WINTER 20

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MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

The Ache of Motherhood

New mothers are dying at alarming rates. Is a shortfall in mental health care making the problem worse? p12

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FEATURES

on the cover

Rates of maternal mortality—women's deaths that happen in the months before and after giving birth—are alarmingly high in the United States. Few resources have gone to understanding a key dimension: how mental health plays into the problem.
// Photograph by Eric Ogden

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.

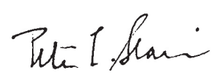
THE WRITER JOHN STEINBECK said that his ideal doctor was "a friend with special knowledge." The primary care physician who could form that kind of sustaining, lifelong bond was once a mainstay of American life. Increasingly, however, that is changing. Now only about half of people between 18 and 30 have a personal physician at all, and that number is bound to get smaller.

The changing landscape of primary care is the result of several factors, some of which are laid out in our article "The Primary Problem." More and more people today, whether motivated by convenience or economic concerns, choose to receive their care à la carte at retail health clinics. And for some individuals, sadly, it's not even a choice, as many areas—both rural and urban—face a shortage of primary care physicians.

Adding to the problem, fewer physicians are going into primary care. Those who do take on a growing list of critical tasks—not only addressing patients' physical ailments but also screening for mental health problems and discreetly asking about conditions at home while racing to document all of these factors in electronic health records. For many doctors, patient rosters are growing while time spent with each patient is shrinking.

It is widely recognized that regular primary care can improve health, save lives and make care more cost-effective. Indeed, primary care represents the foundation of trusting and effective relationships in medicine that not only support and foster good health, but also prevent disease and diagnose problems at the earliest possible time. And primary care is not only important to individual patients, but also to the larger community. Academic medical centers like Massachusetts General Hospital bear a certain responsibility to work collaboratively with communities to improve health care and health access, with primary care as a major focus. Mass General Community Health Associates, for instance, delivers comprehensive primary and preventive community health services to underserved populations around Boston. And our Crimson Care Collaborative enables medical students, in conjunction with faculty, to provide care to local patients who don't have a primary care doctor.

As the story notes, models for primary care are being reinvented around the country. We are proud to be part of that process, through the efforts of the John D. Stoeckle Center for Primary Care Innovation and other initiatives throughout this institution. The bonds that primary care physicians create—and the high-quality care that they bring to their patients—are too precious and too critical to let erode.



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stat

FOCUS

Facial feminization surgery occurs from the neck up, where strangers most often look for clues to a person's gender. Subtle changes there—removing an Adam's apple, lowering a hairline, excising tissue from around the eyelids—can profoundly alter how a transgender woman is perceived. Mae, pictured here, had her surgeries three days before this shot was taken. Photographer Elle Pérez documents the intimate lives of those in the LGBTQ community, and this image was shown as part of the 2019 Whitney Biennial in New York City.

While many insurers now cover the costs of some gender confirmation surgery, facial feminization is widely regarded as unnecessary for the treatment of gender dysphoria. Paying for the procedures out of pocket can cost as much as $50,000, and access can be difficult, as nearly half of the states have no physicians specializing in the procedures. Some are advocating—and litigating—for the facial surgeries to become the standard of care, pointing to recent studies that show better mental health outcomes for those who undergo facial feminization.

ELLE PÉREZ

INTERVIEW

The Beloved Elucidator

Pathologist Husain Sattar is becoming an icon—and a meme—to a generation of medical students.

BY STACY LU

TIM KLEIN FOR *PROTO*

It's not often that the image of a surgical pathologist is plastered on coffee mugs and T-shirts, much less with a caption calling him "my homeboy." But Husain Sattar holds a revered place for recent medical students. Collectively, they have viewed eight million hours of Sattar's Pathoma, *an online prep course for the STEP 1 licensing exam. Many credit him not only with their surviving the test but also with changing how they think about the body and medical education itself.*

Sattar is a leading pathologist for breast cancer at the University of Chicago Medical Center, where he teaches clinical pathophysiology. Every major medical publisher has knocked on his door to ask for the secret behind the success of Pathoma*—which includes a 218-page textbook and an engaging library of videos. But Sattar says the context and the groundwork for his course would be hard to replicate.*

Q: You took time away from medical school to study Islam in Pakistan. How was that an influence for you?
A: One of my teachers never used any notes and would speak about his topic as if he was talking about his own children. He spent so much time and energy synthesizing the material that he could be perfectly comfortable with it. Also, he would present with excitement, regardless of who was sitting in front of him. You would think there were thousands of people in the room, but there were six of us.

Q: How did *Pathoma* come about?
A: When I was studying in Islamabad, I forgot everything I knew from med school. That allowed me to relearn it from a different perspective when I came back. I was removed from how I had been studying for decades, so I was able to see the bigger picture, an ability I think I had lost as a medical student.

I'm not a trained educator, but when I was interacting with students later, a few things became obvious. I saw that they were caught up in the trees and not seeing the forest, as I had been. They were missing the big principles. One pulled me aside and said, "I don't really understand the difference between leukemia and lymphoma," and I said, "Let's take a step back. What's carcinoma?" They couldn't explain it. I came back to my desk and said, "That's it. I'm making *Pathoma*."

Q: Did you have any principles that guided you?
A: I wanted to create something that was a conversation instead of a lecture, as exemplified by my former teacher. I have a minimalist, simplistic view of things, and that drove me to produce the material in a similar vein. In the book, I've organized every page the same way. The videos all have the same structure and tone. These things are soothing to the students. That little bit seems to have made a big difference.

I also wanted to keep the course slim and light. Knowledge has expanded, while the time we have to teach that material has remained constant. Sometimes there needs to be a bridge that allows students to get ahead, a simple idea before things become too complicated. It's nice to know there's a sequence to eventually mastering a topic. I think the students find that very beneficial.

Q: What other improvements might we make in how we teach medicine?
A: Medical students are highly accomplished individuals, but they're kindergartners in the medical field. When I bring in lecturers, they're often not in the same place as the students. I can bring in a world expert to talk about nephrotic syndrome, but it's hard for them to remember what it was like before they knew what that was. It's important to start from zero and review basic principles, recognizing that students are going to learn nuances throughout their lives. Medicine is a marathon, not a sprint.

Q: Has your teaching influenced the way you practice?
A: I do think that it informs the way I look at a slide. I don't want any patient history; I want to assess what I'm seeing without preconceived notions. That allows me to be very broad, and has saved me from a misdiagnosis on many occasions.

Q: What's it like to be a medical celebrity?
A: I'm a relatively introverted, private person, so it's very odd for me. I don't really know much about what goes online, but wherever I go in the world, there are people asking for selfies. I prefer to be alone in a room with my microscope.

BY THE NUMBERS

OK, Millennial

$7 billion

Amount spent annually on gym memberships by American millennials (born 1981–1996), the so-called "wellness generation." That is more than double the amount spent by Generation X (born 1965–1980) or Baby Boomers (born 1946–1964). Millennials have also driven demand for boutique workouts, designer water bottles and high-end sports apparel.

16

Percentage of millennials who don't have health insurance, compared to 12% of Gen Xers and 8% of Baby Boomers. Their generation is the most likely to report zero visits to the doctor's office in the past year and is twice as likely to act on health advice found online.

$5.2 billion

Projected amount spent on fake meat in 2020, a trend driven by millennial appetites and the generation's greener politics. About 26% of millennials identify as vegan or vegetarian, and 34% of meat-eating millennials consume four or more vegetarian dinners a week.

80

Percentage of 10 common health concerns that are more prevalent for millennials than they were for Gen Xers at the same age. Rates of major depression and type 2 diabetes were particularly elevated among millennials, with depression 31% higher and type 2 diabetes 22% higher.

36,000

Number of millennials who died in 2017 from "despair deaths"—drug overdoses, alcohol use or suicide. The number of drug deaths is 400% higher than it was two decades earlier. Factors may include higher debt, economic uncertainty and rising health care costs.

INFOGRAPHIC

How to Green a Hospital

Health care leaders look for ways to scale back an outsized carbon footprint.

In 2019 more than 100 health care organizations—including the American College of Physicians and the American Medical Association—signed a statement drafted by the Medical Society Consortium on Climate and Health. It begins: "Climate change is one of the greatest threats to health America has ever faced," and outlines the need for bold action now.

Fighting climate change might well begin at home. The global health care industry itself is responsible for 4.4% of worldwide emissions of planet-warming greenhouse gases. If the global health care sector were its own country, it would be the fifth largest emitter of greenhouse gases, and the U.S. health care sector alone accounts for 27% of the global health care carbon footprint.

"It's important for health care systems to lead the way in mitigating and decreasing their carbon footprint," said Renee Salas, an emergency medicine physician at Massachusetts General Hospital on *The New England Journal of Medicine*'s Perspectives podcast. "We have the tools to solve this. We have the research and public health infrastructure and the ingenuity."

That ingenuity, in fact, has taken a dizzying array of forms in recent years, as hospitals and health care systems rethink their use of energy, their physical resources and their relationship to the environment.

COOLING

Hospitals need to keep specimens, medications and their rooms cool. But fluorinated gases—specifically hydrofluorocarbons—from refrigeration systems significantly contribute to greenhouse gas emissions.

Thomas Jefferson University Hospital in Philadelphia uses "district cooling," a low carbon, energy efficient system in which cold water is chilled at a central source and circulated to six buildings through an underground piping network.

FOOD

Food contributes about 10% of a hospital's overall waste stream, and products of decomposition, including methane, can yield devastating greenhouse effects.

Massachusetts General Hospital transports food waste to Stonyvale Farm in Exeter, Maine, where it is mixed with manure to create biogas, a combination of methane and carbon dioxide. This biogas is then burned to heat and power more than 1,000 homes in New England.

TRANSPORTATION

Ambulances, employee travel and supply chain transportation account for 7% of health care's global carbon footprint.

Pitt County Memorial Hospital in North Carolina was the first U.S. hospital to install its own on-site biodiesel fueling station. All of its fleet vehicles now run on B20, a blended fuel containing 20% biodiesel.

WASTE

Every U.S. hospital bed generates about six pounds of waste daily, one pound of which is considered hazardous. Reducing this waste saves greenhouse gases both in manufacturing and in waste transportation costs.

The Mayo Clinic operates its own 11-employee recycling facility at its campus in Rochester, Minnesota, where it recycles not only plastic and glass but also surgical blue wrap, which is converted into polypropylene, a common and versatile plastic.

ELECTRICITY

Power generation—both purchased and generated on-site—accounts for nearly half of the health care sector's worldwide emissions.

Prompted by an initiative from international nonprofit Health Care Without Harm, more than 20 health care institutions in 12 countries have recently pledged to use 100% renewable electricity by 2050. U.S. signatories include Partners HealthCare (co-founded by MGH) and Kaiser Permanente.

PHARMACEUTICALS

Manufacturing drugs is one of the most carbon-intensive parts of the health care sector. Epoxides—a commonly used type of chemical—have a particularly large footprint.

In April 2019, Massachusetts Institute of Technology chemical engineers devised an alternative approach to synthesizing epoxides that eliminates carbon dioxide entirely as a byproduct.

ILLUSTRATION BY MSJONESNYC

DEFINED

'pa-sən-jr 'hät'späts

Passenger Hotspots

n: A run of mutations in a tumor genome that don't offer any particular survival advantage.

In cancer cells the genetic code has, by definition, become corrupted somewhere along the line. But a major challenge in cancer genomics has been identifying which mutations are the actual "drivers" of cancer, responsible for unimpeded growth of the cell, and which are just "passengers." A typical cancer genome will have only five to 10 driver mutations but thousands or even millions of passenger mutations along for the ride.

Researchers tend to classify recurrent mutations—those that have been found time and again in the tumors of many different patients—as driver mutations. But new research published in *Science* reveals that some mutations that occur with great frequency are, in fact, dense groups of passengers—passenger hotspots—that come about because of a quirk of cell replication.

One human enzyme, APOBEC3A, has a strong preference for DNA structures called stem-loops, or hairpins, which occur during DNA replication. The stretches of DNA that form hairpins may mutate up to 200 times as frequently as non-hairpin sites, and the mutations occur in a dense group.

The authors note that these passenger hotspot mutations owe their prevalence in cancer cells to their attractiveness to APOBEC3A and "not to any effects on tumor fitness." These findings highlight the importance of being able to recognize passengers—and not to waste therapies or drug development resources on these false culprits in cancer cells.

UPDATE

A Personal "Flybrary"

People with hard-to-treat cancer might get unlikely new allies: 400,000 genetically engineered fruit flies.

BY ADAM BLUESTEIN

Animal models have never been a perfect stand-in for humans, but their use took a giant step forward with CRISPR and other genetic manipulation technologies ("Made to Measure," Fall 2016). The techniques made it much easier to replicate human disease mutations in laboratory animals.

That development has particularly benefited cancer research. Tumors show a wide range of genetic diversity—too wide to replicate easily through traditional breeding techniques—but the new tools have made it possible to engineer features of a single tumor into a mouse. A "co-clinical trial" then can try out a new medication in the mouse first; if it is successful, the same treatment can be given to the human patient.

Mice in that scenario might even be replaced by *Drosophila melanogaster*, the common fruit fly. A team led by Ross Cagan, a developmental and cancer biologist at Mount Sinai Hospital in New York City, used a fruit fly approach to discover an effective treatment for a patient with metastatic colorectal cancer. The results of the trial appeared in the May 2019 issue of *Science Advances*.

The team first sequenced the man's primary tumor and identified mutations that might be fueling its growth. Then the researchers narrowed the field to nine mutations within the tumor, and engineered those nine mutations into a generation of fruit flies.

"THE 3D-PRINTED FRUIT-FLY": JOAQUIN VILLA, IMAGE CREATOR, AND ALICIA HIDALGO (UNIVERSITY OF BIRMINGHAM, UNITED KINGDOM), PROJECT DIRECTOR

GODFREY ARGENT/NATIONAL PORTRAIT GALLERY, LONDON

While the flies were still larvae, they had various treatments mixed in with their food. They received a nutrient mixture that was either plain or mixed with one of 121 drugs that have been shown to have some kind of antitumor effect.

On all of these regimens, fewer than 20% survived. But when researchers tried combining drugs, one pair—a cancer drug and a drug traditionally used for osteoporosis—saw survival rates for the flies triple in some cases. When this combination was administered to the patient, his tumors shrank by 45% and stayed that way for the next 11 months, although new resistant lesions eventually did emerge.

"The signaling pathways involved in cancer are conserved in fruit flies."

A fruit fly may seem a poor stand-in for a human patient, but roughly 75% of human disease-causing genes have a functional counterpart in the fly, according to Norbert Perrimon, a geneticist and developmental biologist at the Broad Institute of MIT and Harvard. *Drosophila* has been used since the early 1900s to study human diseases, including cancer. "The signaling pathways involved in cancer are conserved in fruit flies," he says. "And in fact many components of these pathways were first discovered in the fly."

A London company, My Personal Therapeutics, is trying to make this approach widely available. For each patient, the company engineers five to 20 mutations into about 400,000 flies (called "fly avatars"). Then it laces the flies' food with each of about 2,000 FDA-approved drugs, alone and in combination, including both traditional chemotherapy agents and others with reported antitumor effects. When there is a match—a fly given a particular drug lives much longer than expected—the company replicates the drug screen eight times to make sure the observed effect holds up.

Flies have several advantages over mice in cancer research. "In mice or rats, we can generate only two or three mutations and it takes a year or more," says Nahuel Villegas, chief scientific officer of My Personal Therapeutics. "In flies, we can create 20 mutations in a month and a half and can activate them all at the same time to recreate the patient's tumor." That greater number of mutations more accurately reflects the complexity of real-world tumors, he says, which are typically driven by a dozen or so key mutations. In addition, hundreds of thousands of flies can be handled in a small room and, compared to other models, they eat very little. Because they require only minute doses of drugs, they offer a significant cost benefit when expensive cutting-edge therapies are on the menu.

But the process of testing treatments in this way is still labor intensive, and even with the short reproductive cycles of the flies, agonizingly slow. "One challenge is to build the avatar and perform the screen fast enough to deliver a treatment," Perrimon says. Currently the whole process can take four or five months, but the company aims to shrink the timeline to weeks.

My Personal Therapeutics is now offering its technology commercially to patients worldwide, with a focus on colorectal and GI cancers, and is conducting multi-center clinical studies. Though the company is banking on the success of avatars, its ultimate aim is to build a "flybrary" of data showing which treatments may be successful therapies for patients with particular mutations. The company hopes that future patients will be able to get treatment recommendations based on what worked for previous patients—rather than getting their own personal swarm.

MILESTONE

Women's Work

A pioneer in protein structures also left a legacy for mothers in the sciences.

BY STACY LU

Dorothy Crowfoot Hodgkin was one of the first female scientists to receive a Nobel Prize. Yet another, lesser-known career landmark also casts a long shadow: She took one of the first paid maternity leaves in scientific research.

In the early 1930s, Hodgkin was a teaching and research fellow at Somerville College of Oxford University. She had been captivated by chemistry since her primary school days, and crystals particularly interested her. Two decades earlier, physicist Max von Laue discovered that the diffraction of an X-ray through a crystal could provide a glimpse into the shape of the molecules within. Though the technique was still considered experimental, Hodgkin pushed through the massive calculations it required. After some early success, she acquired insulin—still a novel substance—and wrote about the first time she saw images from the crystals she had prepared: "The moment … when I developed the photograph and saw the central pattern of minute reflections was probably the most exciting in my life."

By 1938, Hodgkin had fully focused on proteins, which presented a daunting challenge in their varied structures. She had begun another momentous undertaking as well, having become pregnant with the first of her three children. Few female fellows were married at the time, and none had become a parent during their fellowship. But the college had never before had a faculty member like Hodgkin. Unusually progressive for the era, members of the college thought, according to a letter from Hodgkin to her husband, that her resignation "... would be a bad precedent and might mean that future married fellows would consider they couldn't have children and they didn't approve of interfering with the course of nature."

With the approval of Somerville's female principal, she was given full pay for leave during an academic term (£100) plus sick leave. She gave an enthusiastic speech to Britain's Royal Society about insulin molecules a month before her December due date, pondered them during her time at home with her new baby, and was back to photographing crystals in August.

Hodgkin had two more children, and Somerville adopted a formal maternity leave policy upon her third pregnancy. She continued to stretch boundaries all the while; in the 1940s, spurred by wartime demand for a drug with seemingly miraculous potential, she worked on the structure of penicillin, a puzzle that took her four years to solve. Knowledge of the drug's structure led to development of semi-synthetic derivatives of penicillin and an array of other new treatments.

Hodgkin paid forward her maternity leave benefit, establishing a day care center at Somerville with some of her Nobel Prize money. Such incentives still make a difference. In the STEM fields, 43% of women and 23% of men do not return to work full time after the birth of their first child, according to a *PNAS* study published in March 2019. The statistics are similarly stark in medicine. While Hodgkin showed that supporting women after childbirth can pay dividends for science, that message has yet to echo in every corner of the field.

POLICY WATCH

Who Needs to Know?

Addiction treatment comes with its own strict privacy rules. Perhaps it shouldn't.

BY ANITA SLOMSKI

CHRIS GASH

Entering a drug rehab program has long come with the promise that the treatment will be kept secret from the rest of the world. Since 1975, a federal regulation called 42 CFR Part 2—or Part 2, for short—mandates this discretion for any addiction program that gets U.S. funding. Even when a patient wants to share the treatment history of a substance use disorder (SUD) with a primary care doctor, those records have to remain segregated from the rest of the medical record so no one else can view them.

Absolute patient privacy can come at a cost, however, and this has come into sharp focus in the trenches of the opioid crisis. Psychiatrist Bruce Schwartz remembers a patient who never told his primary care physician that he was taking methadone, a synthetic opioid, to curb his opioid cravings. The physician unwittingly prescribed opioids for pain, which led to a nonfatal opioid overdose.

Schwartz is president of the American Psychiatric Association and professor and deputy chair of psychiatry and behavioral sciences at Montefiore Medical Center in New York City. He believes that Part 2 rests on outdated ideas about addiction that not only put patients in danger but "perpetuate the stigma of this medical problem and prevent people from seeking treatment," he says.

Many of the leading voices in addiction recovery have called for reform of Part 2. "The protections were visionary and necessary in the 1970s, but now they serve as a barrier to coordinated care," says Jennifer Lohse, vice president and general counsel for the Hazelden Betty Ford Foundation, the largest not-for-profit SUD treatment provider in the country.

In August 2019, the U.S. Department of Health and Human Services proposed a series of updates to Part 2, citing the opioid crisis as a primary reason for the changes. If they go into effect, physicians or other providers who see patients after their recovery treatment would still need consent to acquire the SUD treatment records, but they would be able to incorporate some of that information in patients' electronic medical records. Those would then be available to any treating clinician, such as an emergency physician. Another proposed change would seek to avoid prescribing errors by giving providers access to a database showing whether a patient is receiving medications to treat substance abuse.

Not everyone is happy about these moves. Some patient advocacy groups and treatment programs contend that entering addiction history in an electronic medical record could lead to disastrous consequences. Though medical records are protected by the Health Insurance Portability and Accountability Act (HIPAA), which restricts who can see them without a patient's consent, that law doesn't apply to some third parties—law enforcement, insurers, employers and the courts. If information about a stay in rehab, for example, is added to a medical record and seen by one of those entities, a patient could risk losing a job or custody of children, be denied insurance or be subject to arrest.

"Weakening the current protections for patient privacy contained in Part 2 will not fix what is broken," said H. Westley Clark in a statement from the Legal Action Center, an advocacy organization for people with addiction and other issues. "Instead, it will drive even more people away from substance use disorder treatment and penalize the over 20 million people in recovery from substance use disorders." Clark is the former director of the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment.

Others say the proposed Part 2 rule changes don't go far enough. They want to get rid of any requirement for special patient consent to gain access to SUD records. "We want to eliminate all barriers between physicians, counselors, pharmacists and others involved in the patient's care," says Lohse of Hazelden Betty Ford, one of more than 50 groups, including the American Psychiatric Association, that have formed a partnership to advocate for having SUD records subject only to existing HIPAA laws, without the extra steps of Part 2.

> Patient privacy can come at a cost, a truth that has come into sharp focus during the opioid crisis.

Lohse argues that most patients seeking treatment have no expectation of absolute secrecy beyond the confidentiality afforded throughout health care. And quality treatment for SUD increasingly involves multiple providers, including primary care physicians whose medical records fall under HIPAA, not Part 2. "Worries about privacy are not keeping patients from seeking care at non-Part 2 facilities," she says. As for concerns that HIPAA records are vulnerable to law enforcement, she says the Part 2 reform would actually strengthen law enforcement protections for SUD patients.

The American Medical Association takes a middle-of-the-road position on SUD patient privacy. "We know there is value in having SUD information available at the point of care, but we believe it's important for patients to decide whether they want to disclose this information," says Laura Hoffman, assistant director of federal affairs for the AMA. "We also want patients to continue to have the option to confidentially access care at a Part 2 program so that they have somewhere to seek treatment without the fear that someone will find out about it."

SECOND OPINION

Promise in Voice Diagnosis

Imagine getting a meal at a food court in a major international airport. As you are enjoying your sandwich or cappuccino, you close your eyes and soak in the conversations around you. You may not understand much of what is being said, but you can often identify the panicked voice of a parent who has momentarily lost sight of their child, stress in the voice of a couple having a disagreement, or the kindness in the voice of a stranger giving directions to another traveler. It is possible to infer a range of emotions from these fleeting snippets of conversation.

"Something in Your Voice," (Fall 2019) discusses how studying such vocal cues over time could help diagnose mental illness. But caution needs to be taken to ensure that the algorithms used in clinical settings are able to differentiate short-term emotions—similar to those observed at an airport—from long-term mental health conditions. Unusual talkativeness, for example, may indicate a hypomanic episode of bipolar disorder, but it really depends on the specific individual and what is considered "unusual" for them. Otherwise we risk labeling any bubbly teenager as manic. So, although there is a lot of promise in using voice in the diagnosis of mental illnesses, more attention should be paid to individual differences—that is, when an individual shifts from their baseline behavior. These "shifts" can be crucial for diagnosis and most skilled psychiatrists are adept at noticing them.

Tanzeem Choudhury // Professor of Information Science and Computing, Cornell University/Tech, Ithaca, New York

An Enduring Mystery

"Back From the Brink" (Fall 2019) provides a fascinating overview of the phenomena of near-death experiences (NDEs). A vitally important question regarding NDEs is whether or not they are explainable by physical brain function. I began exploring this question more than 20 years ago when I developed the non-profit Near-Death Experience Research Foundation (NDERF).

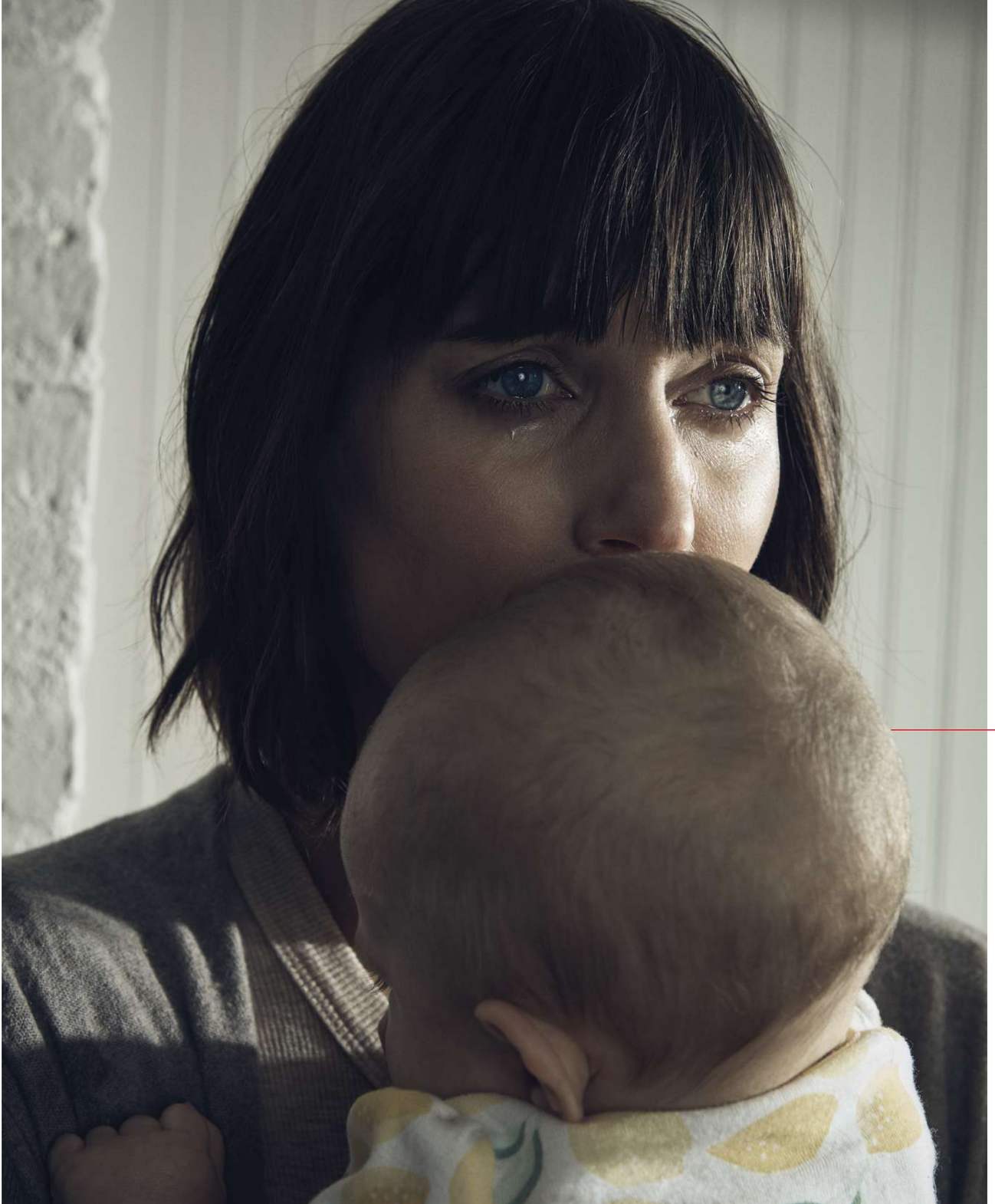
Near-death experiences often occur immediately following cardiac arrest. About 20 seconds after cardiac arrest EEG measurements of brain activity are generally flat, indicating no significant brain cortical activity. Yet people with NDEs often report accurate observations from this time. Such occurrences are medically inexplicable.

NDEs are typically highly lucid experiences, and the sequence of events commonly observed during NDEs (such as an out of body experience, passing through a tunnel, entering an unearthly realm) is reported with remarkable consistency among thousands of NDEs.

The suggestion that near-death experiences occur independently of physical brain function is relevant to a broad spectrum of scholarly interests including medicine, science, philosophy and religion.

Jeffrey Long // Radiation oncologist and founder of Near-Death Experience Research Foundation, Houma, Louisiana

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



New Mothers on the Brink

They are dying at alarming rates in the United States. Treating mental illness, an often overlooked cause, could save many lives.

By Anita Slomski // Photographs by Eric Ogden

Kim Manfredi fantasized about crashing her car into a massive tree, but was terrified that if she told anyone, her six-month-old son would be taken away. Alicia Nelsen worried obsessively about her newborn but couldn't understand why she wasn't deeply in love with him. Anxiety kept her from sleeping more than two hours a night, a panic attack landed her in the emergency room and once, in a rage, she kicked a hole in a wall of her house.

After enduring months of severe postpartum depression, both mothers tried to end their lives with drug overdoses. Manfredi's husband rushed her to the ER after finding her unconscious; an inpatient stay in a psychiatric ward was followed by months of counseling and a course of drug therapy. Nelsen awakened from her overdose, confessed to her husband that she had tried to kill herself and embarked on a long road of recovery involving medication and psychotherapy. The women finally emerged from their anguish and became the kinds of mothers they desperately wanted to be. Now both of them are advocates for sufferers of postpartum depression and mood disorders, and both run peer support groups.

While many of these women feel blindsided by their mental state, experts find it unsurprising that mental health issues might arise or intensify amid the stress of pregnancy and early motherhood. "If you have a history of depression or anxiety, you're going to be more vulnerable during

pregnancy or postpartum," says Edwin Raffi, a perinatal and reproductive psychiatrist at Massachusetts General Hospital's Center for Women's Mental Health.

The experiences of Manfredi and Nelsen—and of many others whose suicide attempts succeed—represent a little-known subset of a broader problem. American women die in alarming numbers during pregnancy or in the first year after giving birth, and the rate of such deaths in the United States is comparable to those in Afghanistan, Lesotho and Swaziland. These statistics, and the headlines that have accompanied them, have brought unprecedented efforts to prevent or treat the medical problems—hemorrhage, preeclampsia, infection and cardiomyopathy—that often lead to those deaths. A new program created by the American College of Obstetricians and Gynecologists, for example, trains hospital obstetrical teams how to respond to childbirth emergencies.

Yet a significant fraction of those maternal deaths involve new mothers who commit suicide or accidentally overdose on substances. Almost a third of young, healthy mothers who die before their babies' first birthday fall into one of those two categories, according to a number of state medical committees that have been looking into the problem. "According to some reports, suicide and drug overdose actually cause more deaths than postpartum hemorrhage, cardiovascular events or other pregnancy-related medical problems," says Kimberly Mangla, a perinatal and reproductive psychiatrist at Columbia University Vagelos College of Physicians and Surgeons.

Mothers at risk of suicide are often not identified in the same way as those who have more straightforward medical problems. "Although major depression is relatively common during pregnancy and postpartum, many women suffer in silence, afraid of the stigma of admitting their sadness and that they can't bond with their babies," Raffi says. And even when clinicians do find women suffering from mental illness during the perinatal period—from the beginning of pregnancy through the first year after childbirth—as few as one in 10 gets appropriate care and recovers. Not only is screening for depression and other conditions inadequate, says Lee S. Cohen, a perinatal and reproductive psychiatrist who directs the MGH Center for Women's Mental Health, but "women are failed on the other side of screening because of all of the obstacles in getting treated."

Now a few initiatives are beginning to tackle this overlooked, more complex part of maternal mortality. "Women are literally speaking to us from their graves, telling us how they came to die," says Marcela Smid, a maternal-fetal and addiction specialist at the University of Utah who sits on one of Utah's investigative committees. "It's our job to learn as much as we can from them and to try to prevent these kinds of deaths in other women."

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When a maternal death occurs, a maternal mortality review committee, or MMRC, will sometimes step in. Created by state or local governments, these bodies are charged to look into the deaths, report them to the Centers for Disease Control and Prevention and make recommendations about future prevention. Not all states even have the groups, many do little more than look at hospital records and death certificates and few measure the mental health aspects of the problem. Some MMRCs, however, have recently taken on this last task and appointed suicide experts, forensic pathologists and psychiatrists to help determine the causes of all maternal deaths that occur during the perinatal period.

In 2016, Colorado's MMRC reported that 30% of the maternal deaths in the state over a nine-year period had been caused by accidental overdoses or suicide. In Utah, in a similar span, pregnancy-associated maternal mortality rose 76%, largely because of a spike in drug-related deaths fueled by the opioid epidemic. According to CDC data, the number of women using opioids at the time of delivery more than quadrupled between 1999 and 2014, from 1.5 to 6.5 per 1,000 deliveries.

The work of California's MMRC has been particularly revealing. A special committee that included a medical examiner, psychiatrists, criminal justice experts, psychologists and obstetricians looked at "any woman's death where there was an inkling of suicide," according to Elliott Main. Main is a clinical professor of obstetrics and gynecology at Stanford University and medical director of the California Maternal Quality Care Collaborative, which has been credited with cutting the state's maternal mortality rate in half. He was particularly interested in piecing together which drug-related deaths might actually have been suicide attempts. "We interviewed family members and studied toxicology reports to rule out accidental overdose," he says.

The committee found that suicide accounted for 4% of California's pregnancy-associated deaths from 2002 to 2012. Main says he believes that all of the new mothers who committed suicide had a "good to strong chance" of being alive today if medical professionals had intervened with proper treatment. Most had mental health conditions before becoming pregnant and nearly a third used illicit drugs—missed opportunities to get women into treatment and on to recovery.

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Specialty doctor groups and the U.S. Preventive Services Task Force endorse screening all pregnant and postpartum women for depression. But physicians in one specialty—pediatrics—might be particularly well positioned to spot problems. A depressed new mother will most likely take her infant to the recommended seven well-baby visits, even if she doesn't have the energy, motivation or insurance coverage to seek care for herself. Earlier this year, the American Academy of Pediatrics called for screening postpartum women for depression and postpartum psychosis, a rare and much more serious problem that often leads to suicide, during four of the well-baby visits. They also noted that fewer than half of pediatricians currently looked for depression in new mothers.

"Many women suffer in silence, afraid of the stigma of admitting their sadness."

Another entry point is the HealthySteps pediatric program, which promotes healthy development for babies and toddlers and primarily focuses on low-income parents. Its protocols mandate maternal depression screening in the 164 pediatric practices that integrate HealthySteps in their practices. "It's going to much more difficult to improve developmental and emotional outcomes for a six-month-old if mom is depressed," says Rahil Briggs, national director of HealthySteps. When a mother screens positive for depression or substance abuse, a HealthySteps specialist, most often a psychologist or social worker in the pediatric practice, makes a referral to in-house or community mental health services and follows up to ensure she gets treatment.

Yet even when physicians provide all recommended screenings, some women in emotional distress will insist they don't have a problem. To help those new mothers, Colorado's Department of Public Health is experimenting with a public awareness campaign about postpartum depression that is designed to bring family and friends into the equation. "We need to involve partners, grandmas and best friends who can spot symptoms of depression," says Mandy Bakulski, maternal and infant wellness manager at the Colorado Department of Public Health & Environment.

As part of this campaign, young mothers and fathers have written blogs and appeared in videos to explain postpartum depression in English and Spanish, and hotlines have been set up to answer questions. The department has also worked with Medicaid to approve reimbursement for three depression screenings during pregnancy and the first postpartum year. Screenings of new moms during well-baby visits are now also covered.

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These and other initiatives help identify women in emotional distress. But the next step—finding appropriate treatment in an overburdened mental health system—can be even more challenging. "We know that a very small proportion of women who screen positive for depression will get an appointment with a mental health provider," says Nancy Byatt, associate professor of psychiatry and ob/gyn and population and quantitative health sciences at the University of Massachusetts

Medical School in Worcester. One study found that only 8.6% of pregnant women and just 6.3% of postpartum women received adequate treatment for their depression.

To combat that part of the problem, Emily Miller, assistant professor of obstetrics and gynecology, psychiatry and behavioral sciences at Northwestern University Feinberg School of Medicine in Chicago, launched a program that embeds psychotherapy and perinatal psychiatry services into Northwestern's obstetric clinics. That means an obstetrician can now send a woman with mental health disorders down the hall to Collaborative Care Model for Perinatal Depression Support Services (COMPASS). If a patient's problems aren't complex, the OB may be encouraged to handle them with support from COMPASS staff, who keep tabs on all referred patients. "Every week, an OB, a psychiatrist, a psychologist and social workers review every woman's progress and we'll change the care plan until she gets better," Miller says. "This frees up our perinatal psychiatrist to see the most complex patients without a long wait."

with perinatal psychiatrists. "By leveraging digital technology, a psychiatrist in Casper, Wyoming, can get the same consultation from a perinatal psychiatrist as a psychiatrist on Beacon Hill in Boston," Cohen says.

Other approaches help obstetricians and other primary care providers not only to recognize illnesses in perinatal treatment but also to provide mothers with immediate help. For example, the state-funded Massachusetts Child Psychiatry Access Program for Moms offers telephone consultations with five perinatal psychiatrists for advice on treating women with depression and other psychiatric problems. "When providers know they can call an expert for help, they feel much more comfortable managing these illnesses themselves," says medical director Byatt, who started the program in 2014.

In about one in five cases, the specialists on the phone will conclude that a woman needs to be under the care of a psychiatrist—and will see that patient face-to-face within two weeks, making recommendations to her OB on how to manage her care until she can be treated by a local psychiatric provider.

> "We need to involve partners, grandmas and best friends who can spot symptoms."

Still, there aren't nearly enough perinatal psychiatrists to go around, so the MGH Center for Women's Mental Health trains other physicians to deliver specialized treatment to perinatal women. Perinatal psychiatrists at the center evaluate women with complex mental health disorders and develop treatment plans for community psychiatrists to follow—an approach that enables center specialists to consult on the care of 1,200 women each year. Psychiatrists located far from the hospital can take the center's online course in reproductive psychiatry and consult by phone

Encouraged by the success of this program, which has provided consultations for 1,471 physicians in Massachusetts, 14 programs in other states have received funding to replicate the model.

Byatt, however, wants treatment for depression by an obstetrician to become as commonplace as managing diabetes. To that end, she and her colleagues at the University of Massachusetts Medical School created a second program—an intensive intervention called the PRogram in Support of Moms (PRISM). The program trains nurses and social workers already working in OB practices to develop a registry of patients with depression and to keep close tabs on their progress for up to 12 months postpartum. That approach is now being tested in a randomized trial funded by the CDC.

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Obstetricians often are wary about prescribing antidepressants to perinatal women, but they frequently don't hesitate to give them opioids. In Utah, for example, 42% of women covered by Medicaid and about 20% of privately insured women get opioids for pain during pregnancy. Nationally, three-quarters of women who have a caesarean delivery and one in four who have a vaginal birth are prescribed opioids, according to a recent study in *JAMA*. This widespread prescribing leads to some 77,000 women a year who continue to fill opioid prescriptions for months after birth—and some may be headed toward opioid addiction, says Smid of the University of Utah.

Of course, many women are already there, and during pregnancy and the first postpartum year they face several distinct dangers. Often they'll stop using drugs once they learn they are pregnant. "Some of my patients with the most severe opioid use disorder have private insurance, are married and have jobs, and are very good at hiding their drug use," Smid says. Yet trying to wean themselves from opioids on their own increases the odds of adverse outcomes, and as many as 80% of women who stop taking drugs during pregnancy will relapse within a year postpartum.

Legal issues further complicate matters. Many clinicians don't screen pregnant women for substance use in part because they fear what may come next. "You want to screen to give women the treatment they need, but you don't want to leave a woman vulnerable to potential prosecution," says Northwestern's Miller. In 23 states and the District of Columbia, a pregnant woman found to be using illegal drugs can be charged with child abuse, and in even more jurisdictions,

health care providers must report suspected prenatal drug use to child welfare authorities. In addition, when opioids or other drugs are found in a newborn, mothers may lose custody, at least temporarily. "We are criminalizing a medical problem," Smid says. "The goal should be for moms to disclose drug use so they can get treated and get healthy. But most women are terrified of talking about drug use or relapses because they are acutely aware of the consequences."

Pregnant women with opioid use disorder who are receiving medication-assisted therapy (MAT) have improved outcomes for themselves and their babies compared to women who are not on MAT, and are less likely to have accidental or intentional overdoses. But one option for MAT—going to a methadone clinic—often isn't available in rural areas, and even in cities it may be challenging for mothers, especially with children in tow. The other drug for MAT, buprenorphine, is more convenient, but only providers who complete eight hours of training can prescribe it, and those clinicians can treat only a limited number of patients.

The HOPE Clinic at MGH attempts to overcome some of these barriers by providing a network of coordinated care, with a goal of helping patients navigate pregnancy, early parenting and substance use recovery at the same time. "Many are struggling with social-environmental stressors and barriers to care, such as homelessness, lack of insurance, trauma, violence or a partner who has substance use issues," says MGH's Raffi, who also works at the clinic. "And there's a lot of guilt and shame. We want to help the recovery of mothers with substance use disorders, aid their mental health care and prevent tragedies such as suicide, infanticide or death by overdose." Women can continue receiving services, including parenting education and recovery coaching, at the clinic for up to two years after giving birth. Other integrated models for addiction treatment have started to pop up in other places, and the CDC recently partnered with 12 states to increase access to treatment for perinatal women with opioid use disorder.

The momentum for mental health services marks a welcome change, says Stanford professor Main, and one long in coming. But innovations in screening for suicide and drug overdose risk shouldn't stop at perinatal women, he says. "Women shouldn't die during pregnancy or postpartum, so they serve as the canary in the mineshaft as a warning for problems in our system," he says. "A perinatal woman's suicide gets attention. But for every suicide, there are 100 or more people with mental health issues that aren't being treated. We need to do a much better job helping all of these people."

DOSSIER

"Association of Punitive and Reporting State Policies Related to Substance Use in Pregnancy With Rates of Neonatal Abstinence Syndrome," by Laura J. Faherty et al., *JAMA Network Open*, November 2019. This analysis found that states that criminalized substance use during pregnancy were associated with greater rates of NAS.

"The California Pregnancy-Associated Mortality Review: Pregnancy-Associated Suicide, 2002–2012," by California Department of Public Health, Maternal, Child and Adolescent Health Division, 2019. This report looks at 99 pregnancy-associated deaths from suicide.

"Maternal Self-Harm Deaths: An Unrecognized and Preventable Outcome," by Kimberly Mangla et al., *American Journal of Obstetrics & Gynecology*, March 2019. The authors outline the barriers and biases that thwart pregnant women from seeking mental health care.

Long the bedrock of medicine, the practice of primary care has been in need of a reinvention. Several models show promise. None of them will be cheap.

The Primary Problem

By Linda Keslar // Illustrations by Michael Waraska

After her residency, Julie Gunther took a standard position for a new family physician, signing on with a large medical system in southern Idaho where she stayed for five years. “My vision was to serve my community as a sort of Marcus Welby,” Gunther says, a nod to the compassionate and fictional family doctor who appeared on television in the late 1960s. But the reality was nothing like that. Administrative hassles were always front and center, and the few minutes she had with her patients were scarcely enough for her to get to know them. “I was always apologizing for being late,” she says. “I felt like my patients were being pushed through in an assembly line.”

More and more primary care physicians have the same complaint. Their offices are crowded with aging baby boomers and they’re besieged by paperwork and mushrooming requirements for preventive care, charged with improving patients’ health while also controlling costs. “We’re being asked to do more with fewer resources and less time,” says Bruce Landon, an internist at Beth Israel Deaconess Medical Center in Boston.

Fewer patients have a personal primary care physician—a recent survey showed that nearly half of those 18 to 29 years of age were going without—but most experts still believe that primary-care-centered medicine is worth preserving. Office appointments with an internist, family practitioner or pediatrician make up more than half of all patient

encounters with doctors, and during these visits physicians diagnose and treat the vast majority of medical ailments and chronic diseases. These visits can keep small health problems from becoming big ones, says Joshua Metlay, chief of general internal medicine at Massachusetts General Hospital. "Primary care has been demonstrated to make a real difference in health outcomes," he says.

Removing these providers from a patient's life comes at a cost. The United States spends more per capita on health care than any other country, yet ranks 43rd in life expectancy—a discrepancy partly tied to a lack of preventive care, which in turn may be related to not seeing a generalist physician who conducts regular screenings.

The problem is not a new one, and rethinking the role of frontline physicians has led to decades of tinkering with alternative models. In recent years, physician burnout—an epidemic with a steep human cost—has given these efforts a special urgency. While outcomes of the first generation of experiments are rolling in, other innovative delivery models, many started by physician entrepreneurs, are beginning to upend notions about how, when and where primary care doctors see their patients.

These efforts, each very different, aim to re-engineer and strengthen primary care—and they call for a new level of investment, both from insurers and patients. "We're in a moment in which the old model is collapsing," says Alan Glaseroff, a family physician and professor at the Stanford Medicine Clinical Excellence Research Center in California. The new models will need to move quickly to take their place.

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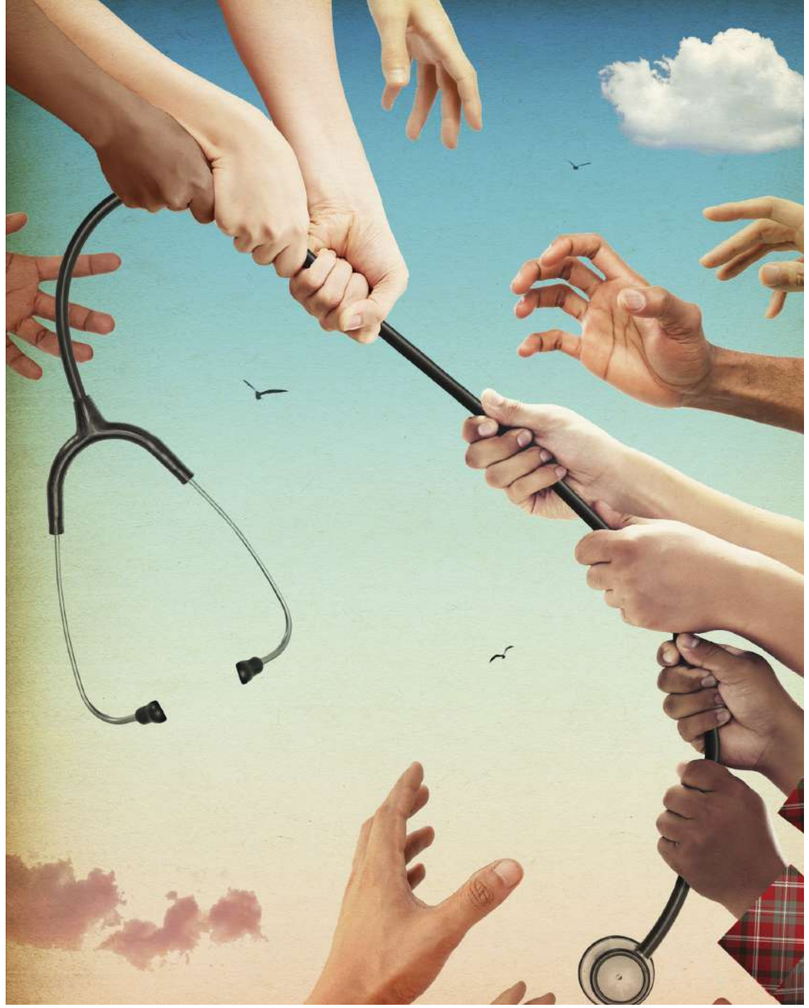
A landmark 1978 report from the Institute of Medicine defined primary care as "accessible, comprehensive, coordinated and continual," to be placed in the hands of "accountable providers." Yet the same report noted that the supply of physicians delivering primary care was and would continue to be inadequate.



Then, as now, physicians-in-training were more likely to opt for narrower specialties that offered higher incomes, and only about one-third of the nation's 700,000 practicing physicians today are primary care physicians. That percentage is likely to get slimmer. More than one in four primary care physicians is age 60 or older, and just about a fifth of medical graduates now choose primary care residencies—increasingly a pragmatic choice because starting salaries for primary care doctors don't make much of a dent in the average medical student debt of $200,000.

The typical primary care physician now has a panel of 2,300 patients and must see 20 to 30 of them every day. The demand for their services seems to outweigh supply. More than an eighth of U.S. residents live in a county with a shortage of primary care physicians, and in some metropolitan areas, patients have to wait almost six months to see a doctor. When they finally do get in for a visit, they're typically ushered out of the exam room in 15 minutes or fewer. Even after those 20 to 30 patients are gone, their physicians must spend hours updating electronic health records (EHRs) and other paperwork. Many physicians complain of feeling like they're on a treadmill, losing the struggle to provide timely, high-quality care—and feeling the toll on their mental health. Every day, on average, a doctor commits suicide. "That's basically a whole medical class's worth of physicians that we're losing every year," Gunther says.

Efforts to rescue primary care have been sporadic and wide ranging. Many are built around or inspired by the "patient-centered medical home," or PCMH. The "home" is figurative, referring to a team-based approach designed to help physicians navigate their patients through their "medical neighborhood" of specialists, hospitals, home health care and other services, and to connect them to appropriate community resources. It was developed by the American College of Physicians and promoted by the American Academy of Family Physicians and other physician groups as a way to treat the "whole patient." For physicians, the team approach also considerably relieves the sole provider facing a mountain of patients and administrative tasks. The program has been adopted by many organizations, including Medicare and Medicaid, especially to manage the care of those with complex or chronic conditions. Fees paid by the government may be tied to performance metrics that measure quality, cost or patient engagement, and for insured patients, insurer costs can include additional monthly payments.

During the past decade, the PCMH has been widely tested by the federal government and states. One federal PCMH experiment, Comprehensive Primary Care Plus (CPC+), launched in 2017, aims to expand the reach of a promising earlier pilot. With almost 3,000 practices participating, CPC+ is the biggest, most ambitious reform effort yet for the federal Center for Medicare and Medicaid Services.

South Arkansas Medical Association Healthcare Services, a CPC+ participant, delivered traditional fee-for-service primary care until 2012, says Gary Bevill, a founding physician of the group. Now daily practice has changed from the ground up. Each physician is assigned to a team, or pod, that also includes nurses, care coordinators and care managers—people who can review patient charts before appointments, manage and check referrals and arrange transitions to other types of care. With that infrastructure in place, Bevill and other physicians can enter an exam room and focus solely on their patients. "I've already reviewed the EHR, so I don't have to have my nose in a computer," Bevill says. During four years in the earlier pilot, the practice not only saw big improvements in patient outcomes but also in employee and patient satisfaction.

About one in five primary care physicians currently practices in some variation of the PCMH. The Cleveland Clinic and the University of Colorado Health System have tested or implemented a version of the home model. Bellin Health in Green Bay, Wisconsin, has rolled it out over its entire system, which encompasses 140 primary care teams in 32 locations. During a five-year transition, teams using the model scored higher on most quality metrics. Patient engagement and staff satisfaction increased, and clinician satisfaction scores almost tripled. "Medicine isn't an individual activity anymore, and for this to work, physicians have to work as leaders of a team," says James Jerzak, the Bellin Health physician lead for team-based care, who helped implement the pilot. "Working as part of a team makes it fun to practice medicine again. It's more satisfying for the staff and better for our patients, too."

It was a rare case in which a better model for doctors and patients also meant a healthier bottom line. Improved efficiency has enabled doctors and other providers to see more patients, expanding access to primary care in the communities in which Bellin operates. And even though the health system hired additional staff, invested in training and technology and redesigned facilities, revenue also increased, with the team-based model credited for an average boost of $724 per patient yearly in some segments.

It's not yet clear, however, whether larger-scale PCMH projects can actually both save money and improve care. Evaluations of federal efforts so far show modest improvements at best. Researchers concluded that the pilot that preceded CPC+ had no significant impact on physician burnout, Medicare spending or quality of care, although practices did report enhanced access and improved care management for high-risk patients. Gains from the first year of CPC+ also appear to be limited.

> Rethinking the role of frontline physicians has led to decades of tinkering with alternative models.

And instituting some version of the medical home carries a hefty price tag, costing practices in excess of $100,000 per physician per year, according to one study. During the pilot's first two years, practices received median government subsidies of $115,000 per clinician in care management fees, and median care management fees for the newer CPC+ program have ranged from $88,000 to $195,000.

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Other approaches to improve the lot of the primary care physician also rely on finding new ways to fund more staff and longer visits. "We've fundamentally changed the traditional primary care model," says Rushika Fernandopulle, co-founder and chief executive officer of Boston-based Iora Health, a primary care provider, which launched in 2010. Iora receives fixed, per-patient monthly fees—a system called "capitation"—from

the employers, unions and health insurance organizations that contract with it. Because those fees won't rise to cover the cost of extra care, Iora has an incentive to promote patient health, and its providers work with patients on a range of measures to reduce expensive emergency room and hospital stays. That means not only getting patients to adhere to care plans and take prescribed medications but also, when possible, to eat well and exercise regularly. "We get paid for helping keep people healthy," Fernandopulle says.

In some 50 practices across the country, physicians at Iora are on integrated teams that include nurse practitioners and behavioral health specialists, among others. A health coach is also assigned to help patients understand and follow through on recommended care. Each doctor is responsible for fewer than 1,000 patients—less than half the size of patient panels in other kinds of practices. Physicians have more time to see patients in the office and to communicate with them between visits. Patients interact with their care teams through phone calls, emails and texts an average of 16 times per year, and come into the office six times. Iora will also arrange transportation to the office for those who might not otherwise be able to get there.

According to the company, hospitalizations and emergency room visits have fallen by more than a third, and patient scores for controlling hypertension, diabetes and other chronic conditions are above national averages. Patients give Iora high marks for satisfaction and engagement, and employee attrition has declined.

CareMore Health uses a similar, capitated model to deliver a more well-rounded experience, including clinics with gyms where patients can work out and, in one notable innovation, a reinvention of the house call. In Connecticut, CareMore serves 2,100 high-needs patients almost exclusively through home visits by physicians, nurse practitioners and medical assistants, with social workers, behavioral health specialists and others brought in as needed. "Seeing patients where they live adds familiarity to the physician-patient relationship," says Sachin Jain, the physician president and CEO of CareMore. "We get a window on their social determinants of health, the economic and social conditions that can significantly affect their health."

Jain says their model has led to sharp reductions in hospital admissions and emergency room visits for their patients, who include Medicare Advantage and Medicaid beneficiaries. Another metric of success is the number of requests for information Jain gets from other groups that want to partner to set up a CareMore program. "We're not even close to where we could be in terms of impact," he says.

> Models that require additional fees would disproportionately harm people who can't afford to pay.

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All of these models aim to improve the lot of primary care physicians, reducing their burdens and strengthening connections to patients. One model that predates the latest experiments is concierge medicine—in which patients pay retainer fees to physicians on top of normal payments from insurers in return for increased access and additional services. Physicians, in turn, can often afford to spend more time on each case. Another increasingly popular experiment along those lines is "direct primary care," or DPC, which largely leaves health insurance out of the equation. Patients are charged a flat monthly or annual fee, typically much lower than the price of concierge medicine, for a limited set of primary care services. Those may include real-time access, extended visit times and, in some cases, home visits.

This was the route Julie Gunther chose after leaving her large Idaho group. At her direct primary care practice in Boise she charges adult patients $79 a month for around-the-clock access by phone or email. Core services include physicals as well as diabetes and weight management. Other services are offered à la carte, and patients get large discounts on medications, lab work and imaging. "I love practicing medicine this way," Gunther says. "It puts the physician-patient relationship back at the center."

During the past decade, more than 1,200 physician practices have moved to this model, according to the Direct Primary Care Coalition. One big perk is being able to treat many fewer patients than in other settings. A survey by the American Academy of Family Physicians, which supports the concept, found that the average panel size for DPC practices is 600—roughly a fourth of the average for other primary care doctors.

Proponents of the model contend that it delivers better care at lower prices. Such claims have yet to be confirmed, however, says Paul George, associate professor of medicine at Warren Alpert Medical School of Brown University. "We don't have peer-reviewed data to support anecdotal claims by individual practices," he says.

Other policy experts worry that the DPC model—and other models that call for the limited number of primary care physicians to see fewer patients—will exacerbate physician shortages. "Every time a primary care physician moves to DPC, what other provider is going to take care of the large number of patients that doctor no longer sees?" asks Carolyn Engelhard, associate professor at the University of Virginia School of Medicine and the Frank Batten School of Leadership and Public Policy. "Are the patients who are left out just going to have to walk into the emergency room?"

Engelhard and other critics also worry that a shift to DPC and other models that require additional fees would disproportionately harm people who can't afford to pay. The DPC Coalition insists, for its part, that DPC practices serve diverse patient panels that include low-income patients and those who are chronically ill. Some practices have sliding fee scales for patients who may make too much to qualify for Medicaid but who still can't afford other insurance coverage.

Few of these innovations can promise to broaden access to primary care—a particular concern considering that the Association of American Medical Colleges predicts a nationwide shortfall of as many as 55,000 primary care doctors by 2032. An increasing number of patients, particularly those who are young and healthy, are skipping traditional primary care, opting instead to visit drop-in urgent care centers and retail clinics, and only when they need immediate medical attention. Their relationship to medical care is closer to that of a customer and doesn't include the traditional physician-patient bond, a dynamic that has been shown in some cases to improve outcomes, George says.

The solution that addresses every part of this conundrum—exhausted physicians, patients who have trouble getting access to a personal doctor and payment models that don't cover the bases—still seems far away. But as the spirit of experimentation takes hold, and practices refine dozens of approaches, some material improvements are coming to light and, eventually, catching on. "Different health systems in different parts of the country are seeking solutions to different problems," says Metlay at MGH. "I think it's likely we'll end up with an array of primary care models—because no one size is going to fit all."

DOSSIER

"Transforming Health Care from the Ground Up: Top-Down Solutions Alone Can't Fix the System," by Vijay Govindarajan and Ravi Ramamurti, *Harvard Business Review*, July–August 2018. Two business professors analyze bottom-up innovations as solutions for transforming health care delivery.

"Powering-Up Primary Care Teams: Advanced Team Care With In-Room Support," by Christine Sinsky and Thomas Bodenheimer, *Annals of Family Medicine*, July–August 2019. The authors discuss obstacles that face a new model of primary care provided by a physician-led team.

"Direct Primary Care: One Step Forward, Two Steps Back," by Eli Adashi et al., *Journal of the American Medical Association*, August 2018. Experts weigh in on the promise and flaws of DPC models currently underway.

The Insomnia Genes

Poor sleep affects almost half of the country, and solutions have been hard to come by. Tracing the problem to its genetic roots may stop the tossing and turning.

By Jane Palmer

Mornings start at 3 a.m. for Shawn Radcliffe. Without setting an alarm, he wakes up like clockwork in the pre-dawn hours, does some writing and then some yoga, sometimes followed by a run. “I really like the mornings,” Radcliffe says. “I’m alone and it is a beautiful time.” He goes to bed between 9 and 9:30, which means he rarely sleeps more than six hours a night. But at 48 his health is good, he feels happy and well rested, and his unconventional sleep cycle doesn’t seem to have any ill effects.

Radcliffe’s relationship with sleep hasn’t always been so harmonious. In college he stayed up late to study, drank tea and soda to keep going and suffered from insomnia and fitful, fragmented sleep. He finally solved those problems when he started practicing yoga and meditation, limited his caffeine intake and learned how to switch off his mind at night. But he also had to accept that sleeping at an unusual time and for fewer hours than most people do was part of his internal machinery, and it wasn’t going to change.

Evidence is growing that genetic makeup has much to do with when, how long and how well a person sleeps, and also plays a role in some types of insomnia—the inability to fall asleep or stay asleep. Just this past October, sleep researchers established that yet another gene—the third discovered so far—appears to share responsibility for the kind of “short sleep” that Radcliffe currently experiences, which appears to carry no negative health consequences. Insomnia, in contrast, does impair health and well-being,

and it affects one-third to half of the U.S. population, making it the most common sleep disorder.

"Insomnia can harm people mentally and physically," says Philip Gehrman, a psychologist who works in the department of psychiatry at the University of Pennsylvania and whose current research involves the genetic roots of insomnia. "It is tied to depression and anxiety and can depress the immune system," he says. And current therapies leave much to be desired. Sleeping pills, the most common treatment, don't work for everyone, may lose their effectiveness over time and can lead to daytime drowsiness, attention deficits, memory loss and even dangerous episodes of sleepwalking. A second approach, cognitive behavioral therapy, involves trying to change attitudes about sleeplessness with the goal of reducing sleep anxiety. This treatment, which also involves establishing rigid sleep routines, isn't easily accessible to most people and can be challenging to do without support.

"If a treatment for insomnia means you have to wake up every day at the same time, flip on a light, sit in front of that light for half an hour"—a typical cognitive behavioral treatment—"you're asking an awful lot from a person," says Jacqueline Lane, a geneticist at Massachusetts General Hospital. "These treatments can be really difficult to maintain."

Better alternatives are needed, and getting there means delving deeper into the genetic underpinnings of sleep. Yet that, too, poses challenges. "Every major neurotransmitter is involved in regulating sleep, and sleep is the product of so many different biological systems that there are bound to be a large number of genes that influence it," Gehrman says. "It makes for a very complicated situation."

Moreover, environmental and social factors can also influence when humans sleep and for how long. "There is a biological tendency for us to go to sleep and wake up, but we often override that, because we have to stay up to meet a deadline, to study for an exam or to spend time with our families," says neurologist Louis Ptáček of the University of California, San Francisco, co-senior author of the October 2019 *Science Translational Medicine* study that identified the third gene implicated in short sleep.

Such factors can make untangling the genetic complexities of sleep even more difficult—and during the past 35 years, as modern genetic tools have revolutionized research into many neurological disorders, discoveries about sleep have lagged behind. That's beginning to change, largely thanks to a giant, recently established database that pairs genetic information about people with data about their sleeping habits. The resource has helped researchers probe the core components of sleep—sleep-wake times, sleep length, sleep quality—and is slowly helping them parse the intricacies of insomnia.

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Every minute, thousands of tiny biological "clocks" are at work in the body. Found in nearly every tissue and organ, the clocks control the daily rise and fall of body temperature, metabolism, the release of hormones—and sleep. They're coordinated by a single master clock, a cluster of 20,000 neurons in the brain's hypothalamus called the suprachiasmatic nucleus, or SCN. The SCN uses signals from the eyes, cued to the waxing and waning of daylight, to "tell the time" and synchronize the internal army of clocks. The system is responsible for circadian rhythms, plus it controls the production of melatonin, a hormone that helps humans sleep. When morning light hits the optic nerves, this master clock reduces the output of melatonin, and as daylight fades, it produces more.

The other major process affecting sleep is sleep homeostasis, an internal biochemical system. This "sleep drive" is low after a good night's sleep, but as the day progresses, the chemicals behind the drive build until—normally late at night—the urge to sleep becomes overpowering. In the 1980s, scientist Alexander Borbély from the University of Zurich in Switzerland proposed a two-process model that married the two systems. Circadian time oscillates like a wave in humans, making us sleepy at night and wakeful in the morning. On a separate track, the longer people are awake, the more they feel their "sleep drive."

PREVIOUS PAGE: FLORA HANITIJO

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Evidence is growing that genetics has much to do with when, how long and how well a person sleeps.

This accounts for the fact that people who miss a night's sleep may fall asleep during the day, even though the body's clock is saying "be awake." While Borbély's model is highly simplified—it doesn't take into account the nature of stress, arousal or other factors—researchers have found it a useful framework for investigating the genes behind sleep, which may play into two or more interlocking mechanisms.

Forays into identifying individual genes associated with the timing of sleep started in the 1970s. By 1984, scientists Jeffrey Hall and Michael Rosbash at Brandeis University in Waltham, Massachusetts, and Michael Young at the Rockefeller University in New York City had found the period gene in fruit flies. Mutations of this gene could shorten or lengthen the flies' daily cycles of activity. These scientists later discovered additional genes affecting circadian rhythms and eventually were able to explain the key workings of the biological clock—an achievement that led to a Nobel Prize in Physiology or Medicine in 2017.

As helpful as these discoveries have been, translating molecular findings about fruit flies into a meaningful understanding of human sleep has proved difficult. One tool for doing that is the genome-wide association study, or GWAS, which lets researchers compare the sequenced genetic data from large numbers of people—some who have a particular health problem and some who don't—and look for potentially significant differences. By 2015, however, only two GWAS's had been conducted on insomnia, and neither gleaned significant insights.

One likely reason for the inconclusiveness of those studies was the relatively small number of participants. One looked at 10,038 people in Korea, and the other considered 2,323 Australian twins. "To do this type of analysis you need very large numbers—often more than a single research group can come up with," says Allan Pack, founding director of the Center for Sleep and Circadian Neurobiology at the University of Pennsylvania Perelman School of Medicine.

It turns out that one resource—the UK Biobank, created in 2006—had those large numbers. The database boasts detailed health information, including genetic data and answers to a questionnaire about sleep habits, for 500,000 people. In addition, one in five of the UK Biobank participants spent a week wearing a monitor that recorded information about activity, rest times and sleep patterns.

Recently an international group of researchers, led by the University of Exeter and Massachusetts General Hospital, analyzed the genetic data of 453,379 people from the UK Biobank who had responded to the question, "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" Nearly a third had answered "usually," which researchers took as an indication that they suffered from symptoms of insomnia.

The scientists also looked at activity tracker data, which told them how efficiently the research subjects slept and whether they were awake in the middle of the night. Using a GWAS approach, they identified 57 regions of the genome, containing 236 genes, that were associated with insomnia symptoms. That marked a significant advance on previous studies, which had found only seven areas of the genome linked to insomnia. The

team published its findings in *Nature Genetics* in March 2019.

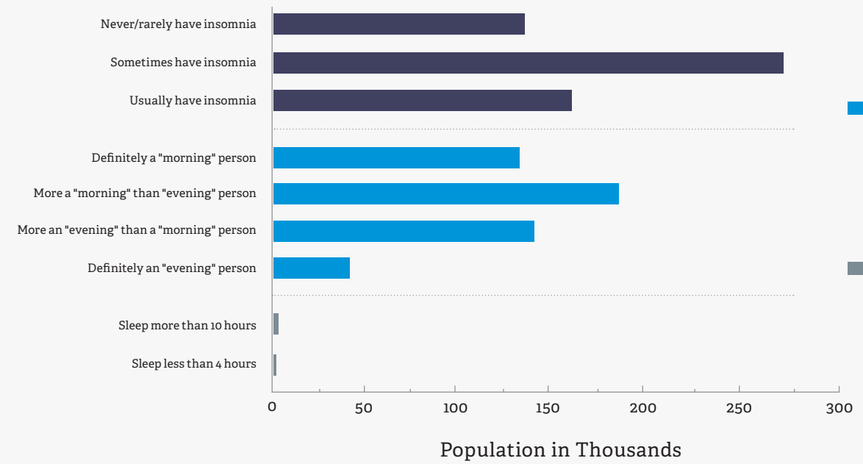
These early results were encouraging—all of the identified regions could be possible therapeutic targets—and the team continued to look into related issues, including how many hours a study participant habitually slept. They found 78 associated gene regions, some of which overlapped with the areas implicated in insomnia. Sleep quality was the next target, which they explored using activity tracker data showing when people went to bed and when they finally got to sleep, how long they slept and how broken up or fitful their sleep was. Inspecting data from the UK Biobank as well as information from three additional studies, the team ultimately associated sleep quality with 47 gene regions.

Of particular interest was an uncommon variant of one gene, PDE11A, which appeared to affect both sleep quality and sleep length. "Occasionally you find one thing that looks very clear in a study and it's like, 'Yes. This is the spot. This is it,'" MGH geneticist Lane says. Previous studies had suggested that this gene could be a good target for treating neuropsychiatric disorders such as depression or anxiety, so its connection with sleep was illuminating.

Apart from these specific insights, the researchers also came away with a more general sense of how genes affect sleep. Many of the gene regions identified by the activity tracker data, for instance, were linked to the production of serotonin, a neurotransmitter known to play a role in the sleep cycle,

Shades of Restless

Responses to the UK Biobank questionnaire, with more than half a million respondents, point to several atypical dimensions of sleep. Finding the intersections and genetic roots of these abnormalities may help researchers parse the secrets to better sleep.



INSOMNIA: About 75% of respondents answered yes to the question, "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" About a third say this is a usual occurrence, which is the hallmark of chronic insomnia.

CHRONOTYPE: Responses to these questions can indicate a different "set point" for the circadian clock. But the relationship between the times a person prefers to be awake—morning or evening—and insomnia remains unclear.

SLEEP DURATION: Some genes associated with "short sleep" have been located and are correlated with depressive symptoms and insomnia. The genes behind long sleep—or hypersomnia—are tied to depression, schizophrenia and type 2 diabetes.

JOSE LUIS PELAEZ/GETTY IMAGES

bolstering the case that it may promote deeper sleep and improved sleep quality. They were also able to pinpoint what insomnia *wasn't*. Previous researchers had mapped regions associated with chronotype—someone's propensity to go to sleep earlier or later than most people do. The newly identified gene regions for insomnia and poor sleep quality had little overlap with those.

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Lane believes this new evidence, taken together, suggests that there are important distinctions to be drawn between unconventional sleep cycles and true insomnia. Some people seem able to sleep less or more than average and may have earlier or later wake-up times, with no ill effects whatsoever. "But if someone takes a long time to fall asleep, and wakes up five times during the night, then it seems very clear that there are health consequences," Lane says. "And these findings indicate that insomnia is a true disorder."

Perhaps most illuminating is that researchers also found significant overlap between the genes implicated in insomnia and those related to depression, anxiety and other psychiatric conditions. "Now the question is whether some sleep traits are closer to psychiatric traits than they are to other sleep traits," Lane says. "When we talk about sleep and psychiatric traits, are we talking about different things? We think of them as very separate beasts, but they are not all that separate."

Such findings indicate that beneficial treatments for insomnia might focus on reducing anxiety and treating mood disorders. They could explain why cognitive behavioral approaches—which can focus not only on sleep habits but also on a person's thoughts and emotions involving sleep and sleeplessness—are often successful.

It is more than likely that there are different types of insomnia, Lane says, driven by discrete genetic forces. For example, one gene associated with insomnia is also involved in restless legs syndrome, a sleep disorder characterized by an uncomfortable, irresistible urge to move the legs. A genetic approach could try to identify different forms of the disorder so that physicians can offer more personalized diagnoses. "It will help to subdivide people who might be better candidates for one kind of treatment versus another," Lane says.

> There are important distinctions between unconventional sleep cycles and true insomnia.

But tailoring treatment is still a long way off. The recent GWAS's are a starting point, and the next step will be to pinpoint the active genes and understand how they influence sleep. "If you find the causative gene, then that takes you into exploring new pathways, and it opens up an entirely new area of biology," says Pack from the University of Pennsylvania.

Pack has established a pipeline with other researchers to follow up on the GWAS he conducts. Starting with a gene region, one of his collaborators will home in on a gene of particular interest. Then Alex Keene, associate professor of biological sciences at Florida Atlantic University in Boca Raton, tests the effects of variants of that gene in animal models.

Keene suggests that this methodology may be particularly helpful for a complex disorder like insomnia that's likely to involve many genes, each of which makes only a small contribution to the final trait. "It is not going to be one gene or one genetic mechanism that explains why you or I might sleep less than the average person," Keene says. It is only in working through the possibilities, one by one, that researchers can slowly build up a genetic picture of how the disorder occurs—and eventually arrive at an age of new therapeutic targets, which may bring a better night's sleep for everyone.

DOSSIER

"Genetics of Sleep Disorders," by Philip Gehrman et al., *Psychiatric Clinics of North America*, December 2015. This study provides an overview of the history of and advances in the genetics of sleep disorders.

"Biological and Clinical Insights from Genetics of Insomnia Symptoms," by Jacqueline Lane et al., *Nature Genetics*, February 2019. Lane provides a detailed description of the GWAS's looking at the genetics of insomnia for subjects in the UK Biobank.

"Genetic Studies of Accelerometer-Based Sleep Measures Yield New Insights into Human Sleep Behaviour," by Samuel Jones et al., *Nature Communications*, April 2019. Using accelerometer data from more than 85,000 UK Biobank participants, the researchers looked at sleep quality, quantity and timing, and identified 47 genetic associations.

THE ART OF ACTIVE SURVEILLANCE

Sometimes prostate cancer is best served by a wait-and-see approach. Yet many patients and doctors can't stand the thought of doing nothing. What would change their minds?

By Timothy Gower // Illustrations by Keith Negley

When men receive a diagnosis of prostate cancer, which kills more than 30,000 Americans each year, they tend to be "like deer caught in the headlights," says Mark Lichty. For his part, Lichty felt terrified and uncertain when he received his diagnosis in 2005 and a urologist recommended removing his prostate.

That procedure, a radical prostatectomy, is standard treatment; a common alternative is to use radiation therapy to destroy the tumor. Yet although both approaches can be effective and save many lives, they can also negatively affect the quality of life. Some two out of three men who undergo prostatectomy and more than half of men whose prostates are irradiated have long-term erectile dysfunction. Surgery causes short-term urinary incontinence in most men, and for one in five, that becomes a long-term condition. And there are persistent bowel problems for one in six patients who get radiation therapy.

Lichty had watched his father suffer what he describes as "gruesome" side effects of treatment in his losing battle against prostate cancer, and Lichty decided he didn't want to follow suit. He rejected his urologist's recommendation, choosing instead to put off surgery in favor of what was known then as watchful waiting—having his cancer closely monitored for signs of progression. It was a bold move, and among the medical professionals who urged him to have immediate treatment was his wife, a nurse practitioner. "She thought I was perhaps a bit off the edge," Lichty says.

But Lichty, who co-founded a support organization called Active Surveillance Patients International in 2018, held firm to his plan, and now, almost 15 years later, routine monitoring shows that his cancer remains in check.

In the years since Lichty made his decision, the strategy now known as active surveillance (AS) has become much more common. Major medical organizations recommend it as the preferred option for most men with low-risk prostate cancer, who account for about half of all diagnoses. Today some men with somewhat riskier tumors are being offered AS, too. Yet while the proportion of men who choose AS has nearly tripled in the United States since 2010, more than half of Americans who have low-risk prostate tumors still have them treated with surgery or radiation, choosing to live with the accompanying harms despite an equivocal benefit. "If this were like an appendectomy, where you have the operation, you recover and then you're back to normal, it would be another story," says University of Toronto urologist Laurence Klotz, an early proponent of AS. "But it's not like that. To undergo unnecessary radical treatment for a disease that doesn't pose a threat to the patient's life is obviously a problem."

In countries such as Canada and Sweden, the overwhelming majority of eligible men choose AS. Yet although some doctors in the United States have been offering AS as an option since the 1990s, acceptance has been relatively slow. Many patients and their physicians are understandably reluctant to leave a potentially deadly tumor in place, even when the risk is small. Moving more patients to AS may require making better data available to them as well as improving how tumors are detected and assessed for risk. It might also mean changes in how physicians portray AS, a tricky course of treatment that is less a magic pill than a conversation that can last for years.

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Researchers and clinicians have understood for decades that prostate cancer often poses little risk. When Klotz completed his residency and fellowship in the late 1970s and early 1980s, "it was widely known that low-grade prostate cancer was indolent in many cases," he says. A few small studies had shown no ill effects in many men whose disease wasn't treated. And surgeons who performed procedures to address urinary problems caused by enlarged prostates often detected small cancers in the gland—but didn't raise the alarm. "I was trained to not tell the patient he had cancer," Klotz says. "We were told to use euphemisms like: 'We found a few abnormal cells,'" a practice he says was widespread.

The majority of men who did get a cancer diagnosis at the time had incurable disease that was either locally advanced or had spread to other organs. That changed in the early 1990s, however, with the arrival of the prostate-specific antigen (PSA) assay, a blood test that measures levels of a protein that rises when prostate cancer is present.

The test has known flaws: PSA can also rise for other reasons, such as noncancerous inflammation of the prostate, which can cause false-positive results. Yet the test can also catch cancer at an early stage, when it's likely to be treatable. When the PSA test became available, urologists embraced it as a screening tool, and that led to a surge in prostate cancer diagnoses, the majority of which involved tumors that were small and confined to the gland. Yet in the decade after PSA testing was introduced, more than 90% of those diagnosed with low-grade tumors had radical prostatectomies or radiation therapy.

Like Klotz and a few others, Peter R. Carroll, a surgeon and professor and chair of the department of urology at the University of California, San Francisco, was troubled by that apparent disconnect between the promise of a new cancer screening tool and a surge in potentially unnecessary surgery and radiation. He was one of a small group of clinicians who began suggesting that some men with apparently low-risk cancers could be monitored, at least initially, instead of being sent to the operating room.

It seemed like a logical approach, and in 1995, Klotz and his colleagues began tracking a group of men who chose it. That led many other urologists to condemn what they saw as undertreatment. "I heard statements like, 'Klotz doesn't care if his patients die,'" he recalls. "But as the data matured, it became apparent that patients weren't dying. And they were avoiding a lot of overtreatment."

Large, long-term studies by Klotz, Carroll and others indeed have shown that men with low-risk prostate cancer who choose active surveillance rarely succumb to the disease. In one 2015 study of 1,298 men, researchers at Johns Hopkins University found that fewer than 1% died of prostate cancer or developed a metastasis over a 15-year period. Moreover, several clinical trials have found that men with low-risk prostate cancer who adopt AS die of prostate cancer about as often as those who receive immediate surgery or radiation—infrequently, in both cases.

As the results of these long-term studies have emerged, AS has become widely accepted, at least officially. The American Urological Association and the National Comprehensive Cancer Network now consider AS the preferred option for people with low-risk prostate cancer. And although criteria for defining low-risk vary, the ideal candidate for AS typically is someone whose tumor is small and confined to the prostate and who has a PSA lower than 10 nanograms per milliliter (ng/ml). That patient also must have had a biopsy of prostate tissue resulting in a score on the Gleason scale—used for gauging how aggressive a tumor may be—of no higher than 6. (Studies have shown that approximately half of prostate cancer diagnosed in the U.S. is Gleason 6 or below.) Guidelines from 2016 suggest that certain patients with intermediate-risk (Gleason 7) tumors could be offered AS, too, though those men are more likely to require treatment eventually, and most U.S. doctors remain uncomfortable with delaying their surgery or radiation.

The Science of Thinking It Through

Shared decision-making protocols can lead to better, more confident choices.

Some patients who choose aggressive treatment for their prostate cancer never have the chance to think through the options with the help of clinicians. Patients who opt for active surveillance (AS), on the other hand, may feel anxious and uncertain about their choice.

Both groups stand to benefit from efforts to deepen the decision-making process. In shared decision-making—a concept that dates to the early 1970s—patients are given an extra helping of information and support from clinicians when they need to consider difficult choices. This process results not only in more confidence about their decisions, but also, often, in choosing more conservative treatments.

Some decision-making involves tools that lay out treatment options in simple language. Researchers and clinicians at Thomas Jefferson University's Sidney Kimmel Cancer Center in Philadelphia have developed a program in which men with low-risk prostate cancer receive unbiased information about surgery, radiation and AS. A nurse walks patients through these treatments, answers questions and helps them gain more clarity about which option is best for them. Afterwards, the men and their physicians choose a treatment plan. In a 2016 study, 83% of low-risk patients, who initially believed that surgery or radiation were their only options, chose AS after engaging in shared decision-making. "The patients felt as though someone took the time to ask them what was important to them," says medical sociologist and study lead author Ronald Myers.

Other programs make sure that patients meet a range of clinicians who will provide multiple points of view. At Massachusetts General Hospital, men with prostate cancer can be referred to the Claire and John Bertucci Center for Genitourinary Cancers Multidisciplinary Clinic, where they meet with cancer specialists in urology, radiation oncology and medical oncology, all in the same room at the same time. The beauty of this approach, says radiation oncologist Jason Efstathiou, co-director of the clinic, is that it brings patients together with specialists who can each explain their views on the pros and cons of the management options. In a 2012 study, Efstathiou and his colleagues found that men with low-risk prostate cancer who visited the clinic were twice as likely to choose AS. A 2018 study in the *Journal of the American College of Radiology* found that such multidisciplinary clinics made a big difference: 63% of men with low-risk disease changed their treatment decisions to AS after going through the shared decision-making process that the clinics offered.

Then again, some physicians still appear reluctant to offer AS, period. A 2019 study in *The Journal of Urology* surveyed urology practices across southeastern Pennsylvania and New Jersey and found that although some doctors had all of their low-risk prostate cancer patients in AS, others had as few as 10%. A study in Michigan found that among 30 urologists in one practice, the prevalence of AS ranged from 95% to none.

Some clinicians who don't recommend AS may simply be slow to change their ways. "In many disciplines, the way you're trained is the way you treat," Carroll says, and for some doctors, learning about AS shook the foundation of their medical education. "The idea that you'd find a cancer and not treat it was something both patients and their physicians had a hard time considering," Carroll says.

In other cases, patients want their doctors to be aggressive about ridding them of cancer. "I believe a lot of overtreatment has been driven by patients, and you can't blame them," says biostatistician Andrew Vickers of Memorial Sloan Kettering Cancer Center in New York City, who studies prostate cancer and AS. A meta-analysis of studies that included 7,627 men in AS protocols found that 20% of cases in which monitoring was abandoned in favor of treatment happened "because of patient choice or anxiety."

Their concern is not out of left field. About one in three men who adopts an AS regimen eventually does get "upgraded," with follow-up testing indicating a malignancy dangerous enough to warrant surgery or radiation. Informed patients who know these statistics may worry that delaying treatment could make their cancer deadlier (though that doesn't appear to be true).

But some patients may lack a complete picture, either of the scope of their risks or the process of AS itself. Enrolling a patient relies on a physician navigating a complex conversation that encompasses not only the statistical realities of AS but also questions about quality of life. If the goal is to get more suitable patients into this protocol, then advances need to happen on two fronts: finding more effective ways for a physician to discuss the road ahead, and providing more reassuring data about whether tumors are likely to turn lethal.

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Patients might be more likely to risk AS, for instance, if there were better ways to spot a prostate that does need immediate attention. Biopsies can be hit or miss, with the needles used to retrieve prostate tissue for testing inserted more or less at random. A more effective approach could be to use multiparametric magnetic resonance imaging (mp-MRI) to map where potential tumors might lie. Research shows that mp-MRI targeted biopsies find a greater number of aggressive tumors than standard biopsies, and a study published in *JAMA Network Open* in September 2019 found that undergoing a pre-biopsy scan can reduce the risk to as low as 8% that a man in AS will need to be upgraded. Study author Leonard Marks, a urological surgeon at the Ronald Reagan UCLA Medical Center in Los Angeles, says he believes mp-MRI should be performed to help guide biopsies in men entering AS programs.

So far, only about one in five prostate biopsies performed in the United States is guided by mp-MRI, Marks estimates. One reason it's not more widely used may be the expense, which some insurance companies don't cover. Another issue: "Performing and interpreting a prostate MRI requires advanced training, which many radiologists lack," he says.

Newly available genetic tests that gauge whether a prostate tumor is likely to spread and turn deadly might also help, and several studies have shown that these tests are beginning to influence men's decisions about whether to choose AS. According to the University of Toronto's Klotz, however, the tests are likely to be most valuable for men with intermediate-risk tumors who are on the fence about AS. "These tests definitely have a role, but it's for a minority of patients," Klotz says.

Other kinds of innovations might help physicians convey the advantages of AS. Vickers and several colleagues at Sloan Kettering, including surgeon Behfar Ehdaie, collaborated with Deepak Malhotra, a professor at the Harvard Business School and an authority on negotiation, to develop a systematic approach to counseling patients that uses principles from the behavioral science of decision-making. For example, social scientists know that when people aren't sure how to behave, they tend to look at what their peers typically do. So if a good candidate for AS is agonizing over his decision, a physician might advise the patient that AS is the choice of most of that doctor's patients who have low-risk prostate cancer. "We can talk about why you might be different, and I'll explain the other options," the doctor might say, "but you should know that's what most men do." In a 2017 study published in *European Urology*, Vickers and his colleagues showed that using this and related techniques increased the proportion of men in their clinic who chose AS by 9 percentage points—a change that reduced overtreatment by 30%, according to their calculations.

"Some clinicians who don't recommend AS may simply be slow to change their ways: "In many disciplines, the way you're trained is the way you treat."

A more radical proposal is to change the way low-risk malignancies in the prostate (and elsewhere, including the breast and thyroid) are discussed. "Patients report their anxiety skyrocketing when they hear the word 'cancer'; they feel a sort of mental paralysis that stops them from hearing anything else," says Kirsten McCaffery, who studies health literacy at the University of Sydney School of Public Health in Australia. McCaffery's research shows that people who are told they have "lesions or abnormal cells" rather than cancer are less likely to opt for unnecessarily aggressive treatment.

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The move toward greater acceptance of active surveillance has played out against a different, though related, conversation about the advisability of screening for prostate cancer at all. In 2012, the United States Preventive Services Task Force (USPSTF), an advisory panel, recommended that men skip the PSA test, because the panel's research showed that the test's downsides—particularly its knack for identifying meaningless tumors that may prompt aggressive treatment and its accompanying harms—outweighed its benefits. But in 2018, the USPSTF softened its stance, recommending that men ages 55 to 69 should talk to their doctors and decide for themselves whether to have the test. A primary reason for the change of position, the panel noted, was that more men were enrolling in AS regimens. That meant fewer men were being needlessly harmed by a PSA-aided cancer diagnosis.

Klotz says he hopes the trend of more men opting for AS will "rehabilitate" PSA screening, which he believes is valuable. The test often detects deadly tumors as well as harmless ones, and when the USPSTF recommendation led to lower rates of screening, higher numbers of men began to be diagnosed with advanced disease. And death rates from prostate cancer, which had been falling for years, flattened. Having AS as an option can make prostate cancer screening more appealing, and if more men choose it, more serious tumors are likely to be caught in time for life-saving treatment. "Reducing the burden of treatment for a lot of these patients," Klotz says, "could ultimately result in a decrease in prostate cancer mortality."

DOSSIER

"Active Surveillance for Prostate Cancer: How to Do It Right," by Juan D. Garisto and Laurence Klotz, *Oncology*, May 2017. The authors, who include an AS pioneer, offer an evidence-based rationale for this treatment approach and guidelines for administering it.

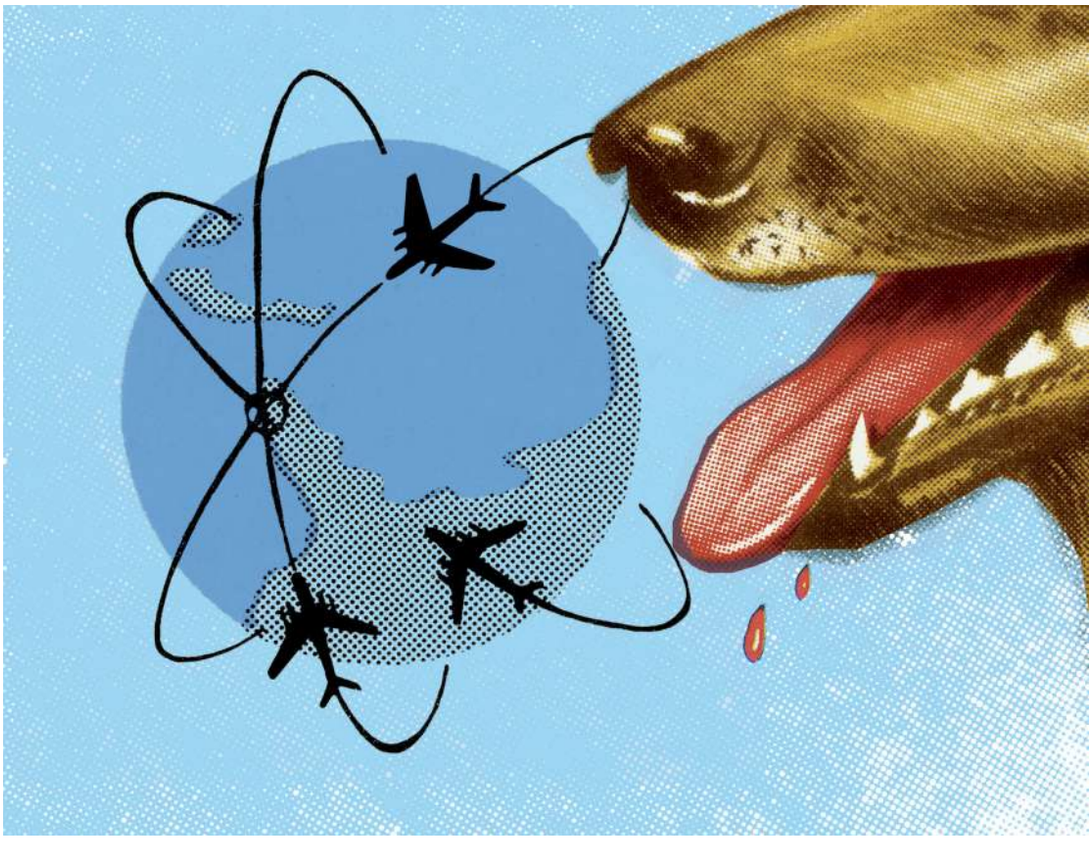
"Active Surveillance for Low-Risk Prostate Cancer in Black Patients," by Brandon A. Mahal et al., *The New England Journal of Medicine*, May 2019. This letter examines recent trends in the use of AS in black men with low-risk prostate cancer.

"Renaming Low Risk Conditions Labelled as Cancer," by Brooke Nickel et al., *BMJ*, August 2018. In this paper, the authors argue that removing the "cancer" label from low-risk prostate malignancies, as well as rarely lethal forms of other cancers (such as breast and thyroid), could reduce overdiagnosis and overtreatment.

FIRST PERSON

Worse Than Its Bite

BY LIBBY RYAN



I love to travel. For a girl prone to panic attacks, it's the ultimate test of my self-confidence. But that challenge became a nightmare when I went on a solo trip to Thailand and got nipped by a street dog.

The injury was small—barely a scratch. But the country has seen outbreaks of rabies, which I learned from a session of frantic Googling from my hostel bunk bed. With no one to help me and trying to stifle my worry, I discovered that I had only a short window to get a vaccine before a potential virus would set in.

I soon found myself in an emergency room in Ayutthaya, a small city outside Bangkok. I was armed with a scrawled note that read "dog bite" in Thai. The hospital was bustling and crowded. Initial examinations were happening on a plastic bench right there in the waiting room.

I got shuffled from place to place until someone on staff examined my ankle. We communicated through a mix of rapid Thai (them), tearful English (me) and wild hand gestures (the Thai grandmother seated next to me who'd become very invested in my diagnosis). They settled on giving me antibiotics, a tetanus shot and the first rabies shot.

I held it together until I felt myself getting dizzy, at which point I realized I didn't know how to call for help in Thai. Overwhelmed and full of drugs, I collapsed.

Any doctor I'd seen in the United States would have had a fit if I had fainted in their office. But no one even noticed the 25-year-old Caucasian passed out in the examination room, on the bed where they had propped me. When I came to, they just handed me instructions with a schedule for my next four vaccine injections.

That businesslike nonchalance came as a shock to me, and it was characteristic of my next two clinic visits too, in Bangkok and Chiang Mai. Google had by now informed me that a U.S. doctor would certainly have given me a dose of rabies antibodies, an expensive ($40,000!) but reassuring weapon against infection. My first Thai doctor told me it was "too late" and the second said I was "probably fine."

At both hospitals, I cried ragged anxiety tears, barely feeling the well-practiced nurses prick my arm. By now my confidence in finishing this Thailand trip was shaken, and at every jungle waterfall or ancient temple my anxiety told me to go home. At least there I could pepper the doctors with questions. I wouldn't have to climb over a language barrier for conversations that were short and mostly one-sided.

But I tried to remain calm, despite the worry. And I stayed the whole trip. When I finally set foot in the United States, I was somehow calm and assured getting my fourth and fifth shots. The doctor who gave me the last one wasn't sure he had the same brand of vaccine that the other U.S. physician had given me, and in fact had never given a rabies shot before. I think he was taken aback by my command of the protocol, and my barrage of questions.

Which vaccine was this? Did he know that I had received a Chinese rabies vaccine in Thailand, and would this be compatible? Would it work in tandem with the other U.S. vaccine? We pulled up the research on his computer and pieced it out together. It was fine, he told me, and I took a deep breath. He gave me my final shot. This time, no tears.

When the results of the rabies test came in several months later—full immunity and no sign of the virus—I took a picture of myself smiling in front of that clean bill of health. I put it in my scrapbook next to my favorite snapshot at an elephant sanctuary. Both were proof I'd been brave enough to finish out a dream trip, all by myself.

COLLAGE WITH GETTY IMAGES

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