SPRING 20

proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

Can We Get There Any Faster?

In the push to find COVID-19 treatments, next-generation trial designs get their moment to shine. p12

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on the cover

Vaccines have historically taken years to test and bringing new drugs to market can cost billions. How can both of those be streamlined in the time of COVID-19? Innovative trial designs, in development for a decade, may hold an answer.
// Illustration by Kacper Kieć

proto: a prefix of progress, connoting first, novel, experimental. Alone, it conjures an entire world of the new: discoveries, directions, ideas. In taking **proto** as its name, this magazine stakes its ground on medicine's leading edge—exploring breakthroughs, dissecting controversies, opening a forum for informed debate.

AS COVID-19 CASES STEADILY MOUNTED at Massachusetts General Hospital, so did the questions: Were there better ways to minimize clinicians' exposure? Could personal protective equipment (PPE) be manufactured or reused in new ways? How could we better treat the very sick patients? Just how many patients would we get? Might a vaccine arrive in time to be useful in this pandemic?

On March 16, the hospital's research arm—a $1 billion enterprise—announced it was shutting down lab operations. When it did, thousands of researchers turned on a dime to seek answers to these questions and more.

The innovation that has emerged has been staggering, and so has its pace. To manage a firehose of ideas, committees and centers sprang up overnight, including a center that has enlisted thousands of researchers to work on devices, diagnostics, data analytics and therapeutics. A booth to protect clinicians testing potential COVID-19 patients was designed and installed in less than two weeks. Researchers' work in understanding how hydrogen peroxide vapors could decontaminate N95 respirators led, also in a matter of weeks, to the decision to use this technology to preserve these vital protective devices for hospitals across the state. In the nearby city of Chelsea, the hardest hit community in the state, MGH led free testing of its citizens and also descended on Chelsea streets to collect samples for antibody testing to get a better picture of the city's rate of infection: nearly one-third. Within Boston, the city, its public health commission and the hospital have done the same.

The holy grail—a vaccine—is, of course, a major focus as well, with the Ragon Institute of MGH, MIT and Harvard pivoting away from its usual HIV/AIDS work to develop a vaccine for COVID-19. In another vaccine effort, a collaboration with affiliate Mass Eye and Ear is looking at using an adeno-associated virus as a vector. On the treatment front, MGH has been involved in drug trials for remdesivir, chloroquine, favipiravir and nitric oxide. In an attempt to speed what can be an agonizingly slow timeline for new therapies, many of these studies are platform trials. The focus of this issue's cover story ("When a Cure Can't Wait," p. 12), this innovative trial design allows for quicker moves away from treatments that don't seem to be working, redirecting study participants into more promising arms and reducing the number of trial subjects traditionally required.

This is just a sampling of what is happening at MGH, and what is sure to continue in the coming months. Even during the time this issue is being printed and mailed, yet more knowledge about the coronavirus will have been amassed. We know that necessity begets invention, but it has been extraordinary to witness scientists examine this problem from every possible angle and take advantage of every literal and figurative chink in its armor.

stat

FOCUS

The shortage of masks was felt in China first, a topic explored here by Hong Kong artist Tommy Fung. His work uses surrealism to explore social and political truths, but during the COVID-19 pandemic he notes that the real world became "even more surreal."

By late March, a national survey found that 92% of U.S. cities did not have an adequate supply of face masks for their first responders and medical personnel. Especially in short supply were N95 masks, which filter out 95% of airborne particles and are the standard for those working on the front lines. Hospitals bid against one another to secure them, driving the prices up to 15 times their normal cost. While domestic manufacturers struggled to keep up, the focus quickly turned back to China, which before the pandemic had produced half of the world's medical masks.

Chinese factories quickly ramped up their production on masks of all grades. While there has been concern about quality issues, new measures from the government—and the seizing of 89 million faulty products in late April—calmed concerns somewhat. The shortage is ongoing.

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INTERVIEW

Bullies on Notice

Toxic work environments are bad for science. Morteza Mahmoudi is on a crusade to clean them up.

NICK HAGEN FOR *PROTO*

The journey through scientific training can hang, at certain moments, on the goodwill of a single professor or principal investigator. What happens when that person treats you inhumanely? Bullying in academic environments has come under much greater focus in recent years, with high-profile cases coming to light in the United States and Europe.

Morteza Mahmoudi, a nanoscientist at Michigan State University, has become a vocal advocate for the victims of this largely hidden problem. Last year he helped launch the Academic Parity Movement, a nonprofit that aims to outline the costs of academic bullying and show ways to help root it out.

Q: What is academic bullying?
A: Some of it is the same kind of bad behavior you find in any other profession. Say a young post-doc is made fun of in group meetings or is privately berated by her superior. That is clearly recognizable. But in higher education, bullying can take other forms. Let's say that post-doc led a project for three years, but her boss felt that he should really get the entire credit. Her name might be buried in a list of authors on a paper or taken off altogether. She might be pressured not to speak at conferences, or to sign away patent rights to a discovery. All of these things have happened, and they are devastating to the mental health and careers of these young researchers.

Q: How extensive is academic bullying in clinical medicine?
A: A recent paper in *The New England Journal of Medicine* suggested that 30% of residents experienced verbal or physical abuse. I should note that there has historically been a lack of data for any of this kind of behavior, driven in part by fear from bullying targets. One study asked them how many trusted their institutions enough to report an incident. The answer was 2%.

Q: What is behind that lack of trust?
A: There are several reasons, including a fear of retaliation. This might take the shape of a bad recommendation for a future job. It can also be the fear of an unfair internal investigation. For international students, visa cancellation is another major worry. Without protocols in place, or an independent board that can evaluate these situations, there is nowhere for the target to turn, and that encourages silence.

Q: What are the consequences for medicine?
A: Studies have found that bullying is extremely costly both for the scientific community and the public. The authors of that *NEJM* study found that bullying made those residents more likely to experience burnout and suicidal thoughts. We know from multiple studies that burnout has adverse effects on patient care and increases the risk of errors.

Q: Are there solutions to these problems?
A: Yes, we've started to see more sweeping responses. In 2018 the Wellcome Trust in the United Kingdom decided to yank a major £3.5 million grant from a famous genetics professor. She had resigned from her position following an independent investigation into her bullying behavior. Wellcome also barred her from applying for further grants for two years. It was the first test of a pioneering anti-bullying and anti-harassment policy the charity had just instituted.

Q: And are academic institutions following suit?
A: Many are trying their best. Here at Michigan State, we are working to create a dedicated budget to help with these issues and to enhance the efficacy of offices of academic bullying. We need to increase awareness and simplify reporting. But what we really need is integrated collaboration among all the stakeholders and to look for permanent solutions. Institutions and funding agencies should share data about problematic principal investigators. A center for excellence in higher education should be created and establish a very clear definition of academic bullying, and this should be shared with all staff, including PIs.

Q: What is your aim with the Academic Parity website?
A: Today, we are using it to create awareness and collect stories. We have received more than 150 so far. Many are heartbreaking. The long-term goal is to create a community with lawyers and psychiatrists to help people who are targets. We are also running a global survey to help identify trends.

I think this work helps all of us, even the perpetrators. One thing we keep in mind is that the academic bullies among us may not be aware of the consequences of their actions for targets, for patients, for academic institutions and even for science. If they knew, surely they would change.

BY THE NUMBERS

COVID-19 Vaccines

0

Number of vaccines for any human coronavirus, of which there are hundreds. Vaccines are sold, however, for coronaviruses that affect cattle, cats, chickens, dogs and pigs.

8

Number of potential COVID-19 vaccines in clinical trials as of early May 2020. More than 115 others are in some phase of development.

$14 million

Lower-end cost of developing a single epidemic infectious disease vaccine to large final trials, according to a 2018 study published in *The Lancet*.

1 billion

The number of doses of a vaccine Johnson & Johnson plans to provide worldwide on an "affordable" and "not for profit" basis. The company has backed a favored candidate under development at the Ragon Institute of MGH, MIT and Harvard, and expects it to be in clinical trials by September.

7

Number of factories Bill Gates intends to fund, each one producing a separate promising vaccine candidate. He has said this will waste "a few billion dollars," as only one or two will actually be viable.

$300 million

The money put aside by the U.S. government for buying vaccines and treatments. Vaccines typically range in price from about $10 to $230.

INFOGRAPHIC

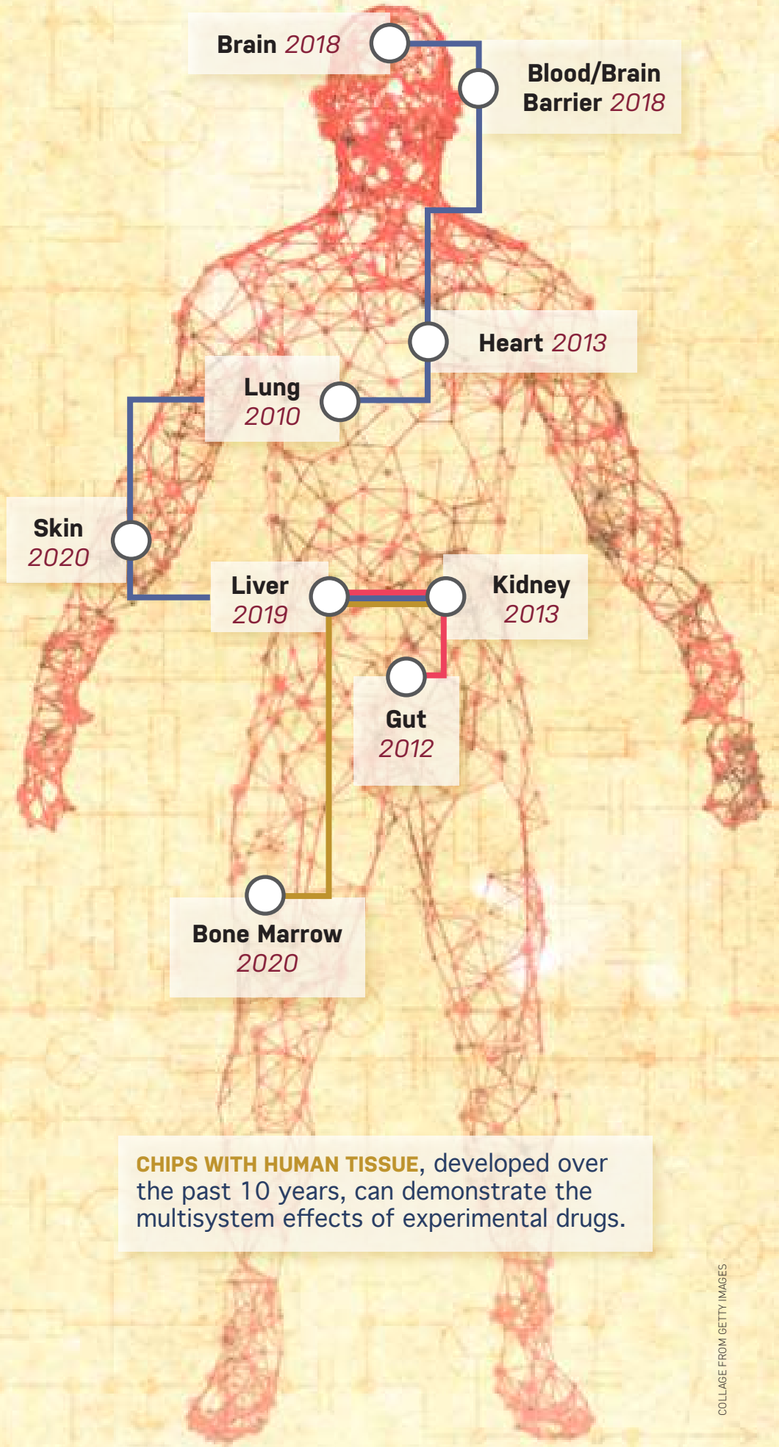
The Body on Chips

An engineered model of human physiology hits an important milestone.

Typically, animals are the first stop in seeing how a drug works, and researchers use them to see how well it is absorbed, distributed and metabolized in the body. But animal testing often doesn't translate well to humans, and it also carries a high financial—and ethical—cost.

In 2010 a team at the Wyss Institute at Harvard offered an alternative with their first "organ on a chip." The devices are the size of a computer memory stick and contain living cells from human organs. Those cells are cultured on one side of a porous membrane, and vascular tissue cells line the other, allowing the two compartments to exchange molecules—including drugs—as they would in the human body.

In early 2020, the teams hit their target to have a complete human "body on chips," which would consist of at least ten types of organs. By sending fluids from one chip to another—which is done by a device they call "the interrogator"—the researchers can explore the multisystem effects of drugs on real human tissues. The model has already delivered critical insights about how particular compounds might work in the body and where they might prove toxic. Their use in the future as a first stop for experimental drugs may pay big dividends, improving the success rate of those that make it into human clinical trials.



CHIPS WITH HUMAN TISSUE, developed over the past 10 years, can demonstrate the multisystem effects of experimental drugs.

COLLAGE FROM GETTY IMAGES

WYSS INSTITUTE AT HARVARD UNIVERSITY

Proof of Concept Study (2020)

The first organ chip, which modeled a human lung, was developed in 2010. In 2012 the organization that funds breakthrough technologies that might help with national security, DARPA, issued a challenge to create such chips for each of the major organs and the technology to replicate multi-organ system responses. In January the Wyss Institute published a study showing that it had achieved this goal. In their experiment, the group linked eight chips, passed blood substitute among them and correctly predicted the distribution of a particular chemical over the course of three weeks.

Nicotine Metabolism Study (2020)

Nicotine chewing gum, an anti-smoking aid, is also being investigated as a drug that might help with neurodegenerative and inflammatory bowel diseases. To study its effects in the body, researchers coupled a human gut chip with liver and kidney chips. They could study nicotine's first pass through the intestinal wall, through the vascular system, to the liver where it is metabolized, and finally to the kidney where it is excreted. The researchers were able to quantify the concentration of nicotine metabolites in each organ and to quantitatively predict the drug's pharmacokinetics—the way drug levels change in blood over time—which closely matched data from human studies.

Cisplatin Study (2020)

The team also investigated the pharmacological effects of cisplatin, a chemotherapeutic drug commonly used in cancer treatments. It is administered intravenously and can be toxic to the kidneys and bone marrow. When researchers linked a bone marrow chip to the liver and kidney chips, the model accurately predicted changes of cisplatin levels in blood over time and cisplatin breakdown products in the system. It also accurately predicted the toxicity of the drug in the bone marrow, matching data from previous clinical studies in humans.

THE INTERROGATOR is what the team calls the instrument that links the organ chips. The robot uses a pipette to rapidly transfer drops of liquid between the vascular channels of the chips, simulating the flow of fluids in the human body.

INVESTIGATIONS

What About Generation COVID-19?

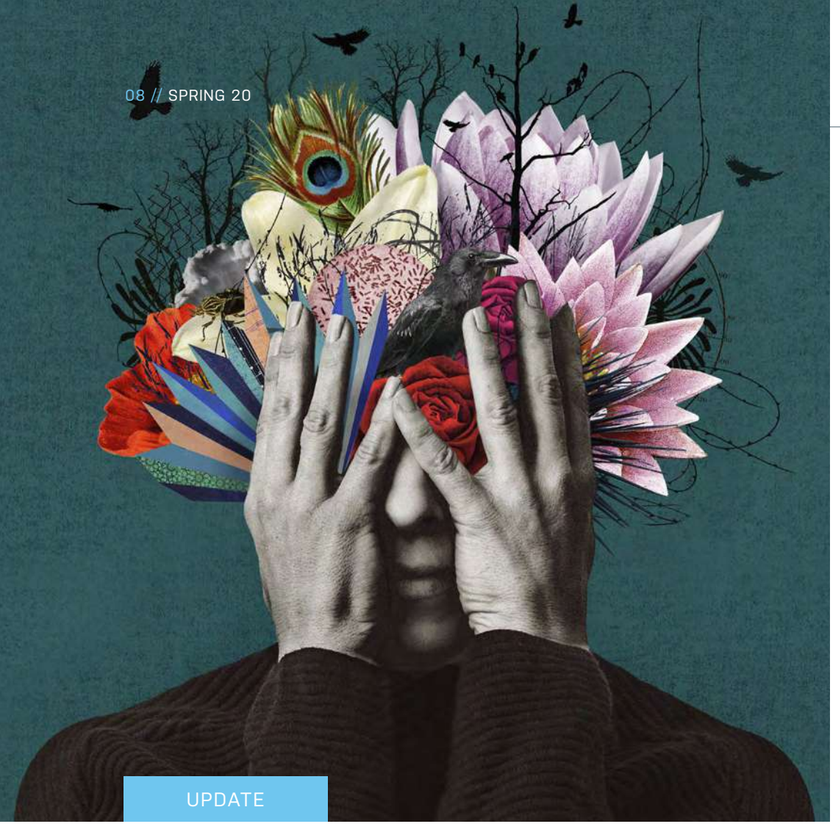
The rites of childhood are being rewritten, and researchers are trying to map the long-term effects.

Children may be less susceptible to the worst outcomes of COVID-19, but the social response to the pandemic will leave a deep impression on them. More than 55 million were sent home from school earlier this year, and prospects for the fall are anything but clear. "We have to think about how this affects the development of kids," says Larry Amsel, a child psychiatrist at Columbia University.

Amsel led the largest longitudinal study of children directly affected by the terrorist attacks of September 11, and found that the event caused adverse effects well into adulthood. Currently he is surveying millions of young adults of college age displaced by the COVID-19 pandemic. Many of them were on the verge of starting their adult lives, he says, and now find themselves living with their parents: "For some, their whole identity has been shattered."

Other research looking at Generation Z is underway, including a study in Baltimore looking at hundreds of minority parents and their children. They are finding that Chinese American families are experiencing increased stigmatization as a result of the outbreak. Another study, published in April, found that the lockdown in China had a more pronounced effect on the mental well-being of teenagers than on adults in their fifties.

The questions are still taking shape, says Amsel, and the challenges of conducting studies in the current environment are not small. His advice to fellow researchers is to acknowledge that conventional approaches may need tweaking: "We have to keep our eyes open."



UPDATE

The Secret Is Inside You

Can microbial communities help treat depression?

BY CHRIS WOOLSTON

Doctors and psychiatrists have long suspected that diet can alter a person's temperament, and studies over the past decade have turned those suspicions into hard data. It now seems clear that a healthy diet can lower the risk of depression and other mental disorders. What is also clear is that some of that effect may be tied to bacteria and other residents of the digestive tract. "These bacteria are little factories producing all sorts of chemicals," says John Cryan, a professor of anatomy and neuroscience at University College Cork in Ireland. Cryan and others are trying to sort out what materials might be most useful in boosting mood with the hopes of someday concocting a "psychobiotic"—an infusion of microbes that works as one of the "New Tools for Depression" (Spring 2018).

That gut microbes play some role in mood has been boosted by recent research. In a 2019 article in *Nature Microbiology*, a team of European researchers surveyed the gut bacteria in more than 2,100 people through genomic screening. They identified two genera of bacteria—*Coprococcus* and *Dialister*—that were sparse in people with depression. The study also found that *Coprococcus* and another bacterium, *Faecalibacterium*, were especially abundant in people who reported a high quality of life.

Study co-author Jeroen Raes, a microbial immunologist at VIB-KU Leuven in Belgium, notes that both *Coprococcus* and *Faecalibacterium* can produce butyrate, an anti-inflammatory compound. The study doesn't prove any cause and effect, but the possibility is intriguing to those who have long suspected that an inflammatory response plays a role in mood disorders. "It's tempting to think that inflammation in the gut could be related to inflammation in the brain, which could in turn be related to depression," he says. Raes and his colleagues also showed that many gut bacteria have the genetic capacity to either produce or metabolize neuroactive compounds such as dopamine and serotonin.

Teasing out which bacteria are particularly helpful might guide future clinical trials of probiotics, although "that part of the field needs to catch up," says Cryan. He and colleagues identified 20 such clinical trials in a January 2020 issue of the *Harvard Review of Psychiatry*, but the studies used widely varying designs that made it hard to draw generalized conclusions.

Cryan points to one Iranian double-blind, placebo-controlled study. As reported in *Clinical Nutrition* in 2019, depressed individuals who took a probiotic capsule containing strains of *Lactobacillus helveticus* and *Bifidobacterium longum* for eight weeks showed improvement in depression symptoms compared with a placebo.

Probiotics aren't the only way the microbiome can be enlisted to improve mental health. Valerie Taylor, a psychiatrist at the University of Calgary in Canada, is actively studying a more direct approach: fecal transplants from healthy volunteers. She's currently recruiting patients with bipolar disorder, and is about to start a study of people with major depression. "The premise of a fecal transplant is you're trying to reset the microbiome of someone who is unwell," she says. The studies will track any improvement in symptoms as well as any changes in the microbial community.

A fecal transplant—an entire colony of microbes taken from a healthy donor—may be a blunt approach, and not without its own dangers, but the insights could help lead the way to psychobiotic capsules and other interventions, Taylor says. "Right now, we don't even know what normal looks like, and we don't know what abnormal looks like," she says. "We're trying to find the things that we need to target."

Cryan is studying the possibility of using diet to create a depression-resistant gut microbiome. He's partly inspired by a 2017 study showing that a 12-week Mediterranean-style diet reduced symptoms of major depression. "I fervently believe that the beneficial effects of that trial are because of the microbiome," he says. He has started a pilot study to see whether a similar diet—ramped up with extra fiber and bacteria-rich fermented products—could alter the gut bacteria community and ease feelings of stress and depression. "We're very excited about developing a psychobiotic diet," he says.

The potential of a bacterial remedy for depression has grown stronger but Cryan says it will take more studies to win over the doubters. "I see a long way to go toward convincing a very conservative medical community," he says.

MARTIN O'NEILL

POLICY WATCH

The Autopsy Ascendant

The traditional post-mortem undergoes a reinvention.

BY LINDA KESLAR

Nationwide, the practice of the hospital autopsy is at historic lows, performed on fewer than one in 20 patients. The procedure is most frequently performed when a death is related to a crime or is otherwise suspicious, and in many cases those are performed by medical examiners, who are sometimes but not always physicians. A growing number of academic institutions, however, are trying to bring the procedure back into the fold to fulfill one of its core historic roles—as a source of discovery.

The resurgence owes a lot to a model called the rapid research autopsy. In this approach, normal and diseased tissue samples are obtained within hours of a patient's death, rather than the 12 to 48 hours for a traditional autopsy. Pathologists, oncologists and technicians work together to extract targeted, predetermined samples of tissue. These can be immediately cultured to create living cell lines, preserved in liquid nitrogen or in paraffin blocks or, in some cases, implanted in animal models.

This approach has been especially helpful in studying cancer. Researchers can sample large volumes of tissue from different areas of the body, gaining clues about how a cancer changes as it spreads. "We can't do all the science we need on a small biopsy," says Jody Hooper, a physician who runs the rapid research autopsy program at Johns Hopkins Medicine. "The rapid autopsy gives us the opportunity to compare different sites and different time points of a tumor."

Hooper wrote an article in *Cancer* that outlined recent insights from rapid autopsies. Different studies have looked at a range of cancer types and helped researchers trace the origins of a particular case from an initial founder cell to the development of metastases, showing exactly where and sometimes how resistance to a treatment takes hold.

James Stone, a physician who heads autopsy services at Massachusetts General Hospital, notes that the approach can have very practical applications. A team from Mass General Cancer Center recently used the process to identify, for the first time, specific genetic mutations that contributed to resistance to a promising group of targeted cancer drugs.

CHRIS GASH

Autopsies have also stepped up in another way in 2020: Stone is currently performing them on those who have died from COVID-19. His lab is providing these COVID-19 infected tissues to laboratories throughout the Boston area, where some of the most concentrated research on the pandemic is located. "They are going to be vital for understanding the complications of the virus," says Stone. Laboratories around the world are piecing together how the disease progresses in the body and what systems—the gut, kidneys, heart and brain—it affects. "Core to this will be the lessons that these patients who succumb to COVID-19 can teach us," he says.

MILESTONE

God Panels, Then and Now

Who most deserves a medical device? A brief history of an impossible conversation. BY STACY LU

In the summer of 1961, six men and one woman were called to meet in a ground-floor library in Seattle, near Swedish Hospital. Their job was not easy: Review short biographies of various patients and decide which would be given a new life-saving treatment. The panel consisted of a minister, a housewife, a banker and other members of the local community. The seven were officially called the Admissions and Policies Committee of the Seattle Artificial Kidney Center, but soon became known as the "God committee."

The hand of God, in this case, was dialysis. While a machine for treating acute kidney failure had become available in 1943, it wasn't until 1960, when Belding Scribner at the University of Washington invented the Teflon shunt, that safe, regular dialysis became possible. It could pull patients back from the brink of death. The Kidney Center eventually had only three machines, though, and treatment was expensive, costing $15,000 a year for each patient.

Physicians identified scores of candidates. Scribner, however, felt that having doctors choose who got the treatment—and who didn't—would create an impossible ethical bind, requiring them to pretend to be impartial about their own patients. Instead he asked the King County Medical Society to convene a panel of citizens to decide who would receive it.

The committee quickly got to work, and the way its members made their decisions has become a fascinating—and sometimes chilling—crash course in bioethics. Their first decision was that dialysis should go only to Washington taxpayers, because their money had funded the research. That still left them the task of deciding which residents most deserved the chance to live.

A prime factor was how well the patient was likely to do with the treatment. Physicians had warned that patients over the age of 45 were more likely to develop serious medical complications. But the panel's

THE ARTIFICIAL KIDNEY BOARD, 1962
The anonymous members of the Admissions and Policies Committee of the Seattle Artificial Kidney Center. These ordinary citizens met to debate who ought to get access to a limited number of life-saving dialysis machines.

LAWRENCE SCHILLER/POLARIS COMMUNICATIONS/GETTY IMAGES

conversation took this in other directions as well. One member urged that a man's church work should be considered, because "moral strength" would help him endure the twice-weekly, overnight dialysis sessions.

A recurring theme was the "social worth" of the individual, saving those who had the most to give back. This slowly evolving calculus factored in the applicant's age, number of dependents, educational background and potential for future contributions to society. The group also became absorbed in whom each patient would leave behind. "For the children's sake, we've got to reckon with the surviving parent's opportunity to remarry," said one panelist, a labor leader. "A woman with three children has a better chance to find a new husband than a very young widow with six children."

The panelists themselves never felt easy about their roles. The sole medical professional among the seven said that "one can just never face these situations without feeling a little sick inside." The group had also enrolled a pastor, who initially refused before he joined. "I felt I was being asked to do something not within my power ... I told them 'I do not choose to play God.'"

History knows about their deliberations because reporter Shana Alexander spent six months studying the new technology and observing the committee. Her article, one of the longest *LIFE* magazine had ever published, talked about the "medical miracle and a moral burden." The story ignited a national controversy that led to additional articles, documentaries and books—the first national debate on bioethics.

Many were aghast. One issue was that the panel's math favored those who led conventional lives—married white people with children and steady jobs. As the *UCLA Law Review* noted in 1968, "the Pacific Northwest is no place for a Henry David Thoreau with bad kidneys." Scribner was astonished by the publicity and defended the committee as a "fairly reasonable and simple solution to an impossibly difficult problem," while lamenting that it had taken attention away from the medical breakthrough.

Eventually, dialysis machines became more affordable and widely available. The God committee in Seattle, and a few that had sprung up after it, disbanded. Medicare began to cover the procedure in 1972, and the End Stage Renal Disease Program is now the nation's longest-standing entitlement program.

But scarcity is a perennial problem in medicine. The environs of Seattle also saw the first U.S. deaths in the COVID-19 pandemic, in which ventilators—devices that can assist breathing—became critically important and in short supply. The question of who most deserved one sparked another national conversation.

In Washington state, those decisions are to be guided by a document on scarce resource management, one of many that were created in the years after 9/11 at the prompting of federal agencies. Most of these guidelines were created with the input of physicians and bioethicists, but some states also sought input from average citizens. Washington was one of these.

In 2010, the state posted ads online and put up flyers in community centers. They asked for volunteers to join an eight-hour discussion on who ought to get scarce resources in the event of a severe influenza pandemic.

The attitudes of the 123 participants—representing a cross-section of races, ages and income groups—held, in large measure, to the precedents of the God committee. They believed that resources should go to patients most likely to survive, and that some—health care workers in particular—were worth saving first. As uncomfortable and imperfect as their conclusions might be, their talks fulfilled the same critical function: that clinicians on the front lines do not have to bear the weight of these terrible decisions alone.

SECOND OPINION

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

Medical Distancing

"The Primary Problem" (Winter 2020) accurately reviews challenges and solutions to primary care. At this moment in history, as the coronavirus pandemic rages, primary care is undergoing dramatic change: Most visits are now e-visits through patient portals, phone visits (patients make an appointment for their clinician to call them at a specified time), or video visits. To ensure social distancing we now have medical distancing.

Research studies show that a great deal of health care can be conducted through these "distance visits," with high quality and patient satisfaction. Distance visits take less time for clinicians and staff and allow patients to avoid leaving work or school, arranging child care, fighting traffic, finding parking and sitting in the waiting room.

But we still need research to determine if such a change improves patient access and reduces clinician burnout. At long last, Medicare, Medicaid and private insurers are starting to pay for distance visits.

The burning question: Will this transformation continue after the virus has been tamed? If the temporary policy of paying for distance visits is made permanent, primary care will likely rebalance its visit types, perhaps 50:50 face-to-face versus distance visits. Such a transformation could be a small silver lining to the terrible toll of the coronavirus.

Thomas Bodenheimer // Founding director, Center for Excellence in Primary Care, University of California, San Francisco

A Mother's Physical Bond

As a reproductive psychiatrist, I was very interested in *Proto*'s story "New Mothers on the Brink" (Winter 2020), which discusses interventions for treating perinatal mental health.

In the stressful time of COVID-19, addressing mental health during pregnancy and postpartum has become even more important. The pandemic elicits a complex—and fraught—set of decisions about childbirth. Health care professionals must weigh strict physical distancing rules against the known benefits of continuous labor support and physical closeness between a mother and her newborn. The World Health Organization, for example, stresses the benefits of physical contact, including mother-infant bonding, avoidance of maternal stress and increased likelihood of breastfeeding.

But many hospitals have had to enforce visitor restrictions (and, in some cases, visitor bans), and to make decisions about whether newborns should be separated from a mother with a known or suspected COVID-19 infection—which the CDC recently stated should be determined on a case-by-case basis.

While we are accustomed to balancing risks, the pandemic brings with it a new conundrum: the need for physical distancing and the importance of physical connection.

Lucy A. Hutner // Reproductive and adult psychiatrist, Women's Mental Health Consortium, New York City

When A Cure Can't Wait

COVID-19 treatment trials will need to be nimble. Is this the moment for adaptive designs to step into the limelight?

By Carrie Arnold // Illustrations by Kacper Kieć

Even as the world was learning about an unusual viral pneumonia surging in Wuhan, China, scientists at the National Institute of Allergy and Infectious Diseases (NIAID) were launching a global trial of a possible treatment. Their first candidate—an antiviral medication known as remdesivir—was given to human subjects barely a month after the first cases were reported. But the standard and time-tested approach to measuring the worth of remdesivir and any other treatments for COVID-19 seemed glaringly at odds with the need to operate at the speed of a global catastrophe.

For 50 years, the gold standard for evaluating new drugs has been the two-armed randomized controlled trial (RCT). The model is nothing if not straightforward: Participants are assigned to one of the trial arms, the first of which gets the experimental drug while the second is given a placebo or the standard existing treatment. Augmented over the years by safeguards for patients and other rules to keep the results fair and accurate, this process has been the road by which most current prescription drugs have arrived on the market. But setting up such a trial for each promising COVID-19 treatment might take years, and by assigning half of these

ailing patients to a placebo or a less effective treatment, hundreds could be denied their best chance to get better.

For Clifford Lane, NIAID deputy director for clinical research and special projects, that model simply wasn't a match for the moment, especially with the sheer number of new and existing treatments that U.S. teams would need to explore simultaneously. "There were a lot of things we thought might be worth testing," says Lane, who was selected to join a World Health Organization team on a trip to Wuhan to help study remdesivir. "Rather than running a whole series of independent trials, it made sense to use one design where you could put the most promising drugs first, bring in others later and get rid of those that weren't working sooner rather than later."

That alternative approach is known as an adaptive trial, an emerging model that adds (or removes) additional arms and protocols to a trial and evaluates the drugs' effects by means of complex statistics. Something similar had worked well during the 2014 outbreak of Ebola in West Africa that caused more than 11,000 deaths. To search for effective therapies, Lane and his colleagues first gave trial participants ZMapp, an antibody-based drug, and compared their progress with those of a control group receiving "supportive care," which included fever reduction techniques and intravenous hydration. When ZMapp proved to be no worse than the standard approach, the same study simply changed its shape during its next implementation in the recent Ebola outbreak in the Democratic Republic of Congo: The control group was switched over to ZMapp, which researchers compared against three additional drugs, including remdesivir. Ultimately this way of conducting a clinical trial rapidly proved that two other antibody medications, MAb114 and REGN-EB3, performed best. As soon as that was known, all subsequent patients were randomized to receive MAb114 or REGN-EB3.

That dramatic success demonstrated that nontraditional trial designs could be critically useful during an infectious disease crisis. "Despite being in the middle of an outbreak, and amid tremendous social disruption, it was possible to conduct rigorous research and come up with valid answers," Lane says. Now, NIAID scientists have engineered similar trial designs to test COVID-19 treatments. One approach—to use the same control group to gauge the effectiveness of several candidate treatments—enables researchers to enroll fewer trial participants overall. The adaptive trial design also means that drugs that work well early on could become the standard of care for later patients.

The Design Fit for a Pandemic?

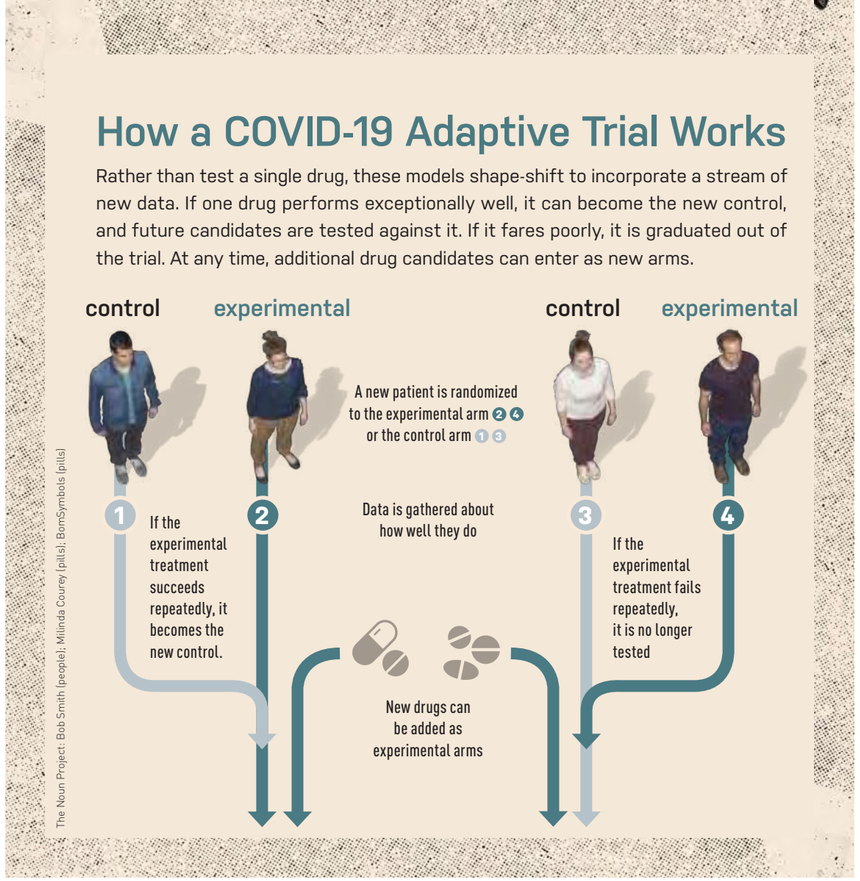
By mid-April, the U.S. Food and Drug Administration had consulted on 72 active COVID-19 trials under its Coronavirus Treatment Acceleration Program (CTAP). The treatments they are looking at run the gamut: antiviral medications, investigational immunotherapies and "convalescent plasma" taken from survivors, among others.

Many of the biggest trials are taking an adaptive approach, and not only those in the United States. The World Health Organization is conducting an adaptive multinational trial, and other adaptive trials are up and running in Austria, Denmark, France, Norway and Spain, according to Andre Kalil of the University of Nebraska Medical Center in Omaha. Kalil himself is leading one of the first U.S. trials—the Adaptive COVID-19 Treatment Trial (ACTT), a 75-site effort sponsored by the National Institute of Allergy and Infectious Diseases.

The design of ACCT offers advantages, Kalil says: "Adaptive trials offer the fastest detection of benefits or harms from experimental therapies." A drug that isn't helping can be removed from the trial, and one that is showing benefits can be moved to its control arm.

Getting physicians to enroll COVID-19 patients in these trials—in any of the trials under way—will be a critical step fighting the pandemic. Many physicians have resorted to "compassionate use" of unproven therapies, says Kalil. "Giving experimental, unproven drugs outside a randomized trial, without controls, will never allow patients and doctors to know whether the drugs help or harm," he says. "Without randomized trials, there will be no discovery of safe and effective new treatments."

On whether the pandemic will be a turning point for the acceptance of adaptive trials, Kalil is mildly optimistic. But all parties in U.S. research—the FDA, the pharmaceutical industry, and funding agencies both federal and private—will need to get on board for them to be more widely used.



This is just one way to configure an adaptive trial, and the ingenious products of this experimental field are known, collectively, as complex, innovative designs (CIDs). While a fleet of CIDs have been enlisted in the pandemic, they owe a debt to 10 years of groundwork and refinement in other fields.

The largest, longest-running adaptive platform trial, I-SPY2, has enrolled more than 1,700 women with high-risk breast cancer and evaluated 20 therapies since 2010. Regulatory agencies have historically been skeptical of the many innovations used in I-SPY2, but that has been changing, and in September 2019, the Food and Drug Administration issued its draft guidelines to help CID trials get past regulatory hurdles. Efforts inspired by the I-SPY2 approach are now being used in prostate cancer, pancreatic cancer, Alzheimer's disease and glioblastoma. This spring the first patients were scheduled to enroll in the HEALEY ALS Platform Trial, the first CID platform for ALS, led by Merit Cudkowicz, chief of neurology and director of the Sean M. Healy & AMG Center for ALS at Massachusetts General Hospital.

These new types of trials are also now being used to evaluate treatments for COVID-19. With millions of lives in the balance, the world is watching to see just how well they work.

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In the history of clinical trials, one of the first landmark experiments commenced aboard the *Salisbury*, a 50-gun British warship, on May 20, 1747—and is the reason International Clinical Trials Day is celebrated on that day. The ship's surgeon, James Lind, wanted to resolve a debate about the best way to combat scurvy, an incapacitating and sometimes deadly disease. He gave oranges and lemons to a handful of sailors and different treatments to others, then saw who fared better in the end. (The citrus diet won out.)

Two centuries later, Austin Bradford Hill, an English statistician and epidemiologist, introduced another crucial idea: The treating physician shouldn't choose or know which patients received the treatment. The random, secret assignment of test subjects to one or the other arm of a trial would reduce the chance of bias by a doctor, who might otherwise skew results by giving a promising treatment to patients considered most likely to improve. Hill used the method in 1948 to gauge the effects of the antibiotic streptomycin on tuberculosis. Additional rules further improved objectivity. Researchers had to keep the questions they asked patients relatively simple, for better standardization, and weren't allowed to change anything once a trial was under way. All of these led to a process through which the potential benefits of a drug could be observed in the most rigorous fashion.

But that rigor increasingly comes with an administrative burden and a steep price. Today the road to FDA approval of a new treatment normally proceeds in three (sometimes four) phases, which progressively ramp up requirements for showing safety and efficacy. Most drugs don't make it to phase 3, which enrolls hundreds or thousands of patients and measures results against existing treatments. All told, only about 12% of medicines that enter clinical trials come out the other end with the FDA's stamp of approval, according to a 2016 study published in the *Journal of Health Economics*, which also pegged the average cost of bringing a new drug to market at $2.6 billion (although other research has argued that figure is probably lower).

A portion of that expense can be attributed to conducting clinical trials, with the average cost of a phase 3 trial pegged at $19 million by a 2018 *JAMA Internal Medicine* study, the first to compile such an estimate. Tim Cloughesy, a neuro-oncologist at the University of

California, Los Angeles, and global principal investigator of the GBM AGILE Trial for glioblastoma, says that six recent phase 3 trials for that deadly brain cancer collectively added up to $600 million. Such price tags, and the need to recruit large numbers of patients, make modern RCTs untenable in many cases, Cloughesy says. "We need a better way to evaluate therapeutics," he says.

But high costs and long timelines aren't the only drawbacks of traditional RCTs. There is often an inherent conflict between the scientific needs of drug trials and participants' ongoing clinical care, a disparity that has been cited in multiple studies as a barrier that discourages physicians from enrolling their patients. That reluctance means research subjects can be very hard to find. A 2015 report published in the *Journal of the National Cancer Institute* found that one in five oncology trials fails because it can't recruit enough participants.

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Proponents of CID believe that it can address many of the drawbacks of the traditional drug development pathway by designing a single study that is made up of phase 1, 2 and 3 trials all "soldered together" into one. They contend that asking multiple questions and evaluating many therapies in a single trial requires fewer patients, reduces overall costs and increases the likelihood that trial participants will receive beneficial treatments.

"Our objective has always been to deliver better therapy to patients—those in the trial and those outside the trial," says Donald Berry, a professor in the department of biostatistics at the University of Texas MD Anderson Cancer Center in Houston. Barry has helped develop alternative trial designs that use something known as Bayesian statistical analysis to calculate probabilities and refine models based on early results.

One trial to emerge from experiments with Bayesian analysis was I-SPY2, a collaboration between Berry and Laura Esserman, a surgeon and oncologist who directs the Carol Franc Buck Breast Care Center at the University of California, San Francisco, School of Medicine. Known as an adaptive platform trial, I-SPY2 started in 2010 by testing one potential breast cancer therapy—and another 19 since then—in women whose tumors had a high chance of metastasizing. The adaptive design included randomization algorithms that adjusted the likelihood that a patient would be randomized to a particular arm of the trial based on how well that arm was performing. Therapies that performed well in phase 2 of I-SPY2 would then "graduate" to phase 3 trials outside of I-SPY2.

Berry and Esserman also designed I-SPY2 so that the control arm could be changed as the trial progressed. Initially, controls received the best treatment currently available. But in this trial, if a new drug proved better, it became the new standard of care and was substituted for the original control group therapy. That aspect became critical for infectious disease trials, including those for COVID-19. It ensures two things—that participants in the control group wouldn't get what had become substandard treatment, and that additional drug candidates would be compared with the new state of the art. "We found that patients' outcomes were getting better and better over the course of the trial," Berry says.

The I-SPY2 team published their answer for a number of therapies in *The New England Journal of Medicine* in July 2016. They showed that the new therapies had met prespecified criteria that will be used to trigger critical changes—such as adjusting the probabilities that someone will be randomized into one arm or another, and when a drug will be added to or removed from a trial.

Yet even as more researchers consider the possibilities of CID trials, inherent limitations may restrict their use for now. For example, the Bayesian statistical analyses that are essential to CID trials require specific training and advanced computing skills, and their complexity may create a "black box" effect that prevents the clinicians conducting trials from truly gauging the results. As a byproduct of these algorithm-driven treatment courses, a drug that appears to be effective in one CID trial may fail in another, says John Ioannidis, professor of medicine and a clinical trials expert at Stanford University, who considers this lack of reproducibility a major drawback. Sarah Blagden, an oncologist at the University of Oxford, says she believes CID trials hold great potential, but cautions that too few have been done for scientists to verify that, in fact, they are better, faster and cheaper than the traditional trial pathway. Getting to that point will require more time—and more trials. "Although cost-effectiveness assessments are being done, we do not yet have a definitive answer as to whether conducting a single, complex study is better than the traditional, separate study route," she says. "But instinctively, it seems likely."

Those new trials, however, are beginning to materialize. The COVID-19 global clinical trial will be a major testing ground. Another effort slated to take off this year is a large platform trial at the Healey Center for ALS at MGH. A team led by Cudkowicz will initially evaluate three new drugs, with several more slated to be added later. Each potential ALS therapy will have its own arm, with 120 participants taking the new drug and 40 serving as a control group. But those same 40 controls will be utilized in all three arms, and together those arms of the trial will require just 480 participants—compared with a total of 720 that would otherwise have been needed. "We wanted to show that you could have a very patient-friendly design and get clear answers faster," Cudkowicz says. In addition, adding new treatments can be done much faster because a new drug protocol is just added as an amendment to the master protocol.

The groundwork that all of this lays for the COVID-19 response could not be more critical. "In these trial designs we have a tool that, we hope, can not only give us good information but also let us help as many of our enrollees as we can," NIAID's Lane says. That proposition, if it holds out, could be a major step forward for other research and treatment questions long after the current crisis is over.

These trials will get their biggest test as they're used to evaluate treatments for COVID-19.

DOSSIER

"Challenges with Novel Clinical Trial Designs: Master Protocols," by Michael Cecchini et al., *Clinical Cancer Research*, January 2019. This article lays out some of the common issues relating to innovative clinical trials.

"Effective Delivery of Complex Innovative Design (CID) Cancer Trials—A Consensus Statement," by Sarah P. Blagden et al., *British Journal of Cancer*, January 2020. The authors provide an overview of complex, innovative design.

"I-SPY 2—Toward More Rapid Progress in Breast Cancer Treatment," by Lisa A. Carey and Eric P. Winer, *The New England Journal of Medicine*, July 2016. This editorial looks at how the I-SPY 2 trial is advancing breast cancer treatment specifically and medical science as a whole.

THE CASE AGAINST VAPING

As COVID-19 makes lung health a national concern, experts take another look at the dangers of e-cigarettes.

Farrah Kheradmand was puzzled by what she saw under the microscope. The slides contained lung tissue, stained purple and red, of mice that had been exposed to the aerosols produced by the "vaping" of electronic cigarettes. In the tissue, macrophages, a type of immune cell, were not only enlarged but also bulging with translucent fats. "There were these glistening, large, abnormal buildups of lipids," she says. "I was really taken aback—it was unlike anything I'd ever seen in a healthy mouse."

Kheradmand, a pulmonologist and professor at Baylor College of Medicine in Houston, was investigating with her team whether e-cigarettes are a safer alternative to conventional tobacco cigarettes. It was a question that often came up at Houston's Michael E. DeBakey Veterans Affairs Medical Center. "I was actually getting cornered in the hallways by vets asking me, 'Can I switch to vaping? I hear it's better for you,'" Kheradmand says.

That safety argument has helped to attract millions of users over the past decade. Cigarette smoking exposes smokers to scores of chemicals known to be deadly and is linked to one in five deaths annually in the United States, killing about 480,000 people. E-cigarette manufacturers argue that their product, on the other hand, is inherently safer. Users breathe

By Linda Keslar // Photos by Joe Toreno

in a vaporized liquid that contains only nicotine, a few solvents and sometimes a flavoring such as menthol or cherry.

Doubts had already taken root about the safety of vaping, and now, as the pandemic spread of a respiratory disease has taken more than 1.2 million U.S. lives, the question has become more urgent. The virus that causes COVID-19 preys on the lungs, and although there are few solid data points yet, the National Institute on Drug Abuse has warned that vaping could cause underlying health problems that complicate coronavirus symptoms. Kheradman's study provides one chilling example. Most vaping mice models who were then exposed to a flu virus—another pathogen that causes respiratory illness—died shortly after.

Kheradmand's study and other research suggest that vaping weakens defenses in fighting infection and compromises the immune system, says Jonathan Winickoff, a pediatrician and director of pediatric research at the Tobacco Research and Treatment Center at Massachusetts General Hospital. "We don't have any direct studies yet, but it's likely vaping increases the risk of severe symptoms and complications in people infected with COVID-19," he says. The physical act of lifting the vaping device to the mouth may increase the chance of the user becoming infected—"you're spreading whatever is in your hand into your body"—and an increased need to cough or expectorate could help spread the disease further. Massachusetts has issued a health alert that vaping can exacerbate the risks of spreading COVID-19, and Winickoff expects other states to follow suit.

This isn't the first—or even the greatest—alarm bell to be sounded about e-cigarettes. In 2019 a shocking number of vaping-related lung illnesses and deaths began to reach the news, and that summer, the Centers for Disease Control and Prevention began tracking cases it classifies as EVALI—for "e-cigarette or vaping product use-associated lung injury." Before the pandemic, more than 2,800 people had been hospitalized around the country, and as of February 2020, there had been 68 confirmed deaths. Most of those who have gotten sick were 24 or younger.

Youth vaping rates have been on the rise since 2011, and in just one year, from 2018 to 2019, the reported use of e-cigarettes by U.S. middle school and high school students rose from 3.6 million to more than five million, representing 11% of those in middle school and 28% of high school students. The use of the products in that age range alone constitutes a health crisis, as nicotine exposure during adolescence can cause addiction and harm the developing brain, says Nii Addy, associate professor of psychiatry and cellular and molecular physiology at Yale School of Medicine. Studies in young mice suggest nicotine exposure can lead to long-term problems, and because the human brain isn't fully developed until around age 25, these "may be effects that we see in people down the road," Addy says. Potential problems include attention disorders, impulse control issues and a higher risk for substance misuse, he says.

In 2018 the U.S. surgeon general declared e-cigarette use among youth "an epidemic," and there have since been attempts to ban or restrict the practice, and not only for the young. New York state's Academy of Family Physicians asked for a ban of all e-cigarettes during the entire COVID-19 pandemic, noting that the risks, while still unknown, were potentially great. Measuring the precise nature of those risks remains a task for labs and institutions across the country.

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Smoking a traditional cigarette produces more than 7,000 chemicals, 93 of which the Food and Drug Administration has classified as harmful or potentially harmful. But no one knows exactly what chemicals are in e-cigarettes, which come in a range of models and can emit different toxicants. What *is* known is that vaping devices are becoming more and more powerful, designed to deliver larger aerosol clouds and elevated doses. Users can also modify their devices and the aerosols they vape. The EVALI investigation, for example, has been complicated by the fact that patients reported using so many different products.

"E-cigarette smokers aren't going to die from the same diseases that cigarette smokers die from because e-cigarettes just don't deliver those same carcinogens," says Thomas Eissenberg, professor and co-director of the U.S. Center for the Study of Tobacco Products at Virginia Commonwealth University in Richmond. "But e-cigarettes do deliver things that may be just as toxic." For example, a 2009 FDA report on the dangers of e-cigarettes noted that scientists, analyzing cartridges from two leading brands, found diethylene glycol, a toxic chemical used in antifreeze, as well as nitrosamines and other carcinogens.

When it issued that report, the agency asked health professionals and consumers to detail serious adverse events from vaping or product quality problems. That information was reviewed alongside other evidence in a 2013 summary by researchers at the University of California, San Francisco. The authors noted that serious health issues and hospitalizations because of congestive heart failure, hypotension, pneumonia and chest pain had been reported to the FDA. "Even that early, there was a fair amount of evidence that e-cigarettes were more dangerous than they looked," says Stanton Glantz, principal investigator at the UCSF Tobacco Center of Regulatory Science and an author of the review.

But conflicting information also emerged. A 2015 review by Public Health England in the United Kingdom, an agency similar to the CDC, surveyed the opinions of a dozen experts and contended that e-cigarettes are "around 95% less harmful than smoking." Indeed, U.K. public health officials continue to encourage physicians to promote e-cigarettes to help smokers quit. That "around 95%" estimate, not tied to any hard data, is nevertheless widely cited. "People use that claim as a reason to keep using e-cigarettes," Eissenberg says. "Or if they've never used nicotine before, they hear 95% safer and figure, 'That's safe enough for me.'"

THE U.S. SURGEON GENERAL DECLARED E-CIGARETTE USE AMONG YOUTH "AN EPIDEMIC," AND THERE HAVE BEEN ATTEMPTS TO BAN THE PRACTICE. YET THE NOTION THAT VAPING MAY BE SAFER THAN SMOKING PERSISTS.

A 2018 report from the National Academies of Sciences, Engineering and Medicine evaluated 800 peer-reviewed scientific studies on the human health effects of e-cigarettes. It wasn't quite as sanguine. Although the report did conclude that e-cigarettes are less hazardous than combustible cigarettes, with a vaper's exposure to harmful substances "significantly lower" than it would be if smoking cigarettes, the report did note that e-cigarettes generate potentially toxic chemicals, in addition to nicotine. "The report found no evidence of long-term harms to health, but acknowledged that this was based on a limited body of evidence available at the time," says Nancy Rigotti, director of the Tobacco Research and Treatment Center at MGH, who served on the report's panel of experts. "And most of the studies reviewed tested earlier generations of devices. I think it's fair to say the needle has moved since then."

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Recent research shows a much starker picture. In an analysis of 28,000 adults in the Population Assessment of Tobacco and Health (PATH) study, researchers at the University of Rochester in New York found that people who vaped were nearly twice as likely to struggle with wheezing as people who didn't regularly use tobacco. Wheezing, caused by narrowed or abnormal airways, often precedes other serious health conditions including sleep apnea, emphysema, heart failure and lung cancer.

Another risk comes from the toxic chemicals such as acetaldehyde and formaldehyde—both known carcinogens—that have been detected in e-cigarette aerosols. The metal heating coils in the devices can also cause users to inhale lead, chromium, manganese and nickel, according to a study conducted at Johns Hopkins Bloomberg School of Public Health in Baltimore. And the flavoring compounds are also under scrutiny. E-cigarette makers aren't required to disclose all of the chemicals they use to flavor their products, but there's growing evidence that some can be dangerous. "Flavorings were designed for food, and are rarely tested for inhalation," says Maciej Goniewicz, a toxicologist at Roswell Park Comprehensive Cancer Center in Buffalo and co-director of the Western New York Center for Research on Flavored Tobacco Products, a collaboration between

Roswell Park and the University of Rochester Medical Center.

Goniewicz's team has launched a five-year clinical study that is tracking a group of 100 volunteers who vape. Every month a small bus drives to retail e-cigarette outlets, staffed by a certified phlebotomist and pulmonary function technician who evaluate the users for potential health effects, through metrics that include samples of blood, urine and exhaled breath. They also collect data about the devices and flavorings each person has been using. "Changing flavors is quite common and we want to see how that may affect users' respiratory symptoms," Goniewicz says.

Other studies on flavorings home in on two chemicals: diacetyl and 2,3-pentanedione. Known for its buttery aroma, diacetyl is safe when eaten, but in its inhaled form it has been linked to a serious lung disease called bronchiolitis obliterans—also known as "popcorn lung," because it was first observed in workers at popcorn factories. After that health risk was established, 2,3-pentanedione was sometimes substituted for diacetyl. But studies have shown respiratory injury in rats and mice that inhale either of these chemicals, and researchers at the Harvard T.H. Chan School of Public Health and the University of Pennsylvania recently published a study showing their negative impact on cultured human lung tissue. They also discovered links between the chemicals and chronic obstructive pulmonary disease, asthma and other conditions.

E-CIGARETTE MAKERS AREN'T REQUIRED TO DISCLOSE ALL OF THE CHEMICALS THEY USE TO FLAVOR THEIR PRODUCTS, BUT THERE'S GROWING EVIDENCE THAT SOME CAN BE DANGEROUS WHEN HEATED AND INHALED.

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Kheradmand's mouse study, funded by the National Institutes of Health, was designed to look for a link between vaping and emphysema, a condition caused most frequently by smoking tobacco in conventional ways. In emphysema, lung air sacs become damaged, causing shortness of breath. To test for the effects of vaping, one group of mice was exposed to e-cigarette vapors containing nicotine and two common vaping solvents. A second group received vapors with the solvents but no nicotine. These groups were compared with mice exposed to tobacco smoke or to clean air.

The mice inhaled tobacco smoke or e-cigarette vapors for four months, the equivalent of people who began smoking as teens and continued into their fifties. The mice exposed to cigarette smoke had severely damaged lungs and excessive inflammation, much like human smokers with emphysema. Kheradmand and her team expected to see similar results in the other groups but didn't find them. Then a team member showed her the slides of the lung tissue from vaping mice that revealed extensive cell damage. "I honestly did a double take," she says. "Where is this fat coming from?"

Further experiments showed that chronic exposure to e-cigarette solvents alone, without nicotine, was enough to disrupt the basic biology of the mouse lungs. One of the two solvents was vegetable glycerine, a type of fat. But the immune cells hadn't guzzled the fat directly from the vapor, as Kheradmand initially suspected. Instead, the accumulated lipids came from an abnormal turnover of the lungs' protective fluid layer—a process that involves macrophages, which essentially went into overdrive in reaction to the chemicals. When researchers then infected this group of mice with small amounts of a flu virus, their weakened ability to battle infection killed most of them.

Kheradmand notes that while her team was working on the mouse study, several reports came in of e-cigarette users developing a form of pneumonia. "The staining of cells within their lungs looked identical to what our mice had," she says. E-cigarette users could also be more vulnerable to serious illness from COVID-19, she adds. "It's more important than ever to explore how vaping might make our lungs weaker or more vulnerable to disease, as we face a pandemic that essentially targets that organ."

Now, Eissenberg is recruiting adult vapers to investigate whether Kheradmand's findings hold true for humans. "Her study is incredibly important, a stunning finding and potentially a big warning sign about the long-term health effects of e-cigarettes," Eissenberg says.

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With potential risks coming in from many quarters, regulators have increasingly been called on to come down hard. "We know far less today than we should and we have allowed the e-cigarette industry to conduct basically an experiment on our entire population," says Matthew Myers, president of the Campaign for Tobacco-Free Kids. In early April, the House Oversight Committee urged the FDA to "clear the market" of e-cigarettes because they might increase the number of serious cases of COVID-19.

Even before the pandemic broke, some tougher laws began to kick in. A statute that took effect in late 2019 raised the federal minimum age for purchasing tobacco products—including e-cigarettes—from 18 to 21. Then in January, the FDA announced a ban on sales of all cartridge-based fruit-, mint- and candy-flavored e-cigarette products. As of September 2020, all e-cigarette makers must submit an extensive application to the FDA with a health and safety review of vaping products they want to remain on the market.

There is still one argument in favor of e-cigarettes—that they might indeed be an effective aid for people who want to stop smoking regular cigarettes. E-cigarettes aren't approved by the FDA for that purpose, and numerous studies evaluating their effectiveness as a smoking cessation tool show mixed results. Still, some researchers and public health experts believe that vaping offers a net public health benefit if it replaces conventional smoking. If most current U.S. smokers switched to vaping e-cigarettes over the next 10 years, there could be as many as 6.6 million fewer premature deaths and 86.7 million fewer life years lost, according to researchers at New York University School of Global Public Health.

"There's just incredible disagreement within the public health community over whether e-cigarettes cause more problems than they solve," says Michael Siegel, a professor at Boston University School of Public Health. He says he believes that overregulation of e-cigarettes could make things worse, with both vapers and former smokers turning to smoking if e-cigarettes are banned.

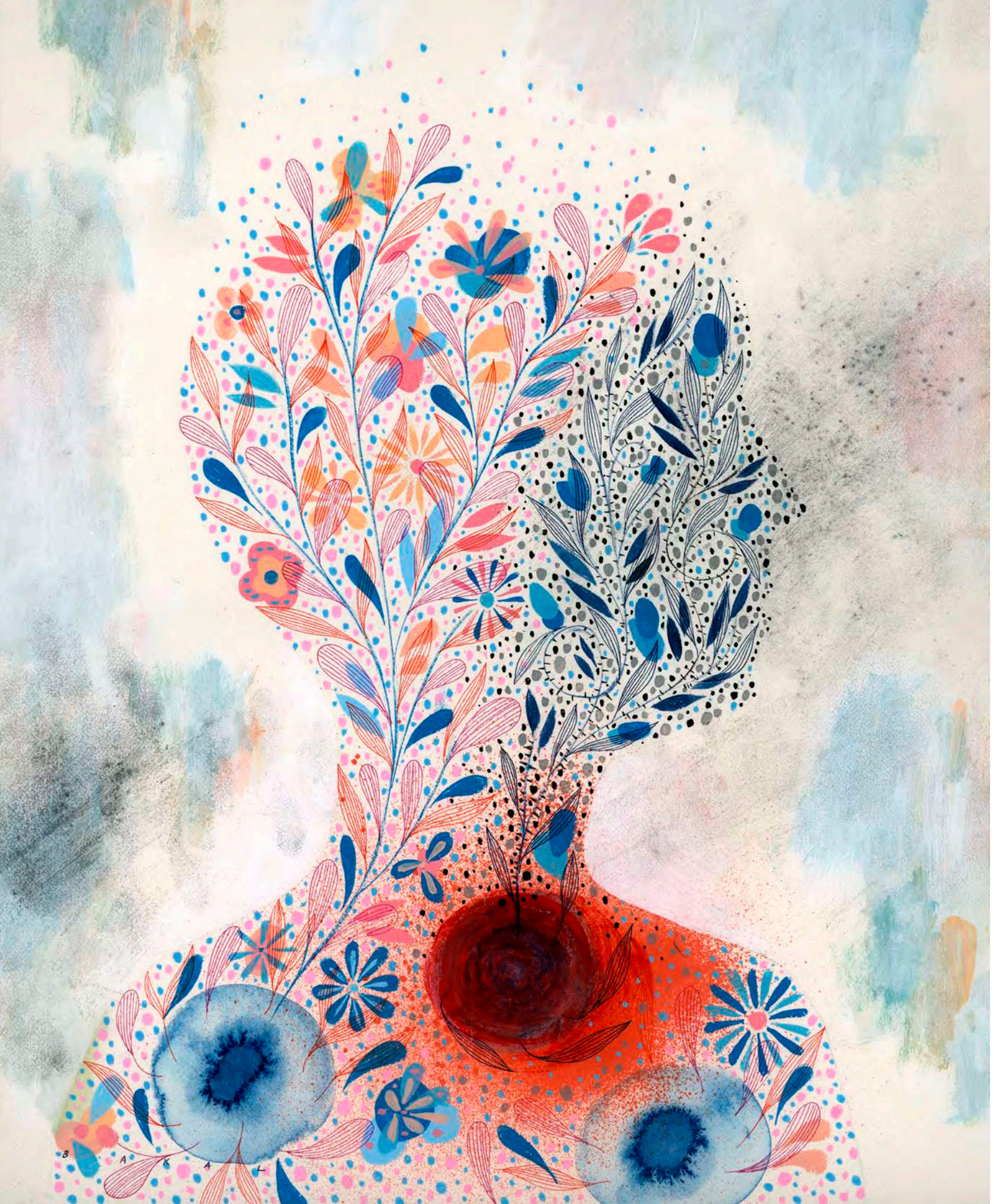
Against this shifting backdrop of research and regulation, physicians are left to grapple with how to provide care and guidance to adult smokers, users of e-cigarettes and the large numbers of young people now dealing with nicotine addiction as a result of vaping, says Winickoff. He notes that the stay-at-home orders caused many parents to discover their children's vaping habits for the first time. That led to worried calls about how vaping might put them more at risk for the disease. "There's plenty yet to learn about vaping and COVID-19, but the time to act on current information is now," he says. "The good news is that the crisis has created a real opportunity to talk about the dangers—and to help current users to quit."

DOSSIER

"Electonic Cigarettes Disrupt Lung Lipid Homeostasis and Innate Immunity Independent of Nicotine," by Matthew C. Madison et al., *The Journal of Clinical Investigation*, September 2019. This study shows how chronic exposure to vaping harms the lung cells of mice.

"Invalidity of an Oft-Cited Estimate of the Relative Harms of Electronic Cigarettes," by Thomas Eissenberg et al., *American Journal of Public Health*, October 2019. The authors reexamine the 2013 claim that e-cigarettes are "95% safer" than combustible cigarettes.

"Cardiovascular Risk of Electronic Cigarettes: A Review of Preclinical and Clinical Studies," by Nicholas D. Buchanan et al., *Cardiovascular Research*, November 2019. In this review, the authors conclude that e-cigarettes harm cardiovascular health.



EVERY TUMOR BEGINS WITH A GENETIC MUTATION. UNDERSTANDING HOW THEY OCCUR AND WHAT THEY DO MAY REVOLUTIONIZE CANCER TREATMENT.

EVERYTHING CHANGES

Virtually every time a cell divides, some small error is introduced into its genomic code. That error might mean nothing at all, or it might lead to a modest change in the function of a cell. On a geologic time scale, a pileup of these tiny mutations is the basis for all evolution, how one species becomes another by developing claws, a shell or a complex brain. But at the speed of a single human life, that progression is slow and mostly silent. "The enzymes in your cells have to copy six billion letters with every division," says Moritz Gerstung, a computational cancer biologist at the European Bioinformatics Institute in Cambridge, England. "That they only make about one mistake per division is remarkably good."

Still, with cells dividing roughly 10 quadrillion times during a human lifetime, an accumulation of tiny mistakes can sometimes yield deadly effects. One of the most familiar is cancer. This happens when DNA "processing errors," coupled with damage from external carcinogens and other factors, cause mutations that allow cells to go into reproductive overdrive, growing out of control and eventually overtaking healthy cells, bypassing the body's ability to police and repair errors and eventually crowding out the body's healthy tissue.

One of the most successful recent frontiers in cancer research, powered by advances in genomic sequencing, has been to pinpoint which mutations initiate cancer and explore how each one may help tumor cells thrive. Creating a rogue's gallery of mutations and their functions has led to earlier and more accurate diagnoses, treatments that can narrowly target the mutation's effects and an overall better prognosis for many cancer patients.

By Adam Bluestein // Illustrations by Scott Bakal

Now a flood of new research is vastly expanding what is known about mutations—how they arise and what transforms them into agents of disease. In one landmark development, an international team of scientists analyzing the largest set of cancer sequencing data ever assembled has produced the most extensive catalog of cancer-causing mutations. The Pan-Cancer Analysis of Whole Genomes (PCAWG) Consortium launched a flurry of publications in February 2020 that detailed a host of insights both profound and useful.

These and other recent discoveries are bringing into focus a more complex and fascinating picture of the role of mutation in cancer. Mutations—even those that are quite dangerous—may be more widespread than researchers had thought, and may lie dormant in the body for much longer than previously believed, relying on a particular cascade of factors to kickstart the disease. Researchers are also seeing how the position of mutations in chromosomes may hold clues to understanding their impact, and how their location in the body may lead to wildly different outcomes for the same genetic error.

EFFORTS TO TRACE THE COURSE OF THE MUTATION MAY LEAD TO CHANCES TO INTERVENE EARLY.

One major result of this work is a changing view of mutation itself. It is increasingly seen not as an error of the body but as its natural background activity, one that has a profound effect as humans age and minor transcription errors add up. Although it can't be stopped, mutation can be better understood, and today's efforts to trace the course of the mutations may lead to opportunities to intervene early and more effectively, signaling a turning point in the way that cancer is diagnosed and treated.

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One surprise of recent research is just how widespread potentially deadly mutations may be. That was clear in the results of a study published in November 2018 in *Science*, in which researchers at the Wellcome Sanger Institute near Cambridge, England, looked at esophageal tissue from deceased donors. New sequencing methods allowed them to examine small populations of cells and see which mutations those cells held in common. None of the donors had esophageal cancer, and the researchers expected to see fewer mutations than in, for example, the skin, which is subjected to the mutagenic effects of the sun. While there were, indeed, fewer than in the skin, the esophageal mutations were still manifold. People in their early twenties carried several hundred mutations per cell, and in samples from older donors, there were more than 2,000 mutations per cell.

More surprising than the sheer number of mutations in normal tissue, though, was how many of those alterations involved genes known to be mutated in cancer. Tissue samples from middle-aged and elderly donors, although they showed no signs of cancerous lesions under a microscope, had "mutant clones"—clusters of cells with cancer-like mutations—colonizing more than half of their surface. These mutant clones behaved like cancer in that they multiplied rapidly in order to gain a competitive advantage over neighboring cells. But they weren't cancer.

In these samples, the most prevalent cancer-driving mutations affected the TP53 and NOTCH genes. Mutations in TP53 are found in about half of all cancers, but they were also found in up to 37% of these esophageal cells from healthy donors. Even more unexpected was the prevalence of mutations in the NOTCH1 gene, which helps to control cell division. Because it's mutated in about 10% of esophageal tumors, the NOTCH1 gene has been widely assumed to be a "driver mutation," crucial for helping cancer cells proliferate. But the Sanger Institute researchers were shocked to find NOTCH1 mutations in up to 80% of the noncancerous esophageal cells taken from older donors. That suggested that mutant versions of this gene, by themselves, might not be sufficient to push cells into malignancy.

Iñigo Martincorena, who co-led the study, has speculated that in a healthy body, clones with different mutations arise and compete for available space and resources—and that rivalry somehow keeps each of them in check, by not allowing any single population of mutated genes to dominate. And tolerating a certain amount of DNA damage as normal seems to be biologically advantageous, says Serena Nik-Zainal, a clinician scientist at the Medical Research Council Cancer Unit at the University of Cambridge. Because the vast majority of mutations aren't particularly harmful, responding to every nick and scratch as if it were a three-alarm fire can be too "expensive" from a cellular survival standpoint. In conditions of high DNA damage—such as exposure to ultraviolet light or to carcinogenic chemicals—focusing too much energy on repairing the genome perfectly could exhaust a cell and kill it. Nik-Zainal hypothesizes that the abundance of mutations in normal cells reflects not a compromised ability to repair DNA, but rather a management strategy.

The research underscores the idea that the mere presence of certain mutations isn't sufficient to initiate the disease. It takes additional outside factors to create an environment in which cancerous cells take over. "A mutated genome may contribute to the potential for malignant transformation, but it does not on its own always determine it," Nik-Zainal says.

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Why do some cells, even when they are riddled with driver mutations—like the cells in that healthy esophageal tissue—not progress to cancer? One reason that mystery has been so difficult to solve is that malignancies don't develop all at once, or steadily. Rather, they appear to grow in a series of clustered events that may stretch over long periods, even decades, and a typical cancer diagnosis occurs at age 60 or older. By that time, a tumor's genome already reflects a life's worth of genetic changes, and it can be almost impossible to reconstruct when and how mutations led to cancer.

It would be ideal to flash back in time and somehow take genetic snapshots of a growing tumor from the time it was a single healthy cell. A team led by Gerstung at the European Bioinformatics Institute has figured out how to do that, virtually, devising a method to reconstruct the evolution of a tumor from a single biopsy. These researchers detailed "life histories" of 38 cancer types for an analysis published in *Nature* in February 2020.

They took advantage of the fact that tumors contain cells from multiple generations. Sets of mutations in each generation evolve further away from their common genetic ancestor and also tell a story of what mutations happened at each phase. So by sequencing cells from different parts of one tumor, researchers were able to deduce the most recent common ancestor for all of them. From there, they could continue to work backward to infer what happened during previous rounds of mutation and cell division. Gerstung's team identified other mutations in the cell that occur as a normal part of aging and used them as markers—something like the rings of a tree—to gauge when particular cancer-specific mutations occurred.

The scientists were surprised to find how early some important cancer-causing mutations showed up. In brain cancer, for example, one crucial driver mutation that alters chromosomal structure sometimes develops even before birth. "That is absolutely astonishing," Gerstung says. "How these people lived so long with such a dramatic alteration before it led to disease is a big unanswered question."

For most cancers, though, the period between the first cancer-causing mutation and diagnosis is shorter—a matter of several years, not several decades. The team also found that, once the first mutation occurred, a cell typically required an increasingly narrow set of additional changes to become cancerous. It turns out that common driver mutations that are shared by many cancer types—involving TP53 and KRAS genes, for example, and noncoding changes affecting the TERT gene—tend to occur early in cancer evolution. In fact, half of all early-stage mutations in cancerous tumors involve just nine genes. It's only later that a tumor is likely to differentiate itself with a more specific, diverse set of mutations that involve about 35 genes. Gerstung's group identified timelines of mutation in colorectal cancer,

glioblastoma and pancreatic cancer, among others, about which little had been known.

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But knowing when cancerous changes occur and what genes they're likely to involve still leaves the question of how and why mutations sometimes cascade into cancer. Important clues can be found by examining underlying patterns of DNA damage known as mutational signatures, and in recent years, there has been a push to catalog the signatures that specifically give rise to driver mutations. The Pan-Cancer (PCAWG) Consortium has put out the most extensive analysis yet of these signatures.

Mutational signatures take researchers a step beyond knowing which genes are mutated, to understanding how they got that way—an interplay of natural failure of DNA repair, for example, and damage caused by internal processes, smoking or too much sunlight. Each type of damage leaves a particular mark, or signature—a characteristic pattern of messing with the cellular DNA. Tobacco, for example, changes the DNA base chemical cytosine to adenine.

The PCAWG researchers identified 97 distinct mutation signatures across 38 types of tumor. The majority of these involved so-called single-base substitutions, in which a single DNA base letter replaces another. Others involved double-base substitutions, affecting two DNA bases, and insertions or deletions of small sections of DNA.

Knowing these signatures can help clinicians spot weaknesses—and even offer clues for treatment. For instance, some cancer cells carry a signature that indicates they have a limited ability to make routine DNA repairs. That characteristic helps the cancer cells mutate and expand, but it can also be used against them. With more mutations, "the cell has more liabilities, more degraded functioning," says Gad Getz, director of bioinformatics at the Mass General Cancer Center, who co-led the PCAWG Consortium study. "It's sicker than those without mutations." Through radiation or chemotherapy, clinicians can prod tumor cells to mutate so much that they become no longer viable. PARP inhibitor drugs, for example, are specifically designed to target tumor cells with defective DNA repair mechanisms.

But this approach to treatment doesn't always work, and deliberately mutated cells may evolve resistance to the therapies. So Getz and others are now working to characterize the mutational signatures and drivers of treatment-resistant tumors, too, which could improve treatment of recurrent cancers.

By using whole genome sequencing data, another team of researchers in the PCAWG Consortium was also able to identify patterns of larger-scale DNA damage—so-called "structural variants." Those involve rearrangements of large chunks of DNA across chromosomes, rather than just a few DNA letters getting altered within specific genes. These seismic rearrangements of DNA are a significant factor in many cancers.

"When people think about mutations, they think of changing one DNA base letter into another letter," says Rameen Beroukhim of the Dana-Farber Cancer Institute in Boston. "But a primary way that cancer becomes cancer is to add copies of genes that it likes"—in other words, those that help promote malignancy—"and delete copies of genes that it doesn't like."

In fact, 23 of the 25 most frequent genetic changes in cancer involve structural changes of whole chromosome arms. During those changes, sections of a chromosome can break away, adding or eliminating one or more copies of hundreds or thousands of genes all at once.

For a February 2020 paper published in *Nature* as part of the PCAWG Consortium, an international team led by Beroukhim analyzed nearly 2,700 whole cancer genomes in the largest study to date of genomic rearrangements. The researchers identified 16 structural variant patterns that play a role in many cancers.

These changes, Beroukhim says, "can screw up the biology of a cell in ways we still can't understand." But solving those mysteries could hold enormous potential for new treatment approaches. "If we can understand structural rearrangements, the therapeutic possibilities are very large and pretty much untapped," he says.

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Another recent insight is that driver mutations work in remarkably specific ways depending on where in the body they occur. Although a handful operate in similar ways across multiple types of cancers, they are the exception, not the rule, says Stephen Elledge, a geneticist at Brigham and Women's Hospital in Boston.

In research published in March 2018 in *Cell*, scientists in Elledge's lab ran experiments on three types of cells—breast, pancreatic and connective-tissue cells called fibroblasts—and were startled by how differently each tissue responded to the same genes that regulate cell proliferation. Genes that drove proliferation in one kind of tissue had no effect in another and actually suppressed proliferation in still another.

How can the same DNA code be translated so differently in different locations? Elledge's team had the idea that such tissue-specific responses to cancer mutations might be largely the result of the "epigenetic" landscape—the array of chemical markers that attach to DNA and alter how its code is read, and the distinct chemical environments different types of cells have, which affect how their genes operate. Epigenetic differences can turn cancer genes on or off, for example.

The epigenetic state of a cancer cell is also likely to influence how particular tissue types respond to therapies and how they may evolve resistance. Inhibiting the gene RAF, for example, is effective in slowing down melanomas. But it has little impact on colorectal cancer in which the same mutation plays a role. That's because tumor cells in the colon express a tissue-specific "growth factor" protein that's not present in skin cells, and that protein helps tumor cells in the colon survive the treatment. Better understanding of such differences could help researchers find tissue-specific vulnerabilities that could be targeted for true precision treatments.

Understanding in much finer detail how cancer develops—including a more precise knowledge of driver mutations and the events that cause them, and a better grasp of how the same mutation might operate in different parts of the body—could lead to new ways to intercede and stop its growth. "As sequencing costs keep decreasing, one can imagine a day when every patient will have their tumor genome sequenced as a standard step," says MGH's Getz. "This information could flow into diagnosis and early detection, and could help identify potential vulnerabilities of newly discovered cancers as well as those already being treated."

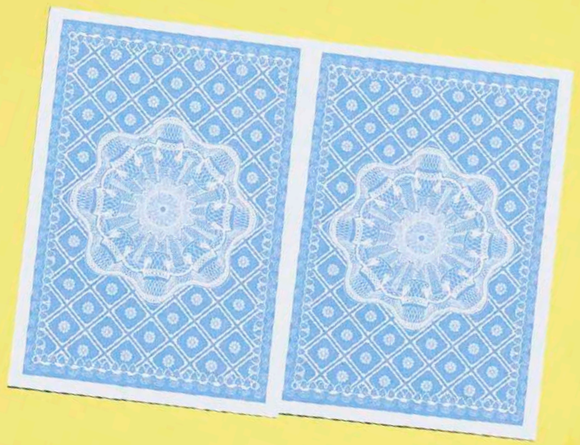
"ONE CAN IMAGINE A DAY WHEN EVERY PATIENT WILL HAVE THEIR TUMOR GENOME SEQUENCED."

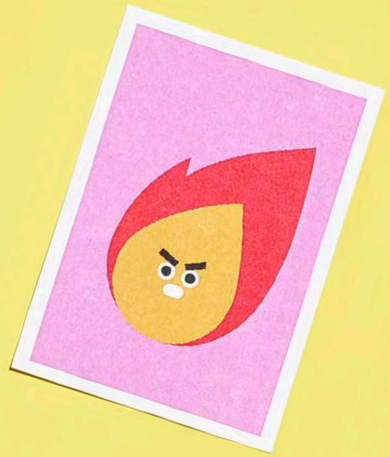
DOSSIER

"Somatic Mutant Clones Colonize the Human Esophagus with Age," by Iñigo Martincorena et al., *Science*, November 2018. This study describes a surprisingly high prevalence of mutations in the tissue of healthy donors.

"Global Genomics Project Unravels Cancer's Complexity at Unprecedented Scale," by Marcin Cieslik and Arul M. Chinnaiyan, *Nature*, February 2020. Across six papers in this issue of *Nature*, the PCAWG Consortium provides the most comprehensive analysis of cancer genome so far.

"A Compendium of Mutational Signatures of Environmental Agents," by Jill E. Kucab et al., *Cell*, May 2019. A short video abstract in this study explains the creation of a "reference library" to better understand mutational signatures that arise from environmental exposures.

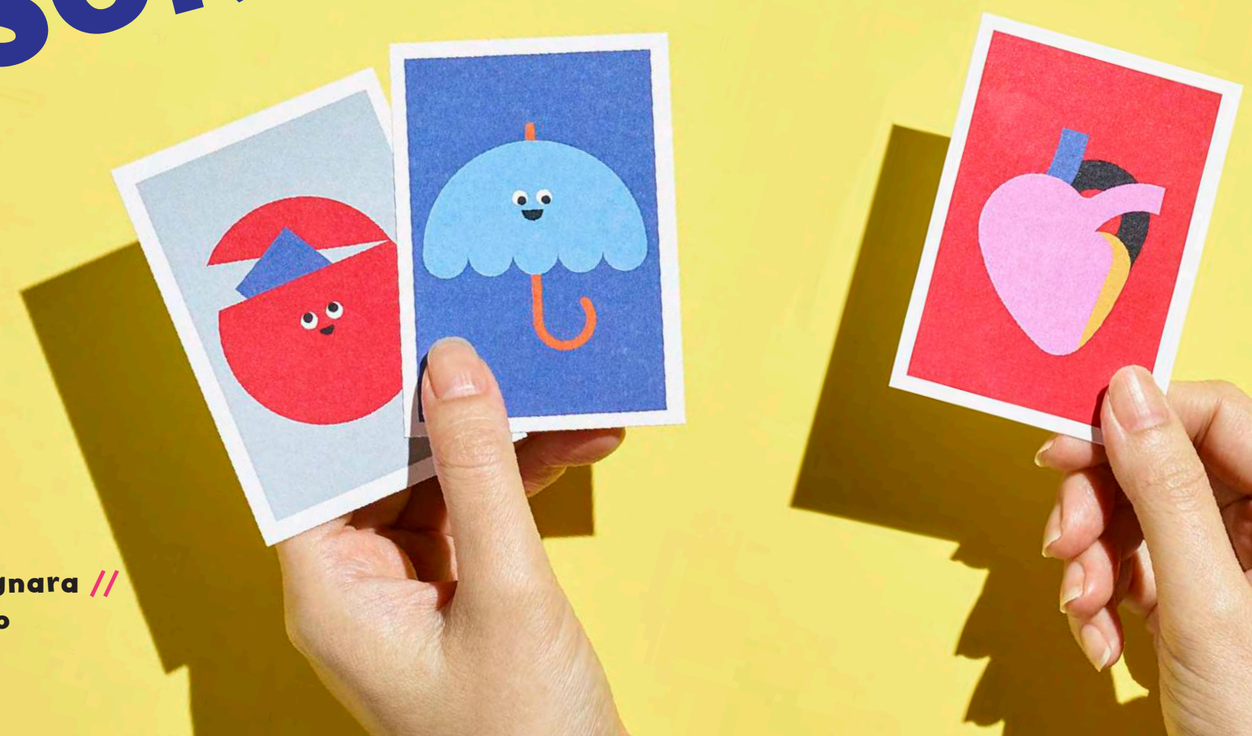




the PERSONALITY GAME

Character traits can influence heart health, cognitive decline and other health factors. Are people prisoners of their dispositions?

By Anita Slomski //
Illustrations by Giacomo Bagnara //
Photographs by Victor Prado



In the 1980s, a young psychology professor in California was looking for a new way to approach an old riddle: why some people enjoy good health while others fall ill and die prematurely. Beyond the physical circumstances that set one life apart from another, wouldn't mental factors play a part as well? Centuries of speculation had swirled around that question: pessimism, hypercompetitiveness, lack of religious devotion, being unsociable—all of those traits had at one time or another been thought to make people less well. But Howard Friedman, now distinguished professor of psychology at the University of California, Riverside, wanted good data—a smoking gun.

Friedman found a wealth of that data in Stanford University archives that had been amassed about 1,500 people, all born between 1900 and 1925. They had been followed from childhood through their adult years as part of the Terman Study, which examined leadership potential in intellectually gifted kids. In his landmark 1993 paper, Friedman reported that children whose parents and teachers rated them, at age 10, as particularly conscientious—well organized, persistent, responsible—were 30% less likely to die during any particular year in their adult lives than their less conscientious peers. In a less positive finding, the most cheerful and optimistic kids—who may have had a more laissez-faire attitude about their lives—were about 6% more likely to die.

"Friedman put personality and health research on the map with that study," says Benjamin Chapman, associate professor of psychiatry and public health at the University of Rochester Medical Center. The research spurred interest in the connection between personality traits, disease and mortality, he says, and helped launch a new wave of investigation.

Recent work has taken these ideas in striking new directions. One study tied hostility in older women to a significantly higher risk of developing diabetes. In Europe, one broad measurement of personality known as Type D—which lumps together those more likely to experience social inhibition, irritability, anger and fear—is now considered so robust a risk factor for cardiovascular disease that it is included in the European Cardiovascular Prevention Guidelines.

Chapman's own latest study, published last year in *JAMA Psychiatry*, brings this thinking to one of the most pressing issues in neurology: the origins of Alzheimer's disease. His work demonstrates that a personality type in adolescence could predict, with impressive consistency, the people who would develop dementia more than 50 years later.

"The evidence that personality contributes to disease is consistent and powerful," says Mark Blais, director of the Psychological Evaluation and Research Laboratory at Massachusetts General Hospital. "Personality influences our habits, the friends we make, the careers we choose, how far we go in school, our lifestyle—and all of that has health consequences, both positive and negative."

Personality is statistically as important as blood pressure, obesity or cholesterol in predicting disease risk.

Personality traits can also have more direct, physiological effects on health. Excessive, chronic worry, for instance, can increase the production of stress-related hormones and chronic inflammation, which in turn can lead to diseases of the heart or immune system. "Personality is statistically as important as blood pressure, obesity or cholesterol in predicting disease risk," Friedman says.

Researchers envision a future in which doctors might give patients a quick personality survey as part of a medical exam and use the results to modify a treatment strategy. Studies have shown, for example, that personality predicts how likely people are to adhere to a treatment regimen, how well they cope with a diagnosis, how quickly they recover from serious illness and how willing they are to make changes to benefit their health.

Future research may also determine whether there are effective interventions to help people tweak their own settings—to alter damaging personality traits or to pump up those that are beneficial. The trick may lie in starting early, when personality is most malleable. "We can teach adolescents and college students the skills to improve self-control," says Brent Roberts, a professor of psychology at the University of Illinois, "which is a key factor to avoid some of the health problems they'll suffer later in life."

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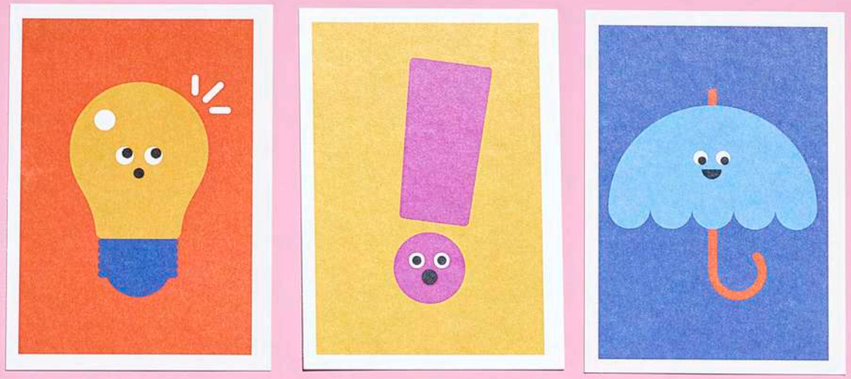
The Type A personality was the first notable modern foray into linking disposition with disease. The term was coined by two cardiologists in the 1950s to describe common traits of their patients who had had heart attacks. These patients were perfectionists who were also super-competitive, impatient and wanted to achieve at all costs. People with relaxed, easygoing personalities—Type B—had a lower risk.

The research drew critics and the approach failed to catch on, in part because many found the divide into only two types of people crude and rigid. The second half of the twentieth century saw a number of attempts to create a more flexible system of personality factors, one that could be used across studies and diseases. By the 1990s, this had coalesced into the Big Five, a collection of widely observed traits. The Big Five consisted of conscientiousness, neuroticism, openness, extraversion and agreeableness. Each of those qualities existed on a spectrum from high to low. "Before the Big Five, the research on personality and health was a mess," says Robert Wilson, professor of neurological sciences at Rush University in Chicago. "The Big Five imposed a common language."



A person can be measured on any of these traits by how far from the average they score. The units are standard deviations, and most people fall within two standard deviations of the average for any personality trait. With this measurement in place, researchers could begin to explore correlations in finer detail. A 2017 study at Northwestern University Feinberg School of Medicine in Chicago, for instance, showed that subjects who were high in conscientiousness, extraversion and agreeableness had a lower risk of mortality, with conscientiousness as the most influential trait. And those who were high in neuroticism were more likely to die prematurely.

More precisely, one standard deviation in neuroticism increased the risk of an early death by 5%. The highest scores for neuroticism—falling, say, four standard deviations above the average—increased the risk to 20%.

Those broad outlines of those findings—that conscientiousness and neuroticism have a profound impact on health—appear in study after study. Count yourself lucky if you rank high in conscientiousness; that is, you are goal-oriented, delay gratification, follow rules, are organized and have good impulse control. Highly conscientious people tend to go to college, achieve career success, and have more stable marital and social connections. All of these correlate strongly with good health, and the group's being more likely to achieve above-average socioeconomic status alone reduces the risk of developing 18 diseases or health conditions, according to new research from Finland. The most conscientious people also tend to take better care of their health and better cope with stress.

Contrast them with people who rank high in neuroticism, making them prone to anger, frustration, jealousy, depression and anxiety. High neuroticism and low conscientiousness are associated with health-damaging behaviors that include overeating, smoking and a lack of exercise. The negative emotions of neuroticism may contribute to chronic stress, which in turn may help spur physical harm in the form of excessive levels of triglycerides, cortisol and inflammatory C-reactive protein. The cards are indeed stacked against them.

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Rush University began its Religious Orders Study in 1993. Its object was to look at aging and the brain by closely following the lives of 1,100 Catholic priests, nuns and brothers. From the outset, the study was designed to look at the role played by personality traits. "We were taking a chance, hypothesizing that personality and its influence on thinking and behavior might predict cognitive decline and dementia," says study researcher Wilson.

It had already been observed that Alzheimer's disease tends to bring personality changes—toward greater neuroticism and less conscientiousness—and that those shifts sometimes come years before the usual signs of dementia. The big question for Wilson was the order of events: whether people who display these traits are at higher risk for Alzheimer's or whether their increasing neuroticism and declining conscientiousness might be symptoms of the disease.

During their lifetimes, the volunteers have regular exams of cognition and personality assessments. The study has found that those who ranked highest in neuroticism at older ages had a threefold higher risk of both developing Alzheimer's disease and experiencing more rapid cognitive decline than those who scored lowest. At the other end of the scale, participants who scored high on conscientiousness had an 89% reduction in risk of Alzheimer's disease compared with those who had the lowest scores.

Researchers then autopsied the brains of deceased study participants to look for physical changes. That's where the shock came. Most of the brains, whether or not the person had dementia, showed surprisingly similar signs. Almost three of four participants who died in their eighties and nineties had the same amyloid-beta plaques and tau protein tangles that are hallmarks of Alzheimer's disease, regardless of whether they had experienced cognitive problems.

"It's very common in old age to have these kinds of dementia-related pathologies—the plaques and tangles—and those pathologies do affect cognitive function," Wilson says. "But the pathologies explain only about half of who gets Alzheimer's disease. There are other factors at play, and we think personality-driven behaviors and lifestyle account for a very meaningful 15% to 20% of the risk."

But how does that personality-driven part of the risk work? Wilson is looking into how neuroticism seems to affect memory and thinking in old age. He believes that chronic psychological distress may cause as-yet unidentified structural and neurochemical changes in brain regions that regulate stress-related behavior and memory—a distinct novel mechanism. The brains of those in the study who had ranked high in conscientiousness, on the other hand, showed better functional and structural characteristics in the frontal lobe.

"We have no evidence yet that personality causes the underlying pathologies of

dementia," Wilson says. "We think instead that personality affects your ability to tolerate and be less vulnerable to the dementia-related changes that normally occur in old age," helping your memory and cognition remain intact, he says. Data taken from a second longitudinal study begun in 1997, Rush's Memory and Aging Project, involves a more diverse group of subjects from all walks of life but has yielded results similar to those from the Religious Orders Study.

A new study from the University of Geneva in Switzerland also suggests that personality can affect the structure of areas of the brain related to memory. The 65 elderly study participants underwent functional and structural brain imaging for almost five years. The researchers found that people who scored low in agreeableness (who were unpleasant, not afraid of conflict, anti-conformists) and high in openness (curiosity, desire to learn, interest in the world) had distinct brain features. They showed less lost volume in the hippocampus, temporal lobe and other regions that tend to deteriorate during normal aging and especially after the onset of Alzheimer's disease.

Personality can affect the structure of areas of the brain related to memory.

Although being a highly agreeable person—cooperative, wishing to please others, eager to avoid conflict—is generally considered a positive personality trait, it might not hold a continued value for brain health. "In older age, agreeableness may have a deleterious effect on brain integrity when the need for social adaptation is less imperative," says study leader and psychiatrist Panteleimon Giannakopoulos, professor and department head of the Geneva University Hospitals of Psychiatry, whose findings were published in *Neurobiology of Aging*. Other studies have shown that high agreeableness in older people tends to be associated with less effective executive performance and other cognitive functions, Giannakopoulos says.

Additional compelling evidence that personality is a risk factor for Alzheimer's disease comes from another recent study, which links personality in the teenage years to the development of dementia 50 years later. Chapman, from the University of Rochester Medical Center, analyzed the personality profiles of 82,000 people who underwent personality tests in 1960 as part of Project Talent, a national study of U.S. teenagers. He then scoured Medicare records of Project Talent participants when they were about 70, searching for those who had received a dementia diagnosis.

The personality tests for Project Talent had been administered before the advent of the Big Five, but children who had shown higher levels of vigor (roughly corresponding to the extraversion category on the Big Five), calm (low neuroticism) and maturity (high conscientiousness) had a lower risk of dementia, and teens who scored at the other end of the scale for those traits—low extraversion, high neuroticism and low conscientiousness—were more likely to develop dementia.

"The kids who were bursting with energy and said that their lives were full of fast-paced activities probably liked to exercise during adulthood and may have felt they had purpose in life and more social engagement," Chapman says. Vigor had a protective effect regardless of whether the teens came from rich or poor families.

Chapman is now looking at specific causes of death of Project Talent participants. In general, those who as children scored high in vigor, calm, maturity and social sensitivity had the lowest rates of premature deaths. Not so for the teens who were most impulsive. Chapman wonders whether he'll find that many of the latter group have deaths related to overeating, drinking and smoking.

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If mounting evidence shows that personality affects health, that leads to another question: Are personality traits innate or can they be modified? Also, can interventions by physicians nudge patients toward the healthier outcomes of "better" personality traits?

Researchers long believed that personality is immutable, but that view has changed. "We know now that personality develops until about age 35," says MGH's Blais, who notes that upbringing and early life experiences play a big role in shaping personality. "But after that point, life-changing events—positive or negative—and even aging itself can alter personality traits. We know that, even after personality has stabilized, some traits can be reduced if they are extreme or increased if they are too low."

Roberts, at the University of Illinois, looked at some of the ways that this might happen. In a study published in 2017, he examined the results of 207 clinical trials in which therapists were experimenting with some new type of therapy—a variation on standard cognitive behavioral therapy, for example. The investigators in those studies measured personality traits of the participants before and after the intervention, in addition to the behaviors they were most interested in changing, such as depression, anxiety, substance abuse or being overweight. "The studies showed without a doubt that personality can change, and much faster than we thought, especially regarding the trait of neuroticism," Roberts says.

"Training programs in which participants learn some type of life skill appear to be especially effective in changing personality traits," he says. "For example, a mindfulness intervention was associated with changing conscientiousness, agreeableness, empathy and emotional stability among medical residents."

On average, the six- to eight-week psychological interventions in these studies changed personality by about half as much as would normally happen between ages 20 and 60, Roberts says. "That is a remarkable amount of change—half a life's worth of change in a few weeks," Roberts says.

In a similar vein, an ongoing study is exploring whether psychological interventions for heart disease patients might be helpful. MGH psychiatrists Jeffery Huffman and Christopher Celano are studying whether positive psychology exercises can enhance happiness, gratitude and optimism in patients with heart disease or diabetes—and, as a result, promote well-being and better health behaviors and cardiac outcomes. "Basically, they're treating neuroticism without identifying it as such, and we are getting promising results altering behaviors," says Nicholas Kontos, a psychiatrist at MGH.

It will be fascinating if clinicians can bring personality research into the clinic to predict disease or to tailor treatment to a patient's personality traits. But perhaps more important is using this knowledge to keep people healthy, says UC Riverside's Friedman. "We can't expect physicians to undo all the habits that began in their patients' lives many years before," he says. "Nor should we attempt to make everyone highly conscientious and expect them to follow the same path to college and beyond."

Instead, Friedman urges a conceptual shift in how we think about health. "It is much more than the absence of disease," he says. "We need to put more emphasis and resources on prevention, and we need to emphasize the social and educational variables that we now know lead to good health—having a purpose, meaningful work, positive social ties and the leisure to enjoy nature. Ultimately, the study of personality and disease is so important because it forces us to think about what it means to be a healthy person," he says.

DOSSIER

"Personality Traits and the Risk of Coronary Heart Disease or Stroke in Women with Diabetes—an Epidemiological Study Based on the Women's Health Initiative," by Junmei Miao Jonasson et al., *Menopause*, October 2019. This paper outlines how postmenopausal women with diabetes who score high in hostility have a higher risk for coronary heart disease.

"Association Between High School Personality Phenotype and Dementia 54 Years Later in Results from a National U.S. Sample," by Benjamin P. Chapman et al., *JAMA Psychiatry*, October 2019. Using a cohort of more than 82,000 study participants, the authors demonstrate that personality traits in adolescence may predict who gets dementia by age 70.

FIRST PERSON

Turning Patient

BY LIZ MONTGOMERY

As a registered nurse in Manhattan, I saw the coming of the pandemic firsthand. I'd seen the overflow of patients in the ER, the staff burdened more than we could have ever imagined. We went about our tasks with a minimum of protection and using the same mask shift after shift.

With my own severely compromised immune system—a run-in with stage-4 cancer nine years ago—I knew I was personally at high risk. I had lost, among other things, my spleen, the gatekeeper of pathogens. But I did my work because it was a time when every one of us was needed. When my own coughing and respiratory distress began, the decision to walk into our emergency room was something I did not take lightly.

The last thing I wanted to do was waste the staff's time or become another burden for the already encumbered. Still wearing my scrubs, I left my unit. I walked into the ER. I was convinced and half hopeful the doctors would tell me my symptoms were psychological, a response somehow to these rows of patients experiencing their signature distress. But after my own abnormal CT scan and dropping oxygen saturation, I was admitted into an isolation room.

I've been hospitalized a hundred times during my battle with cancer; being a patient was not new to me. But the thought of this particular contagious illness terrified me. Awaiting results from my nasal swab, I thought about the people on ventilators, and about those who had already died, and I wondered whether I would ever see my family or my dog again. Every time I attempted to cough, it felt as if a knife was stabbing my lungs. I looked out my hospital window to an empty, dark avenue and alternated between being mentally strong and agonizingly depressed.

The clinicians who took care of me couldn't have been more compassionate, despite their obvious fatigue. I profusely apologized for being another patient, and each time they told me not to worry. It was curious to watch them, knowing what I knew—that they were moving through their shifts hour by hour and saved their crying for when they got home.

At the same time my own nurse manager was texting me: When would I be back to work?

Finally, a pulmonologist entered my room, his hazel eyes full of sympathy. "Your COVID test came back—negative," he said. But even looking at him through his mask and shield, I could tell he wasn't smiling. He explained that my right lung had several nodules and then asked if I had heard of nontuberculous mycobacteria. I only knew of it in AIDS patients. This rare lung infection had somehow set up a home in my frail lungs and would require a year or more of antibiotics and potentially surgery. He said it was an unfortunate time to be diagnosed with dangerous lung disease, when pulmonologists were in such high demand.

He wanted to send me home as quickly as possible so I wouldn't catch the virus or anything else. "But I'm a nurse," I said, to which he just shrugged his shoulders.

I went home to my empty apartment. Messages from my boss continued: "So do you have COVID-19?" I somehow felt guilty that I didn't; it would have been easier to explain. It still hurt to breathe, but in a way, knowing that it wasn't caused by the virus stranded me very much on my own.

When you are working on the wards, you feel you have a bit of control—over your life, over a virus we still know so little about. And frankly, for health care workers, it's during times like this that we thrive. We step up to assist the helpless, to aid those in crisis.

What do nurses like me do when we aren't able to help? When we're benched for the season, watching from the sidelines? My first job is to get better, of course. But beyond that, all I can do, all most of us can do, is send my love and support to my peers who continue to show up.

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