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MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

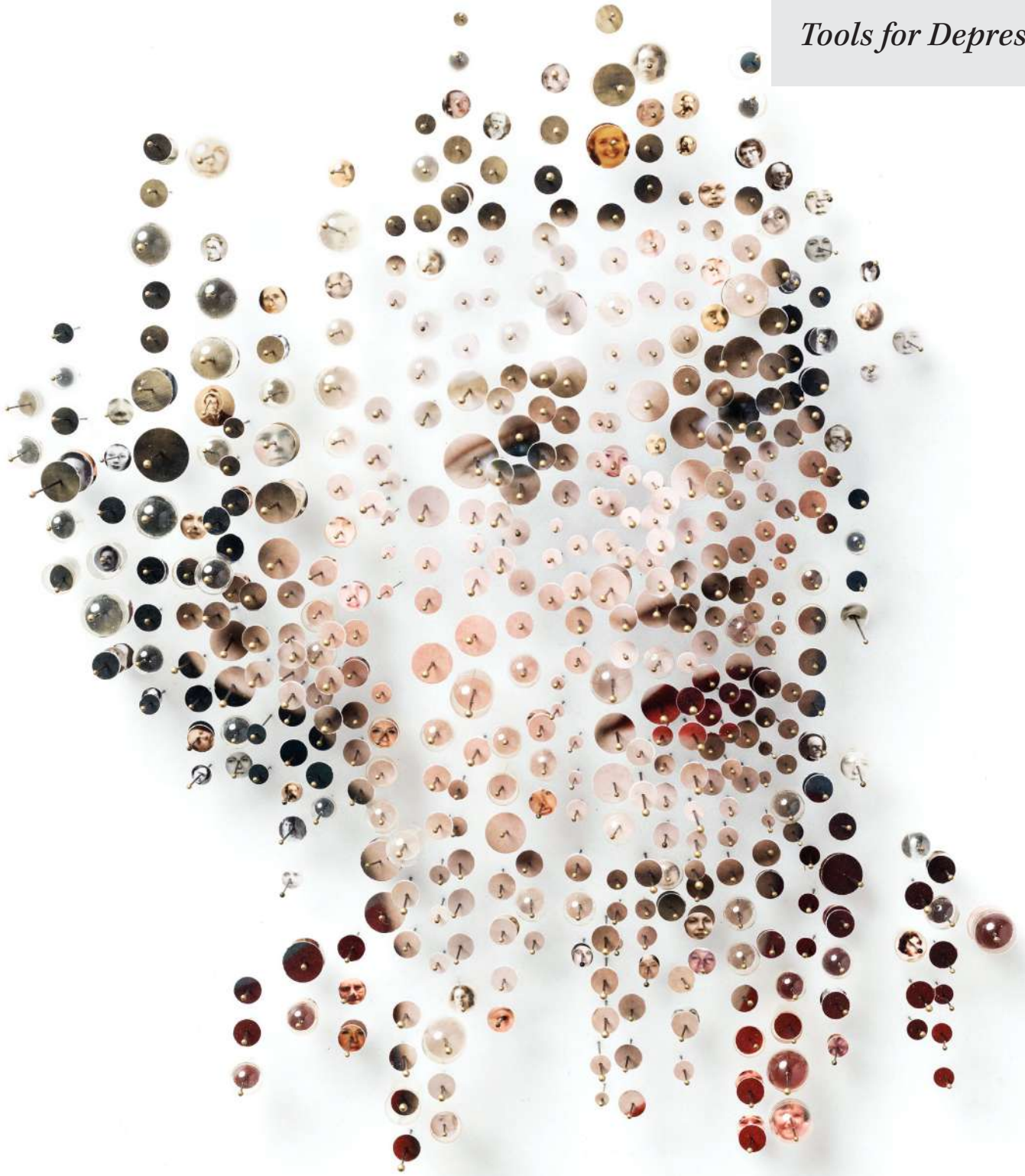
SUMMER 18

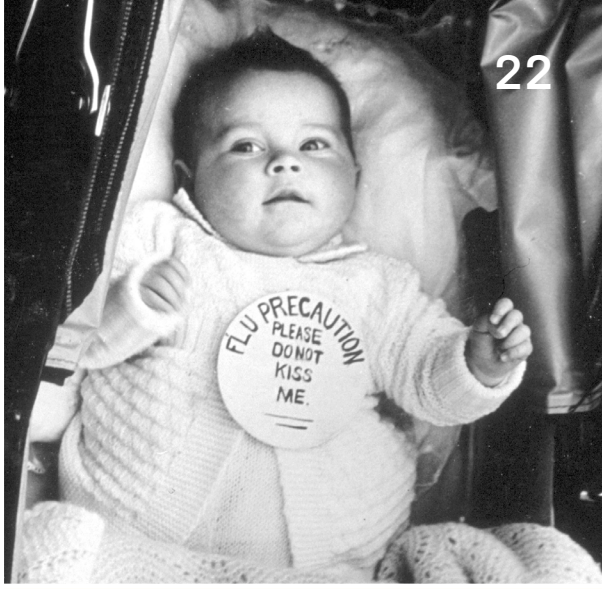
Family Secrets

A trove of genealogical and medical records in Utah helps researchers zero in on the genetic roots of disease. p10

Fake Medical News p16

Tools for Depression p28





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on the cover

Sickness travels through the tapestry of every family. When several generations of medical histories are paired with DNA samples, researchers can quickly home in on rare genetic variants that are the primary culprits. // Photo Illustrations by Michael Mapes

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.

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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 July 2017 cover of *Time* magazine carried a sobering message: "Depression afflicts 300 million people. One-third don't respond to treatment." Indeed, the numbers are staggering. In the United States alone, depression each year affects nearly 7% of adults and 13% of adolescents. This common and complex disorder can interfere with the ability to function, think, act, participate, respond, work, sleep, learn, engage and socialize. It can bring about feelings of sadness, emptiness, hopelessness, worthlessness, irritability and guilt. Left untreated, depression also can lead to catastrophic outcomes and has been a major factor in the alarming 25% increase in the nation's suicide rate between 1999 and 2014.

It has been more than 30 years since the antidepressant Prozac came on the scene, ushering in a new generation of psycho-pharmaceuticals called selective serotonin reuptake inhibitors—SSRIs—that have enabled millions of people to regain control over their moods and their lives. While the medicine chest of antidepressants has continued to grow and new approaches to psychotherapies and other treatments have evolved since then, there has been no similar kind of game-changing breakthrough to help those who have not responded to available treatments. There is, however, some interesting—and promising—work on the horizon.

In this issue of *Proto*, we look at "New Tools for Depression," which examines a wave of innovative treatments directed at easing the impact of this pervasive, debilitating health condition. Perhaps of greatest interest right now is ketamine, a short-acting anesthetic that has shown stunning success in stopping major depression—and suicidal thoughts. While ketamine has some significant drawbacks, including its potential for diversion for abuse or hallucinatory effects at high doses, its overarching benefits have led several major pharmaceutical companies to explore it as a foundation on which to design what could become a totally new category of antidepressants. Beyond ketamine, hope also lies in several clever nondrug interventions, such as simply raising the body's temperature or using innovative and more intense forms of cognitive behavioral therapy.

The Massachusetts General Hospital Department of Psychiatry, like other major psychiatric research programs around the world, continues to explore many avenues that could lead to better, faster and safer treatments to ease the burden of depression. We may not know today what the next transformative treatment will be, but one thing is clear: It can't come soon enough for the millions who continue to struggle with the devastating effects of depression.

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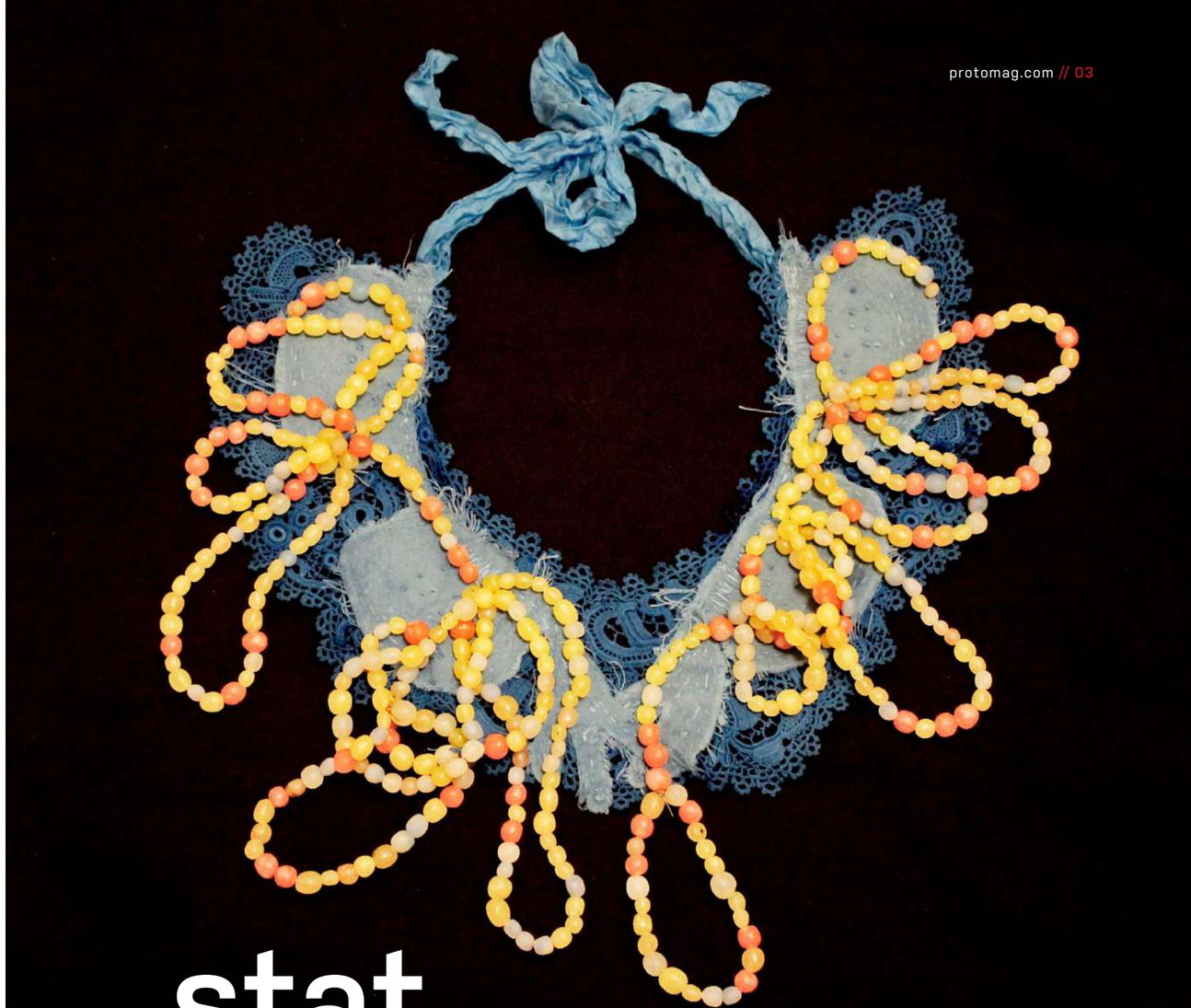


ANNA DUMITRIU

stat

FOCUS

This beaded necklace takes its inspiration from an antibody found in HIV-positive patients. Its twists mirror those of the 21 amino acids that compose the protein, and each bead contains copies of the amino acid it is meant to represent. They are anchored on fabric that has been dyed with Coomassie Brilliant Blue—a stain used in laboratories to visualize and separate proteins.

The piece is a collaboration between artist Anna Dumitriu and Xiang Li, a biomedical engineer at the University of California, Irvine. Li's lab is trying to introduce an additional amino acid—sulfotyrosine—into this protein structure, so that it can better block HIV infections. Through his close work with Dumitriu to create the necklace, Li discovered errors in his own models, which he was then able to remedy.

INTERVIEW

The Walk-In Genome Clinic

Consumers are curious about their DNA, and Bryce Mendelsohn thinks hospitals should give them answers.

BY HEATHER STRINGER

In November, the Food and Drug Administration announced that it would simplify the approval process for direct-to-consumer genomic tests. This move is likely to boost the number of people who get at least part of their genome sequenced—a number that may reach as high as 2 billion by the year 2025, according to a 2015 PLoS *study. That doesn't guarantee, however, that once people acquire their genomic data, they will be able to understand it.*

"Expecting people to manage their genetic testing process is like asking them to interpret their own MRIs," says Bryce Mendelsohn, a geneticist and assistant professor of pediatrics at the University of California, San Francisco, School of Medicine. Mendelsohn is the lead clinician at the Preventive Genomics Clinic, where healthy patients can get their genes sequenced and interpreted by medical professionals. The effort—one of a handful of similar initiatives—aims to improve overall genetic literacy.

TIMOTHY ARCHIBALD FOR *PROTO*

Q: Why did your team open this clinic?
A: More and more of our patients were coming in with direct-to-consumer test results. Many were confused or anxious, which could have been avoided if they had done their testing and counseling through medical channels. That kind of clinic didn't exist, though, so we decided to build one ourselves.

Q: What's wrong with DNA tests from private companies?
A: One problem is that these companies screen for a very narrow range of diseases and the most common mutations linked to them. So when a commercial test doesn't raise any alarms, it doesn't necessarily mean that someone is risk-free. Another problem is that people can panic when they test positive for a gene associated with a serious disease, such as early-onset Alzheimer's. But they may not know that genes are only part of the equation.

Q: Is there an educational component to what you do?
A: Absolutely. Our product is education, not a test. When someone comes in, one of the first things I ask is, "What motivated you to come here?" Many have some risk factor—a family history of cancer, a mother who died of ALS, or an ethnicity associated with a certain disorder. I explain what current technology can do and what it can't—and of course sometimes it won't be helpful at all in their case. If they decide not to get further screening, that's okay with us.

Q: Are people generally well informed?
A: I find it is very mixed. Some patients ask informed and detailed questions. At the other extreme, some buy into concepts about what genetic screening can and can't do that are not widely accepted. So there's really a huge spectrum.

Q: What tests do you offer?
A: People can screen for their genetic risk of adult diseases, or do "carrier screening," which looks for diseases that might be passed on to children. They can also get a pharmacogenetics test, which looks at how their bodies might be predisposed to respond to certain medications.

We can also sequence their whole exome—all of the genes that produce proteins. Patients then possess all of their most significant genetic data, which can then be referenced as more discoveries are made.

We bill insurance for all tests, but most people end up paying because the tests are still considered elective. The first three tests are $250 each and whole exome sequencing costs $3,500, although this price will probably come down with time.

Q: Are you opposed to consumer genetic tests?
A: The consumer demand for these tests is not currently something that brick-and-mortar academic centers can keep up with, even if this model spreads. But I think there are any number of ways to deliver better information and counseling with genetic data, even with these companies. What matters is that it is accessible and of high quality—and perhaps as importantly, that it is motivated by a desire to inform and empower, and not just to sell tests.

BY THE NUMBERS

Community Health Centers

27 Million

Americans who use community health centers: nonprofit clinics that deliver affordable health care to patients with no insurance or inadequate coverage. The number of people who rely on these centers has nearly tripled since 2001.

1,200

Infants saved in the summer of 1908 because of Sara Josephine Baker's home-visiting program, which taught new mothers to care for their babies. She also created milk stations that gave out free, clean milk to struggling mothers. These projects served as models for early community health centers.

53

Years since the nation's first federally funded community health center, Columbia Point Health Center, opened its doors. The facility provided medical services to underserved populations in Boston during the social justice movements of the 1960s.

93

Percentage of families who visited community health centers in 2015 with incomes below the federal poverty level. Fewer than half of all center patients were covered by Medicaid, and nearly a third were under the age of 18.

70

Percentage of funding for these centers that comes from federal sources. Funding expired briefly last year and many are concerned that the overall plan is in jeopardy. A 2009 study showed that these centers save the national health care system $24 billion annually.

JUSTIN GABBARD

UPDATE

A Gentler Gene Edit

Re-engineered cells are making waves in cancer treatment. But there may be a safer way to achieve the same effect.

BY GRACE NIEWIJK

After nearly two decades of clinical trials, the first gene therapy was approved in the United States in August 2017. It is a landmark in immunotherapy, which enlists the body's own immune cells to fight disease ("Kept at Bay," Fall 2015). The new treatment, chimeric antigen receptor (CAR) T-cell therapy, was developed at the University of Pennsylvania and uses modified immune cells to treat blood cancers. It has succeeded in some cases where standard methods have failed.

"People who were on their deathbeds with no chance of survival now have an 80%, even 90% chance," says Samuel Katz, a hematopathologist researching CAR T cells at the Yale School of Medicine. But these new treatments are far from perfect, he says, and new methods are needed to head off dangerous side effects and to bring down costs.

In CAR T therapy, physicians remove some of a patient's T cells—a type of immune cell—and rewrite the cells' DNA by means of a disarmed virus. This causes the cells to begin producing CAR proteins. The cells are then returned to the patient's body, where those proteins lock on to cancer cells so that T cells can finish them off.

While the therapies are effective, they have drawbacks. CAR T therapies are costly, at more than $475,000 per patient. And even after the cancer has been eradicated, the CAR T cells continue to reproduce and may attack healthy cells. This creates a risk of autoimmune disease, which can cause

T CELLS ARE GATEKEEPERS FOR THE BODY, AND SOME FORMS OF IMMUNOTHERAPY GENETICALLY ALTER THEM TO PERFORM THAT DUTY MORE EFFECTIVELY.

fevers, neurological damage and other organ dysfunction.

But gene editing isn't the only way to get T cells to make CAR proteins, says Katz. The current approach changes the cell's DNA "blueprint," ensuring that it will always produce CAR. A less permanent solution would be to send a one-time message to the ribosome, the part of a cell that creates proteins. This message would be in the form of mRNA—a type of cellular communication that Peter Rabinovich, Katz's colleague at Yale, learned to forge in the early 2000s.

An mRNA message would last only about an hour, after which the cell would stop producing CAR proteins. The proteins produced in that short time would stay on the outside of the cell, doing their job, until they degraded in three to five days, at which point the cell would return to normal.

This temporary approach could prevent CAR T cells from overstaying their welcome. "If you have any toxicity from the mRNA treatment, you'd expect that it would be very short-lived," says Nabil Ahmed, who researches CAR T therapies at Baylor College of Medicine in Houston.

Using mRNA reprogramming also has potential cost advantages. The virus-infected CAR T cells needed for today's treatments must be custom designed, tested and manufactured for each patient, a cumbersome process that has halted the development of some gene therapies and slowed others down by years.

In contrast, synthetic mRNA is relatively cheap and easy to manufacture, requiring little in terms of specialized equipment or ingredients. It could be mass-produced and used on a wide range of patients. Ahmed explains, "mRNA is a drug. It can be made and put in a bottle."

While using mRNA to make CAR T cells might take a few days, says Katz, "virus-reprogrammed CAR T cells take weeks or even months to prepare. And sometimes patients don't have that kind of time."

Some experts are skeptical about an mRNA approach, however. "My concern would be that it wouldn't last long enough," says Helen Heslop, president of the American Society of Gene & Cell Therapy. "Short-term persistence may not be sufficient to control the cancer."

The scientific jury is still out regarding how long CAR T cells need to remain in the body, says Katz, although multiple doses of mRNA-reprogrammed cells might be given until the cancer is eradicated. Neither he nor Ahmed, however, can say whether multiple doses of mRNA cells would be as effective as the existing approach to gene therapy.

Other methods for making safer CAR T cells are also under way, so if the promise of mRNA isn't borne out, alternatives are in the wings. "The CAR T cells we're using today are going to be viewed as primitive in fewer than five years," predicts Michael Bishop, who oversaw early CAR T clinical trials as director of the cellular therapy program at the University of Chicago Medical Center: "With the next generations in development, we'll be able to turn them on and off, enhance them and have greater efficacy in treating cases that we once viewed as hopeless."

MILESTONE

False Starts

A failed birth control drug gives a boost to cancer treatment.

BY NAOMI ELSTER

The success of the first oral contraceptive in 1960 led to both a cultural revolution and a surge in fertility research, as the pharmaceutical giants of the day raced to find better contraceptives. One candidate turned out to be a great success—in treating cancer.

Arthur Walpole ran his laboratory in Manchester, England, at Imperial Chemical Industries (ICI, now part of AstraZeneca). He was briefly commissioned to run drug discovery programs for breast cancer and birth control simultaneously. Walpole believed that estrogen might play a role in each, and looked for compounds that would block the hormone in the body, keeping a special eye out for those that would be mild enough for patients to take regularly.

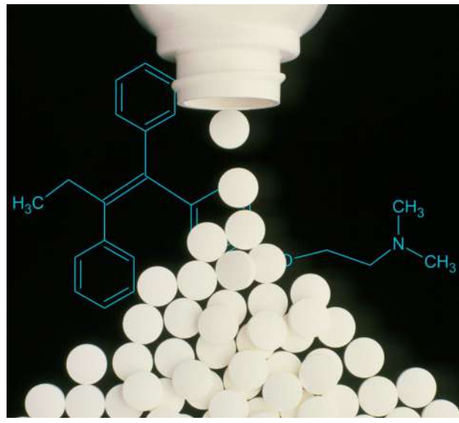
The company soon shifted its cancer efforts to another division, but Walpole didn't want to abandon promising research. And studying breast cancer and birth control at the same time had its advantages: It was especially difficult to obtain a legal abortion in Great Britain in the 1960s, which made conducting contraceptive trials, with their risk of unwanted pregnancies, problematic. He could, however, test his drugs for their ability to block estrogen in women with breast cancer. This would serve as an initial step for later contraceptive trials.

In 1969, 46 breast cancer patients at Christie Hospital in Manchester received one of the more promising chemicals—tamoxifen—overseen by oncologist Moya Cole. Patients showed remarkable recoveries, with many tumors receding significantly.

Most breast cancers, it would later be discovered, contain a receptor for estrogen and rely on the hormone to survive. Blocking the estrogen receptor dealt a severe blow to such cells. Cole noted in her review of the trial in 1971 that not only did the drug work, but patients had a "low incidence of troublesome side effects." This was unheard of at a time when other cancer treatments were highly toxic.

The top brass at ICI were reportedly less than impressed. They reminded researchers that they were supposed to be looking for a birth control drug. The prognosis for breast cancer patients at the time was not good, and the market for such a treatment was not expected even to cover research costs.

When ICI ordered the termination of tamoxifen's development, Walpole threatened to resign, and ripples of despondency fanned out through the research community. But the company soon reversed its decision, and by 1973 the program was back up and running.



JAMES KING-HOLMES/SCIENCE PHOTO LIBRARY

Today, tamoxifen is on the World Health Organization's list of essential medicines, and the drug has been connected to the survival of more than 400,000 breast cancer patients. A milestone study in 1988, 30 years ago, concluded that tamoxifen could in certain cases be used without traditional chemotherapy—making it the first standalone targeted cancer therapy.

This lesson—that cancer treatments could be tailored to the unique mechanisms of each kind of malignant cell—became one of tamoxifen's greatest legacies. The insight led to many other targeted treatments and paved the way for an age of personalized cancer medicine.

POLICY WATCH

A Delicate Matter

Fecal microbiota transplants run into a semantic crisis.

BY MARCIA LERNER

CHRIS GASH

Fecal matter continues to show extraordinary promise as a treatment for microbial imbalances. In the first randomized controlled trial, in 2013, a fecal microbiota transplant (FMT) from a healthy donor worked so effectively to counter *Clostridium difficile*—a drug-resistant and often deadly bacterium that thrives in a depleted microbiome—that the study was halted midway. FMT has also shown promise in treating Crohn's disease and multiple sclerosis and in fighting other multi-drug-resistant bacteria.

But with FMT's growing acceptance as a treatment comes a curious question: What is it? Donated fecal matter, rich in microorganisms that live in the human gut, isn't easily classified under current regulatory categories. Is it a medicine? A kind of tissue? Or something else entirely? A designation governs rules for its safety and effectiveness, so the topic is both pressing and hotly debated.

In 2013, the Food and Drug Administration classified FMT as a biological product and drug. But drugs require consistency from batch to batch and dose to dose, a virtual impossibility for a substance that contains a microbial colony, explains Diane Hoffmann, director of the Law and Health Care Program at the University of Maryland Francis King Carey School of Law. The drug designation also requires that physicians file an investigational new drug (IND) application for each use outside of a clinical trial, a hurdle that many thought was unnecessarily cumbersome for a material so ubiquitous to the human experience.

Physicians and patients pushed back, and later that year the FDA announced that it would exercise "enforcement discretion"—a classification that permits more leeway as the particulars of a new treatment are worked out. In this case, the FDA would overlook the IND requirement for treating cases of recurrent *C. difficile* infection (RCDI). In 2014, it clarified that enforcement discretion only applies if the donated stool comes from a source known to the patient or the physician, and the physician must oversee the screening process.

This requirement posed another challenge, particularly in rural areas. Finding appropriate stool donors isn't as easy as it might seem. A good donor must be in excellent health to reduce the chance of passing on infections, and should be screened for an ever-expanding list of conditions, as varied as obesity and depression, that seem to be tied to the many organisms that call the microbiome home.

Screening donors on an individual basis is not only expensive—it is also not for the squeamish. Carolyn Edelstein is the executive director of OpenBiome, the first stool bank, which operates in the Boston area and provides physicians and researchers with prescreened fecal matter. Before stool banks existed, Edelstein says, physicians had "shelves and shelves of blenders" in which, if they got as far as finding and screening a donor and acquiring a sample, they would need to puree the donation so it could be siphoned through a colonoscopy tube. The blenders had to be thrown away afterward, as they could not be properly sterilized. It was not a sideline most doctors found alluring.

The 2014 FDA guidelines provided no role for—or regulation of—such organizations. "Limiting donations to people the patient or physician knows would eliminate the possibility of using a stool bank," says Hoffmann.

The guidance was updated in 2016, allowing physicians to use a hospital stool bank, but even then the stool sample had to be obtained under the direction of the treating physician. That didn't offer much of an improvement.

In a recent issue of *Science*, Hoffmann and other policy experts and researchers proposed a three-track FMT regulatory system. In the first track, treating a patient for a *C. diff* infection using stool from a known donor would be considered the "practice of medicine"—in other words, it wouldn't be regulated by the FDA. FMT for other conditions would require more oversight, including filing an IND, with a special exemption for some patients in life-threatening situations.

Track two would lay out regulations for stool banks, which would be treated similarly

With fecal matter's growing acceptance as a treatment comes a curious question: What is it?

to establishments that provide human cells and tissues. Registration, screening and testing rules would be put into place, and stool banks would need to report outcomes and other data to a national registry. Finally, track three would apply to "modified stool-based products," such as a new generation of pills. These would be regulated in much the same way as other kinds of experimental drugs.

Elizabeth Hohmann, an infectious disease physician at Massachusetts General Hospital, has been researching and administering FMT since 2012, amid the shifting regulatory landscape. "We need to proceed with as much caution as possible," she says. While some of the first, typically older patients to require FMT were facing life-threatening conditions, today more patients are younger and expected to live a very long time after the procedure: "Changing the microbiome might affect that patient over decades."

And does she think the substance in question is closest to a tissue, a drug or another existing category of treatment? "None of the above," Hohmann says. "The microbiome is different."

SECOND OPINION

Optimizing Science

If we are to retain our best and brightest scientists, research institutions and funding organizations are due for some self-reflection on how policy affecting scientists is formed. The culture of science is often one of optimization, because that is how science itself is conducted. The reality, however, is that optimization in the science world has often ignored the human circumstances of life as a scientist.

Optimizing for risk and perceived return on investment has disadvantaged young scientists and created a competitive environment in which our most talented principal investigators end up spending more time on grant-related activities than research. Optimizing for translational value has come at the cost of basic research that leads to our most incredible breakthroughs.

As "A Future Defunded" (Winter 2018) illustrates, we are losing many of our best scientists because certain policies treat science as a production pipeline rather than a career. It is essential that we find ways to ease the burden of competing for funding, to create stable career options worthy of talented postdocs—even if there is not a faculty position available for them—and to formally seek input from young scientists as we try to solve these problems. A generation of American science is at stake.

Justin Q. Taylor // Co-Founder, Academics for the Future of Science, Massachusetts Institute of Technology, Cambridge, Mass.

Technology and Education

"The Dawn of the Bionic Pancreas" (Winter 2018) is a poignant and timely article on the trials and tribulations of living with type 1 diabetes and how the growing use of technology and artificial intelligence is improving both health outcomes and quality of life. Although the artificial pancreas or fully "closed loop" insulin delivery systems in development are confined to research studies, a hybrid version (Medtronic MiniMed 670G) has hit the market, and more are on their way.

But it is important to keep in mind that technological advances in diabetes management cannot succeed unless patients remain active participants in their care, making healthy meal and physical activity choices to work in concert with the medication regimen.

At NewYork-Presbyterian and Weill Cornell Medicine, we empower our patients and give them the knowledge and tools they need to take control of their lives and their disease. Comprehensive diabetes education to master new automated devices, along with mobile health and other forms of remote decision support, will offer ongoing guidance to make it easier to live well with diabetes.

Jane Jeffrie Seley // Diabetes Nurse Practitioner and Program Manager, Inpatient Glycemic Control, NewYork-Presbyterian and Weill Cornell Medicine, New York, N.Y.

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

Genealogy databases are a new frontier for disease research, pinpointing the genes that stalk families across generations.

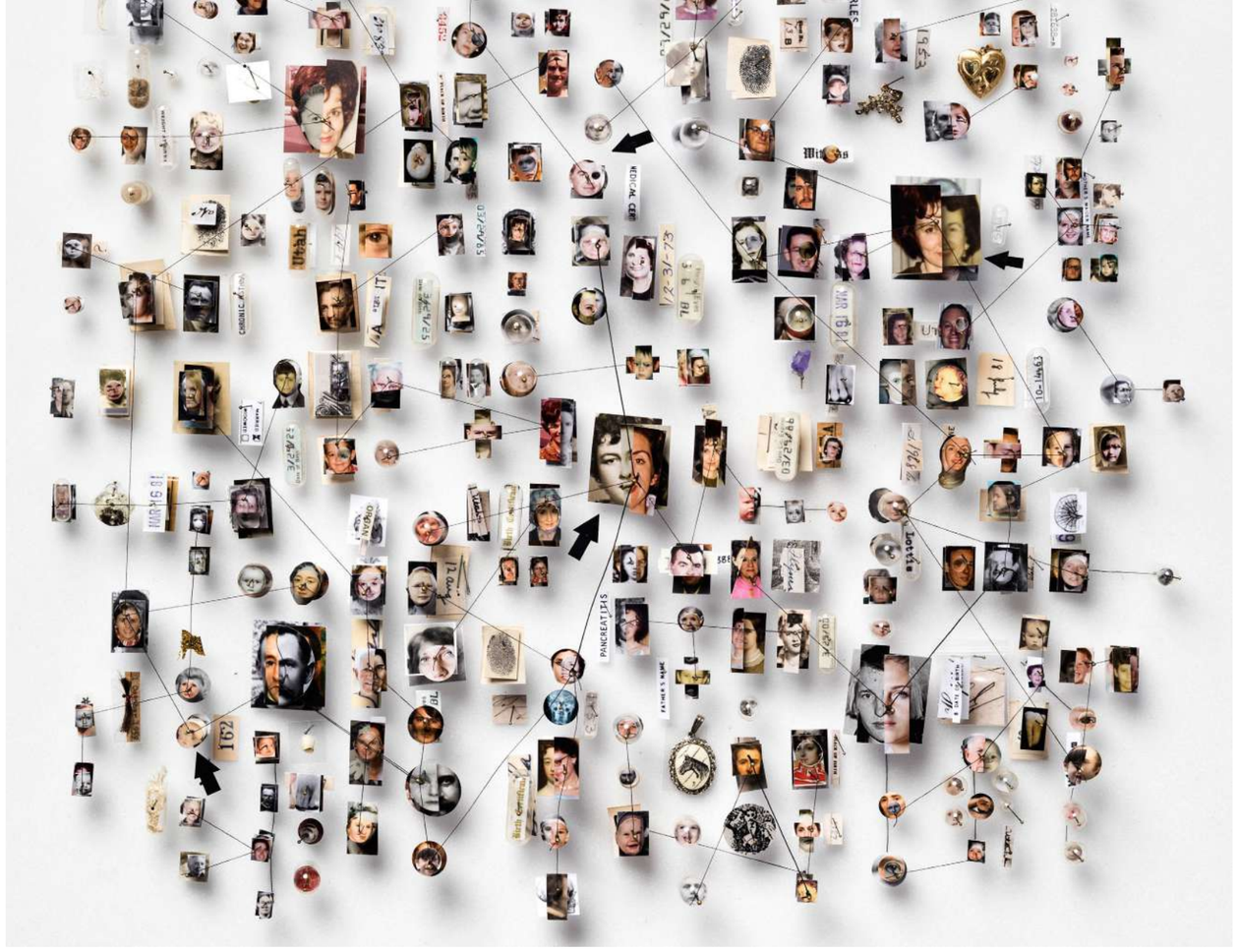
Knots *in the* Family Tree

By Adam Bluestein // Photo Illustrations by Michael Mapes

The pedigree chart of Family 709 tells a grim story, with black diamonds indicating the death by suicide of 27 distant cousins across the branches of an eight-generation family tree. In another chart, for Family 553615, black diamonds mark the suicides of 81 descendants of a single couple who lived in the early 1800s.

Of all the approaches to solving Utah's suicide problem—the state's suicide rate is the nation's fifth highest, and suicide is the leading cause of death there for young men—genealogy might not be the first to spring to mind. Yet researchers have suspected for some time that genes play an outsize role. Adopted relatives of those who have killed themselves have no more risk of suicide than the population at large, but for biological kin, the risk is four times greater; the identical twin of a suicide victim may carry up to 11 times the normal risk.

Family 709, Family 553615 and others like them fall far outside the norm, with a rate of suicide 4 to 10 times higher than that of the overall population. In trying to understand what might set them apart genetically, Hilary Coon, professor of psychiatry at the University of Utah, can draw on two resources unavailable almost anywhere else. One is DNA samples that the Utah state medical examiner has collected from nearly 5,000



suicide victims. The other is the Utah Population Database, or UPDB, one of the most comprehensive human databases, with extensive family pedigrees—genealogical records for Utah families that trace many to forebears in the 1700s and 1800s.

Exploring the medical histories of extended families can help refine and focus genetic investigations, and for Coon, it provided valuable leads. By cross-referencing public records—Utah death certificates started noting suicide as a cause of death in 1904—with Utah's genealogical database, Coon was able to get de-identified family structures of 200 large families with evidence of a high risk of suicide. She chose to study 10 of those families—the ones with the highest risk and the most DNA available.

A genetic analysis of those samples pointed Coon toward 10 chromosomal locations where the sets of distant cousins who died by suicide shared unusual genetic variants. She and her colleagues are studying those sections in detail, using whole genome sequences to home in on particular variations in the DNA. If they find one or more variants that have an evident role in increasing suicide risk, it might be possible to design a drug or other therapy that could act on that gene. Meanwhile, identifying individuals at greater risk through a genetic test could help with early intervention.

Medical histories of extended families can help refine and focus genetic investigations.

Coon's study is one of more than 50 that are part of the Utah Genome Project at the University of Utah. That work combines the latest tools of genetic research—next-generation DNA sequencing and advanced data processing—with one of the oldest: the family tree. By making use of Utah's unique wealth of genealogical records and meshing them with a trove of sequenced DNA, researchers in the state hope to sift out new heirlooms from the past: concrete genetic discoveries that lead to new treatments and better genetic insights.

• • • •

Utah's non-native population descends overwhelmingly from settlers belonging to the Church of Jesus Christ of Latter-day Saints, commonly known as Mormons. Mormons today account for more than 60% of the state's approximately 3 million residents. The UPDB is in part a product of their church—knowing the names of dead ancestors allows relatives to perform "proxy baptisms" for those who may have died unbaptized, giving them a chance at salvation in the afterlife. As a result, Mormons have become some of the world's foremost genealogical record-keepers. The names of the Mormon dead and their living offspring are carefully archived by the Genealogical Society of Utah, which houses hard copies of ancestry records in a secure, underground facility.

During the 1970s, these genealogical records led to the establishment of the UPDB. It can cross-reference the family trees of more than 11 million people from millions of linked pieces of information, including death certificates, data from the Utah Cancer Registry, and electronic health records from the University of Utah and Intermountain Healthcare, which provide care for roughly 85% of the state's population. About 3 million living people listed in the UPDB have ancestry records going back at least three generations. In 2017, the Genealogical Society of Utah supplied records for an additional 90 million, representing deceased relatives of families in the UPDB, many of whom lived outside the state and country.

The only comparable resource is the deCODE database of Icelandic families, which biotech company Amgen acquired in 2012 for $415 million. DeCODE has genealogy records tracking Iceland's population of about 350,000 all the way back to a handful of ninth-century ancestors, and the company has collected more than 10,000 whole genome sequences from current Icelanders.

The UPDB is managed for public benefit by the Huntsman Cancer Institute at the University of Utah. It is used primarily for medical research and fields hundreds of requests each year. The wealth of ancestral records allows for a genealogical approach to understanding disease that has been largely pushed aside for the past 20 years—not because it wasn't effective but because it was hard.

"Historically, we recognized the importance of families in understanding human disease before we knew anything about DNA," says Scott Hebbring, an investigator at the Marshfield Clinic Research Institute's Center for Human Genetics in Wisconsin. But the challenge of finding large families to study, and the declining costs of sequencing, prompted a shift in the mid-2000s toward very large studies of unrelated people, called genome-wide association studies (GWAS).

With a GWAS, researchers can survey the DNA of hundreds or thousands of unrelated people, connect that genetic data to health records and let software find mutations shared by those with a particular disease. Such studies have revealed nearly 40,000 potential connections between areas of the human genome and complex but common conditions such as type 2 diabetes and Parkinson's and Crohn's diseases. But translating those tantalizing findings into diagnostic tests or treatments has often proven difficult.

In part that's because GWAS can identify many genes associated with a disease, but the roles of individual genes may be quite minor. For example, many genes discovered through GWAS raise or lower cholesterol levels by 5% or so—an increment too small to target with a drug. By focusing on families with a high incidence of a disease, however, researchers may be better able to spot rarer variants—the smoking-gun genes—that have a larger impact, says Will Dere, a biopharmaceutical-industry veteran who now heads the University of Utah's Program in Personalized Health. "From my drug-discovery perspective, that's appealing. Histories and generations help separate the wheat—the clinically meaningful gene variant—from the chaff."

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Many studies of disease genetics have focused on parent-child or sibling pairs, because those relationships are easy to find. But the UPDB makes distant relatives—and their medical histories—easier to find as well, which confers two distinct advantages. When a study focuses only on close family relationships, any illnesses they share may be the result of confounding factors that come from a shared environment, rather than just the genes they have in common. That's less likely to be a problem if relatives are further apart on the same family tree.

Second, studying two distant relatives makes it much easier to find troublemaking genes. That's a matter of math. Parents share roughly half of their DNA with their children, and siblings share roughly the same amount with each other. For more distant relatives, the number of shared inherited variants drops by half with each degree of separation. First cousins have only about 12.5% of their human DNA in common, and with each branching, that number goes down further. If two far-flung family members share a rare condition, the culprit genes will be lurking within a relatively small pool of their shared DNA—only a few dozen rare coding variants, versus hundreds or thousands shared by a closer relative.

The genes identified through this process may be beneficial. Lisa Cannon-Albright, a professor and division chief of genetic epidemiology at the University of Utah School of Medicine, and geneticist John Kauwe at Brigham Young University in Utah, used the UPDB to find a rare variant of the gene *RABI0* that may provide resilience against Alzheimer's disease. Major risk factors for Alzheimer's include age and a particular variant of the *APOE* gene

called *APOE*e4, which can increase the likelihood of developing late-onset Alzheimer's by as much as twelvefold. But a small percentage of people who have the *APOE*e4 variant appear untouched by its effects, living well beyond 75 years without symptoms of cognitive decline. A beneficial genetic mutation may exist that counteracts the "bad" one.

For their study, published in *Genome Medicine* in 2017, Cannon-Albright and her colleagues began with some 5,000 residents of Cache County, Utah, who have been followed for more than 15 years in a study on aging and dementia. Because nearly all of these subjects were in the UPDB, the researchers were able to find those with a strong family history of Alzheimer's and to break them into two groups—one consisting of 232 people, living and dead, who had never shown symptoms of cognitive decline, even though they had the normally damaging *APOE*e4 variant, and another of 581 people diagnosed with dementia.

With the Kauwe Lab, Cannon-Albright's team was able to pinpoint variants in the *RAB10* and *SAR1A* genes that hadn't been seen before and that were shared by members of the pedigrees. Then they were able to validate their findings by checking two independent DNA databases of Alzheimer's patients and elderly controls, finding that the variant in *RAB10* appeared to confer protection against Alzheimer's in those groups, too.

Brain cells in mice pointed to a likely biological mechanism: Changes in *RAB10* affected another gene, *APP*, involved in the production of amyloid proteins—an excess buildup of which is a hallmark of Alzheimer's disease. This suggests that *RAB10* could be a particularly promising target for prevention and treatment.

Amgen has taken a similar tack in developing a cardiovascular drug that mimics the lack of a particular gene discovered in Icelanders. People without the gene have a 35% lower risk of having a heart attack. Developing a drug that "silences" the gene might confer protection in people who have it. "Looking at pedigrees allows us to focus our attention in promising places," says Cannon-Albright.

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Some of the greatest leaps have combined genealogical tools with an ever-increasing trove of genomic data. In the past three years, the USTAR Center for Genetic Discovery at the University of Utah, which processes genomic data for the Utah Genome Project and external collaborators, has analyzed tens of thousands of genomes. Yet with so much information at their fingertips, the challenge for researchers becomes "how to get the data to tell us what it knows," says Nicola Camp, a statistical geneticist in the Huntsman Cancer Institute.

In a recent study of breast cancer, Camp and her colleagues tried to ascertain whether there were inherited genetic variants that predisposed women to develop particular types of tumors. Breast cancer tumors can be classified into four main subtypes determined by looking at patterns of expression across a panel of dozens of genes. Those with particular subtypes are more likely to succumb to the disease than those with other subtypes.

Using the UPDB and Utah's cancer databases, Camp identified 11 extended families containing an unusually large number of people with breast cancer. She expected to find a preponderance of certain subtypes within distinct pedigrees, but the samples didn't fit the expected pattern. That made her question the standard model. "We weren't convinced that the existing four categories really told us what we wanted to know," Camp says.

"Histories and generations help separate the wheat—the clinically meaningful gene variant—from the chaff."

So she took a different tack and looked at about 1,000 cancer patients in a Kaiser Permanente database. Rather than sorting them into the usual subtypes, her team used a method called principal component analysis to derive biomarkers that explained the most common patterns of gene expression across the panel. It discovered five multigene tumor characteristics—an alternative representation of expression diversity, distinct from the four standard categorical subtypes—and found that these were consistent across other cancer databases, too. Then, back with the original high-risk pedigrees, the researchers found that two of the new multi-gene tumor characteristics did a much better job of explaining the excess of cancer in those extended families than the four subtypes had done. That discovery might eventually lead to better diagnosis and treatment.

"There was information in the genes that was important, and the pedigrees themselves told us we weren't looking at it in the right way," Camp says.

The potential breakthroughs made by Coon, Camp, Cannon-Albright and other researchers in Utah and Iceland may have much to do with the special resources in those places. Still, it's possible to build other useful genealogies—and to do so rather quickly. Cannon-Albright is working with the U.S. Department of Veteran's Affairs to create a genealogy database that will eventually link all 24 million VA patients to ancestry and health records. "It's a massive amount of data, but it's not that hard to do with publicly available records," says Cannon-Albright. Starting with a birth certificate, researchers can usually find who someone's mother and father were, and death and marriage records can also help.

Using health records is another way to construct genealogies, says Hebbring of the Marshfield Clinic Research Institute. He was coauthor of a 2017 paper in *Bioinformatics* that outlined a strategy for predicting people who are related, using basic demographic data—last name, date of birth, home address and gender—available in most electronic health records. (All demographic data was de-identified to protect patient privacy, as it is in all of these genealogical databases.) Two people sharing an address are likely to be related, especially if they share a last name. Factor in ages and you can make a good guess about familial relationships—parent-child or siblings. Using an algorithm to analyze records of 2.6 million people in Marshfield's electronic health records, Hebbring and his coauthors predicted the composition of 173,368 family units of two to five generations with remarkable accuracy. The work showed that other medical systems with decent electronic records might be able to build genealogies in a similar way.

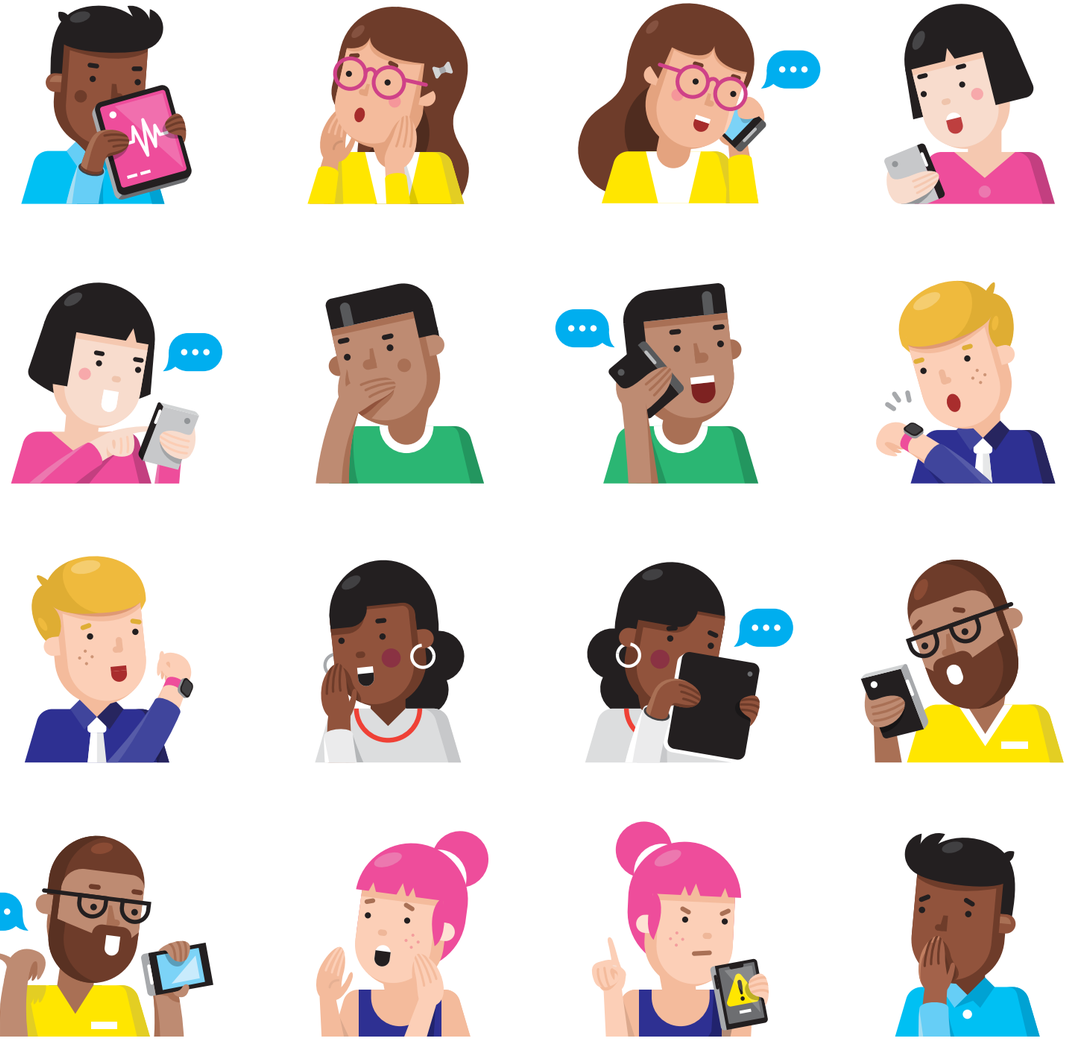
Meanwhile, a growing number of national genome projects also have the potential to generate genealogical data. At least 50 such projects are under way around the world, in the United Kingdom, Saudi Arabia, Singapore, China and other countries. "Most national studies are often treated as large sets of unrelated individuals, but in reality, everyone is related somehow," says Hebbring. "If you have hundreds of thousands of people in a study, there will be a few brothers, sisters, children, cousins—but there will also be many more distant family relationships."

The race to mine such data for important genes is heating up. In 2015, for example, both Amgen and Regeneron launched *PCSK9* inhibitors, potent new cholesterol-lowering drugs based on a variant discovered in French families that researchers at University of Texas Southwestern Medical Center in Dallas linked to very low cholesterol levels. This heralds a bright future for genealogy studies and even promises a kind of poetic justice. Disease-causing genes have always stalked families across generations, bringing tragedy in their wake. Now, by looking across generations, researchers will be able to follow the trail to new cures.

DOSSIER

"Variant *ASGR1* Associated with a Reduced Risk of Coronary Artery Disease," by Paul Nioi et al., *The New England Journal of Medicine*, June 2016. This study of Icelandic pedigrees identifies a protective gene variant that significantly reduces heart-disease risk.

"Linkage, Whole Genome Sequence, and Biological Data Implicate Variants in RAB10 in Alzheimer's Disease Resilience," by Perry G. Ridge et al., *Genome Medicine*, November 2017. This study uses a Utah population to discover a potential protective gene variant in Alzheimer's disease.



false information online has hit a high-water mark, and many offenders are stories about health and medicine. can anything be done to set the record straight?

going viral

the rise of fake medical news

Last winter, the website YourNewsWire published a story with this headline: “CDC Doctor: ‘Disastrous’ Flu Shot Is Causing Deadly Flu Outbreak.” Appearing during one of the worst flu seasons in years, the article quoted an anonymous physician at the Centers for Disease Control and Prevention who warned that nearly all the people dying of the flu had one thing in common: They had gotten flu shots. “This scares the crap out of me,” says the physician in the article. The story also cast Big Pharma as a co-conspirator for failing to disclose to the public the toxic chemicals contained in the vaccine.

None of this was true; the entire story, including the quotes, was fabricated. Yet that didn’t stop the piece from going viral on the internet, popping up on a variety of alternative-health and conspiracy-theory websites. The story was widely shared on Facebook, generating about 500,000 engagements in January alone—more than any story that week from the *Wall Street Journal*, NPR, ABC, CBS, CNN or Fox News. It also generated thousands of online comments, some fanning broader fears about vaccinations, with “anti-vax” campaigners writing to support the story’s claims and even purported incidents in which the flu shot itself caused paralysis or even death. Although several fact-checking websites poked holes in the story’s narrative, that did nothing to slow its momentum.

Welcome to the world of fake medical news. During and after the 2016 U.S. presidential campaign, the phrase “fake news” marked a new phase of distrust in media, serving on the one hand as a way for politicians to denounce any news coverage they didn’t like, and describing

by linda keslar //
illustrations by michael brandon myers

on the other a proliferation of stories that were baldly untrue. The medical realm is not immune and has become home to some of the most egregious examples. "There's no empirical way to measure it, but my sense is that of all the categories of fake news, medical news is the worst, and there's more of it out there," says Kelly McBride, vice president of the Poynter Institute, a nonprofit journalism school in St. Petersburg, Fla.

Watchdog groups have identified hundreds of websites purveying fake medical news, and countless more fly under the radar. This misinformation runs the gamut from truly ridiculous to more subtle misreporting and overhyping of stories from mainstream news sources. Motivations of its creators vary, but fake medical news can earn clicks and "likes," which can translate to ad revenue, or further an agenda that targets evidence-based medicine.

the ascendance of the internet and social media has raised the dissemination of unreliable medical news to new heights

Deliberately false information can also drive the sale of expensive, unproven treatments. "These schemes are bilking consumers out of millions and millions of dollars," says Richard Cleland, assistant director at the Advertising Practices division in the Bureau of Consumer Protection at the Federal Trade Commission in Washington D.C., which has taken action to shut down offenders.

Moreover, after a fake news story is posted, there's little that can be done to retract the information. "Once it's on the internet, it's there forever," says Joseph Jankovic, a neurologist who heads the Parkinson's Disease Center and Movement Disorders Clinic at Baylor College of Medicine in Houston. Would-be miracle cures for Parkinson's are a "major, major problem," he says. "I have to spend a lot of time in patient visits debunking unreliable information from the internet."

Beyond the chaos they sow, and beyond instances of fraud and unreliable cures, fake medical news also undermines—sometimes intentionally—trust in the medical establishment, according to Melissa Zimdars, an assistant professor at Merrimack College in North Andover, Mass., who has analyzed more than a thousand fake news websites. Health care practitioners, researchers and government health agencies all are weakened by an atmosphere in which the reliability of the authorities is suddenly suspect. "The way health and medicine are discussed and oversimplified in the news is already problematic," she says. "But that's made so much worse by websites that destabilize how much the public can rely on science and research."

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Fake news in medicine is nothing new. "Bogus medical information has been circulating in one form or another since at least the Middle Ages," says Jonathan L. Stolz, a retired physician and medical historian in Williamsburg, Va. In the latter part of the nineteenth century, for example, newspapers were crammed with false advertising for questionable elixirs, such as Mrs. Winslow's Soothing Syrup, the effects of which relied on high concentrations of alcohol and other questionable ingredients, including morphine.

In the 1950s, another category of fake news—misleading industry-funded research—made its debut when tobacco companies underwrote studies to downplay the health hazards of cigarettes. They also launched a far-reaching public relations campaign that included "A Frank Statement," which the industry placed in hundreds of U.S. newspapers. During the "more than 300 years tobacco has given solace, relaxation and enjoyment to mankind," the ad read, "critics have held it responsible for practically every disease of the human body. One by one these charges have been abandoned for lack of evidence."

Holding scientific and medical claims to account, meanwhile, has traditionally been a weak spot even for mainstream publications, says McBride. "Journalism is very much about trying to simplify and distribute information about what's new and where advances have been made. That's incompatible with the scientific process, which can take a long time to build a body of evidence." Moreover, science stories are often far from provocative. "Good information can be really boring," she says.

The decline of print media, bringing a loss of editors and fact-checkers to verify accuracy, has meant fewer gatekeepers in vetting the quality of information, says Leticia Bode, an assistant professor and media technology researcher at Georgetown University in Washington, D.C. The ascendance of the internet and social media has also raised the dissemination of unreliable medical news to new heights. Online search technology relies on algorithms that automatically—and opaquely—determine what people see, often without concern for substance or accuracy. That reliance on automation encourages the unscrupulous to game the system. "You can figure out how to get your links to rise to the top of search results," Bode says.

Even those who run reputable websites feel compelled to churn out click-worthy stories, because those clicks are how success (and revenue) is now defined. There are fewer incentives for articles that probe deeply into complex subjects, says Rick Weiss, director of SciLine, a service for journalists based at the American Association for the Advancement of Science (AAAS) in Washington, D.C. "Journalism just isn't adequately performing a key function it was meant to perform, which is to screen information and provide the public with material that it can reasonably believe," Weiss says.

The way news is consumed has also shifted the role of editor to users, who have more freedom than ever before to choose the stories they find compelling, with no imperative to screen for truth. On platforms such as Facebook, now the nation's single-largest social media news source, people share what they like, including posts from blogging platforms that anyone can use. This has created an online world of echo chambers, populated by the opinions of celebrities and other nonexperts who cast themselves as credible sources on medical issues, says Zimdars. "On the internet, you can always find someone to agree with you and reinforce your beliefs," she adds.

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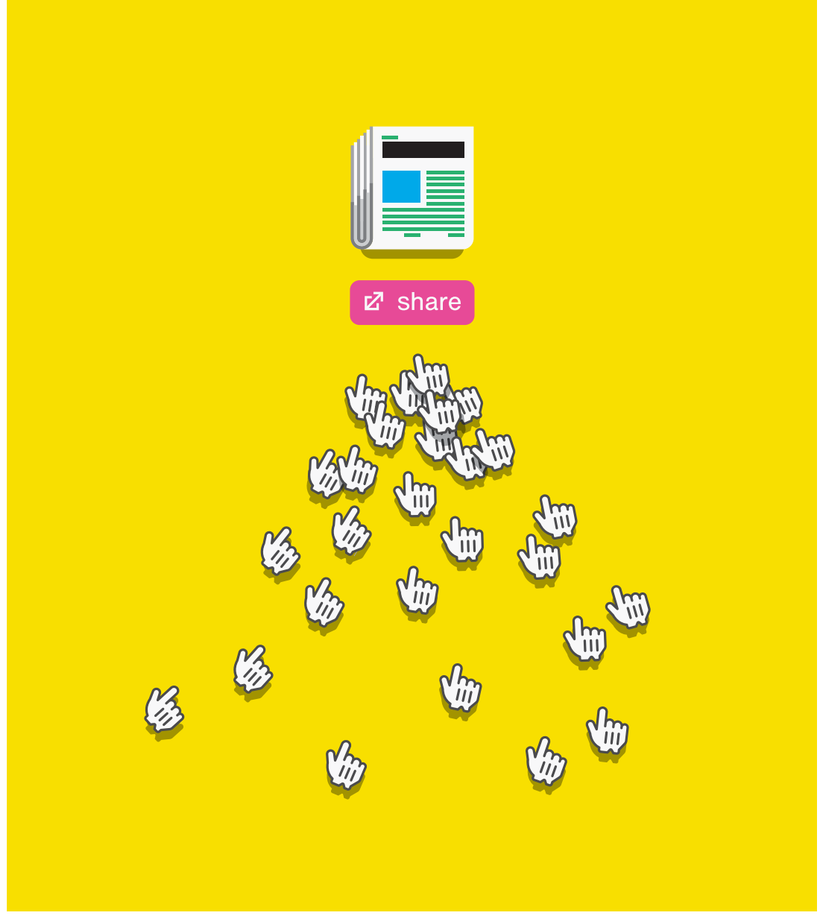
Academic research is only beginning to explore the causes and effects of fake news. In one massive study—"The Spread of True and False News Online," published in *Science* in March—researchers at the Massachusetts Institute of Technology reported the results of a decadelong project probing the habits of millions of Twitter users. They found that false news of all kinds reached more people more quickly than true stories did. The top 1% of false information diffused to as many as 100,000 people, according to the study, while accurate stories rarely reached more than 1,000.

In a separate research project that looks specifically at fake medical news, Zimdars has analyzed about a dozen questionable websites. Most, like YourNewsWire, include junk medical news as part of their overall content, while a smaller number are exclusively devoted to it. The "fraudulence" of mainstream medicine was also a common theme, says Zimdars. "The typical refrain is that Big Pharma is rigged and researchers are controlled by business interests," she says. "The intent is to make readers fear well-researched, traditional medical treatments."



That approach can be especially effective when a legitimate debate about research and therapies exists, Zimdars says. Steven Nissen, a cardiologist at Cleveland Clinic, points to statins as a prime example. Statins reduce cholesterol levels and cut the risk of cardiovascular disease, and are among the most widely prescribed treatments. Yet there is a growing debate about whether the drugs should be prescribed to patients who have no history of heart disease. Meanwhile, statins have spurred a torrent of fake or dubious medical stories.

Only about half of the people prescribed a statin continue taking the medicine after six months, a rate that is "shockingly low," says Nissen. He believes that an "internet cult" of misinformation is partly to blame. In an editorial in the *Annals of Internal Medicine* last August, he recounted that when he typed "statin risks" into a search engine, he got more than 3.5 million hits. Many of the links were to websites created by people with little or no scientific expertise and which relied heavily on misleading claims. In contrast, when he searched "statin benefits," he got 655,000 results. "I have scores of patients who have stopped taking statins based on fears that mainly come from the internet," he says, noting that the consequences can be deadly. Multiple studies have found that patients who discontinue statins are up to five times more likely than those who continue on the therapy to develop cardiovascular disease, and those who abandon statins may have twice the risk of dying prematurely.

Fake medical news also often exploits the hopes of patients desperate for a cure. Last January the website Natural News, which averages more than six million monthly visitors, ran this story: "Top 8 ways to HEAL America from cancer—when every US hospital goes 100% ALL NATURAL with therapy." It listed therapies—turmeric, vitamins, oxygen and cannabis among others—that would be better treatments than radiation, chemotherapy or other conventional approaches.

That kind of questionable medical advice has real consequences, says Skyler Johnson, a physician specializing in radiation oncology at Yale New Haven Hospital. "I have seen patients with curable cancer who come in with printouts of internet stories like this one, which they've usually gotten from well-meaning family members or friends. This helps them decide to choose alternative medicine over recommended cancer treatment," he says. Yet that choice could be deadly, according to a 2017 study by Johnson and a team of Yale scientists, who compared the two approaches in hundreds of patients with breast, prostate, lung and colorectal cancers. They found that using alternative treatments instead of receiving medically advised cancer care could double a patient's risk of death from cancer.

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The Food and Drug Administration and the FTC have some power to censor online medical content when it is used to advertise fraudulent products. During the past year, for instance, the FDA issued warning letters to more than a dozen companies that the agency said were illegally selling products on the internet that fraudulently claimed to prevent, treat or cure cancer. The FTC, which coordinates its efforts with the FDA, has filed 120 cases during the past decade challenging medical claims for supplements. It has also tried to crack down on fake online medical content that the agency considers deceptive marketing.

Weight-loss supplements and drugs claiming to reverse age-related mental decline are two of the biggest categories for bogus products, according to the FTC's Cleland. "Those generate heavy online traffic, with lots of money changing hands," says Cleland. But he notes that the agency doesn't have the resources to keep up with that volume, and even the relative handful of regulatory actions from the FTC and FDA don't always stick. Some companies simply change their names and reintroduce disguised versions of their websites and the disputed products.

Other solutions are needed, Cleland says. Yet much of what exists or has been proposed depends on consumers themselves blowing the whistle on false or exorbitant claims. Both the FTC and FDA websites feature links for reporting fraud and unlawful sales of medical products, and Quackwatch, a website run by retired North Carolina psychiatrist Stephen Barrett, provides guidance on spotting fraudulent sites. Snopes.com is dedicated to weeding out fake news stories in general, and HealthNewsReview.org focuses exclusively on the accuracy of medical news.

Moreover, dozens of major global news sites as well as social media platforms, including Facebook and Twitter, are experimenting with "trust indicators"—flags on an article that show whether it is news, opinion, analysis or advertising; give details about the site's funders; and, for some articles, provide sources used to back up its claims.

Other institutions are also working on ways to combat fake medical news and to encourage factual reporting. The AAAS, for example, recently launched SciLine, a service that connects journalists with credible science experts when they write or produce stories about science and medicine. The nonprofit also posts background summaries of science-related topics in the news. "There are a lot of people who now do fact-checking after a story is published," says SciLine's Weiss. "We want to help journalists have the resources so their work is accurate when it's first published, rather than worrying about how to correct bad information once it's out there."

Facebook often finds itself in the middle of debates about fake news, medical and otherwise. Yet its attempts to address the issue have gained little traction and have sometimes had unintended consequences. In December, for example, the company announced that it would no longer use red flags to identify questionable stories—because sometimes the flags increased traffic to those pieces.

health care practitioners, researchers and government health agencies are weakened by an atmosphere in which the reliability of the authorities is suddenly suspect

Other Facebook initiatives have included adjusting its newsfeed algorithm to give preference to posts shared by friends and family, rather than those from third-party organizations, and a new process for vetting content that asks users what news sources they find trustworthy. "We decided that having the community determine which sources are broadly trusted would be most objective," Facebook founder Mark Zuckerberg wrote on his Facebook page.

Although these and other policies may affect how people distribute and consume news, Zimdars questions how useful they'll be. She notes that sharing posts among friends and family members who likely have similar views will only reinforce the "echo chamber" effect that already plagues so many online interactions. "How will Facebook prevent this process from being gamed by the mobilized readers of consistently inaccurate websites?" she asks.

More thoroughgoing reforms will be needed. An essay from 16 political scientists and legal scholars, published in the issue of *Science* that contained the MIT fake news study, called for interdisciplinary research to redesign the "information ecosystem in the 21st century." The experts said changes were needed "to reduce the spread of fake news and to address the underlying pathologies it has revealed.... How can we create a news ecosystem and culture that values and promotes truth?"

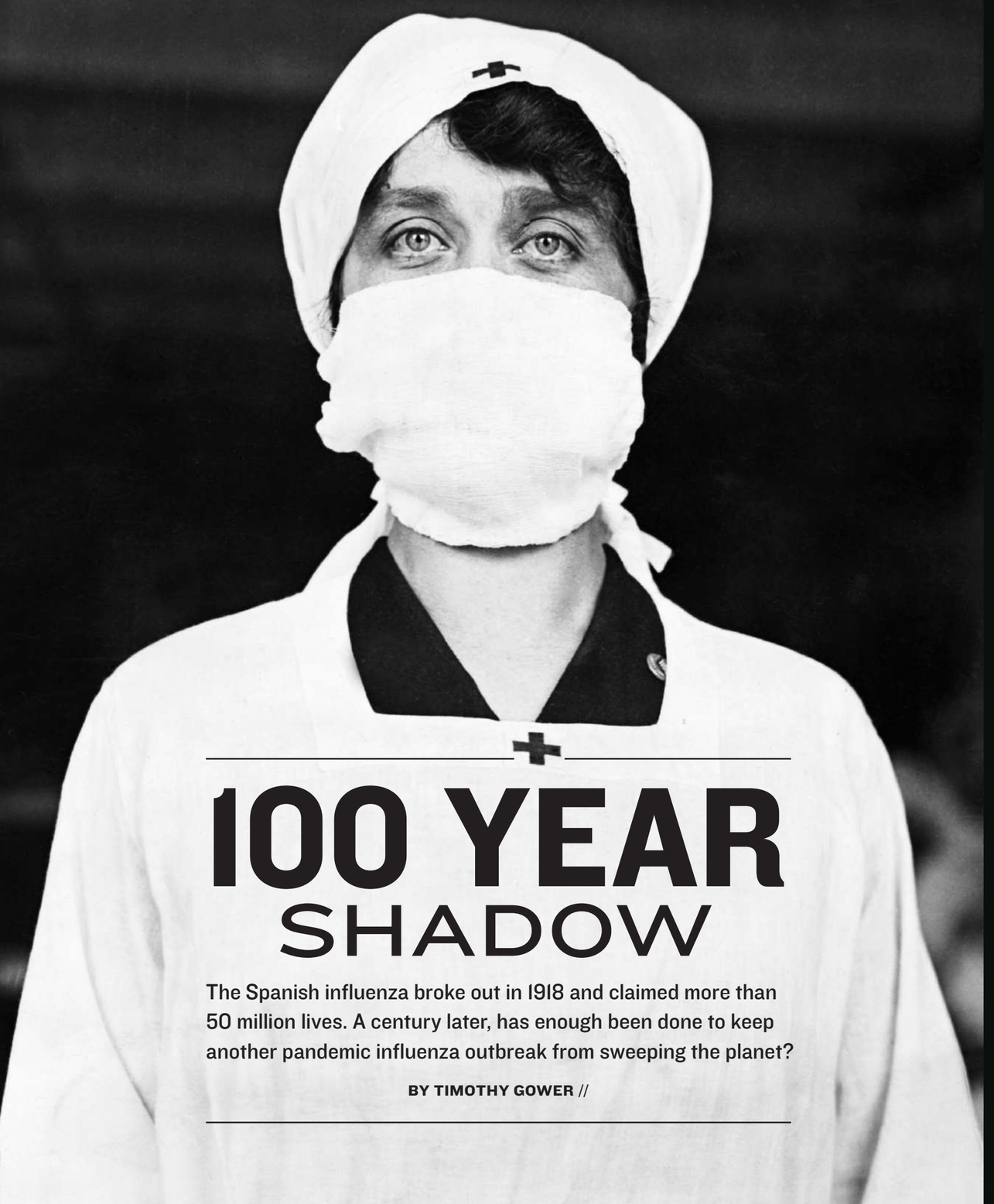
Until fixes are identified and put in place, fake medical news will continue to be produced and widely shared. In a disturbing follow-up to the YourNewsWire story about dangerous flu shots, the site identified a CDC scientist who had disappeared and later drowned as the source of its "scoop." The website even implied that the missing scientist was the victim of a deliberate government conspiracy to silence him. After that story also went viral, generating more than 170,000 Facebook engagements within a week, police investigators and the scientist's family dismissed the rumors—noting, among other things, that he hadn't worked in the CDC's infectious disease unit and wouldn't have had access to information about the flu vaccine. The site took no notice and both articles are still live, gathering more views and shares by the day.

DOSSIER

"The Spread of True and False News Online," by Soroush Vosoughi et al., *Science*, March 9, 2018. This study on fake news, the largest to date, examines the habits of 3 million Twitter users and documents how misinformation spreads.

"I Do Not Believe You: How Providing a Source Corrects Health Misperceptions Across Social Media Platforms," by Emily K. Vraga and Leticia Bode, *Information, Communication & Society*, April 19, 2017. This investigation looks at mechanisms for correcting health misinformation about the Zika virus circulating on Facebook and Twitter.

"Science Reporting in the Age of Fake News," by Carl Zimmer, lecture delivered at American Association for the Advancement of Science event, Oct. 12 2017. Science writer Carl Zimmer talks about the history of fake science news and its implications for public policy.



100 YEAR SHADOW

The Spanish influenza broke out in 1918 and claimed more than 50 million lives. A century later, has enough been done to keep another pandemic influenza outbreak from sweeping the planet?

BY TIMOTHY GOWER //

Influenza viruses cause epidemics in the United States every year, year after year. Sometimes they are mild, with relatively few infections and low mortality. Other years they leave a deeper mark, as was the case this past winter, with news of overflowing intensive care units and of children who fell ill one day and perished the next. While infectious disease experts and others who study the flu are never certain of just how bad a season will be before it hits, they say that one thing is easier to predict: Some day, sooner or later, the world will likely face another serious pandemic—one that evokes the tragedy that struck in 1918.

The "Spanish flu"—misnamed, since no one is certain where it first struck, although many historians place its origins in Haskell County, Kansas—remains one of the worst known plagues in human history. When it arrived, the First World War had been raging for several years, building an international network of transmission routes. The war also put hundreds of thousands of soldiers in close, unsanitary conditions. By early spring, a strain of influenza virus began causing a number of deaths across the United States and other countries. The final estimated toll, when the disease had run its course in 1920, was between 50 million and 100 million people worldwide.

Medicine is better suited, in nearly every respect, to confront pandemics today. Seasonal flu vaccines are widely available; antibiotics can treat secondary bacterial infections, which were a major cause of deaths in 1918; and antivirals can both prevent the disease and control symptoms. Intensive care units provide life-saving technology that includes mechanical ventilators for damaged lungs, the lungs being where most secondary infections strike. Not least, epidemiologists can track the path and severity of an outbreak to help organize preventive efforts and treatment.

Yet there have been four pandemics since 1918, most recently in 2009, that have together killed more than 2.5 million people

worldwide. A virus that carries the pathogenic punch of the 1918 influenza could still prove devastating, says virologist Jeffery K. Taubenberger of the National Institute of Allergy and Infectious Diseases (NIAID)—especially for people around the globe who lack access to advanced medical care. "Many would not be much better off than in 1918," says Taubenberger, who believes another death toll of tens of millions would not be out of the question.

Flu viruses change frequently, and if a newly evolved virus is so unlike previous pathogens that humans have no preexisting immunity to it, the risk of a pandemic becomes especially great. On the lookout for such a virus, health officials are currently most concerned about the H7N9 avian virus, which originated in China in 2013 and has killed more than 600 people. In its current form, H7N9 virus doesn't seem able to be readily transmitted among humans, but mutations could give it

A MICROBE THAT CARRIES THE PATHOGENIC PUNCH OF THE 1918 INFLUENZA VIRUS COULD STILL PROVE DEVASTATING.

that ability. "If that happens, we would likely have a pandemic," says Tim Uyeki, a medical epidemiologist in the influenza division of the Centers for Disease Control and Prevention. "That is what keeps me up at night—literally."

The best solution for heading off a new pandemic would be a universal vaccine—one that protects against not only known variations on the flu virus but any new subtypes that might appear. Such a vaccine would also help with the scattershot protection offered by current flu shots, which are reformulated each year to protect against the strains that seem to pose the greatest danger. Today's flu vaccines reduce the risk of developing the disease by, at most, 60%. In bad years, that advantage may drop to 10%.

Infectious disease experts emphasize that current influenza vaccines nonetheless offer crucial protection, especially by making the disease less toxic in people who become infected. A 2017 study found that unvaccinated flu patients in the hospital were two to five times more likely to die than those who had received flu shots. Still, today's vaccines are routinely stymied by the flu virus' uncanny ability to mutate, rearranging its genetic makeup in subtle and significant ways that help it hide from the immune system. The next generation of vaccines in development takes that shape-shifting into account and tries to find a way around it—by, among other methods, focusing the power of the immune system on parts of the virus that don't change. The work carries a sense of urgency, taking place as it does under the specter of 1918 and the probability that an especially deadly flu season will yet again be upon us.

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Scientists first isolated the influenza virus in the early 1930s, more than a dozen years after the 1918 pandemic; a decade later the first flu vaccines became available in the United States. Each February, an advisory board at the Food and Drug Administration identifies the flu strains that are known to be circulating and selects which ones manufacturers should include in vaccines to be sold in the United States the following fall.

Most flu vaccine is still produced as it has been for 70 years—by slowly growing viruses in eggs, a complex, multistep process that takes about six months. By the time a batch of flu vaccine is ready—just in time for the U.S. flu season—the dominant strains in circulation may have changed. Flu viruses change frequently, and protein structures in the virus can subtly drift as it is passed from person to person. One of the key proteins that can change is the hemagglutinin, the structure the vaccine trains the immune system to guard against. If that structure has changed significantly, the vaccine becomes less effective. Moreover, viruses undergo mutations to survive and reproduce in eggs, and mounting research suggests that this phenomenon can play a significant role in spoiling the match between flu strains included in seasonal vaccines and the viruses in circulation.

To overcome the problem of mismatched vaccines, some researchers are looking at the "conserved" parts of the flu virus—the ones that generally don't change. To understand this, consider that the flu virus is studded with mushroom-shaped surface proteins: hemagglutinin and another, called neuraminidase. The head portion of hemagglutinin attracts the most attention from the human immune system, which attacks it with proteins called antibodies to eradicate the virus. Hemagglutinin heads, however, also happen to be the sites of frequent antigenic changes, which create new strains the immune system doesn't recognize. That helps explain why vaccines often fail to protect against the flu.

One potential solution, then, is to redirect the immune system's attention from the head to the stalk, which doesn't undergo these mutations, says microbiologist Peter Palese of the Icahn School of Medicine at Mount Sinai in New York City. Past attempts tried simply to chop off the heads and hope the immune system would refocus attention on the stalk. But headless stalks turned out to be too structurally unstable to be used in vaccines aimed at inducing protective antibodies.

Palese and his colleagues created a structure called a chimeric hemagglutinin (cHA), which tricked the immune system into making protective antibodies against the stalk as well as the conserved neuraminidase. They started with a virus that sickens humans, removed the hemagglutinin heads, and in their place fused on the heads of "exotic" hemagglutinins, borrowed from avian flu strains that are harmless to people. In animal studies, repeated inoculations with a cHA-based vaccine persuaded the immune system to ignore the strange head and instead to direct antibodies against the stalk and the neuraminidase, says microbiologist Florian Krammer, Palese's colleague at Mount Sinai and a frequent co-investigator.

In theory, this kind of universal vaccine would train the immune system to recognize a portion of the virus that remains unchanged in all forms of influenza—both seasonal flu and any new, particularly virulent strains. So far, says Palese, the cHA-based vaccine has worked beautifully in mice and ferrets, protecting them against every strain of flu virus the research team has tried, including some from as early as 1934. "Our dream," says Krammer, "is to be able to vaccinate kids twice, maybe three times, and have them never need another flu shot." Two human trials, supported by pharmaceutical giant GSK and the Gates Foundation, are in progress.

Meanwhile, other groups are trying new ways to make vaccines with headless hemagglutinin. A team led by scientists at NIAID has made headless stalks more stable by anchoring them to the blood protein ferritin. With such a vaccine, the body detects the presence of hemagglutinin, and the immune system responds as it would to a real virus, says John Mascola, director of NIAID's Vaccine Research Center. In a 2015 study published in *Nature Medicine*, Mascola and his colleagues reported that a vaccine made with headless hemagglutinin stalks protected mice and ferrets from a dose of H5N1 avian flu that was lethal to unvaccinated lab animals.

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Other groups are looking past the virus's heads and stalks. Microbiologist Ted M. Ross, director of the University of Georgia's Center for Vaccines and Immunology, leads a team that hopes to achieve a universal vaccine by creating a comprehensive structure that contains every likely epitope in a single antigen. Ross developed a technique—computationally optimized broadly reactive antigen, or COBRA—that draws from databases of genetic data on hundreds of strains of influenza viruses that have been reported over the years. The goal is to identify the most dominant hemagglutinin epitopes—the parts of antigens that antibodies attack—and use their genetic sequences to create one encyclopedic synthetic molecule. This would then be introduced into the body, stimulating an immune response to all possible flu viruses—theoretically, even strains of the influenza viruses that don't yet exist.

Ross and his colleagues have used a COBRA-derived vaccine to inoculate mice and ferrets against all strains of H1N1 and H3N2 flu—the viruses widely circulating now in people—as well as the H5N1 avian virus, which is rare but often deadly in humans. Ross says his experimental vaccines guard against 90% of all known strains, at least in animals. It remains to be seen how durable that protection will be, "but if it lasts for four or five years, that's better than what we're doing now," says Ross. Drugmaker Sanofi Pasteur has licensed this technology, which is currently being developed for possible testing in humans.

PREVIOUS PAGE: BETTMANN/GETTY IMAGES AND JONATHAN NACKSTRAND/GETTY IMAGES; THIS PAGE: BETTMANN/GETTY IMAGES AND JUNKO KIMURA/GETTY IMAGES; NEXT PAGE: PA IMAGES/ALAMY

Still other vaccine developers are looking beyond antibodies altogether, with the goal of stimulating a different mechanism of the human immune system. "There is a kind of hierarchy in the immune response," says Tamar Ben-Yedidia, chief scientific officer of the biotechnology company BiondVax in Ness Ziona, Israel. B cells in the immune system generate the antibodies that often block a flu virus's infection of a cell. But if antibodies fail, T cells confer another layer of protection, producing immune modulators called cytokines that directly attack infected cells and stop influenza from proliferating. Moreover, immunity based on T cells remains high after recovery from the flu, reducing the risk of reinfection, even by other subtypes of the disease.

There are limits to what T cells can do, however. The immunity they provide declines after each flu infection, until they are no longer at high enough levels to protect, says Sarah Gilbert, a vaccinologist at the University of Oxford and cofounder of biotech firm Vaccitech. Vaccitech and BiondVax are both developing vaccines designed to boost the T cell response against the influenza virus. In one trial, BiondVax's vaccine, known as M-001, was given to elderly men and women before they received the traditional flu vaccine, improving their immune response. More intriguing, three years later the tests performed on stored blood taken from these men and women showed that antibodies spurred by the vaccine also neutralized the H3N2 virus that caused widespread illness in the 2014–2015 flu season, suggesting that the injection might guard against viruses that evolve and circulate in the future. BiondVax is now preparing phase 3 clinical trials.

Similarly, Taubenberger and his colleagues at NIAID have tested a vaccine cocktail containing hemagglutinins from four subtypes of avian influenza—H1 and H3, which are subtypes that have caused pandemics and annual epidemics in humans, and H5 and H7, from avian viruses that have also caused lethal infections. This not only protected mice from those flu subtypes but also from H2 viruses, H6 viruses and other influenza subtypes that were lethal to other animals. How could it protect against types not included in the vaccine? Taubenberger says that part of the explanation may be that their vaccine cocktail, which triggers production of protective antibodies, may also stimulate T cells.

TOPICAL NEWS AGENCY/GETTY IMAGES AND JAM MEDIA/GETTY IMAGES

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Despite the promise of these disparate approaches, a truly universal influenza vaccine is likely decades away, says Anthony Fauci, director of NIAID, which earlier this year unveiled a strategic plan for creating a safe and effective universal influenza vaccine. Still, Fauci believes that broadly effective vaccines that protect against more than one subtype of the flu could be available much sooner. "There is going to be universal flu vaccine 1.0, then 2.0 and so on," says Fauci. "We're not going to get the right answer the first time."

CREATING BETTER FLU VACCINES WILL REQUIRE NOT ONLY PATIENCE BUT A KNOWLEDGE OF HISTORY.

Other researchers question whether there will ever be a single flu vaccine that can provide all or even most people with something approaching total immunity. One somewhat controversial theory holds that a person's immune system may be "imprinted" by the first flu virus it encounters and then will primarily produce antibodies to that virus subtype, paying less attention to others. That hypothesis isn't universally accepted, but if true, the immune systems of older people might be too rigid to respond to a universal vaccine. Very young people, in contrast, who have never been exposed to the flu, would have immunological clean slates and could be strong candidates. "With a universal vaccine you could conceivably produce generations of young people who might develop immunity to new flu strains and new pandemics," says Taubenberger, "but this kind of approach might not help fiftysomethings like me."

In the meantime, researchers continue to look for ways to make conventional flu protection more effective. "If you could narrow the window, then you could better match them to evolving strains of a virus," says Uyeki.

HARRY SHEPHERD/GETTY IMAGES AND NOAH SEELAM/GETTY IMAGES

That means moving away from egg-based vaccine production, says Andrew Pavia, chief of the division of infectious diseases at University of Utah Health, an academic health care system in Salt Lake City. One current vaccine, FluBlok, is cultivated in insect cells and can be ready in six to eight weeks. Although it's FDA-approved for use only in those who have egg allergies, in a 2017 study FluBlok provided better flu protection than a standard flu shot. Pavia believes that wider use of adjuvants, added ingredients that increase the immune response to influenza, could help reduce the flu's annual impact, too.

Emerging technology could also speed production of vaccines in the event of a pandemic. For example, genetic vaccines, such as DNA and mRNA, currently under investigation could be ready within a few months after the genome of a pandemic virus is sequenced, says Mascola. The vaccines that Mascola and his colleagues have tested contain only the genetic sequence for hemagglutinin and therefore don't form a full virus. "Muscle cells take up the DNA and make part of the flu virus—for instance, just the hemagglutinin—and the body produces an immune response to that protein," says Mascola. In a 2017 study by NIAID scientists, 30 healthy adults were vaccinated with an H7 DNA vaccine, an inactivated H7N9 vaccine prime, or both. In the study, most of the participants who received the priming H7 DNA vaccine had at least a fourfold increase in antibodies against the H7N9 virus, compared with those who received only the H7N9 vaccine.

Creating better flu vaccines will require not only patience but a knowledge of history, says Taubenberger. It would be a mistake to believe that the terrifying virulence of the 1918 pandemic was an outlier caused by strange mutations in the virus that are unlikely to recur. "There are other viruses out there in the wild that share those features," says Taubenberger. "Something like this could happen again."

DOSSIER

"Reconstruction of the 1918 Influenza Virus: Unexpected Rewards from the Past," by Jeffery K. Taubenberger et al., *mbio*, September 2012. This article explores how reassembling the 1918 flu has led to insights about influenza virus biology and pathogenesis.

"Chasing Seasonal Influenza—The Need for a Universal Influenza Vaccine," by Catherine I. Paules et al., *The New England Journal of Medicine*, Jan. 4, 2018. This article outlines why the world needs a broadly effective flu vaccine, and why everyone should still get the current imperfect version.

***The Great Influenza: The Story of the Deadliest Pandemic in History*, by John M. Barry (Penguin Books, 2004).** This heavily researched narrative chronicles the 1918 influenza pandemic and the first "great collision between nature and modern science."

After decades of glacial progress on treating mood disorders, researchers have found a new generation of treatments that show real promise. But will they offer the relief patients have been waiting for?

New Tools for Depression

By Anita Slomski // Illustrations by Martin O'Neill

Could an overactive immune system make you depressed? In the late 1990s, psychiatrist Andrew Miller and his colleagues began to notice that patients with cancer, cardiovascular disease, obesity and Crohn's disease—all conditions that cause higher than normal levels of inflammation—often suffered from elevated rates of depression. He also observed that many patients who took medication to tamp down their immune system, thereby reducing inflammation, also saw their depressive symptoms ease.

But when Miller tried to interest pharmaceutical companies in studying the effect of immunosuppressants on depression, he got turned down again and again. "I lost count of the number of lunches I had with drug company executives, but the answer was always no,"

says Miller, who also serves as the director of the Immunology Program at Emory University School of Medicine in Atlanta. Drugmakers didn't want to risk having a depressed patient attempt suicide while taking their medication, forever branding the drug with the "black-box warning" of potential suicide that every conventional antidepressant medicine already carried.

Finally, a research proposal from Miller won a competition sponsored by Centocor, a drug company eager to develop neuropsychiatric treatments; with funding from the National Institute of Mental Health (NIMH), Miller and his colleagues launched the first trial of immunosuppressants in 2008 for severely treatment-resistant depression with 60 patients. When Miller reported in 2013 that severely depressed trial participants who had significant inflammation got well after three infusions of infliximab, an antibody used to treat Crohn's disease and rheumatoid arthritis, other drug companies finally took notice. Although it has taken a while for this fledgling field to develop, there are now several trials testing immunosuppressants for treatment of depression, bipolar disorder and schizophrenia.

That research, like other work aimed at finding new and better treatments for major depression, must seem long overdue to the more than 16 million adults in the United States who suffer from the condition—which may involve profound, unrelenting sadness and an inability to muster what's required for day-to-day living. "Yet progress in developing therapies has been glacial," says David Mischoulon, director of the depression clinical and research program at Massachusetts General Hospital.

The first drugs with antidepressant properties were discovered serendipitously in the 1950s, and most people who are diagnosed with depression today are prescribed medications intended to have similar effects. "We've invented the same drugs over and over again," says psychiatrist and researcher Roy Perlis, director of the Center for Quantitative Health in the psychiatry department at MGH.

Those conventional antidepressants often work, but they're not effective for everyone, and usually they begin helping only after many weeks. The landmark NIMH STAR*D trial, completed in 2006, found that only 27% of depressed people taking antidepressants experienced remission within the first 12- to 14-week course. Others didn't feel better until they had tried several different drugs, and one-third never got full relief.

The immunosuppressant approach, like virtually every other treatment for depression, new or old, works only for some people. In Miller's trial, just the participants with the highest levels of inflammation experienced significant relief from their depressive symptoms, and those with low levels of inflammation actually tended to fare worse than the placebo group. Moreover, the side effects of drugs that suppress the immune system may mean that using such treatments is worth the risk only in the most severe cases.

Knowing more about how depression functions in the brain would help in the search for new treatments, and in recent years researchers have made great strides in learning how both to map and to alter the physiology of brains that malfunction in mood disorders. "We now have a vast number of tools available to study the biology of depression, from the molecular level to the cellular level to brain circuits," says Carlos Zarate, chief of experimental therapeutics and pathophysiology branch at NIMH. "Optogenetics, for example, allows researchers to use light to control brain cells. That helps them isolate particular circuits in the brain and see how they interact with each other."

That more intimate knowledge has led to a new generation of possible therapies, including short-term treatments that may work quickly to resolve an episode of depression without committing a patient to long-term maintenance doses of antidepressants. The search for better treatment has also led to promising, if unconventional, approaches that include whole-body hyperthermia and the use of psychoactive drugs, two areas studied by Charles Raison, a professor at the School of Human Ecology and School of Medicine and Public Health at University of Wisconsin, Madison. "After decades of the antidepressant doldrums," he says, "this is a very exciting time in depression research—one that I didn't think I would see in my lifetime."

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Some of the most widely used antidepressants originated in the middle of the past century as drugs to treat tuberculosis and schizophrenia. They failed to cure those diseases, but physicians noticed that using them made patients decidedly happier. Researchers worked backward to figure out how the treatments functioned, and by 1965 they had found that the drugs affected the concentrations of three neurotransmitters that serve as chemical messengers in the brain and play primary roles in depression. Serotonin is vital to regulating sleep, appetite, mood and pain perception; norepinephrine is involved in energy and arousal systems; and dopamine is important in motivation and reward. The most widely prescribed antidepressants are selective serotonin reuptake inhibitors, or SSRIs, which temporarily increase the amount of serotonin in the brain.

But three sometimes-faulty neurotransmitters scarcely offer a complete explanation of what goes awry in the brain during major depression. Many other neurotransmitters may also be implicated, and there are billions of chemical reactions related to mood, along with exquisitely complicated circuitry connecting the many brain regions that regulate emotions. This complexity means that what is monolithically labeled depression actually arises from a wide variety of causes, grouped into multiple subtypes that are still largely undefined. "A handful of subtypes probably account for most depression, but there are likely to be many others that affect fewer people," says Perlis. Those differences in how depression arises and manifests help to explain a phenomenon that has long plagued researchers: Possible treatments, hailed because of their clear effectiveness in some patients, fail in clinical trials involving wide swaths of the population because one size does not fit all.

As some depression pathways become clearer, researchers have been able to devise novel therapies that target different points along the way—from drugs that quiet or rev up brain signaling to more precisely targeted electrical devices that can sense when and where there's a problem. "If you interrupt the chain of events that leads to depression at any point, then the patient gets better," says Miller.

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One of the most promising recent discoveries is the use of the anesthetic ketamine and its derivatives. Ketamine blocks receptors for glutamate, a neurotransmitter involved in cognition and emotion. Researchers believe that excess glutamate in someone who is depressed, along with high levels of the stress hormone cortisol, lead to reduced neuronal resilience in response to stress. By blocking glutamate receptors, ketamine launches a cascade of events in the brain, including release of GABA (gamma-aminobutyric acid), a calming neurotransmitter, as well as increased levels of proteins that help new synapses form within a day.

Ketamine was approved by the Food and Drug Administration in 1970 as a short-acting anesthetic, and the drug, which distorts the senses and causes dreamy detachment as well as euphoria, was used on injured soldiers in Vietnam and emerged

A BRIEF HISTORY OF DEPRESSION TREATMENTS

335–280 BC

BLOODLETTING

Greek physician Herophilos, now known as the Father of Anatomy, endorses bloodletting as a treatment for mood disorders, based on the belief that they stem from imbalanced humors in the body. This treatment persists well into the 19th century.

Faculté de Médecine Université Paris Descartes

Science History Images/ Alamy

1st Century

A SHOCK TO THE SYSTEM

The medical guide *De Medicina* lists treatments for depression, such as rubbing water infused with the herb vervain on a shaved head or starving and flogging a patient to shock the mind and body back into health.

1621

MUSIC

Robert Burton produces *The Anatomy of Melancholy*, in which he recommends music as "a sovereign remedy against despair and melancholy [that can] drive away the devil himself."

Wellcome Collection

Wellcome Collection

1796

ENVIRONMENT

Quaker William Tuke founds The York Retreat in England. It becomes a flagship of the "moral treatment," which aims to cure mental illness through kindness and patience, a pleasant environment, walks and recreation.

1898

WATER

The American Journal of Psychiatry recommends opium and hydrotherapy, such as taking prolonged hot baths Other sources call for needle showers, steam chambers or the Scotch douche: strong jets of alternating hot and cold water.

Wikipedia Commons

(Continued on page 34)

as a recreational drug in the mid-1990s. In 2000, ketamine was tried for the first time with depressed patients. A single 40-minute intravenous infusion of the drug lifted symptoms for a handful of patients within four hours and continued its antidepressant effects for up to 72 hours. When the same patients got a placebo infusion, it didn't help at all. Several follow-up studies also showed the potential of the drug.

The success of these trials was a milestone in the search for new treatments. "Ketamine's rapid and profound antidepressant effects showed us that it was possible to develop truly new antidepressants, and that has encouraged the entire field to come up with new approaches," says Perlis. Many physicians now administer ketamine to depressed patients "off label," because that use of the drug has not yet been approved by the FDA.

But several trials of ketamine-like drugs are now in progress. At least one new treatment is likely to pass muster with the FDA by late this year or early 2019. That drug, esketamine, can be delivered through a nasal spray. Janssen, a subsidiary of Johnson & Johnson, recently completed part of a phase 3 trial of the therapy, and the FDA has granted it "breakthrough therapy" status for its possible use as a depression and imminent suicide risk treatment.

Ketamine's fast action may also prove valuable for preventing suicide. Michael Grunebaum, associate professor of psychiatry at Columbia University Medical Center, conducted a study of 80 severely depressed people—half of whom were already taking antidepressants—who said they were considering suicide. Half of the patients, by random assignment, were given intravenous ketamine, and the others received the intravenous sedative midazolam, a benzodiazepine sedative that lasts in the body about as long as ketamine, but with no established antidepressant or antisuicidal effects. Among those receiving ketamine, 55% showed a robust reduction in suicidal thoughts in one day, versus 30% of those who got midazolam. "It's quite dramatic to see the people in the ketamine group be more hopeful, have more energy and talk about wanting to get on with their lives within 24 hours," says Grunebaum.

Esketamine and all ketamine drugs stimulate an opioid receptor in the brain, and have the potential for addiction and abuse. Chronic, heavy ketamine use is known to cause long-term memory and cognitive problems. If approved by the FDA, however, esketamine will be administered only in physicians' offices, perhaps once or twice a week, and at much lower doses than it would take to get high. "The onus will be on physicians who treat depression with esketamine to make sure the drug is not diverted," says Michael Thase, an investigator for the esketamine trials and director of the Mood and Anxiety Program at the Perelman School of Medicine at the University of Pennsylvania.

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Psychiatrist Charles Raison was a co-investigator with Andrew Miller on the immunosuppressant trial for treating depression. Raison's most recent research is inspired by ancient practices for adjusting mental states. "Sweat lodges, which cause hyperthermia, and psychedelic drugs are two of the oldest strategies that people have employed to alter consciousness," says Raison. Rather than "gerrymandering the brain" with a steady stream of antidepressant medications, he explains, it might be more effective to investigate treatments that deliver a single, profound shift to brain pathways—physical events that cause prolonged antidepressant effects.

For a whole-body hyperthermia study published in *JAMA Psychiatry* in August 2016, Raison put subjects into a Heckel device: a bed equipped with infrared lights and coils and covered by a fabric tent. Half of the depressed participants received a mild-intensity heat treatment designed to raise core body temperature to 101.3 degrees Fahrenheit, which took an average of 107 minutes, while the placebo group received only slight warming. Actual core body temperatures of both those who were given the active treatment and those who received the placebo varied among participants, and those who became the hottest experienced the strongest antidepressant effects. Raison found that the treatment boosted levels of interleukin-6, a signaling molecule of the immune system that has inflammatory and anti-inflammatory effects. (Intense exercise can also hike interleukin-6.) While some people got no benefit from the heat treatments, those who did respond continued to feel less depressed throughout the six weeks of the study.

In Raison's view, treating psychiatric disorders with controlled psychoactive substances in a safe environment also revives an approach that may have been effective before the advent of modern medicine. The FDA has given a group called the Multidisciplinary Association for Psychedelic Studies approval to conduct large-scale clinical trials of MDMA, also known as molly or ecstasy, for people with post-traumatic stress disorder (PTSD). This approval stems from several previous studies by the same researchers. In one of these, 68% of participants who had suffered PTSD for an average of 18 years no longer had symptoms one year after a single treatment of MDMA. Equally dramatic results were found for depression. A group of Johns Hopkins researchers treated 51 people with depression and life-threatening cancer with a single dose of hallucinogenic psilocybin mushrooms or a placebo. After six months, 60% of participants who received psilocybin were no longer depressed, and 67% cited the drug-induced experience as one of the five most meaningful in their lives. Psychedelics are currently being studied for the treatment of several other conditions, including obsessive-compulsive disorder and alcohol and drug abuse, as well as for smoking cessation.

Raison is developing additional large-scale studies to evaluate the use of psilocybin as a clinical treatment for major depression. Psilocybin and other psychedelics, he says, acutely reduce the activity of the brain's default mode network, composed of brain regions that become active when the brain is resting and not engaged by a cognitive task. In depression, the default mode network may be overactive, leading to negative ruminations and preoccupations. By suppressing the default mode network, psychedelic agents allow contact among brain areas that don't normally communicate, helping break the tenacious hold of negative emotions. "These brain changes appear to induce powerful emotional experiences that help the brain reassemble itself differently and with more flexibility, leading to long-term changes," says Raison.

(Continued from page 32)

Bettman/Getty Images

1917

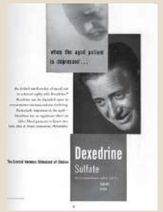
THERAPY

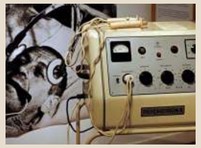
Sigmund Freud publishes *Introduction to Psychoanalysis*, establishing the "talking cure" to treat those afflicted with depression. He also recommends the use of cocaine, but later repudiates the drug.

1937

AMPHETAMINES

Amphetamines are included in treatment guidelines for mild depression and related conditions. By the mid-1940s, more than 1 million amphetamine tablets are taken daily in the United States to improve mood and lose weight.





Arterre Picture Library/Alamy

1938

ELECTRICITY

The first human electroconvulsive therapy (ECT) is performed in Rome. Initially used to treat schizophrenia, ECT is found to be highly effective in severe depression. It is still used today.

1951

IPRONIAZID

Patients with tuberculosis, treated with the experimental drug iproniazid, begin laughing and dancing in hospital corridors. The drug is used until 1961 as an antidepressant, followed by imipramine, a failed treatment for schizophrenia.

1960s

MORE THERAPY

American psychiatrist Aaron Beck develops cognitive behavioral therapy to help depressed patients break the cycle of negative thinking. This will become one of the most studied forms of talk therapy.

Courtesy of Beck Institute for Cognitive Therapy

1987

PROZAC

Prozac hits the market, and by 1990, 2 million people worldwide are taking the drug, which targets serotonin. This and other SSRIs become first-line treatments for the condition.

Will & Deni McIntyre/Getty Images

In a very different approach to a similar end, deep brain stimulation (DBS) provides pulses of electricity from an implanted battery pack to electrodes implanted in the brain. DBS has long been used to treat Parkinson's disease, obsessive-compulsive disorder and epilepsy. But its path to federal approval as a therapy for depression has been rocky, despite persistent evidence that DBS can have an effect.

In 2003, neurologist Helen Mayberg, a neurosurgeon and a psychiatrist then at the University of Toronto, implanted the first DBS device in a severely depressed patient in a brain region called Area 25, deep in the brain's cingulate cortex. Area 25 is involved in regulating emotions, motivation and the way people evaluate themselves relative to others. The brain region is overactive in depression and suppressed after the condition is successfully treated. Delivering a continuous current to Area 25 is the most direct, powerful way to affect depression, according to Mayberg's data. "DBS doesn't repair what is broken; it puts the brain in a different rhythm that allows normal functioning to occur," she says.

One subject whose depression had failed to respond to 100 treatments of electroconvulsive therapy—a treatment of last resort—recovered after DBS. "It was transformative for her," says Mayberg. Encouraged by such results, both St. Jude Medical (now Abbott) and Medtronic in 2009 were pursuing FDA approval for DBS devices to treat depression. Both trials were stopped early, however, when patients showed only mild improvement. In the randomized St. Jude trial—in which all patients had DBS devices implanted, but only half had them turned on—22% of treated patients reported improvement, versus 17% in the group with inactive devices. Results of the Medtronic trial were similar, also falling short of researchers' hopes.

But here, says Mayberg, is where it gets interesting. When the St. Jude trial ended, participants were given the option of either having their devices removed or allowing them to continue to stimulate their brains while researchers followed the patients' progress. Of the 90 participants originally recruited, 77 opted to keep their DBS, which was switched on for all of them. Two years later, the depression symptoms of half of the trial subjects had been reduced by at least half. One in four participants had no lingering symptoms of depression. Those were very promising results in patients who had been severely depressed for an average of 12 years, says Mayberg. At Medtronic, 28 of the 30 study participants opted to keep their devices and most of them also experienced significant improvements.

Now, Mayberg, who heads the new Center for Advanced Circuit Therapeutics for the Icahn School of Medicine at Mount Sinai in New York City, has a grant from the NIMH BRAIN Initiative to study the mechanism of Area 25 DBS and how the brain changes in response. Also being funded by NIMH BRAIN Initiative, along with $30 million from the federal Defense Advanced Research Projects Agency (DARPA), is a parallel DBS project at Massachusetts General Hospital to treat soldiers and veterans with severe depression and PTSD. Darin Dougherty, director of the neurotherapeutics division at MGH, who served as lead investigator for the Medtronic DBS trial, is taking a different approach this time, alongside the project's 50 other researchers. Instead of using DBS electrodes to stimulate the brain constantly, the new devices record brain activity and provide a pulse of electricity only when they detect problems in a brain area associated with symptoms of depression.

"Because depression is so heterogeneous, there is no single neurocircuit for it," says Dougherty. The device he and his fellow researchers are developing for DARPA measures signals associated with dysfunction in known behavioral circuits, such as those associated with reward and fear, and delivers electrical pulses to normalize those signals when needed. "This is a personalized, responsive approach that treats specific symptoms of depression," says Dougherty. "The brain is an electrochemical organ, and I'm confident we'll find an approach with electricity that works on this circuit-based disorder. We just need to crack the code, and now we have the tools to do that."

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Drugs and devices aren't the only tools for treating depression. Psychotherapy has long been an effective alternative, with effects comparable to taking antidepressants but with less than half the drugs' risk of disease relapse. "Antidepressants modify a stress response, but they don't cure depression," says Penn's Thase, who studies cognitive behavioral therapy (CBT), which teaches depressed patients strategies to break harmful habits and negative thought patterns. "When you stop taking an antidepressant, the therapeutic element is gone and you're again at risk of getting depressed."

While CBT isn't new—it was developed in the 1960s—researchers are now experimenting with novel methods of delivering it. Thase is investigating ways to make CBT more accessible—for example, with therapy delivered primarily through web-based modules. In a recent study, that approach was compared with traditional weekly CBT sessions with a therapist. "We took the material that therapists cover in good CBT and put it in an interactive format with video vignettes, self-help exercises and guidance through homework assignments," says Thase. Depressed participants who received the Internet-assisted therapy also received five hours of face-to-face contact with therapists—compared with 13 hours of in-person therapy in the conventional CBT group. At the end of 16 weeks, the groups reported nearly identical rates of recovery, but the computer-assisted therapy cost participants $928 less. "Internet-assisted therapy makes therapists three times more efficient and reduces the cost of treatment by two-thirds," says Thase.

Another new strategy tries to predict which treatment pathway will have the best effect. Many patients get talk therapy and antidepressant medications, which can be more powerful in combination, but for most patients neither approach succeeds at first. Now there is evidence that some depressed brains may respond to one approach and not the other. That makes it important to choose the right therapy from the start.

Helen Mayberg has conducted a series of brain-imaging studies to find biomarkers that will predict which patients are most likely to respond to either approach. Using positron emission tomography (PET) and functional magnetic resonance imaging, Mayberg has found distinct patterns of neural activity and connectivity in people who get better taking antidepressants versus those who respond to CBT. The diagnostics can help predict optimal treatments as well as which ones to avoid.

"On a PET scan, for example, if you have high metabolic activity in the insula, you'll do great on drugs but terrible in CBT," Mayberg says. "And if you have low activity in that region, the reverse is true. Understanding these different brain patterns should eventually help us find a clinical test that will predict who is a candidate for which therapy."

Never before have there been so many new breakthroughs. David Mischoulon of MGH finds the new research lines both promising and a call for renewed efforts. "The more we learn, the more we realize the limitations of the current available treatments," he says, "and how much work we still need to do before we can get a handle on this disorder."

DOSSIER

"Neuroimaging-Based Biomarkers for Treatment Selection in Major Depressive Disorder," by Boadie Dunlop and Helen Mayberg, *Dialogues in Clinical Neuroscience*, December 2014. This paper looks into developing brain biomarkers to better determine individualized depression treatments.

"The Role of Inflammation in Depression: From Evolutionary Imperative to Modern Treatment Target," by Andrew Miller and Charles Raison, *Nature Reviews Immunology*, January 2016. The authors investigate how a genetic bias for inflammation can promote depression.

"Treating Refractory Mental Illness With Closed-Loop Brain Stimulation," by Alik Widge et al., *Experimental Neurology*, January 2017. The report looks at progress toward creating more targeted deep brain stimulation.

FIRST PERSON

Finger to G_d

BY ELI REITER

Before I even rub the sleep from my eyes, I tally the sins I am about to commit: Shower. Get in a car. Ride to the hospital. I might be almost 39 for 39 *melakhot*, an important Hebrew word I'll happily explain in just a minute.

First let me catch you up on Eli's adventures in the outdoors. I had been hiking in Olympic National Park, about three hours from Seattle. That day's hike brought me to the top of a mountain near Hurricane Ridge. It was all so beautiful up there, waterfalls and emerald forests, an experience of nature that is hard to get between a Brooklyn apartment and the subway.

It wasn't until I got back to the parking lot that nature, in the form of a tree root, had her little joke. I tripped and fell down—hard. My pinky swelled up until it was huge. It was a pinky pregnant with another pinky.

I asked the locals about the nearest hospital and they told me it was in Forks, Wash. That's the town in the *Twilight* books, they said helpfully. I got there and met with a doctor who was not, thankfully, a teenage vampire.

"I showed your X-ray to a doctor in Seattle," said the medical professional (after ordering a suspicious number of blood tests). "You need to get surgery soon."

I decide to head for the suburbs of Seattle and throw myself on the mercy of my cousin's family. They volunteer to host me during my surgical ordeal. Unfortunately, the only day my emergency surgery can be done before the July 4 holiday is a Saturday, the day when I am supposed to be observing Shabbat law.

For thousands of years, observant Jews in my orthodox tradition have refrained from 39 activities—the melakhot—on every Sabbath. Prohibitions include writing, carrying objects, and operating electronics and machinery. There are big stretches of Brooklyn, including hospitals, which have made this kind of thing easier to observe. Redmond, Washington—not so much.

During my medical consultation, I stealthily send a Facebook message to a friend in rabbinical school: "They say I have to get surgery tomorrow. What can I do, and what can't I do?" When you are at risk of losing organs or your life, he writes me, much is permitted. But I'm not convinced that my pinky situation qualifies.

I head home that night, dreading the next day. My Seattle family is sympathetic, but they don't follow the same religious rules that I do. I try to explain the situation, as I make their kitchen kosher for Friday night Shabbat dinner. This, by the way, is a complicated process of dipping utensils into a large vat of boiling water with one hand and consulting with a New York rabbi with the other, phone cradled in a plaster cast. If you ever need to do this in a Pacific Northwest kitchen, here's a hot tip: a crab sieve is a great way to boil a drawer-full of forks and spoons at once.

The family says they'll make the day as easy as they can. They will drive me and run interference. The solution is not ideal in my head, but I let them do this for me.

At the hospital I can't uphold the Sabbath at all. Despite my family's desire to help, I have to sign my name I don't know how many times—liability, medications, insurance. The hospital staff just doesn't know how to handle me. They are solicitous about my body, but draw the line at my soul.

I go under, and the next thing I know it's over. The door of the recovery room opens and my cousins are there to pick me up, the broken wanderer far from home.

We ride home together in my cousin's car. Yes, this is a prohibited activity, and the whole day has become an exercise in showing how imperfect I am.

But I will have to have my reckoning later, I think. Right now I am whole again. I am on the mend, and with family that just wants to see me well.

COLLAGE IMAGES: GETTY IMAGES

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