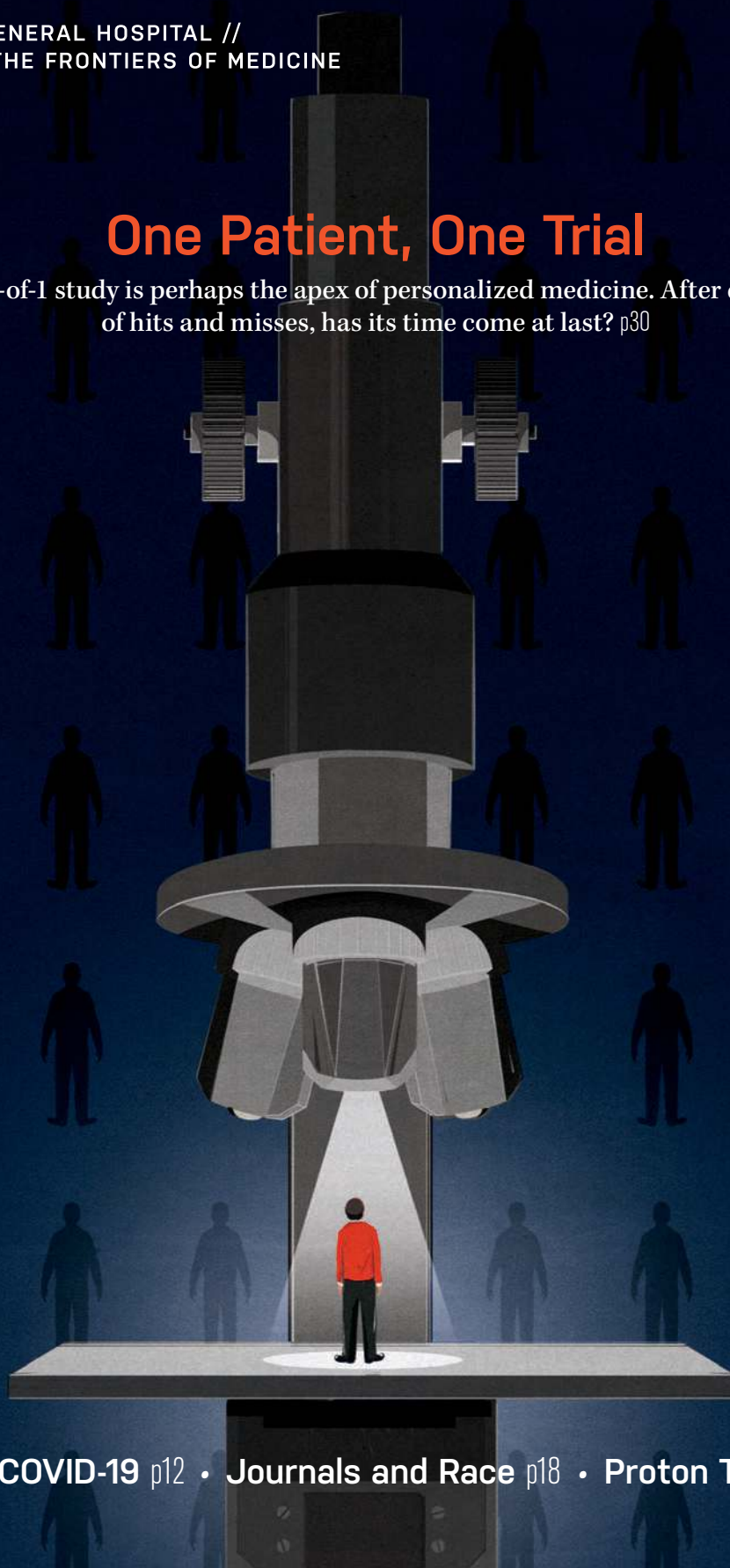


proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

One Patient, One Trial

The N-of-1 study is perhaps the apex of personalized medicine. After decades of hits and misses, has its time come at last? p30





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on the cover

Large randomized trials help establish typical patient responses. But is any patient typical? The N-of-1 model is an effective, if time-intensive, corrective. // Illustration by Andrea Ucini

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 1,043-bed academic medical center located in Boston. It is a founding member of Mass General Brigham (formerly Partners HealthCare) and is the original and largest teaching affiliate of Harvard Medical School.

This magazine is intended to present advances in medicine and biotechnology for general informational purposes. The opinions, beliefs and viewpoints expressed in this publication are not necessarily those of MGH. For personal health issues, MGH encourages readers to consult with a qualified health care professional.

EVERY DAY, THE FRANCIS H. BURR Proton Therapy Center at Massachusetts General Hospital teems with patients, many of them children. The crucial questions about who can benefit most from proton therapy—explored in the article “A Time for Protons”—often don’t apply when it comes to the youngest patients. This highly targeted form of radiation therapy can treat a long list of pediatric malignancies, including many kinds of brain cancer and bone cancer, lymphoma and other tumors. Proton therapy’s great advantage in young patients is its ability to limit collateral damage to healthy tissue. For each treatment for each patient, extensive imaging is used to design individually machined brass disks that focus the beams of protons, delivered at 400 million miles an hour, precisely where they are needed to attack and kill tumor cells. Children receiving this therapy may be spared the negative effects of conventional radiation on young and growing bodies.

The first MGH patient to receive proton therapy, in 1973, was a four-year-old boy with a pelvic tumor. He was treated in Cambridge at the Harvard Cyclotron Laboratory, a physics research facility where MGH physicians pioneered proton therapy. They built on an idea set forth in 1946 by Harvard physicist Robert R. Wilson, who had collaborated on creating the first atomic bomb and wanted to put the remarkable properties of protons to peaceful use. The opening of the Burr Center in 2001 made proton treatment accessible to many more children and adults. Since then, the demand for proton therapy has grown, and in 2020, the MGH opened a second facility, the Gordon-Browne Proton Therapy Center.

As the wonders of protons have become increasingly apparent, dozens of proton therapy centers have opened and now operate across the country and around the world. Thousands of patients at those facilities are being enrolled in clinical trials to determine when proton therapy is the right choice for attacking specific kinds of cancers and which patients will benefit most from this powerful and precise tool. Amid this rapid expansion of technology, scientists at the MGH—ground zero for proton therapy—have continued their legacy of building upon and refining the more than five decades of vital research into this life-saving and game-changing treatment.



DAVID F.M. BROWN, M.D.
President
Massachusetts General Hospital



MARCELA DEL CARMEN, M.D., M.P.H.
President
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stat

FOCUS

The holiday snowflake shares a radial symmetry with many kinds of viruses. That similarity struck Edward Hutchinson, a senior lecturer at the MRC-University of Glasgow Center for Virus Research. In 2019, Hutchinson put together a small booklet of virus patterns with instructions for cutting them out as decorations for the holiday season. He included helpful information explaining their symmetry and some of “the things that make virus particles beautiful.”

When the holidays of 2020 rolled around, the beauty of viruses was a harder sell. Hutchinson added a few patterns to last year’s book, which included (clockwise from the top right) an RNA vaccine, the SARS-CoV-2 virus, the adenovirus used in viral vector vaccines and the coronavirus neutralized by antibodies. In July 2021, the project was awarded the Microbiology Society’s Outreach Prize, in part for helping “people to understand what was causing the pandemic and how control measures worked, in an accessible and non-alarming way.” The patterns can be downloaded on the website of the Center for Virus Research.

VICTOR PRADO

LOOK AT YOU, PRETENDING TO BE ALL PROFESSIONAL!

THE ONLY PRETENDING I'M DOING IS THAT YOU EXIST!

INTERVIEW

Drawing the Line

Shirlene Obuobi—cartoonist and physician—shows how dark days sometimes call for a light touch.

As a physician, Shirlene Obuobi, 29, is just starting out, working on a cardiology fellowship after completing her residency at University of Chicago Medicine. But as a cartoonist, Obuobi is already a practiced hand. Her online persona, Shirlywhirl, M.D., is a favorite comic of medical Twitter and Instagram, and she recently signed on for a recurring column in Medscape.

OPPOSITE PAGE: PHOTO BY TIM KLEIN; ILLUSTRATION BY SHIRLENE OBUOBI; THIS PAGE: THE NOUN PROJECT

Shirlywhirl, M.D., mostly explores the joys and frustrations of hospital work—wrestling with the “coverage cobra” of insurers and striving for elusive moments of work/life balance. But in 2020, the tenor of the strip shifted. Confronted with the pandemic and a national crisis in racial injustice, Obuobi’s comics took on a much more serious tone—an evolution that brought her work to a much wider audience.

Q: Do any of your comics from the past year especially stand out for you?

A: I did a series about doing rounds on the COVID intensive care units. I was really proud of that piece. We didn’t have cameras on the units, so my comic provided a window into them—the dedication of my teams and also some of the frustrations we felt. A lot of fellow health care workers saw themselves in what I drew. And a lot of people who weren’t health care workers, when confronted with the human aspects of treating COVID—well, they were taken aback. That felt good and cathartic.

Q: You produced several long, serious comics last year. In another you took on the police killings of Black people, and the first line read: “I was twelve years old the first time the police were called on me.”

A: You know, when an event like that happens, there’s often an effort to tarnish the victim’s character—to come up with reasons outside of their race why that person may have been targeted.

When you go to elite, predominantly white institutions and are able to code-switch the way I can, you kind of fall into this category of an “acceptable” Black person. But this comic allowed me—a physician, someone who perhaps my peers respect—to show that I am not immune to racism in America. In that comic, I depict an experience when I was twelve during which cops were called on me because I was running around a hotel. And similar things have happened to so many other Black people, with terrible consequences.

Q: How can a comic help with weighty topics like this?

A: Comics are so underrated! There are so

many things to say about this, but I’ll just focus on the speed at which they can be processed. In the medical profession we have so many essays and papers to consider, on top of very busy lives. Comics can be an easier way to address some topics. They take seconds to read, and they spark conversations, often with people on different levels of the medical hierarchy.

What I write about ... they’re not exactly taboo topics, but in medicine, we don’t really talk about the ways that social inequities influence health. We’re a very cerebral group; we like to talk about basic science research and clinical trials. So I’m happy if one of my comics can give someone a laugh and maybe allow us to refocus on other important topics for a little bit.

Q: Is there a “moral” to Shirlywhirl?

A: To best serve our patients, we really need to look for diversity. And I’m not just talking about diversity in terms of race and gender. It’s also diversity of thoughts and experience and talents. Not everybody has to be the focused researcher. Some people love to write and focus on communication. Other people are good at advocacy and political action. We should be finding those talents and nurturing them, rather than trying to create some mold of a perfect doctor.

There are so many ways medicine can help our patients and help the world. Through this work, I kind of found my own way to reconcile the various parts of myself. But there are so many people with so many talents out there, and I sometimes worry we’re letting all of that go to waste in this field. Let’s think about the many ways that we can really use our peers and celebrate their differences. 🍷



BY THE NUMBERS

Hyperprolific Authors

262

Number of scientists who published at least 72 papers—one paper every five days—in any calendar year between 2000 and 2016. About half of them work in biomedicine.

165,000

Dollars given by Chinese universities to Chinese scholars for papers published in high-impact journals. Cash incentives may be a driving force for hyperprolific authors from many countries. Malaysia and Saudi Arabia offer these bounties, although China banned the practice in 2020.

70

Percentage of hyperprolific authors who said they made minor contributions on at least 25% of those papers. Only 1 in 10, however, said they didn’t approve the final versions of most of their publications.

10-fold

Increase in published papers, on average, by cardiologists when they become directors of major research or clinical centers. While research time typically goes down in these positions, leaders often receive credit for research performed under their watch—a possible contributor to hyperprolific tallies.

33.4

Percentage of researchers who admitted to adding “honorary” authors to their manuscripts even though those authors did not deserve credit. The names were added to papers as a compliment to a mentor, to avoid conflicts at work or to increase the likelihood of a major journal accepting the manuscript.

INFOGRAPHIC

Organoids Grow Up

The model tissues, barely a decade old, have become more clever and complex—and increasingly useful. BY JOSHUA KRISCH

Organoids—cells coaxed to grow into tiny, three-dimensional tissues—have changed the face of basic science. Because they possess key qualities of human organs in miniature, “organoids opened the door to deep analysis of human tissue in a laboratory setting, in a way once possible only with animal models,” says Christina Faherty, a molecular biologist at Massachusetts General Hospital. Advances in the field have led to even more ingenuity. At MGH, for instance, Faherty and colleagues are studying the *Shigella* bacterium and how it infects the human intestine. They grew an organoid that

included a variety of intestinal cells, including some that produce mucus and others that “sniff” for bacterial intruders. Then they splayed those across a membrane to test how different strains of *Shigella* infect each cell type. The model led to new findings on a disease that infects 165 million people per year and kills more than 600,000. “We’ve never before had such a versatile prototype for human disease,” Faherty says. Organoid researchers across the globe have moved to do the same for hundreds of other conditions. [P](#)



BACTERIAL INFECTION
Faherty Lab, Massachusetts General Hospital
Shigella infect half a million Americans each year, and antibiotic-resistant strains are on the rise. These organoids capture the nuances of intestinal tissue to provide authentic models for *Shigella* infection, complete with mucus production.



SNAKE BITES
Clevers Lab, University Medical Center Utrecht, the Netherlands
Tomorrow's antivenoms and venom-based drugs may owe their existence to today's venom gland organoids. Snake venom gland organoids have recently arrived, and a biobank of organoids from other venomous animals is on the way.



DRUG TOXICITY
Little Lab, Royal Children's Hospital Melbourne, Australia
Three-dimensional bioprinting has recently given rise to a kidney organoid with mature nephrons—the tiny basic unit of the kidney, which contains 26 different interacting cell types. Such a model could be used to test the toxicity of new drugs and treatments.



TUMORS
David Jones Lab, Memorial Sloan Kettering Cancer Center, New York
Patients suffering from many cancer types have had their tumors biopsied then replicated as organoids. Increased savvy in using this technology may soon allow physicians to test and tailor treatments to their patients.



DRY EYES
Clevers Lab, University Medical Center Utrecht, the Netherlands
Dry eye disorders are hard to study without looking at tear production up close. Tear duct organoids can be coaxed into crying—swelling without producing tears—in the lab. Such organoids may also pave the way for tear duct transplants.



SKIN DISEASES
Koehler Lab, Boston Children's Hospital
Scientists have been growing skin in the lab for decades, but recent organoids include skin tissue with fat, nerves and hair. These could eventually help test how drugs interact with human skin, and may lead to advances in treating severe burns.



SEIZURES
Novitch Lab, University of California, Los Angeles
The newest brain organoids have neurons that network, producing coordinated waves of electrical activity. In one study, researchers tracked electrical pulses resembling seizures. The tissue was grown from patients with Rett syndrome, which is characterized by such events.



COVID-19
Blish Lab, Stanford University Palo Alto, California
Organoids were key in demonstrating that lung cells begin dying en masse only three days after severe COVID-19 infection. They have also shown that the virus targets not only alveoli—tiny air sacs in the lung—but also club cells, which line the tissue leading to the air sacs.



CONGENITAL EYE DISORDERS
Little Lab, Royal Children's Hospital Melbourne, Australia
The optic cup organoid—which has both brain and eye tissues—has allowed scientists to observe precisely how retinas, lenses and corneas develop in human embryos, a crucial step in studying birth defects and congenital eye disorders.



TASTE TROUBLES
Jiang Lab, Monell Chemical Senses Center, Philadelphia
Organoids have been coaxed to develop taste buds that detect salty, sour, sweet, bitter and umami flavors. Studies of these organoids have shed light on the genes and signaling pathways involved in taste receptor cell differentiation and proliferation.



HEART ATTACKS
Mendjan Lab, Austrian Academy of Sciences, Vienna
Scientists recently developed the first human heart organoids, smaller than sesame seeds and complete with beating chambers. Designed to function like the hearts of month-old embryos, these organoids may increase our understanding of congenital heart defects and heart attacks.

NEXT GENERATION

Skies of Gray

New research looks into young people's anxiety around environmental collapse.

BY TIMOTHY GOWER

Yet another awful effect of climate change has been the emergence of climate anxiety, also called eco-anxiety. This dread of future extinctions and severe climate events happens disproportionately to the young, who will bear a warming planet's greatest burdens. One new global study, to appear in *The Lancet Planetary Health*, is by far the largest of its kind, including 10,000 people between the ages 16 and 25. Participants from 10 countries were asked how they felt about climate change and their government's reaction to it. More than half of respondents said that thinking about climate change left them sad, anxious, angry, powerless, helpless and guilty; 59% described themselves as “extremely worried,” while nearly half said that their feelings negatively affected their daily lives. Many said they felt betrayed by inadequate governmental response to climate change. “This study confirmed what those of us who work with kids have known for some time,” says Elizabeth Pinsky, a pediatrician and child psychiatrist with Massachusetts General Hospital. “I have patients who say, ‘I have no future, so what's the point?’” Some complain of chronic nervousness, poor sleep and an inability to shut off thoughts about climate change “to the point where it can cause significant distress or impairment,” she says. Pinsky notes that research on climate anxiety is in its infancy, so there is as yet no diagnostic criteria or established treatment. When it occurs alongside conditions such as anxiety disorders or depression, however, treatment might take the form of talk therapy or medication. Not all of the young who worry about the planet's future are paralyzed by their fears. “Feelings of dread and despair about climate change are normal,” Pinsky says, and can be channeled into activism, such as organizing a beach clean-up. For parents, however, simply encouraging a child to attend a march isn't enough. Listening to and not dismissing a child's fear about the future is critical, Pinsky says, as is involving the whole family in thoughtful climate-related discussions and decisions around the home. Pinsky feels that past sources of generational angst—such as Cold War-era fears—may have echoes in the current climate crisis. “It brings comfort to know that people have experienced existential threats before,” she says, “and yet they persevere.” [P](#)

POLICY

One for All

A global pandemic treaty—a health plan on par with nuclear and climate deals—is now in the works. Does it stand a chance?

BY LINDA KESLAR

The decision-making arm of the World Health Organization, the World Health Assembly, begins to meet in special session on November 29, 2021. Delegates from its 194 member states will meet virtually and in person to focus on one question: whether to begin the process of creating an international “pandemic treaty.”

The uneven, uncoordinated responses to the COVID-19 pandemic so far have sharply underscored the need for global cooperation. Even now, experts argue that worldwide health authorities should be working together to monitor regions where the next dangerous pathogen might take hold. Many voices have called for a coordinated, equitable policy for producing and distributing protective equipment, effective treatments and vaccines. When one country is unsafe, they say, all countries are unsafe.

Some laws already on the books could help. In 1969, the WHO adopted what would become the International Health Regulations, which are binding on all of WHO’s member states. The code stipulates, for instance, that countries must notify the WHO within 24 hours of any event that might lead to an international health crisis. It also prohibits countries from enacting travel bans or taking other extreme steps in advance of scientific consensus. Yet these statutes and many others were violated during the COVID-19 pandemic, in part because the WHO system has no mechanism for enforcement.



A legally binding treaty with more bite—such as those that govern nuclear arms control and climate policy—might discourage scofflaw attitudes. “In every phase of this pandemic, there has been no solidarity and no global cooperation,” says Lawrence Gostin, professor and faculty director of the O’Neill Institute for National and Global Health Law at Georgetown Law. “But we can’t let the world unravel.”

“The politics of creating an enforceable treaty are likely to be devilishly tricky.”

No single government or institution, no matter how powerful, can address the threat of future pandemics alone.”

“The politics of creating an enforceable treaty are likely to be devilishly tricky, and countries around the world have been eval-

uating whether such an agreement is in their best interests,” says Ilona Kickbusch, founding director and chair of the Global Health Centre at the Graduate Institute in Geneva. Notably missing from the initial treaty supporters are the United States and China. The Biden administration, although not directly opposing the proposal, has expressed concerns that negotiating a treaty now could derail the momentum necessary to tackle the worsening pandemic. But more than 60 countries have now joined a “Friends of the Treaty” group that supports the initiative, Kickbusch says: “From some countries, we are seeing a very, very strong commitment.”

But broadening that commitment and getting a treaty negotiated and signed could depend on support from outside the halls of policymakers. “If we are serious about getting a pandemic treaty in place, it’s important that we involve scholars, academics, human rights lawyers, civil society groups and affected communities,” says Allan Maleche, executive director of the Kenya Legal & Ethical Issues Network on HIV and

ILLUSTRATION BY CHRIS GASH

MILESTONE

Shots Unfired

The Boer War was an early turning point in vaccination history.

BY HANNAH THOMASY

Sir Arthur Conan Doyle arrived in Bloemfontein, South Africa, in April 1900, less than a year into the Second South African Boer War. At 41, the creator of Sherlock Holmes was too old to join the British Army, but his services as a physician were sorely needed.

For the next few months, Doyle and the staff of Langman Hospital—a field hospital set up on a cricket pitch on the outskirts of the city—struggled under the number of those sick and dying with typhoid. “For more than two months the hospitals were choked with sick ... nearly all enterics [typhoid fever patients] ... As many as fifty men died in one day, and more than 1,000 new graves in the cemetery testify to the severity of the epidemic,” wrote Doyle in *The Great Boer War*.

More than 8,000 British troops succumbed to the disease, a bacterial infection that spreads quickly and can perforate the bowel. Vaccination might have helped to blunt these numbers significantly—the first typhoid

rent contagion is under control. “We’re in a public health emergency,” says Kelley Lee, a professor of global health governance at Canada’s Simon Fraser University. “Negotiating a new treaty will take three to five years. We need to consider whether that process should take priority over ending the current pandemic and understanding why countries are not adhering to the obligations already in place.”

Still, others are optimistic that the WHA meeting now underway will lay a path for future action and could save untold numbers of lives in future pandemics. And while it’s possible to delay action, the shadow of COVID-19 may be just the impetus to make global consensus possible. “We experienced a once-in-a-lifetime level of suffering, death and economic destruction,” says Georgetown’s Gostin. “So if not now, when?”



vaccine had been developed a few years before the start of the war. But it was still considered experimental and side effects could be severe. The British army opted to make it voluntary, and the vast majority of the troops refused it.

Other nations would not take the same tack. Germany, for instance, had a long tradition of mandatory vaccinations for its troops, and typhoid vaccinations began in 1904 for German armies stationed in German South West Africa (later Namibia). Contemporary studies showed that many lives were most likely saved.

The lessons of both the British and Germans in South Africa were front of mind as the nations prepared for World War I. “More died from the bacilli of this disease than from the bullets of the Boers,” Sir William Osler

reminded British Parliament. While the vaccine was still not compulsory for British soldiers, more than 90% chose to be inoculated during the final three years of the Great War.

Less fortunate, however, were the Africans they left behind. While typhoid has been virtually eradicated in high-income countries, populations in the world’s developing countries, largely unvaccinated, have seen the disease persist and mutate. Extensively drug resistant (XDR) typhoid, which is resistant to at least five antibiotic classes, appeared in Pakistan in 2016. By the end of 2020, the CDC had identified nine cases of XDR typhoid spread across six different U.S. states in people with no history of travel to Pakistan. True safety against typhoid, it would seem, calls for a global, coordinated response.

UPDATE

AI, Explain Thyself

Policymakers call for algorithms in health care to become more transparent. But at what cost?

BY STEPHEN ORNES

The past decade has seen machine learning—finding patterns in vast piles of data—in a state of vibrant growth. The number of life science papers on machine learning numbered just under 600 in 2010; by 2019, there were more than 12,000. The applications in medicine are potentially lifesaving and include the ability to help physicians home in more quickly on the right diagnosis (“Doctors in the Machine,” Winter 2015).

The FDA has already approved 29 medical devices that use machine learning in some way, with dozens of others in the pipeline. Translational research teams are also looking to find room in clinical practice for an astonishing range of its insights, including which patients are most likely to miss an insulin dose and who might attempt suicide in the next six months.

But there is a downside. Human researchers are, by and large, unable to follow the logic behind many of these algorithms—including almost all of those used in FDA-approved technologies. The insights are created by passing the information through “hidden layers” of complex networks to develop predictive patterns—a black box approach where the logic becomes opaque.

“To say that an algorithm is a black box means that it wouldn’t be interpretable even by the people who designed it,” says Boris Babic, a professor of philosophy and statistics at the University of Toronto. The parameters and their relationships become



LAURA CARLIN

so complicated, he says, that it becomes mathematically impossible to piece together how the inputs lead to the outputs.

Some might argue: So what? If the algorithms have predictive power, then let the black box be black. But others are concerned about dangerous assumptions that machines might cook up or “catch” from the data they import. Where a tool is learning from human example, for instance, it might perpetuate existing biases—clinicians’ tendencies to take women’s accounts of pain less seriously than men’s, for instance.

Researchers and policymakers have increasingly called for algorithms that can explain what they’re doing. The U.S. National Institute of Standards and Technology held a workshop earlier this year to lay out new benchmarks. The Royal Society issued a policy brief in favor of explanations, and the European Union, after it passed the General Data Protection Regulation in 2016, has increasingly advocated a “right to

explanation” about the algorithms that affect people’s lives.

Will explanations of an algorithm really solve problems of bias and unintended consequences? “This notion of requiring an explanation is typically pitched as a way to allay ethical and legal concerns,” says Babic. “But it’s not going to be an effective one.”

In a recent editorial in *Science*, Babic and his colleagues—including legal researchers and computer scientists—issued a warning about so-called “explainable AI.” Efforts to increase transparency run the risk, at a minimum, of misleading an audience and potentially undermining these programs’ predictive power—their chief advantage over human analysis.

“Researchers pursue explainability in two primary tracks,” Babic explains. One is through “interpretable AI,” which focuses on developing new models for prediction based only on steps and connections that

can be reported in an understandable way by the program. While this introduces constraints, in some situations, he says, it’s possible that an interpretable program would equal or exceed a black box in accuracy. This would not be true in all cases, however.

“The other track,” Babic says, “is more worrisome.” It involves designing a separate algorithm that closely approximates the findings of a black box—except that this second program employs only functions that users can understand. It finds a pattern in the data to fit the conclusions. While comforting, Babic says, these approximations are far from being the same as the real thing: “A bad explanation is worse than no explanation at all.”

SECOND OPINION

Nocebo a No Go

Regarding the nocebo effect sidebar in your article on cholesterol deniers (Spring 2021), the conclusions from the experiment quoted from *The New England Journal of Medicine* are just the opposite of what is stated in the sidebar. [Ed. *This piece outlined an experiment in which a patient was rotated through statins, placebos and no medication. The patient discovered that side effects happened primarily on months without statins.*]

One must think of the effect of statins as similar to scurvy. The effect of inhibiting proper wound healing appears only a month or more after the deficiency (in scurvy) or inhibition (with statins) is established. It is not surprising that the effect of a month of statin “therapy” is delayed into the month that is statin free! Since good healing also takes weeks, it is not surprising that the symptoms of poor healing of simple tendon strains occur on the two non-statin months of the study design.

From personal experience, the effects take different times to appear in different tendon groups. The failure of hand tendons to heal comes before problems with ankles,

Some scientists do see a potential limited role for such post hoc models. Matt Turek, who leads an explainable AI program at DARPA, the research and development arm of the Department of Defense, can imagine situations where a provisional explanation for a complex prediction would be useful, as long as users were warned about its limitations. “I think about it in terms of a spectrum of explanation technologies,” he says.

Turek also points to ongoing “interpretable AI” efforts at universities across the country to develop complex algorithms that can, in some sense, explain what they’re doing. A group at the University of California, Berkeley, for example, in 2016 developed a type of “black box” algorithm that could

feet or knees. I have now observed five such personal episodes. And the healing process after stopping statins invariably takes more than a month.

If one tries to prove the absence of tendon effects by only asking about Achilles tendon pain or rupturing, one is missing the point of a migrating tendonitis association with statin therapy. Indeed they are wonder drugs. But let us not deny that there are side effects when the opposite is the truth!

Alex M. Saunders, M.D. // Redwood City, California

Response from the study authors:

The reader is correct that SAMSON is not

MISSED THE LAST ISSUE?
All stories from *Proto* Spring 2021 are available at [protomag.com](https://www.protomag.com).

produce text-based explanations of why it made its choices.

And the current roadblocks could even lead to improvements. “In some cases, we’ve found that by using explainable AI techniques, we improved past performance,” he says, explaining that certain algorithms seem to “get better” when they’re forced to explain themselves.

Medicine is not the only field grappling with this issue—AI has also been pulled into the sensitive fields of criminal justice, self-driving cars and predicting who is likely to repay a loan. In all of these cases, people can be harmed by AI. “We need explanations—especially in domains where serious outcomes happen when things go wrong,” Turek says.

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

able to comment on the etiology of symptoms in patients whose symptoms arise several months after commencing statins. We explain in the manuscript that to be confident the monthly blocks were long enough for patients’ symptoms to arise, we only recruited patients whose side effects had previously arisen within two weeks.

However, while SAMSON can’t provide information on the patients with side effects arising over a longer period, the vast number of randomized controlled trials that preceded it can. A meta-analysis of 10 primary prevention trials by Finegold et al. has shown discontinuation rates in patients taking statins was 12.1% and 13.4% in those taking placebo. We would never claim this means statins don’t cause side effects in some patients. But side effects are sufficiently rare that in a meta-analysis of thousands of patients, sugar tablets were actually worse tolerated.

James Howard // Clinical Lecturer, National Heart and Lung Institute, Imperial College London

MORE THAN 670,000 FLAGS across 20 acres in Washington D.C. are one effort to commemorate the enormity of the COVID moment. Each flag represents an American who has died from the virus, and more are added daily. The installation, "In America: Remember," was created by Suzanne Brennan Firstenberg.

THE MOURNING AFTER COVID-19

Some people who lose loved ones to COVID-19 will face an inconsolable grief—a second epidemic the nation is poorly prepared to handle. // by Kristen French

ALLISON BAILEY/ASSOCIATED PRESS

In June 2020, Kristin Urquiza's father caught the COVID-19 virus. Two weeks later, the 65-year-old was dead. Like so many others bereaved by COVID-19, Urquiza didn't get a chance to say goodbye or to hold a funeral with loved ones. It seemed as though her dad had just vanished. In the aftermath of his death, she rode rolling waves of rage that alternated with profound sorrow. "I couldn't live with it," she says. She needed to break the cycle of her grief, but didn't know how.

Many people in her father's neighborhood—a predominantly Latino area of south Phoenix—were also suffering. Citywide, infections had surged 151% over the first half of June, which was just after the city's stay-at-home order expired in May and before a June 15 mask mandate. His neighborhood had notched some of the highest case counts, in part because many of the residents worked front-line jobs at hospitals, restaurants, grocery stores and other essential businesses, putting them at high risk. Many households struggled financially—Urquiza's father had just been laid off from his manufacturing job—and those who died often left their loved ones in a precarious economic place.

Urquiza began to worry about the next wave of victims: the bereaved and grieving. Many of them would face tragedy without even her modest resources, which had allowed her to see a psychiatrist and pay for antidepressants and anti-anxiety medication. To help herself and others lost in grief, she drew on her experience in social and environmental justice advocacy to create a national organization called Marked by COVID. The nonprofit offers online support groups, engages in political advocacy and sponsors regional and national memorials for those who lost loved ones to the pandemic. Connecting with other people in similar circumstances, she says, helped her get through the most acute stages of her pain.

A national body of mourners has taken shape in the wake of COVID-19. They grieve not only the more than 700,000 U.S. deaths brought by the virus but also hundreds of thousands who have died from related causes: missed physician visits and canceled procedures caused by overcrowded hospitals or fears of catching the virus, and a spike in substance-misuse deaths provoked by the pandemic's economic and emotional stresses. If every death affects between two and



LEFT: In Columbia, national protests made COVID grieving even more complicated.
RIGHT: Mourners honor COVID-19 victim Maria Estela Maris Melo at her funeral in the Nossa Senhora Aparecida cemetery in Manaus, Amazonas state, Brazil.



LEFT: A funeral service in New Rochelle, New York, for Conrad Coleman Jr., a 39-year-old who died from COVID-19 just two months after his father also died from the virus.
RIGHT: Relatives wait to receive the body of a loved one at a mortuary in New Delhi.



10 people, as research estimates, the global count of pandemic mourners may lie somewhere between 8 million people—roughly the population of New York City—and 40 million people, the population of California.

Grief is a natural waypoint in life. The experience of it is “as individual as our lives,” wrote the late Elisabeth Kübler-Ross, author of the landmark *On Death and Dying*, which introduced her popular five-stage model of grieving. But while some grief is natural and even valuable, when extreme or disordered, the emotion brings a biological toll. Of special concern to psychiatrists is prolonged grief disorder (PGD), a condition added only last year to the Diagnostic and Statistical Manual of Mental Disorders, or DSM-V. PGD is defined as almost daily yearning for a deceased loved one, a condition that causes long-term, clinically significant distress or impairment that can lead to suicidal behavior and correlates with early mortality and increased rates of heart disease and cancer.

Under normal circumstances, 10% to 15% of bereaved people are thought to develop PGD. But pandemic-era deaths were largely unexpected and sudden, often coupled with financial woes and experienced without the normal channels of social support. All three of those factors are associated with a higher risk of PGD and may have doubled or tripled its prevalence, some researchers estimate.

The consequences could be especially grave in BIPOC (Black, Indigenous, people of color) communities, which have experienced some of the pandemic’s greatest losses. An August 2020 survey found that 39% of Black Americans and 31% of Hispanic Americans knew someone who had died from the virus, compared with only 18% of white Americans. These communities also experienced greater pandemic-related job losses, were already underserved by mental health services and suffer from other systemic health inequities.

“People of color, but especially African-Americans, have such a long history of brutal loss,” says Katherine Shear, a psychiatrist at the Columbia University School of Social Work and founding director of the Center for Complicated Grief. “Those traumas get transmitted across generations, and in combination with ongoing, current racism and disparities—this is hugely impactful in how deeply someone is going to experience a COVID death,” she says.

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On Nov. 28, 1942, the Coconut Grove Fire tore through a nightclub in Boston, killing 498 people. The deadliest nightclub fire in history, it became the subject of the first-ever systematic study of the physical and psychological features of grief. Erich Lindemann, a German-American psychiatrist,

collected extensive data from bereaved family members. Two years later, he published “Symptomatology and Management of Acute Grief,” a paper that established many of today’s standards of psychological care after disasters. Lindemann, who later became chief of psychiatry at Massachusetts General Hospital, found that acute grief often caused hostility, guilt, and a loss of social habits. He had seen similar reactions in patients who’d had organs removed, and he concluded that losing a human relationship was similar to losing a part of oneself.

Although research on grief advanced significantly over the next half century, few psychiatrists treated it as a distinct medical condition, says Holly Prigerson, a professor of geriatrics at Weill Cornell Medicine and co-director of the Weill Cornell Medicine Center for Research on End-of-Life Care. In the 1990s, when Prigerson began to study bereavement, any pathology that arose from grief was characterized as depression. But Prigerson’s studies led her to identify a collection of symptoms associated with mourning that were distinct from depression and often had specific medical consequences. In 2009, Prigerson and her colleagues published results of the Yale Bereavement Study and presented a comprehensive proposal for a new diagnostic entity: prolonged grief disorder.

ABOVE LEFT: HECTOR PERTUZ/GETTY IMAGES; ABOVE RIGHT: PHOTO BY MICHAEL DANTAS/AFP/GETTY IMAGES

ABOVE LEFT: PHOTO BY JOHN MOORE/GETTY IMAGES; ABOVE RIGHT: PHOTO BY PRAKASH SINGH/AFP/GETTY IMAGES

PGD is described as an experience of prolonged yearning and numbness, a state that can give rise to mistrust, bitterness or a feeling that life is meaningless. Some people with PGD have confusion about their identity after the loss, or may avoid confronting the reality of it. All find it difficult to move on with life. Prigerson and her colleagues also found that PGD, as proposed, was distinct from other mental disorders—major depressive disorder, generalized anxiety disorder and post-traumatic stress disorder (PTSD)—and its victims had an increased risk of future psychiatric diagnoses, suicidal ideation, functional disability and low quality of life.

PGD has distinguishing genetic and biological characteristics. Those who suffer PGD appear to have distinct patterns of expression in immune system genes—specifically, in the type I interferon pathway, which governs immunity against some viruses, bacteria and other invaders. In bereavement, people with PGD also appear to have higher levels of inflammatory biomarkers, such as IL-1RA and IL-6, circulating in the blood as well as patterns of cortisol dysregulation that are consistent with chronic stress.

Like many psychiatric conditions, the causes and severity of PGD extend beyond biology to life circumstances and even cultural elements. “This kind of suffering owes something both to nature and nurture,” says

Prigerson. She offers the parallel of someone who has a genetic vulnerability to alcoholism, but who may only become addicted if she is exposed to certain life stressors and lives within a culture that condones alcohol consumption. While the diagnostic criteria for spotting PGD are straightforward—debilitating grief that lasts a year or more, or more than

The global count of pandemic mourners may lie somewhere between 8 million people ... and 40 million people.

six months for children and adolescents—the causes are complex, as is the question of effective treatment.

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Helping those who are lost in mourning may be bound up in a more fundamental question: What is profound grief? Comparing it to other known brain phenomena, research from the past decade suggests that PGD may

share the greatest similarities with addiction. For a 2008 paper, Mary-Frances O’Connor, a psychiatrist who directs the Grief, Loss and Social Stress (GLASS) Lab at the University of Arizona, worked with women suffering from prolonged, unabated grief. In the laboratory, they were hooked up to fMRI brain scans and triggered with stimuli related to the deceased. The scans showed activity in the brain’s nucleus accumbens region, in neural reward pathways that are active in addiction. Those experiencing routine and shorter-lived periods of grief showed activity only in the pain centers of the brain.

“It was a novel idea—that yearning for a deceased loved one is the same as craving,” says Eric Bui, a psychiatrist at the Center for Anxiety and Traumatic Stress Studies and Complicated Grief at Massachusetts General Hospital and president of the International Society for Traumatic Stress Studies. More recent studies have provided further evidence of a link between PGD and a number of reward-related regions of the brain, as well as to altered signaling of oxytocin, a hormone involved in social bonding and attachment.

These findings have led a few researchers to consider treating PGD with medications designed for depression and addiction. Antidepressants haven’t been effective in clinical trials, but there is some hope for naltrexone, a medication often successfully



LEFT: A couple cries after leaving a stone for a COVID-19 victim at the “March of the Stones” tribute in Buenos Aires, Argentina. RIGHT: Gertrud Schop lights candles in Zella-Mehlis, eastern Germany, for each of the more than 8,000 COVID-19-victims.



LEFT: A mourner at the Paramo de Guerrero nature preserve near Cogua, Colombia, where trees are planted with the ashes of COVID-19 victims. RIGHT: A woman at the Old Town Square in Prague, where thousands of crosses have been drawn as a tribute to victims.



used to treat alcohol and gambling addictions. Earlier this year, Prigerson launched a clinical trial that will be the first to study naltrexone for PGD. Naltrexone blocks opioid receptors in the brain, inhibiting the release of dopamine, which in turn inhibits the reward pathway. Prigerson is hoping that naltrexone will stop the “reward” triggered by a loved one’s memory. That could, in turn, free someone from the most severe symptoms of the condition and allow that person to adjust to a new reality.

So far, though, only a handful of psychotherapeutic treatments have proved to be effective, including cognitive behavioral therapy and exposure therapy. The most effective is a 16-week course of weekly one-on-one psychotherapy, a protocol developed and validated by Columbia’s Katherine Shear. Her complicated grief therapy—also known as prolonged grief disorder therapy (PGDT)—has more in common with PTSD treatment than with therapies for depression or addiction. She does, however, include a module called “motivational interviewing,” which has been successful in addiction treatment.

The PGDT therapist helps bereaved patients through seven “healing milestones” that enable them to understand the grief and their own emotional responses, strengthen their current relationships and help them find new ways to live with reminders and memories of the person who died. “We help people revise the mental

representation of their deceased significant other so that the representation can still provide support and comfort,” says Shear. “That requires accepting the reality that the person is gone and not coming back.” In clinical trials, this approach has been shown to help resolve the symptoms of disordered grief in 70% of cases among older adults and 50% in the general population.

So far, the only treatment proved to be effective is a 16-week course of weekly one-on-one psychotherapy.

But talk therapy is expensive and time-intensive, and it relies on a mental health care network that is already overstrained. Some researchers are now looking at ways to make Shear’s CGT model more accessible. For instance, Naomi Simon, a professor of psychiatry at NYU Grossman School of Medicine and director of the division of Anxiety and Complicated Grief Disorders, is developing a “step care” approach. Therapists would start with group-based psychoeducation and

mind-body approaches and only “step up” to individual psychotherapy for those who really needed it. And Eric Bui has submitted grant proposals for novel uses of artificial intelligence—using data to predict which mourners might need extra help in moving on.

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As efforts to amend PGDT suggest, delivering real help to those who need it can be tricky—particularly in communities of color, which have suffered the greatest losses. Beyond the expense and time required to deliver such therapies, few clinicians have training in grief support, and there are no graduate programs in grief and bereavement, says Robert Neimeyer, a psychology professor at the University of Memphis and director of the Portland Institute for Loss and Transition, which offers training and certification in grief therapy.

Grief support often falls to hospice workers, who are required to provide this kind of care to bereaved family members for up to a year in order to receive Medicare reimbursement, says Amy Tucci, head of the Hospice Foundation of America. Yet Medicare offers few guidelines about what such care should entail, and hospice workers get little or no training in grief support. Proposed national mental health legislation would change that, providing more funding for grief training, grief support staffing and grief services.

In the meantime, already overstretched community organizations have been doing their best to get support to the bereaved quickly. One of those, in the Harlem neighborhood of New York City, is the Hope Center, a mental health treatment facility that is connected to a Baptist church, a liaison meant to help overcome the stigma against mental health care in the Black community. Early in the pandemic, the center’s wait-list doubled for free grief therapy services, which are modeled after Katherine Shear’s treatment program at the Center for Complicated Grief and provided by licensed clinicians, says Lena Greene, the center’s executive director. The Hope Center enlists its pastors and other staff to conduct assessments to identify those who might need further mental health treatment.

To reach those who don’t have access to one-on-one services or who aren’t ready for that kind of counseling, the Hope Center also offers support groups and group events. Shear has given talks—“healing conversations”—about grief and this fall, the center planned to host a conference on mental health, spirituality, racism, grief and loss. To get a better sense of the problem in the Harlem community—and a better understanding of how grief interacts with racism and trauma—the center will roll out a survey in early 2022.

“The majority of the people we see are African American,” says Greene. “They have been dealing with these historical traumas, so we make sure that our therapists are addressing

systematic injustices and talking about the impact of racism on people’s ability to cope on a daily basis.” Greene is also working with a team of pastors to help a Missouri church replicate the Hope Center model.

Harlem has the Hope Center, but many other underserved communities are still desperately short on grief support. Online groups fill some of the gaps, but can’t substitute of in-person counseling. Chris Kocher launched and ran the nation’s largest network for gun violence survivors and the families of shooting victims, and when the pandemic began, he created the online COVID Grief Network. In asking local communities what they needed, Kocher found that although online peer support was appreciated, many people also wanted local, physical spaces and in-person access to mental health professionals who would show up week after week.

Leaders of COVID-19 support groups are hoping for help from the Biden administration and wrote a letter in February 2021 urging the president to allocate funds to grief support, including grief training for the public and for social workers, psychologists, teachers and clergy. So far, though, the only two measures taken on the federal level have been a new federal bereavement leave policy and reimbursement of up to \$9,000 in funeral expenses for those who died of COVID-19. That leaves most of the grief response to local volunteers, many of whom are running out of steam. And as the one-year anniversaries of

more U.S. COVID-19 deaths arrive, more cases of prolonged grief will rise to the surface.

“We have to address the monumental pandemic of grief and trauma that we’re living through,” says Kristin Urquiza, whose father’s death is still fresh in her memory. “So far, mutual aid community groups like Marked by COVID have been leaning on one another and doing our best. We’ve pulled together to funnel the generosity of practitioners and artists into helping our communities,” she says. But it’s not enough to match the need. ☹

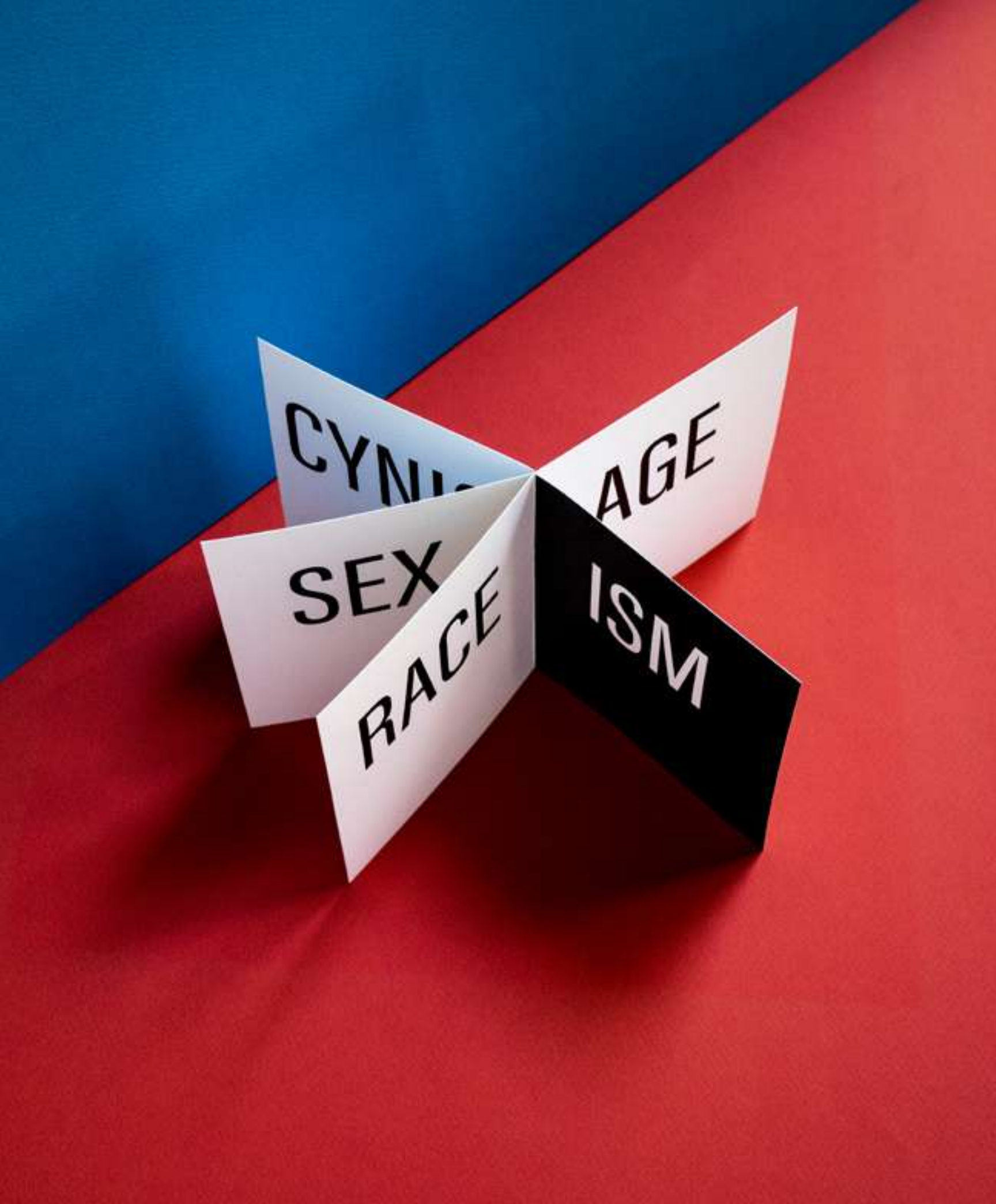
DOSSIER

“History and Status of Prolonged Grief Disorder as a Psychiatric Diagnosis,” by Holly G. Prigerson et al., *Annual Review of Clinical Psychology*, January 2021. A detailed review explores the evolution of psychiatric views of grief over the 20th century, including current diagnostic formulations for prolonged grief disorder.

“Complicated Grief Therapy for Clinicians: An Evidence-Based Protocol for Mental Health Practice,” by M. Katherine Shear et al., *Depression & Anxiety*, October 2019. A detailed description of the evidence-based psychotherapeutic protocol developed by Katherine Shear looks at the treatment of complicated grief, also known as prolonged grief disorder, including ways of implementing its seven core themes.

ABOVE LEFT: (PHOTO BY MANUEL CORTINA / SOPA IMAGES/SIPA USA)/SIPA VIA AP IMAGES; ABOVE RIGHT (PHOTO BY JENS SCHLUETER / AFP) (PHOTO BY JENS SCHLUETER/AFP VIA GETTY IMAGES)

ABOVE LEFT: PHOTOGRAPHER: NATHALIA ANGARTZ/BLOOMBERG VIA GETTY IMAGES; PHOTO BY MICHAL CIZEK/AFP VIA GETTY IMAGES



Confronting Bias in Journals

Medical journals have a blind spot when it comes to race.
But a blueprint for change is beginning to emerge.

BY LINDA KESLAR // ART BY STEPHEN DOYLE

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ast February, the *Journal of the American Medical Association* aired a podcast episode that would spark a heated conversation throughout the medical community. It featured two editors—both white male physicians—from its network of publi-

cations discussing the hot-button topic of structural racism. To promote the podcast, the journal posted the tweet: “No physician is racist, so how can there be structural racism in health care?”

The podcast was offered for continuing medical education credit, meaning that it was a nationally approved resource for physician learning. But neither physician is considered an expert on racism, and it didn’t take long for one of the men—host Edward Livingston, then deputy editor of *JAMA*—to voice skepticism about whether it was possible now for racism to be embedded in society. After all, he said, it has been illegal under civil rights legislation since the 1960s. “Structural racism is an unfortunate term ...” Livingston said in the podcast. “Personally, I think taking ‘racism’ out of the conversation would help. Many people like myself are offended by the implication that we are somehow racist ...”

Although Livingston’s guest, Mitchell Katz, president and CEO of the largest municipal health system in the United States and deputy editor of *JAMA Internal Medicine*, attempted to provide a more nuanced take, the podcast failed to address the considerable evidence that structural racism and health inequalities are indeed embedded in medicine. The podcast, unsurprisingly, was not received quietly.

“It was difficult for me to even get through it,” says Ron Wyatt, a Black physician who co-chairs the Institute for Healthcare Improvement’s equity advisory group. “It was a case study of bias and racism stereotypes in health care and a perfect example of the audacity of whiteness.”

Wyatt and many others view the *JAMA* podcast as symptomatic of a much wider problem: Medical journals, in their role as gatekeepers of scientific knowledge, are overdue for a reckoning. While Livingston may question the idea of structural racism, the evidence for it has been extensively documented through decades of research into racial bias in housing segregation, job discrimination, substandard public education, exposure to environmental hazards, psychological stress and inadequate health care. While journals might be expected to lead the charge rooting out this bias, mounting research shows how many of them may be party to it, ignoring, minimizing and

mismanaging issues of race, ethnicity, gender and other disparities.

“This isn’t just an example of one time when someone misspoke,” says Julie Silver, associate chair in the Department of Physical Medicine and Rehabilitation at Massachusetts General Hospital and a longtime advocate for addressing racial and other disparities in the medical workforce. “It’s the result of decades in which leading medical journals haven’t addressed equity on their editorial boards or published studies on racism or the social determinants of health.”

That lack of diversity, in turn, ultimately hurts patients, too. Journal editors influence what medical topics are priorities, and that helps shape the nature and direction of scientific research. Moreover, persistent systemic bias can lead to flaws in understanding about physiology and treatment.

For example, a 2013 study in the *American Medical Association Journal of Ethics* found that because of myths perpetuated in the scientific literature—in this case, that people of color have a higher tolerance for pain—Black and Hispanic people received inadequate pain management compared with white patients. A 2016 survey of white medical students and residents published in the *Proceedings of the National Academy of Sciences of the United States of America* showed that half endorsed at least one false belief about physiological differences between Black and white people, including that Black people’s nerve endings are less sensitive than whites’. Demonstrating the impact of such beliefs, a study published last July in *The New*

England Journal of Medicine that reviewed 2016 and 2017 Medicare claims data discovered that annual pain medication doses for Black patients were more than a third lower than prescriptions for white patients.

Now, finally, many top journals and less well-known publications are attempting to change, with broad efforts to investigate and address forms of bias. Yet even—and perhaps predictably—in the face of these initiatives, some voices are pushing back, arguing that the proposed remedies could undercut journals’ quality and scientific integrity. While the proponents for change see these objections as symbolic, rearguard actions, many worry that the pushback could have a more lasting effect, dampening the momentum for real change.



In an 1884 address to the American Association of Medical Editors, president Leartus Connor described medical journals as “the greatest factor of modern medical progress” and an ambitious convergence of “a medical school, a residency program, a clinical preceptor, a set of textbooks and a medical society unto itself ... the great unifier of the past and present, the diffuser of all new facts ...” Medical journals continue to be the primary conduit through which medical knowledge is created and, to some extent, how medical culture takes shape.

Historically, white men have held the majority of editorial positions at U.S. medical journals, and an audit in 2020 by Raymond Givens, a physician at Emory University Medical Center in Atlanta, found a continuation of the

status quo. At the time, only one of 51 editorial board members of *The New England Journal of Medicine* was Black, one was Hispanic and six were Asian. That same year in the *JAMA* Network of 12 journals, approximately 90% of top editorial positions were occupied by whites. Currently, only four of the *JAMA* Network journals are being led by women.

“That lack of diversity continues to contribute to inequities in how research is conducted and published today,” says Melissa Simon, vice chair for clinical research at the department of obstetrics and gynecology at Northwestern

University’s Feinberg School of Medicine and founding director of the Center for Health Equity Transformation. Journals are complicit in perpetuating inequalities, says Simon, who is Latina. “It’s deep and baked into the system,” she says. “And who gets to sit at the table and who has a voice at every step of the way is critical.” What top-tier journals decide to publish also influences whose careers move forward. “To be highly regarded in your field, you need to have publications in high-impact journals,” she says.

Increasing numbers of studies have documented how this lack of editorial diversity has undercut interest in research about minority groups and supported prevalent and persistent disparities in peer review and authorship. Consider that in more than 200,000 articles that the top four medical journals have published in the past 30 years, fewer than 1% even had the word “racism” anywhere in the text, according to a study published last April in *Health Affairs*. “Science begets science,” says Simon. “So when you

have science that filters out nondiverse eyes and opinions, you get science that benefits one group and can disadvantage another.”



Excluding marginalized voices is one issue. The other is what to do about problematic research and opinions that do make their way into the journals—something that is increasingly litigated on social media and other public forums. Recently, Twitter critics took aim at a paper published in *JAMA* in September 2020 that tied higher rates of COVID-19 infection in Blacks, compared with rates in white people, to differences in the expression of a gene in the nasal epithelium. None of the three authors of the *JAMA* paper were white. Yet many commenters criticized the paper as “racist medicine,” citing increased concerns in the research community about using social constructs of race as a proxy for genetic makeup. Others noted medicine’s long history of blaming the health woes of Black people on supposed genetic differences instead of larger,

structural factors. The clinical relevance of the gene’s expression is still unknown.

Another study that drew fire examined racial bias as a design flaw in pulse oximeters, oxygen sensors crucial in monitoring the status of COVID-19 patients. The devices were developed and tested largely on people with white skin, and the study’s authors later referenced three decades of evidence that pulse oximeters perform differently in patients with different skin tones. Here, the outrage was directed toward a subsequent letter published in *NEJM* that challenged the original study’s use of the phrase “racial bias.” “Medical devices such as pulse oximeters are blind to color and cannot exhibit such a bias,” the author of the *NEJM* letter wrote. Critics questioned why *NEJM* published the letter.

A March 2020 article in the *Journal of the American Heart Association* has been a particular focus of controversy. The paper criticized diversity initiatives in cardiology, arguing that data from the past 50 years show that affirmative action and other mandated diversity initiatives have failed to contribute significantly to rising numbers of Black and Hispanic clinicians or to improve patient outcomes. Its author, cardiologist Norman Wang at the University of Pittsburgh Medical Center, proposed that medicine adopt race-neutral policies in hiring. “Ultimately, all who aspire to a profession in medicine and cardiology must be assessed as individuals on the basis of their personal merits, not their racial and ethnic identities,” he wrote.

Critics on Twitter called the article “shocking.” But after the *JAHA* retracted Wang’s article and apologized, Wang asserted that he stood by his findings, and he has filed lawsuits against the University of Pittsburgh Medical Center and the American Heart Association, which owns the journal, alleging that he was demoted and defamed because his views were unpopular. Proponents have lined up on both sides of the debate.

Emory’s Givens questions the processes that were in place among *JAHA* reviewers. “Where was the voice in the room that said



WHILE JOURNALS MIGHT BE EXPECTED TO LEAD THE CHARGE ROOTING OUT THIS BIAS, MOUNTING RESEARCH SHOWS HOW MANY OF THEM MAY BE PARTY TO IT.

“this is going to cause a tremendous firestorm,” he asks. Givens believes the same could be said of the *JAMA* paper about gene expression in the epithelium, a view he expressed in a letter to that journal last fall. “These are elite journals and the journal editors are very bright people,” he says. “But when it comes to issues of race and science, something goes haywire and their ability for nuanced thinking is blunted.”



In recent years, medical journals have made efforts to improve inclusion and diversity, and the uproar about the *JAMA* podcast has brought renewed urgency to those efforts. “There’s simply no excuse at this point for inequities to exist on journal editorial boards for women or minorities,” says Julie Silver.

Many leading journals have published plans that prioritize equity across leadership, authorship and content, and in May, the AMA released a blueprint for dismantling structural racism within the organization and medicine

probing the issues of race and diversity. And late last year, Winfred Williams, associate chief of the MGH Division of Nephrology and founding director of the MGH Center for Diversity and Inclusion, became the journal’s first Black deputy editor.

Williams says that during his first year, he has reviewed manuscripts related to his clinical expertise in nephrology and other diseases but also a flood of submissions covering diversity in medicine. “Part of my role is to bring a new perspective on these issues,” Williams says. “Leading journals have long published studies that simply don’t include enough participants from racial and ethnic groups that are disproportionately affected by certain illnesses.”

A new *NEJM* protocol for submissions will require a table that breaks out whether the disease or condition being considered has a greater burden for specific groups, and the participation rates of those groups in the research. That information will then be posted with published articles. “We can take

dedicate financial resources to support new equity initiatives and staff development.

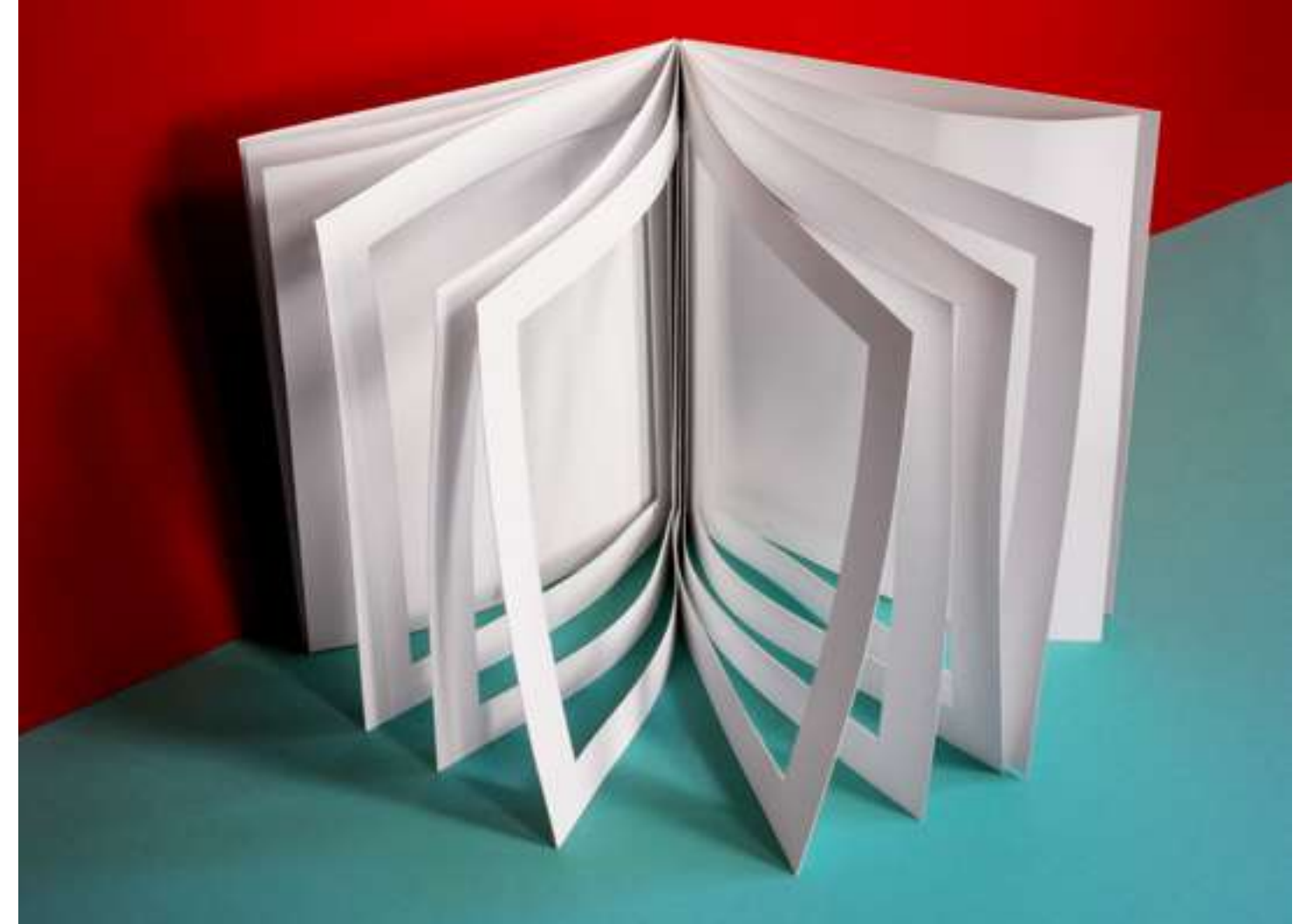
Better compensation for editors and reviewers could help, says Julie Silver at MGH. Most leading journals pay their top editors handsomely yet ask peer reviewers to serve gratis. “Inviting diverse people to work for free is ethically and financially problematic, particularly when there are few opportunities at the top for women and minority groups,” says Silver.

In a paper last year in *Health Affairs*, Rhea Boyd, a pediatrician and public health advocate who teaches about structural inequality and health, and her colleagues laid out other proposed remedies, including setting rigorous standards for publishing on racial health inequities—for example, by defining race in the experimental design of the study and specifying, within a sociopolitical rather than a biological framework, why race is being used. But she also proposes that journals make public the histories of article submissions—draft revisions, reviewer comments, rejections and where rejected articles ultimately get published—and use that information to help understand how the medical canon excludes certain types of studies and what can be done to address that.



Within a week of the February airing of the *JAMA* network podcast on racism in medicine, the American Medical Association issued a statement. The organization affirmed the existence of structural racism while saying that both the tweet and podcast were “inconsistent” with the AMA’s views and policies. It announced an independent investigation into the incident and the resignation of Edward Livingston, who hosted the podcast. Harold Bauchner, *JAMA*’s editor in chief, was put on administrative leave and resigned in June.

While perhaps justified, the staff changes seem like a small step on the long road to transforming the way race, gender and other biases are addressed. Bigger changes are needed. “The science is really just developing, and the stakes are high,” Wyatt says.




While there is broad agreement within the AMA on the need to address inequities in health care, many delegates felt the AMA’s strategic plan to address health inequities and embed racial justice should have been presented to the House of Delegates for debate. This year, a group of AMA delegates wrote to the association’s leaders in a letter that was leaked online. The letter called out portions of the AMA’s new plan for health equity as, at times, “divisive, accusatory and insulting” and asked how one could question the plan without being labeled racist. One complaint was that “white males are repeatedly characterized as repressive and to some degree responsible for the inequities.” Suggesting that firing the *JAMA* editors over the podcast was “perhaps precipitous, possibly a blot on free speech and also possibly an example of reverse discrimination,” the letter requested an independent group be charged with reviewing the podcast and preparing a report.

Although the dissenters’ letter didn’t dissuade AMA delegates from pushing ahead

with the new policies, it is an example of the kind of pushback being seen, particularly on social media, from those who have voiced worries that the growing focus on racism and other biases has the potential to constrain medical discovery if it suppresses work by those with other priorities.

But Samir S. Shah, a pediatric hospitalist at Cincinnati Children’s Hospital Medical Center and editor of the *Journal of Hospital Medicine*, continues to champion reform. A first and important step is to make sure that all voices are heard, Shah says. “Diversity isn’t the goal in and of itself, but for our journal, it’s one important step,” he says. “We were one of the first journals to develop a systematic process for gathering information from authors on race, ethnicity and gender”—information that the editorial team then used to compose lists of scholars from whom to solicit review articles and editorials and “determine whether there are biases.”

“In the end, discussions about diversity and structural racism are for the greater

good,” Shah says. “This is something we have to really lean into with intention. Change is never easy.” 

DOSSIER

“Medicine’s Privileged Gatekeepers: Producing Harmful Ignorance About Racism and Health,” by Nancy Krieger et al., *Health Affairs Blog*, April 2021. This in-depth analysis of the 50 highest-impact health journals documents a persistent absence of articles relating to race and health.

“Gender, Race, Ethnicity, and Sexual Orientation of Editors at Leading Medical and Scientific Journals: A Cross-Sectional Survey,” by James W. Salazar et al., *JAMA Internal Medicine*, June 2021. In the first study to assess the diversity of editors at 25 leading medical and scientific journals, researchers found that about 77% of the 368 editors identified as white (compared to 1.1% Black) and more than 88% identified as heterosexual.

THOSE WHO INVESTIGATE STRUCTURAL RACISM BELIEVE BIGGER CHANGES ARE NEEDED.

at large. Weeks later, a *JAMA* editorial detailed new strategies to address “inclusion and anti-racism in all journal-related activities.”

Other top-tier journals are taking similar steps. Since Eric Rubin became editor of *NEJM* in September 2019, the journal has added four editors and four editorial board members. Among this new group, four are people of color. In June 2020, the journal created a Race and Medicine page on its website, which has since published more than 100 articles

steps to ensure that research papers really reflect gender, race and ethnicity appropriately in the study’s sample,” Williams says.



The IHI’s Ron Wyatt considers such changes to be largely positive, but he also notes that past flurries of self-scrutiny and promises to improve were quickly replaced by business as usual. “I’m optimistic, but with a lot of caution,” he says, noting that journals need to



A Time for Protons

Proton therapy has been a cutting-edge cancer therapy for decades. Can researchers at last zero in on its best applications?

Peter Vieira was 39 when he was diagnosed with a malignant brain tumor, a stage 2 astrocytoma the size of a golf ball lodged in the temporal lobe of his brain. Although the cancer was growing slowly, its location meant treatment would be perilous. The first step was to excise the tumor, but because it was in the brain, Vieira's surgeons couldn't remove an additional swath of healthy tissue to make sure they had all of the cancer cells. Radiation therapy could kill the straggler cells, but with conventional photon radiotherapy, which uses high-powered x-rays, some radiation would pass through the cancer, bringing not only an immediate risk of damage to the brain or pituitary gland but also elevating the risk of other cancers years later.

Vieira's doctors suggested an alternative. They invited him to join a clinical trial assessing proton therapy, a different kind of radiation treatment. That technology, in use for decades, relies on proton particles split from hydrogen atoms and then

spun around an accelerator called a cyclotron, extracted and guided by magnetic fields to the tumor. A key advantage is that the energy of the protons can be precisely calibrated, which means that technicians can control how far they penetrate into the body. Proton therapy can hit a tumor with a heavy dose of DNA-altering radiation that is released there, like a tiny precision strike, going no farther. Vieira agreed to try it.

For many cancers, this more targeted approach to treatment should be ideal. "A technique that can achieve a higher dose of radiation to the tumor while delivering equal or less radiation to normal tissues—that is by definition a superior treatment," says Helen Shih, medical director of the Massachusetts General Hospital Proton Therapy Centers, where Vieira was treated. And since the tool's origins at the dawn of the Atomic Age, increasingly sophisticated forms of proton therapy have been developed and deployed to treat an ever wider range of

BY MONIQUE BROUILLETTE // ILLUSTRATIONS BY EDWARD CARVALHO-MONAGHAN

malignancies. It is now routinely recommended for most pediatric cancers and adult head and neck cancers—applications that speak to its specific advantage, namely a precision that can help avoid debilitating side effects and reduce the risk of later cancers. That precision also makes it a sought-after tool for prostate cancer, where incontinence and impotence are often a risk, and others have looked at its usefulness in breast and lung cancer treatment.

To meet increasing demand, hospital centers that offer the proton therapy have sprung up around the world. As of last October, they numbered 40 facilities in the United States and more than 100 globally. MGH, a pioneer in proton therapy and the first to have a treatment center, opened a second center in 2020, and other big names in cancer treatment—Memorial Sloan Kettering, MD Anderson, Johns Hopkins, Mayo Clinic—now also offer it. Japan has 24 centers and a handful of others exist in Germany and the United Kingdom, while Denmark and Norway have recently joined the movement.

PROTONS COULD BE GUIDED TO HIT A TUMOR AND NOTHING ELSE.

The future of proton therapy, however, depends heavily on the technology finding its therapeutic groove. The centers are very expensive to build and operate—the cost of treatment is often several times that of conventional radiotherapy, and insurance companies have long been reluctant to reimburse patients, denying as many as two-thirds of requests for coverage. In a 2016 editorial, Anthony Zietman, currently the interim chief of radiation oncology at MGH, lamented that proton therapy was still trying to shake off a reputation for being “exotic, expensive and irrelevant.” The field has made advances since then, but still

lacks key clinical trial data to support many of its applications.

Major efforts now in progress, however, appear to be on the cusp of changing that. Trials like one that helped Vieira with his brain tumor aim to determine how, and how extensively, proton therapy works, and that data will be the key to determining its place in cancer treatment in the coming decade.



Proton therapy can trace its origin to 1930 and the invention of the cyclotron. That massive machine, created by Ernest Lawrence at the University of California, Berkeley, was designed to break apart the nucleus of hydrogen atoms into their subatomic parts—positively charged protons and uncharged neutrons—and then accelerate them around a track using an electromagnetic field. Its original purpose was to probe the secrets of matter. But in 1943, a cyclotron at Harvard University was sold to the U.S. government for \$1, dismantled and sent to Los Alamos, New Mexico. There it was used

in the Manhattan Project, the secret effort to create an atomic bomb.

As part of that agreement, the government promised either to return the cyclotron when it was no longer needed or to pay for the construction of a new one. And after the war, physicist Robert R. Wilson, a veteran of the Manhattan Project, came up with an idea that would put that new Harvard cyclotron to peaceful use. Eager to atone for his involvement in building the bomb, Wilson, then an associate professor of physics at Harvard, published an article, “Radiological Use of Fast Protons,” in the November 1946 issue of *Radiology*. Wilson suggested that the properties of protons “make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose.”

In the article, Wilson pointed out the unusual behavior of protons. The particles tend to travel through materials in a straight line until they come to a stop and release all of their energy. That large jolt is called “the Bragg peak,” and Wilson surmised that it could be a boon to cancer therapy. Unlike high-powered X-rays, which have a tendency to scatter and irradiate adjacent tissue, protons could be guided to deliver DNA-altering radiation to a tumor and hit nothing else.

The cyclotrons in existence at the time, Wilson noted, weren’t powerful enough to create a beam of protons that could reach a human tumor. But newer machines, then planned or under construction, would have a far greater range. “It is clear,” he wrote, “that such protons can penetrate to any part of the body.”

After Wilson’s article was published, physicists and physicians began to explore how this new kind of treatment, which seemed at least theoretically feasible, might be developed. The first patients to receive proton therapy were treated at the Berkeley Radiation Laboratory in Berkeley, California, in 1954, and in 1957, at a facility in Uppsala, Sweden.

But most of proton therapy’s early history involved close collaborations between the Harvard Cyclotron Laboratory (HCL) in



Cambridge and physicians at MGH. In 1971, Herman Suit, head of radiation oncology at the hospital, recruited a British physicist, Michael Goitein, who threw himself into nascent efforts to explore the possibilities. In spring 1972, Goitein organized a one-day symposium that brought together MGH physicians and nuclear physicists from Harvard, MIT and the Princeton Particle Accelerator Laboratory. Out of that forum came not only a consensus that proton technology had therapeutic possibilitie, but also a plan to explore them on-site.

By 1973, the project was ready for its first patient, a four-year-old boy with a pelvic tumor. Because the HCL facility lacked a gantry—the movable arm that in modern systems can pivot around a patient—patients had to be positioned in whatever way made their tumor most accessible to the giant machinery. Some sat or stood, and they had to remain as still as possible so that the proton beams could reach their target.

In those early days, physicists, doctors and patients had to share space with graduate students from the physics department who took over the HCL in the afternoon. Then, as now, extensive imaging had to precede each treatment, to determine the exact size and location of the tumor and create a plan for positioning the proton beam. That preparation was done at MGH, with patients then ferried, often by taxi, on the 20-minute ride to the lab in Cambridge.

Ultimately, some 4,500 MGH patients were treated at the HCL. By the early 1980s, however, two things were clear: Proton therapy could be an extremely effective way to treat many cancers, and the hospital needed a proton therapy treatment center on its own campus. After a decade of planning and fundraising, construction began on a cyclotron, two gantries and three treatment bays. Finally, in 2001, MGH opened the Francis H. Burr Proton Therapy Center, the first hospital facility created to provide proton therapy.

Costs Less, Hits the Spot

The next generation of proton therapy will bring down high startup costs and boost both accuracy and effectiveness.

TAILORING TO FIT

New research is looking at biological differences among patients and organ systems to determine which might benefit the most from proton therapy. Such a handbook would help to minimize the most dangerous damage to nearby tissue.

REAL-TIME IMAGING

Today, proton therapy must be preceded by advanced, precise imaging to guide the procedure. But what if imaging and therapy could happen simultaneously? MRI-guided therapy systems being developed would allow the proton beam to strike even moving cells and tissues in the lung and gut.

MOVING PATIENTS

To ensure accurate tumor targeting, patients are typically immobilized on a table while a large metal gantry, weighing 100 tons or more, pivots to deliver the proton beam. But patients could instead be moved around the beam, an approach that could be accomplished using a robot with real-time positioning feedback.

WORKING SMALLER

Reducing the size of proton systems—which can be the size of a football field—would allow them to be retrofitted into existing buildings, reducing construction costs. On average, one-room systems cost about between \$20 and \$40 million to build, compared with up to \$225 million for multiroom systems.

Today, treating one person's cancer with proton therapy may cost from \$30,000 to \$120,000, compared with just \$8,000 to \$15,000 for a course of conventional radiation therapy. That much higher price tag, one of the main concerns for the future of proton therapy, factors in the much higher cost of building and maintaining these facilities, the complicated engineering that goes into running the equipment and the expertise needed to tailor treatments.

In many cases, however, the side effects of the alternative—conventional radiation therapy—can also be expensive, both in human suffering and medical costs. MGH's Helen Shih notes that in head and neck cancers, for example, patients who undergo traditional radiation therapy may suffer a range of ills: permanent dry mouth that prevents swallowing and causes choking, dental and spinal deformities, damage to the thyroid gland, chronic pain and cognitive dysfunc-

Harald Paganetti, director of physics research in the Department of Radiation Oncology at MGH, notes that proton therapy should be a better choice in most cases when judging by the dose distribution alone. "If you simply look at it from a physics perspective, protons and photons give the same amount of radiation to the tumor, but the dose that goes to the surrounding tissues with proton therapy is much smaller, on the order of two to five." That underscores why proton therapy is so beneficial for children, whose young tissues are more susceptible to the harmful effects of radiation. Evidence shows that children who receive proton therapy have a much lower incidence of cognitive decline, for example, than those who got conventional therapy. "There is clearly an advantage for pediatric cases," he says. "But for others, the benefits are less clear."

Evidence of the comparative merits of the two kinds of radiation is only now begin-

wonders whether the choice of radiation-induced lung injury as a primary endpoint might have limited the 2018 study's ability to detect a potential benefit for proton therapy in reducing overall side effects. "I suspect that if the study had used the overall rate of severe toxicity—which includes a wide range of side effects—as its endpoint, it may have reported more of a benefit for proton therapy," Baumann says.

In 2019, Baumann was the lead investigator for the first large-scale review comparing proton beam therapy and conventional therapy across multiple cancer types for patients treated with concurrent radiation and chemotherapy. The study, published in *JAMA Oncology*, analyzed data from about 1,500 adult patients with 11 kinds of cancer. Patients receiving conventional treatment were more than twice as likely to experience a severe toxicity that leads to hospitalization or an emergency room visit, they found. In addition, the patients' abilities to perform routine activities were half as likely to decline for the proton therapy group. The study did not include prostate cancer patients or breast cancer patients who were rarely treated with concurrent chemotherapy and radiation.

And in 2020, a study published in the *Journal of Clinical Oncology* showed positive results for esophageal cancer patients. Patients were randomized to traditional or proton radiotherapy, and those who received proton therapy had significantly fewer adverse events and an improved survival rate. According to an accompanying editorial, this was the first clear victory for proton therapy in a head-to-head contest with conventional radiation.

Further evidence should come in the next few years from several large randomized clinical trials. The biggest of those is the COMPARRE (COMparative Study of Outcomes with Proton and Photon Radiation in Prostate CancER), begun in 2018 and led by researchers at the University of Florida, which plans to recruit 1,500 patients for each arm of the study. And the RADCOMP trial, launched

THIS WAS THE FIRST CLEAR VICTORY FOR PROTON THERAPY IN A HEAD-TO-HEAD CONTEST.

tion. Symptoms can be so severe that they result in the need for a feeding tube.

For head and neck cancers, insurance companies do often approve proton therapy. But for many other conditions—especially those such as breast and prostate cancers that affect large numbers of patients—they have shown reluctance. Their decisions are buoyed by a 2014 report for the Institute for Clinical and Economic Review, a Boston nonprofit that evaluates the cost-effectiveness of medical care, which stated that the cost of proton therapy was justified for only a few select types of cancer, including pediatric and brain and spinal tumors.

ning to be amassed, and it promises to show just where proton therapy can do the greatest good—and where it might not be needed. The first randomized trial to evaluate proton therapy in lung cancer, for example, was published in the *Journal of Clinical Oncology* in January 2018. Proton beam therapy and traditional radiotherapy, it showed, were equally effective in treating the tumor and showed no difference in a common side effect that results in severe inflammation in the lung that sometimes requires hospitalization.

Brian Baumann, a radiation oncologist at Washington University School of Medicine in St. Louis and the University of Pennsylvania,



in 2015 and led by researchers at MGH, the University of Pennsylvania and Memorial Sloan Kettering Cancer Center, is recruiting patients to see whether proton therapy can reduce cardiovascular events—heart attacks, arrhythmias and valve disorders—related to radiation treatment in breast cancer patients. According to Shannon MacDonald, an MGH oncologist and lead investigator of the trial, the proliferation of proton therapy centers will make it easier to recruit patients and collect needed data.

MGH's Anthony Zietman agrees. "We've reached a critical mass with the number of proton centers in America," he says. "Now we can actually do multicenter trials and get them done quite quickly to answer questions about where the benefit lies and where it doesn't."

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Even as research ramps up, the technology of proton therapy is changing rapidly, as engineers explore ways to bring down the cost and make the systems easier to install. When the first MGH proton center was built 20 years

ago, the massive component parts came first, and an entirely new building had to be designed to fit around them. New, smaller cyclotrons may be able to fit in existing spaces.

Other advances are improving accuracy. Pencil beam scanning, for example, introduced during the past decade, allows the proton beam to penetrate the tumor more precisely, layer by layer. Increasingly, real-time imaging systems are built in, so that protons can be more accurately applied even to moving tumors, such as those in the lungs. "That lets us control the beam to improve accuracy even more," says Aswin Hoffmann, a medical physicist at OncoRay in Dresden, Germany.

These efforts to reduce costs and increase performance, alongside results from the major trials now underway, could go a long way toward answering lingering questions. "At the end of the day, if protons could be as affordable as any other kind of radiation, and as easy to deliver, there would be no discussion," says Helen Shih. "We would all be using protons."

"The two sides of the equation are research and cost," adds Zietman. "On one side, you

can target the patients who benefit most from this treatment, while on the other side, you work to decrease the costs. And that way you increase value all around." 

DOSSIER

"Three Ways to Make Proton Beam Therapy More Affordable," by Thomas Bortfeld and Jay Loeffler, *Nature*, September 2017. The paper explores advancements in engineering, physics and health care policy that could bring down the cost of proton beam therapy. They include shrinking the size of accelerators, making the tool more accurate and broadening coverage.

"Can Proton Therapy Be Considered a Standard of Care in Oncology? Lessons from the United States," by Anthony Zietman, *British Journal of Cancer*, March 2020. This brief summary of the evolution of proton beam therapy looks at present and future challenges, as well as the role that the United Kingdom might play in conducting research.



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LARGE TRIALS DELIVER RESULTS BASED ON AVERAGES, NOT INDIVIDUALS. THE N-OF-1 MODEL IS A PLUCKY—BUT LABOR-INTENSIVE—WAY TO RIGHT THE SYSTEM.

Frustrated by his experiences with statins, “Noah” let his doctor enroll him in a clinical trial. He knew that he needed to lower his cholesterol, but all three drugs he had tried seemed to cause debilitating muscle pain—a common reaction to statins that has puzzled many physicians because the original studies testing the drugs for safety and efficacy showed that such outcomes should be rare.

The trial Noah’s physician proposed was unusual. The gold standard for knowledge in medicine has been, for many decades, the randomized control trial (RCT), which typically involves a large number of subjects randomized into either experimental or control arms, with the results assessed to see which alternative offers the better benefit. If a large number of patients do well with the new treatment, it’s considered a success. If only a few patients benefit, the control is considered the better course. But the

trial that Noah would undergo had only one patient—Noah himself—and success would be gauged on his reaction alone.

For the next year, Noah would act as both the control and the experimental arms of his own study. He would take a statin for four months out of the year (not necessarily consecutive), four months of a placebo and four months of no medication. Each day he would record any side effects. While he did this, 48 other patients were enrolled in similar, stand-alone studies. The findings of each trial would be personal. For instance, two participants found that during their months on statins they experienced disabling side effects, which went away when they took the placebo or no medication. “There was nothing in these patients’ histories to indicate they would have trouble taking a statin,” says James Howard, a cardiologist at Imperial College London and the trial’s investigator.

BY ANITA SLOMSKI // ILLUSTRATIONS BY ANDREA UCINI

But for Noah, something more surprising happened. “He nearly left the trial after the first few months because he felt so dreadful,” says Howard. “But that was when he was on placebo. The fourth month, when he was actually on the statin, he felt fine.” Reviewing the final data, Noah was “gobsmacked” that his response to statins appeared to be more psychological than physical. The evidence argued that pain stemmed from the “nocebo effect”—because he expected to feel terrible taking statins, he did. It convinced him to go back on the medication, and in the four years since, his muscle pain hasn’t returned.

Noah’s trial had an N of 1—in clinical research, N denotes a study’s number of subjects—and now the N-of-1 model for this kind of personalized scrutiny is experiencing something of a renaissance. At first glance, an N-of-1 trial resembles any medical encounter in which a patient visits a physician to find treatment that works. But the average patient journey falls far short of the rigor of clinical research. “Physicians do a considerable amount of trial-and-error prescribing, which can be very flawed,” says Heather Kaplan, associate professor of pediatrics at Cincinnati Children’s Hospital Medical Center. “We start patients on a new drug and ask how they feel. If they say OK, they may stay on the drug for years, even though the improvement they describe may not actually be directly related to the new drug.”

The N-of-1 trial, in contrast, offers a framework for gathering information “systematically and rigorously,” Kaplan says. She is conducting N-of-1 trials on children with inflammatory bowel disease, with the goal of discovering, with confidence, which participants can control the disease through diet. For kids who respond to a dietary intervention, the trial investigates what specific diet works best.

Although huge RCTs can predict treatments that benefit the average patient, “I’ve never met an average patient,” says neurologist Steven Arnold, managing director of the Interdisciplinary Brain Center at



Massachusetts General Hospital. The success of any treatment is influenced by genetics, the patient’s progression in a disease, other illnesses the patient may have, and environmental and lifestyle factors such as levels of exercise and stress. Typical parallel-group RCT trial results may not account for these, Arnold says, and it falls to the physician to map the best treatment in a personalized way.

The N of 1 is a tall order, however, and such trials have historically required more effort than most physicians can give. That may be changing, however, says Ian Kronish,

associate professor of medicine and co-director of the Hypertension Center at Columbia University Irving Medical Center. Digital medical devices and smartphones can now seamlessly track and transmit data, enabling doctors and patients to create N-of-1 trials to shape joint decisions, and genetic analysis of individual patients has become more accessible. For conditions that are hard to measure objectively, such as cognitive decline, N-of-1 trials may offer new pathways to improvement. And for patients who fall outside the treatment norm, these studies are a way to

find the most effective treatment. Patients may serve not only as guinea pigs but as research architects and investigators.

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The legacy of N-of-1 trials in mainstream medicine dates to the 1980s and the work of physician Gordon Guyatt. In a 1986 article in *The New England Journal of Medicine*, in which the term “N of 1” first appears, Guyatt and his colleagues at McMaster University in Ontario, Canada, note the physician’s “paradox” of having to use large RCTs to guide individual treatment when, in those trials, “experimental therapy almost never benefits every patient randomly assigned to it, and it usually harms at least some ... [and] even when a relevant randomized trial has generated a negative result, at least some patients will appear to have benefited.”

The paper described a trial designed to test drugs on a single patient, a 65-year-old with uncontrolled asthma. “We found out the therapy we were giving the patient was killing him,” recalls Guyatt, now distinguished professor of health research methods, evidence and impact at McMaster. The N-of-1 trial tested the patient’s response to two of his four asthma medications. For each drug, the patient alternated the medication and a placebo—neither he nor Guyatt knew which was which—while the patient kept a careful log of his symptoms and ability to breathe.

This N-of-1 trial involved multiple rounds of treatment—a typical strategy today, in which a patient may cycle between treatment and placebo three or four times—and the random, blinded order of the intervention improved the odds that the patient’s response wouldn’t be influenced by a placebo or nocebo effect. Before the trial, Guyatt and the patient both suspected that one of the drugs was the source of the disabling side effects. Yet it turned out that the other—theophylline, which causes extreme reactions in some people and is no longer as widely used—was the culprit. “Once we stopped theophylline, the patient was 100 times better,” says Guyatt.

Guyatt conducted 57 N-of-1 trials during the next few years for McMaster physicians and their patients. The trials produced definitive answers to a clinical or statistical question in 50 cases, and 26 doctors changed their treatment recommendations based on the results. The process was time-consuming and cumbersome, however, and referrals eventually dried up. But word spread, and Eric Larson, now senior investigator at Kaiser Permanente Washington Health Research Institute, created his own N-of-1 service at the University of Washington in 1993, inspired by one of Guyatt’s talks. Larson’s group completed 34 trials before his effort also ended, in this case through lack of funding.

Those issues—too little interest among physicians and not enough financial support—led to a long dry spell for this kind of research. “What Guyatt and Larson attempted to do with N-of-1 trials went against an ingrained mindset that large randomized controlled trials were the only way to evaluate a drug or therapy for safety and efficacy,” says Nicholas Schork, deputy director and distinguished professor of quan-

For the latest generation of N-of-1 champions, one of the model’s most compelling uses is to sort out therapy for medical disorders that are highly variable from one patient to another. Obesity, pain, asthma and other conditions can be difficult to treat because patients tend to have idiosyncratic responses to therapies.

Taking on the problem of lower back pain, a recent series of 60 N-of-1 trials compared Swedish massage to yoga and found that the subjects, indeed, differed widely in their responses. “For some, massage dramatically reduced pain and the number of medications they required,” says Karina Davidson, senior vice president of research and director of the Center for Personalized Health at Northwell Health in New York, who conducted the study. “Other patients responded only to yoga, others felt better on both interventions and some responded to neither.” Because the N-of-1 trials tested every patient on each therapy, the patients and their doctors were able to use the resulting data to see whether, and to what degree, these treatments could reduce the need for pain medication.

ONE COMPELLING USE IS FOR MEDICAL DISORDERS THAT ARE HIGHLY VARIABLE.

titative medicine at the Translational Genomics Research Institute in Phoenix. “There wasn’t much desire to detect individual variability in the response to a drug.”

Those problems were exacerbated by a lack of sophistication in data collection and analysis. That’s different today, says Schork. “In an era where there is now tremendous interest in individual variation as well as better biomarkers and wireless devices for continuous monitoring, N-of-1 trials just make a lot of sense,” he says.

Medically complex patients—often excluded from conventional trials, which try to minimize variables in test subjects—are another example of the variability that makes a good candidate for an N-of-1 study. Alzheimer’s disease, for instance, afflicts older people who are more likely to have multiple additional conditions, one reason that parallel-group RCTs for the disease are hard to implement. “Alzheimer’s is very complex, with symptoms and progression of the disease varying considerably depending

on how much amyloid and tau is in the brain, whether vascular or inflammatory factors are driving the disease and so on,” says Arnold. To control for all of that, a conventional RCT would need 2,000 people per arm, he adds.

But N-of-1 trials embrace such variability. Arnold is conducting a pilot study on patients with mild cognitive impairment to determine who might benefit from Ritalin to improve memory and decision-making. The trial is divided into four-week treatment blocks during which each patient takes a placebo or Ritalin for two weeks at a time. Then the blocks are repeated two additional times while patients play daily computer brain games, and periodically take memory and thinking tests. At the end, Arnold will analyze each person’s performance to see who might benefit from the drug.

Such N-of-1 trials might move the needle in finding good, useful treatments for neurodegenerative conditions. With mild

In all of these cases, the N-of-1 approach can lead to better, individualized treatment recommendations, in part because the trials involve the patient in the process. As with the statin study at Imperial College London, looking at the data can sometimes provide powerful feedback to the patient that leads, in turn, to more satisfaction and better adherence.

The University of Queensland in Australia has embraced N-of-1 trials for a number of conditions, including insomnia, menopausal symptoms, traumatic brain injury, Parkinson’s disease and palliative care. In a series of N-of-1 trials involving 71 patients with chronic pain or osteoarthritis pain, 65% adjusted their pain medications after participating in the trials. One year after enrolling in other personalized trials, seven of 10 participants with attention deficit hyperactivity disorder and 45% of patients with chronic neuropathic pain stayed on the therapies that proved to work best for them during their trials.

the treatment they were scheduled to have and reminded them to fill out daily questionnaires about pain levels and side effects.

The patients in the N-of-1 study arm had similar pain scores and patterns of opioid use as patients in the control group, but N-of-1 participants reduced their use of NSAIDs and were more likely to experience a clinically meaningful improvement in pain-related functioning six months out and reported better shared decision-making with their doctors about pain medication. Of the N-of-1 participants who filled out questionnaires after the trial, four in 10 said that data from the trial had given them insight into managing their pain and that they would consider changing their pain medications as a result.

The failure to cut opioid use shouldn’t be laid at the feet of the N-of-1 trial, says Richard Kravitz, the trial’s principal investigator and distinguished professor of internal medicine at the University of California, Davis. Patients saw the evidence that other, less dangerous treatments were just as effective as opioids. But the pull of habit may have been more powerful than convincing data. On the other measures, however, “I think we had clinically important results,” he says.



The N-of-1 model unquestionably requires more effort and more resources than other ways to determine the best treatment for a particular patient, and if the responsibility falls to overstretched primary care physicians, the approach is unlikely to take off. Moreover, the N-of-1 model has its detractors, including pioneer Gordon Guyatt. “Intuitively, N-of-1 trials should be great,” he says. “But if you randomize 50 people to N of 1 and 50 to usual care, there isn’t much of a difference in outcomes.”

For now, Kravitz sees a limited scope for N-of-1 trials. “I think they’ll have niche applications—for statin withdrawal, for example, and perhaps when a patient and doctors are trying to decide between a cheap drug that’s pretty good and an expensive one that looks

SUCH TRIALS MIGHT MOVE THE NEEDLE ON TREATING NEURODEGENERATIVE DISEASES.

cognitive impairment and Alzheimer’s, for instance, behaviors affected by the disease can be hard to standardize across hundreds of patients. But one patient might be measured on her bridge playing ability, while another could be tested on his reaction times in a driving and navigation game. Similarly, neuropsychiatric dimensions of advanced disease, such as agitation, depression or anxiety, can manifest in very personal ways that thwart larger treatment studies. But personalizing the measure—putting a sensor on a suitcase that a patient pulls out of the closet when she feels stressed—can generate relevant data about whether a certain treatment is working.

One of the most ambitious N-of-1 studies in the United States was designed to help patients with chronic musculoskeletal pain reduce their use of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), both of which have adverse effects and limited long-term effectiveness. The study randomly assigned 215 people to usual care (continuing pain treatments recommended by their physicians) or to an N-of-1 approach. For N of 1, each person chose two pain treatment regimens from among eight categories that included both drugs and alternative medicine therapies such as massage and exercise. Once those were locked in, a phone app randomized the treatment sequences, notified patients of



marginally better in large randomized studies. If an N-of-1 trial finds that the two drugs are comparable for that person, the patient could opt for the cheap drug and save money.”

But other N-of-1 research now being done by MGH’s Steven Arnold, Columbia’s Ian Kronish and many others suggests that the impact of individualized trials is only beginning to be explored. For conditions that are notoriously difficult to treat effectively, such as irritable bowel syndrome and dementia,

there are broad possibilities for using N of 1 to sort through patients’ individual responses to therapies. “The beauty of an N-of-1 trial is that I can confidently tell a patient whether or not a drug is good for them,” says Arnold. “This approach also eliminates a lot of bias, not only the placebo effect that a patient may experience, but also wishful thinking by a doctor who just wants a patient to get better.”

Karina Davidson at Northwell Health, meanwhile, is creating N-of-1 “kits” that

give Northwell physicians and their patients everything they need to systematically test patients’ responses to a series of antihypertensive medications. A second kit, for stress reduction, will be marketed directly to consumers.

And physician Alexander K. Smith, writing in *JAMA Internal Medicine*, described his experience with an informal N-of-1 trial he designed for himself. After Smith was diagnosed with eosinophilic esophagitis, a chronic immune disease that damages the esophagus and can cause food to get stuck, his gastroenterologist prescribed a “cruel” elimination diet to find the foods that made his condition worse. Conducting his own N-of-1 study, Smith quickly discovered that dairy products were the offending foods. That spared him having to avoid wheat, soy, eggs, seafood and nuts for months, as his doctor had suggested. Rather than abandon N-of-1 trials, Smith urges researchers and clinicians to find their best applications. “Think creatively [to find ways that] N-of-1 trials might simplify treatment regimens, improve patient compliance and reduce health care costs,” he says.

DOSSIER

“N-of-1 Trials in Healthcare,” *Healthcare*, March 2021. This special issue includes 13 articles on N-of-1 trials, highlighting pilot studies that focus on a range of diseases and exploring the barriers and opportunities. The editors emphasize the importance of such trials in a time of movement toward personalized medicine and patient-centered health care.

“Experimental Designs to Optimize Treatments for Individuals: Personalized N-of-1 Trials,” by Karina Davidson et al., *JAMA Pediatrics*, February 2021. The article explores the advantages of personalized trials for children and discusses methodologies through which N-of-1 trials could determine optimal treatment of attention deficit hyperactivity disorder.

FIRST PERSON

Reunion

Dad—thinning waves of white hair mostly covering the scar on the back of his head—fondles a goblet of Barolo and swallows the last of it. A shot glass full of grappa waits on the table. I catch the gaze of my wife and our two teenagers. My mother looks for something in her lap.

Where, I wondered, was the man from nine months earlier—weak, grimacing, shaky. The man who confided: “I want you to know how ashamed I feel,” and who, for the first time, referred to himself as a “high-functioning alcoholic.” As sick and broken as that guy was, I wanted him back.

We bid my parents goodbye last summer, hoping they would have a smooth move from their home in the Northeast to a gated community in Florida. That state was facing the peak of its COVID crisis. “Be careful,” I’d say, in call after call. And yet, somehow, they were always in a store, at the bank, in a restaurant; a parade of electricians, painters and landscapers marched through their house. Over FaceTime, I could see masks hanging from their chins.


My father, characteristically, resisted his retirement and fixated instead on a task—completing what amounted to the final brief of his legal career. But the stress, compounded by the move, computer problems and a new difficulty maintaining focus, sent him into a tailspin. A lifelong drinker, he was now finishing a fifth of vodka every other day. When Mom started complaining about him being “out of it,” I chalked it up to the usual.

The first time he went to the ER was to stitch up a large, unexplained cut on the back of his head. Two weeks later he was back, after he fell on his way to bathroom, soaked himself in urine and couldn’t get up. He was in intensive care for a week. Scans and blood tests showed one underlying cause for his falls—alcoholic liver disease and a form of muscle wasting called alcoholic myopathy.

But the reason for his rapid cognitive decline remained unclear. I located a neurologist affiliated with a top-rated national clinic, hoping the doctor could tease out the threads of alcoholism, depression and family history of dementia to deliver an explanation—and with it, some indication of what lay ahead.

As for so many people of my age, it fell to me to steer my parent’s illness—research his providers, schedule appointments, coordinate care with doctors, physical therapists and the insurance company. I was disappointed, but sadly not shocked, to find that no one wants to talk about substance use disorder in older adults. Nearly one in five people over age 60 has a problem with controlled substances. “ETOH,” the diagnostic shorthand for ethyl alcohol, was all over my father’s medical records. Where were the referrals to counseling? The neurologist ordered a cognitive assessment and multiple screenings for mercury. But they never asked if my father knew where to find an AA meeting.

It took my going to Florida to get him into support groups. He got an AA sponsor. And even though the cognitive tests had shown significant and likely permanent impairment, even though he refused to take dementia medications he’d been prescribed, he started getting not only stronger, but mentally sharper, too. He remembered things. Over my objections, he was cleared to drive again.

And here he was, back to visit for my daughter’s graduation—mentally “together,” more or less. And drinking. Gently, I bring up the dark days of last year. I mention a study on COVID in older adults who had no traditional symptoms—cough, shortness of breath—but who did report confusion and forgetfulness, along with weakness and falls. “Maybe,” I say, “that helps explain why you were so out of it.” He looks at me, confused: “What?! I was out of it? When?” We remind him of the lost months. “Well,” he says, with a shrug, “I was probably drunk!” He laughs. No one laughs with him. 



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