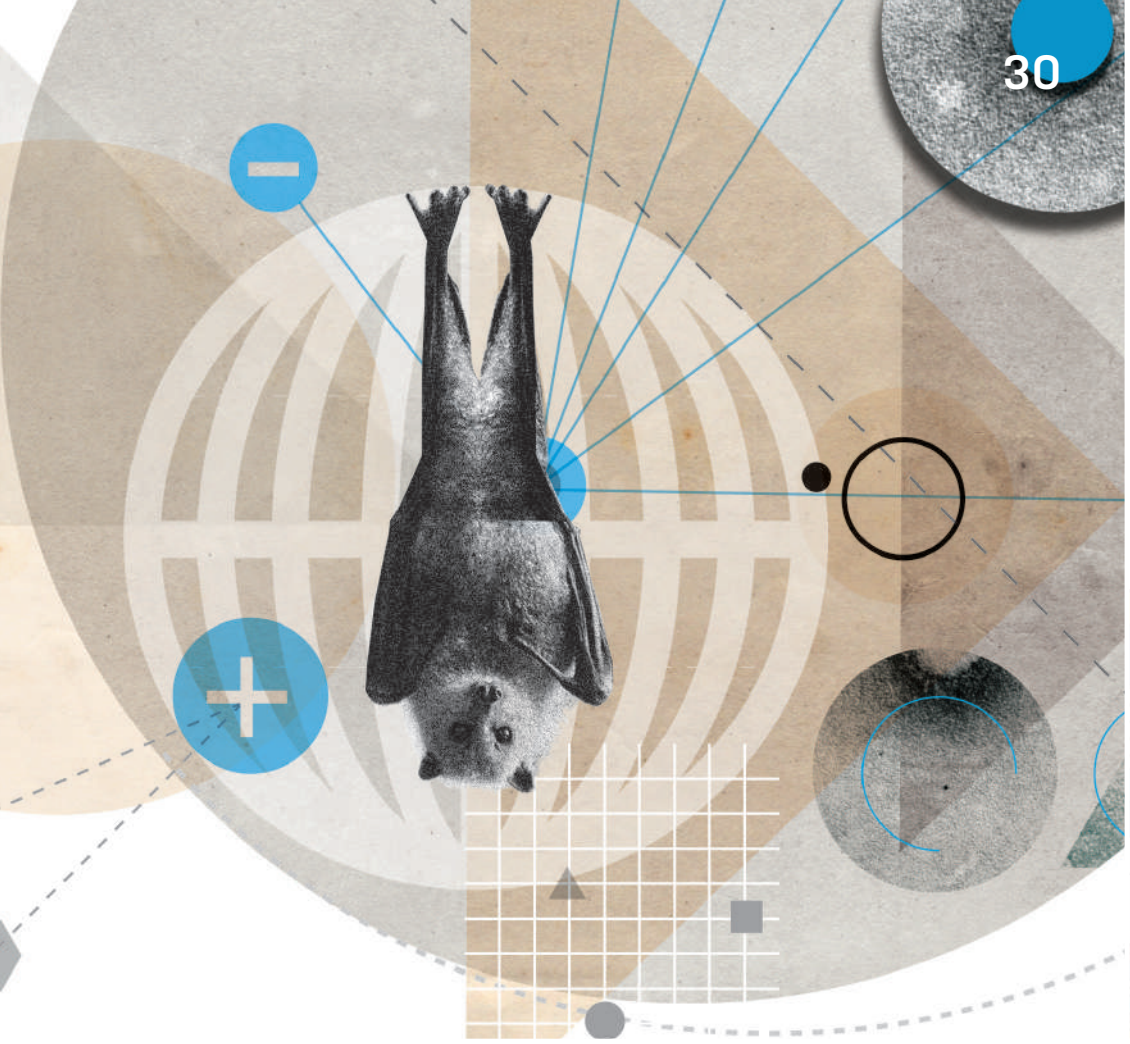
FALL 19

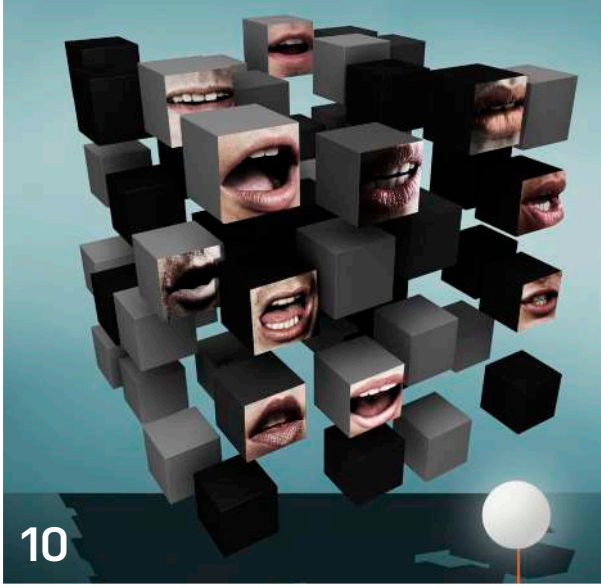
proto

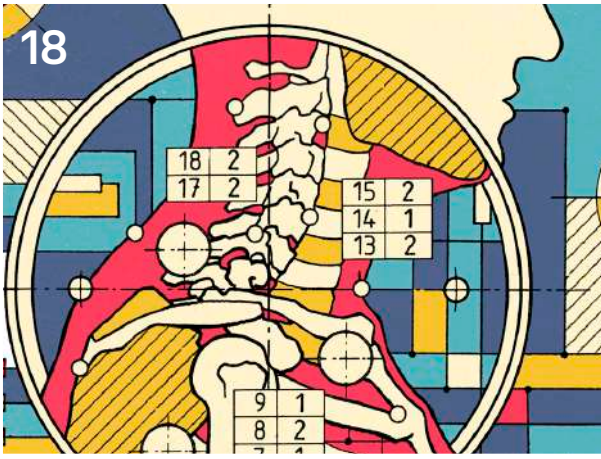
MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

"They Told Me I Died"

Near-death experiences are a puzzle for researchers, clinicians and the people who go through them. p24







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FALL 2019

STAT

POST-OP

FEATURES

on the cover

When the body comes close to death, the mind can undergo a life-altering experience. Understanding these moments better may lead to more compassionate care for the people who have them as well as fresh insights about the brain.
// Illustration by Prologue

proto: a prefix of progress, connoting first, novel, experimental. Alone, it conjures an entire world of the new: discoveries, directions, ideas. In taking **proto** as its name, this magazine stakes its ground on medicine's leading edge—exploring breakthroughs, dissecting controversies, opening a forum for informed debate.

proto

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Founded in 1811, Massachusetts General Hospital is a 1,000-bed academic medical center located in Boston. It is a founding member of Partners HealthCare and is the original and largest teaching affiliate of Harvard Medical School.

THE FIRST VACCINATION IN THE UNITED STATES happened July 8, 1800, in Boston, when physician Benjamin Waterhouse administered the new smallpox vaccine to his five-year-old son, Daniel. And it worked. In the more than 200 years since, vaccines have proved themselves time and again to be safe, efficient and compellingly effective—especially in saving the lives of children.

But in recent decades, a troubling and misplaced fear of vaccines has spread throughout society, causing far too many to reject what is arguably the best weapon available to prevent deadly disease. An effective vaccine for Lyme disease, for example, was introduced in 1998, but it failed because of public skepticism and the threat of lawsuits. Meanwhile, known pathogens continue to spread and new infections emerge because of such factors as climate change, human encroachment and overcrowded living conditions.

Developing vaccines to combat new diseases takes time and ingenuity. Some efforts, like creating a universal flu vaccine, have not yet succeeded, though promising studies are bringing that goal within sight. In addition, new techniques that leverage advances from many fields—including genomic sequencing, computer modeling of proteins and new ways of measuring cell function—could trim years, and possibly decades, from the traditionally tedious vaccine development process. (“To Build a Better Vaccine,” page 30).

Central to the next generation of safe and effective vaccines will be a more precise understanding of the immune response. The Ragon Institute, a pioneering collaboration among Massachusetts General Hospital, MIT and Harvard, received a record donation of $200 million this spring from Phillip and Susan Ragon. This flexible funding enables scientists to pursue bold and unconventional ideas for harnessing the power of the immune system to treat and prevent some of the world’s most devastating human diseases. The Ragon Institute has been close on the trail of an HIV vaccine, with one candidate currently being tested in a large efficacy trial in Africa. The researchers at Ragon have also used these resources to make progress on a universal flu vaccine and are exploring vaccine technology as a way to treat solid tumors.

We need to continue to build upon our understanding of the body’s immune response to pathogens, and we need new ideas about how best to fortify the vital first line of defense. Indeed, at stake are millions of lives that could be saved by the next vaccine . . . and the next.

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stat

FOCUS

Fixed-wing drones, carrying up to three units of blood, have been flying from a distribution center in western Rwanda to clinics as far as 50 miles away. Photographer Jason Florio visited the rural nation to capture the use of these “sky ambulances,” as the locals call them. Blood was among the first commercial products ever delivered by drone, the result of a partnership between the Rwandan government and Zipline, a San Francisco robotics firm. Zipline now also delivers a wide range of other products—including vaccines, contraceptives and drugs to treat HIV and malaria—in Rwanda and Tanzania, and in April the company struck a deal with Ghana to launch the world’s largest drone delivery service. Those drones will make as many as 600 deliveries per day and serve about 12 million people.

Regulatory and security issues in the United States have made drone deliveries slow to catch on. But the U.S. Department of Transportation recently selected 10 states to test the logistics of using drones as part of a Federal Aviation Administration pilot program. Medical supplies were a first priority, and in March drones started delivering samples between the campuses of WakeMed hospital in Raleigh, North Carolina.

JASON FLORIO/REDUX

INTERVIEW

Seeing Past the Scale

Obesity expert Fatima Cody Stanford looks at how physician bias around weight causes harm to patients.

BY STACY LU

Do doctors have a weight problem? Studies show that physicians, no less than members of the general population, show a marked bias against people who carry extra pounds. In the examination room, such attitudes can cause real harm, as physicians tend to spend less time with these patients and can overlook their non-weight-related symptoms.

Fatima Cody Stanford is an obesity medicine physician at Massachusetts General Hospital and researches the effects of bariatric surgery and weight loss medications on adults and children. She also studies how bias against people who are overweight can shortchange patients, and how physicians can begin to see—and treat—the whole person.

TONY LUONG FOR *PROTO*

Q: How can weight bias affect a patient's health?
A: People who report that they have experienced bias about their weight are more likely to develop type 2 diabetes and metabolic disease. They are more likely to binge eat and less likely to exercise. Patients who feel they've been "fat shamed" have an increased risk of depression, anxiety and low self-esteem. And when these shaming behaviors come from a physician, the patient is more likely to avoid seeking medical care in the future.

Even when physicians don't shame patients for their weight, their bias can show up in other ways. One patient went to her primary care provider with joint pain, but the physician wouldn't send her to an orthopedist because obesity was assumed to be the culprit. The patient ended up having a huge cancer in her hip. Sometimes all we see is the obesity.

Q: Your research shows that weight bias is particularly harmful to children. Why?
A: The health effects of weight stigma accumulate over a lifetime. It shapes patients' lifelong relationships with health care, which they see as a system that accuses them but doesn't help them. Parents also report that they feel blamed, which can lead to families missing medical appointments.

Q: Why does bias persist in medicine?
A: We do a good job of learning about diseases that may result from weight gain, such as diabetes and sleep apnea. But most of us don't learn enough about obesity itself to perceive it as a disease, even though the American Medical Association classified it that way in 2013. Instead we tend to think of obesity as a behavior or a character flaw, something that can be solved solely by eating less and exercising more. When weight loss doesn't happen, we jump to the idea that patients are not adhering to treatment plans.

Q: How does it help to think of obesity as a disease?
A: It changes the idea that a patient is the primary or only contributor to obesity. When we see obesity as a disease, we take the time to learn about the complexity of its contributing factors, such as genetics, psychosocial factors or environmental toxins. It means that we take more seriously the current interventions for weight loss, such as bariatric surgery or medications, which my research shows are effective.

In a survey I published in 2015 in the *International Journal of Family Medicine*, we found that primary care doctors don't feel they have the knowledge to treat obesity medically, especially in recommending bariatric surgery. There's a particular squeamishness on the part of pediatricians. But I've had patients who had surgery at 15, and their metabolic profile, their weight status and their outlook on life completely changed. We are able to place several obesity-related diseases in remission when we acknowledge obesity and treat it as a disease. If someone comes into my office with poorly controlled type 2 diabetes and dangerously high blood sugar, it would be medical malpractice for me to let that patient go home with the mantra to just "eat less and exercise more."

Q: How can doctors advise weight loss without seeming to be biased?
A: Using people-centric language helps. Patients are not obese; they have obesity. In some cases it can be severe, but not "morbid"—which is a loaded term. Be direct with your patients but acknowledge that they are human beings who deserve respect. Give them the license to express who they are and why they struggle with their weight. Just withhold the judgment.

BY THE NUMBERS

Fashion Scrubs

12

Published editions of *The Physician Himself*, a guidebook on physician comportment written in 1890. Regarding dress, it suggests: "Do not altogether ignore the fashions of the day, for a due regard to the customs prevailing around you will show your good sense and discretion."

3

Height, in stories, of a billboard in Times Square this April announcing the latest Grey's Anatomy line of scrubs by Barco Uniforms. The company was the first to introduce the idea of the "fashion scrub" in 1965. Barco ads of the time, featuring model Cheryl Tiegs, helped launch her career.

1,800

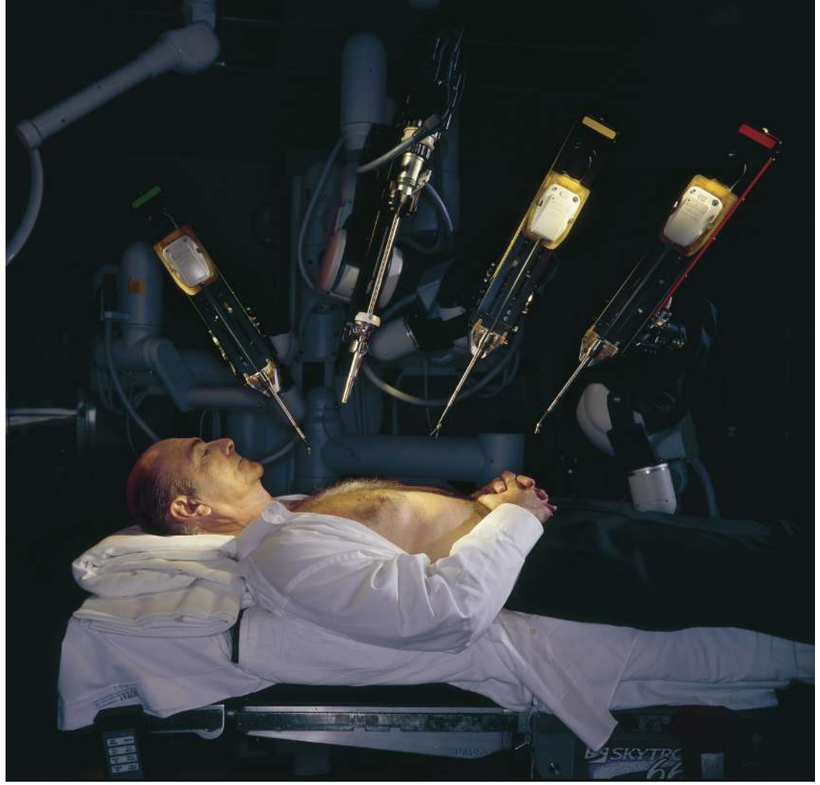
Square feet of space in the first scrubs pop-up shop, on Melrose Place in Los Angeles. The shop offered designs by the company FIGS, which reignited a "designer" scrubs movement in 2013. Between 2014 and 2017, the company's revenue increased 9,948%.

24

Largest women's clothing size in the Curve scrubs line from Jaanuu, a brand launched in 2013 that describes itself as "runway inspired." The Curve line doesn't charge more for plus sizes, a practice still common elsewhere in the industry.

90

Percentage of American health care professionals who must purchase their own uniforms, helping make scrubs a $10 billion industry in the United States and about a $60 billion one worldwide.



UPDATE

Is the "Robot Surgeon" Worth It Yet?

Despite a massive investment by hospitals, the jury is still out on how these machines affect outcomes.

BY STEPHEN ORNES

In 2000 the U.S. Food and Drug Administration approved the first complete robotic surgery system, a four-armed, multimillion-dollar behemoth called the da Vinci. Since then, the technology has become commonplace. "A robotic prostatectomy for prostate cancer is now the standard of care," says Michael Palese, chairman of urology at Mount Sinai Beth Israel Hospital in New York City, noting that nine out of 10 prostatectomies are now performed robotically.

Twelve years ago, *Proto* asked whether the technology would ever improve on the skill, technique and experience of unassisted human hands ("The Robot Surgeon," Winter 2007). "It's great to have new technology," said the late Lawrence Cohn, former chief of cardiac surgery at Brigham and Women's Hospital, "but at the end of the day, you'd better have at least as good a result as you did with the old technique, or you're just kidding yourself."

Dozens of studies have tried to compare the outcomes of robotic surgery and traditional surgery, but many questions remain. One issue is that research into the technology often involves physicians with a vested interest in the success of surgical robots. A review published in the March 2019 issue of *Annals of Surgery*, for instance, looked at 33 major studies, more than half of which reported positive results for robotic surgery. But nearly all of that published work included authors who received money from robotic surgery companies. Researchers who got more than $9,550 were more than twice as likely to report the beneficial outcomes of robotic surgery compared to researchers who received less money, the authors found.

Economic motives aside, the expertise required to guide robotic surgery may itself constitute a research bias. "Many studies are done by single centers with considerable experience," says surgeon Kyle Sheetz at the University of Michigan's Center for Healthcare Outcomes and Policy in Ann Arbor, "but their outcomes may not be generalizable to surgeons across the country, who are familiar with the devices to varying degrees."

> "At the end of the day, you'd better have at least as good a result as you did with the old technique."

In other words, surgeons who have done only a few supervised operations with robotic devices may be allowed to do procedures on their own, and their results might not match those in the journals, performed by robot-savvy surgeons, Sheetz notes. In a letter published in *JAMA* in April, he recommended that hospitals and institutions establish more rigorous credentialing requirements.

There may also be issues with the kinds of surgery the robots perform. In February the FDA sent a special alert stating that the safety and effectiveness of robotic surgery for cancer treatment, including mastectomies, "has not been established," and noted that preliminary evidence might link it to shorter survival with some cancers. An international trial published in *The New England Journal of Medicine* last October found that cancer-related hysterectomy via minimally invasive robot-assisted or laparoscopic surgery was associated with lower three-year survival rates compared to open surgery. And even though some hospitals have begun using robots for minimally invasive mastectomies, there have been no clinical trials establishing that the robotic version of the procedure is more beneficial for patients than conventional surgery.

In other cases, robotic procedures may be as effective as laparoscopic surgery, but introduce higher price tags because hospitals must buy and maintain the expensive machines. A 2017 *JAMA* study involving nearly 24,000 patients who had undergone a kidney removal found that using robotics didn't introduce any complications, but it did affect costs: Robotic surgery added an average of around $3,000 per patient.

Whatever its dangers or merits, robotic surgery is not going away anytime soon. As of the end of last year, 3,196 da Vinci machines have been installed in the United States, each at a cost of up to $2.5 million, and at least four other robot systems are scheduled to debut as early as this year. Michael Palese at Mount Sinai is optimistic that robotic surgery will continue to evolve. "As competition increases, costs will come down," he says. "And the techniques, and the surgeons who use them, will keep improving."

MAX AGUILERA-HELLWEG FOR *PROTO*

MEDICAL ARCHIVES OF THE JOHNS HOPKINS MEDICAL INSTITUTIONS

MILESTONE

A Glove Story

The common surgical glove has an amorous past.

BY STACY LU

William Halsted is considered the father of American surgery for a number of reasons, among them his work advancing the procedures for gallstone removal and the radical mastectomy for breast cancer. But he is less well known for his role in introducing the surgical glove—and his mixed motives in its development.

Halsted cut a dashing figure, though a tragic one. He nearly destroyed his early career with an addiction to cocaine, a substance he had been testing for its anesthetic power. After being treated for the problem—with morphine, to which he also became addicted—a friend found him a job at Johns Hopkins Hospital in 1886.

Halsted quickly showed himself to be brilliant and fastidious, and the hospital appointed him its first chief surgeon. At his side was Caroline Hampton, the nurse in charge of his operating theater. Hampton was born in South Carolina and grew up on a plantation that was burned down in 1865 by Union troops. Impoverished, she left her family to enroll in nursing school at New York Hospital, and relocated to Baltimore for work.

Halsted found Hampton a capable and "unusually efficient woman," and so it was with some distress that he learned that, after surgeries, she would develop dermatitis from mercuric chloride, the antiseptic Halsted used in surgery. Noting her plight, the normally reserved doctor took the gallant step, not of replacing the nurse, but of asking the Goodyear Rubber Company to make two sets of thin rubber gauntlets—gloves with extended cuffs—expressly for Hampton. "On trial these proved to be so satisfactory that additional gloves were ordered," he noted.

Their colleague William Osler, often described as the father of modern medicine, began to observe that relations between the two might be veering from the strictly professional. "One Sunday morning I went in the Pathological Laboratory and found Dr. Halsted teaching her osteology—demonstrating the fibula. I then knew all was 'up with him.'" A week after that, the two announced their engagement, and the couple were married in 1890.

It took another seven years for gloves to catch on widely among surgeons. Though Halsted used antiseptics during surgery and believed that minimizing infection could be done through the use of small, clean cuts, he found that the bulky early gloves interfered with manual dexterity. It was Halsted's colleague Joseph Bloodgood, the director of surgical pathology, who showed that they greatly reduced the risk of infection. Later, Halsted wondered how "we could have been so blind as not to have perceived the necessity for wearing them invariably at the operating table."

The Halsteds remained married until William's death in 1922; Caroline died two months after him. Their legacy partly lives on in research on the gloves they helped bring about. Most recently, that work has focused on the tendency of gloves to become perforated during procedures. That happens as often as 17% of the time, and it has led to research into embedded disinfectants, double gloving and new glove models that can indicate when they have been punctured.

An early twentieth-century rubber surgical glove with the seal of the Stanley Supply Co. of New York stamped on the cuff

POLICY WATCH

Saving Stark

Can the embattled reform law adapt to a newer model of health care?

BY LINDA KESLAR

SEBASTIEN THIBAULT

The 1980s saw both a steady expansion of Medicare and a bipartisan concern about its rising costs. One of the era's signature pieces of reform legislation came from a California congressman, Pete Stark, who proposed a commonsense rule: Physicians should not refer their Medicare patients to another provider if the transaction would benefit the physicians financially. Several statutes built around that idea became known, collectively, as the Stark Law.

"Financial interest can corrupt decision-making," says Claire Sylvia, a partner in the San Francisco office of Phillips & Cohen, a law firm that has handled a number of Stark cases. "That's particularly a problem when a person's health is at stake, and the money being spent is taxpayer money."

Yet while the law has been successful at curbing misconduct, it has also recently run headlong into a different reform movement: the drive to shift health care away from payment for individual services and toward bundled, or "value-based," care.

The Stark Law often butts up against a signature creation of the Affordable Care Act: the accountable care organization, or ACO. These voluntary associations of practitioners coordinate services to reduce costs in return for a cash incentive from Medicare. For instance, the 70 physicians who make up the cardiology section of Illinois-based AMITA Health Medical Group are part of an ACO that includes certain nursing homes and home care agencies, with whom they partner for seamless care.

"We can't direct patients to these specific organizations within our ACO, even if that helps us deliver better patient care—because of Stark," says Cathie Biga, president and CEO of Cardiovascular Management of Illinois, which helps to administer the program. "Instead, we have to give Medicare beneficiaries and their families a list of post-acute-care facilities in the area and let them make a choice."

To ease such conflicts, legislators over the years have loaded up Stark with numerous exceptions, waivers and workarounds. But many of these amendments apply only to federally sponsored ACOs, which are not the only efforts to build bridges and reduce costs.

Even with waivers, however, ACOs often worry that they might run afoul of some part of the byzantine law, says Kevin McAnaney, a lawyer who helped draft the original Stark rules. Compliance burdens are costly and there remain areas of legal uncertainty. "Stark is definitely holding back the adoption of value-based payment models," he says. "Health care systems aren't willing to take the risk." This has led some erstwhile Stark proponents—including Pete Stark himself, who served in Congress until 2013—to call for repealing the law entirely.

Yet Stark still fulfills its original purpose, which is to penalize those who try to game the Medicare system. Last year, Health Management Associates, formerly a U.S. hospital chain headquartered in Naples, Florida, agreed to pay more than $260 million for compensating physicians who referred patients to them, among other charges. William Beaumont Hospital in Detroit paid $84.5 million to settle allegations that it provided free or substantially discounted office space and staff to reward physicians for patient referrals.

Last year, the U.S. Department of Health and Human Services said that reexamining the Stark rules was a top priority, and the federal Centers for Medicare & Medicaid Services opened the issue for comment. It received 375 letters from concerned parties, including the American Medical Association and other industry leaders. Many asked for additional exceptions for value-based payment arrangements and models for coordinating care, which they said are needed to reduce costs and deliver higher quality care. This past spring, CMS Administrator Seema Verma indicated the Stark Law would receive a major update sometime this year, with what she characterized as "the most significant changes" to the law since its inception.

There is a similar push to reform the law on the legislative front, with Congress considering two bills that pursue different objectives. The Medicare Care Coordination Improvement Act of 2019, pending before the House Subcommittee on Health, proposes eliminating some Stark restrictions. But the Promoting Integrity in Medicare Act of 2019, also pending, would tighten the law—altering exceptions it sees as having gone too far, including one that allows physicians in some specialties to refer patients to imaging, radiation and other therapies that are provided in their offices and in which they have a financial interest. Closing that loophole alone could save an estimated $3.3 billion in Medicare reimbursements over a 10-year period, according to a 2017 analysis conducted by the nonpartisan Congressional Budget Office.

> "Stark is definitely holding back the adoption of value-based payment models."

Some experts worry that the current push for change could jeopardize what Stark has accomplished. Genevieve Kanter, an economist and assistant professor at the Perelman School of Medicine at the University of Pennsylvania points to research showing that ACOs and other care coordination programs may turn out to be not as good at improving care and reducing costs as proponents had estimated. Gutting Stark to help those groups "could lead to few gains and substantial losses," Kanter says. "Stark is badly in need of critical reexamination, but there are a lot of open questions. Consumer protection still needs to be a priority."

SECOND OPINION

Perception Shift About Organs

Given the persistent organ shortage, it has become critical to identify innovative ways to help more patients. The *Proto* article "Rethinking the Perfect Organ" (Spring 2019) outlines a few promising solutions for how we can increase transplant rates and reduce organ discard. These new strategies and policies, however, will not create the desired changes on their own. Many of them require a shift in perception on the part of health care systems, providers and patients—and a better understanding of the perceptual obstacles we face.

"Increased risk" donor organs present a case in point. These organs—typically from a donor who had an STD, or was a sex worker or intravenous drug user—present an extremely low chance of transmitting HIV or hepatitis C. But transplant providers vary in their willingness to offer increased risk organs to their patients, and patients, for their part, may not accurately perceive the risk of disease transmission.

What is needed, then, is a new body of research that looks into the root causes of such perceptions. Insights can help shed light on the common, perhaps tacit, values that unintentionally cause us to discard organs that might be saving lives. When we know what these factors are, we can more effectively implement strategies to counter them, and deliver healthy organs to a larger number of patients.

Elisa J. Gordon // Professor of Surgery/Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, Illinois

A Global Approach to ME/CFS

As "Energy Crisis" (Spring 2019) so eloquently points out, even today myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) resists easy categorization. How do we begin to understand the biological underpinnings of this complex, multisystem disease?

Big data may hold the answer and help us unlock some of the questions that ME/CFS researchers and clinicians have grappled with for years. By looking at health information across whole populations, we can identify patterns of similarity that help us characterize subtypes of the disease and develop personalized therapies.

Efforts are under way at our organization, Solve ME/CFS Initiative, to establish a global registry and biobank in collaboration with others around the world. Researchers who study the disease will be able to access this patient data only if they agree to share their results and methodologies with others using the registry. Our hope is that this will break down data silos and allow for a unified global approach to ME/CFS research, helping knit together some of the myriad scientific hypotheses and generate a comprehensive disease model.

Sadie Whittaker // Chief Scientific Officer, Solve ME/CFS Initiative, Los Angeles, California

WHAT'S YOUR TAKE? **Send your comments or suggestions for future topics to protoeditor@mgh.harvard.edu.**

Something in Your Voice

Machine analysis of speech can help pinpoint those with mental health issues. But the new technology also raises troubling questions.

By Kristen French // Illustrations by Matthieu Bourel

Debbie Gingrich saw things turn for the worse in 2016, when Cincinnati schools experienced an unexplained surge in youth suicides. Suicide is the second most common cause of death for teens and young adults in the country, but its prevalence in Cincinnati had mostly held steady for the previous 15 years. Now the area was seeing an alarming spike. The trend continued into January 2017, when an eight-year-old boy killed himself after reportedly being bullied at school, and another six students took their lives soon after. Parents and school officials were desperate with worry, and the local medical community hunted for a way to identify the children most at risk. "In the mental health world, we don't have the equivalent of an X-ray to detect a broken bone," says Gingrich, director of behavioral health at The Children's Home, which provides mental health support to troubled minors. "Everyone wants to know, 'What can we do to save a life?'"

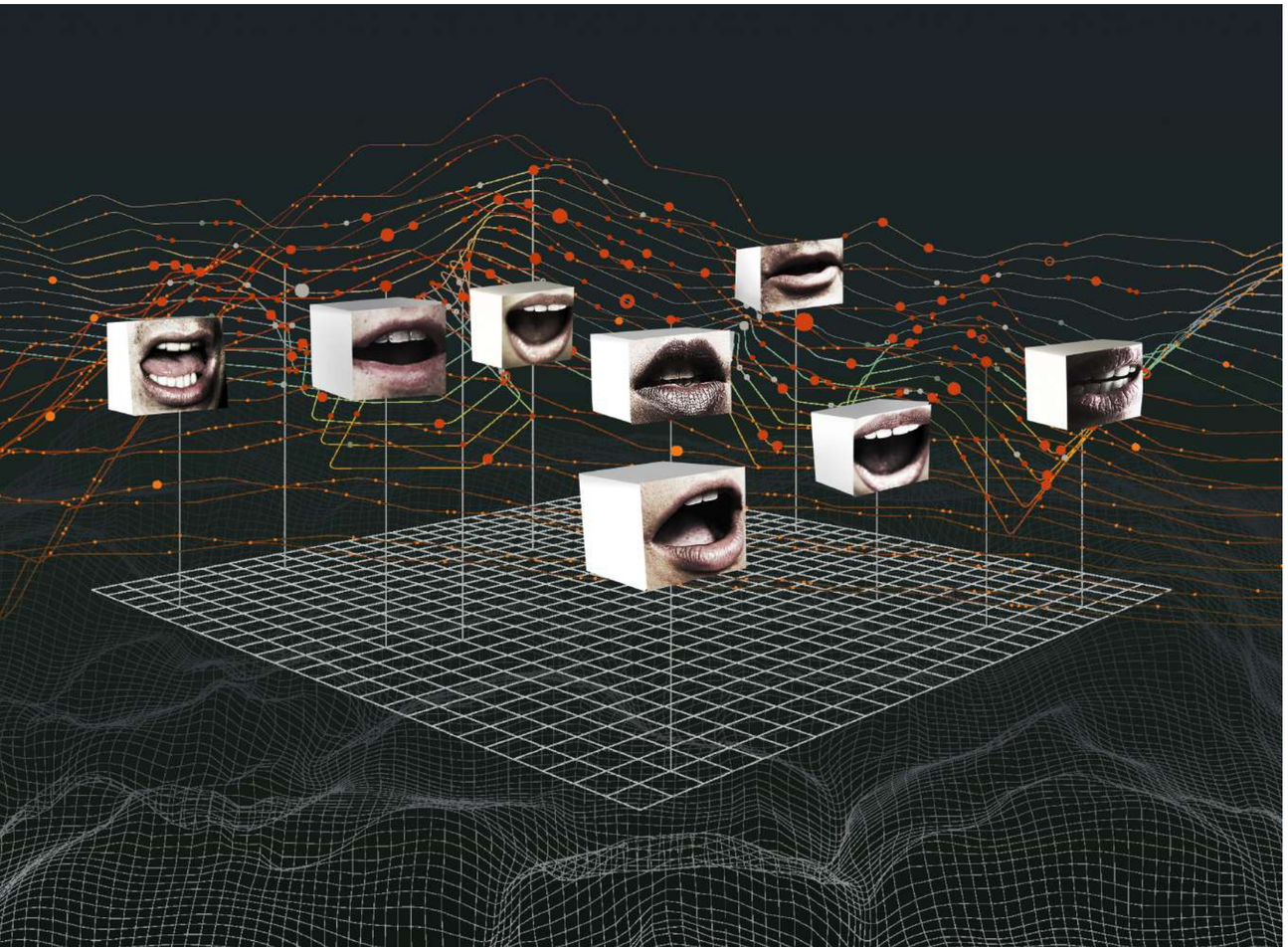
One answer, the Cincinnati schools decided, was to try an experimental artificial intelligence technology. It promised to detect telltale signs of suicidal intent hidden in human speech. Developed by John Pestian, a professor in the divisions of biomedical informatics and psychiatry at Cincinnati Children's Hospital Medical Center, the machine-learning algorithm sifts through recordings of a patient's voice to analyze a combination of signals, some of which no human could detect: minute changes in inflection or delays in the nanoseconds between words and syllables.

Pestian's algorithm had been trained by scanning suicide notes and recordings of patients who had recently survived a suicide attempt. In one study from 2016, his team

tested the algorithm on recordings of 379 patients. Some of them had attempted suicide in the previous 24 hours; some had mental illness, according to psychiatric assessments, but had not attempted suicide; and a third cohort fit neither category. By screening the content of the tapes alone, Pestian's algorithm was able to assign patients to the correct category 85% of the time.

Pestian's algorithm made its appearance in a few Cincinnati schools this spring. In the first phase, counselors made mental health assessments of the students using the usual tools but also recorded them on a custom mobile phone app. Researchers looked to see whether the voice analysis matched up with the psychiatric surveys and opinions of the professionals. It performed well enough that the technology rolled out at about 20 schools this fall, recording interviews with thousands of students. The researchers hope it will help direct the right students to psychiatrists for further evaluation and head off tragedies for at least a few.

Speech analysis is a promising frontier in the emerging field of computational psychiatry, which applies the tools of artificial intelligence to mental health. Using high-powered machines to sort through piles of data, researchers try to spot patterns in cognition, behavior or brain function that can help them understand and detect mental illness. On the speech front, these programs automate detection of linguistic and vocal patterns that only a highly trained psychiatrist might pick up, as well as some acoustic clues the human ear can't perceive. Algorithms created by scientists at Harvard, MIT, Columbia and Stanford, among others, have so far been able to use as little as a minute of speech, collected with consent, to identify people with post-traumatic stress disorder, depression, schizophrenia, psychosis and bipolar disorder. These automated assessments have been found to align with the opinions of trained psychiatrists between 70% and 100% of the time.



As a mental health crisis unfolds in the United States and suicide rates hit their highest levels since World War II, many people are pinning their hopes on AI to help at a time when the psychiatric field is severely understaffed. The U.S. Department of Defense is funding ongoing research to develop AI tools that can detect PTSD—to determine whether a soldier back from war is psychologically suited for redeployment, for instance. Silicon Valley is investing heavily, too. Earlier this year, for example, Google launched a partnership with The Trevor Project, a nonprofit that works in suicide prevention for LGBTQ youth. The project will use proprietary technology from Google that can detect and analyze human emotions in voice and text to help alert counselors to a patient's possible suicide risk.

Plentiful real world data, collected from smartphones and social media—and, perhaps one day, voice-activated assistants such as Amazon's Alexa or Google Home—are helping scientists develop clinical tools that promise a way to scan for mental illness cheaply, remotely and noninvasively. "You don't have to biopsy someone, you don't even have to draw their blood," says Charles R. Marmar, chair of the department of psychiatry at New York University School of Medicine who specializes in PTSD. "All you have to do is record them."

But with that ease comes a round of questions, both clinical and ethical. Who should collect this data, and who should analyze it? How confident can researchers be about AI diagnoses? And if a machine delivers an incorrect assessment about a person's mental health, what can be done to head off dangerous consequences?

• • • •

Each year the United States spends more than $201 billion on mental health services, making it the most expensive category of illness to treat. Yet there is a shortfall of providers. Over half of U.S. counties don't have a single social worker, psychologist or psychiatrist. Unlike in other medical fields, there's no blood test or biomarker to speed diagnosis. Uncovering a mental illness still largely relies on a single expert going through the time-consuming process of conversation and observation.

Even then, the science is far from exact. Serious mental illnesses are categorized based on symptoms set forth in the *Diagnostic and Statistical Manual of Mental Disorders*,

Signs in the Sounds

The speech of someone with depression can carry a number of linguistic and acoustic markers.

1 First person

A higher incidence of first-person singular pronouns, such as I, my and me, is one of the most robust language markers for depression, and may even be helpful in flagging likely future depression before it's fully formed. A recent meta-analysis found that this characteristic of depressed speech appears to hold true across demographic lines.

2 Articulation errors

Imprecise consonant and vowel production are also common. According to one analysis, depressed speakers make 71% more "speech errors" than non-depressed speakers. These may include word omissions, transpositions and substitutions of incorrect but similar sounding words.

3 Pause length

The duration of pauses is also longer, on average, in most depressed patients. As early as the 1980s, researchers found that patients who transitioned from depressed mood states showed a decrease in pause duration of more than 50%.

4 Negative emotion words

Researchers at the University of Pennsylvania recently looked for words most strongly associated with future depression status. Many of these reflected states of sadness, loneliness, hostility and rumination.

5 Monotone pitch

Some of the earliest investigations into the acoustic aspects of depressed speech found consistent abnormalities, including reduced pitch range, reduced variation in intonation and reduced linguistic stress. Such speech may sound dull and "lifeless."

6 Tense vocal quality

Depressed speech is often described as having a throaty, strained or tense quality. MRI studies have shown that this is associated with increased vocal tract tension.

or DSM. Yet there is considerable diagnostic overlap among these conditions.

Anxiety, difficulty with concentration and changes in energy level, for instance, could indicate bipolar disorder, PTSD or depression. At least half of patients receive more than one psychiatric diagnosis, according to a 2018 study published in *JAMA Psychiatry*. And settling on the right one sometimes takes years.

In 2013, just prior to publication of the fifth edition of the *DSM*, Thomas Insel, then head of the National Institute of Mental Health, became so frustrated with the reference book that he publicly denounced it in his director's blog on the NIMH website. He wrote that it lacked scientific "validity" and that "patients with mental disorders deserve better." Insel championed moving research away from *DSM* categories, instead focusing less on symptoms and more on the causes of these conditions, a shift that he called a first step toward "precision medicine" in mental health. A research group at NIMH began to define criteria for a new classification system for mental health disorders. One of those criteria is language.

Machines can now sort through vast troves of data, looking for patterns humans might miss.

Insel believes that natural language processing, a marriage of data science and linguistics, could be a game-changing biomarker for mental health, offering objective measures of how the mind is working. He now serves as president of Mindstrong Health, a technology company that measures mental health via mobile phone use data, and is optimistic about the potential of digital technology to usher in a new age in mental health diagnosis and treatment. "Over the next decade, the use of AI tools to classify language may transform the field, giving community health workers and emergency room physicians the tools of a master clinician," he says.

Using language for diagnosis is as old as the field of psychiatry itself. Sigmund Freud was famously inspired by slips of the tongue, which he believed could reveal unconscious urges. In the early 1900s, Swiss psychologist Eugen Bleuler and his then-assistant Carl Jung pioneered the use of word association, one of the first observational, empirical tests used in psychoanalysis. A delayed response time or jarring word associations could indicate psychological conflicts and help point toward a diagnosis.

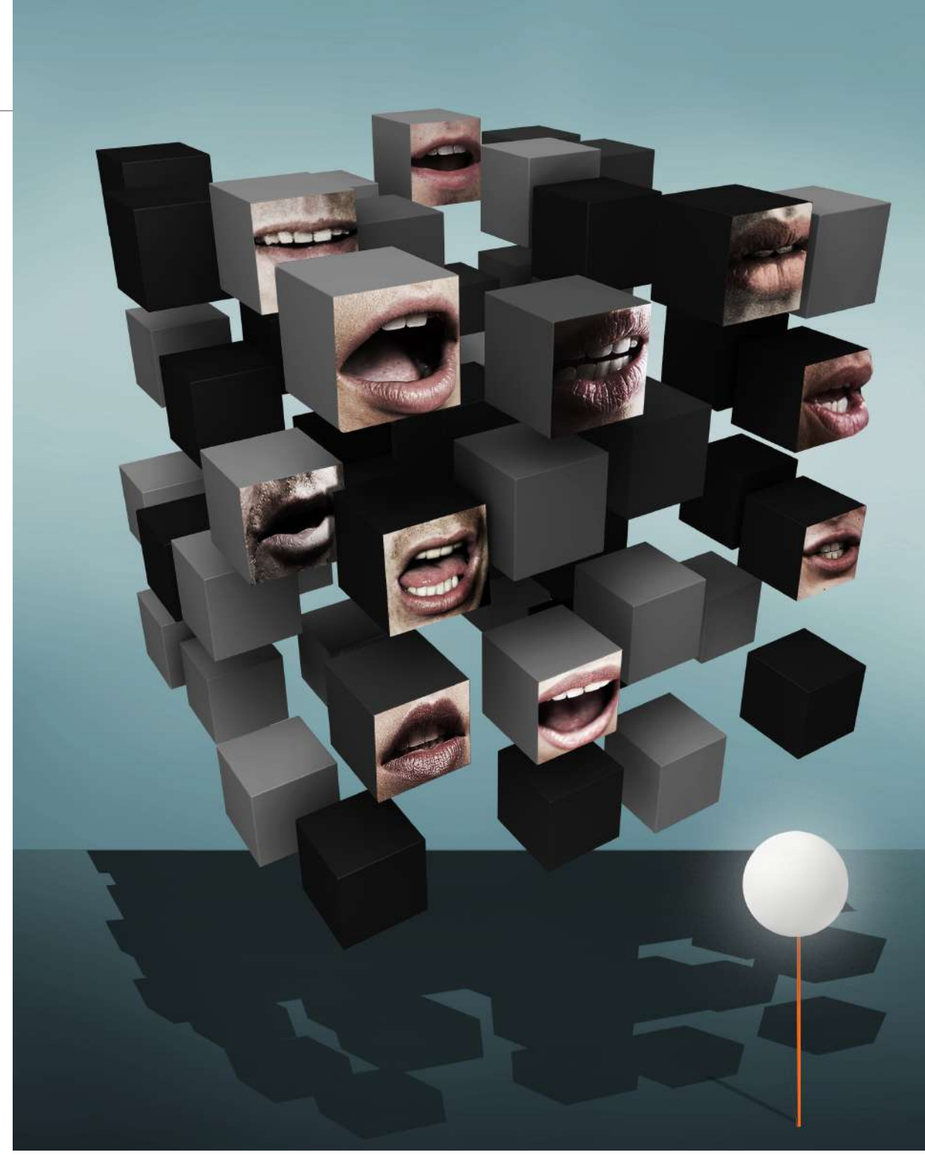
After World War II, researchers began looking beyond the linguistic content of speech toward acoustic content, or meanings hidden in the sounds of speech itself. For example, NASA began taking recorded language samples from astronauts to analyze their stress levels, among other metrics, and in the 1990s, the Department of Defense started testing voice analysis for lie detection to replace the much maligned polygraph.

Today, psychiatrists are trained to look for speech traits in interviews with patients: Unusual talkativeness can indicate a hypomanic episode in bipolar disorder; reduced pitch and a slower speaking rate can indicate severe depression; and jarring breaks in meaning or coherence from one sentence to the next might suggest schizophrenia.

The first attempts to measure the language of mental illness quantitatively began in the 1980s, when a University of Maryland psychiatrist named Walter Weintraub began hand-counting words in speeches and medical interviews. Weintraub noticed that higher ratios of "I" and "me" in a person's speech were reliably linked to depression. In the next decade, American social psychologist James Pennebaker created software that counted individual words and classified them into more than 80 linguistic categories—words that expressed insight or negative emotion, for example. Language that favored some of these categories correlated with mental health issues. Analysis of the auditory features of mental illness kicked off around 2000, when a team from Vanderbilt and Yale found that fluctuations in voice "power," among other features, could serve as an indicator of depression and suicidality.

More recently, advances in AI have transformed this approach to understanding speech. Machines can now sort through vast troves of data, looking for patterns humans might miss. Improvements in mobile phone recording technology as well as the advent of automated transcription over the past decade have also been critical to the field, making rigorous large-scale studies possible for the first time, according to Jim Schwoebel, CEO and founder of NeuroLex Diagnostics, which is working to build a speech analysis tool for primary care physicians to screen for schizophrenia. In the past several years, scientists have continued to refine their analytical tools, in some cases devising studies with larger sample sizes by extracting data from social media posts instead of working only with small cohorts in the lab.

Researchers with the University of Pennsylvania's World Well-Being Project and Stony Brook University in Long Island, New York, for instance, have been collecting written language samples from social media. They recently published a study showing how one of their AI programs was trained to scour the Facebook posts of 683 consenting users—114 of whom had a depression diagnosis in their medical records—and could predict the condition up to three months earlier than clinicians could. With a vast database of people sharing thoughts and feelings in public, and the computing power to sift through it and look for patterns, the internet becomes a laboratory of speech.



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But it is with the spoken voice that AI has really been able to break new ground, as computers learn to detect changes in sound that even a highly skilled psychiatrist would never pick up. In work supported by the Department of Defense, for instance, a team of researchers from New York University's Langone Medical Center are collaborating with SRI International, the nonprofit research institute responsible for creating Apple's voice assistant Siri. This past spring they published results showing that their program had identified imperceptible features of the voice that can be used to diagnose PTSD with 89% accuracy.

The production of speech uses more motor fibers—the nerves that carry messages to muscles and glands—than any other human activity. Speech involves more than 100 laryngeal, orofacial and respiratory muscles, creating a neurologically complex behavior that produces subtle variations in sound. The engineers at SRI International isolated 40,526 features of the human voice and asked their program to listen to half-hour speech samples taken from 129 male veterans who had been to war in Iraq and Afghanistan.

The team, led by NYU psychiatrist Charles Marmar, was able to identify 18 voice features that were present in all speakers but had a different pattern in PTSD cases. These included a narrower tonal range (fewer highs and lows), less careful enunciation, a more monotonous cadence and vocal changes caused by tension in throat muscles or by the tongue touching the lips.

"We thought the 18 features would reflect high levels of anxious arousal," says Marmar, "but they didn't. They reflected monotonous speech, slowed speech, less bursty speech, flatter speech, less animated speech. In other words, low energy, atonal and unemotional." Marmar thinks that this may result from studying soldiers five to eight years after they served in a war zone, and that this long window after the event may have led to a numbing of emotions as a defense mechanism against long-term stress mixed with alcohol and other problems.

Marmar's team now wants to repeat this analysis using a sample that includes both male and female veterans and nonveterans. If the AI continues to show high marks, the

team plans to use the program to test the effectiveness of a new drug for PTSD, studying the voice quality of a group of veterans before and after they take the treatment.

Another complicated but critical task for AI is to predict a future mental health event, such as an episode of psychosis, which can take the form of delusions and incoherent speech. Evidence suggests that the earlier mental illness is caught and treated, the better the outcome, so predictive powers would be particularly valuable.

One lab making headway in this regard is run by Guillermo Cecchi, a computational biologist at IBM Research in New York. Cecchi and his team are building an automated speech analysis application for a mobile device. In a study published in 2018, his algorithm was able to use a few minutes of speech collected during interviews to identify those who would develop psychosis over a two-and-a-half-year period. It accomplished the task with 79% accuracy—a rate validated in two additional studies. The computer model was also found to outperform other advanced screening technologies such as neuroimaging and electroencephalograms, which record brain activity.

"Language is one of the best windows into mental processes that we have," says Cecchi. "Now we are using machine learning techniques and AI techniques to quantify what was mostly based on the particular experience of a well-trained psychiatrist or neurologist." He envisions such tools serving as "stethoscopes of the mind," available in the office of every psychiatrist, neurologist and social worker—and in every patient's pocket.

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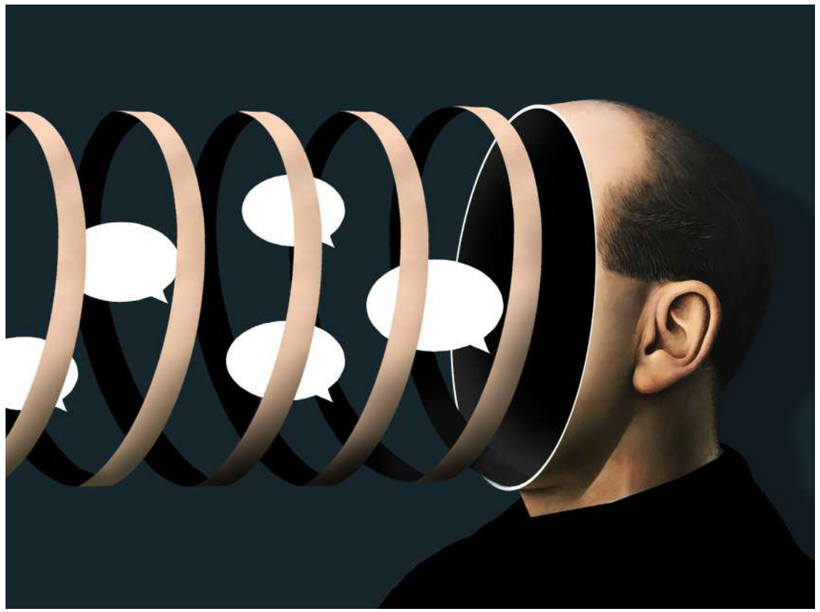
A number of barriers stand between these early efforts and their wider adoption. One of them is the scarcity of good training data, as the number of voice samples teaching the current generation of AI is still relatively small. Even the most rigorously tested models learn from, at most, a few hundred professionally diagnosed psychiatric patients. And larger samples can be difficult to collect and share among researchers because of medical privacy concerns—a problem that affects medical AI projects in every field.

"It's encouraging that these pilot projects are showing us what's possible with voice analysis, but it's kind of just the beginning," says John Torous, director of the division of digital psychiatry at Beth Israel Deaconess Medical Center in Boston. "No one has found a way to capture clinically actionable and useful data at the population level." Most researchers agree that sample sizes need to be in the tens of thousands before these projects can have full confidence that the algorithms work.

One of the biggest problems with a small sample size is that the AI can falter when it encounters a speech pattern it hasn't adequately trained on, such as a linguistic subculture. Apple's voice assistant Siri, for instance, still struggles to handle questions and commands from Scottish users. IBM's Cecchi notes that research participants, who mostly belong to similar socioeconomic and linguistic groups, likely have trained existing AI algorithms to recognize vocal cues that will not be relevant for other populations. "We study the temporal structure of your voice, its cadence. That can vary by culture," says Cecchi.

But such problems may be easier to solve than larger, ethical questions. One well-known concern is that AI can propagate bias. When a model makes a diagnosis, it is only as good as the human psychiatrists it has learned from, but racial biases are well known to exist in current mental health care settings. An African American patient with the same symptoms as a white patient is more likely, for instance, to be diagnosed with schizophrenia and less likely to be diagnosed with a mood disorder. So AI may simply carry those errors forward, and to a wider population.

One response is to increase the "explainability" of AI models. Machine learning algorithms are generally considered "black box"



Many pin their hopes on AI to help at a time when the field is severely understaffed.

models that present results without offering researchers any sense of how the machine arrived at the final answer. But the Navy Center for Applied Research in AI, via funding and research from the Department of Defense's investments arm, DARPA, as well as IBM, are working to create AI that can explain how it came to its conclusions. Other teams are laboring to develop AI programs that can effectively communicate how much uncertainty is involved in a prediction. That information would help practitioners understand how much weight to give AI in making clinical decisions. "It's very important that the AI be explainable, so that we can fiddle with the knobs and address where these AI formulations are coming from," says Cecchi.

Another major concern is who should have access to these diagnostic tools. Facebook already has a function that scans posts by members and flags those who might be at risk of suicide. Facebook users can't opt out, and since last fall, the tool has been involved in sending emergency responders to check on 3,500 users who were thought to be in danger. Yet despite criticism of the intrusiveness of the function, Facebook has declined to release data or publish findings related to the interventions.

As the relics of voice recording become a part of daily technology use—Amazon's voice-controlled Alexa device apparently keeps its voice data and transcripts forever, for example—many people worry about police, employers or private companies snooping into the mental health of those who use the devices. "We need regulation," says Jim Schwoebel of NeuroLex Diagnostics, "because right now, at least in some states, you can capture and reproduce someone's voice without their consent." And there are currently no laws to prevent discrimination based on speech.

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Behind all these concerns is a nagging question: What happens when an AI-derived conclusion is wrong? In mental health care, small errors can be catastrophic, and false positives—in which someone might wrongly be flagged as being bipolar, for example—can do significant damage. "Just having that diagnosis can make people feel sick and change their view of themselves," says Steve Steinhubl, director of digital medicine at Scripps Research Translational Institute in San Diego. "That's something we need to be really cautious about, especially if it's just coming from a digital interface with no face-to-face conversation."

Even as these and other concerns are raised, companies working in the field of computational speech analysis are forging ahead. Some are looking for ways to collect population-size samples of data. Schwoebel is building something he calls the Voiceome, a gigantic online repository of speech and voice data contributed by volunteers. Others, like the project in Cincinnati schools and the phone screening with The Trevor Project, are looking to bring diagnostic and prognostic tools into real-world applications.

Sonde Health, based in Boston, is doing both. Sonde is building a mobile phone platform that uses vocal analytics, licensed from MIT, with the potential to monitor and screen patients for depression from samples of speech of as short as six seconds. The Sonde app is already being used in India for research purposes through partnerships with hospitals and rural clinics. The company has audio files from 15,000 people that it is analyzing for signs of a range of mental and physical health conditions.

In Sonde's grand plans, the platform will be available to patients everywhere, and it will be able to diagnose dementia, Parkinson's and other conditions that go beyond its initial scope. CEO and cofounder Jim Harper says the company intends the platform to be used by both patients and health care providers.

Harper imagines a future in which people could choose to have a voice screening device set up in their homes, passively monitoring speech for clues to changes in mental and physical health. The app he's imagining would work much like the recently released Alexa Guard, which tunes devices to listen for breaking glass or a smoke alarm to alert people who are away from home.

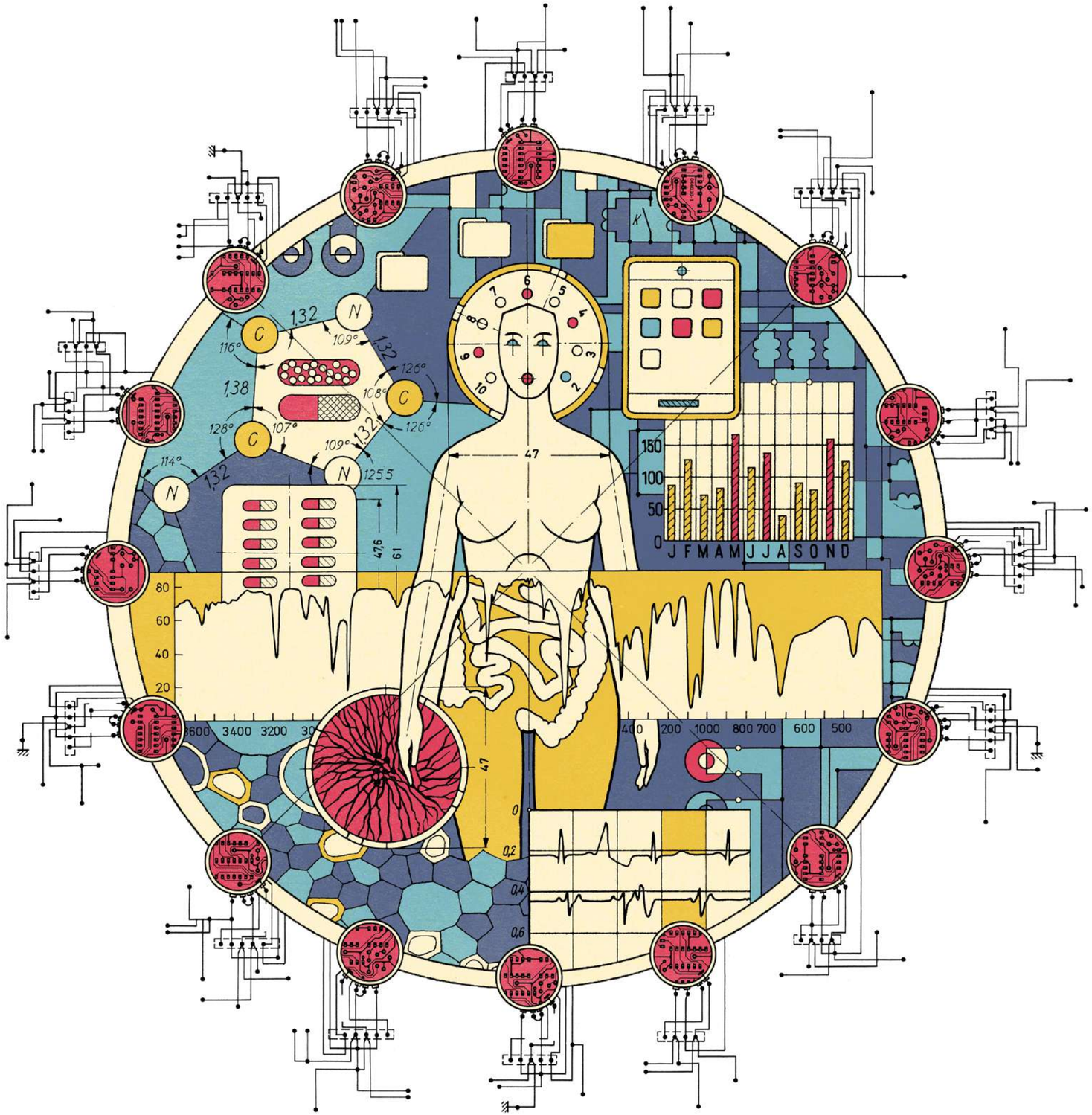
But he's cautious, too. He can see how a tool that suggests a mental health diagnosis can too easily be misused, employed for harm rather than good. "That's not a world any of us wants to live in," he says.

DOSSIER

"The Psychological Meaning of Words: LIWC and Computerized Text Analysis Methods," by James W. Pennebaker and Yla R. Tausczik, *Journal of Language and Social Psychology*, December 2009. This paper details some of the earliest efforts of applying computational analysis to text.

***Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again*, by Eric Topol (Basic Books, 2019).** In his forward-looking book, Topol discusses how AI will transform the doctor-patient relationship.

"Rise of the Machines? Machine Learning Approaches and Mental Health: Opportunities and Challenges," by Paul A. Tiffin and Lewis W. Paton, *The British Journal of Psychiatry*, August 2018. This editorial focuses on the potential benefits and limitations of machine learning approaches to mental health.



What Blockchain Could Do

Beneath the hype is a technology that could solve many logistical problems that plague medicine.

By Linda Keslar // Illustrations by Christian Gralingen

Every year in the United States, billions of dollars' worth of unopened, unexpired prescription drugs are destroyed or tossed in the garbage—at a time when a quarter of the U.S. population says it can't afford prescribed medicines and sometimes goes without. Many states have set up donation and reuse programs through pharmacies, charitable clinics and hospitals, but such programs have done little to solve the big problem of wasting perfectly good, desperately needed medications.

Good Shepherd Pharmacy, a nonprofit in Memphis, has been part of an effort to collect unsold medicine from drug manufacturers and wholesalers, with the goal of dispensing it to uninsured and low-income patients. But the initiative has gotten bogged down by the hands-on work it demands from participants, according to Phil Baker, founder and CEO of Good Shepherd. "There's a lot of paperwork and phone calls," he says. So his pharmacy, along with Lipscomb University's College of Pharmacy in Nashville and the University of Memphis, recently announced the first steps in an effort to track prescription waste more easily and link needy patients with prescription drugs. The backbone of this global network is blockchain.

Blockchain technology may evoke cryptocurrencies and overhyped Silicon Valley startups, but at its root, blockchain is a way to share information securely by also sharing the responsibility for keeping it safe. For Baker and his partners, for instance, the technology would facilitate the tracking of unused medications. Rather than having a central administrator manually verify every time a drug changes hands, participants

will share that role. They'll record and store data about donated medications on a shared electronic ledger and verify their authenticity by tracing a medication back to where it was manufactured and forward to where it's needed. "This is an example of how blockchain can help save lives," Baker says.

For the better part of a decade, blockchain has been hailed as a technology that will change how almost everything—information, goods, money—gets created, distributed and consumed. Experiments are taking place across the landscape of American business, and that includes hospitals and research laboratories. Indeed, plans for blockchain in health care outpace those of any other sector, according to a recent Stanford Graduate School of Business study.

The challenge will be to find the right fit, which means identifying problems that can be solved by a technology that can streamline and secure the movement of data. Electronic health records (EHRs) have been an early target. They're now the lingua franca of health care, and patient medical data has taken root in the records of insurance companies, hospitals and the offices of physicians and other providers. But not all of these records are accessible to everyone who might need them. In the city of Boston alone, 26 EHR systems are used by more than a dozen hospitals, with patient data often dispersed across multiple platforms—making it nearly impossible to consolidate every patient's individual encounters into an accessible, comprehensive health record.

Plans for blockchain in health care outpace those of any other sector.

Blockchain, at least in theory, could provide the infrastructure for a decentralized EHR system that would allow selective access to that data and let it be updated safely and securely. "Blockchain has unique qualities that could provide a lattice work needed to transform interoperability and the future of health care," says Mutaz Shegewi, research director for IT transformation strategies at IDC Health Insights near Boston.

Yet even as blockchain pilot programs and trials move forward, the technology appears to be less of a quick fix than a long-term experiment, with successes and failures that outline its potential and limitations. The task ahead will be to separate help from hype. "There are two major questions," says Tim K. Mackey, an associate professor in the department of anesthesiology at the University of California, San Diego School of Medicine and director of the Global Health Policy Institute, a UCSD affiliate. "How is blockchain an appropriate fit for the challenges we face in health care?" he says. "And how does technology measure up in terms of cost and efficiency?"

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To understand how blockchain works, consider how a company traditionally keeps track of its business. For every transaction, buyer and seller maintain a record of what is bought and sold—a process that was once practiced in handwritten ledger books, but which now almost always happens digitally. Yet each participant's ledger remains separate and isolated from all of the others, and a lack of transparency across different companies' systems can lead to discrepancies, disputes and fraud. Intermediaries—lawyers, accountants, banks and government regulators—are needed to resolve problems and keep goods and information flowing.

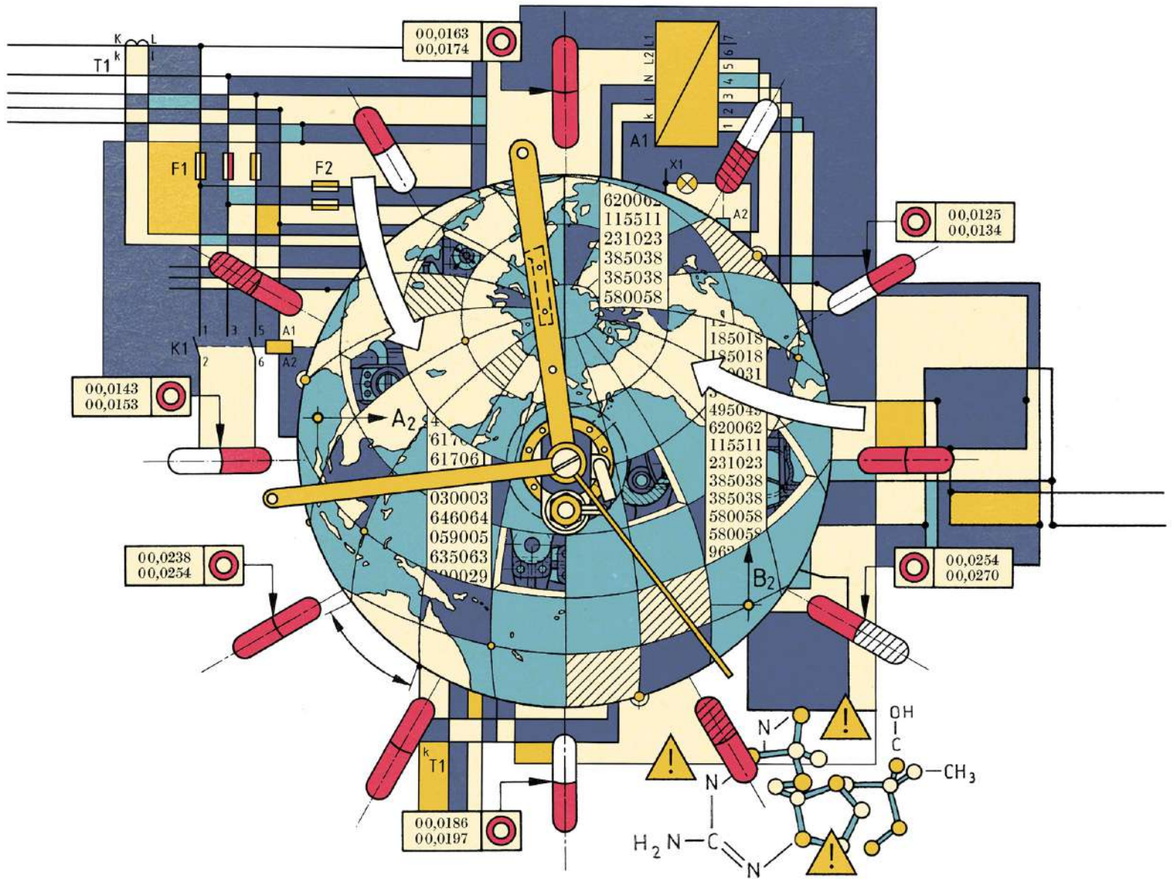
Blockchain takes a different approach. It uses a form of record-keeping that participants agree to share: a "distributed ledger." In blockchain, each network member, known as a node, can add information—a block—to the shared ledger in real time, as well as read and review the blocks others have added. Each node is assigned a kind of password, a private digital key that verifies the user's identity. Each block also has a unique identifier called a hash, which is determined via a complex mathematical process that is very difficult for outsiders to decode—one reason blockchain technology is considered so secure.

When a member of the blockchain network makes any transaction—a manufacturer, say, ships a product to a distributor, and receives payment—other members are notified electronically. If they confirm the transaction, a new block is created, which includes a hash. Each time another block is added, its new hash is automatically applied to all previous blocks, linking them—the "chain" in blockchain.

If someone goes back and attempts to change data in a prior block—to fix an inaccurate payment, for example—the hash value of that block will change and won't match those of successive blocks. Those data have fallen out of the chain, and making the chain whole again requires all members seeing and approving the change—and updating the hashes in all subsequent blocks.

This transparent process helps ensure trust among members of the blockchain network, allowing it to operate as a single "source of truth" for authorized participants, says Mutaz Shegewi. The encryption and node systems also keep data remarkably safe from intrusions by unauthorized outsiders.

Blockchain originated in 2008 as a tool to power Bitcoin, the first unregulated cryptocurrency, a form of electronic cash that can be created and exchanged without the involvement of any government or financial institution. Now, a decade later, there are well over 2,000 cryptocurrencies, all of which depend on some version of a blockchain network. For a currency—a kind of shared truth, which fundamentally



depends on no counterfeit blocks entering the system—the technology has been an ideal fit. But in the years since blockchain's introduction, innovators in many other fields have also seized upon the technology as a way to make other kinds of transactions more transparent and more secure.

In 2016 the Office of the National Coordinator for Health Information Technology, part of the U.S. Department of Health and Human Services, challenged researchers and health care organizations to explore how blockchain could be used in their fields. The research team of Noah Zimmerman, director of the Center for Biomedical Blockchain Research at the Icahn School of Medicine at Mount Sinai in New York City, recently published a "landscape map" that counts 159 current blockchain projects in health care, roughly three times the number just two years earlier. In Zimmerman's opinion, "many of those efforts are still half baked or overly optimistic, with a disconnect between what blockchain technology could enable and our most pressing problems in health care." Fewer than one in six companies on his list has a functioning prototype, and even fewer have launched a product. Yet despite the shaky foundations, Zimmerman believes their collective impact will someday be profound.

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Some blockchain ideas are already in motion, demonstrations of what John Bass, founder and CEO of a blockchain startup in Nashville (Hashed Health), calls "low-hanging fruit" that demonstrate how the technology can deliver real value.

For the past two years, for example, U.S.-based Spiritus Partners has worked on a pilot project with National Health Services Scotland and other participants to test how blockchain might be used to track medical devices. "We're interested in whether a device is safe at the point of care—in an acute care setting, outpatient facility, or at home, or as an implant," says Susan Ramonat, CEO of Spiritus Partners.

The pilot demonstrated how a blockchain system could provide a useful record of medical devices as they pass through a chain of custody during their lifespans. With tagging, tracking and scanning technologies, the simulation showed how those who used the device could produce a traceable, certifiable update on its service history and condition. Spiritus is now creating a consortium of

providers, medical device manufacturers and third-party service providers to launch a more ambitious demonstration in the United States by mid-2020, says Ramonat.

Other medical resources depend on constant input and updating from many sources. Consider the lists of providers covered under various health insurance plans—directories that patients can consult on the plans' websites when they're looking for a new doctor. The provider information, maintained separately by each health plan, is often wrong or outdated, and coordinating input from insurers, physicians and other participants is time-consuming and expensive, racking up an estimated annual cost of $2.1 billion, according to statistics from the Council for Affordable Quality Health Care. So seven major health care companies, working together in what they call the Synaptic Health Alliance, are experimenting with blockchain to make provider data more accurate, while reducing administrative burdens.

In a 2018 white paper, the group described a blockchain that lets any alliance member input, validate, update and audit provider data within the network. In a recent trial in Texas the results were promising, and the Alliance is moving toward full deployment in the state, says Kyle Culver, a Synaptic Health Alliance co-founder and director of emerging technologies at Humana, an alliance member.

Health organizations must also validate the credentials of physicians and other providers, and there's no easy way to collaborate on maintaining those records. Last year, the Professional Credentials Exchange, known as ProCredEx, in partnership with Hashed Health, announced a collaboration testing blockchain to streamline this process and build a faster, more secure exchange, says Anthony Begando, ProCredEx CEO, who expects to release early results of the project next year.

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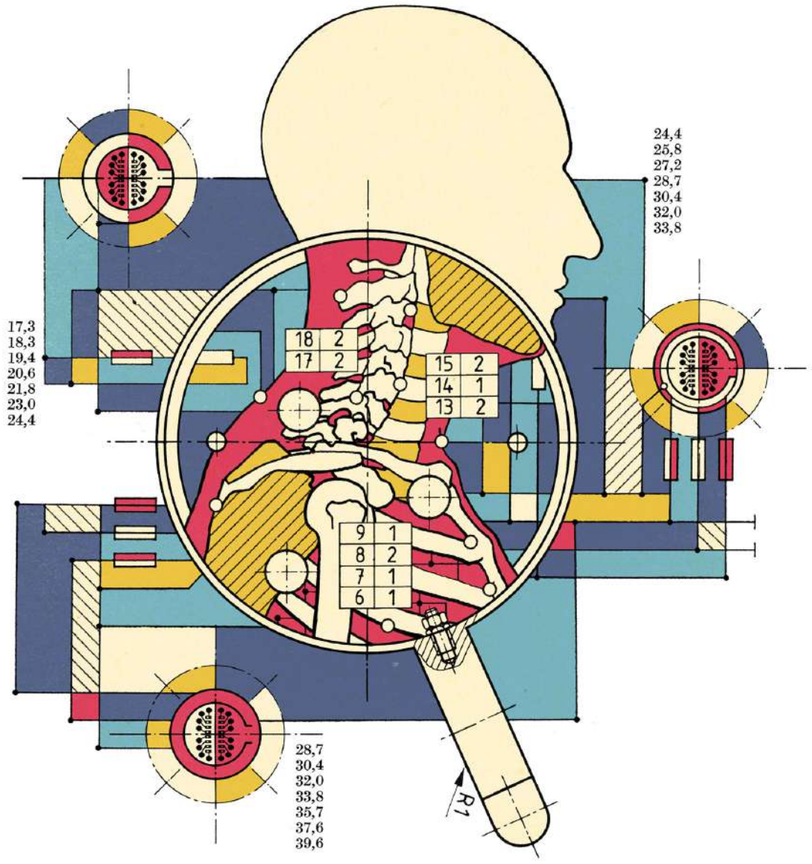
If most blockchain projects aren't visible to health care consumers, Nebula Genomics in Boston could emerge as a notable exception. The company, which provides genome sequencing services, was co-founded by George Church, a professor of genetics at Harvard Medical School and a giant in the field of genomics. Nebula has touted its mission of using genetic data to advance biomedical research. While other direct-to-consumer DNA-testing companies have stated similar goals, several have also been criticized for selling data to drugmakers without their customers' knowledge or permission, a practice that led the U.S. Federal Trade Commission to open a probe into how those firms handle patient information.



Nebula promises a much greater degree of control for its genetic donors, and part of the company's solution will use blockchain technology. The Nebula website will provide a marketplace that allows researchers to promote their projects and seek research subjects. Blockchain should enable customers to see which projects are requesting their data and authorize or deny access. Those who do choose to participate will be compensated with digital Nebula "tokens," which are already being used to reward users for completing surveys, referring friends and uploading data. The tokens can be redeemed to defray the cost of personal genome sequencing—Nebula offers whole genome sequencing that can be paid for in this way—and once the research blockchain is in place, tokens will help users buy additional tests and more in-depth interpretation of personal DNA data, says Dennis Grishin, co-founder and chief scientific officer of Nebula.

And consumers in the Arizona Care Network, one of the largest accountable care organizations in the country, also will soon be able to take advantage of blockchain information sharing. ACN has adopted a mobile app called Care.Wallet that will allow its physicians to check on patients' benefits details and eligibility and enable patients and providers to share administrative and financial data.

About 10% of ACN's 300,000 members have type 2 diabetes. A version of Care.Wallet initially being offered to these patients in two Arizona counties is the first blockchain-enabled diabetes care network. The app offers patients information about diabetes, helps them coordinate care and offers a host of resources. "Blockchain is enabling organizations like ours to have direct interaction with patients, insurers and providers, automatically synchronizing shared information and updating everyone on the chain in real time," says David Hanekom, CEO of ACN.

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IDC Health Insights predicts that blockchain adoption in health care will increase eightfold by 2022. Yet for now, it remains a technology in its infancy, and one recent survey of health care organizations found that only 6% were building blockchain programs and just 3% had pilot programs underway. Nearly two in five weren't doing anything at all.

One issue is money. "Because most blockchain solutions have never matured beyond pilot projects, it's hard to answer the question of what the actual costs are of developing and implementing such a system," says Tim Mackey at the UCSD School of Medicine. Despite blockchain's reputation for security, there are worries about when problems do happen. The technology's defining characteristic—a lack of centralized control—means that when a problem occurs, there's no single entity that can shut down a network. And a security issue with one blockchain node, unlikely as it may be, can affect all of the others. "Health care institutions will need strong vulnerability management programs and shared security standards," says Mitch Parker, executive director of information security and compliance at Indiana University Health. "We really need to address these things before we start broadly implementing the technology," he says.

In addition, perhaps the greatest hope for blockchain—that it could solve the many problems of EHRs while giving patients more control over them—may be further off than the pioneers had hoped. Pilot projects have been slow to roll out, impeded by technical challenges and regulatory obstacles. "Blockchain was initially viewed as a possible way to start over and rebuild EHRs," says Parker. "But we're finding that's not possible right now, and instead we're implementing blockchain as a way to augment the systems we already have."

Another hurdle is that blockchain can't yet support the speed and volume requirements of EHRs. At Beth Israel Deaconess Medical Center in Boston, for example, hundreds of patient record transactions are processed per second—whereas blockchain systems, because of their decentralized architecture, can currently handle just seven transactions per second, says Manu Tandon, chief information officer for the center.

Still, for blockchain pioneers such as Phil Baker at Good Shepherd Pharmacy in Memphis, the technology is already making a difference. The network has taken its first steps toward using blockchain to re-dispense oral doses of chemotherapy drugs for cancer, a month's supply of which can cost more than $30,000. Its proof-of-concept project expanded inventory collection beyond traditional sources, such as pharmaceutical companies, to include individuals, who are the largest potential source of unused medication. Now any of these donors can contribute unused cancer drugs, and patients can register to request them. So far, the consortium has collected a stockpile of medicine worth more than $2.2 million that it is distributing through partner pharmacies in Tennessee, Georgia, Iowa and Texas.

For blockchain pioneers the technology is already making a difference.

Those donations and more to come, distributed through a widening network, provide an early demonstration of how blockchain can be put to work: solving problems that once seemed intractable, and saving money and lives along the way.

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"Top 10 Blockchain Predictions for the (Near) Future of Healthcare," by John D. Halamka et al., *Blockchain in Healthcare Today*, January 2019. The peer review board of this new journal discusses lessons learned about blockchain in 2018 and identifies 10 major themes for the technology's future applications.

"'Fit-for-Purpose?'—Challenges and Opportunities for Applications of Blockchain Technology in the Future of Healthcare," by Tim K. Mackey et al., *BMC Medicine*, March 2019. This article summarizes views from experts at the forefront of blockchain conceptualization, development and deployment in health care.

"Blockchain: The Future Is Here," by MIT Technology Review editors, *MIT Technology Review*, May/June 2018. This issue, entirely devoted to the topic of blockchain, is a detailed primer for understanding the new technology and its ramifications.

Back From the Brink

Near-death experiences have been the domain of pseudoscience. But clinicians ignore them at their peril.

When lightning struck orthopedic surgeon Tony Cicoria by an outdoor pay phone, he was lucky that a nearby intensive care nurse immediately began administering CPR. He survived, but it took many years for Cicoria, who at the time in 1994 was 42 and chief of orthopedics at Chenango Memorial Hospital in Norwich, New York, to make sense of it, especially the memories between the moment the lightning stopped his heart and when it started pumping again. He recalls watching people clustered around his lifeless body and the sensation that he had morphed into a ball of energy, able to pass through walls as he looked for his children. He says he saw scenes from his life play out and felt "absolute love and peace" as he was immersed in a bluish-white light.

This was a near-death experience, or NDE, and in its wake, Cicoria's life took a bizarre turn. He became obsessed with playing classical piano and composing music—despite consciously remembering nothing from his childhood piano lessons. He achieved some fame as a musician and performed internationally, but now considers the years he spent relentlessly pursuing his music while also working as a surgeon a "destructive element of my NDE" that ultimately cost him his marriage and time with his kids. "For a long time, I was convinced that the only reason I survived was for the music, which I pursued with a vengeance to my own detriment," says Cicoria. These days he practices orthopedic surgery part-time in Damariscotta, Maine, and says he has finally achieved a balance between his music and the rest of his life.

By Anita Slomski // Illustrations by Prologue

MY WHOLE LIFE UNFOLDING BEFORE ME

There is no precise definition of NDEs—the term is widely used to describe a conscious experience of a close brush with death, as when the heart stops beating—and the exact prevalence of such experiences is also subject to debate. NDEs may happen to about one in 10 survivors of cardiac arrest, and NDEs also occur after accidents or when people are gravely ill. Yet despite this uncertainty, there is a large body of writing on the topic, from both professionals and self-styled experts. Those who study NDEs have observed that for many, like Cicoria, the event sparks a profound psychological shift that can alter the course of careers and relationships. Accounts of those life-changing moments can also, curiously, share common elements. Many people report leaving their bodies and rushing toward a bright light or recount intense feelings of peace and review scenes from their lives. Indeed, fascination with NDEs and what they may say about the mind and an afterlife has led to a flood of books, websites and even some peer-reviewed research.

Yet for those who want to understand the nature of this phenomenon, there's still little to go on. While some people consider an NDE an encounter of a spiritual or religious reality, neuroscientists propose that NDEs involve aspects of the brain, a supremely complex organ, that aren't yet understood, says Brian Edlow, associate director of the Center for Neurotechnology and Neurorecovery and director of the Laboratory for NeuroImaging of Coma and Consciousness at Massachusetts General Hospital. "The brain can create very complex realities, such as psychosis or what happens after taking a hallucinogenic drug, that are beyond our ability to comprehend today," Edlow says. "There's no reason to doubt that NDEs exist, but I don't think anyone understands them well enough to have firm convictions about what is happening."

Still, says Edlow, there is value in trying to unravel how NDEs happen. "If we can identify the brain structures or connections that are preserved and remain active in people having an NDE, perhaps we can use that resilience for other purposes—for instance, to predict who might be more likely to recover consciousness after brain injury," he says.

The psychological impact of an NDE seems important in itself, since the mental state may carry into encounters with physicians and others who care for those who have had the experience. About one in 20 NDEs is distressing rather than uplifting, and those who experience hellish images may struggle for years to come to grips with what they've witnessed. Those who have positive NDEs, meanwhile, may have less anxiety about dying. Some researchers have proposed using pharmacologically induced NDEs—or even a virtual-reality NDE—as an approach to alleviate anxiety about death, or to model the life-transforming aspects of an NDE as a potential treatment for anxiety, depression and other stresses that face the living.

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Most attempts to explain near-death experiences in medical terms run aground on basic facts of human physiology. The brain needs blood, oxygen and glucose constantly, and when the heart stops pumping blood, the brain shuts down in 20 seconds—which should make any conscious experience impossible. Until the heart's rhythm is restored and normal blood flow resumes throughout the body, the chest compressions of CPR can force only 15% to 20% of normal blood flow to the brain. "That's typically not enough to activate metabolism in the brain," says Sam Parnia, associate professor of medicine and director of the Critical Care and Resuscitation Research Program at New York University's Langone Medical Center.

In fact, most people who are revived by CPR can't remember the time before their heart stopped, let alone what happened while they lacked a pulse. "As a result of resuscitation, the brain swells and memory circuits are affected by the lack of oxygen," says Parnia, who has written extensively about the physiological effects of cardiac arrest, death and NDEs and is leading studies on the quality of brain resuscitation following cardiac arrest. "This insult to the brain causes people to lose memory for events prior to a cardiac arrest or accident and afterwards. Days of memory can be wiped out. Yet people who have near-death experiences can recall them in great detail and say they are more real than any other experiences they've had."

FOR THOSE WHO WANT TO UNDERSTAND THE NATURE OF THIS PHENOMENON, THERE'S STILL LITTLE TO GO ON.

Those who appear to be lifeless may, however, retain sufficient consciousness to register part of what's happening during efforts to revive them, says Kevin Nelson, professor of neurology at the University of Kentucky in Lexington, who has written a book about brain function during spiritual experiences. "During resuscitation, you're likely to have varying degrees of blood flow to the brain, which may allow consciousness to be gained and lost," he says. "With cardiac arrhythmias, the heart alternates between pumping blood efficiently and inefficiently to the brain. It is very common during a medical crisis for consciousness to wax and wane.

"The richness of the NDE narratives demands a rich engagement of the brain that involves multiple mechanisms, not all of which we understand," says Nelson, who notes that there is no scientific evidence that people can have an experience of anything without brain function. "NDEs must occur before cardiac arrest or after a patient has been revived," he says. "Having an NDE and remembering it requires a functional brain."

Another hypothesis for how NDEs might occur is that a critical mass of brain cells large enough to form a neural circuit could, theoretically, continue functioning while disconnected from other parts of the brain that have shut down while a patient is unresponsive, says MGH neurologist Edlow. Yale researchers recently demonstrated that they could restore basic cellular activity in the brains of pigs that had been dead for four hours. It's possible that in humans, select neural networks important in conscious thought remain active for longer after the heart stops than is generally thought possible.

Others in the medical field have proposed an idea that runs counter to this current understanding of the body. Psychiatrist Bruce Greyson, who has studied NDEs for 40 years, believes that consciousness may somehow exist outside the brain and outside the body itself during an NDE. The human brain might act as a filter, giving access only to thoughts essential to survival, suggests Greyson, professor of psychiatry and neurobehavioral sciences at the University of Virginia Health System. When the brain shuts off as someone approaches death, perhaps it gains access to thoughts that until then were unavailable, Greyson says.

That idea appeals to Tony Cicoria, who for years had a running debate with eminent neurologist and author Oliver Sacks about NDEs. The late Sacks interviewed Cicoria in 2006 and featured him in a 2007 *New Yorker* article and in Sacks's book, *Musicophilia: Tales of Music and the Brain*. After that, Sacks periodically sent Cicoria articles and explanations of how NDEs were manifestations of brain anatomy and neural circuitry under insult. But Cicoria was never convinced. "Consciousness survives death," says Cicoria. "People who have an NDE come back with something they didn't have before. In my case, it was music."

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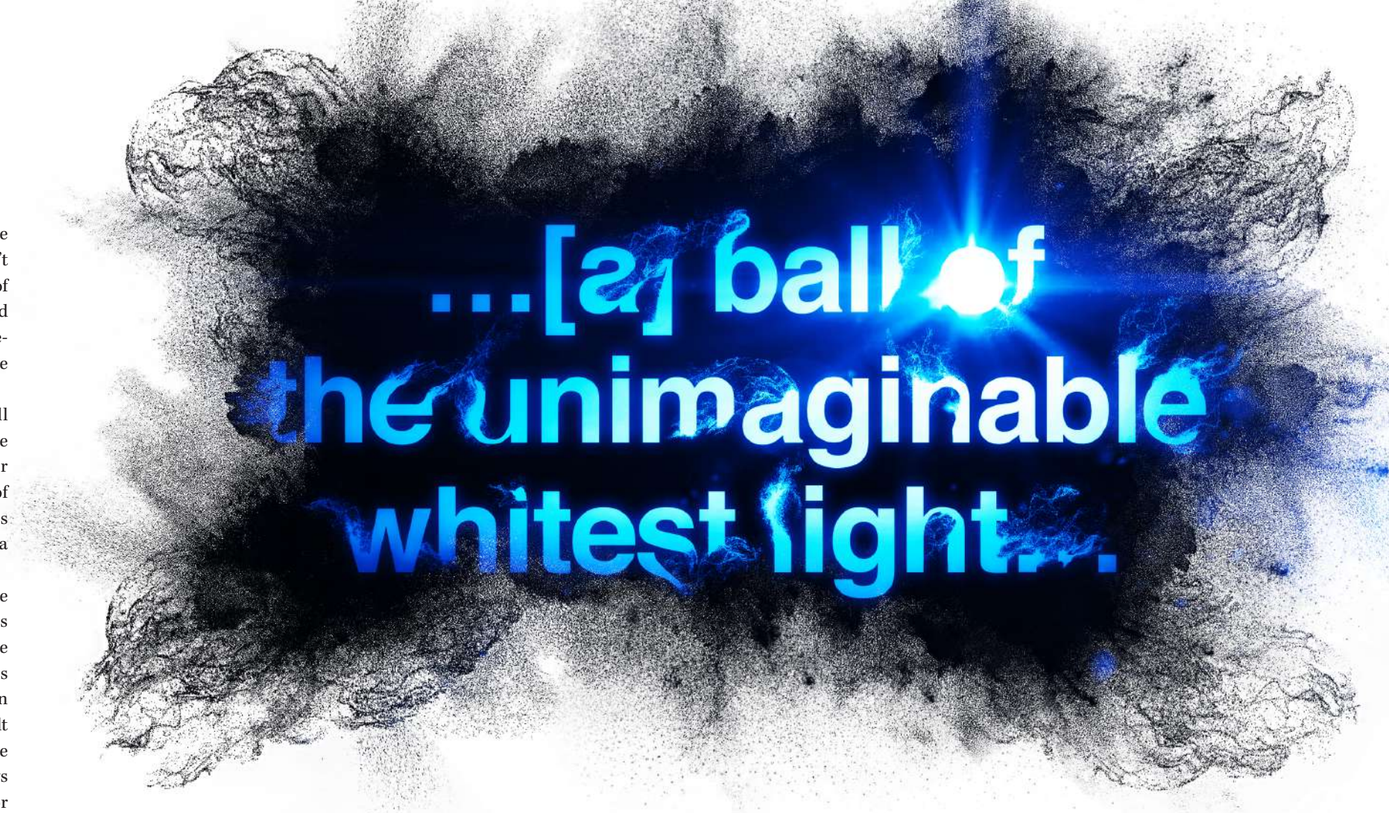
Neurologists may be a long way from determining exactly what causes a near-death experience. "If someone says they went to another realm, how do you corroborate that?" Greyson says. Yet he believes that to focus on explanations of how and why NDEs happen may be asking the wrong questions. How the experiences change people is much more interesting and important, he says, and much easier to study. "Many NDEs are followed by dramatic changes in attitudes, beliefs and values, which can put a strain on relationships," says Greyson, who has interviewed more than 1,000 people who have had



NDEs and has counseled many patients struggling to come to grips with their experiences. Divorce and job shifts are common, he says. People with highly competitive careers, for example, may end them, while police officers or military personnel may decide they can no longer carry a gun. Those who have undergone what they consider religious experiences may not be able to relate to a nonspiritual spouse. "People also report being less afraid of death after an NDE, they engage more in life and may have a new sense of purpose, and they are more altruistic and humanistic," he says.

After his NDE, Tony Cicoria took stock of his professional life and decided that "moving down the path of academia, publishing articles and organizing orthopedic spine meetings was no longer that important," he says. "I let go of some of those things and became more empathetic and aware of people's feelings."

An NDE can also profoundly affect family members. After her mother's near-death experience 27 years ago, Julie Supple decided to leave a career in real estate to train as a hospital chaplain. "I wasn't particularly religious before my mother's NDE, but I recognized the meaning and power of her experience," says Supple, who is now a chaplain at MGH. "It caused me to question my priorities and was life changing for me."

People who have distressing NDEs, however, may find them particularly difficult to incorporate in their lives. These NDEs typically involve hostile or terrifying encounters with malevolent beings, or with a vast emptiness that evokes sadness.

Some people interpret hostile or frightening NDEs as a call to change their ways, and they often become dogmatically religious, according to Greyson. Others may explain them as hallucinations, perhaps resulting from drugs they've been given in the hospital. Those in a third group may attempt to repress the memory of a dark NDE and often land in psychotherapy—only to have a therapist seem to dismiss the NDE and prescribe medication to quash the anxiety, says Greyson.

"I DIDN'T NEED A BRAIN SCAN TO TELL ME WHY MY LIFE HAD BEEN DRAMATICALLY ALTERED."

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Several years ago a neighbor told ophthalmologist John C. Hagan III about his NDE. The neighbor explained that during exploratory surgery, a surgeon had accidently lacerated his liver, causing uncontrolled bleeding and cardiac arrest. In the next 40 minutes, the man's heart stopped several times, requiring him to be defibrillated. After he was revived, he told his medical team what he remembered—that he had gone to heaven, seen God and talked to his deceased mother. The response from his physicians was greatly upsetting to him. "They said, 'Don't tell anyone about your hallucination or people will think you have brain damage,'" says Hagan.

That felt wrong to Hagan, and he resolved to learn everything he could about NDEs and to pass along his knowledge to other physicians. As the editor of *Missouri Medicine*, Hagan has published a series of physician-bylined articles about NDEs, and he lectures on the subject around the country in hospital grand rounds, which he says often draw standing-room-only crowds. "I'm not invited to talk to physicians about the supernatural or about heaven and hell," he says. "Rather, I talk about NDEs as a medical syndrome that physicians need to recognize. They don't have to buy into patients' interpretations of what has happened to them, but they do need to understand that this is likely to be a life-changing event and that an inappropriate response can create harm."

But talks at grand rounds are often all physicians hear about NDEs, and because these patient experiences fall outside their areas of expertise—or the comfort zone of what they're prepared to discuss—patients who have had NDEs often are referred to a hospital chaplain.

MGH chaplain Kate Gerne recalls one referral, a patient in her eighties who was facing major surgery and who told Gerne about an NDE that had occurred 60 years earlier during childbirth—and that had taken away the patient's fear of death. "She had felt such peace then, and she remembered the details as if it had happened yesterday," says Gerne, who notes that it's not unusual for patients to confide in her about long-ago NDEs that they've never disclosed to anyone else. "They've been afraid they would be considered crazy if they talked about their experiences," she says.

Yet when patients are made to feel comfortable discussing an NDE, it may not only relieve their anxiety but also ease the grieving process of family and friends when death occurs. When chaplain Julie Supple was called to the bedside of a dying patient to provide end-of-life support to her and her family, the woman's daughter told her about her mother's NDE two weeks earlier after cardiac arrest. Once terrified of dying, the mother said she had experienced a place of great love where she was greeted by departed friends and family members. Although she didn't want to leave what she perceived as heaven, the mother knew she had to return to the living to say goodbye to her family and tell them not to grieve when she died. "I told the family that the NDE was a gift that allowed their mother to replace dread of dying with peace," says Supple. "For the daughter, losing her mother suddenly and without knowledge of her NDE would have been very different and much more painful," she says. With her own mother, says Supple, "knowing that she was going to the beautiful place she described from her NDE and that she was at peace brought all of us comfort when she died."

At MGH, a chaplain is paged to support the family whenever a patient undergoes resuscitation, and patients who are successfully revived will get a visit from a chaplain. Often, those patients are starting to process why they survived and what that may mean for the rest of their lives. "Many times, these patients are so sick that the medical team is focused on taking care of their medical needs," says chaplain Erica Long. "Patients are comfortable talking to a chaplain because we offer a spiritual context and can help them create meaning and personal growth from their traumatic, life-threatening event."

After Cicoria went public about his near-death experience, his hospital in New York would occasionally ask him to talk with patients who reported having an NDE or to terminally ill patients who were anxious about dying. Cicoria would tell those who were near death that he had visited a place of love and peace during his own NDE and he reassured those who were bewildered by an NDE that they weren't crazy. "I told them that what they experienced was real and not their imagination," he says.

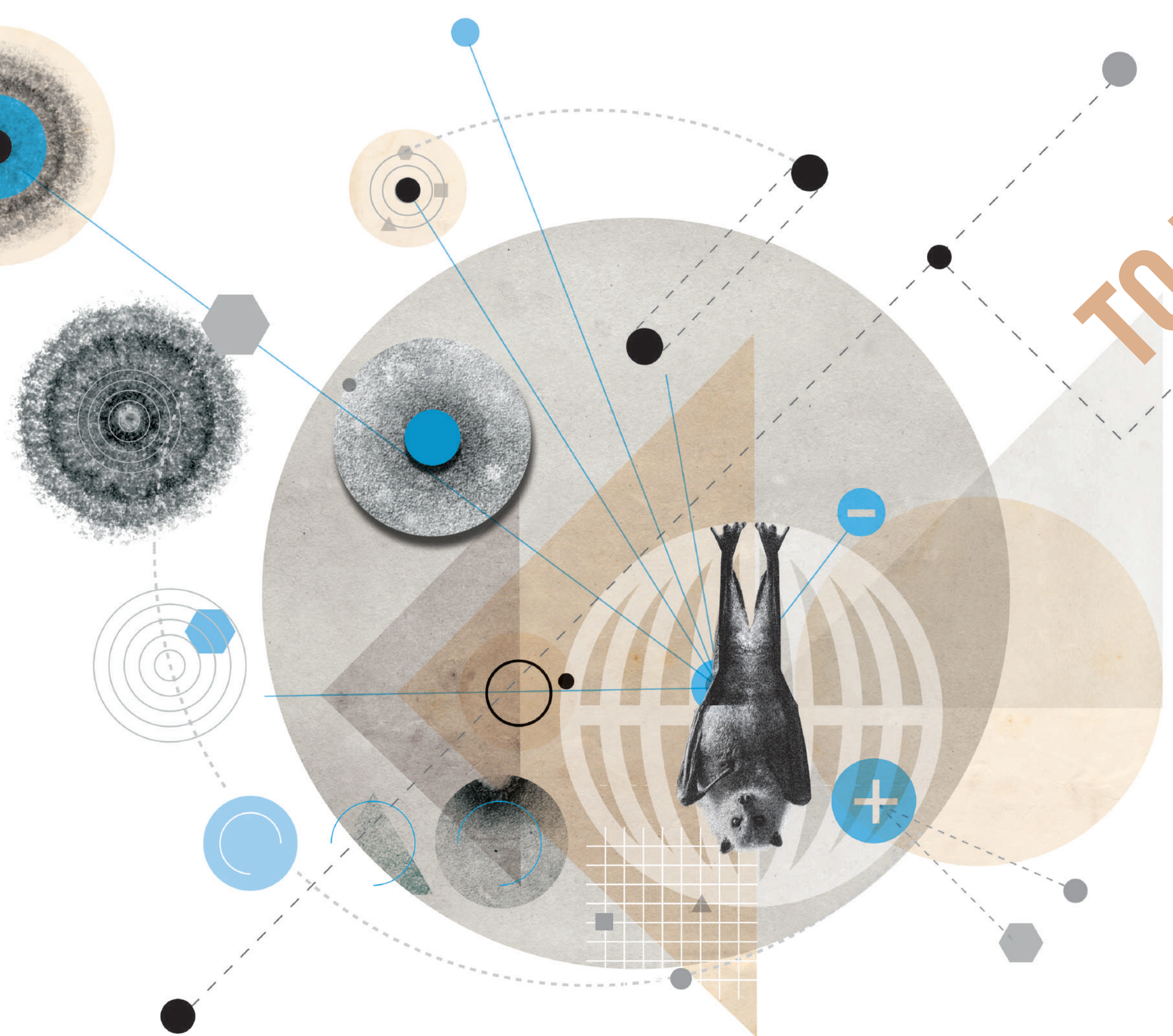
In his *New Yorker* article, Oliver Sacks wrote that he had "never met another person with a story like Tony Cicoria's," referring to the physician's musical talent that emerged only after he had nearly died. Sacks concluded that the lightning had somehow reorganized Cicoria's brain: "I suspected that his brain must be very different now from what it had been before he was hit by lightning," he wrote. Cicoria, however, declined Sacks's offer to do a scan of his brain to see what answers it might reveal. "I knew what I knew," he says. "I didn't need a brain scan to tell me why my life had been dramatically altered."

DOSSIER

"Characteristics of Memories for Near-Death Experiences," by Lauren E. Moore and Bruce Greyson, *Consciousness and Cognition*, May 2017. In this study of individuals who had a close brush with death, the researchers found that their NDE memories were more vivid and detailed than memories of real events.

The Spiritual Doorway in the Brain: A Neurologist's Search for the God Experience, by Kevin Nelson (Dutton/Penguin Group, 2011). Nelson relates specific stories of NDEs and offers possible neuroscientific mechanisms behind these experiences.

The Science of Near-Death Experiences, edited by John C. Hagan III (University of Missouri Press, 2017). This collection of essays by prominent NDE researchers includes accounts by physicians who have experienced NDEs and how they've reconciled their journeys to another realm with science.



TO BUILD A BETTER VACCINE

Waiting a decade or more for new vaccines may be a thing of the past, thanks to the revolution of rational vaccine design.

By Adam Bluestein //
Illustrations by Chad Hagen

The English physician Edward Jenner achieved his first major scientific recognition after describing the life cycle of the cuckoo bird. But it was the publication of another work in 1798, 10 years later, that would become his legacy and one of medicine's best ideas. By inoculating humans with a virus found in cows, he was able to trigger a protective immune response against smallpox, resulting in the first demonstration of vaccination. Vaccines for polio, rabies, typhoid and cholera followed, and today the vaccines for measles and five other diseases prevent as many as three million deaths a year, according to the World Health Organization.

Yet as essential as vaccines are, the process of creating new ones has never been quick. It took nine years from the time that the measles virus was first isolated in 1954 until the licensing of the first commercial vaccine. Manufacturing also takes time, and the measles vaccine today is still made much as it was back then—by culturing a large quantity of live virus, and then weakening it by growing it in eggs. That "attenuated" virus, like Jenner's cowpox virus, doesn't cause the disease, but it prompts the immune system to produce antibodies and activate T cells, imprinting a lasting "immune memory" that allows the

body to respond quickly when it encounters the real thing.

Vaccines made in this time-tested way are highly effective against known threats. But older methods of developing vaccines are no match for a host of emerging—and reemerging—pathogens that call for a tailored and speedy response. The 2015 breakout of an obscure virus called Zika in Brazil "came out of nowhere," says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID). Last year the Ebola virus roared back with a vengeance, so far taking more than 2,000 lives in the war-torn Democratic Republic of Congo after killing more than 11,000 people earlier this decade. Its comeback prompted the Emergency Committee of the World Health Organization to declare a global health emergency in July, the fifth such declaration since the first emergency committee was formed in 2005.

Fauci points to several factors that have fueled these and other epidemics. Human encroachment on otherwise pristine environments increasingly brings people into contact with animals and their diseases. "About 70% of all new infections that attack people originate in animals," he says. Floods and other natural disasters, intensified by climate change, displace about 25 million people every year and create conditions that may foster outbreaks. War and civil unrest displace roughly 16 million refugees annually, sending many of them to crowded, unsanitary camps that can become disease incubators. When an outbreak of a new pathogen happens, there's little time to go through the traditional steps of vaccine development—isolating an infectious agent, growing sufficient amounts to make a batch of vaccine and culturing it long enough to render it safe for humans. By then, says Fauci, "the outbreak will probably be out of control."

Against this backdrop, infectious disease research has taken on a new urgency, leading to an emerging paradigm for developing vaccines. Rational vaccine design, also known as synthetic vaccinology, uses twenty-first-century technologies to modernize an eighteenth-century idea—replacing the "natural" approach of traditional vaccines with those that are "rationally" engineered to elicit a particular immune response. It begins with the genetic sequence of the pathogen that has been collected in the field. That data can be emailed to a lab, eliminating the risk of shipping and handling infectious material. Aided by a level of computing power unimaginable when the measles vaccine was developed, scientists then are able to identify antigens, the parts of a virus or bacteria that will trigger an immune response, and then create optimized copies of them. These synthetic antigens go into vaccines that can be delivered in new ways—as a nanoparticle, an engineered virus or a snippet of genetic code. The entire process can produce vaccine candidates within months, versus the many years needed by approaches used just a few years ago. In this new age, says Fauci, "forget about growing anything in eggs."

Infectious disease research has taken on a new urgency, leading to an emerging paradigm for developing vaccines.

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Before researchers can design a new vaccine, they have to know what they're up against, and that means identifying infectious culprits that may cause a pandemic. Because so many pathogens originate in animals, surveillance efforts have largely focused on areas that are home to many species and where computer modeling suggests a heightened risk. This has given rise to an increasingly sophisticated network of "listening stations" around the world. USAID's PREDICT project, for example, has monitored hot spots in some 30 countries in Africa, Asia and Latin America since its founding in 2009. By analyzing samples from animals and people who come in contact with them, PREDICT has already discovered hundreds of viruses that could cause disease in humans.

Today, infectious agents are almost always identified by sequencing their genomes. Starting in 1999, when genetic data for the West Nile virus became available during an outbreak, sequencers have become standard diagnostic tools, even at remote clinics on the front lines of new outbreaks. Using computational tools, pathogen hunters scan samples of water, soil or food to detect potentially dangerous pathogens before they infect humans.

While older field tests could detect just a few known pathogens, new tools can help scientists who don't even know what they're looking for. VirCapSeq-VERT, for example, is a custom sequencing system developed by W. Ian Lipkin, a professor of epidemiology, pathology and neurology at Columbia University's Mailman School of Public Health and Vagelos College of Physicians & Surgeons. It works as a universal virus detector, which means that clinicians can take a sample of a person's blood and detect the genetic signature of virtually any virus known to infect humans and other vertebrates, as well as from novel viruses loosely related to known ones.

Now Lipkin is working on tools that can also allow researchers to assess qualities about a virus that might make it harder to treat and vaccinate against, and has built sequencing systems that detect bacteria and genes for virulence and antibiotic resistance. Lipkin says the new tools will be able to provide a report within hours of obtaining a sample, helping researchers "recognize a threat and appreciate it in its full complexity."

On the receiving end of this information from the field might be someone like Mark Poznansky, director of the Vaccine and Immunotherapy Center at Massachusetts General Hospital. In 2014 Poznansky led a multi-institution project called VaxCelerate II that looked into Lassa, a virus that causes hemorrhagic fever in humans. His team received Lassa's genomic sequence by email and developed a vaccine candidate within just 90 days, a feat that offers a kind of step-by-step playbook for rapid rational vaccine design.

The first task for the MGH researchers was to "decode" the digital version of the Lassa genomic sequence, which meant determining the full set of proteins produced by the virus. Then, using bioinformatics tools that search databases on virus biology and protein structures, they started to home in on specific antigens that could be used in a vaccine to trigger the immune system.

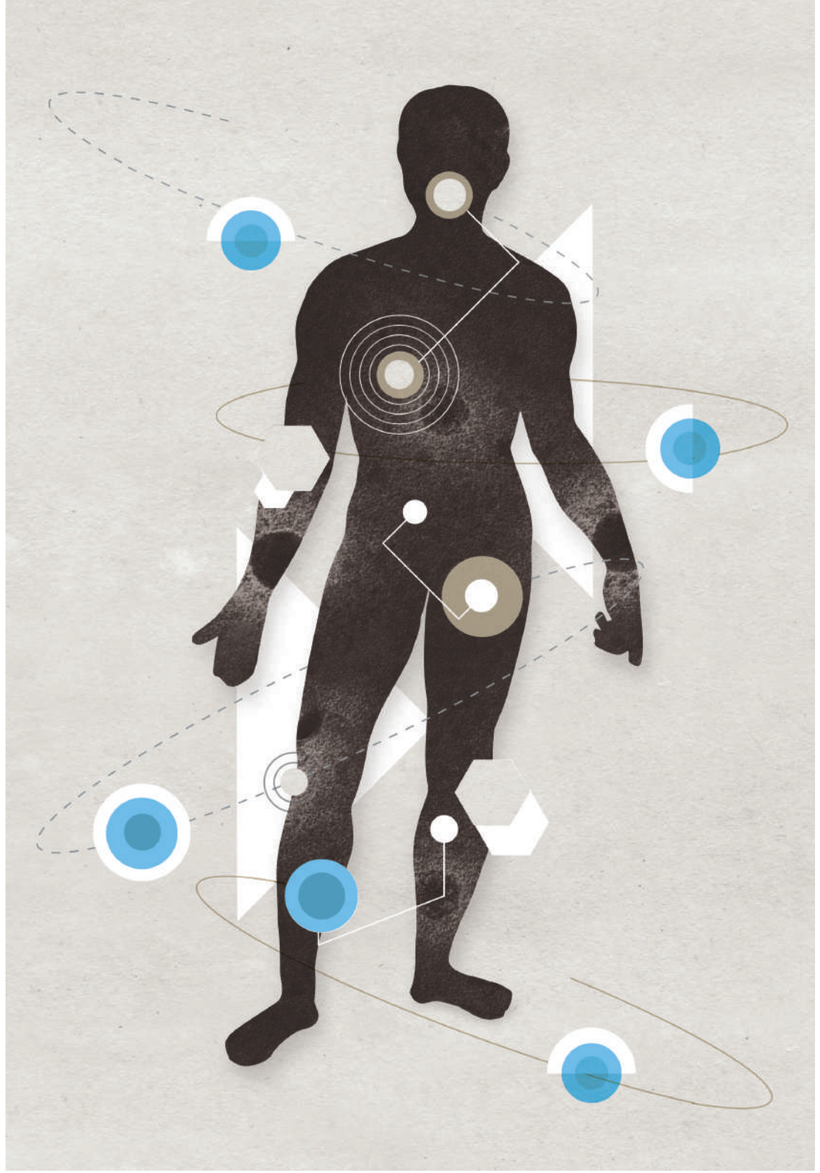
Traditional vaccines contain lots of antigens because they include whole pathogens in killed or attenuated form. Many of these structures serve no useful purpose in the vaccine, however, and some can even trigger a potentially dangerous phenomenon called antibody-dependent enhancement, in which antibodies responding to a virus actually help it enter a cell or replicate. Rationally designed vaccines aim to be more selective, presenting the immune system with just a few select proteins or fragments of proteins that stand in for the whole virus. In this case, after determining which antigens to focus on, Poznansky's team identified specific features on the protein's surface—called epitopes—that immune system cells were most likely to recognize and attack. Then the researchers chemically synthesized antigens that mimicked those features.

Compared to vaccines made of whole viruses, these rationally designed vaccines are safer to manufacture because there's no need to work with infectious agents. The process is also faster, sidestepping the long process of weakening the virus in an egg medium. The main question is how best to deliver the synthetic antigens into the body. In the case of the Lassa vaccine, the researchers chose to inject them in the blood as a mixture of proteins that would assemble themselves into free-floating chains that would, in turn, trigger the production of Lassa antibodies.

The researchers in Poznansky's lab then tested the vaccine, first in human cell cultures and later in "humanized" mice engineered to generate human-like immune responses. Testing an immune response can be complex, involving many types of cells, and until recently, this was done mostly through flow cytometry, a method in which cell samples are suspended in fluid, labeled with fluorescent markers and injected in a device that illuminates them with a laser beam, one cell at a time. Analyzing the intensity of each fluorescent marker allows scientists to measure up to 20 aspects of a cell simultaneously, at a rate of thousands of cells per second.

In an effort to maximize the information gained from samples, researchers in the Vaccine and Immunotherapy Center used a newer method, mass cytometry. For this method, the same antibodies that are usually fluorescently tagged are instead labeled with heavy metal ions, which can provide an extremely detailed analysis in a single experiment. Using a tiny blood sample from a humanized mouse, for example, mass cytometry can measure more than 40 parameters simultaneously, showing how a test subject's entire inflammatory and immune system is responding to a vaccine.

Mass cytometry produces "hundreds of thousands of data points," says Poznansky, and making sense of that massive amount of



data can be challenging. To interpret these datasets, Patrick Reeves, senior scientist and project leader in the Vaccine and Immunotherapy Center, and his team are using new visualization tools that show mass cytometry data, and other forms of big data, as "architectural layouts" of the immune and inflammatory response. Some visualizations resemble abstract art, with clusters of colors indicating surges of immune cell activity and expression of immune and inflammatory molecules. Others resemble mandalas, with the spokes and concentric rings of a wheel and squares of color showing activation of particular immune system components. "Patrick's images let us see multiple aspects of a mouse or human immune response to a vaccine or infection over time," says Poznansky.

The VaxCelerate II Lassa vaccine platform has been licensed to a biotechnology company, which means that it could soon be ready for use in high-risk areas. And Lassa is not the team's only success. Q fever is an animal-borne disease that can infect humans; it garnered attention when U.S. troops in Iraq and Afghanistan became infected with it when they inhaled bacteria from local livestock. In 2018, using a process similar to that used for Lassa, VaxCelerate produced a vaccine candidate for Q fever that is now being tested.

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The VaxCelerate vaccine approach delivers antigen epitopes, tiny fragments of protein, directly into the patient's body. But other new vaccines, including some of the first developed for Zika, take a different approach, using DNA or RNA with genetic instructions that allow the body's own cells to manufacture the vaccinating proteins. To make these vaccines, scientists insert short DNA sequences into small circular molecules called plasmids—a sort of key ring to hang genes on. When the plasmids are injected into a muscle cell, that genetic code is translated, causing the cell to produce key proteins that trigger an immune response. One DNA vaccine for Zika is now being tested in an international clinical trial.

As efficient and direct as this method is, however, it does require one interim step. DNA relies on a molecule called messenger RNA, or mRNA, to forward genetic coding instructions to the cellular machinery that actually makes proteins. RNA-based vaccines skip that step by delivering mRNA directly into the cells. In several clinical studies, RNA vaccines have performed better than DNA vaccines. That may be because, unlike DNA vaccines, RNA vaccines don't have to find their way into the cell nucleus, where DNA is transcribed. Instead, they need only penetrate the outer cell wall. Also, delivery via RNA greatly reduces the risk of its code becoming integrated in the patient's genome, which could have unintended effects.

RNA vaccines have their own drawbacks, however. They tend to become unstable in the body and quickly lose effectiveness. To address that problem, researchers are trying new approaches, such as manipulating the RNA sequence to make it easier to store in the cell, or binding RNA to other molecules that protect it. These stabilized RNA vaccines also can be held for long periods at room temperature, making them attractive for use in countries in which refrigeration may not always be available. An RNA vaccine against rabies is currently in clinical trials, and other vaccines against influenza, HIV, tuberculosis and Zika are at earlier stages of development.

"Gene-based vaccines are potentially very fast and flexible," says John Mascola, director of the Vaccine Research Center at NIAID. Both DNA and RNA vaccines spur the body to make antigens that closely resemble natural viral epitopes, adding to the vaccines' effectiveness. Producing gene-based vaccines is also less expensive than making a traditional vaccine, and the new vaccines can be manufactured in quantity in a matter of weeks.

Gene-based vaccines can be delivered in other ways as well. Viral-vector vaccines use common human or animal viruses that have been engineered to be noninfectious and incapable of replicating. Because they have a real virus as a "chassis," viral-vector vaccines are highly effective at infiltrating host cells and transferring their cargo of genes, which makes the cell produce antigenic proteins for as long as a few days. These vaccines also have inherent "adjuvant" properties—they trigger the production of cytokines, inflammatory proteins that spur a stronger response from antibodies and T cells, which contain and clear a pathogen—and they are relatively easy to produce in large amounts in industrial bioreactors. This is the approach used to make several current vaccines, including the first Ebola vaccine to be widely deployed, which uses a common pig virus as a vector. It was found to be safe and protective in a large 2015 study and has been used to vaccinate more than 200,000 people in the current outbreak in the Eastern Democratic Republic of Congo.

Before researchers can design a new vaccine, they have to know what they're up against, and that means identifying infectious culprits.

New ways to design and manufacture vaccines also promise to transform the fight against a more familiar but no less deadly foe—the seasonal influenza virus, which infects tens of millions in the United States alone. While the flu is not a new disease, there are many strains of influenza, and they mutate quickly, making it hard to predict exactly what will show up in a particular flu season. If a vaccine is a poor match, there is seldom time to prepare a new formulation, which normally must be slowly cultured in eggs. Researchers have long hoped to circumvent this guessing game by creating a universal flu vaccine that would work for all or most flu strains.

Several universal flu vaccines are now in clinical trials, including Biondvax's M-001, a peptide vaccine (similar to Poznansky's Lassa vaccine) that contains nine viral epitopes common to 40,000 influenza viruses listed in the NIH database. In spring 2019, the NIH's Vaccine Research Center Clinical Trials Programs started enrolling volunteers for the first in-human trial of its experimental universal flu vaccine, H1ssF_3928. Another—Medicago's MT-2271—delivers key proteins from multiple flu strains in the form of virus-like particles (VLPs). A VLP is a type of nanoparticle that has a dense, repetitive arrangement of proteins on its surface. Its structure closely resembles that of real viral particles, so it often elicits a more robust immune response than other kinds of vaccines that isolate a particular antigen or epitope. There are already VLP vaccines approved for hepatitis B and for human papilloma virus, and VLPs can be produced rapidly through a variety of methods, including growing them in the leaves of tobacco plants.

If rational design—through nanoparticles, DNA vaccines or other novel means—can master the common flu vaccine, which is given 150 million times each year, the lives saved in the United States alone could be in the hundreds of thousands. "We're certainly not there yet," says Anthony Fauci, "but we're way ahead of where we were a couple of years ago, and we are clearly making very positive progress toward a universal flu vaccine." The discovery of that vaccine and others will be a major leap forward for one of medicine's best ideas.

DOSSIER

"Emerging Viral Diseases From a Vaccinology Perspective: Preparing for the Next Pandemic," by Barney S. Graham and Nancy J. Sullivan, *Nature Immunology*, December 2017. This review covers new paradigms in rapid vaccine development, with case studies on the Ebola and Zika viruses.

"Next-Generation Sequencing of Infectious Pathogens," by Marta Gwinn et al., *JAMA Insights*, February 2019. Researchers provide an overview of the emerging technologies for identification and characterization of viruses.

"VaxCelerate II: Rapid Development of a Self-Assembling Vaccine for Lassa Fever," by Pierre Leblanc et al., *Human Vaccines & Immunotherapeutics*, January 2015. This paper outlines the process used to successfully develop a candidate vaccine for Lassa fever, beginning with the genomic sequence of the virus.

FIRST PERSON

The Checklist

BY KRISTEN HAUNSS

It was a Monday. Another day, another doctor.

I clenched my jaw in dread. I had been in the ICU again recently, and the upshot of that visit was that I needed to add yet another specialist to my team. But despite more than a decade of first appointments like this, it still gave me butterflies. To calm myself, I ran down the list.

Will she be prepared? Hear me? Communicate? Be a team player? Do I trust her?

I was diagnosed 13 years ago with reflex sympathetic dystrophy, also known as complex regional pain syndrome. It was a relief to finally have a name for the agonizing little mysteries that had refused to add up: the purple tint of my foot, the sensitivity to touch that made socks impossible to wear, the ankle that swelled to the size of a basketball, leaving scores of shoes collecting dust in my closet. And of course the pain, burning and relentless.

When the diagnosis came, I thought a remedy was the next stop. But the orthopedist shook his head. I would need to deal with my RSD/CRPS from now on, and he said that the best thing would be to assemble a solid team of medical professionals—a neurologist, a pain management physician and a physical therapist at a minimum—to help me navigate my new life.

It's daunting to find the people you can trust with your future, but I went out and found them. More complications, including two pulmonary embolisms, meant that my team got even bigger. Through it all, I slowly gained the expertise I would practice today—the ability to figure out what doctors I could work with, which I had come by after learning who I *couldn't* work with.

There were the doctors who wouldn't listen when I shared my concerns and doctors who prescribed medicine I'd already tried and knew wouldn't work. The shortest appointment was with a doctor who told me she would never see me or speak to me, and all questions should be directed to a nurse practitioner. Her introduction lasted three minutes, and on the fourth I grabbed my crutches and walked out.

Those failures rattled around in my head as I sat there waiting. It's uncomfortable to be a patient, on an exam table in an ill-fitting gown, waiting to be judged. So to steel myself I had my tool ready—a private, "Team Haunss" physician checklist—which went into motion when the doctor walked through the door.

Is this doctor prepared? This one walked in and smiled, and after introductions she showed me that she had read my chart and knew my tangled, extensive history. She noted the medicines I couldn't tolerate and the tests I'd already completed. She also knew a lot about RSD/CRPS. Check.

Does this doctor listen? Does she talk to me or down to me? I told her that twice we'd been able to head off a fatal complication because my team listened when I said something was wrong, even when other doctors dismissed me. She said she understood and that my concerns would be heard. Check.

Do I trust her? We talked about a treatment plan and all the moving pieces and professionals it would take to get it right. She made sure I was on board, answered all my questions, and at the end assured me: "We'll get through this."

Check, check, check. Internally I heaved a sigh of relief that I wouldn't have to turn this one down and start from scratch. "Welcome to the team," I thought, and walked to my next appointment.

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