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Fortifying Our Defenses

EARLY STUDIES SHOW THAT TO FIGHT NEW VARIANTS LIKE OMICRON BOOSTERS ARE NECESSARY

Plus:

IS "BAD" CHOLESTEROL ALL THAT BAD?

THE PANDEMIC'S EFFECT ON CANCER

THESE GUT BACTERIA ARE ASSOCIATED WITH AGING

WITH COVERAGE FROM nature

Liz Tormes

Our Best Bets against COVID

Vaccines remain the strongest protection against severe illness and death from COVID, even as the Omicron variant runs like wildfire through the U.S. population. In fact, as Ewen Callaway reports, a booster shot of the Pfizer vaccine is holding strong against serious cases of the disease according to early reports (see "Omicron Is Likely to Weaken COVID Vaccine Protection–but Boosters Could Restore It"). Vaccines are also the best bet for protecting children and help to reduce transmission (see "The Benefits of Vaccinating Kids against COVID Far Outweigh the Risks of Myocarditis"). The take-home message is that the vaccines work and that as many of us who can get them should.

Also in this issue, reporter Natalie Healey takes a close look at one of the long-held beliefs about hearth health (see "Is There More to a Healthy-Heart Diet Than Cholesterol?"). And a growing list of successful treatments is coming out of gene therapy, as journalist Jim Daley writes (see "Four Success Stories in Gene Therapy"). As always, here's to your health.

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Health & Medicine

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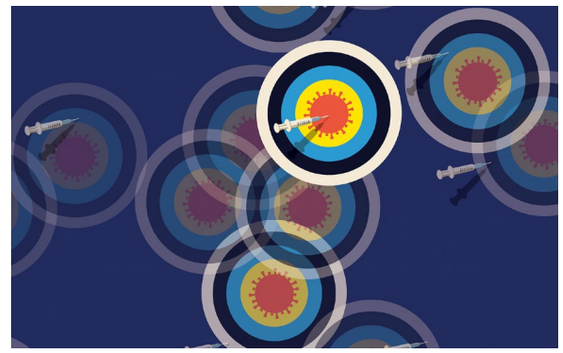

Chris Gash

On the Cover

Early studies show that to fight new variants like Omicron boosters are necessary

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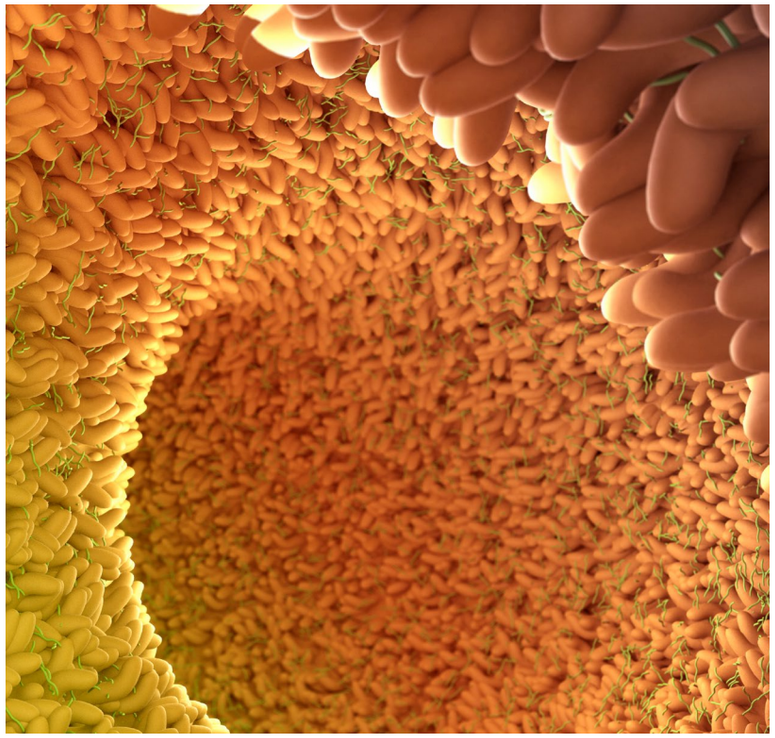

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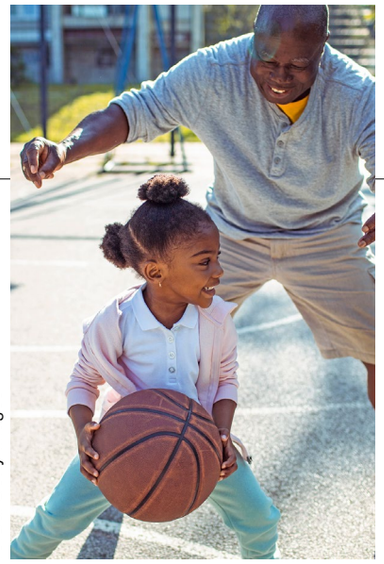

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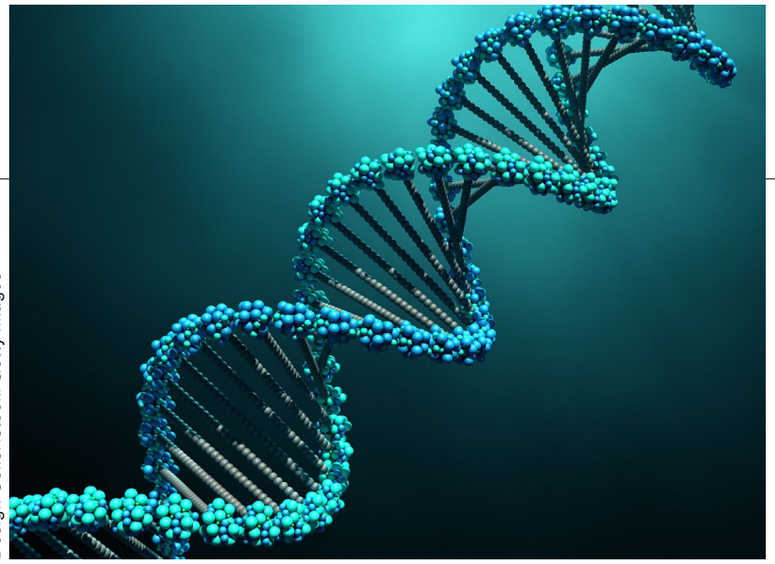

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NEWS

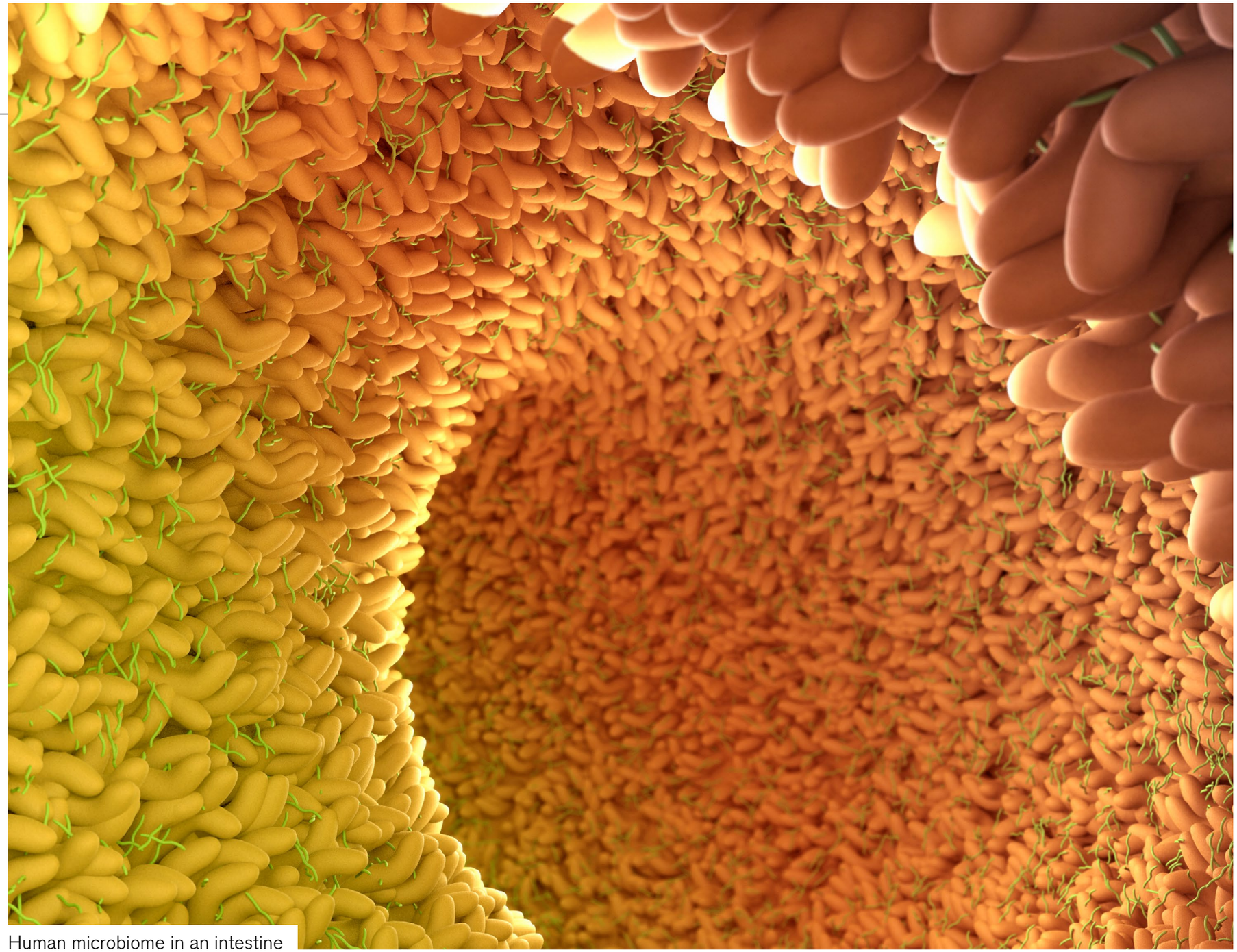
FEATURES

OPINION

Gut Bacteria Change as You Get Older—and May Accelerate Aging

Microbe types in older people's intestines are different and are linked to disease

The body's constellation of gut bacteria has been linked with various aging-associated illnesses, including cardiovascular disease and type 2 diabetes. Now a study has found that aging itself is associated with microbiome changes and that these alterations are distinct from those connected to diseases or medication use. The findings raise the possibility that shifts in gut bacteria help to drive the aging process—and that protecting these microbes could help people lead longer, healthier lives.



Human microbiome in an intestine

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In the new study, published in *Cell Reports* on September 28, researchers at Cedars-Sinai Medical Center in Los Angeles sampled bacteria from the small intestines of 251 people between the ages of 18 and 80 who were undergoing upper endoscopies, when a doctor sticks a small probe down the throat and past the stomach. Usually researchers study gut bacteria through stool samples. But those microbes, coming from the very end of the bowel, can be quite different from bacteria in the small intestine, closer to the stomach. That's where most digestion and nutrient absorption occurs. "All the magic happens in the small intestine," says study co-author Mark Pimentel, a gastroenterologist at Cedars-Sinai.

After analyzing the samples, the researchers found that aging was linked with changes in bacterial populations. Older people had more bacteria from the families Enterococcaceae, Lactobacillaceae, Enterobacteriaceae and the genus *Bacteroides*, "and those are all groups of bacteria that can cause disease in humans," says Heidi J. Zapata, an infectious disease specialist and immunologist at the Yale School of Medicine, who was not involved in the study. *E. coli* bacteria, which belong to the Enterococcaceae family, for instance, can cause diarrhea and urinary tract infections. Overall bacteria diversity also declined as people got older, going down as people headed toward age 80. Low diversity has been linked to health problems too, Pimentel says. Studies have found a relation between low bacterial diversity and Crohn's disease, irritable bowel syndrome and colorectal cancer, among other conditions.

It is not crystal clear how changes to the microbiome might drive aging, or if they really do. Research in rodents has shown that disruptions to gut bacteria can make it harder for intestinal stem cells to regenerate. This could affect metabolism as well as the overall health of the intestinal barrier; problems with that barrier have been tied to aging and age-related conditions such as liver disease, metabolic diseases, inflammatory bowel diseases, and lung and brain problems. The microbial changes that occur later in life may also create a more inflammatory environment in the gut, helping to drive the aging process. When researchers transplanted gut microbes from older mice into younger germ-free mice in a 2017 study, the young mice developed inflammation that is indicative of aging.

Because the new study only found associations, it does not prove that these changes cause aging. Instead gut bacteria might change after people get older. "We really don't know the chicken or the egg here, but we need to find out," Pimentel says. He hopes to tease out answers in future studies, including additional experiments that transplant "older" microbiomes into young animals to see if it makes them age faster or become ill. It would also be interesting, he says, to study the microbiomes of healthy centenarians and identify differences that could play a role in healthy aging.

It's also unclear just how broadly applicable the new findings are, though, because the patients were undergoing upper endoscopies—and "endoscopy is not something people happily volunteer for," says Elena Biagi, a researcher who studies the microbiome at the University of Bologna in Italy, who was not involved in the study. These people may have had underlying medical issues that prompted them to get endoscopies, so their gut bacteria may not have been representative of normal, healthy individuals.

The researchers were also able to figure out that medication use and the presence of disease affected the small intestine microbiome, separate from aging. They found, for instance, that the more medications people took, the more *Klebsiella* bacteria they had in their intestines—but that the abundance of *Klebsiella* was unrelated to their age or the number of diseases they had. *Klebsiella* can cause hospital-associated infections, including pneumonia, surgical site infections and meningitis, and these bacteria are often antibiotic-resistant. They also found that people with underlying conditions, regardless of their age or medication use, tended to have more *Clostridium* bacteria in their intestines, which can cause dangerous *C. difficile* infections.

If in future studies, researchers do show that microbial changes drive the aging process rather than the other way around, then protecting the microbiome through healthy lifestyle choices or targeted medical interventions may keep people healthier for longer. Pimentel says eating well and exercising almost certainly help. Zapata encourages people to also be judicious in their use of antibiotics—to avoid taking them when they aren't needed and to take targeted antibiotics rather than drugs that kill off a broad array of bacteria. After treatment with broad-spectrum antibiotics, gut bacteria tend to grow back with less diversity, she says, and more unhealthy kinds of bacteria can thrive.

"An unbalanced microbiota can definitely lead to infections and disease," Zapata says. "It is important to understand these changes that happen as we get older to try to see if we can improve the aging process."

—Melinda Wenner Moyer

Investigating Antidepressant's Surprising Effect on COVID Deaths

Researchers are still puzzling over what this drug does at the molecular level to help COVID patients

Basak Gurbuz Derman/Getty Images

Researchers reported last October that an inexpensive, widely available pill substantially reduced hospitalizations and deaths in a large study of individuals with mild COVID symptoms who were at high risk for complications. It is the only existing oral medication with promising peer-reviewed data from multiple randomized COVID trials—and it is already used by millions of people worldwide. The drug is fluvoxamine, and it is approved in the U.S. for treating obsessive-compulsive disorder and depression. So how did this antidepressant end up in a trial for treating COVID?

"Drugs don't know what their original indicated purpose was, they just do what they do, and they don't usually do only one thing," says Angela Reiersen, a child psychiatrist at Washington University in St. Louis. Along with her Washington University psychiatry colleague Eric Lenze, Reiersen conducted a smaller randomized trial in 2020 that suggested fluvoxamine could keep newly infected COVID patients from deteriorating.

Fluvoxamine is best understood for its impact on serotonin—a chemical messenger linked to mood and anxiety disorders. But the drug has other molecular targets. One is a protein called the sigma-1 receptor, which regulates the release of inflammatory molecules, including several that escalate in people with severe COVID. In a 2019 study, University of Virginia scientists chemically induced sepsis, a life-threatening infection complication, in mice. They observed that animals lacking the sigma-1 receptor developed severe inflammation, and many died. Yet in normal mice, a shot of fluvoxamine quieted the immunity overdrive and helped the animals survive.

That study caught Reiersen's attention: the same overdrive immune response seen in those mice was a central feature observed in children who had come under her care because they had a rare genetic disorder—Wolfram syndrome—that led to psychiatric symptoms. When the pandemic hit and reports emerged that some people with COVID worsen because their inflammatory response goes haywire, Reiersen recalled the mouse study and wondered if fluvoxamine could also keep immune responses from spiraling out of control in these individuals.

She approached Lenze about testing fluvoxamine as an early COVID treatment, and he was game. Many modern mental health drugs in fact came from serendipitous observations of mood and behavior improvements with drugs developed for unrelated reasons—to fight nausea, for example, or to treat infectious diseases such as tuberculosis. So when Reiersen proposed repurposing fluvoxamine as a potential COVID treatment, "I remember saying, 'Hey, you know, we owe psychopharmacology to the infectious disease field,'" Lenze says.

"Wouldn't it be good to pay them back on this one?"

Curiously enough, others who pivoted their research during the pandemic have also converged on the sigma-1 receptor. In a notable case, a team searched for drugs that block interactions between human proteins and proteins in SARS-CoV-2, the virus that causes COVID. One of the two sets of drugs that emerged from this systematic analysis, published in 2020 in *Nature,* was compounds that bind the sigma-1 receptor.

Andrea Fekete, a nephrologist and CEO of SigmaDrugs, a biotech spin-off of Semmelweis University in Budapest, has used fluvoxamine and other sigma-1-receptor-targeting drugs to protect rats from fibrosis, or tissue scarring, in renal disease. She and her colleagues are now conducting a clinical trial to see if 200 milligrams of fluvoxamine daily can prevent lung fibrosis in hospitalized COVID patients with moderate disease. Recently a small open-label study found that two weeks of fluvoxamine reduced mortality in COVID ICU patients who chose to receive the drug, compared with those who refused it, suggesting fluvoxamine could also help people with more advanced disease.

Other researchers have turned their attention to antidepressants more broadly. Early in the pandemic, Nicolas Hoertel, an associate professor of psychiatry at Paris University and a psychiatrist at Corentin Celton Hospital in France, noticed something intriguing: mentally ill patients—even elderly ones—were not getting COVID nearly as seriously nor as often as hospital staff did. He called up his former colleagues in New York State, and they, too, noted that although emergency units were packed, there were surprisingly few psychiatric patients. In the spring of 2020 "I was thinking, What could explain this?" Hoertel says.

By that time scientists were zeroing in on overexuberant inflammation as a key feature of severe COVID. As it turns out, people with depression have high levels of some of the inflammatory proteins that are elevated in people with COVID, and many antidepressants have anti-inflammatory properties. Hoertel wondered if COVID patients who happened to be taking antidepressants had better outcomes.

Following that hunch, his team combed through databases at dozens of Paris-area hospitals and showed that, indeed, COVID patients admitted to the hospital who were already taking an antidepressant had a 44 percent reduced risk of intubation or death. In a separate analysis, researchers tracked comorbidities and outcomes in people hospitalized for COVID in Germany and found that depression was the only condition associated with lower odds of death.

It was hard to explain these observations, however. In the Paris study, several—but not all—of the drugs associated with better COVID outcomes were selective serotonin reuptake inhibitors (SSRIs). Several—but not all—activated the sigma-1 receptor. Hoertel and his co-workers were puzzled as to why certain antidepressants appeared to help COVID patients, whereas others seemed to have little effect. Last November he received an e-mail with a possible answer.

The message came from Erich Gulbins, a molecular biologist at the University of Duisburg-Essen in Germany. In it, Gulbins described a paper his team was about to publish showing that the five antidepressants associated with a COVID benefit in Paris hospitals also block SARS-CoV-2's entry into human nasal epithelial cells grown in a lab dish. And those drugs have something in common: they inhibit acid sphingomyelinase, the key enzyme in a biochemical pathway that processes fats into forms that can help viruses enter cells. Some antidepressants are among the dozens of so-called FIASMA (functional inhibitor of acid sphingomyelinase) drugs known to block this pathway. When Hoertel and his colleagues scoured hospital records again, they found that patients who were taking FIASMA medications (a broader drug class than antidepressants) had lower odds of intubation or death despite being generally older and having more advanced disease.

It is not yet clear if fluvoxamine's COVID benefit derives from its binding to the sigma-1 receptor or its effect on the acid sphingomyelinase, or a combination of these and other potential mechanisms. Some wonder if fluvoxamine might also help treat COVID by directly suppressing SARS-CoV-2—similar to

oral drugs recently developed by Merck and Pfizer that have not yet been authorized for use in the U.S.

Matt O'Meara, a computational pharmacologist at the University of Michigan Medical School, who was one of the authors of the human-viral protein analysis published in *Nature,* thinks the mouse sepsis study points to the sigma-1 receptor as a primary way fluvoxamine helps against COVID. By showing that clinically relevant concentrations of fluvoxamine could block a strong inflammatory immune response in living animals, O'Meara says, "that's very strong evidence that this is a reasonable mechanism."

In addition, he and his colleagues have conducted lab-dish experiments in which they have assessed the growth of SARS-CoV-2-infected cells mixed with increasing concentrations of fluvoxamine. Their data, still unpublished, show that fluvoxamine had little effect on viral infection even at concentrations high enough to be toxic to the cells, O'Meara says.

Hoertel and his colleagues' studies on antidepressants and FIASMA drugs raise another question: Could the antidepressant fluoxetine (Prozac)—a drug that, like fluvoxamine, binds the sigma-1 receptor—have a similar benefit in treating COVID? That would be an attractive possibility because fluoxetine is better tolerated and more widely prescribed than fluvoxamine. If targeting the sigma-1 receptor is the prime mechanism, some think it is unlikely that fluoxetine would help against COVID because it binds to that receptor about 10 times more weakly than fluvoxamine.

Fluoxetine has not yet been investigated in a randomized trial for treating COVID. But researchers at Stanford University and the University of California, San Francisco, have a forthcoming paper that will report their analysis of electronic health records to look for a potential link between preexisting fluoxetine use and COVID outcomes among more than 80,000 patients nationwide.

While these questions about how antidepressants help against COVID are being investigated, "what I think, in fact, is the most likely [answer] is that we have a contribution of different mechanisms," Hoertel says. "I mean, we know that, in biology, nothing is simple."

—Esther Landhuis

Cannabis Use in Pregnancy Is Linked to Child Anxiety, Hyperactivity

Changes in the activity of immune system genes in the placenta could explain the association, researchers speculate

As with most decision points around pregnancy, cannabis use is a fraught subject. Researchers can't assess it in randomized trials, because dosing pregnant people with the psychoactive substance is unethical. The next best thing is studies with enough participants who use cannabis on their own, allowing for comparisons with those who do not.

The findings of one such study, published on November 15, 2021, in the *Proceedings of the National Academy of Sciences USA,* highlight symptoms of increased anxiety, hyperactivity and aggression in children whose parents used cannabis during pregnancy. And its analysis of placental tissue points to changes in the activity of immunity-related genes.

Today pregnant people "are being bombarded with a lot of ads to treat nausea and anxiety during pregnancy" with cannabis, says the

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paper's senior author Yasmin Hurd, director of the Addiction Institute at Mount Sinai. "Our studies are about empowering them with knowledge and education so that they can make decisions."

The results are "very striking, very much a first," says Daniele Piomelli, a professor and director of the Center for the Study of Cannabis at the University of California, Irvine, who was not involved in the work. Pregnancy studies in rodents and even in sheep, which have a placenta more like ours, have required cautious interpretations of findings that show effects on offspring behavior and function, he says. The new study is one of the first to tackle the question in people "in a systematic way," Piomelli adds.

Hurd and her colleagues worked with 322 parent-child pairs, beginning with profiles of genetic activity in placental samples taken at birth. When the children reached about three years of age, samples of their hair were tested for levels of stress hormones. From ages three to six, they also underwent recordings of their heart-rate variability, another indicator of stress response, and evaluations for anxiety, aggression and hyperactivity. The researchers used statistical methods to exclude effects from cigarette smoking, parental anxiety and other factors that could confuse associations with cannabis use.

In the placental tissues, gene activity was altered with cannabis exposure during pregnancy: genes related to the inflammatory response showed decreased function. Anxiety and hyperactivity levels were higher in children from cannabis-exposed pregnancies and were associated with the placental gene patterns. The researchers speculate that a decline in the activity of immune-related genes in the placenta might explain the behavioral findings.

"We always have to interpret human studies with a grain of salt," Piomelli says, because factors other than cannabis could still be the true cause of the behavioral outcomes, including experiences after birth. Although the researchers in this study "did a really good job" of controlling for these factors, he says, "there is only so much one can do."

Anxiety is an example of a potential confounding factor, says Mitch Earleywine, a professor of psychology at the University at Albany, State University of New York, who was not involved in the study. Anxiety has some genetic underpinning, which parents can pass to children. For this reason, he says, "I'm not sure that cannabis is really the issue" instead of genetics. Earleywine is also an advisory board member of the National Organization for the Reform of Marijuana Laws (NORML), which advocates for the legalization of cannabis.

Hurd agrees that human studies will always involve elements that can muddy the findings. "Yes, genetics plays a role, maternal anxiety plays a role, their postnatal environment plays a role," she says. But even with all of that, the associations her group found with cannabis are results that "I don't think we can ignore."

For parents who used cannabis during pregnancy and find these results potentially unsettling, "the human organism is very resilient," Piomelli says. "Appropriate care and love and attention to your kid can certainly reduce any potential harm." Hurd says that one strategy to reduce harm is to be alert to signs of anxiety or hyperactivity in children and get them help right away.

—Emily Willingham

COVID Can Cause Strange Eye and Ear Symptoms

From conjunctivitis to vertigo, coronavirus infections can affect disparate senses

Red eyes, ringing ears, sensitivity to light, trouble hearing: although a loss of taste and smell have become well-known sensory symptoms of COVID, accumulating research suggests that vision and hearing are also frequent targets of SARS-COV-2, the virus that causes the disease.

More than 10 percent of people who get COVID develop some type of eye or ear symptom, according to the latest data, and both categories are among the complaints that can end up persisting for a long time. As researchers work to understand how the virus infiltrates our senses, their findings suggest that people may need to broaden the scope of warning signs for when to get tested. Instead of just a fever, cough, or changes in taste and smell, the first signs of illness might include irritated eyes, hearing

problems or balance issues.

Nearly two years into the pandemic, research on COVID's effects on the eyes and ears suggests that scientists have much more to learn about how the virus affects our bodies and nervous systems, experts say. "The data are growing to suggest that there are more neural consequences of this infection than we originally thought," says Lee Gehrke, a molecular biologist at the Massachusetts Institute of Technology.

Aliëna Pasko/EyeEm/Getty Images

THE EYES HAVE IT

One of the first people who tried to warn the world about COVID was Li Wenliang, a Chinese ophthalmologist in Wuhan. He most likely caught the virus from an asymptomatic glaucoma patient, according to Bhupendra Patel of the University of Utah's John A. Moran Eye Center, who co-authored a 2021 review of research on COVID's ocular symptoms. Li died from his illness early in 2020, but his case was not the only early clue that eyes might play a role in the virus's spread. From the beginning of the pandemic, reports included red eyes as a common symptom.

That was not surprising to scientists. During the 2003 SARS outbreak, researchers in Singapore detected the virus that causes that disease in patients' tears. And in Toronto, the risk of infection was higher among health-care workers who did not wear eye protection. But because COVID causes severe respiratory problems and other symptoms and because most eye doctors closed their offices during lockdowns, eyes were overlooked at first, Patel says.

Over the pandemic's first year and a half, accumulated data have established that about 11 percent of people with COVID develop some kind of eye issue, according to a review of multiple studies. The most common symptom is conjunctivitis, or inflammation of the eye lining. This condition affected nearly 89 percent of people with eye symptoms, researchers in Iran reported in a 2021 meta-analysis that included 8,219 COVID patients across 38 studies.

Other ocular symptoms can include dry eyes, redness, itching, blurry vision, sensitivity to light and the feeling that there is a foreign particle in the eye. People on ventilators often develop a type of eye irritation called chemosis, a swelling or bulging of the eye membranes and eyelids, Patel says. He suspects that as many as one third of people with COVID have some type of eye issue—even if it is just red eyes that do not bother them. And some eye issues are not visible. Patel and his colleagues are working on a study, not yet submitted for publication, that he says will be among the first to report that the virus can cause inflammation in the tissue behind the eyeball.

Eye symptoms can show up early or late in the illness, adds Shahzad Mian, an ophthalmologist at the University of Michigan. He and his colleagues reported ocular signs and symptoms in nearly 10 percent of 400 patients hospitalized in Michigan in March and April 2020.

A person who has COVID can shed the virus through their tears, sometimes long after they have recovered from the illness. One early COVID patient was a 65-year-old woman who traveled from Wuhan to Italy in January 2020 and was soon admitted to a hospital with a cough, sore throat and conjunctivitis in both eyes. Even though her eyes were better by 20 days after she was admitted, researchers detected viral RNA in eye swabs on day 27. In the Lombardy region of Italy, research-

ers found SARS-CoV-2 on the surface of the eyes in 52 out of 91 patients hospitalized with COVID in the spring of 2020, sometimes even when their nasal swab was negative.

The virus may also able to get into the body through the eyes, studies suggest—either from eye rubbing and the direct transfer of tears or from respiratory droplets that happen to land on the eye. When drops containing SARS-CoV-2 were put into the eyes of rhesus macaques in a 2020 study, the animals got sick. A monkey intervention study cannot reveal whether or how often people get infected through their eyes in real life, but the virus appears to be able to replicate in eye tissue and then make its way into the nasal passages, Mian says. Eye involvement "may be a portal for COVID in addition to being just a symptom," he says.

As many as 6 percent of people will show symptoms in their eyes before any other signs of COVID, Mian says. Red eyes or irritation could be a sign that someone has the illness, especially if there is a known exposure or other symptoms. "As a parent or as a patient or as a community member, you should be aware that if you have conjunctivitis in this day and age, you want to make sure that it's not COVID," he says.

INSIDE THE EARS

Hearing and balance changes can also be signs of SARS-CoV-2 infection, says Zahra Jafari, an audiologist and cognitive neuroscience at the University of Lethbridge in Alberta. In a 2021 meta-analysis, she and her colleagues found dizziness or vertigo in 12 percent of COVID patients, a ringing in the ear known as tinnitus in 4.5 percent and hearing loss in 3 percent. One hypothesis of how SARS-CoV-2 might affect the ears, she says, is that inflammation caused by the virus may directly impact the auditory system. The virus could also invade a barrier between the bloodstream and inner ear.

Confirming those mechanisms has been difficult because the inner ear is notoriously hard to study, Gehrke says. Encased in bone and located deep inside the head, it is inaccessible, and animal models do not always help. Mice are not natural hosts for RNA viruses, so the commonly used lab rodents do not work particularly well as a stand-in for SARS-CoV-2 infection.

To investigate what might be happening inside the ears of people with COVID, Gehrke teamed up with researchers at several other labs to grow human ear tissues using stem cells. With those tissues, the team was then able to show that two types of inner ear cells have the genes for making proteins—including ACE-2 receptors—that allow SARS-CoV-2 to get into cells.

Hair cells, which are important for both hearing and balance, can also be infected by the virus, the researchers reported in *Nature* last October. The team was able to confirm that inner ear infection with the virus is possible by studying human tissue that had been removed as part of surgeries that were scheduled as treatments for other disorders. The findings are "highly suggestive that, indeed, SARS-CoV-2 patients might have hearing loss associated with virus infection due to infection of the hair cells," Gehrke says.

Most of the time, both eye and ear symptoms get better on their own, experts say. But research is starting to suggest that in both cases, COVID-induced symptoms can become long-lasting. Patel knows of two cases in which COVID patients have lost sensation in their corneas, which can cause those corneas to break down, even with minor trauma. That breakdown can lead to corneal infection, damage and ultimately blindness. Multiple case reports include ear-related symptoms that stick around even after people recover from the illness, Jafari says.

Although damage to sight and hearing still appears to be less common than loss of smell and taste—which can affect 40 percent or more of people with COVID—studies on eyes and ears lend insight into the many and often still mysterious ways that the virus can go to work inside the human body, experts say.

The research also illustrates how intertwined our sensory organs are. Nasal passages butt against Eustachian tubes and eyeballs. "The nerves that allow you to taste, the nerves that allow you to smell, and the nerves that allow you to feel corneal sensation—these are all part of the central nervous system where the brain connects to these different parts," Patel says. Vision, smell and taste—"these are all connected."

—Emily Sohn

Physical Activity Could Be an Evolutionary Adaptation for Grandparenting

It may force energy shifts to repair and maintenance, which could slow aging and make us more available to care for younger generations

vorDa/Getty Images

Lifelong physical activity can help our span of good health run almost the length of a lifetime. In this way, remaining active later in life promotes humans' wherewithal to support the survival of their grandchildren—and their genetic lineage into future generations—say the authors of an essay published last November in the *Proceedings of the National Academy of Sciences USA*.

The piece builds on anthropology's "grandmother hypothesis," which posits that people typically live for several decades because young humans require significantly more care than the immature offspring of many other species.

In the new work, evolutionary biologist Daniel Lieberman of Harvard University and his colleagues assert that maintaining physical activity into the later stages of life slows aging, or senescence, and protects against chronic disorders, facilitating a healthier longevity. This "health span," or prolonged stretch of relatively disease-free years, allows older people to remain physically active and contribute to caring for later generations, the authors suggest. To learn more about these ideas and the evidence for them, *Scientific American* spoke with Lieberman.

[*An edited transcript of the interview follows.*]

This essay offers two related hypotheses, both with physical activity at their center. Why is physical activity such a focus?

It has long been known that humans evolved to live past our normal reproductive age. The key argument of this paper is that physical activity is part of that equation. We evolved to live past the age of reproduction in order to be physically active. In turn, that physical activity helps maintain our health span so that we can stay healthy for several decades after we stop reproducing.

All organisms have to allocate energy, and there are two ways we do that as a result of physical activity. One is to decrease how much [energy] we spend on fat storage and reproduction, and the other is to increase energy that we spend on repair and maintenance. The argument is that there was evolutionary selection for physical

activity and also evolutionary selection for these various physiological responses to physical activity—these energy-allocation responses that promote health. As we get older, the repair-and-maintenance pathway becomes more important.

People with ovaries undergo a cessation of reproductive capacity, whereas people who make sperm can do so for a lifetime. How does this hypothesis apply to both?

The benefits of living to be a grandparent apply to both men and women in terms of hunting and gathering so that you produce food for your children and grandchildren. In both sexes, the grandparents benefit from the consequences of that energy allocation that slows senescence, especially those that are related to repair and maintenance. I went for a run this morning and produced all of these reactive oxygen species [oxidative molecules that can cause tissue damage], and my body was producing antioxidants to counter those. If I hadn't gone for a run, I wouldn't have produced as much of those antioxidants.

What is the biological explanation and evidence in support of these hypotheses?

We've long known that physical activity is good for us because it prevents overly high levels of reproductive hormones, such as estrogen and testosterone, and it prevents us from storing abnormally high levels of fat. Those are obvious benefits of physical activity that are well known, a consequence of energy allocation.

The more novel hypothesis that [my colleagues and I are] proposing is that when you exercise, you get what is called an "afterburn." You're spending energy after you stop exercising. Initially it was thought that this energy, which we call "excess postexercise oxygen consumption," was a replacement for oxygen debt. But we now know that energy replacement is only a fraction of that increased metabolic rate.

Our argument is that afterburn is a sign of investment in repair and maintenance to deal with the stresses of physical activity, such as tearing muscles and pumping out reactive oxygen species, that cause DNA mutations. The good news is that because we evolved to be physically active, we also evolved a diverse array of repair-and-maintenance mechanisms that respond to that physical activity. We basically overshoot with those responses.

Can you give an analogy for this process?

Imagine you spill some coffee on the kitchen floor, and then you clean it up. You clean it up such that the floor is now cleaner than it was before you spilled the coffee. Physical activity turns on all of these repair-and-maintenance mechanisms, and because you don't want to undershoot, you overshoot. The result is a benefit. We never evolved not to be physically active, and we never evolved not to turn these on. Otherwise, exercise would be bad for us, and even the most hard-hearted cynic agrees that exercise is not bad for you.

Why do you distinguish between physical activity and exercise?

Physical activity is just moving and using your body to do something, such as gardening, hunting and gathering, or going shopping. Exercise is discretionary voluntary physical activity for the sake of health and fitness. It's a very modern activity—lifting weights and getting on a treadmill have no function other than health and fitness. As the world has changed, we've replaced human labor with machines, and we now have to do something really weird, which is to exercise.

How do these ideas fit with the "grandmother hypothesis," this concept that we live beyond our ability to pass genes to future generations so we can help nurture children during their lengthy period of maturation?

We're saying that the physical activity proposed by the grandmother hypothesis—and we shouldn't leave grandfathers out—that physical activity is also part of the way in which the health span has increased. Physical activity is both a consequence and a cause of that elongated health span.

In the essay, you highlight the protective effects of physical activity as we age, particularly against cancer and heart disease. How is that thought to work?

Most people know that physical activity is important to prevent heart

disease, but the evidence on the importance of physical activity in preventing cancer is also substantial.

Physical activity lowers estrogen and progesterone levels and lowers risk for breast cancer quite substantially—by some estimates by 30 to 40 percent. There are other factors—reducing inflammation, for example. One of the things that physical activity does is: it causes your muscles to produce anti-inflammatory molecules, and muscle is a major regulator of inflammation. Physical activity also lowers blood sugar levels, and most cancer cells are kind of sugar-hungry. Physical activity lowers levels of insulin, and insulin is associated with increased risk of cancer. For almost every cancer, there are activity effects that have been shown, some quite dramatic.

For heart disease, one of the reasons that cardio exercise is so beneficial is that it promotes a suite of responses that keep our arteries elastic, increase capillary growth and make the heart stronger. All of these prevent hypertension and congestive heart failure and decrease risk of atherosclerosis. There's compelling evidence that physical activity is good for the cardiovascular system because of these repair-and-maintenance mechanisms. You've got to stress the system in order to get benefit. You don't need pain, but maybe you need strain. Perhaps the saying should be "no strain, no gain."

How much physical activity would it take for us to match the "dose" that earlier humans got?

[My colleagues and I reviewed] some evidence that hunter-gatherers get about two and a quarter hours of moderate to vigorous physical activity a day, and those doses are clearly protective. But there are plenty of epidemiological and longitudinal studies showing that lower doses also are protective.

We have this idea that as we get older, it's normal to take it easy, retire, be less active. But we also know that physical activity is really important for health. And as people get older, it becomes more important, not less important. You don't need to run marathons or bike across America or swim the English Channel. Just moderate levels of physical activity are incredibly beneficial.

—Emily Willingham

The Smartest Way to Use Rapid At-Home COVID Tests

The self-administered tests are sold over the counter, holding out the promise of safer gatherings. But interpreting results requires savvy

As COVID-19 vaccines became widely available in the U.S., some people who had put life plans on hold earlier in the pandemic decided not to wait any longer. One of them was *Scientific American* senior health editor Tanya Lewis, who got married in August 2021. But in the weeks leading up to the wedding day, infections of the novel coronavirus, or SARS-CoV-2, had started to rise again nationwide. So the wedding was held outdoors and limited to fewer than 40 guests, with all the adults confirming they were vaccinated—and Lewis handed out over-the-counter antigen tests for the coronavirus just before the ceremony, then asked guests to take them. These relatively low-cost tests return results within 15 to 30 minutes. "I wanted to make sure that I had one extra layer of protection," she says.

Her strategy seems to have worked out well. None of the tests—performed by putting a nasal swab and some reagent drops on a test card or test cassette that quickly displays two lines for positive or one for negative—returned a positive result, and no one reported infections in the following days.

But the accuracy of antigen tests varies. These assays correctly identify a SARS-CoV-2 infection in 72 percent of people with symptoms and 58 percent of people without them, according to a review study published in March. And timing matters. The tests detect an average of 78 percent of cases in the first week of symptoms but only 51 percent during the second week, the researchers found. If antigen tests had been Lewis's only layer of defense (beyond the setting and hosting a mini wedding with all adults vaccinated), this strategy would have held the potential to disrupt her important day with misinterpreted or false test results. How should people use over-the-counter antigen tests? And if they do, what should they be wary of?

At-home antigen tests are expected to become more widely available later

this autumn: the Biden administration has committed to address shortages with the purchase of hundreds of millions of the assays. The tests are useful as a quick, initial screen for SARS-CoV-2 infection prior to traveling, attending an event, or even going to work or school, particularly if one is experiencing mild or moderate symptoms. Repeated antigen testing at frequent intervals is ideal to increase the chances of spotting an infection if more accurate polymerase chain reaction (PCR) tests are not available.

One small study found that antigen testing every three days is 98 percent accurate at detecting SARS-CoV-2 infections, but there is no magic number for how often concerned individuals should take these tests, experts say. People who test positive (or "detected") should take the result seriously and seek health care. A negative test can ease anxieties, at least for the time being—but people with symptoms should still follow up with a more accurate test.

Antigen tests, which detect pieces of the virus's proteins, are considered less sensitive to low amounts of virus than the more accurate PCR tests. The latter, for which results can take a day or more to come back from a lab, detect pieces of the virus's genetic code. If a person with very low viral levels in their nose took both tests at the same time, they would be more likely to receive a positive or detected result on a PCR test than on an antigen test. A person who had been recently infected might slip past an antigen test because the virus would not have had much time to replicate in the nose.

In that regard, antigen tests arguably are more likely than PCR tests to only return a positive result when a person's case reaches the threshold of infectious—not when they are just infected. For instance, the accuracy of Abbott's BinaxNOW clinical antigen test increases from about 85 to 95 percent among symptomatic people with higher amounts of virus in their nose, the company states.

This feature of the rapid tests can hold some public health benefits, says Monica Gandhi, an infectious disease physician at the University of California, San Francisco. Antigen tests are "good for detecting the amount of virus in your nose that's usually associated with transmission," she says, "which is actually exactly what you want to know." Gandhi describes

ljubaphoto/Getty Images

PCR tests as "too sensitive" when it comes to determining infectiousness and says antigen tests are often superior in this area.

Many experts agree that infected people with low levels of virus in their nose (usually described as a low viral load) typically do not spread the virus. So if the goal is simply to make sure that test takers are less likely to infect anyone else—rather than identifying every infected person even if they are relatively unlikely to spread the virus—an antigen test often fits the bill, Gandhi says. Lewis says this was part of her rationale for using them.

But Omai Garner, a clinical microbiologist at the University of California, Los Angeles, cautions against assuming that antigen tests rely on the correct threshold of infectious-

ness. "I am unaware of a study that ties infectiousness to antigen-test positivity," he says. Garner adds that antigen tests pick up too few infections in people who are experiencing no symptoms. One type of antigen test detected SARS-CoV-2 infections in only 41 percent of infected people without symptoms, according to a Centers for Disease Control and Prevention study published in January.

If picking up all possible infections is a concern, why bother with antigen tests at all? One answer is that speedier results can at least help quickly flag many or most of the infectious test takers, allowing them to receive care sooner and to isolate before infecting others.

Any infection test can only capture a snapshot in time. With antigen tests, that captured moment is only 15 to 30 minutes prior to results, so they are capable of revealing a sufficient viral load before an infected individual would likely have much time to interact with many others. Because the more sensitive PCR results take longer, any virus present in an infected person's nose could multiply while they wait—or a person who was uninfected at

"I am unaware of a study that ties infectiousness to antigen-test positivity."
—Omai Garner

testing time could catch the virus.

A rapid test an hour or two before going to school, work or some other gathering provides an up-to-date (if imperfect) answer on whether the test taker could spread the coronavirus that day, says Clare Rock, an epidemiologist and infectious disease specialist at the Johns Hopkins University School of Medicine. "You are getting that real-time information," she says. For multiday situations such as going to work or school throughout the week, such tests would ideally be taken daily (or at least randomly) to potentially detect getting infected in the window between tests and to spot infections in which the viral load increased to the point that it triggered detection that slipped past the initial test. At about $20 per test, however, the costs mount quickly.

Antigen tests also run the risk of a false positive result, particularly in areas with moderate or low transmission. But false negative results are more common. Incorrectly swabbing one's nose—or reading the test results before or after the specified time window—can also yield inaccurate results.

Antigen tests clearly have limitations. In short, if a person with no symptoms tests positive, especially in an area of low transmission, that result is on shaky ground. People in these cases should also follow up with a PCR test, Gandhi says. And the CDC recommends that symptomatic people with a negative antigen test should follow up with a PCR test within 48 hours.

One way to view rapid at-home tests is as an extra precaution—not a license to throw caution to the wind. "They're not a stand-alone tool to use and say, 'Okay, I've tested myself, and I don't need to do any of the other prevention pieces,' " Rock says.

This is how Lewis treated the antigen tests at her wedding. Layered measures relieved her of constantly worrying about COVID-19 at her small outdoor gathering. "I felt reasonably safe," she says. "I mean, as safe as you can feel."

—Tara Santora

Can Intense Exercise Lead to ALS?

New studies show a possible connection. But debate over such an association will continue

Lou Gehrig was a star baseball player who led the New York Yankees to six World Series titles before he was diagnosed with a devastating disease in 1939, when he was still in his mid-30s. The disease, amyotrophic lateral sclerosis (ALS), causes the motor neurons that enable muscle movement to deteriorate, gradually leading to the loss of the ability to move, eat, speak and even breathe. Gehrig's illness, which had already been documented for decades, helped raise public awareness before the first baseman passed away in 1941—so much so that "Lou Gehrig's disease" later became a common name for the condition.

There is a long list of professional athletes who, like Gehrig, died from ALS. Among professional soccer players in Italy, for example, there have been reports of a higher than average number of ALS cases.

Lou Gehrig delivers his farewell speech at Yankee Stadium on July 4, 1939.

Stanley Weston/Getty Images

Researchers have also found similarly elevated rates among athletes in the U.S. National Football League. These observations have led many scientists to wonder whether doing elite sports—or, more broadly, engaging in intense exercise—might increase the risk of developing the neurodegenerative disease.

Despite the many studies that have examined whether physical activity is tied to ALS, researchers have yet to pinpoint a clear answer. Some investigations have revealed a link, while others have not. These conflicting findings have led some researchers to examine whether other, related factors, such as metabolism or genetic predisposition, might provide alternative or complementary explanations. “Once you take this evidence all together, it looks like there is something else underlying this association rather than physical activity alone,” says Valentina Gallo, a neuroepidemiologist at the University of Groningen in the Netherlands.

TOO MUCH MOVEMENT?

The idea that physical activity might be involved in ALS goes back decades. During a 1962 conference, British neurologist MacDonald

Critchley pointed to Gehrig's case and noted that the fact that he was a professional athlete might not be a coincidence. "Nothing has been said about the possible role in ætiology of a previous habit of athleticism," Critchley said at the time. "I have the uncomfortable feeling that a past history of unnecessary muscular movement carried out for no very obvious reason may be followed in later life by the development of motor neurone disease in a statistically significant number of cases."

In the years that followed, many investigators set out to assess whether this hunch was correct. Some studies—such as those of Italian soccer players or American football players—suggested that there was, indeed, something about high levels of exercise that increased the risk of the illness. Researchers also reported that certain jobs that required strenuous physical labor, such as metalworking or farming, could increase the likelihood of a diagnosis. Other studies, however, failed to find a heightened risk of ALS in individuals who had some of those occupations—or among people who, in general, had a very active lifestyle. "Physical activity is a very tricky exposure to evaluate in terms of types, intensity and duration" says Elisa Longinetti, a postdoctoral researcher at the Karolinska Institute in Sweden. "That's why I think we've found so many conflicting results in several studies investigating its effect on ALS."

"I have the uncomfortable feeling that a past history of unnecessary muscular movement carried out for no very obvious reason may be followed in later life by the development of motor neurone disease in a statistically significant number of cases."
—MacDonald Critchley

One of the challenges in doing this research is determining how best to measure the level of physical activity a person was exposed to throughout their life. In a study published on October 20 in *Neurology*, Angela Rosenbohm, a neurologist at Ulm University in Germany, and her colleagues tried to get a better estimate of people's lifetime physical activity by asking them very specific questions about the types of activities they engaged in during work and leisure and how those activities changed across different life stages.

The team recruited people from a large database that comprised all newly diagnosed ALS cases in Swabia, a southwestern region of Germany. For each patient, the researchers also enrolled two healthy subjects who were randomly selected from the general population. They ended up with 393 participants with ALS and 791 healthy recruits. Participants were asked to report how much physical activity they had engaged in at age 20, 30, 40, 50 and 60—as well as the type, duration and intensity of the activities they were involved in (for example, whether a given activity was work-related and if it made them break out into a sweat).

This study revealed that physical activity and ALS may be connected in a more complex way than previously considered. The researchers found that only those who had high levels of physical activity from their occupation—but not from leisure activities—had an increased risk of ALS. Rosenbohm says that rather than being a consequence of physical activity, this link may arise from other underlying factors, such as higher levels of toxins or pollutants in workplaces where the most physically demanding jobs take place—which would be consistent with what has been reported in other studies. She adds that professional athletes (who were not explicitly examined in this study) may be exposed to pesticides on the field.

Rosenbohm's team found that while there was no correlation between general exercise levels and risk of ALS, there was an association between the former and outcomes of the disease. People who were very active or sedentary were more likely to die from ALS earlier than their moderately active counterparts. It also suggests that moderate exercise might benefit people with the disease—both after diagnosis and before their symptoms appear.

The researchers also discovered that, around five to 10 years before they were diagnosed, many patients with ALS reported a steep drop in their physical activity, which was much more pronounced than that seen in healthy individuals—suggesting that the disease may cause changes in the body that start many years before the deterioration of motor neurons begins.

But Rosenbohm's study, like many others that have come before it, has one major limitation: it relies on participants' self-reports. Gallo explains that it is difficult for people who have a disease in which movement is impaired, such as ALS, to remember past physical activity in an unbiased way. The only method to truly remove this bias, Gallo adds, is to document physical activity levels in a so-called prospective cohort study, which observes a large group of people over time. In any such group that is followed for long enough, some individuals are expected to be diagnosed with ALS. But these resource- and time-intensive studies are few and far between.

In 2016 Gallo and her colleagues conducted such a study of ALS using data on 472,100 people from 10 different European countries that had been collected between 1992 and 2002 for a long-term investigation on cancer and nutrition. All the subjects filled out a questionnaire about their physical activity, both during work and leisure time. Information on deaths and causes of death were also available. By the time this study took place, 219 of these individuals had died from ALS. The team found that, contrary to the many retrospective studies on the topic, being active appeared to very slightly decrease—rather than increase—the risk of dying from the disease.

ALTERNATIVE EXPLANATIONS

Studies suggest that there may also be other explanations for the link between intense physical activity and ALS.

One idea is that exercise alone might not heighten the risk for ALS in the general population but could be harmful for people who are genetically predisposed to the disease. In a study published in *EBioMedicine* this spring, researchers reported that higher levels of past physical activity were associated with earlier disease onset only in patients with a mutation in the *C9ORF72* gene—the most common cause of inherited ALS. Additionally, they found that exercise altered the amount of protein produced by the *C9ORF72* gene. The authors of the paper say that their findings may explain the inconclusive effects of exercise reported in prior studies, most of which did not examine the role of genes.

Another hypothesis is that it is not the exercise itself but rather a person's metabolism that is the real culprit. Researchers have found, for example, that people with a higher body mass index are less likely to develop ALS and that losing weight after developing the disease leads to more rapid progression.

"It seems that the people who develop ALS have a sort of accelerated metabolism," says Alberto Ascherio, a neuroepidemiologist at Harvard University. Ascherio and his colleagues have found signs of abnormal metabolism in blood samples collected from people years before they were diagnosed with ALS. This suggests that something is happening in patients long before their symptoms appear—which is consistent with the reduction in physical activity that Rosenbohm's team observed in its latest study, Ascherio adds. "What that is, we are still unable to pin down," he says.

The question of whether altered metabolism is a cause or an effect of the disease remains unanswered, however. "There is a huge wealth of evidence showing that patients with ALS have increased metabolism," Gallo says. But in most cases, "these are people with the disease already, so you don't know if this led to the development of the disease or if it was actually a consequence of the disease."

The bottom line, according to Ascherio, is that the connection between intense physical activity and increased risk of ALS is too uncertain to make specific recommendations about whether people should be more or less active to stave off the disease. ALS is a relatively rare condition—so even if working out less would be protective, it is important to remember that exercise can help prevent other, more common illnesses, such as cardiovascular disease, stroke and dementia, Ascherio adds. "Keep enjoying your physical activity," he says.

—Diana Kwon

A woman wears a COVID-19 face mask as she walks in Manchester, England, on December 8, 2021. A year ago the U.K. began its COVID-19 vaccination campaign. A year later, amid concerns that vaccines are less effective against the more transmissible Omicron variant, the government is pushing booster jabs and reintroducing public safety measures seen earlier in the pandemic.

Omicron Is Likely to Weaken COVID Vaccine Protection—but Boosters Could Restore It

The rapid spread of new variants such as Omicron offers clues to how SARS-CoV-2 is adapting and how the pandemic will play out over the next several months

By Ewen Callaway

Christopher Furlong/Getty Images

Ewen Callaway is a senior reporter at *Nature*.

THE FAST-SPREADING Omicron SARS-CoV-2 variant is highly likely to compromise some of the protection from vaccines, suggest the first laboratory studies of Omicron's ability to evade immunity.

But the preliminary results—released in December by teams in South Africa, Germany, and Sweden, as well as the Pfizer-BioNTech collaboration—hint that protection conferred by existing COVID-19 vaccines won't be totally wiped out, and that boosters should improve immunity to Omicron.

"We're likely to see reduced effectiveness of vaccines against preventing infection," says Penny Moore, a virologist at the University of Witwatersrand in Johannesburg, South Africa, who co-authored one of the studies. "I think it's a strong argument to get boosters out there."

The studies, which measure the capacity of antibodies in people's blood to block the infection of cells in a dish, have not yet been peer reviewed, and do not tell researchers the extent to which vaccines' ability to protect against COVID-19—in particular, its most severe forms—could be compromised by Omicron.

"We still need to wait for more effectiveness data and clear signals from the places where this is blowing up first," says Ben Murrell, an interdisciplinary virologist and immunologist at the Karolinska Institute in Stockholm, who co-led one of the studies.

MANY MUTATIONS

Researchers in Botswana and South Africa identified Omicron in late November, and teams worldwide have since been racing to understand the variant's properties and the risks it poses. Preliminary data from South Africa and elsewhere suggest that the variant is highly transmissible—spreading several times faster than Delta—and might have the capacity to infect people who are immune to other variants.

Omicron carries a large number of mutations in its spike protein—the prime target of immune responses—and some of these changes, when present in other variants, affect the ability of antibodies to recognize the virus and block infection.

Scientists used two types of laboratory assay to test how well Omicron can evade neutralizing, or virus-blocking, antibodies triggered by vaccination and infection. One approach uses infectious SARS-CoV-2 particles, typically isolated from individuals infected with Omicron. The other employs pseudovirus particles—a genetically modified version of another virus (often HIV) that uses the SARS-CoV-2 spike protein to infect cells.

The results from the four separate teams all suggest that Omicron blunts the potency of neutralizing antibodies more extensively than any other circulating SARS-CoV-2 variant. But the magnitude of Omicron's impact varied between the different studies, which examined blood from people with different vaccination and infection histories.

A study led by virologist Alex Sigal of the African Health Research Institute in Durban, South Africa, found that serum—the antibody-containing portion of blood—from 12 people who received the Pfizer-BioNTech vaccine was 40 times less potent against Omicron, on average, compared to an earlier strain of SARS-CoV-2. That was similar to two other studies: one reported by Pfizer and BioNTech in an December 8 press release, and the other released on Twitter by virologist Sandra Ciesek at Goethe University in Frankfurt, Germany.

A fourth study, led by Murrell and virologist Daniel Sheward, also at the Karolinska Institute, reported a smaller reduction in levels of Omicron neutralizing antibodies in two different groups of participants: 17 healthcare workers, who had all been previously infected, and 17 Swedish blood donors. The researchers cannot determine the vaccine status of the anonymous blood donors but say they will soon update their paper with vaccination information from the healthcare workers.

Despite differences in the labs' results—which are common in such virus neutralization assays—their conclusions are similar and show that Omicron's effects on neutralizing antibodies are "not complete knockouts," says Murrell. "The magnitude is still a little up for question."

BOOSTER PROTECTION

The results suggest that vaccines are likely to be significantly impacted by Omicron—but precisely how much is hard to say. Sigal's team found that people who were previously infected before vaccination tended to have higher levels of neutralizing antibodies against Omicron than vaccinated people with no known history of infection. "I

think retaining some neutralization against Omicron can only be helpful," says Moore, a co-author on the study, whose lab is also working on neutralization experiments.

A prior case of COVID-19 isn't the only way to improve antibody levels against Omicron. The Pfizer-BioNTech study found that people who had received a third dose of its vaccine had neutralizing antibody levels against Omicron comparable to those against other SARS-CoV-2 variants that were raised by two vaccine doses. Based on those results, "we expect significant protection against any type of COVID-19 mediated by Omicron in individuals who have received the third vaccine," BioNTech CEO Uğur Şahin said at a press conference on December 8.

Danny Altmann, an immunologist at Imperial College London, agrees that jacking up antibody levels with booster shots should help protect against Omicron, in the same way that boosters have improved protection against the Delta variant. "Omicron is scarier than anything we've known before, because it's a little bit worse still than Delta. But we were in quite a bad situation with Delta in unboosted populations," Altmann says.

Jesse Bloom, an evolutionary biologist at the Fred Hutchinson Cancer Research Center in Seattle, says that it will be important to determine the extent to which immune mechanisms other than neutralizing antibodies, such as T cells, ameliorate severe disease caused by infection.

It will also be important to see further studies confirming the latest results, because variables such as the type of cell used can affect their conclusions, says Pei-Yong Shi, a virologist at the University of Texas Medical Branch in Galveston. "In the next week or 10 days, there will be a lot of confirmatory results coming out," he says. SA

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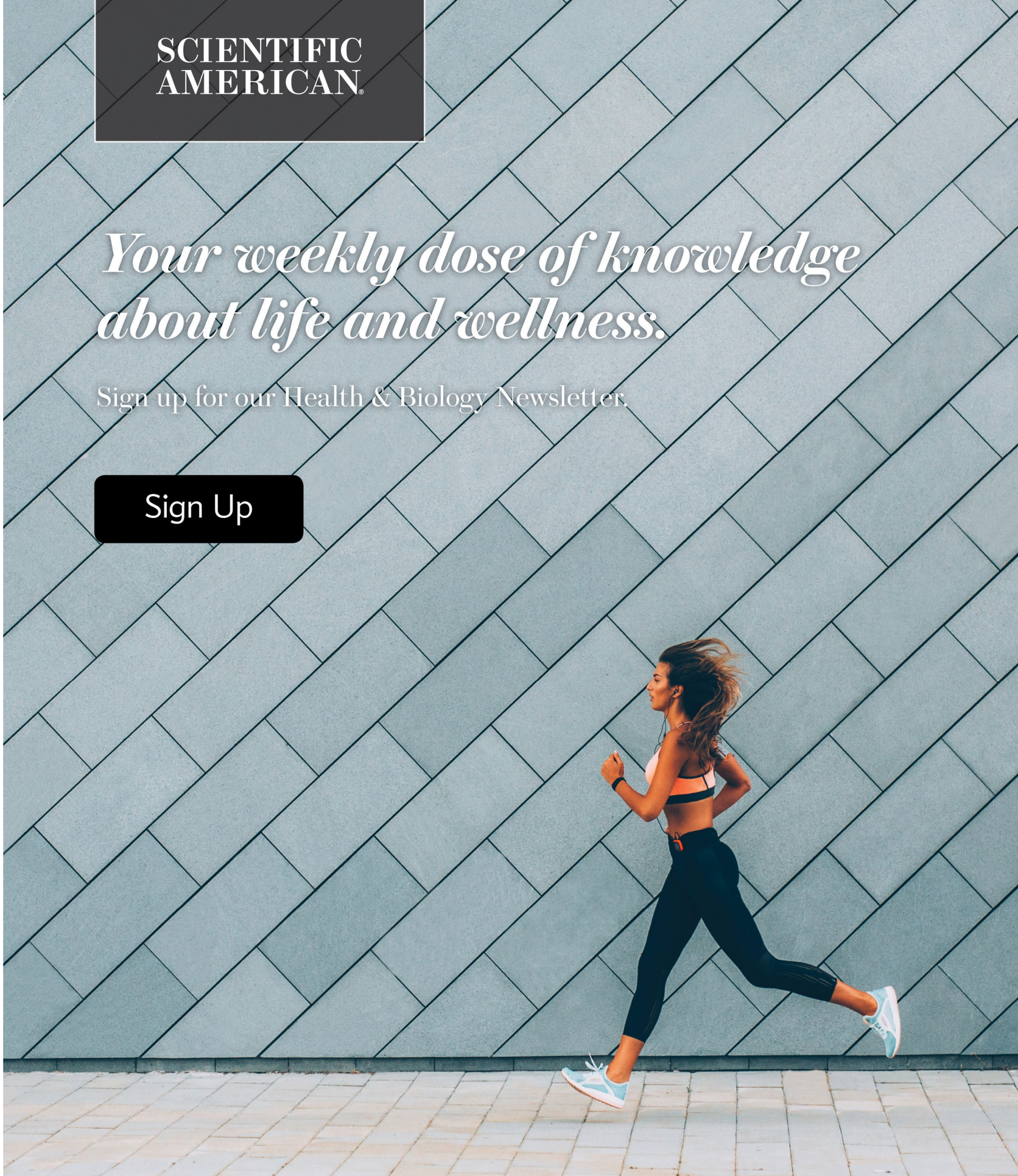


A child is prepared to receive a dose of the Pfizer-BioNTech COVID-19 vaccine at a high school in Lansdale, Pa., on November 7, 2021.

Hannah Beier/Bloomberg via Getty Images

The Benefits of Vaccinating Kids against COVID Far Outweigh the Risks of Myocarditis

Vaccination is likely to prevent many more COVID cases than it is to cause a rare and nonfatal heart side effect in five- to 11-year-olds

By Tanya Lewis

Tanya Lewis is a senior editor at *Scientific American* who covers health and medicine. Follow her on Twitter @tanyalewis314

PARENTS WHO ARE CONSIDERING WHETHER TO vaccinate their child against COVID may have heard about the risk of a rare side effect called myocarditis, an inflammation of the heart tissue that has occurred in some teenagers and young adults who have received an mRNA vaccine. These parents may be wondering, "Is this something I should be worried about for my child?"

Here is what scientists know: Vaccine-related myocarditis is extremely rare; estimates vary, but the highest figures suggest there have been fewer than 200 cases per million fully vaccinated males ages 12 to 15, the youngest age group for which such data currently exist. Only about 30 cases per million have been reported in vaccinated females of that age. Pfizer, whose mRNA vaccine was recently authorized for use in five- to 11-year-olds, says it did not observe any myocarditis cases in its clinical trial for the latter age group (it would be nearly impossible to design a trial large enough to detect such a rare effect). Scientists expect it to be even rarer in five- to 11-year-old kids compared with teens, because myocarditis from any cause is less common in the younger age group. The vaccine dose authorized for that group is lower as well.

The risk of getting COVID itself is much greater. From the beginning of March to October 10, over 1.9 million children in the U.S. ages five to 11 contracted the disease, according to data from the Centers for Disease Control and Prevention. More than 8,300 kids in that age range were hospitalized with COVID, and 94 died. In addition to causing an acute infection, COVID can also trigger a sometimes deadly inflammatory syndrome known as MIS-C, which is most common in the five to 11 age group. And, as in adults, COVID in children can also lead to lingering symptoms—such as fatigue, shortness of breath, or neurological issues—known as long COVID. Vaccination helps protect kids from all three conditions.

Scientists at the Food and Drug Administration have modeled the risks to children from COVID itself versus vaccine-related myocarditis. Their model compares the likely number of COVID cases, hospitalizations and deaths prevented among vaccinated kids aged five to 11 with the estimated number of "excess," or vaccine-related, myocarditis cases, hospitalizations and deaths (which were extrapolated from the risks in 12- to 15-year-olds). The model considers males and females separately, as young males have a higher risk of myocarditis compared with young females.

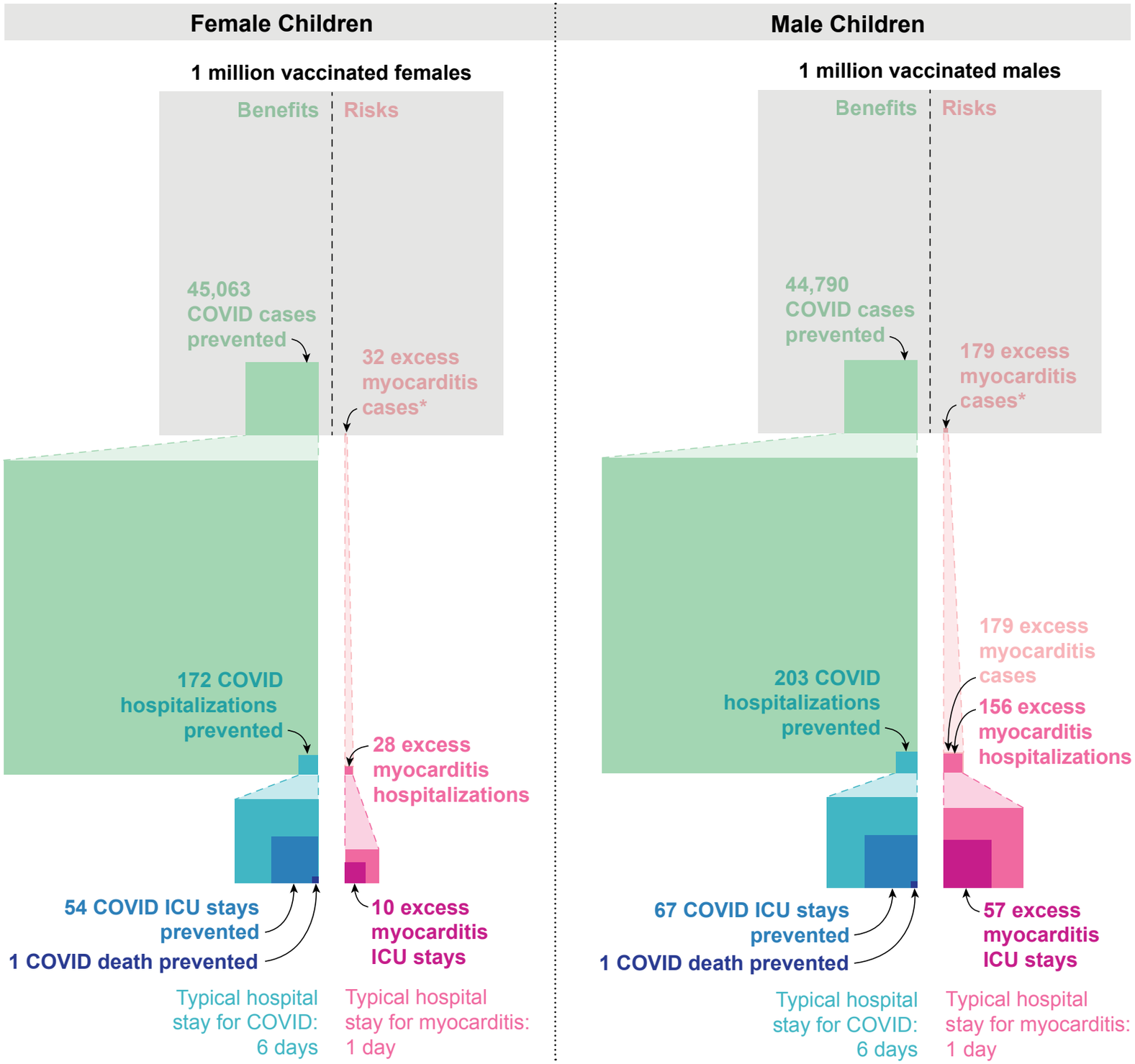
Ultimately the model indicates that the number of COVID cases prevented by vaccination vastly exceeds the number of excess myocarditis cases and that the number of COVID-related hospitalizations exceeds those for vaccine-related myocarditis as well. The model also suggests COVID vaccination will prevent one death per million vaccinated kids; no deaths from myocarditis are expected. The benefit-risk ratio of vaccination is even more pronounced for female children, for whom myocarditis is expected to be extremely rare.

The model's main scenario was based on the incidence of COVID in the U.S. as of September 11, 2021, and assumed a vaccine efficacy of 70 percent against disease and 80 percent against hospitalization. FDA researchers also modeled the risk-benefit trade-off for vaccinating kids under higher and lower rates of COVID transmission and hospitalization. Under the lower-transmission scenario, the risks of myocarditis from vaccination could potentially exceed the benefits of vaccination, especially for males. But under the higher-transmission scenario, the benefits of vaccination significantly outweighed the myocarditis risk. And if the rates of vaccine-related myocarditis in younger kids turn out to be lower than those in teenagers, as expected, the scale tilts even further in favor of vaccination.

"What we know from the adolescent and young adult age group is that the vaccine-associated myocarditis was a very rare occurrence," says Sallie Permar, chair of the pediatrics department at Weill Cornell Medicine and pediatrician in chief at New York–Presbyterian Koman-

COVID Vaccination for Children: Benefits versus Risks

These graphics quantify the benefits and risks of the Pfizer vaccine in male and female children, ages 5–11, assuming COVID case rates equivalent to those during the week of September 11, 2021 (about 148,000 weekly average).



Amanda Montañez; Source: U.S Food and Drug Administration, Vaccine and Related Biological Products Advisory Committee Meeting, October 26, 2021 (*data*)

sky Children's Hospital. Those who do develop this side effect typically have some chest pain and feel bad for a day, and blood tests show some inflammation of the heart, Permar says. They may be hospitalized for monitoring and treated with ibuprofen and usually walk out after a day. "That is completely different than the myocarditis that we see that's associated with virus itself," Permar says.

Myocarditis can also be triggered by infections, including COVID, which is far more likely to do so than vaccines are, Permar says. Moreover, COVID-related myocarditis symptoms are usually much more severe than those seen in vaccine-related myocarditis, with the former leading to an average hospital stay of six days instead of one, she says. Infection-related myocarditis often requires lifesaving interventions such as medicines that help keep the heart pumping or even a heart-lung bypass machine—and such cases often result in lasting heart damage.

As of December 1, 2021, about 4.2 million children between the ages of five and 11 had gotten at least one dose, according to the CDC. Vaccinating children protects not only them but people around them, too. This is especially important as winter approaches in the U.S. and people are spending more time indoors and with the new and potentially more transmissible Omicron variant circulating.

"Your children deserve to be protected against this virus as much as adults do," Permar says. "The more people we get vaccinated," she adds, "the better off we'll be." SA

**The values shown reflect vaccine-related myocarditis rates in 12–15-year-olds, the closest demographic for which data are available. Scientists believe that case rates are likely to be significantly lower in the 5–11 age group.*

Low-density lipoprotein, or "bad" cholesterol, is an accepted cause of heart disease.

Juan Gaertner/Science Photo Library/Getty Images

Is There More to a Healthy-Heart Diet Than Cholesterol?

A high-fat diet is thought to increase the risk of a heart attack. But some say that the long-held dogma of "bad" cholesterol might be flawed

By Natalie Healey

Natalie Healey is a journalist in London.

SHORTLY AFTER THE END OF the Second World War, large numbers of wealthy businessmen in the U.S. began dying from heart attacks. Shocked by the obituaries mounting up in his local newspaper, physiologist Ancel Keys decided to investigate. His findings would fundamentally change the way we eat for decades to come.

Keys couldn't understand why high-powered U.S. executives, with access to plentiful food, had much higher rates of coronary heart disease than did people in post-war Europe, where food shortages were common. Then it dawned on him: could there be a correlation between fat in the diet and heart disease? Keys presented his diet–heart hypothesis with gusto at a World Health Organization meeting in 1955. Six years later, his face appeared on the cover of *Time* magazine, in which he urged readers to shun fatty foods such as dairy products and red meat.

Keys's Seven Countries Study, launched in 1958, explored the diet, lifestyle and incidence of coronary heart disease in nearly 13,000 middle-aged men in Finland, Greece, Italy, Japan, the Netherlands, the U.S. and Yugoslavia. The findings showed that blood cholesterol levels and heart-attack death rates were highest in countries with diets high in saturated fat, such as the U.S. and Finland. Around the time that Keys was setting up his trial, the Framingham Study of more than 5,000 residents of a Massachusetts town identified high cholesterol as a major risk factor for coronary heart disease.

Landmark studies such as these laid the groundwork for the introduction of dietary guidelines in the U.S. and the U.K. during the 1970s and 1980s. The recommendations advised citizens to reduce their consumption of saturated fat to about 10 percent of their total energy intake, to lower cholesterol in the blood and therefore decrease the chances of a heart attack. In the public consciousness, a low-fat diet has been synonymous with good health ever since.

But not everybody agrees. Uffe Ravnskov, a Danish independent researcher based in Lund, Sweden, dismisses the relationship between dietary fats, cholesterol and coronary heart disease, calling it "the greatest medical scandal in modern time." Critics such as Ravnskov say data points in Keys's Seven Countries Study were cherry-picked to fit the conclusion. For instance, Keys did not include data from France, where the occurrence of heart disease was comparatively low at the time despite the nation's high-fat diet. Ravnskov's International Network of Cholesterol Skeptics, which has around 100 members—some of them cardiologists—says millions of people have been "badgered" into eating a "tedious and flavorless diet" out of fear for their hearts.

CHOLESTEROL CONFUSION

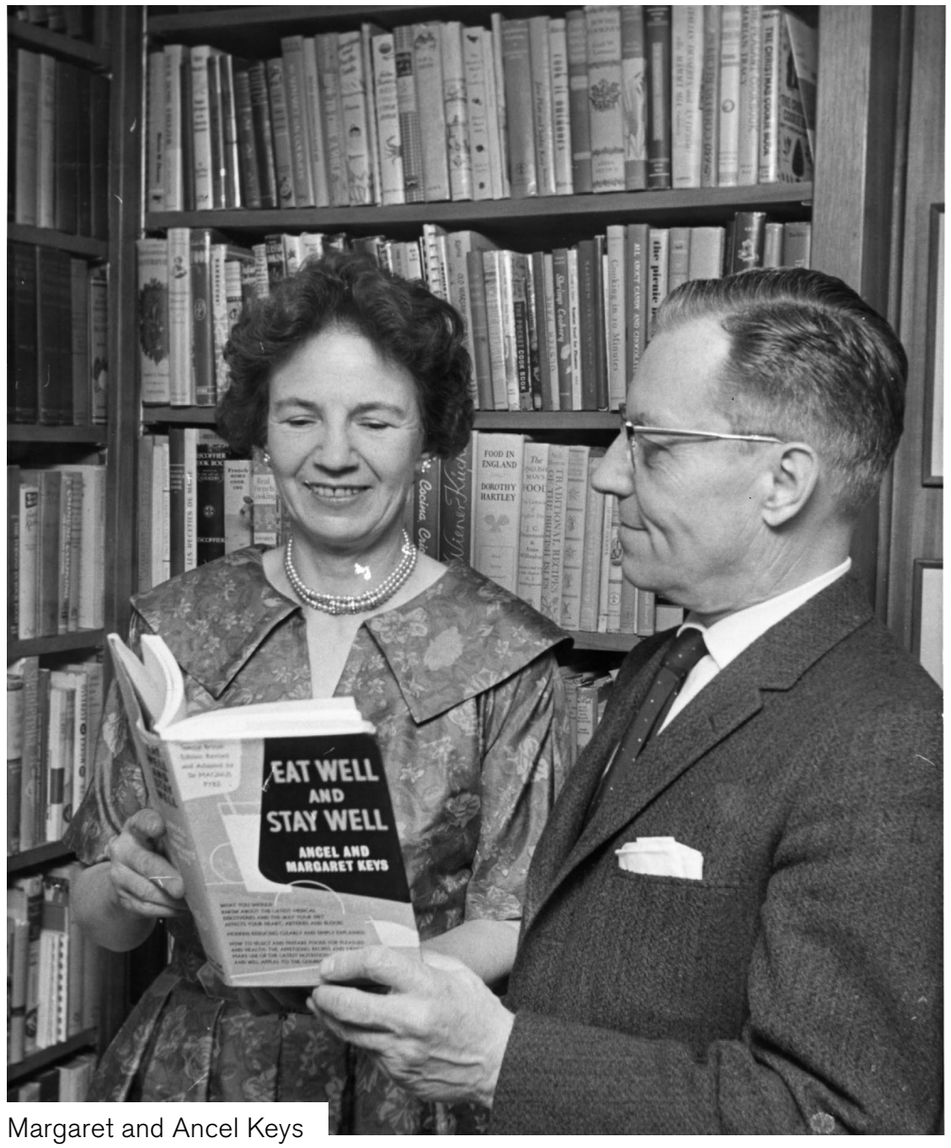
Robert DuBroff, a cardiologist at the University of New Mexico in Albuquerque, used to take the theory linking lipid in the diet with heart disease as gospel. But around 15 years ago, he noticed editorials critiquing the dogma were cropping up in the scientific literature. The debate prompted him to revisit the Framingham Study. He was surprised to find that the cholesterol levels of those who developed coronary heart disease and those who did not were pretty much the same, except when total cholesterol was either exceptionally high (more than 380 milligrams per deciliter) or low (less than 150 milligrams per deciliter). "For the vast majority of patients in the middle, cholesterol levels really did not distinguish those who did or did not develop heart disease," DuBroff says.

When cholesterol is implicated in causing cardiovascular problems, it is not the lipid itself that is the culprit, but rather the lipoproteins that carry cholesterol to and from cells. Broadly, these can be categorized into two groups: high-density lipoprotein (HDL), colloquially referred to as good cholesterol; and low-density lipoprotein (LDL), or bad cholesterol, that clogs arteries and increases the risk of heart attacks. This distinction was determined in the 1950s by U.S. physician John Gofman. His experiments analyzing the blood plasma of people who had had a heart attack found big increases in the levels of LDL, whereas HDL levels were lower than normal. The cholesterol theory gained widespread acceptance in 1984, when a trial of around 3,800 people found that those with lower levels of LDL had a reduced risk of having a heart attack or of needing bypass surgery.

The link between LDL and heart disease is indisputable, says Jane Armitage, an epidemiologist at the University of Oxford. As evidence, she points to studies of

people with familial hypercholesterolemia—a condition that arises from a mutation in the gene encoding the LDL receptor protein. This protein usually removes LDL cholesterol from the blood, but in people with the condition it is faulty. As a result, people with familial hypercholesterolemia have abnormally high levels of LDL cholesterol and, if left untreated, are up to 13 times more likely to develop coronary heart disease than someone without the mutation.

The advent of statins—medication that lowers LDL by inhibiting a cholesterol-producing enzyme in the liver—reinforced the view that LDL cholesterol has a substantial role in heart disease. In the early 1990s, the Scandinavian Simvastatin Survival Study showed that the statin simvastatin was effective at lowering LDL cholesterol and reducing the risk of a heart attack. Since then, numerous randomized clinical trials have shown that statins reduce heart attacks, strokes and death. A review in 2016 concluded that, for every 10,000 people with vascular disease, a daily statin would prevent 1,000 heart attacks, strokes and coronary artery bypasses. "For people to doubt that statins save lives in high-risk people seems to be just extraordinary in the light of the very strong evidence," says Armitage.



Margaret and Ancel Keys

Some researchers, however, still have their doubts. DuBroff argues that the substantial body of evidence supporting statins has never been properly validated. His systematic review of published clinical trials comparing several cholesterol-lowering drugs with placebos found that the medications did not necessarily reduce the risk of death. And although most specialists broadly consider the evidence for statins to be strong, the same can't be said of cholesterol-lowering drugs with different mechanisms of action, such as fibrates and ezetimibe, he says. "If this concept of lowering cholesterol is valid," he asks, "then why aren't these other agents equally effective at reducing cardiovascular events?"

FAT OR FICTION

Armitage insists that the cholesterol theory is scientifically sound, but she admits it is difficult to draw direct conclusions about heart disease from dietary studies. In gold-standard randomized controlled trials, people replace saturated fats in their diets with polyunsaturated fatty acids, such as those found in vegetable oil, and this reduces the levels of LDL cholesterol in the blood. But, curiously, most trials have failed to show a mortality benefit. Many other dietary studies looking at heart disease are observational and rely on participants completing a food questionnaire from memory—a method that has its limitations. "Such approaches give a general indication of the types of food that are associated with heart disease," says Tim Chico, a cardiologist at the University of Sheffield. But, "an association doesn't prove that there is a causal link," he adds.

This swirl of contradictory findings could indicate that the perils of eating saturated fat have been overstated and that other dietary components that contribute to the pathogenesis of heart disease might have been overlooked. Four years before Keys appeared on the cover of *Time,* British physiologist John Yudkin floated the idea that the real danger to public health was sugar. His findings were largely ignored at the time. In 2016, however, it was revealed that influential research in the 1960s that had downplayed the role of sugar in coronary heart disease had been funded by the sugar industry.

Shortly after this revelation, results from the PURE (Prospective Urban Rural Epidemiology) study suggested that diets high in carbohydrates, not fats, are the ticket to an early grave. The study found no association between high-fat intake and the occurrence of heart attacks or cardiovascular disease. Moreover, it suggested that diets high in saturated fat actually reduced the risk of stroke by roughly 20 percent. "Emerging data are showing us that refined sugars are likely the main culprits in our diet, not fat," says lead researcher Mahshid Dehghan, a nutritionist at the Population Health Research Institute in Hamilton, Canada. But PURE was an observational study that relied on questionnaires and so had the same limitations as many

Pete Hohn/Star Tribune via Getty Images

other nutritional studies.

DuBroff stops short of calling himself an all-out cholesterol skeptic, but he is convinced that placing the blame on bad cholesterol gives, at best, a partial picture. “Focusing just on LDL is an oversimplification of a very complex disease process,” he says. He points out that research co-authored by Ravnskov found that people with the highest level of LDL cholesterol seem to live longer than those with the lowest levels. And research in 2019 suggested that levels of a particular subclass of LDL might be a better predictor of heart attacks than is the total amount of LDL present. Clearing up the confusion about the effect of cholesterol, DuBroff says, will require more research into other biochemical mechanisms and dietary components that could cause heart disease, such as insulin resistance and inflammation.

Despite critics poking holes in his most famous work, Keys’s lifestyle seemed to have worked for him. He died in 2004 at the age of 100, having followed a Mediterranean diet (rich in olive oil, starchy foods and vegetables, and low in saturated animal fat) for most of his life. This is the plan Chico recommends for his patients. He’s not fussed if they want to forgo the pasta and also make the diet low in carbohydrates. “Why does it have to be an either–or?” he says. “I would very much like to see a more constructive discussion about how we tackle the multiple influences of heart disease, rather than a popularity contest between one or the other.” SA

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Four Success Stories in Gene Therapy

The field is beginning to fulfill its potential. These therapies offer a glimpse of what's to come

By Jim Daley

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AFTER NUMEROUS SETBACKS AT THE TURN of the century, gene therapy is treating diseases ranging from neuromuscular disorders to cancer to blindness. The success is often qualified, however. Some of these therapies have proved effective at alleviating disease but come with a high price tag and other accessibility issues: Even when people know that a protocol exists for their disease and even if they can afford it or have an insurance company that will cover the cost—which can range from $400,000 to $2 million—they may not be able to travel to the few academic centers that offer it. Other therapies alleviate symptoms but don't eliminate the underlying cause.

"Completely curing patients is obviously going to be a huge success, but it's not [yet] an achievable aim in a lot of situations," says Julie Crudele, a neurologist and gene therapy researcher at the University of Washington. Still, even limited advances pave the way for ongoing progress, she adds, pointing to research in her patients who have Duchenne muscular dystrophy: "In most of these clinical trials, we learn important things."

Thanks to that new knowledge and steadfast investigations, gene therapy researchers can now point to a growing list of successful gene therapies. Here are four of the most promising.

GENE SWAPS TO PREVENT VISION LOSS

Some babies are born with severe vision loss caused by retinal diseases that once led inevitably to total blindness. Today some of them can benefit from a gene therapy created by wife-and-husband team Jean Bennett and Albert Maguire, who are now ophthalmologists at the University of Pennsylvania.

When the pair first began researching retinal disease in 1991, none of the genes now known to cause vision loss and blindness had been identified. In 1993 researchers identified one potential target gene, *RPE65*. Seven years later Bennett and Maguire tested a therapy targeting that gene in three dogs with severe vision loss—it restored vision for all three.

In humans, the inherited condition that best corresponds with the dogs' vision loss is Leber congenital amaurosis (LCA). LCA prevents the retina, a layer of light-sensitive cells at the back of the eye, from properly reacting or sending signals to the brain when a photon strikes it. The condition can cause uncontrolled shaking of the eye (nystagmus), prevents pupils from responding to light and typically results in total blindness by age 40. Researchers have linked the disease to mutations or deletions in any one of 27 genes associated with retinal development and function. Until gene therapy, there was no cure.

Mutations in *RPE65* are just one cause of inherited retinal dystrophy, but it was a cause that Bennett and Maguire could act on. The researchers used a harmless adeno-associated virus (AAV), which they programmed to find retinal cells and insert a healthy version of the gene, and injected it into a patient's eye directly underneath the retina. In 2017, after a series of clinical trials, the Food and Drug Administration approved voretigene neparvovecrzyl (marketed as Luxturna) for the treatment of any heritable retinal dystrophy caused by the mutated *RPE65* gene, including LCA type 2 and retinitis pigmentosa, another congenital eye disease that affects photoreceptors in the retina. Luxturna was the first FDA-approved in vivo gene therapy, which is delivered to target cells inside the body (previously approved ex vivo therapies deliver the genetic material to target cells in samples collected from the body, which are then reinjected).

Spark Therapeutics, the company that makes Luxturna, estimates that about 6,000 people worldwide and between 1,000 and 2,000 in the U.S. may be eligible for its treatment—few enough that Luxturna was granted "orphan drug" status, a designation that the FDA uses to incentivize development of treatments for rare diseases. That wasn't enough to bring the cost down. The therapy is priced at about $425,000 per injection, or nearly $1 million for both eyes. Despite the cost, Maguire says, "I have not yet seen anybody in the U.S. who hasn't gotten access based on inability to pay."

Those treated show significant improvement: Patients who were once unable to see clearly had their vision restored, often very quickly. Some reported that, after the injections, they could see stars for the first time.

While it is unclear how long the effects will last, follow-up data published in 2017 showed that all 20 patients treated with Luxturna in a phase 3 trial had retained their improved vision three years later. Bennett says five-year follow-up with 29 patients, which is currently under-

going peer review, showed similarly successful results. "These people can now do things they never could have dreamed of doing, and they're more independent and enjoying life."

TRAINING THE IMMUNE SYSTEM TO FIGHT CANCER

Gene therapy has made inroads against cancer, too. An approach known as chimeric antigen receptor (CAR) T cell therapy works by programming a patient's immune cells to recognize and target cells with cancerous mutations. Steven Rosenberg, chief of surgery at the National Cancer Institute, helped to develop the therapy and published the first successful results in a 2010 study for the treatment of lymphoma.

"That patient had massive amounts of disease in his chest and his belly, and he underwent a complete regression," Rosenberg says—a regression that has now lasted 11 years and counting.

CAR T cell therapy takes advantage of white blood cells, called T cells, that serve as the first line of defense against pathogens. The approach uses a patient's own T cells, which are removed and genetically altered so they can build receptors specific to cancer cells. Once infused back into the patient, the modified T cells, which now have the ability to recognize and attack cancerous cells, reproduce and remain on alert for future encounters.

In 2016 researchers at the University of Pennsylvania reported results from a CAR T cell treatment, called tisagenlecleucel, for acute lymphoblastic leukemia (ALL), one of the most common childhood cancers. In patients with ALL, mutations in the DNA of bone marrow cells cause them to produce massive quantities of lymphoblasts, or undeveloped white blood cells, which accumulate in the bloodstream. The disease progresses rapidly: adults face a low likelihood of cure, and fewer than half survive more than five years after diagnosis.

"Completely curing patients is obviously going to be a huge success, but it's not [yet] an achievable aim in a lot of situations."
—Julie Crudele

When directed against ALL, CAR T cells are ruthlessly efficient—a single modified T cell can kill as many as 100,000 lymphoblasts. In the University of Pennsylvania study, 29 out of 52 ALL patients treated with tisagenlecleucel went into sustained remission. Based on that study's results, the FDA approved the therapy (produced by Novartis as Kymriah) for treating ALL, and the following year the agency approved it for use against diffuse large B cell lymphoma. The one-time procedure costs upward of $475,000.

CAR T cell therapy is not without risk. It can cause severe side effects, including cytokine release syndrome (CRS), a dangerous inflammatory response that ranges from mild flulike symptoms in less severe cases to multiorgan failure and even death. CRS isn't specific to CAR T therapy: Researchers first observed it in the 1990s as a side effect of antibody therapies used in organ transplants. Today, with a combination of newer drugs and vigilance, doctors better understand how far they can push treatment without triggering CRS. Rosenberg says that "we know how to deal with side effects as soon as they occur, and serious illness and death from cytokine release syndrome have dropped drastically from the earliest days."

Through 2020, the remission rate among ALL patients treated with Kymriah was about 85 percent. More than half had no relapses after a year. Novartis plans to track outcomes of all patients who received the therapy for 15 years to better understand how long it remains effective.

PRECISION EDITING FOR BLOOD DISORDERS

One new arrival to the gene therapy scene is being watched particularly closely: in vivo gene editing using a system called CRISPR, which has become one of the most promising gene therapies since Jennifer Doudna and Emmanuelle Charpentier discovered it in 2012—a feat for which they shared the 2020 Nobel Prize in Chemistry. The first results from a small clinical trial aimed at treating sickle cell disease and a closely related disorder, called beta thalassemia, were published this past June.

Sickle cell disease affects millions of people worldwide and causes the production of crescent-shaped red blood cells that are stickier and more rigid than healthy cells, which can lead to anemia and life-threatening health crises. Beta thalassemia, which affects millions more, occurs when a different mutation causes someone's body to produce less hemoglobin, the iron-rich protein that allows red blood cells to carry oxygen. Bone marrow transplants may offer a cure for those who can find matching donors, but otherwise treatments for both consist primarily of blood transfusions and medications to treat associated complications.

Both sickle cell disease and beta thalassemia are caused by heritable, single-gene mutations, making them good candidates for gene-editing therapy. The method, CRISPR-Cas9, uses DNA sequences from bacteria (clustered regularly interspaced short palindromic repeats, or CRISPR) and a CRISPR-associated enzyme (Cas for short) to edit the patient's genome. The CRISPR sequences are transcribed onto RNA that locates and

identifies DNA sequences to blame for a particular condition. When packaged together with Cas9, transcribed RNA locates the target sequence, and Cas9 snips it out of the DNA, thereby repairing or deactivating the problematic gene.

At a conference this past June, Vertex Pharmaceuticals and CRISPR Therapeutics announced unpublished results from a clinical trial of beta thalassemia and sickle cell patients treated with CTX001, a CRISPR-Cas9-based therapy. In both cases, the therapy does not shut off a target gene but instead delivers a gene that boosts production of healthy fetal hemoglobin—a gene normally turned off shortly after birth. Fifteen people with beta thalassemia were treated with CTX001; after three months or more, all 15 showed rapidly improved hemoglobin levels and no longer required blood transfusions. Seven people with severe sickle cell disease received the same treatment, all of whom showed increased levels of hemoglobin and reported at least three months without severe pain. More than a year later those improvements persisted in five subjects with beta thalassemia and two with sickle cell. The trial is ongoing, and patients are still being enrolled. A Vertex spokesperson says it hopes to enroll 45 patients in all and file for U.S. approval as early as 2022.

DERAILING A POTENTIALLY LETHAL ILLNESS

Spinal muscular atrophy (SMA) is a neurodegenerative disease in which motor neurons—the nerves that control muscle movement and that connect the spinal cord to muscles and organs—degrade, malfunction and die. It is typically diagnosed in infants and toddlers. The underlying cause is a genetic mutation that inhibits production of a protein involved in building and maintaining those motor neurons.

The four types of SMA are ranked by severity and related to how much motor neuron protein a person's cells can still produce. In the most severe or type I cases, even the most basic functions, such as breathing, sitting and swallowing, prove extremely challenging. Infants diagnosed with type I SMA have historically had a 90 percent mortality rate by one year.

"If we could figure out why this exon was being skipped and if we could find a solution for that, then presumably this could help all the [SMA] patients."
—Adrian Krainer

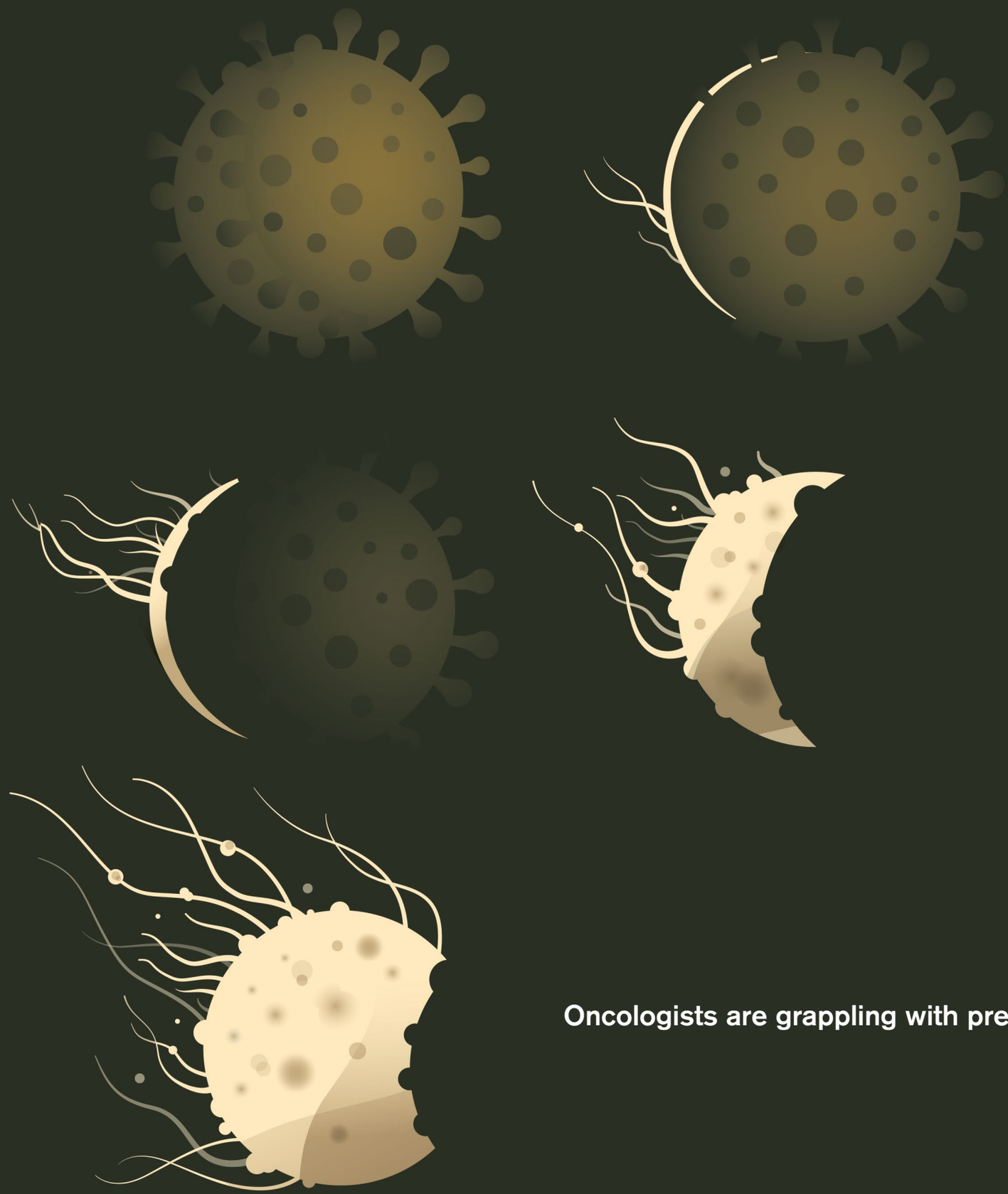
Adrian Krainer, a biochemist at Cold Spring Harbor Laboratory, first grew interested in SMA when he attended a National Institutes of Health workshop in 1999. At the time, Krainer was investigating how RNA mutations cause cancer and genetic diseases when they disrupt a process called splicing, and researchers suspected that a defect in the process might be at the root of SMA. When RNA is transcribed from the DNA template, it needs to be edited or "spliced" into messenger RNA (mRNA) before it can guide protein production. During that editing process, some sequences are cut out (introns), and those that remain (exons) are strung together.

Krainer realized that there were similarities between the defects associated with SMA and one of the mechanisms he had been studying—namely, a mistake that occurs when an important exon is inadvertently lost during RNA splicing. People with SMA were missing one of these crucial gene sequences, called *SMN1*.

"If we could figure out why this exon was being skipped and if we could find a solution for that, then presumably this could help all the [SMA] patients," Krainer says. The solution he and his colleagues hit on, antisense therapy, employs single strands of synthetic nucleotides to deliver genetic instructions directly to cells in the body [see "The Gene Fix"]. In SMA's case, the instructions induce a different motor neuron gene, *SMN2*, which normally produces small amounts of the missing motor neuron protein, to produce much more of it and effectively fill in for *SMN1*. The first clinical trial to test the approach began in 2010, and by 2016 the FDA approved nusinersen (marketed as Spinraza). Because the therapy does not incorporate itself into the genome, it must be administered every four months to maintain protein production. And it is staggeringly expensive: a single Spinraza treatment costs as much as $750,000 in the first year and $375,000 annually thereafter.

Since 2016, more than 10,000 people have been treated with it worldwide. Although Spinraza can't restore completely normal motor function (a single motor neuron gene just can't produce enough protein for that), it can help children with any of the four types of SMA live longer and more active lives. In many cases, Spinraza has improved patients' motor function, allowing even those with more severe cases to breathe, swallow and sit upright on their own. "The most striking results are in patients who are being treated very shortly after birth, when they have a genetic diagnosis through newborn screening," Krainer says. "Then, you can actually prevent the onset of the disease—for several years and hopefully forever." SA

This article is part of "Innovations In: Gene Therapy," an editorially independent special report that was produced with financial support from Pfizer.



The COVID Cancer Effect

Oncologists are grappling with predicting—and mitigating—the effects of the pandemic

By Usha Lee McFarling

Illustration by Harry Campbell

Usha Lee McFarling is a Pulitzer Prize–winning science and medical writer based in Los Angeles. Follow Usha Lee McFarling on Twitter.

AS the novel coronavirus swept through Boston in March 2020, Toni Choueiri was worried. He was concerned not only about the rapid rise in COVID infections but about the swift shutdown in cancer screenings.

In Boston—and around the nation—colonoscopy suites stood empty as patients refused to come in, terrified of setting foot in any hospital or clinic. Screening center schedules, once full of mammography appointments, cleared dramatically. Hospital corridors quieted; screening center workers were sent home. Hospital administrators struggled to find enough PPE to take care of urgent surgeries, and elective procedures fell to the wayside. As COVID cases surged frighteningly across the country, cancer detection seemed to be the last thing on anyone's mind.

Choueiri, who directs the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute, saw a steep drop in new consultations in the pandemic's early months. The veteran oncologist feared that the lack of screenings, which aim to detect cancer at its earliest stages, would lead to a tidal wave of missed diagnoses. He worried about tumors seeding, taking hold, growing and metastasizing without being detected. He envisioned a future with streams of patients who had cancers so advanced he could no longer cure them.

Driven by these concerns and a desire to know exactly how bad the problem was, Choueiri and his colleagues turned to the data. Their study, published in *JAMA Oncology* in January 2021, showed a steep drop in screening from March to June of 2020 in his health system, Massachusetts General Brigham. More than 60,000 patients are typically screened there for cancer in a three-month period; in the first three months of the pandemic, he says, fewer than 16,000 came in for tests. In those early days National Cancer Institute officials estimated the pandemic would result in 10,000 excess cancer deaths in breast and colon cancer alone over the coming decade.

Screenings for some cancers fell by 90 percent when COVID struck, making a postpandemic surge of cancer deaths seem a foregone conclusion. As the pandemic wore on, some cancer centers began to report a worrisome increase in advanced cancer diagnoses. But as more time passed and screenings resumed, the outlook grew less dire. COVID may prove to be a grand experiment assessing the import of cancer screening, and results are beginning to trickle in. But because both the disease and its epidemiology are so complex, those results may take years, or even decades, to become clear.

SKIPPED SCREENINGS

One patient whose pandemic screening turned up early-stage breast cancer was Senator Amy Klobuchar of Minnesota. After delaying the procedure, she had a routine mammogram in February 2021. With surgery and radiation completed and a good prognosis in hand, Klobuchar is urging others not to put off their screenings. "I hope my experience is a reminder for everyone of the value of routine health checkups, exams and follow-through," she wrote in a recent blog post.

Cancer kills some 600,000 people in the U.S. every year. Screening tests such as Pap smears, mammograms, colonoscopies, lung scans and prostate-specific antigen tests clearly save lives: although rates vary by cancer type, five-year survival is consistently higher when the disease is caught in its early stages. Yet as the pandemic spread throughout the U.S. and the world, rates of those routine screenings fell precipitously. This was especially true for colonoscopies, the most invasive screening and an exam that many avoided even before the pandemic. Choueiri's health system usually performs more than 9,000 colonoscopies in any three-month period; in March, April and May of 2020, there were just over 1,700 in total. Similar drop-offs were seen across the country, where in some cases up to 95 percent of colonoscopies were missed in the first months of the pandemic.

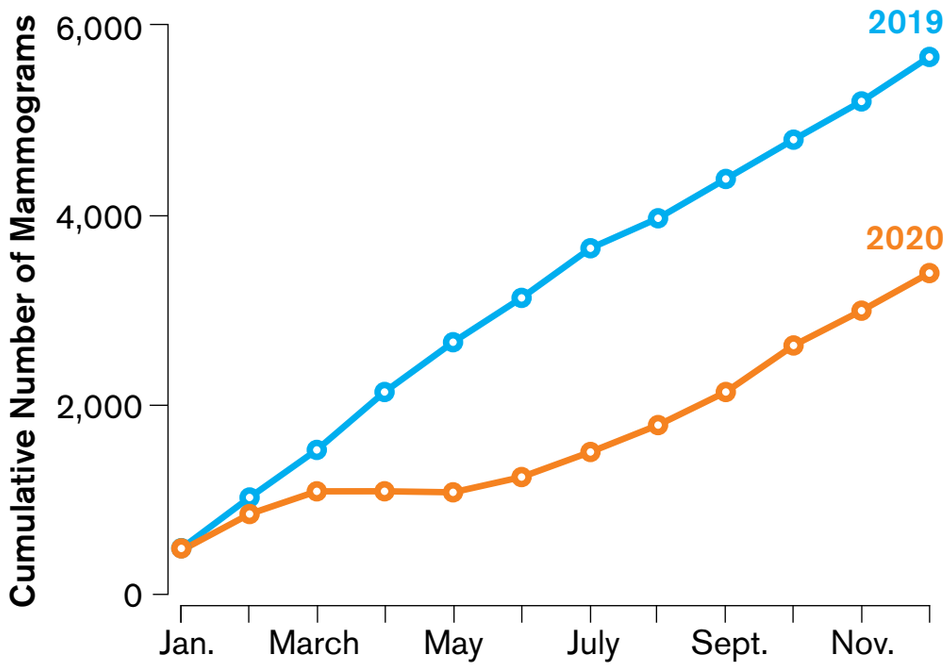
Screening rates synchronized with pandemic waves, bouncing back in the summer of 2020 before falling during subsequent surges. Those who never rescheduled may be up to two years behind. "Between the peaks, what we didn't see was sufficient recovery," says Karen E. Knudsen, chief executive officer of the American Cancer Society. "We've made progress getting people back in the door, but there's a large population that is underscreened. We don't know the impact of this yet, but it's definitely a problem."

One major issue, Knudsen says, is that people who miss screenings aren't always flagged for follow-up. And some tests, such as those for prostate cancer, are harder

to track using medical records because of how they are coded. In fact, she says, determining how many people are overdue for screening is virtually impossible because of the diverse settings in which patients receive screenings and because there is no national infrastructure that tracks them in real time. "We don't know who didn't come back," Knudsen says.

According to a study published in *JAMA Oncology* in April, nearly 10 million people missed screenings for breast, colon and prostate cancer between March and May of 2020, but no one knows how many of those tests remain unscheduled. Those who missed screenings, Knudsen says, are likely to be people who haven't been screened before, because they either just became eligible during the pandemic or were already hesitant. "We can infer that hesitancy is only enhanced with COVID," Knudsen says.

Case Study: Breast Cancer Screening before and during COVID in a San Francisco Hospital



Jen Christiansen; Source: "Trends in Breast Cancer Screening in a Safety-Net Hospital during the COVID-19 Pandemic," by Hana I. Velazquez et al., in *JAMA Network Open;* August 6, 2021 (*data*)

TRACKING MISSING PATIENTS

Coaxing overdue patients into a clinic is one of Rachel Issaka's primary concerns. Issaka, a gastroenterologist and assistant professor at the Fred Hutchinson Cancer Research Center and University of Washington, says it is critical that health systems track down these missing patients. A study she published in June found that hundreds of colonoscopies were canceled between March and May 2020, and more than half of those people had not yet returned. Of those who did, more than 5 percent had new cancers. That implies that around 5 percent of the people who haven't returned may also have cancer, she says, but won't know it. Similar scenarios are likely playing out at health systems across the country; a study that surveyed gastroenterology practices last year found that two thirds did not yet have a plan in place to follow up on missed appointments, although some have now begun this work in earnest.

Issaka is working diligently to contact and shepherd in her more skittish patients. One powerful tool is at-home detection tests for colon cancer. A low-cost fecal immunochemical test, or FIT, can detect blood or tumor DNA in stools and catch 70 percent of colon cancer cases. But a positive FIT result requires a follow-up colonoscopy, and scheduling that, Issaka says, remains challenging.

Telehealth has proved a surprisingly effective way to persuade overdue patients to visit the clinic. A study published in *JAMA Oncology* last spring examined the precipitous drop in breast, colon and prostate cancer screenings and found that telehealth patients were more likely to come in for exams. Patients who are concerned about in-person screenings can use telehealth appointments to talk with their primary care physicians about setting up a plan based on personal and familial risk factors, says the American Cancer Society's Knudsen. "Screening is knowledge. It's power," she says.

Although much communication in oncology, particularly of bad news, is best done in person, the pandemic has shown that telemedicine can play an important role in cancer care and should remain in place, says Choueiri, who is also a professor of medicine at Harvard Medical School. "It's helped a lot," he says. "We can stay in touch with patients, maybe even better than before."

The pandemic-imposed challenges to screening prompted the American Cancer Society to create tool kits explaining current screening guidelines in clear and simple language. It is also spreading the word that patient access to screening must be made easier. One way is to move screenings out of hospitals and into clinics and, when possible, even mobile vans. Another is to open up scheduling in off-hours. "Can you do screenings on Saturdays or in the evenings?" Knudsen asks. "Those turned out to be really popular times for mammography."

UNCERTAIN MORTALITY MODELS

There is little doubt that the chaos ushered in by the pandemic will lead to more cancer deaths. But determining how many has been difficult: many cancers are slow-growing, their development can be complex, and factors such as treatment decisions play a big role in outcomes. To assess how missed screenings might affect cancer mortality rates, the National Cancer Institute turned to Oguzhan Alagoz, a professor of industrial and systems engineering at the University of Wisconsin–Madison

whose research involves modeling both cancer epidemiology and infectious diseases.

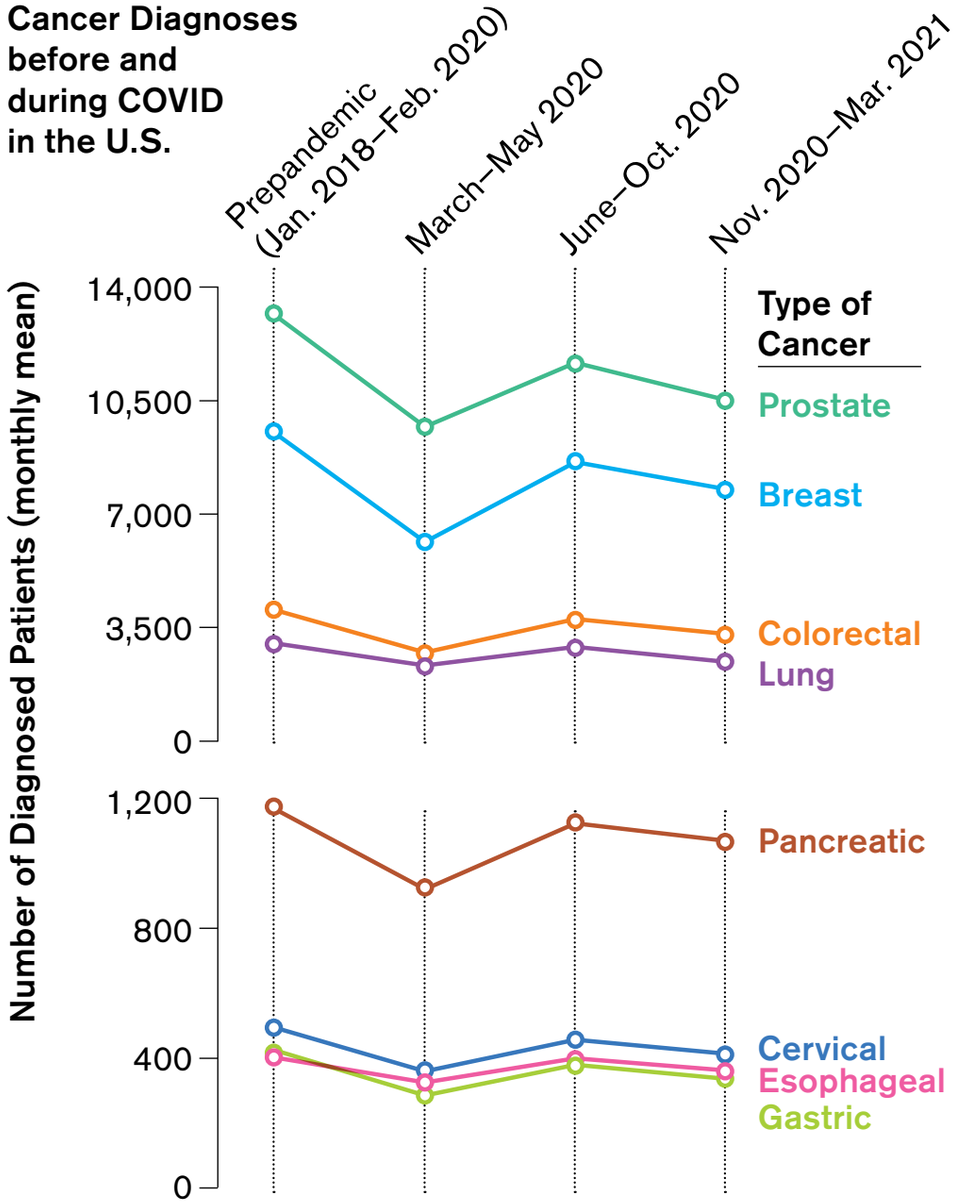
"The question is really interesting because it's a combination of the two areas I work in," Alagoz says. His first estimates, unveiled in a widely read editorial published in *Science* in June by NCI director Normal E. Sharpless, showed that missed screenings might result in 5,000 additional deaths in breast cancer alone over the next decade. A separate group, looking at missed colon cancer screenings, predicted another 5,000 deaths.

When Alagoz produced his breast cancer estimates early in the pandemic, he thought the numbers might not be truly representative. So he worked to refine them, using better data with three powerful cancer models that incorporated numerous factors related to breast cancer—such as delayed screening, treatment effectiveness and long-term survival rates—and the nuanced ways they intersect to affect mortality over time. "Everyone can tell you what will happen immediately, but it's hard to say what's going to happen in five or 10 years," Alagoz says. "If there's a huge increase in smoking, you're not going to see more lung cancer right away. You're going to see that 10 or 15 years down the road."

After a more detailed analysis and after seeing screenings rebound from what he calls the "panic phase" of March and April 2020, Alagoz now says those early mortality numbers were far too high. In revised estimates, published in the *Journal of the National Cancer Estimate* last April, Alagoz and his colleagues suggested the pandemic could lead to 2,500 excess breast cancer deaths in the coming decade, half as many as they had first predicted. "The entire estimate was too pessimistic," he says. "Any individual death is sad, but if there is any silver lining, it's that this isn't as bad as we feared."

One reason death rates may be curbed, Choueiri says, is that oncologists did aggressive triage work to screen and treat patients who needed care most. His hospital system reported fewer missed cancer diagnoses than he expected, and he thinks this was because people at highest risk of cancer and those with palpable symptoms were most likely to be screened even during the pandemic's most dangerous peaks. "Screenings never stopped 100 percent," Choueiri says. "Who were the patients who continued to be screened? They were the highest, highest risk."

Some oncologists say this "risk stratification"—prioritizing screening, diagnosis and treatment for those most at risk or with obvious symptoms—should stay in place after the pandemic ends so treatment can be provided quickly to those who need it most.



Jen Christiansen; Source: "Changes in Newly Identified Cancer among U.S. Patients from before COVID-19 through the First Full Year of the Pandemic," by Harvey W. Kaufman et al., in *JAMA Network Open*; August 31, 2021 (data)

COVID'S LONG SHADOW

Understanding the pandemic's effects on cancer mortality is a complicated task because delayed screenings aren't the only factor involved. Increased alcohol consumption and reduced physical activity—behaviors common during long pandemic lockdowns—can increase cancer risk as well. But postponing an exam can be a major danger. In November 2020 Vincent Valenti, a retired screenwriter in Brooklyn, noticed his voice was hoarse. He attributed it to all the screaming he did on election night. But it persisted for weeks, and his girlfriend encouraged him to get it checked. Valenti, 71, refused. He wasn't going near a hospital or doctor until he was vaccinated. "You walked by hospitals, and there were all these morgue trucks parked outside," he says. "I knew something was wrong, but I wasn't going to go near a hospital." In February of this year, once he had received two doses of vaccine, he scheduled an appointment with an E.N.T. "She

scoped me and jumped back," he says.

There was a tumor on his larynx, stage 3, that had almost reached his lymph nodes. It was a shock to both Valenti and his doctor. He wasn't considered high risk for laryngeal cancer because he doesn't drink heavily or smoke. After seven weeks of chemotherapy and radiation, Valenti says, there was no trace of the tumor, and a recent PET scan confirmed that the cancer did not metastasize. Valenti was told his cancer would likely have been caught at stage 2, or even stage 1, if he had gone in right away.

Research published in *JAMA Network Open* in August shows that Valenti is far from alone. The study reports that diagnoses of eight cancer types dropped nearly 30 percent during the first pandemic wave of 2020, rebounded somewhat during the summer and early fall, then fell by 20 percent during the pandemic's winter surges. Such consistently low numbers indicate that many cases will continue to be undiagnosed, the authors wrote.

Some programs have already reported an increase in the detection of cancers. Lung cancer, the nation's leading cause of cancer death, is of particular concern because it can be so aggressive. The University of Cincinnati's lung cancer screening program was closed for three months. When screening resumed, patients remained scarce, and no-shows were frequent. But among those who did come in, "we noticed we were seeing many more suspicious lung nodules than usual," says Robert Van Haren, a thoracic surgeon and assistant professor of surgery at the University of Cincinnati Medical Center, who analyzed the effect of the pandemic on cancer screenings. "Even small changes in the size of a lung cancer can be important for overall survival," he says. "That's the reason we're concerned about any delays or stoppages."

Whether the pandemic has already caused an increase in dire cancer prognoses more broadly is still an open question. Choueiri hasn't run the numbers and is not sure yet whether his practice is facing more advanced cancer diagnoses. So far the picture is worrisome to him, but it is less so than he originally feared.

"Testing for many cancers, such as mammograms, has largely returned. Why did it return to normal? Simply because the hospitals, and all of us, put measures into place to make this as safe as possible."
—Toni Choueiri

This is largely because screening did rebound. If the pandemic was turning out to be a natural experiment on the toll of missed cancer screenings, thankfully it was one that ended earlier than expected. "Testing for many cancers, such as mammograms, has largely returned," says Choueiri, who has co-authored several studies tracking the pandemic's effect on cancer screening. "Why did it return to normal? Simply because the hospitals, and all of us, put measures into place to make this as safe as possible."

DEEPENING HEALTH DISPARITIES

But timely screening hasn't returned for everyone. Those looking at the data see disturbing gaps in the populations that are coming back and those that aren't, gaps that may be deepening racial and ethnic disparities in cancer care and mortality. At his health system, Choueiri says, fewer Black and Hispanic patients rescheduled mammograms from June to December 2020, even after screenings rebounded in other groups. Van Haren saw something similar in his Cincinnati clinics: more screening no-shows for patients at highest risk of lung cancer death, including those who were current smokers and those who were Black. "It's concerning," Choueiri says. "The pandemic may have accentuated racial disparities related to cancer screening that already existed."

Black people are already 40 percent more likely to die from colon cancer than other groups. Issaka fears those numbers could now grow worse. "Before the pandemic, African-Americans, Hispanics and Native Americans were not screening at high rates. With COVID, my concern was that these same populations that were hard hit by the pandemic wouldn't come for screening," she says. "I worry that five to 10 years from now, we're going to see patients in those groups presenting with advanced disease and higher mortality."

Because colon cancers are usually slow-growing, it's not too late to prevent these deaths. "We need to be very proactive," Issaka says. "We still have the opportunity to turn the tide."

One of the people working to do so is Kathy Briant, assistant director for the Fred Hutchinson Cancer Research Center's office of community outreach and engagement. Cancer-screening outreach was one of the pandemic's biggest casualties, particularly among racial, ethnic and low-income groups that have historically had lower access to screening tests and are far less likely to be up-to-date on cancer screening than white and high-income patients.

Briant has had to mothball the giant inflatable walk-through colon she used to send to events in tribal areas and gatherings of agricultural workers throughout Washington State. She has had to cancel all face-to-face

meetings with at-risk older people, the same ones who are less likely to see her team's YouTube and Twitter messages. Hardest of all, she says, she had had to call off two years of health fairs that, prepandemic, provided information, cancer screenings, free health tests and colonoscopy scheduling.

The communities Briant works with are both the least likely to receive cancer screening and the hardest hit by COVID: minorities, frontline workers, and people who were losing jobs, struggling financially and dealing with SARS-CoV-2 infections. She learned relatively quickly that cancer screening was not a priority for many in these communities. There was fear of COVID, but there were other reasons, too: no time, no child care, a lack of health insurance or the inability to afford copays. In addition, their regular clinics often were too overwhelmed with COVID patients to provide wellness checks or screenings.

People had more immediate needs, such as finding transportation to vaccine appointments and someone to help if they had COVID. Briant's team pivoted from providing grants for cancer screening to helping in other ways. "Our agenda, yes, is cancer screenings, but we had to set that aside and listen to the community," she says. "They were thinking about survival. They were saying cancer screening is not important right now."

Issaka's research confirms what Briant was seeing. One study at her safety-net hospital found that patients already faced multiple obstacles to having a colonoscopy, including lack of transportation, no coordination among specialists to get tests scheduled, and difficulties with the bowel preparation needed for the test. The pandemic added more barriers, she says, such as requiring a negative COVID test before people could even walk through the door.

By responding to more immediate needs, Briant's team hoped to strengthen bonds and increase trust in communities they work with, something that will help them spread the cancer-screening message in the future. Sure enough, as restrictions loosened, she began fielding calls from community health leaders who wanted the inflatable colon sent over. The hypercontagious Delta variant has put those plans on hold—a colon is an enclosed space after all—so they have resorted to a video version until Briant can once again unleash her colon into the world.

COULD WE BE OVERSCREENING?

Another piece of the cancer puzzle that the pandemic experiment may start to solve is a particularly contentious one. As cancer-screening programs continue to grow, an increasingly vocal group of physicians is arguing that too much screening might, at least for some people, be doing more harm than good.

These researchers contend that many patients, particularly those of advanced age, often receive more screening than they require. And those tests can result in more risk than benefit. "One of the biggest risks of cancer screening is the overdiagnosis of cancer tumors that are indolent and will never cause symptoms," says Jennifer Moss, an assistant professor in the department of family and community medicine at Pennsylvania State University, whose research has shown that 45 to 75 percent of older adults receive screening they do not need. She found that for colon, cervical and breast cancers a large percentage of patients were being screened after they had aged out of the recommended age limit. In all three cancers, overscreening was more common for people living in cities compared with those in rural areas.

Unnecessary screenings not only result in false positives but also come with other issues, including unnecessary medical procedures to remove cancers that might not cause harm and side effects, such as perforations during colonoscopies. Now they have the added threat of SARS-CoV-2 exposure. "Many older patients face greater risk from cancer screening than not screening," Moss says. "Especially in a time of COVID."

Moss wants to be clear that people who need screening, based on national guidelines and conversations with their physicians, should get it. And she believes that the pandemic will likely cause an increase in cancer deaths because of missed screenings. But she also thinks the past year and a half will yield important data on missed screenings that were not as consequential, data that could inform future guidelines. "The pandemic will definitely give us insight into when, and how often, and for whom, cancer screening is the most effective," she says.

Choueiri, for his part, is convinced that cancer screening is a singularly powerful tool that can catch cancers at their earliest and most treatable stages. "You don't want stage 1 to become stage 4," he says. "Or even stage 2."

These days his conviction is personal. Unlike many of his patients, who postponed their screenings during the pandemic, Choueiri did not. Because of the pandemic slowdowns, he had extra time on his hands. So, when he turned 45 last year, he took his doctor's advice and scheduled a routine colonoscopy. He didn't think it was urgent—he had no symptoms or family history of the disease. But his test turned up an unexpected precancerous polyp. Now, he says, he will not miss any future screenings. SA

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People visit the *In America: Remember* public art installation memorializing COVID victims near the Washington Monument on the National Mall on September 18, 2021, in Washington, D.C.

Kent Nishimura / Los Angeles Times via Getty Images

PUBLIC HEALTH

Why COVID Deaths Have Surpassed AIDS Deaths in the U.S.

On World AIDS Day, why global COVID deaths are just a fraction of global AIDS deaths

In late October 2021 the U.S. passed a grim milestone: more people in the country had died of COVID-19 in less than two years than the approximately 700,000 who have died in the U.S. in the four decades of the AIDS pandemic.

By World AIDS Day, this gap has grown. More than 800,000 people are known to have died of COVID-19. If current trends continue—and they don't have to—hundreds of thousands of people could die of COVID in the U.S. in 2022, whereas perhaps 15,000 people living with HIV may die next year of any cause.

These dire numbers are worth comparing and considering, with a few caveats.

First, judging deaths in bulk numbers flattens what is actually happening. It is hard to do justice to the more than 100,000 people in the U.S who died by drug overdose during a 12-month period ending in April 2021 (a 30 percent increase from the previous year) and the hundreds of thousands who have died from HIV and SARS-CoV-2. Every person who has died in these pandemics is worthy of being known as they lived and loved in their time on this earth.

Also, we will never truly know precisely how many people have died of AIDS or from COVID.

And yet this milestone is important in its scale. I have known so many people for decades who have lost and mourned loved ones to AIDS; I have seen quite intimately the toll this takes on those who have survived the AIDS pandemic since 1981 and how their individual and collective grief has shaped U.S. politics, protest and the queer community. It is significant and worrying to see four decades of such grief compressed into less than two years. How can U.S. society process such a scale of grief so quickly—especially when COVID has allowed far fewer forms of collective mourning?

The comparative COVID-AIDS death tolls in the U.S. also beg a comparison of global COVID deaths with global AIDS deaths. And here we see something very different. While COVID deaths are now about 110 percent of total AIDS deaths in the U.S., global COVID deaths—more than five million and growing—are less than 20 percent of the more than 36 million people who have died of AIDS.

In terms of virology, the potential for the novel coronavirus to lead to human death much faster than HIV is to be expected. SARS-Co-V2 is a much more efficient virus than HIV, it transmits far more casually, and everything about it is faster than HIV. The novel coronavirus moves through social networks quickly, can take hold in (and transmit through) people in mere days, and can lead to death in weeks (rather than years). According to UNAIDS, annual global deaths from AIDS peaked at about 1.7 million in 2004—about 23 years into that pandemic. COVID has already surpassed this total in a tenth of the time.

And yet that doesn't explain why COVID has already surpassed total AIDS deaths in the U.S. but is less than a fifth of them globally. In some ways, these disparities speak to how the Global South has borne the brunt of AIDS deaths. The U.S. got access to antiretroviral drugs in 1996, and its rate of AIDS deaths immediately plummeted (among people in in the U.S. who got the drugs, anyway). Yet the same drugs did not begin to be rolled out on the African continent until 2003, by which time HIV had created countless orphans and needlessly infected millions of people.

What I find perplexing in some ways is that, similarly to its early access to antiretrovirals, the U.S. had various head starts with SARS-Co-V2 over other countries—more by some metrics. HIV was first noticed in the U.S. long after people were infected and dying, but with the novel coronavirus, the U.S. could have learned from China and Italy, whose earlier experiences gave the U.S. time to prepare. The U.S. also had some of the first COVID medicines and vaccines and, after a rocky start, rolled them out rapidly—at one point vaccinating four million people a day. But it stalled and is currently below number 50 among nations' vaccination rates. Yet through it all, the U.S. has continued to have the highest number of total coronavirus infections and coronavirus deaths (and at times, the highest per capita deaths). Despite being 5 percent of the world's population, the U.S. currently accounts for about 15 percent of the world's COVID deaths and has, at times, accounted for as much as 25 percent.

I think these divergent trends are affected by who was perceived to be the most at risk for HIV and COVID in the U.S. HIV initially transmitted most frequently within the U.S. through anal sex, injection drug use and blood transfusions. Those most affected were marginalized people who had long built solidarity among themselves. And so, even though the transmission modes were stigmatized, queer and Black people and users of injection drugs quickly began using condoms, creating sterile syringe exchanges, and engaging in peer-to-peer education about how to avoid HIV.

But by the time the U.S. had gotten antiretrovirals in the mid-1990s, HIV was circulating in the Global South not just through anal sex, proximity to prisons and the use of injection drugs but, increasingly, through vaginal sex and vertical transmission, from parent to child. At that time in America, many people could get access to good HIV medication, and the virus was pooled within certain communities who couldn't get the drugs; meanwhile, in the Global South, HIV was circulating through a much more general population, whereas no populations had any access to the drugs for nearly a decade.

A different dynamic is developing with COVID in the U.S. While the same kinds of people are most vulnerable to COVID as to HIV, a not entirely incorrect perception among rich people is that they, too, are susceptible to COVID. HIV required marginalized people to collectively care for their communities in very specific ways (such as by using condoms and sterile syringes) during very specific activities. But COVID requires that the entire U.S. population alter many behaviors to

protect one another—and here the U.S. general population diverges extensively from marginalized populations within its own borders as well as with many societies in the Global South. For instance, at the height of AIDS deaths in the U.S., gay men overwhelmingly took on new practices to protect one another, even though they were often accused by straight moralists of "bug chasing"—intentionally trying to get HIV, a desire practiced by an extremely niche group and one never endorsed by formal gay leaders. Yet with COVID, bug chasing has been completely normalized and championed by major conservative radio hosts and politicians.

Thinking about the comparative U.S. and global rates of COVID and AIDS also shows the folly in thinking of the U.S. as a single entity. Health outcomes vary greatly between regions, and the HIV and COVID pandemics within the U.S. are concentrated the most in the Southern states.

Of course, all of this might look very different in the year 2060—the year as far from the first known COVID death as we currently are from the first known AIDS death. For all we know, the U.S. may stabilize with COVID while people in other countries perish without vaccines. But on World AIDS Day, in addition to remembering the dead and supporting the living who are affected by HIV, let us remember there is no contest between these two pandemics. It's not a competition. Despite the particulars of the two viruses, they affect a similar viral underclass. The making of a world free of AIDS would make a world free of COVID (and vice versa) because the same underlying causes are driving both pandemics.

REPRODUCTION

Abortion Doesn't Have to Be an Either-Or Conversation

Treating the decision with nuance and care is essential to reproductive justice

Abortion rights and antiabortion demonstrators hold signs outside the U.S. Supreme Court while the justices conduct a hearing on a Mississippi abortion ban in Washington, D.C., on December 1, 2021.

Graeme Sloan/Sipa USA/Alamy Live News

The language we use to talk about a pregnant person's right to decide whether to continue a pregnancy is full of false binaries: pro-choice versus pro-life, bodily autonomy versus fetal personhood, moral versus immoral. These dualities unnecessarily divide us and prevent deeper conversations about the unique status of pregnancy within our society.

An either-or mentality creates a situation of separate but unequal laws for pregnant people that violate both the human right to bodily autonomy and the guarantee of equal protection under the law.

We, as nurses, midwives and health researchers, know that using a both-and mentality instead of an either-or mentality makes space for multiple truths and nondichotomist positions concerning the decision to continue or terminate a pregnancy. A both-and approach is a hallmark of Black feminism and one that assumes multiple outcomes, multiple discussions or multiple futures as we work together to address the urgent reproductive health crisis in our country.

The primary issue in the *Dobbs v. Jackson Women's Health* Supreme Court case is whether or not Mississippi's 15-week, previability abortion ban is constitutional. When *Roe v. Wade* was argued, however, the word "viability" was never uttered. Court documents show how a Supreme Court clerk suggested that viability be settled on as a legal compromise. That compromise attempted to mark a point in time at which, in the prescient words of Justice Thurgood Marshall, "the State's interest in preserving the potential life of the unborn child overrides any individual interests of the woman."

The binary status of viability and nonviability means that the rights of pregnant people are time-sensitive. As we've learned from the experi-

ences of countless marginalized groups, rights that do not apply to all individuals at all times are not rights but conditional benefits that are inequitably distributed. The emphasis in the abortion debate on viability distracts us from the human rights argument that asserts that bodily autonomy, including the decision to continue or terminate a pregnancy, rests squarely with the pregnant person at all times and in all circumstances.

The whipping of Black enslaved people who were pregnant is a noted instance of the false dichotomy of promoting survival of the fetus at the expense of the pregnant person's humanity and autonomy. To protect these fetuses, the enslaved people's stomachs lay in holes dug into the ground while the rest of their bodies were exposed for punishment. Repeatedly, lawmakers and law enforcers have justified the primacy of fetal rights to restrict bodily autonomy and enforce separate, distinct laws over the bodies and decisions of pregnant people—especially pregnant people of color.

The push for fetal personhood developed alongside, and is in many ways tied to, scientific advances in perinatal-neonatal medicine that enabled the fetus to survive (with extensive technological life support) outside the uterus at earlier and earlier gestations. In this way the fetus and pregnant person became separate entities and separate patients in a health-care setting.

Abortion binaries exist not only in legal settings but in social discourse. For decades a majority of adults in the U.S. have agreed that abortion should be legal in all or most cases. But heterogeneity in views on abortion, particularly across religious affiliations and political ideologies, provides evidence of more nuanced beliefs within groups. Therefore, representations of individuals as either "pro-life" or "pro-choice" do little to identify the granular detail behind an individual's attitudes, beliefs and behavior.

These binary beliefs provide little context around people's life circumstances and the communities in which they belong. Our recent research identified obstetric, women's health and neonatal nurses' attitudes around abortion. We found that on a five-point scale (that is, strongly or moderately proabortion, or strongly or moderately antiabortion, or unsure) that used 14 questions to measure abortion attitudes, one third of the participants ended up in the unsure category. They were neither proabortion or antiabortion. This category also included the largest percentage of those who identified as Christian.

Among nurses who took the survey and reported having had an abortion, nearly one quarter were in the unsure category and 10 percent vocalized antiabortion attitudes, indicating that people's attitudes about abortion are not necessarily indicative of their behavior. This may be evidence of internalized abortion stigma. A lack of concordance between attitudes and actions is neither new nor problematic. Instead it points to the importance of meeting people where they are and respecting their expertise and ability to know exactly what is best of them and their families.

Moving away from binaries and polarities allows us to instead focus on language that helps to create physical and social environments that ensure equitable reproductive health for all, a healthy pregnancy for all who choose parenthood and a safe childhood for all. Research suggests that many people who had an abortion wanted to continue the pregnancy and parent the child but made the choice to have an abortion because they felt they could not adequately or ethically raise a child. They often cited circumstances specific to a lack of resources, whether human, money, space or time.

Often these circumstances could have been ameliorated by enhanced social services, legal protections for pregnant people, paid parental leave and universal chil dcare. Instead they pit the needs of the fetus against the needs of the parent. Policies that are centered in reproductive justice can address the biggest threats to life and livelihood; namely, poverty, health-care barriers, racism and environmental hazards. Meeting these needs could reduce the need for abortion.

Regardless of the decision of the Supreme Court, we as health-care providers and researchers must do a better job allowing for complexity. What do pregnant people want and need? Are we implementing policies that provide financial security, high-quality health care and the social support necessary for those who desire to grow their family while simultaneously ensuring that safe, respectful and stigma-free abortion services are readily accessible?

With the future of safe and legal abortion in the hands of the Supreme Court, we affirm that

bodily autonomy as manifested in abortion is a human right. At the same time, we must improve health care and social services for all people who choose parenthood, especially those historically marginalized.

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