The Ache of Motherhood

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

As the story notes, models for primary care are being reinvented around the country. 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 preventative 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.
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 I licensing exam. Many credit him not only with their success in 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 content 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 medical 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 knew 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 nothing 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 kinder partners in the medical field. When I bring in lecturers, they’re often not in the same place as the students. I can be a world expert to talk about nephritic 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 whenever I go to the office or the coffee shop, people are asking for selfies. I prefer to be alone in a room with my microscope.

BY STACY LU

The Beloved Elucidator

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

In April 2019, Massachusetts Institute of Technology researchers identified 27% of the global health care sector’s carbon footprint as the result of electricity, transportation, cold storage, and pharmaceutical manufacturing. This footprint is outsized relative to the health care’s overall contribution to the national economy as a whole.

At Massachusetts General Hospital, where it recycles not only plastic and glass but also surgical blue wrap, which is converted into polypropylene, a common and versatile plastic.

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.

ELECTRICITY

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

Promoted 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.

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 University Farm in Lincoln, 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.

How to Green a Hospital

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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. “You simulate a tumor,” 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 *Nature Medicine,* which presented a daunting challenge to researchers: to find the mutations driving the disease in the patient’s tumor. Patient’s tumor.

To discover the mutations, the researchers turned to genetically diverse fruit flies. With the short reproductive cycles of the fly, it’s possible to engineer features of a single tumor into about 400,000 flies (called “fly avatars”). Then it laces the flies’ food with each mutation, 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 shrunk by 45% and stayed that way for the next 11 months, although new resistant lesions eventually did emerge.

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 1990s 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 those 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 get 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 promise of a fly personal swarm—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.

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But the promise of a fly personal swarm—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. A London company, My Personal Therapeutics, is now offering a personalized therapy for 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, 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.

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BY STACY LU

Women’s Work

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

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Who Needs to Know?

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

BY ANITA SŁOMSKI

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 physician that they had been prescribed opioids for pain, which led to a nonfatal opioid overdose. “Physicians are held to the same standard of care as anyone else can view them,” he says. “Not every physician shares the patient’s data.”

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-party—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, he says.

“Weakening the current protections for addiction treatment contained in Part 2 will not fix what is broken,” says Dr. E. Wesley 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 Louise of Hazelden Betty Ford Foundation. “We also want to continue to have the option to confidentially access care at a Part 2 program so that we have somewhere to seek treatment without the fear that someone will find out about it.”

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. “We want patients to keep notions that the HIPAA records are vulnerable to law enforcement, she says. The Part 2 rule 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.”

Promote in Voice Diagnosis

Imagine getting a meal at a food court in a major international airport. As you’re 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 still identify the nasal 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. Such abilities are not unusual. In this issue of Communications of the ACM, Tanzeem Choudhury 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—such as those observed at an airport—from long-term mental health conditions. The takeaway is, for example, may indicate a hypomanic episode of bipolar disorder, but it really depends on the specific individual’s condition 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 is in a shift from their baseline behavior. These “shifts” can be crucial for diagnosis and most skilled psychiatrists are adept at noticing them.

An Enduring Mystery

“Back From the Brink” (Fall 2019) provides a fascinating overview of the phenomena of near-death experiences (NDEs). Is it Time for Blockchain?

Near-death experiences often occur im- mediately 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 experi- ences, 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 Lang // Professor of Information Science and Computing, Cornell University/Tech, Ithaca, New York
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.

By 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 succeeded—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, Leso-
tho 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 cardiomyopa-thy—that often lead to those deaths. A new program created by the American College of Obstetricians and Gynecologists, for exam-
ple, trains hospital obstetrical teams how to respond to childbirth emergencies.

Yet a significant fraction of those mater-
nal 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 catego-
ries, according to a number of state medical committees that have been looking into the problem. “According to some reports, suicide and drug overdose account for more deaths than postpartum hemorrhage, cardio-
vascular events or other pregnancy-related medical problems,” says Kimberly Mangia, a perinatal and reproductive psychiatrist at Columbia University Vagelos College of Physi-
cians 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 postpar-
tum, 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 child-
birth—as few as one in 10 gets appropriate care and recovers. Not only is screening for depression or substance abuse inadequate, says Lee S. Cohen, a perinatal and reproduc-
tive 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 facet of mater-
nal mortality. “Women are literally speaking to us from their graves, telling us how they came to die,” says Marcella 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.”

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 36% of all deaths in the state over a nine-year period had been caused by accidental overdoses or suicide. In Utah, in a similarly sized study, pregnancy-associated mater-
nal 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 into the deaths at Stanford University and medical direc-
tor 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 stud-
ed toxicity 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 that he believes all of the new mothers who committed suicide had a “good to strong chance” of being alive today if medical profes-
sionals had intervened with proper treatment. “We need to involve partners, grandmas and obstetricians looked at “any woman’s death where there was an inkling of suicide,” according to Elliott Main. Main is a clini-
cal professor of obstetrics and gynecology at the University of California, San Francisco, and hotlines have been set up to answer questions. The department has also worked with Medicaid to approve reim-
bursement for depression screen-
ings during pregnancy and the first postpar-
tum year. Screenings of new moms during well-baby visits are now also covered.

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 posi-
tive for depression will get an appointment with a mental health provider,” says Nancy Bryant, associate professor of psychiatry and ob/gyn and population and quantitative health sciences at the University of Massachusetts
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.


"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 in perinatal psychiatry. But community providers who work in obstetric practices emphasize that they need access to perinatal psychiatrists. "By leveraging digital technology, a psychiatrist in Casper, Wyoming, can get the same consultation from a perinatal psychiatrist as a psychiatrist in Beacon Hill in Boston,” Cohen says.

Other approaches help obstetricians and other primary care providers not only to recognize illness in perinatal treatment but also to provide mothers with immediate help. For example, the state-funded Massachusetts Child Psychiatry Access Program for Moms (PRISM). The program trains nurses of Moms (PRISM). The program trains nurses who can spot symptoms.”

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 way, an obstetrician can now send a woman with mental health disorders down the hall to Collaborative Care MMs 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 in 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.”

Health care providers must report suspected prenatal drug use to child welfare authori- ties. In addition, when opioids or other drugs are found in a newborn, mothers may lose custody, at least temporarily. “We are crim-inalizing a medical problem,” Smith 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.”

Women pregnant with opioid use disorder who are receiving medication-assisted therapy (MAT) have improved outcomes for their children 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 train- ing can prescribe it, and those clinicians can treat only a limited number of patients.

The HOPE Clinic at MGH attempts to over-come 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 insur- ance, trauma, violence or a partner who has substance use issues,” says MGIF’s Raffi, who also works at the clinic. “And there’s a lot of guilt and shame. We want to help the neces-sity of mothers with substance use disorders, aid their mental health care and prevent tragedies such as suicide, infant death 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 turn from opioid epidemics. In Utah, for example, 42% of women covered by Medicaid and 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 vagi-nal 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 heading toward opioid addiction, says Smid of the University of Utah.

Of course, many women are already there, and during pregnancy and the first postpar-tum 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,” Smith 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 are pregnant with opioid use disorder will relapse within a year postpartum. Legal issues further complicate matters. Many women don’t disclose their pregnancy to their 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 Northwest- ern’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,
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.

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...
A landmark 1978 report from the Institute of Medicine in California demonstrated the need for primary care. The report highlighted the importance of primary care physicians and the need to improve access and quality of care. Yet the same report noted that the public and policymakers were largely unaware of the problems in primary care.

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 39th in life expectancy—a disparity partly tied to a lack of preventive care, which in turn may be related to not seeing a generalist physician who conducts regular screenings.

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 spin new ideas 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 Glassroff, 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.

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 smaller. More than one in four primary care physicians is age 60 or older, and 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 a 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 laid to performance metrics that measure quality, cost or patient engagement, and for insurers, providers, 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 standing up to face a physician assigned to a team, or pod, that also includes nurses, care coordinators and care managers. Physicians, 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, the health system moved from 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 chief physician lead for team-based care. A PCMH model has 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,” Jerzak says.

It was a rare case in which a better model for doctors and patients also meant a health care system was saving money and improving quality. 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 the model can be lost if improvements are not sustained.

And instituting some version of the medical home carries a hefty price tag, costing providers an average of $100,000 per physician per year, according to one study. During the pilot’s first two years, practices received median government subsidies of $15,000 per physician in care management fees, and median care management fees for the newer CPC+ program have ranged from $88,000 to $190,000. 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 tradi- tional primary care model,” says Rashika 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 “capitalization”—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,” says Sachin Jain, the Iora CEO.

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 1,100 patients—less than half the size of patient panels in other kinds of practices.

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

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.

CareMore Health uses a similar, capitalized 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 2,800 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. The 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 the patients who are left out just going 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, catch 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.”


"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 promises and flaws of DPC models currently underway.
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 impact health and well-being.

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
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—the urge to sleep becomes overpowering. In the 1980s, 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

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 complex 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 do a meeting, to study for an exam or to spend time with our families,” says neurologist Louis Parisé 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 sleep 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.

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 waking 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 up until—normally late at night—the urge to sleep becomes overpowering. In the 1960s, scientist Alexander Borbely 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 sleep at night and wake up in the morning. On a separate track, the longer people are awake, the more they feel their ‘sleep drive.’

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 Borbely’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 Jeff 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 looks for genetic differences. By 2015, however, only two GWAS’s had been conducted on insomnia, and neither yielded significant insights.

One likely reason for the inconclusiveness of these studies was the relatively small number of participants. One looked at 10,088 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.
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 fruitful 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 genetiast 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. bolstering the case that it may promote deeper sleep and improved sleep quality. They were also able to pinpoint what insomnia meant. 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.

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 beasties, 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.

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 collaborator’s 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 therapeu tic targets, which may bring a better night’s sleep for everyone.

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

*Genetics of Sleep Disorders,* by Philip Gehman et al., Psychiatric Clinics of North America, December 2019. This study provides an overview of the history 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.

**DOSSIER**

**INSOMNIA:** About 15% 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.

**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.

*More than 10 hours* | *More than 10 hours* | *More than 10 hours* | *More than 10 hours* | *More than 10 hours* | *More than 10 hours*

*Less than 8 hours* | *Less than 8 hours* | *Less than 8 hours* | *Less than 8 hours* | *Less than 8 hours* | *Less than 8 hours*

*Sleep more than a hour* | *Sleep more than a hour* | *Sleep more than a hour* | *Sleep more than a hour* | *Sleep more than a hour* | *Sleep more than a hour*

*Sleep less than an hour* | *Sleep less than an hour* | *Sleep less than an hour* | *Sleep less than an hour* | *Sleep less than an hour* | *Sleep less than an hour*

*INSOMNIA:* About 15% 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.
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.

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?
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 trained to not tell the patient he had cancer," Klotz says. "We were told to use euphemisms like: ‘We found a few abnor-
mal 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 detect 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. A young man who has a PSA above a certain level (4 ng/ml) must meet with a specialist who can each explain their views of 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 the 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.

Researchers have shown that shared decision-making can lead to better, more confident choices. In a 2012 study, Efstathiou and 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 multi-disciplinary 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.

In other cases, patients want their doctors to be agnostic about radium than others. “I believe a lot of overtreatment has been driven by patients, and you can’t blame them,” says biosstatistician 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 7627 men in AS protocols found that 20% of cases in which monitoring was abandoned in favor of therapy 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 regrets doing so. Vickers, who has studied how follow-up testing indicating a malignancy dangerous enough to warrant surgery or radiation sometimes brings 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.

Patients might be more likely to risk AS, for instance, if there were better ways to spot a prostate that doesn’t need immediate attention. Biopsies can be hot 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 urologic 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 urologists lack.”

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, for instance, have been testing a program developed by 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. “I’m a huge fan of social scientists—particularly those in the behavioral science of decision-making,” says Vickers. “We can give patients the tools to make educated choices about their medical care.”

This letter examines recent trends in the use of AS in black men with low-risk prostate malignancies, as well as rarely lethal forms of other cancers (such as breast and thyroid), could reduce overdiagnosis and overtreatment.

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 harmlessly slow-growing forms that may never become dangerous.

A more radical proposal is to change the way low-risk malignancies in the prostate (and elsewhere, including the breast and thyroid) are diagnosed. 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.

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 benefits—mainly its knack for identifying meaningless tumors that may prompt aggressive treatment and therapy that comes with its accompanying side effects—are outweighed by its harms. 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.

“In many disciplines, the way you’re trained is the way you treat.”

**"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.’"**


The authors, who include an AS pioneer, offer an evidence-based rationale for this treatment approach and guidelines for administering it.


"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.

**DOSSIER**
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.
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