

# S T A N F O R D M E D I C I N E

Issue 2 / 2020

special report

## APART YET TOGETHER:

Breaking COVID-19's  
deadly embrace

### Innovating under pressure

Protecting patients,  
protecting health workers

### Testing, testing

Saving lives through diagnostics

### In the eye of the storm

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Facing the unknown, finding answers

### What is this thing?

A primer on the new virus

### Revenge of the viruses

Renowned virus hunter Peter Piot  
fights personal COVID-19 battle

plus

### Confronting the uncomfortable

Neurosurgeon Samuel Cheshier on  
anti-Black racism at Stanford and beyond





S T A N F O R D  
M E D I C I N E

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# HANDS-OFF LEARNING

## HOW A PANDEMIC IS CHANGING MEDICAL EDUCATION

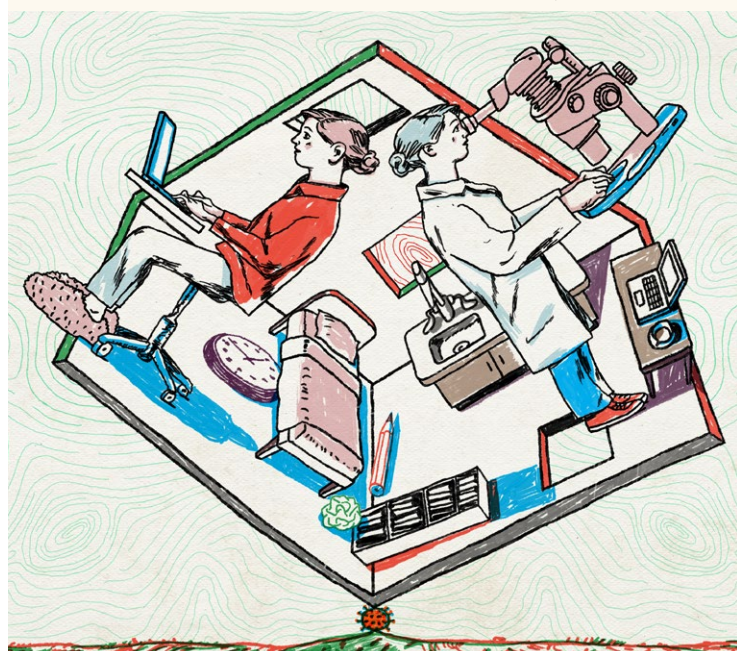
Stanford medical student Kevin Cyr, limited by the pandemic to taking classes remotely, designed a face shield, which was manufactured and distributed to physicians and nurses. His classmate Kiah Williams, exposed to the virus and in quarantine, organized a babysitting service for Stanford physicians suddenly without care for young children. Doctoral candidate Julia McKechnie, forced to postpone her research into dengue virus, switched to processing blood samples from COVID-19 patients.

Shelter-in-place orders, issued in March to combat the coronavirus, disrupted medical education at institutions around the world. But the Stanford University School of Medicine students — who earn medical degrees, master's degrees in physician assistant studies, and doctoral and master's degrees in biomedical sciences — not only generally graduated on time but many also found ways to pitch in.

"As future physicians, we all want to help out," said Cyr, an engineering major. "I'm glad I can provide some expertise."

For the spring quarter, classwork moved online, but many medical and physician assistant students were initially barred from clinical rotations in which they help diagnose and treat patients. Masks, gowns and gloves limit the virus's spread, but supplies were scarce and reserved for health care teams.

Instead, the students joined clinicians on video visits; they also participated in computer-simulated visits that allow them to ask questions, listen to heart and lung sounds, and view lab results. "The real challenge is the examination," said Lars Osterberg, MD, PhD, associate professor of medicine, who oversees the Stanford medical students' clinical education. "Nuances like where you place the stethoscope can't be taught online."



Clinical rotations restarted May 26: Some, including in psychiatry and radiology, work well in online formats and will remain there, Osterberg said; others, including in surgery and obstetrics, must be completed in person.

Starting in June, research labs, most of which had shuttered, reopened for part-time research, allowing the doctoral students to conduct their experiments while social distancing.

Despite the challenges, all 87 of Stanford's graduating medical students and all 27 of the graduating physician assistant students finished on time. A few doctoral students will take longer to wrap up their research, said Sheri Krams, PhD, associate dean for graduate education and postdoctoral affairs, but they tend to graduate throughout the academic year anyway.

"The students have been incredibly resilient through all of this," said Rhonda Larsen, associate director of the program for physician assistants, whose role is similar to that of nurse practitioners. "They've shown amazing patience and a lot of compassion."

When new and continuing medical and physician assistant students arrived on campus in mid-August, they were grouped into small

cohorts that live and study together. They work online as much as possible, but when in-person instruction is required — such as for anatomy, which involves dissecting a cadaver — students wear protective equipment, spread out among classrooms and undergo COVID-19 testing. PhD students, who started in September, are working in their labs in shifts.

The educators see some advantages to the new protocols. Krams has noticed that, with limited time in the lab, doctoral students are more organized about research: "They're using their time quite efficiently," she said.

Lloyd Minor, MD, dean of the school of medicine, noted that students tend to ask more questions during a lecture when classes are taught remotely. And Larsen and Osterberg see the students becoming skilled online practitioners who effectively convey compassion and interpret patients' demeanor through cyberspace. "They're really learning how to use telemedicine," Larsen said, "and that's the wave of the future." — BY MANDY ERICKSON

# STANFORD MEDICINE

## SPECIAL REPORT

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**Web Extra:** Santa Clara County Health Officer Sara Cody on protecting the public from SARS-CoV-2 at [stan.md/saracody](http://stan.md/saracody)



**In the waning hours of 2019, reports emerged of a mysterious cluster of pneumonia cases from an unknown cause.**

Fewer than 60 days later, SARS-CoV-2, the novel coronavirus that causes COVID-19, had gained a foothold on every continent except Antarctica. The speed of the spread of COVID-19 and its devastating impact is unprecedented in modern history. It has challenged the resilience of health care systems, rocked the global economy and disrupted virtually every aspect of public life.

The crisis is far from over, yet I take heart in the scientific collaborations that have unfolded to protect the public, accelerate therapies and clear a path to a globally available vaccine. They give cause for optimism that human ingenuity will eventually win out. I also take pride in the fact that Stanford Medicine has established itself at the forefront of these crucial efforts.

In response to the pandemic, our clinicians, researchers, students and staff quickly mobilized to rise to this challenge. They have led clinical trials, answered fundamental research questions about the coronavirus, brought critical testing capacity to our region, transformed our virtual care capabilities and advised public officials on how to re-open communities safely. This body of work is nothing short of remarkable, and it is my distinct honor to share it with you in this issue of *Stanford Medicine* magazine.

Simultaneously, COVID-19 has laid bare how systemic racism undermines the health and well-being of Black and Latinx Americans. These groups are three times as likely to become infected with COVID-19 and twice as likely to die from it as are white Americans. Communities of color have borne the brunt of this public health crisis, as they have so many others before it.

If we needed to be reminded that racism runs deep in this nation, the tragic murder of George Floyd, under the knee of a Minneapolis police officer sworn to protect and serve, underscores how much progress remains to be made. As Sam Cheshier, MD, PhD, a pediatric neurosurgeon and cancer researcher formerly at Stanford, powerfully writes in this magazine, it is incumbent upon all of us to be actively anti-racist. We must not let this moment pass; we cannot look away.

Overcoming systemic and overt racism requires a sustained campaign greater than the one mobilized to fight COVID-19. It involves individuals changing how they think and act, and elected leaders confronting the effects of policies that have stripped Black and Latinx communities of essential services, affordable housing, a quality education and other opportunities for advancement. Academic medical centers, too, play an important role in bringing forward necessary and long-overdue solutions. We will devote a future issue of this magazine to how Stanford Medicine is actively addressing systemic racism in health care and taking part in the fight for racial justice.

By early October, COVID-19 had killed more than 210,000 people in the United States and a million globally. Vaccines, therapeutics and diagnostics will end this pandemic, but that is not our finish line. We have lifetimes of work ahead of us, especially in confronting the shameful inequities that COVID-19 has exposed. Stanford Medicine is committed to doing this difficult work and will be part of the solution.

Sincerely,  
Lloyd Minor, MD

Carl and Elizabeth Naumann Dean of the School of Medicine  
Professor of Otolaryngology — Head & Neck Surgery



# upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

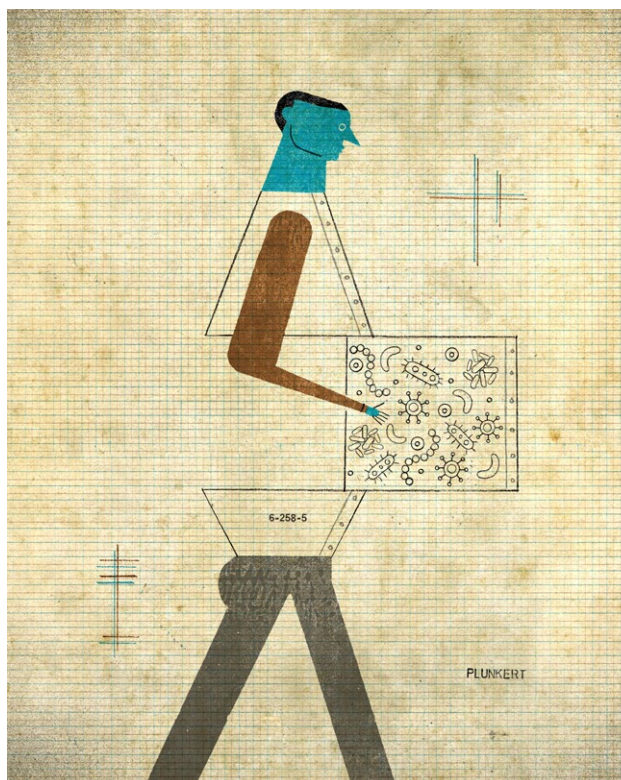
## Gut check

PEOPLE WITH ulcerative colitis — a condition marked by painful inflammation in the colon — could be missing microbes that are key for turning food into crucial substances the body needs, Stanford Medicine researchers found.

There is no cure for ulcerative colitis, and the cause is unknown. But Stanford research described in a Feb. 25 paper in *Cell Host & Microbe* has tied the condition to patients having insufficient amounts of substances called secondary bile acids, which are anti-inflammatory metabolites produced only by gut-dwelling bacteria.

Aida Habtezion, MD, associate professor of gastroenterology and hepatology, and senior author of the paper, said researchers hope the finding leads to “being able to treat it with a naturally produced metabolite that’s already present in high amounts in a healthy gut.”

Researchers compared two groups of patients — one with ulcerative colitis, the other with a noninflammatory condition of the colon — who had undergone an identical corrective surgi-



cal procedure. They discovered that a particular family of bacteria, *Ruminococcaceae*, was depleted in patients with ulcerative colitis. These patients also were deficient in secondary bile acids, the scientists report.

The discoveries raise the prospect that supplementing patients with those missing metabolites — or perhaps someday restoring the gut-dwelling bacteria that produce them — could effectively treat intestinal inflammation in these patients and perhaps those with a related condition called Crohn’s disease, Habtezion said.

## Lyme culprit targeted

SCIENTISTS HAVE FOUND an antibiotic that kills the bacteria that causes Lyme disease and might be effective for the 20% of patients with lingering symptoms that don’t respond to other treatments, a Stanford Medicine study shows.

Jayakumar Rajadas, PhD, assistant professor of medicine, said the intravenous drug azlocillin was tested in mice. Rajadas is the senior author of the study published March 2 by *Scientific Reports*.

Azlocillin is approved by the Food and Drug Administration, but it is not available for clinical use in the United States. Researchers are working with a company to develop an oral form of the drug and plan to conduct a clinical trial.

Stanford has carried out more than **228,000** COVID-19 tests using the assay the virology lab developed at the start of the pandemic. More on Stanford testing at [stanford/COVIDtests](https://stanford.COVIDtests).

## Anti-depressant predictor

A NEW METHOD OF INTERPRETING BRAIN activity has the potential to predict who can benefit from taking an antidepressant, according to a study led by Stanford University School of Medicine researchers.

Treatment for depression often starts with prescribing antidepressants. But finding the right one or identifying patients who don't respond to antidepressants can take months — delaying decisions to try other treatments, said Amit Etkin, MD, PhD, professor of psychiatry and behavioral sciences.

In search of a way to predict which treatment will be effective for an individual patient, the researchers analyzed publicly available data from an earlier joint study from Stanford and the University of Texas-Southwestern called EMBARC, which obtained neuroimaging data from 228 people with depression before and after they were given a placebo or sertraline, an antidepressant marketed as Zoloft.

In the new study, the researchers applied an artificial intelligence technique they developed to identify signatures in the electroencephalography, or EEG, data predicting which participants would respond to sertraline. They focused on EEG because many psychiatrists already have the needed equipment. They published a paper on the approach Feb. 10 in *Nature Biotechnology*.

"It's a method that can work across different types of EEG equipment, and is thus more apt to reach the clinic," said Etkin, who was co-senior author of the paper with Madhukar Trivedi, MD, professor of psychiatry at the University of Texas-Southwestern. Etkin is founder and CEO of Alto Neuroscience, which develops biologically based diagnostic tests to personalize mental health treatments.

## Runner's low

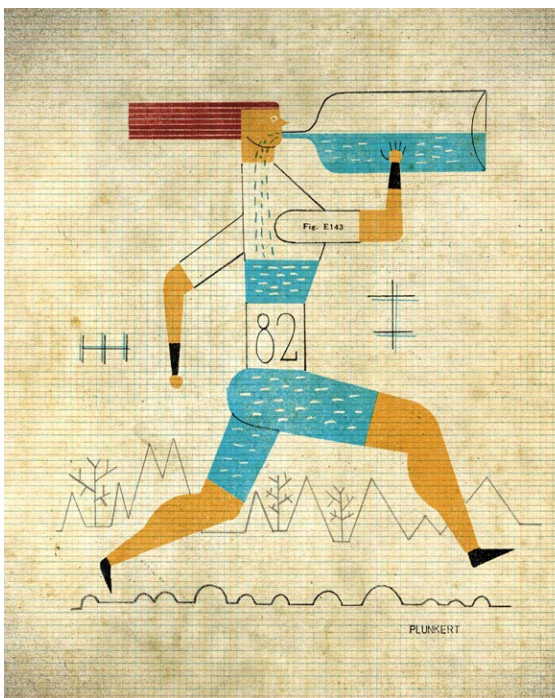
ELECTROLYTE SUPPLEMENTS DO LITTLE to keep sodium levels in balance in endurance events, a Stanford Medicine study published Feb. 25 in the *Clinical Journal of Sport Medicine* showed.

"Electrolyte supplements are promoted as preventing nausea and cramping caused by low salt levels, but this is a false paradigm," said the study's lead author, Grant Lipman, MD, professor of emergency medicine.

Sodium maintains blood pressure and regulates muscle and nerve function, so it's dangerous for levels to be off balance. Hyponatremia occurs when sodium levels are too high, causing dehydration. Exercise-associated hyponatremia, or EAH, occurs when sodium levels drop, causing altered mental status, seizures, pulmonary edema or even death.

To study the usefulness of supplements, Lipman and his collaborators recruited 266 ultramarathoners who ran 155 miles over seven days, across rough desert terrain.

They collected data on a 50-mile day, weighing runners before their race, asking which electrolyte supplements they planned to use and whether they would drink at intervals or when they felt thirsty. Afterward, runners reported how closely they followed their plans, were weighed, and gave a blood sample. Forty-one athletes had sodium imbalances: 11 had EAH, and 30 were dehydrated. Each took supplements, but the type, amount and manner of ingestion showed little to no effect on sodium levels.



## WHAT VAPERS DON'T KNOW

YOUNG ADULTS DON'T KNOW what's in the products they vape and often don't know what brand of vaping products they use, a new study by researchers at the Stanford University School of Medicine said.

For the study, published March 16 in the *Journal of Adolescent Health*, the researchers surveyed 445 California residents ages 17-24 about their use of e-cigarettes, including products from Juul, Suorin Drop, Phix and Myblu.

Researchers said about half of pod-based e-cigarette users were unaware of the product's nicotine content.

"If we asked how many milligrams of nicotine are in a Juul pod, for example, we found the answers were all over the place," said the study's senior author, Bonnie Halpern-Felsher, PhD, professor of pediatrics. "Packaging is so confusing and misleading."

At the time of the survey in early 2019, Juul labels only said "5%." That's been updated — labels now say "5% nicotine." Still, the amount of nicotine per dose is not listed.

"I really hope these findings will be used to further regulate e-cigarettes," said Halpern-Felsher.



## Neurons in action

A GROUP OF Stanford University researchers developed a device that can be implanted into the brain to film the activities of thousands of individual neurons, according to a paper published March 20 in *Science Advances*.

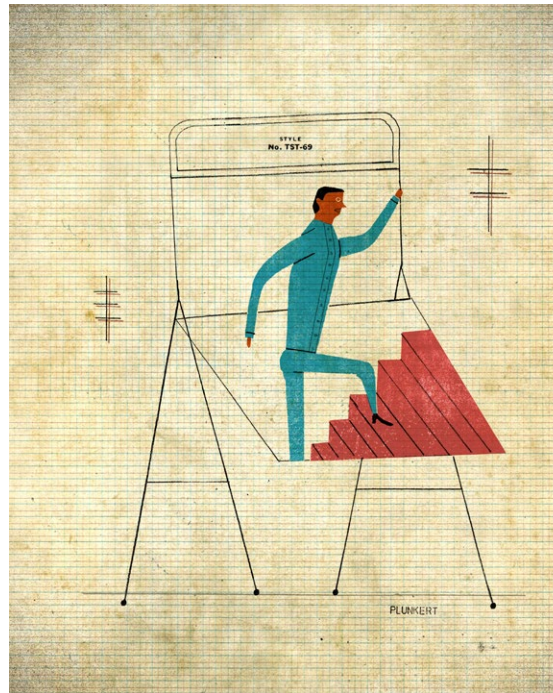
The device, which could be used for research or in prosthetics and has been tested in mice, contains a bundle of microwires that are each less than half the width of the thinnest human hair and are directed into the brain to record passing electrical signals.

"Electrical activity is one of the highest-resolution ways of looking at brain activity," said Nick Melosh, PhD, professor of materials science and engineering and co-senior author of the paper.

"With this microwire array, we can see what's happening on the single-neuron level."

**"If you want to change your behavior, find some other people who are trying to make the same change."**

KEITH HUMPHREYS, PHD



## Social sobriety

THROUGH THE FELLOWSHIP IT PROVIDES, Alcoholics Anonymous helps people quit drinking more effectively than therapy, Stanford Medicine research shows.

More than 2 million people use AA, but mental health professionals are sometimes skeptical of it, said Keith Humphreys, PhD, professor of psychiatry and behavioral sciences. Early on, he was one of the skeptics, thinking, "How dare these people do things that I have all these degrees to do?"

Bill Wilson and Bob Smith created the fellowship in 1935 as a way to stay sober. They formed the first support group in Akron, Ohio, and later developed a 12-step program that includes accepting one's inability to control drinking and helping others stay sober by becoming a sponsor of a new member.

Though AA has been around for decades, researchers only recently developed good methods to measure how well it works, Humphreys said.

He and two other researchers, one from Harvard Medical School and another from the European Monitoring Center for Drugs and Drug Addiction, evaluated AA and counseling designed to facilitate engagement with AA. They analyzed 35 studies that included the work of 145 scientists and the outcomes of 10,080 participants.

In the review, published March 11 in *Cochrane Database of Systematic Reviews*, they found that AA was nearly always more effective than psychotherapy in helping people achieve abstinence.

AA works, Humphreys said, because it's based on social interaction: Members give each other emotional support and practical tips to refrain from drinking. "If you want to change your behavior, find some other people who are trying to make the same change," he said.

## Stanford ranks among the top 20 hospitals

U.S. NEWS & WORLD REPORT has recognized Stanford Health Care's commitment to safety and quality in naming Stanford Hospital 13th in its 2020-21 Best Hospitals Honor Roll.

"We're proud to again be recognized as one of the top hospitals in the country," said David Entwistle, president and CEO of Stanford Health Care. "Our successes are a direct reflection of the tireless dedication, courage and compassion of Stanford Health Care's faculty and staff."

The company uses data on nearly 5,000 U.S. medical centers to rank performance in 16 specialties and 10 procedures and conditions, factoring in patient outcomes, reputation among peers, patient volume, and other considerations.

Lloyd Minor, MD, dean of the Stanford School of Medicine, said being on the honor roll "affirms our talented faculty and staff's commitment to delivering the best possible outcomes for patients through a high-tech, high-touch approach to medicine."







apart yet together

BREAKING COVID-19's DEADLY EMBRACE

It was Friday, Jan. 24, and Amanda Chawla, vice president of supply chain for Stanford Health Care, was knee-deep in a crisis when a colleague relayed a question that gave her pause.

"DO YOU THINK WE'RE GOING TO HAVE A PROBLEM WITH THIS?"

The question had been posed by a nurse who was following the news out of China. Wuhan had just instituted a citywide quarantine that shut down medical supply manufacturing in the region. "The nurse knew that the Hubei province is a major manufacturing hub for medical supplies, including personal protective equipment," Chawla recalled.

Chawla and her colleagues realized immediately that the threat was very real.

Like many other major medical centers, Stanford is on a "just in time" model of medical inventory distribution, including personal protective equipment. As a result, there is rarely more than about three to five days' worth of supplies directly on hand: not enough to combat a worldwide run on manufacturers sparked by what could be a global pandemic.

"Our core mission is to ensure the right items are in the right place at the right time," Chawla said. "It was clear that the inventory on hand, and what we knew was available from our distributors, was insufficient. We had to get ahead of this quickly in order to secure the inventory needed to protect Stanford's workers."

On Monday, Jan. 27, Stanford placed its first bulk order for N95 masks.

The decision to stockpile was prescient. Prior to the arrival of the new coronavirus that causes COVID-19, Stanford Health Care went through about 640 of the disposable respirators each day, but as COVID-positive patients began to show up at the hospital, that rate increased by more than 600% — to about 4,300 N95 masks per day.

Over the next few weeks, the new coronavirus would strain the limits of not just the supply chain at every level but also the organization's physical capacity, the dedication and endurance of its workforce, and its ability to safely care for its sickest patients during a global pandemic.

**A L L**

**T O G E T H E R**

**N O W**

**STANFORD MEDICINE TAKES AIM AT COVID-19**

By Krista Conger

ILLUSTRATION BY JASON HOLLEY



To meet the challenge, clinicians, managers, researchers and staff from across Stanford Medicine — including Stanford Health Care, Stanford Children’s Health, Stanford Health Care – ValleyCare and the School of Medicine — designed diagnostic tests, revamped the flow of patients in its emergency departments, launched drive-through testing clinics and reopened recently decommissioned Stanford

“The responsiveness and dedication of the people of Stanford Medicine in this time of crisis were remarkable,” said Lloyd Minor, MD, dean of the Stanford School of Medicine. “Together we safely cared for our patients, provided intellectual and material resources to our community, and contributed significantly to the growing body of knowledge about this unprecedented global threat.”

**‘EVEN THOUGH**

# **THERE WERE SO MANY UNKNOWN S,**

**OUR PEOPLE CAME ROLLING IN THE DOOR TO HELP.  
THEY WERE RUNNING INTO THE FIRE,  
RATHER THAN AWAY FROM IT.’**

Hospital rooms. They devised models to predict when, where and how urgently infected people were likely to need care, and whether and when hospitals throughout Santa Clara and San Mateo counties were likely to become overwhelmed.

They put in place systems that allowed the organization to quickly cancel elective surgeries, implement telemedicine options for patients sheltering in place, provide testing support to sister organizations, handle tens of thousands of donations of medical equipment and testing supplies, and facilitate an online exchange that allowed Bay Area hospitals to share protective equipment and supplies. To keep everyone in the hospital safe, they instituted universal masking requirements, symptom checks for employees, a robust testing program for patient-facing workers and policies limiting visitors to the hospital.

And they did it all in an atmosphere of uncertainty and fear and under a shelter-in-place order, which made collaboration difficult.

“In the early days, we didn’t know much about what this disease was or how it was transmitted in all instances,” said Alison Kerr, chief administrative officer of clinical operations for Stanford Health Care. “We didn’t know how best to protect ourselves and our families. Not knowing what to be prepared for is hard. It’s scary. But even though there were so many unknowns, our people came rolling in the door to help. They were running into the fire, rather than away from it. It was incredibly inspirational.”

## **MAKING PREPARATIONS FOR THE WORST-CASE SCENARIO**

**I**T’S THOUGHT THAT the first human infection with the novel coronavirus occurred around Dec. 1, 2019, in Wuhan, China. The first suspected case of human-to-human transmission likely occurred in mid-December, and by Dec. 29, local hospitals in Wuhan reported the first four cases of a pneumonia of unknown cause. Ten months later, the virus had infected more than 35 million people and killed more than a million worldwide.

The surge in patients that Stanford expected in March and April didn’t materialize, thanks in large part to the shelter-in-place order issued by six Bay Area counties in March to stop the spread of the virus. But in the first weeks of the pandemic, Stanford Health Care had no choice but to prepare for the worst.

“The county asked us to prepare 200 ICU beds for possible COVID patients,” Kerr said. The hospital had 99.

In early January, however, the hospital was in a watch-and-wait mode as it assessed the news from China. The subcommittee on emerging infectious diseases had a regularly scheduled meeting on Jan. 8 in which they discussed the prevalence of what was then known as Wuhan pneumonia. The same day, the U.S. Centers for Disease Control warned physicians to watch for patients with respiratory symptoms who had recently traveled to China.

"I had a very bad feeling about it, even before we really realized it was a pandemic," said Sasha Madison, director of infection prevention and control at Stanford Health Care. "We were concerned about how a possible shortage of PPE would affect the protection of our health care workers and the care of our patients."

"When we first had an inkling that this could be a problem, I had some informal meetings with infection control experts to outline 'What are going to be the issues? What is the best way to approach them? What do we do now?'" said Norman Rizk, MD, who recently retired as long-time chief medical officer of Stanford Health Care. "It quickly became evident that we needed a central command system with the authority to make sweeping, rapid decisions about how the hospitals would respond to an increase in cases."

But how to identify those cases? Many of the symptoms of COVID-19 — cough, fever, sore throat and fatigue — are shared with other respiratory diseases. Benjamin Pinsky, MD, PhD, the director of the Stanford clinical virology laboratory, realized it would be critical to identify and isolate people infected with the novel coronavirus — to prevent further spread and help health care workers decide when it was necessary to use the personal protective equipment that was likely to become in short supply.

When a research group in Berlin published details on Jan. 10 about a diagnostic test they had developed, including critical genetic information about the virus, Pinsky mobilized his team.

"Ben immediately said, 'We need to get this up and running at Stanford,'" said James Zehnder, MD, professor of pathology and director of clinical pathology at Stanford Health Care. "He had that test ready by the end of January, and we started screening people with respiratory symptoms at Stanford in February." *[For more information about test development at Stanford, see page 20.]*

"I don't know if anyone was completely ready for the magnitude of what was coming. But we had the foresight to do what we needed to do to be prepared," Pinsky said.

Meanwhile, on Jan. 19, a 35-year-old man walked into an urgent care facility in Snohomish County, Washington, just north of Seattle and explained that he'd been coughing and feverish since returning on Jan. 15 from Wuhan.

And the United States had its first case. Four days later, Wuhan announced its lockdown; on Jan. 30, the World Health Organization declared a global public health emergency. A day later, Santa Clara County, where Stanford is located, reported its first confirmed case in a man

who had also recently traveled to Wuhan.

Suddenly, the precautions at Stanford assumed a new urgency. Now it was a race to get ahead of the coming tide of infection.

#### CRITICAL TURNING POINTS HELP LAY THE RESPONSE GROUNDWORK

**T**WO EVENTS WERE CRITICAL to Stanford Health Care being able to prepare for an expected influx of COVID-19 patients. The first was the opening of the new Stanford Hospital in late November, which meant that decommissioned patient rooms in the older hospital were empty and could be tapped for use during the pandemic.

"Our new hospital was the result of more than a decade of hard work and planning, and it enabled us to deliver even more innovative care," said David Entwistle, president and CEO of Stanford Health Care. "We couldn't have anticipated what was going to happen just months later, but the opening couldn't have come at a better time."

The second was a wide-ranging recall of potentially contaminated surgical gowns in early January — the crisis Chawla was dealing with when Wuhan locked down. In response to the recall, Chawla and her team quickly set up a command center to ensure there were enough gowns to prevent a disruption in surgery schedules. This recent experience in rapid crisis response, as well as a heightened awareness of the fragility of the world's supply chain of medical equipment, meant they were primed to tackle this next, even more serious challenge.

"The supply chain is the lifeline and blood of any medical organization," Chawla said. "We cannot be without the appropriate medical supplies. We started to question the reliability of our suppliers; did they really have the inventory we were going to need?" Chawla and her colleagues, including Michael Kohler, the administrative director of procurement operations and strategy, started to work backward, sourcing not just the equipment but also the raw materials necessary for their manufacture.

"As we climbed up the pipelines, we could see that, for example, we were likely to see shortages of certain types of plastics or other materials within a few weeks," Kohler said. "So we started strategizing how to get ahead of this curve. We were scouring not just international suppliers but also Amazon, Home Depot, any place we could think of that might have things like hand sanitizer, disinfectant wipes and other



supplies necessary to keep our health care workers safe. People were working 16 to 18 hours a day seven days a week.”

Despite their efforts, it became apparent that it would be necessary to conserve available protective equipment and explore alternative manufacturing methods for some items. On Feb. 21, Rizk, Dennis Lund, MD, Stanford Children’s Hospital chief medical officer, and David Svec, MD, the chief medical officer of ValleyCare, launched what is now called the clinical oversight resource team, or CORT. It brought together leaders from across Stanford Medicine involved in, for example, laboratory testing, infection prevention, workforce and supply chain management, and occupational health. On Feb. 28, CORT assembled a PPE conservation task force to explore options and implement guidelines for PPE use at the hospitals.

“All the early information we got about COVID came out of Wuhan,” said Lund. “It was fairly apparent early on that children were less affected. At the same time, we realized the adult facilities might be overwhelmed. So, as we thought about our disaster preparedness, we began to plan how we could best support our adult partners with ventilators, ICU beds and doctors.”

Paul King, president and CEO of Stanford Children’s Hospital, said, “Not all our equipment is sized for adult patients, but we were eager to share what resources we could. We also began to consider reducing the number of elective procedures we performed, in part to conserve PPE if needed for the adult hospital, and we discussed expanding our services to include young adults in order to increase bed capacity in the adult facilities. It was a very collaborative effort.”

Also on Feb. 28, Santa Clara County announced the second known case of community spread of the virus in the United States: an older woman with no history of travel outside the country or previous contact with other confirmed cases. Pinsky’s own surveillance diagnostic test also turned up two positive cases in the third week in February. On March 6, Stanford Hospital announced it was caring for COVID-19 patients — including a Stanford faculty member in respiratory distress.

“Early in the morning of Friday, March the 6th, I got a call saying that we had a faculty member who had tested positive for COVID-19 and who was going to be admitted to Stanford Hospital,” Minor recalled. “That call really brought it home how serious this disease is. It was a very tangible indication that we were dealing with a serious, highly communicable disease and that we had to do everything we could to respond to the disease and protect our workforce.”

The virus had arrived at Stanford.

## SHELTERING FROM THE PANDEMIC’S STORM

**M**OST PEOPLE AT Stanford Medicine agree that March was a blur as the hospitals ramped up capacity and the medical school turned the force of its research toward understanding more how the virus spreads and how human bodies respond to infection.

Unfortunately, there were few existing guidelines about how best to care for the sickest COVID patients. In response, a group of experts led by Angela Rogers, MD, a pulmonary critical care specialist, formed the Stanford COVID ICU Task Force to assess and compile information from the virus’s early days in China and New York. Together the multidisciplinary team assembled a set of best-practice recommendations addressing topics as varied as when to ventilate a struggling patient, whether and how to move a patient onto their stomach to aid breathing and circulation — a practice called proning — how to avoid dangerous blood clots caused by the infection, and how to manage a patient’s pain or agitation during treatment. Recommendations were shared in an online living document accessible to other health care workers around the world. *[For more on this, see page 40.]*

Internists — doctors specializing in the care of a wide variety of medical conditions — were recruited from departments across Stanford Medicine to positions in the emergency department and the ICU to prepare for COVID patients. They and other staff anxiously studied videos showing how to put on and take off PPE safely to avoid contamination.

“In times of crisis, it’s all hands on deck,” Kerr said, “whether the staff were patient facing, or involved in the operations of the organization. Everyone just came together to do whatever they could to try to help. Although people were worried, we all knew you have to just shove those feeling down and get things done.”

One important task was to learn how to care for patients in the emergency department and the ICU while limiting the exposure of health care workers and others to infected patients. To do so, they began to use iPads in the emergency department to evaluate patients from outside the rooms and to connect patients and family members. They also learned how to perform chest X-rays remotely. “A nurse in the room would position the plate and we could shoot the X-ray from outside the room,” Kerr said. “This is something we’d never tried before, but it worked quite well.”

Efforts to improve patient care also led to an explosion in clinical research studies across Stanford Medicine, many of which were supported by the enterprise strategy team, led by Priya Singh, chief strategy officer and senior associate dean for strategy and communications. Several researchers participated in multicenter clinical trials of the antiviral drug remdesivir, the use of antibody-rich convalescent plasma from recovered patients and an immune-suppressing monoclonal antibody called tocilizumab. Other studies included an investigation into the use of self-administered nasal swabs to collect samples for diagnosis, an analysis of the sensitivity and usefulness of pooling samples from several people to conserve testing resources, and assessments of the effectiveness of antiviral treatments known to work for other diseases.

“A lot of really rapid, evidence-based practice has come out of this pandemic,” said Samuel Wald, MD, vice president of surgical services at Stanford Health Care. “Many groups within Stanford Medicine came together to not only solve operational and clinical problems but also to publish their findings.”

As the number of COVID patients in the ICU crept up, however, news about how the situation was unfolding in New York City was on everyone’s mind.

“I was worried we were going to be another Mount Sinai,” Kerr said. “We have a special mission in our community to care for the sickest patients. But the average length of an

rush,” he said. “It was like swimming out into Lake Tahoe; you don’t realize how deep it is until you get into it. But we just knew we needed to be compiling some very basic data — case counts, testing rates, and hospitalizations at Stanford and in the surrounding counties — so that senior leadership would have at least a ballpark idea as to the patient load to expect and how much preparation needed to be done. At first, we compiled these data by hand every day.”

This information was relayed to the systems utilization research team headed by clinical associate professor David Scheinker, PhD, who, with associate professor of surgery Kristan Staudenmayer, MD, and professor of medicine Kevin Schulman, MD, used the data to forecast hospitalization trends and bed needs on a hospital as well as county basis.

The scenario the models were predicting was sobering.

“In early March, case counts really started picking up,” Wald said, “and we started talking with leadership about postponing elective surgeries and procedures to create more capacity.” On Friday, March 13, the possibility became a reality.

“We shut off the elective surgical cases essentially overnight,” Rizk recalled. “In one afternoon, we decided not to do the cases the following morning.” Any procedure that could be safely postponed for 30 days or more was put on hold. But patients weren’t abandoned. Within days Stanford Health Care was providing 70% of its care via telemedicine — for example, instructing patients virtually how to remove

**‘IT WAS LIKE**

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**YOU DON’T REALIZE HOW DEEP IT IS  
UNTIL YOU GET INTO IT.’**

ICU stay for a COVID patient is about three weeks, which is much longer than normal. We also knew that other hospitals would be looking to send patients to us. One of the real advantages of being at Stanford was the availability of statistical modeling to predict future demand.”

Nigam Shah, MBBS, PhD, associate director of Stanford’s Center for Biomedical Informatics Research, spearheaded the effort with the Technology and Digital Solutions team. “For the first two or three weeks, it was an adrenaline

a cast, helping a person check their thyroid for irregularities or reviewing a patient’s medications.

For the children’s hospital, Lund said, the original goal for the year had been to achieve 6,000 telehealth or digital health visits in 2020. “But after we got going we did 6,000 in one week,” he said.

On March 16, six Bay Area counties issued shelter-in-place orders, and normal life for those outside the health care world came to a sudden halt.



## TESTING RAMPS UP TO PROTECT CARE WORKERS AND THE PUBLIC

**N**OT ALL THE NEWS was dire. On Feb. 29, the Food and Drug Administration announced that it was relaxing the restrictions on diagnostic tests for the virus developed by certain high-complexity laboratories, including Stanford's. Pinsky was ready. By March 4, Stanford's test was up and running, making it only the second academic medical center in the country with its own test. Within a week, Stanford was testing hundreds of samples per day from around Northern California — vastly increasing information about the spread of the virus in the surrounding communities and feeding valuable data into the research team's model of hospital needs.

Around the first of March, Stanford Medicine leaders realized there was another important population to be tested: the hospitals' staff. Occupational health and safety services had already begun to field an increasing number of calls from worried employees.

"At the time, there was a strong element of fear and anxiety," Wald said. "People were worried not only about what was likely to happen in the community and the hospital but also about their own health as they cared for COVID patients. Would they be infected; would their family be at risk? Usually our own personal safety is not something we are worried about as health care providers."

Singh's team quickly devised a communications strategy, launching a dedicated website and daily email and hosting regular virtual town hall meetings to provide employees the latest information about how Stanford Medicine was handling the crisis and working to protect them.

On March 12, Stanford Medicine launched the Occupational Health Respiratory Evaluation Center and the new Occupational Health Telephone Evaluation Center for employees to receive rapid screening and diagnostic test-

ing, along with advice about how best to protect themselves against infection and when it was safe to return to work after experiencing respiratory symptoms. Stanford Health Care — ValleyCare also offered testing through its occupational health center.

"I don't think there's ever been a scenario where you suddenly have to assess the health of your work force all at once," said Rudy Arthofer, associate chief nursing officer of inpatient access, capacity, and throughput and efficiency.

In mid-April, Stanford Medicine expanded its testing to include all 14,000 patient-facing staff, and by May 4 more than 11,000 employees had been tested. Of those without symptoms, only about 0.3% tested positive, and there were no recorded cases of transmission between health care workers and patients.

"This showed that our PPE guidelines work," said Rizk. "Our staff are not getting infected by the patients they are caring for."

An increasing demand for COVID testing in the community and a need to manage the flow of patients within the emergency department sparked the launch of a drive-through screening and testing site on March 15 in the garage outside Stanford Hospital's emergency department. The drive-through concept was not new; it was first developed at Stanford in 2009 in response to the H1N1 pandemic.

"We set up the garage site within a weekend," Kerr said, "including Wi-Fi access, generators, heaters, computers and nurses in full PPE. If someone just needed testing, we could swab them and send them on their way without them leaving their car. If they were having other medical problems like a heart attack that needed urgent care, we would bring them in. If they were suspected to have COVID and needed a negative airflow room, we would take them to the side of the building to a different door so they didn't have to go through the spine of the emergency department and expose other patients or staff."

Within the larger hospital, others were reconfiguring beds and spaces to accommodate as many COVID patients

**'THERE WAS A STRONG  
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ANXIETY.**

**... USUALLY OUR OWN PERSONAL SAFETY IS NOT SOMETHING WE  
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as possible — a task made significantly easier by the availability of bed space left vacant after the hospital's new building opened in November 2019. But those rooms had already been stripped of all medical equipment and furniture in preparation for the renovation.

On March 17, the hospital began reinstating these rooms. Lacking time to purchase new equipment, workers had to gather ventilators, beds, cardiac monitors, and even chairs and tables from storage rooms and other areas of the hospital left vacant when elective procedures were canceled. On March 30, the rooms were ready for their first COVID patients.

At the same time, workers devised a plan to increase the number of ICU beds in the new hospital on an as-needed basis.

"The new hospital has an air filtration system that is much more flexible than the older hospital," Arthofer said. "Our facility team can convert regular pressure rooms in the new hospital to negative pressure rooms within 12-24 hours if necessary. So we could stay two beds ahead in the ICU. When we got to the point when we only had one left, they would covert two more."

With the bed plan in place and the number of cases rising, the hospital was as ready as possible for the expected surge.

#### SCRAMBLING TO FULFILL PPE AND TESTING SUPPLY NEEDS

**B**EHIND THE SCENES, supply chain experts Chawla and Kohler were battling increasing scarcity of not just personal protective equipment like N95 masks and specialized powered respirators known as PAPRs and CAPRs but also more mundane items like testing supplies and the swabs used to collect patient samples from the back of the nose and throat.

"At one point, we were down to days or even hours of supply for some items," Kohler said. "We were literally shuttling certain lab products around by hand from laboratory to laboratory as needed. When we got one covered, we were low on another."

On March 22, a task force was launched to explore options for 3D printing of swabs, face shields and other items. Soon an ad hoc company created by orthopaedic resident Kim Hall, MD, and a group of Stanford colleagues had designed and printed thousands of face masks. Another local company, Carbon 3D, worked with the group to design, test and validate printed swabs for large scale production by Resolution Medical — answering a nationwide demand for them.

"I've never seen a product come to market so quickly,

in a matter of weeks rather than months or years," said Sridhar Seshadri, DBA, chief administrative officer for destination service lines.

"We got out of a very dicey situation where other organizations struggled," Kohler said.

A call for donations of supplies and equipment by Stanford Health Care president and CEO Entwistle, medical school dean Minor, and Stanford Hospital's board of directors generated 600 to 800 emails each day from the Stanford community and beyond, sparking the creation of a donation center that accepted about 2.8 million items from around the globe.

"We had to get our own customs broker to facilitate the import of all our international donations," Chawla said. "We were able to give back to our community, providing equipment to assisted living facilities, and we worked in partnership with a company called Resilinc to create an online exchange market for hospitals in the Bay Area to share and trade medical supplies."

As the supply chain stabilized, so did the numbers of COVID patients at the hospital — peaking at about 10 to 15 patients per day who needed to be hospitalized. In the last days of March and early April, informatics expert Shah and his colleagues examined each previous days' numbers with bated breath, looking for evidence of worsening trends.

"In mid-March, it wasn't clear if we were going to see numbers similar to New York's," Shah recalled. "Every morning we'd start with counting the numbers and feeding them into the model. Between about March 18 and March 25, it started to look like it wouldn't be as bad as we had feared. Every day we'd watch for upticks, but hospitalizations leveled off by early April."

By mid-April, it seemed the worst had passed. The early shelter-in-place orders in the Bay Area, coupled with social distancing and mask-wearing, had done what they were meant to do: flatten the curve to avoid overwhelming hospitals and health care workers. On April 14, CORT launched a team to facilitate reopening the hospitals and clinics to more normal operations, which they accomplished with the guidance of Singh's strategy group.

The strategy group also facilitated the inception of the recover, restore and reopen committee, comprised of more than a dozen experts across the organization. The committee's goal was to address and provide guidance on the many complex issues facing not just Stanford Medicine but also local governments, schools and communities struggling to achieve a "new normal" after the expected surge.

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apart yet together

BREAKING COVID-19's DEADLY EMBRACE

HOW THE NEW CORONAVIRUS PENETRATES,  
EXPLOITS AND KILLS CELLS, AND HOW AN ARMY  
OF SCIENTISTS AIMS TO DESTROY IT

# the invader

“Know your enemy,” Sun Tzu, the great sage of war, wrote some 2,500 years ago. Today, as COVID-19 spreads around the globe, the greatest army of medical scientists ever assembled is bent on learning all it can, as fast as it can, about SARS-CoV-2, the virus behind the pandemic.

Here’s a primer on viruses in general and SARS-CoV-2 in particular. As researchers learn more and more about the novel coronavirus that causes COVID-19, this knowledge — gathered through unmatched levels of scientific cooperation — is being turned against the virus in real time.

Not that this will be a simple pursuit. Compared with a lab dish, living people are complicated. The cells in that dish aren’t the same as the cells in living tissues affected by SARS-CoV-2. Plus, the environment surrounding, say, a lung cell in a person’s body is different from the one in a culture dish. And then there’s this thing called “side effects.” You don’t see those in a dish. But you may in a COVID-19 patient.

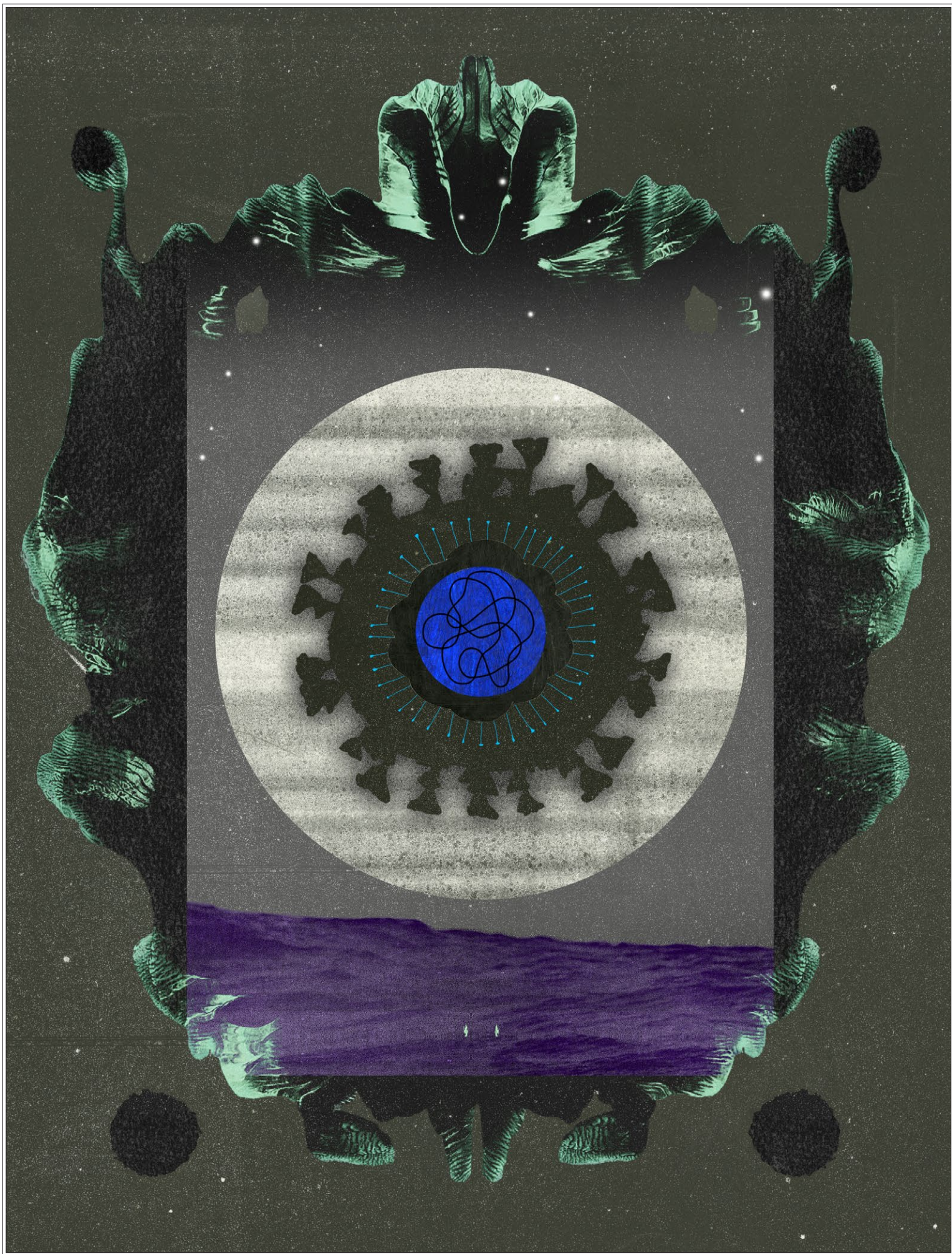
## What, exactly, is a virus, anyway?

Viruses are easily the most abundant life form on Earth, if you accept the proposition that they’re alive. Try multiplying a billion by a billion, then multiplying that by 10 trillion. That — 10 to the 31st power — is the mind-numbing estimate of how many individual viral particles populate the planet.

*By Bruce Goldman*

ILLUSTRATIONS BY JEFFREY DECOSTER







Is a virus a living thing? Maybe. Sometimes. It depends on location. “Outside of a cell, a viral particle is inert,” virologist Jan Carette, PhD, associate professor of microbiology and immunology, told me. On its own, it can’t reproduce itself or, for that matter, produce anything at all. It’s the ultimate parasite.

Or, you could say more charitably, it’s very efficient. Viruses travel light, packing only the baggage they absolutely need to hack into a cell, commandeer its molecular machinery, multiply and make an escape.

There are exceptions to nearly every rule, but viruses do have things in common, said Carette.

A virus’s travel kit always includes its genome — its collection of genes, that is — and a surrounding protein shell, or capsid, which keeps the viral genome safe, helps the virus latch onto cells and climb inside, and, on occasion, abets a getaway by its offspring. The capsid consists of identical protein subunits whose shapes and properties determine the capsid’s structure and function.

Some viruses also wear greasy overcoats, called envelopes, made from stolen shreds of the membranes of the last cell they infected. Coronaviruses have envelopes, as do influenza and hepatitis C viruses, herpesviruses and HIV. Rhinoviruses, which are responsible for most common colds, and polioviruses don’t. Enveloped viruses particularly despise soap because it disrupts greasy membranes. Soap and water are to these viruses what exhaling garlic is to a vampire, which is why washing your hands works wonders.

#### How do viruses enter cells, replicate and head for the exits?

**F**OR A VIRUS TO SPREAD, it must first find a way into a cell. But, said Carette, “penetrating a cell’s perimeter isn’t easy.” The outer membranes of cells are normally tough to get into without some kind of special pass. Viruses have ways of tricking cells into letting them in, though. Typically, a portion of the virus’s cloak will have a strong affinity to

bind with one or another protein that dots the surfaces of one or another cell type. The binding of the virus with that cell-surface protein serves as an admission ticket, easing the virus’s invasion of the cell.

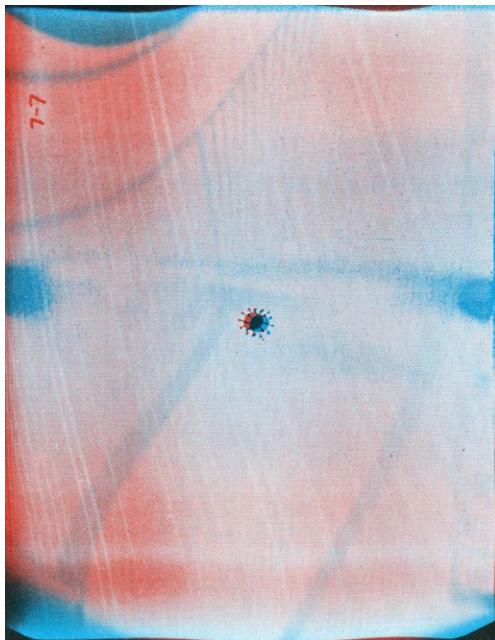
The viral genome, like ours, is an instruction kit for the production of proteins the organism needs. This genome can be made up of either DNA, as is the case with all creatures except for certain viruses, or DNA’s close chemical relative RNA, which is much more flexible and somewhat less stable. SARS-CoV-2’s genome is made of RNA, as are the genomes of most mammal-infecting viruses.

In addition to the gene coding for its capsid protein, every virus needs another gene for its own version of an enzyme known as a polymerase. Inside the cell, viral polymerases generate numerous copies of the invader’s genes, from whose instructions the cell’s obedient molecular assembly line produces capsid subunits and other viral proteins. Among these can be proteins capable of co-opting the cellular machinery

to help viruses replicate and escape, or of tweaking the virus’s own genome — or ours. Depending on the type of virus, the genome can contain as few as two genes — one for the protein from which the capsid is built, the other for the polymerase — or as many as hundreds.

Capsids self-assemble from their subunits, often with help from proteins originally made by the cell for other purposes, but co-opted by the virus. Fresh copies of the viral genome are packaged inside newly made capsids for export.

Often, the virus’s plentiful progeny punish the good deed of the cell that produced them by lysing it — punching holes in its outer membrane, busting out of it and destroying the cell in the process. But enveloped viruses can escape by an alternative process called budding, whereby they wrap themselves in a piece of membrane from the infected cell and diffuse through the cell’s outer membrane without structurally damaging it. Even then, the cell, having birthed myriad baby viruses, is often left fatally weakened.



## **Introducing the coronavirus, and how it latches on**

**N**OW WE KNOW HOW your average virus — an essentially inert particle on its own — manages to enter cells, hijack their molecular machinery, make copies of itself and move on out to infect again.

That just scratches the surface. Of the millions of different viral species identified so far, only about 5,000 have been characterized in detail. Viruses come in many shapes and sizes — although they're all small — and infect everything, including plants and bacteria. None of them works in precisely the same way.

So what about coronaviruses?

Enveloped viruses tend to be less hardy when they're outside of cells because their envelopes are vulnerable to degradation by heat, humidity and the ultraviolet component of sunlight.

This should be good news for us when it comes to coronaviruses. However, the bad news is that the coronavirus can be quite stable outside of cells because its spikes, protruding like needles from a pincushion, shield it from direct contact, enabling it to survive on surfaces for relatively long periods. (Still, soap or alcohol-based hand sanitizers do a good job of disabling it.)

As mentioned earlier, viruses use proteins that are sitting on cells' surfaces as docking stations. Coronaviruses' attachment-enabling counterpart proteins are those same spikes. But not all coronavirus spikes are alike. Relatively benign coronavirus variants, which at their worst might cause a scratchy throat and sniffles, attach to cells in the *upper* respiratory tract — the nasal cavities and throat. The viral variant that's driving today's pandemic is dangerous because its spike proteins can latch onto cells in the *lower* respiratory tract — the lung and bronchial cells — as well as cells in the heart, kidney, liver, brain, gut lining, stomach or blood vessels.

## **Antibody treatments could block binding**

**I**N A SUCCESSFUL RESPONSE to SARS-CoV-2 infection, the immune system manufactures a potpourri of specialized proteins called antibodies that glom on to the virus in various places, sometimes blocking its attachment to the cell-surface protein it's trying to hook onto. Stanford is participating in a clinical trial, sponsored by the National Institutes of Health, to see if antibody-rich plasma (the cell-free part of blood) from recovered COVID-19 patients (who no longer need these antibodies) can mitigate symptoms in

patients with mild illness and prevent its progression from mild to severe.

Monoclonal antibodies are to the antibodies in convalescent plasma what a laser is to an incandescent light bulb. Biotechnologists have learned how to identify antibody variants that excel at clinging to specific spots on SARS-CoV-2's spike protein, thus thwarting the binding of the virus to our cells — and they can produce just those variants in bulk. Stanford is conducting a clinical trial of a monoclonal antibody for treating COVID-19 patients.

A worry: Viral mutation rates are much higher than bacterial rates, which dwarf those of our sperm and egg cells. RNA viruses, including the coronavirus, mutate even more easily than DNA viruses do: Their polymerases (those genome-copying enzymes mentioned earlier) are typically less precise than those of DNA viruses, and RNA itself is inherently less stable than DNA. So viruses, and particularly RNA viruses, easily develop resistance to our immune system's attempts to find and foil them.

The Stanford studies may help reveal whether the precision-targeted “laser” or kitchen-sink “lightbulb” approach works best.

## **The virus breaks into a cell**

**A**SSISTANT PROFESSOR of chemical engineering and subcellular-compartment spelunker Monther Abu-Remaileh, PhD, described two key ways the coronavirus breaks into a cell and seeks comfort there, and how it might be possible to bar one of those entry routes with the right kind of drug.

Here's one way: Once the coronavirus locks on to a cell, its greasy envelope comes into contact with the cell's equally greasy outer membrane. Grease loves grease. The viral envelope and cell membrane fuse, and the viral contents dump into the cell.

The other way is more complicated. The viral attachment can set off a process in which the area on the cell's outer membrane nearest the spot where the contact has been made caves in — with the virus (happily) trapped inside — until it gets completely pinched off, forming an inbound, membrane-coated, liquid-centered capsule called an endosome inside the cell. (To visualize this, imagine yourself with a wad of bubble gum in your mouth, blowing an internal bubble by inhaling, and then swallowing it. In this analogy, you're the cell and all your skin, beginning with your lips, constitutes the cell's outer membrane.)

Enclosed in this endosome is the viral particle that set the



process in motion. The little devil has just hooked itself a ride into the cell's inner sanctum. At this point, the viral particle consists of its envelope, its capsid and its enclosed genome — a blueprint for the more than two dozen proteins the virus needs and the invaded cell doesn't provide.

But the endosome doesn't remain an endosome indefinitely, Abu-Remaileh told me. Its mission is to become another entity called a lysosome, or to fuse with an existing lysosome.

Lysosomes serve as cells' recycling factories, breaking down large biomolecules into their constituent building blocks for reuse. For this, they need an acidic environment, generated by protein pumps on their surface membranes that force protons into these vesicles.

The building internal acidity activates enzymes that chew up the cloistered coronavirus's spike proteins. That brings the virus's envelope in contact with the vesicle membrane and enables their fusion.

The viral genome gets squirted out into the greater expanse of the cell. There, the viral genome will find and commandeer the raw materials and molecular machinery required to carry out its genetic instructions. That machinery will furiously crank out viral proteins — including the customized polymerase SARS-CoV-2 needs to replicate its own genome. Copies of the genome and the virus's capsid proteins will be brought together and re-packaged into viral progeny.

make contact with the membrane of an endosome or lysosome. The virus remains locked in a prison of its own device.

That's what happens in a dish, anyway. But only further clinical trials will tell how much that matters.

#### How the coronavirus reproduces

**S**ARS-COV-2 HAS entered the cell, either by fusion or by sliding in like a Lilliputian aquanaut, stealthily stowed inside an endosome. If things go right for the virus, it fuses with the endosome's membrane and spills its genome out into the (relatively) vast surrounding cellular ocean.

That lonely single strand of RNA that is the virus's genome has a big job to do — two, in fact, Judith Frydman, PhD, professor of biology and genetics, told me — in order to bootstrap itself into parenting a pack of progeny. It must replicate itself in entirety and in bulk, with each copy constituting the potential seed of a new viral particle. And it must generate multiple partial copies of itself — sawed-off sections that serve as instructions, telling the cell's protein-making machines, called ribosomes, how to manufacture the virus's more than two dozen proteins.

To do both things, the virus needs a special kind of polymerase. Every living cell, including each of ours, uses polymerases to copy its DNA-based genome and to transcribe its contents (the genes) into RNA-based instructions that ribosomes can read.

## **A pair of closely related drugs, chloroquine and hydroxychloroquine, have gotten tons of press but, so far, mostly disappointing results in clinical trials for treating COVID-19.**

A pair of closely related drugs, chloroquine and hydroxychloroquine, have gotten tons of press but, so far, mostly disappointing results in clinical trials for treating COVID-19. Some researchers advocate using hydroxychloroquine, with the caveat that use should be early in the course of the disease.

In a lab dish, these drugs diffuse into cells, where they diminish acidity in endosomes and prevent it from building up in lysosomes. Without that requisite acidity, the viral-membrane spike proteins can't be chewed up and the viral envelope can't

The SARS-CoV-2 genome, unlike ours, is made of RNA, so it's already ribosome-friendly, but replicating itself means making RNA copies of RNA. Our cells never need to do this, and they lack polymerases that can.

SARS-CoV-2's genome, though, does carry a gene coding for an RNA-to-RNA polymerase. If that lone RNA strand can find and insert itself into a ribosome, the latter can translate the viral polymerase's genetic blueprint into a working protein. Fortunately for the virus, there can be as

many as 10 million ribosomes in a single cell.

Once made, the viral polymerase cranks out not only multiple copies of the full-length viral genome — replication — but also individual viral genes or groups of them. These snippets can clamber aboard ribosomes and command them to produce the entire repertoire of all the proteins needed to assemble numerous new viral offspring.

These newly created proteins include, notably, more polymerase molecules. Each copy of the SARS-CoV-2 genome can be fed repeatedly through prolific polymerase molecules, generating myriad faithful reproductions of the initial strand.

Well, mostly faithful. We all make mistakes, and the viral polymerase is no exception; actually it's pretty sloppy as polymerases go — much more so than our own cells' polymerases, Carette and Frydman told me. So the copies of the initial strand — and *their* copies — are at risk of being riddled with copying errors, aka mutations.

However, coronavirus polymerases, including SARS-CoV-2's, come uniquely equipped with a sidekick “proofreader protein” that catches most of those errors. It chops out the wrongly inserted chemical component and gives the polymerase another, generally successful, stab at inserting the proper chemical unit into the growing RNA sequence.

### [Coronavirus birth control](#)

**T**HE EXPERIMENTAL DRUG remdesivir, approved for emergency use among hospitalized COVID-19 patients, directly targets RNA viruses' polymerases. Stanford participated in clinical trials leading to this injectable drug's approval. Initially developed for treating Ebola virus infection, it belongs to a class of drugs that work by posing as legitimate chemical building blocks of a DNA or RNA sequence. These poseurs get themselves stitched into the nascent strand and gum things up so badly that the polymerase stalls out or produces a defective product.

“Now, with the drug, the virus starts making a lot of rotten genomes that poison the viral replication process,” said Frydman.

Remdesivir has the virtue of not messing up our cells' own polymerases, said Robert Shafer, MD, professor of infectious disease, who maintains a continuously updated database of results from trials of drugs targeting SARS-CoV-2.

But while remdesivir's pretty good at faking out the viral polymerase's companion proofreader protein, it's far from perfect, Shafer said. Some intact viral genome copies still

manage to be made, escape from the cell, and infect other cells — mission accomplished.

Using remdesivir in combination with some still-sought, as yet undiscovered drug that could block the proofreader might be a more surefire strategy than using remdesivir alone, Shafer said.

### [The final round in the cellular boxing ring](#)

**I**N ADDITION TO REPLICATING its full-length genome, the virus has to make lots of proteins. And it knows just how. Those RNA snippets spun off by the viral polymerase are tailored to play by the cell's protein-making rules — well, up to a point. They fit into ribosomes exactly as do the cell's own strands of “messenger RNA” copied from the cell's genes by its own DNA-reading polymerases. So-called mRNAs are instructions for making proteins.

But there's a hitch: Among the proteins the virus forces ribosomes to manufacture are some that, once produced, bite the hand that fed them. Certain newly made viral proteins home to ribosomes in the act of reading one or another of the cell's mRNA strands, hook themselves onto the strand and stick stubbornly, stalling out the ribosome until the cell's mRNA strand falls apart.

The genomic RNA strands the virus generates, though, all have little blockades on their front ends that protect them from being snagged on the cell's ribosomes by the viral wrecking crew. The result: The cell's protein-making assembly line is overwhelmingly diverted to the production of viral proteins. That's a two-fer: It both increases viral-component production and stifles the infected cell's natural first line of defense.

### [Interferons as a potential treatment](#)

**A**MONG THE CELL'S STILLBORN proteins are molecules called interferons, which the cell ordinarily makes when it senses it's been infected by a virus. Interferons have ways of monkeying with the viral polymerase's operations and squelching viral replication. In addition, when secreted from infected cells, interferons act as “call in the troops” distress signals that alert the body's immune system to the presence and location of the infected cell.

Instead, silence. Advantage: virus.

There are several different kinds of interferons. A clinical trial is underway at Stanford to determine whether a single injection of one of them, called interferon-lambda, can keep just-diagnosed, mildly symptomatic COVID-19 patients out

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apart yet together

BREAKING COVID-19's DEADLY EMBRACE

# TESTING AT THE SPEED OF COVID

STANFORD LAUNCHED ITS OWN DIAGNOSTIC  
WHEN THE PANDEMIC HAD JUST BARELY BEGUN —  
BUT THE CHALLENGES KEPT ON COMING

It was Saturday morning, March 14, and infectious disease specialist Benjamin Pinsky, MD, PhD, was knocking on the locked entry door at the Beckman Center for Molecular and Genetic Medicine while simultaneously fielding a phone call. "Oh, there's someone! I think they are going to open the doors for me."

Pinsky, an associate professor of pathology and the medical director of Stanford's clinical virology laboratory, needed access to the Protein and Nucleic Acid Facility in the building's basement to collect short stretches of DNA called primers — a critical component of a test Pinsky and his colleagues devised to detect the presence in patients of the genetic material of the deadly coronavirus that was sweeping the globe.

Pinsky launched the test on March 4, shortly after the Food and Drug Administration allowed some qualified laboratories to use coronavirus tests that were developed and validated in-house.

Stanford's test was among the first in the nation developed at an academic medical center and the lab quickly became the testing epicenter in Northern California in the early days of the pandemic.

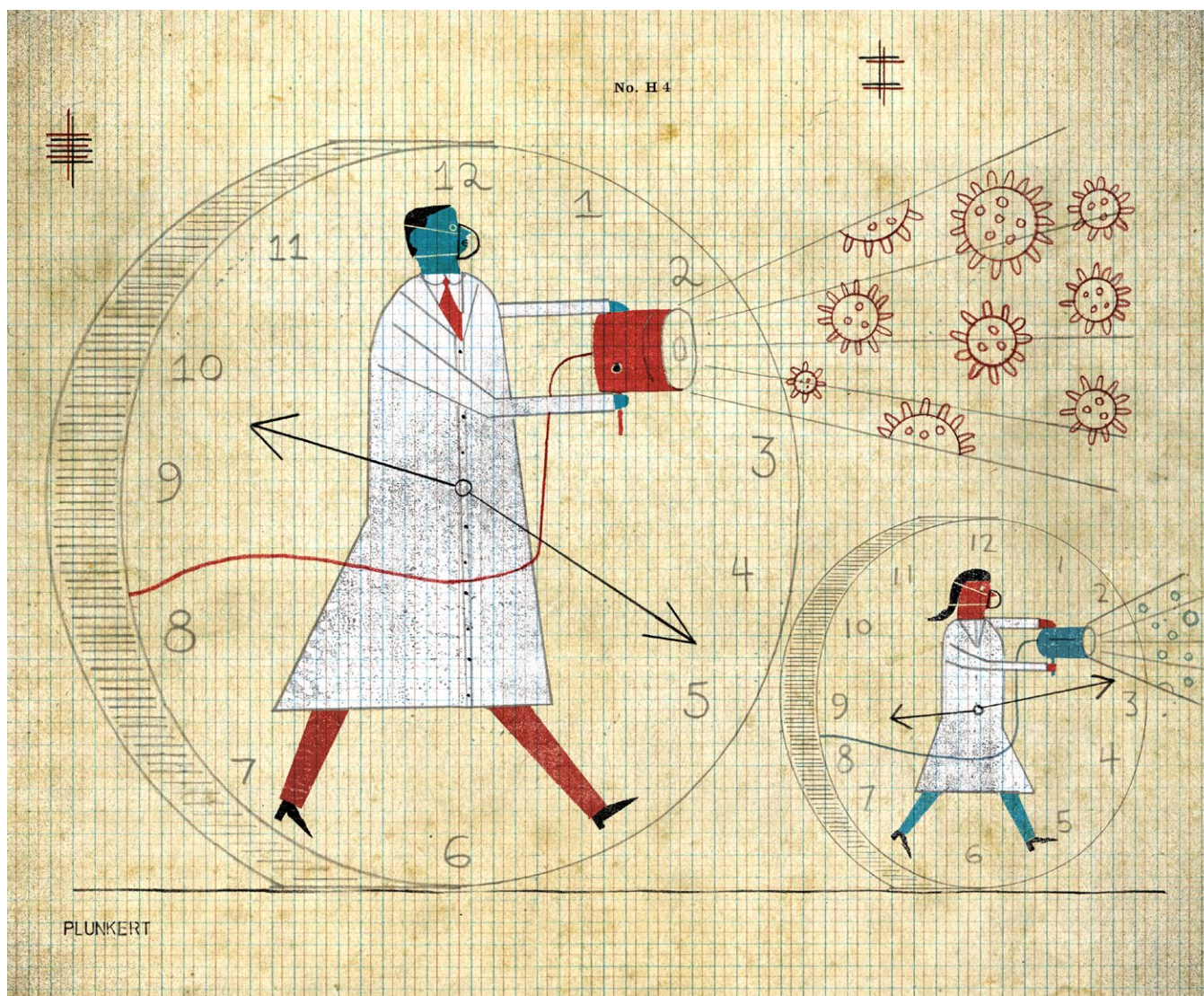
But the development of the test to detect active infection — known as an RT-PCR test — was just the beginning of many challenges. During the next weeks, researchers tackled problems of scarce resources, regulatory hurdles and an increasing demand for tests that could also identify people who had recovered.

The researchers' efforts would help uncover how the new virus spreads, who was at risk and how the body responds to infection. The researchers would also explore whether an infected person could become immune to the virus, and, if so, for how long.

*By Krista Conger*

ILLUSTRATION BY DAVID PLUNKERT





This combination of test development and scientific study in the early days of the pandemic meant that Stanford Medicine became an invaluable resource for public policymakers scrambling to protect California citizens from the virus.

“The rapid implementation of the tests developed at Stanford allowed us to better understand the evolution of the pandemic in the Bay Area and California,” Pinsky said. “It informed our governor and other decision-makers as they established our first shelter-in-place orders, and it limited the initial spread of the infection in the Bay Area.”

But, in early March, the primary concern was how to treat patients who were starting to show up at the hospital with symptoms that raised suspicions of COVID-19 but had no clear diagnosis. And access to testing was scarce across the country.

“The Food and Drug Administration had only authorized the test offered through the Centers for Disease Control, which was in very limited supply,” recalled Christina Kong,

MD, professor of pathology and medical director of pathology and clinical lab services at Stanford Health Care.

Pinsky and his colleagues had been tracking the novel virus in the weeks before it arrived in California. They began working on the PCR diagnostic test in mid-January after a laboratory at the Charité Hospital in Berlin published their PCR method and primer sequences. Pinsky’s laboratory optimized the test in late January and began using it to screen clinical samples from Stanford patients presenting with respiratory illness in February.

“We wanted to know whether the virus, which had been detected in Washington state in late January, was already circulating undetected in the Bay Area,” said James Zehnder, MD, professor of pathology and director of clinical pathology at Stanford Health Care. “In late February, we got our first positive samples. It was clear the virus was here.”

The Stanford researchers were prepared.

"One of the first things that occurred early in my clinical pathology training was the H1N1 flu pandemic in 2009," Pinsky said. "I knew the possibility of a pandemic was part of this sort of a career, and I've monitored several around the world since then. Of course, most of the outbreaks over the past 10 years haven't significantly impacted the United States, so this was different."

#### BECOMING A CORONAVIRUS-TESTING RESOURCE FOR THE BAY AREA

**K**ONG WAS OUT OF TOWN when Pinsky applied for the FDA authorization for their coronavirus test on March 2. When she returned on Friday, March 6, she discussed the test with Zehnder, who suggested that Stanford offer to test patients from other Bay Area facilities that also had possibly infected patients.

"All the hospitals were in the same bind," Kong said. "So we worked through the night to set up a website and a requisition form, and by midday Saturday I was able to contact UCSF and tell them they could start sending us samples."

Calls were soon flowing in from institutions across the country, so researchers had to prioritize. They decided to limit early testing to hospitalized patients in the greater Bay Area who, if positive, would need to be cared for by physicians in personal protective equipment, or PPE.

"We knew PPE was getting to be in short supply, so it would be important to only use it when necessary," Kong said. "We also decided to test only those samples that could be delivered to us by car to limit delays due to transport time."

By March 14, 10 days after the testing was launched, the number of tests completed per day grew to nearly 1,000. But obtaining the test's necessary components — from the DNA primers to the liquid used to transport biological samples to the Stanford lab — from commercial sources quickly became nearly impossible.

"There were massive supply chain failures at all steps, any one of which would have shut our testing down dead in the water," Zehnder recalled. "But this is when being at a place like Stanford is really great. We realized we could make the primers here at Stanford. So we contacted Ian Anderson at the PAN [Protein and Nucleic Acid] facility, and Ian stayed up all night and had them ready for Ben to pick up the next morning."

The researchers also partnered with a local 3D-printing company and Ryan van Wert, MD, a clinical assistant professor of medicine and the assistant director of the Stanford Biodesign Faculty Fellowship, to ensure a stable supply of the swabs needed to collect samples for testing.

"It was incredible to see people from all areas come together and make this happen," Zehnder said.

During the next few weeks and months, the laboratory continued to increase daily capacity from 1,000, to 2,000, to nearly 5,000 tests. They also rolled out in-car, drive-through testing, at first in the parking garage next to Stanford's emergency department and then at locations around the Bay Area. In collaboration with the occupational health department, they also began to test thousands of Stanford Health Care and Stanford Children's Health employees who routinely interact with patients.

Pinsky stopped going home to San Francisco at night and stayed at a hotel near campus to avoid any downtime during a commute that had become complicated. "People kept calling me and I'd have to pull off the road to answer their questions and look up the data they needed," he recalled wryly. "It wasn't the safest situation."

#### THE SCIENCE OF FIGURING OUT WHO'S ALREADY HAD COVID-19

**P**ATHOLOGIST AND IMMUNOLOGIST Scott Boyd, MD, PhD, had also been eyeing the developing situation in China early in the pandemic. Boyd specializes in studying how the human immune system responds to viral infection and allergies. He's particularly interested in the role of antibodies — the protective molecules generated by immune cells called B cells. And he was worried.

It was becoming clear that Stanford should develop another critically important test designed not to detect an active infection, but a past infection of the new coronavirus. Called a serology test, it looks for the presence of antibodies against the virus in the blood of seemingly healthy people.

Learning how many people may have already been infected is an important step in understanding the evolution of the pandemic in California and whether a past infection can protect against, or decrease the severity of, a subsequent infection. It may also help researchers and physicians understand why some infected people become very ill and die and others exhibit few if any symptoms, as well as how long an



'DESPITE THE PRESSURE, THE IDEA OF NOT DELIVERING THE TOOLS OUR PHYSICIANS AND RESEARCHERS NEEDED TO CARE FOR OUR PATIENTS AND EMPLOYEES NEVER CAME UP. THERE HAS BEEN A SENSE OF, "THIS IS WHAT WE WERE TRAINED TO DO, AND WE WILL MAKE IT HAPPEN."'

infected person might be contagious.

Boyd began talking to Taia Wang, MD, PhD, an infectious disease expert and assistant professor of microbiology and immunology, and Peter Kim, PhD, the Virginia and D.K. Ludwig Professor of Biochemistry. Wang and Boyd brainstormed about how to develop the serology test, which uses a technique called an enzyme-linked immunosorbent assay, or ELISA, while Abigail Powell, PhD, a postdoctoral scholar in Kim's laboratory, generated fragments of the virus's "spike" protein, which enables the virus to bind to human cells and enter them.

Boyd and his colleagues, including postdoctoral scholar Katharina Roeltgen, PhD, then used the protein to develop, test and implement a serology assay in Stanford's Anatomic Pathology and Clinical Laboratories that can detect the presence of two types of antibodies — IgG and IgM — that recognize and bind to the receptor binding domain on the spike protein.

"During the last two weeks of March, Katharina and I were working 16-hour days," Boyd said. "Each round of experiments takes four or five hours, and then we'd tweak some conditions and try again. It was a period of intense work. But we were up and running with the test in the clinic by April 7."

Initially, the test was primarily used for Stanford patients but it was soon also used for Stanford Health Care and Stanford Children's Health employees.

Although other commercially available serology tests have struggled to provide the sensitivity and specificity necessary to deliver reliable results, the Stanford test succeeded, delivering about one false positive in every 500 tests, and detecting antibodies in 97% of patients with confirmed infection three weeks after the onset of symptoms.

"Despite the pressure, the idea of not delivering the tools our physicians and researchers needed to care for our patients and employees never came up," Zehnder said. "There has been a sense of, 'This is what we were trained to do, and

we will make it happen.' It is a good feeling to be part of an organization that responds so well to this type of challenge."

#### PUZZLING OUT THE SPECIFICS OF IMMUNITY

NOW BOYD AND HIS COLLEAGUES are trying to learn what it all means. Does the presence of antibodies protect against subsequent infection? Recent research in non-human primates implies it does. But if so, how long do the antibodies and the protection last? How can we use what we've learned to develop the best, longest-lasting vaccines? And how do we respond to other pandemics likely to arise in the next years or decades?

"In many ways, the very earliest days of the pandemic were an exercise in denial," Boyd said. "I had been following the start of the outbreak in China since December; I had all the facts available to me. But even then I had no idea that this would become such a major research topic in my laboratory for what will probably be the next two years or more."

Recently, Boyd, Pinsky and their colleagues found that, intriguingly, the very sickest COVID-19 patients also make the highest levels of antibodies against the spike protein, while patients who are mildly ill make only modest amounts. In patients with mild illness, the antibodies don't seem to last long — dwindling over a period of just a few weeks. The news is preliminary, but suggestive. A similar pattern of antibody expression is seen with other, non-lethal coronaviruses. And the outcome may not be as dire as the news first seems.

"Of course, not having antibodies in the blood doesn't necessarily mean that previously infected people are no longer immune," Roeltgen said. "We can't say that, because we don't know. We might have memory responses in immune cells like T cells that could be protective against a subsequent infection by the virus."

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apart yet together

BREAKING COVID-19's DEADLY EMBRACE

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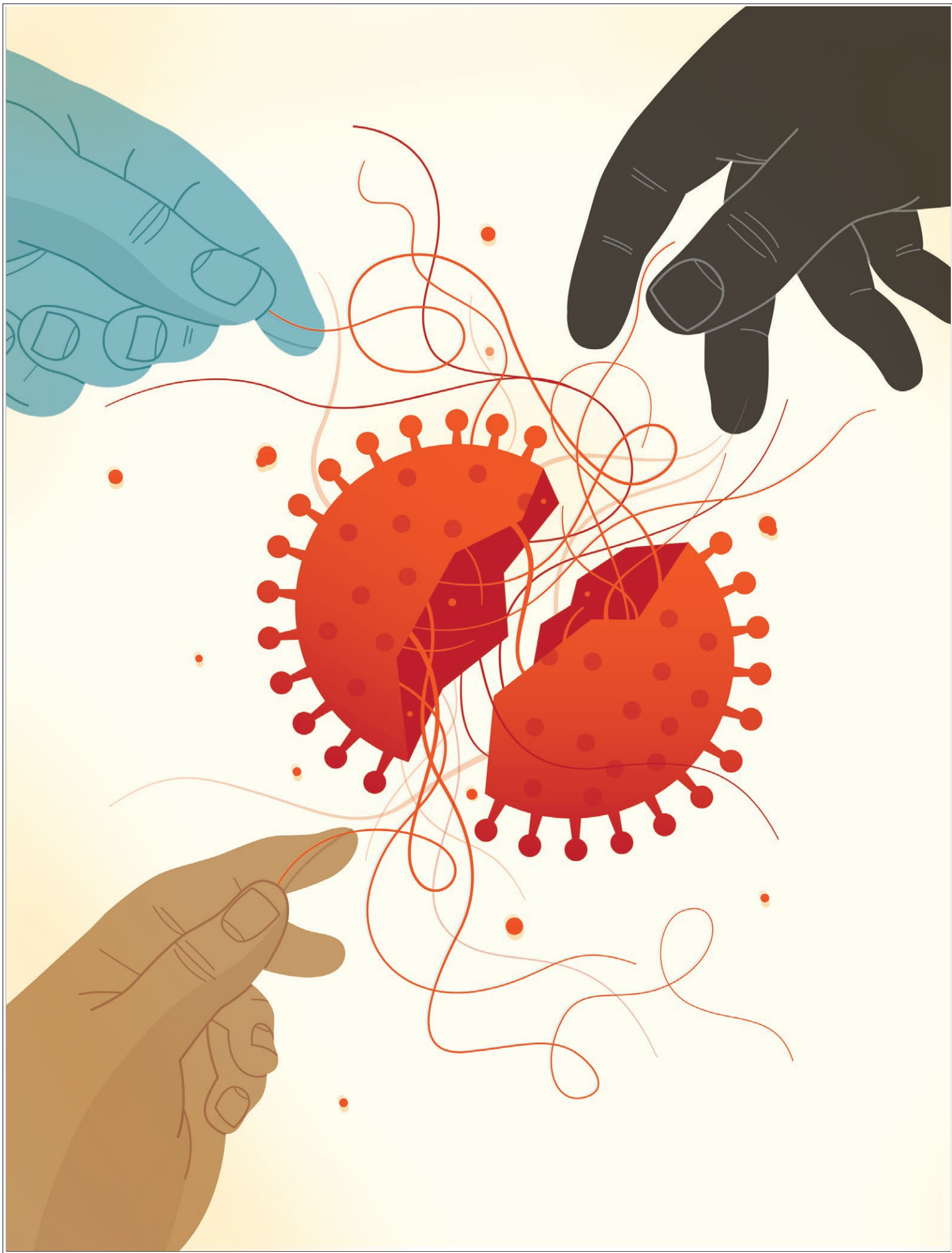
OUT

A SAMPLER OF  
COVID-19 RESEARCH

*By Hanae Armitage*

ILLUSTRATIONS BY HARRY CAMPBELL

With cases of COVID-19 exploding at the beginning of 2020, scientists at Stanford Medicine and around the globe veered onto new research paths. Their purpose: to understand and stop the spread of SARS-CoV-2, the coronavirus that causes COVID-19. Hundreds of COVID-19-related projects have emerged across Stanford's campus. Between scientists harnessing their expertise — such as those in Stanford's clinical virology laboratory who devised an early in-house diagnostic test for COVID-19 — and scientists developing new skills to help combat the virus, the research community is pulling out all the stops. Lawrence “Rusty” Hofmann, MD, for instance, is a radiologist by trade, but was dismayed by an epidemiological problem: Nationally, COVID-19 testing rates were too low to indicate the ebb and flow of the virus at the local level. So he created a method of predicting hot spots of COVID-19 through a project called the National Daily Health Survey, which tracks responses from people throughout the country about their health and whether they have symptoms of the virus.





“In the time that I’ve been at Stanford, I don’t think I’ve ever seen such a large group of people come together with a singular purpose,” said Euan Ashley, MD, DPhil, associate dean of precision health. “It’s been an incredible effort to be part of.”

Alongside Stanford, philanthropies, including the Gates Foundation; the National Institutes of Health; and companies Illumina and Takeda are supporting some of these research projects — just an example of the multibillion-dollar pool of funds that have been allocated to COVID-19 research and relief across the country.

It’s not just labs that are switching course, either. A university effort called the Innovative Medicines Accelerator, intended to help researchers overcome obstacles in developing new therapeutic drugs, has shifted goals and is now boosting nascent COVID-19 projects.

Beyond bench research and epidemiology, Stanford physicians were among the first to participate in clinical trials for COVID-19 treatments, helping to establish the efficacy of remdesivir, a go-to therapeutic for treating the virus. Physicians and clinical scientists are also investigating whether other drugs, such as lambda interferon and favipiravir, expedite patient recovery and slow the disease’s spread.

Here’s a small sample of Stanford researchers’ many efforts targeting COVID-19.

#### CRISPR-BASED NASAL SPRAY OR INHALATIONAL THERAPY TO FIGHT COVID-19

Researchers are using the CRISPR gene-editing system to inhibit the replication of the virus that causes COVID-19.

**WHY IT MATTERS:** A single dose of a nasal spray could provide weeks of protection from acquiring COVID-19; in patients who already have COVID-19 pneumonia, an inhaled version could help treat the infection.

**TIMELINE:** *It’s in early development — a trial in humans is likely two or more years away.*

Four bioengineers are laying the groundwork for a rather futuristic approach for preventing COVID-19 infection:



a nasal spray that harnesses a form of CRISPR that can be programmed to target any virus. The technique aims to arm the body with the ability to stunt infection caused by a range of coronaviruses, including SARS-CoV-2, serving much the same purpose as a vaccine or as a treatment for pneumonia.

A typical vaccine works by priming the host’s immune system with molecules that recognize and attack a specific viral intruder. The CRISPR-based tactic turns that approach on its head, directly targeting the virus instead of revving up host immunity. The team is using a special CRISPR system that deploys a molecule called Cas13D that “digests” or cuts other RNA molecules. It’s also equipped with something called a guide, which helps it target the exact molecules to snip. The idea is to use Cas13D as a first line of defense for the body. In essence, Cas13D would act like a vicious bouncer, stopping the virus from replicating in the host cells it enters by chopping it into tiny pieces.

For now, because tampering with SARS-CoV-2 in the lab requires special clearance, the team is establishing the validity of their approach using coronaviruses that cause common colds.

“The great thing is, coronaviruses across the board tend to interact with the host’s cells and immune system in a fairly predictable manner,” said David Lewis, MD, a professor of pediatrics, immunology and allergy who’s leading the project with

Stanley Qi, PhD, assistant professor of bioengineering and of chemical and systems biology, and Marie LaRussa, PhD, a senior research scientist in the Qi laboratory. “So if we can get this to effectively block the replication of coronaviruses that cause the common cold, for example, it will be a big step in developing this as a prophylactic or treatment for SARS-CoV-2.”

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## A NEW ROLE FOR LAMBDA INTERFERON

Researchers are focusing drug development efforts on patients who are not severely ill in the hopes that these therapeutics will stave off more serious disease.

**WHY IT MATTERS:** Lambda interferon might help patients with mild-to-moderate disease recover more quickly and keep them out of the hospital.

**TIMELINE:** *A clinical trial is underway.*

It’s sensible that the majority of early drug-development efforts against COVID-19, such as studies of remdesivir, were geared toward severe infection. But Upinder Singh, MD, professor of medicine and of microbiology and immunology, and Prasanna Jagannathan, MD, assistant professor of medicine and of microbiology and immunology, are targeting the opposite end of the disease spectrum. Through a clinical trial at Stanford’s COVID-19 clinical trials research unit, Singh and Jagannathan are studying the efficacy of a long-used hepatitis drug known as lambda interferon in patients with COVID-19 who have mild to moderate symptoms.

Many efforts have focused on hospitalized patients. “We of course need to help the critically ill patients, but if you think about COVID-19 infection, 80% are outpatients, and those patients are still suffering — and they’re continuing to shed the virus,” said Singh. “So we wanted to focus on the 80% of people who get mild-to-moderate disease, with the goal of finding drugs that would help people feel better, help avoid hospitalization and limit spread.”

Lambda interferon, a molecule naturally produced by the body, has been safely used to treat thousands of patients with hepatitis infections. It’s a compound that’s naturally released when a virus enters the body, orchestrating other molecules and cells involved in immune function. Essentially, it helps the body gird itself against the intruder. “It’s sort of like, if the virus is a burglar about to enter a home, lambda interferon is the one locking the doors, turning the

lights on and getting the dog,” said Singh.

In Singh’s trial, researchers are testing what happens when the body is given an extra boost, with the goal of catching the infection early and containing it, thereby heading off what could turn into more severe illness and enabling the patient to recuperate at home.

The researchers aim to enroll 120 patients with early, mild-to-moderate COVID-19 infection in the study, which began in April. A randomly selected half of the patients will receive a single injection of lambda interferon, while the other half will receive a placebo — and neither patient nor doctor will know who’s received what.

“We’re going to have to live with this virus for some time and there really isn’t one golden solution,” said Singh. “In addition to vaccine development, social distancing, sheltering in place, masks and hand hygiene, I’m hopeful that this therapy can work in an outpatient setting and help us get back a semblance of normal life.”

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## SWABBING THE BAY AREA

Scientists have investigated new ways to test for COVID-19 in the hopes that less invasive do-it-yourself nasal swabs will expand testing.

**WHY IT’S IMPORTANT:** Expanded testing is critical and still needed.

**TIMELINE:** *Scientists launched a pilot project in September that allows individuals to swab themselves for SARS-CoV-2 and send their samples in for testing.*

Often, the test for a current COVID-19 infection is administered via a swab going deep into the nose, all the way to the back of the throat. Some describe the sensation as akin to “probing your brain.”

Yvonne Maldonado, MD, is more nonchalant. “I’ve had it done,” said Maldonado, professor of pediatric infectious diseases and of health research and policy. “It’s not pleasant but it’s not horrible either.”

This procedure, called a nasopharyngeal swab, and an alternative, an oropharyngeal swab, that reaches a similar area via the mouth, are generally performed by a health care worker. The cells they collect are then processed and tested for the presence of SARS-CoV-2.

Aside from the discomfort, said Maldonado, these methods of testing for SARS-CoV-2 have a few other problems: Deep probing can elicit big coughs or sneezes, potentially expelling droplets of the virus and exposing health care work-

ers to infection; and the need for staff to conduct the test limits how many tests can be done. It's also not clear that a deep sampling method is the most reliable way to detect this virus.

So Maldonado and her colleagues posed a new question: Could people take their own samples using a more shallow, less irritating swab of the nostril and get accurate results?

Such an approach, if as effective as deep swabs collected by health professionals, could open up new research avenues and lead to more abundant testing, something the United States still sorely needs, said Maldonado.

The team conducted a study, published June 12 in the *Journal of the American Medical Association*, comparing the accuracy of self-collected nostril swabs and health care worker-collected oropharyngeal swabs. For 29 of the 30 participants in the study, the accuracy of the shallow swab method was as trustworthy as that of the more invasive test. In theory, folks at home could effectively swab themselves while sparing the tender parts of their sinuses.

The win for self-swabbing has boosted an offshoot project of Maldonado's dubbed CATCH, for community alliance to test coronavirus at home. The goal is to facilitate widespread testing in the San Francisco Bay Area through kits that can be ordered online and sent to individuals by mail.

"The initial goal is to have thousands of people in the Bay Area order and perform these tests, then send them to labs," said Maldonado. "We're starting with this pilot project, but the eventual goal is to have this running across the country."

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#### 'MINI LUNG' ORGANOID MODELS BOOST SCIENTISTS' UNDERSTANDING OF COVID-19

Using miniature, living models of the human lung, researchers are parsing the details of COVID-19 infection.

**WHY IT MATTERS:** Researchers get a more accurate look into how the virus infects the lungs.

**TIMELINE:** The technique is in an early phase of development but researchers are already using it to investigate SARS-CoV-2. There's no better way to research the effects of a virus than



to go directly to its breeding ground; for COVID-19 that means the lungs. And since opening the chest of those infected just to study the virus is not an option, scientists need a way to investigate the novel coronavirus as it exists "in the wild," or at least close to it.

Enter the organoid — a lab-made, miniature replica of a human organ that closely recapitulates the organ's biological function, including what happens when a virus compromises its health. Calvin Kuo, MD, PhD, professor of medicine, is an organoid guru. As good fortune would have it, when the COVID-19 pandemic erupted he and his team had just grown a successful lung organoid, something that's proved finicky and challenging to scientists in the past.

"SARS-CoV-2 became the most pressing virus on the planet and we quickly realized that we had an opportunity, really an obligation, to create a model of COVID-19 lung infection in the lab to be able to better understand the virus," said Kuo, the Maureen Lyles D'Ambrogio Professor of Medicine.

In collaboration with Catherine Blish, MD, PhD, associate professor of medicine, and Manuel Amieva, MD, professor of pediatrics and of microbiology and immunology, the trio of scientists have done just that.



MILLA'S NEW TEST WOULD ALLOW PEOPLE  
TO BREATHE NORMALLY, DECREASING THE RISK OF SPREADING THE VIRUS  
AND INCREASING UTILITY AMONG ALL PATIENTS, EVEN THOSE WITH

# RESPIRATORY

SYMPTOMS, SUCH AS SHORTNESS OF BREATH.

By infecting the lung organoids, which Kuo fondly deems “mini lungs,” with SARS-CoV-2, the team is studying how the virus infiltrates and damages healthy lung tissue and is testing the efficacy of new drugs or preventive treatments.

The researchers have now successfully infected the cells lining the deepest tubes within the lungs, and the air sacs at the end of these tubes, with live SARS-CoV-2 virus. The team was able to see this phenomenon using a laboratory technique developed by Amieva's group that literally flips the organoid model inside out, thereby exposing the tissue that's most susceptible to infection. “Think of it like exposing the insides of a pair of tube socks,” said Kuo.

The researchers are still exploring the genetic pathways that are activated during infection, specifically as they relate to the immune system. In particular, they're interested in a phenomenon called a “cytokine storm,” which occurs in some COVID-19 cases and can lead to death. During this flurry of activity, a variety of immune molecules are unleashed, which may sound like extra protection, but instead overwhelms the body in an onslaught of molecular destruction.

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## SAFER, MORE ACCESSIBLE BREATHING-BASED DIAGNOSTICS

Scientists are trying to see if a simple lung function test can identify those with COVID-19, determine severity of disease and protect health care workers from exhaled particles.

**WHY IT'S NECESSARY:** A standard lung function test can be difficult for people with breathing problems to carry out and can lead people with COVID-19 to expel viral particles into the air, raising the risk of infection for others.

**TIMELINE:** *The research is still early in its development — in a proof-of-principle phase.*

As a pulmonary pediatrician, Carlos Milla, MD, spends a lot of time thinking about how to make breathing tests easier and faster for squirming kids with little lungs. Before

the pandemic, Milla, professor of pediatrics, was working on a new lung function test for small children and babies who have trouble huffing and puffing for standard pulmonary tests. But safety concerns shut down his research as coronavirus cases exploded around the world.

“It occurred to me that our test could serve another purpose — potentially helping both patients and health care workers,” said Milla.

Normal pulmonary tests that evaluate lung function involve a deep and forceful inhalation and exhalation. That's problematic for COVID-19 patients for two reasons. Forceful exhalation of viral particles into the air puts health care workers and staff at higher risk of infection, even when they're using personal protective equipment. Also, sick patients with lung problems aren't always strong enough to inhale and exhale the air necessary for an effective evaluation.

Milla's new test would allow people to breathe normally, decreasing the risk of spreading the virus and increasing utility among all patients, even those with respiratory symptoms, such as shortness of breath.

The test works by measuring the force, duration and other characteristics of an individual's normal breathing. COVID-19 infection changes these parameters in very specific ways, said Milla, allowing clinicians to detect certain breathing-associated details that indicate infection, such as lung tissue stiffness.

In a small pilot group of COVID-19 patients, Milla has shown that the passive breathing test can detect lung abnormalities, and it works for virtually any patient — even people with pulmonary symptoms so severe they require extra oxygen. What's more, almost no extraneous viral particles are exhaled into the open air in the process.

It will take many more patients with varying levels of COVID-19 severity to validate the test and its utility, said Milla. And although a larger study is not yet planned, he hopes the test could be used to predict severity of disease in patients, and as a screening tool to initially detect

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apart yet together

BREAKING COVID-19's DEADLY EMBRACE

# SOUNDING THE MENTAL HEALTH ALARM

THE PSYCHOLOGICAL DISTRESS OF LIVING  
THROUGH A PANDEMIC,  
AND HOW TO BUILD RESILIENCE

*By Erin Digitale*

ILLUSTRATION BY GÉRARD DUBOIS

For many Americans, aspects of ordinary life — working in an office, going to school, eating inside a restaurant, hugging a friend — still feel impossibly unsafe. Amid continued uncertainty about when the COVID-19 pandemic will be brought under control, Stanford mental health experts are planning for the psychological fallout of having an entire population under prolonged stress.

“We’ve all been talking about virus surges. What we’ve been preparing for in psychiatry is a surge in mental health problems,” said child and adolescent psychiatrist Victor Carrion, MD, director of Stanford’s early life stress and resilience program.

Such a surge was well underway as early as March and continues today. In late March, the Kaiser Family Foundation conducted a poll asking American adults whether pandemic-related worries were harming their mental health; 45% said they were. By the end of July, that figure had risen to 53%.

Other indicators, such as more phone calls to hotlines designed for reporting child and domestic abuse, worry experts, too.

The emotional consequences of the pandemic will vary, said Carrion, the John A. Turner, MD, Endowed Professor for Child and Adolescent Psychiatry. Some people are discovering strengths, including the capacity to adapt to the strange circumstances and support their loved ones. But others are finding their coping skills overwhelmed. This group could







experience increases in post-traumatic stress disorder, anxiety and depression, as well as greater rates of substance abuse and domestic violence. Although the pandemic affects everyone, certain groups are more vulnerable, including the young, older adults, people with pre-existing mental health conditions, individuals adversely affected by racism or gender discrimination, frontline health care workers, and people experiencing economic losses. Stanford psychologists and psychiatrists are using a variety of tactics to help.

#### HOW DO DISASTERS AFFECT US?

**P**REVIOUS RESEARCH on the mental health status of those who survive wars, natural disasters and other catastrophes shows that, although they might feel distressed, the majority of people recover without long-term psychological problems. The Stanford experts are seeing this in their day-to-day interactions during the pandemic.

"I've been pleasantly surprised by how resourceful people have been," said Shaili Jain, MD, clinical associate professor of psychiatry and behavioral sciences. "I've had conversations with people who I was concerned about, but they are doing well."

Still, she knows that losses during the pandemic will tip some people from successfully coping into being unable to adapt, with mental health consequences that include PTSD, which is characterized by flashbacks, avoidance of circumstances that resemble the original trauma and emotional numbing.

"I think people have experienced micro-traumas: loss of a way of life, perhaps a job, maybe their perception of how safe and predictable the world is," she said. "And it happened suddenly. The sudden bit is what I, as a PTSD specialist, associate with a traumatic response."

Depending on their proximity to a disaster — whether they're a victim, rescue worker or member of the general population — 5% to 40% of people will experience PTSD. The number rises to nearly 100% in certain situations, such as among children who witness random acts of extreme violence. Incidences of major depression and substance abuse also increase after a disaster, especially in people who have a history of these conditions.

"PTSD correlates closely with economic adversity and unemployment," Jain said. "We know trauma trickles down in financial hardship. Intimate partner violence and family violence go up. We'll see the downstream consequences in the weeks, months and years ahead."

Historically, for every 1% increase in unemployment among adults, there is a 25% increase in child neglect and

a 12% increase in physical abuse of children, Carrion said. Unemployment reached its highest level since the Great Depression, jumping from 3.5% in February to 14.7% in April before declining to 8.4% in September. After an initial decline in calls to trauma hotlines during the earliest days of shelter-in-place orders, child abuse reports rose 22% by the end of March with 70% of reporters identifying abuse perpetrators as family members. Reports of child-abuse injuries in emergency departments also rose.

For people in more stable and safe situations, pandemic-related isolation is still likely to tax their emotional health. This is especially true for people at vulnerable life stages, such as young children, who need interaction to build social skills; teens, who thrive on feeling valued by their peers; new parents, who need in-person help from friends and family during the exhausting newborn days; family members caring for vulnerable adults; and older adults, who are more likely than other age groups to live alone and are more medically susceptible to the novel coronavirus.

"Isolation is very much related to depression, which has significant impacts on health and can lead to suicide," Carrion said.

With kids, he added, stress doesn't need to rise to the level of trauma to harm well-being. "We worry about developmental milestones that may be delayed because play and other social interactions are limited."

Even people with social phobias, who might initially have felt relieved to stay home, can be hurt by isolation, Carrion added: "If people have intense, persistent fear of being embarrassed by others, isolation maintains that anxiety and strengthens the association between anxiety and socializing."

#### HOW TO GET THROUGH

**W**ITH A RESOLUTION to the COVID-19 pandemic still distant, Carrion, Jain and their colleagues are helping others cope.

"Humans can cope with incredibly stressful situations when they feel they're empowered to deal with it," Jain said, noting that good social support is a key protective factor during and in the aftermath of stressful events.

Jain worries about frontline health workers because they're especially likely to show delayed psychological responses; there have even been high-profile instances of health care workers dying by suicide during the pandemic. Not only are they under extraordinary strain from the uncertainties of treating an infectious disease but health care



professionals are also accustomed to temporarily sidelining their emotions to focus on patients' distress, she said.

"It's normal, in the moment, to leave the processing to later, but I think the processing has to happen," Jain said. "When they're ready to do it, it's really good if people are met with a spirit of openness and compassion from whom-ever they want to share with."

One early effort to provide such support was led by Debra Kaysen, PhD, professor of psychiatry and behavioral sciences, and Ryan Matlow, PhD, clinical assistant professor of psychiatry and behavioral sciences. Using principles of psychological first aid, a concept developed by the National Child Traumatic Stress Network in response to disasters, Kaysen and Matlow trained a few dozen colleagues to lead one-hour "connect and recharge" groups online. The groups were offered from March to June for all staff at Stanford Health Care and Stanford Children's Health.

hopes that the shared experience will boost empathy for people in difficult circumstances.

Social support is especially important for kids and teens, Carrion said. "Children are not resilient just by nature of being children," he said, noting the common misconception that children automatically bounce back from bad experiences. Although a consistent predictor of children's resilience is having at least one adult in their lives whom they can count on, other factors also foster resilience, such as perseverance, the ability to think about multiple things at once and consciously regulating emotional responses. Adults can encourage and facilitate these skills by modeling them and by engaging with the children in their lives.

Right now, parents can set their children up for a healthy reaction to the pandemic by giving age-appropriate answers to their questions about the COVID-19 crisis, listening to and helping assuage their fears, helping them maintain virtual

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TO LEAVE THE  
PROCESSING TO LATER,  
BUT I THINK THE PROCESSING HAS TO HAPPEN.'**

"We started each session by offering some psychoeducation — 'Here are the expected responses to a global crisis' — to normalize what was happening, and really just give people a space to talk about what was going on," Matlow said. Participants then discussed their specific concerns and planned strategies they could use to manage stress and meet their own emotional needs. Session facilitators encouraged them to find time for their favorite healthy modes of coping, such as exercise, meditating, improving sleep or making time for a phone call with a supportive friend. The sessions also included opportunities to problem-solve about common challenges, such as how to manage conflict at work or at home when everyone around you is stressed out. Session leaders connected participants to other mental health services if necessary.

Evidence suggests that we can all benefit from emotional support, and that we should keep up with phone calls, video chats and other connections to the people we care about. There may even be hidden social benefits to the pandemic because, unlike previous disasters, it affects everyone. Jain

connections to friends, and giving them a sense of agency — even if it's simply letting them pick a new ice cream flavor for dessert.

"I have been surprised to see how well many children coped with the early phase," Carrion said. "During the first phase of our shelter in place, they may have enjoyed being home and having their parents around a bit more. But as our crisis continues and this is now becoming a chronic stressor, we need to be vigilant of children's reactions."

For teens, maintaining some normal social markers of healthy adolescent development is important, too. Carrion recommends giving them space to interact with their peers without parents around, such as leaving them alone to video chat with friends. It is also important to recognize their opinions and thoughts about current events by including them in conversation and encouraging them to record or write about their experience.

To help support people across California, Carrion is rolling out a statewide program to teach psychological first aid

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## HOW WE CAN BEAT COVID-19 AND FACE DOWN FUTURE OUTBREAKS

Anthony Fauci, MD, has been called America's doctor for good reason. Director of the National Institute of Allergy and Infectious Diseases for 36 years, he has advised six presidents and has led the U.S. response to many health crises, most notably (until recently), HIV/AIDS. Today, he's a trusted source of information for the public about the COVID-19 pandemic, which he calls an infectious disease fighter's worst nightmare.

Fauci's involvement in medicine goes way back: He delivered prescriptions for the Brooklyn, New York, pharmacy his parents owned and was on the pre-med track in college. He graduated first in his class from Cornell University Medical College, now known as Weill Cornell Medicine.

His knack for leadership goes way back, too: He captained his high school's basketball team, despite his less-than-advantageous height of 5 feet, 7 inches.

Lloyd Minor, MD, dean of the Stanford University School of Medicine, spoke with Fauci in July, when the United States was seeing the largest surge in COVID-19 cases to date. When Minor asked Fauci how he saw the pandemic unfolding, Fauci channeled his inner team captain, giving motivating, clear advice on how to win.

"There are things you can do now," he said. "Physically distancing, wearing a mask, avoiding crowds, washing hands. Those things, as simple as they are, can turn it around. And I think we can do that. And that's what we've got to do."

During the discussion, which was streamed live online, Minor talked with Fauci about the state of the COVID-19 pandemic, keys to controlling it and how to prepare for future outbreaks. Their conversation has been edited and condensed for this Q&A.

**MINOR:** How are you dealing with the stress of the pandemic?

**FAUCI:** The worst nightmare of an infectious disease person who's interested in global health and outbreaks is the combination of a new microbe that has a spectacular capability of transmitting and has a considerable degree of morbidity and mortality. And here it is, it's hap-

pened — the worst nightmare, the perfect storm.

It's one of those things where you're really just functioning on adrenaline. Of all the emerging infections that I've had to deal with — starting from HIV in the early '80s, then Ebola and Zika, and anthrax attacks — this is clearly the most challenging because it's so pervasive.

**MINOR:** What do we need to do to better prepare for future pandemics?

**FAUCI:** Let me answer that from the vantage point that I'm most familiar with — as a physician-scientist: What can we do from a scientific standpoint? One thing is to develop new, sophisticated platform technologies — where you can hit the ground running with vaccine development and not have to worry about growing out the pathogen or activating it or attenuating it.

Another thing is to study prototype pathogens to get really good at understanding a particular family of potentially threatening microorganisms. For example, this is the third major coronavirus outbreak we've had in the past 18 years. We had SARS in 2002. We had MERS in 2012. And now in 2019 and 2020, we have COVID. We've got to be able to do universal therapies and universal platform technologies.

Also, we have let the local public health infrastructure in our country really go into tatters. We were so good at controlling smallpox, polio and tuberculosis, we let the infrastructure go unattended. Now, when we need good local public health capability, it's not optimal. We've got to build it up again.

**MINOR:** When you look at the data in communities hardest hit by the coronavirus, it really



LEFT: TIMOTHY ARCHIBALD; RIGHT: KEVIN DIETSCH/POOL VIA REUTERS

highlights health care inequality and issues of access to care in our country. How can we better address this situation?

**FAUCI:** Concentrate resources. In those demographic areas that are suffering most, it's like a broken record. Minority populations are disproportionately negatively impacted by diseases like this. With HIV, 13% of our population is African American, and 45% or more of the new cases are among African Americans. Look at the incidence of COVID-19 infection on the basis of how, in general — I don't like to generalize, but here you have to generalize — how the African American population and the Latinx population find themselves with jobs that don't allow them to properly protect themselves. As everybody's locking down, they're doing the essential jobs that require their physical presence. So they're immediately at more risk of getting infected.

When you look at the prevalence and incidence of comorbidities that make you at higher risk for a poorer outcome, they have most of them: hypertension, diabetes, obesity, chronic lung disease, kidney disease.

**MINOR:** What are we learning from this pandemic about conducting clinical trials during an outbreak?

**FAUCI:** Not too long ago, there was the incorrect assumption that you can't do research in the middle of an epidemic outbreak because it's very important to get whatever treatment you have, whether it's proven or not, to the people. The idea is, they need it and it's better than nothing. That's an understandable approach. But it really is flawed.

The best research you can do is in the middle of an outbreak because you want to help the people who are experiencing the outbreak. You also want to learn from it so you can help that many more people. Until recently, it was felt that, ethically even, you shouldn't do research in an outbreak. We proved that wrong in the Ebola outbreak. We did randomized, placebo-controlled trials, we proved that a couple of therapies worked, and a vaccine was developed. With COVID-19, two drugs have already proved to be beneficial in advanced disease. So clinical research and clinical research infrastructure is a very important part of the response to outbreaks.

**MINOR:** Can you share your thoughts on when a vaccine or vaccines might be available, and about allocation methodology for vaccines

as they move through the various stages of trials and hopefully get to FDA approval?

**FAUCI:** One of the encouraging aspects of having multi-candidate vaccines is that the companies involved, with substantial financial help from the federal government, committed to start producing large numbers of doses even before they're proven safe and effective. If you make a lot of doses and it's not safe and effective, you've lost a few hundred million dollars. If you make a lot of doses ahead of time, and it proves effective, you've gained multiple months in the process.

I'd like to make a reasonable assumption that sometime at the beginning of 2021 we will have a couple of vaccines that are safe and



effective. Obviously, you want to vaccinate everybody, but as doses come online, you're going to have to prioritize. That's where you put together committees of people who understand vaccinology, community representatives and, above all, ethicists who can make sure your decisions about distribution are based on ethical principles of justice and fairness, etc.

**MINOR:** In America today, there's a lot of skepticism about vaccines. What can we, as physician-scientists and leaders, do to gain public trust in vaccines so we can control this pandemic?

**FAUCI:** We've got to engage the community by getting out there, with boots on the ground, to convince people why it's important to

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## 'I'VE TRAINED MY WHOLE LIFE FOR THIS'

In the eye of the pandemic, viral disease expert Bonnie Maldonado still has hope

By Erin Digitale

PHOTOGRAPH BY TIMOTHY ARCHIBALD

**I**N THE 2011 movie *Contagion*, a viral outbreak begins with glitz. After a business trip, Gwyneth Paltrow's character, Beth, is gambling in a Macau casino. It's brightly lit; spirits are high; Beth looks luminous. She shakes hands with a chef who — spoilers ahead — transmits a lethal new virus to her. (The chef's hands carry a virus picked up from an infected pig he prepared for a pork dish; the pig had gotten the virus from a wild bat.)

Following Beth's dramatic death from the new virus, a World Health Organization epidemiologist uses casino security-camera footage to identify Beth as the index case in a pandemic that kills millions. The epidemiologist is one of several scientists whose actions drive the plot.

"I love it because it's not real," said Stanford infectious disease epidemiologist (and sci-fi fan) Yvonne Maldonado, MD, who recently watched the movie during a rare break in the 14-18 hour days she's been working on COVID-19.

"People say, 'How could you watch *Contagion*?' " Maldonado said, laughing. "But why wouldn't I?"

In spite of its unrealistic Hollywood touches — for instance, a vaccine that's ready in just four months — *Contagion* reflects one piece of reality: A global pandemic can put scientists in the spotlight.

That's where Maldonado is now. Across Stanford, California and the nation, people are relying on her acumen as an infectious-disease detective, epidemiologist, collaborator and leader.

"She's said many times, 'I've trained my whole life for this,'" said Clea Sarnquist, DrPH, clinical associate professor of pediatrics and a longtime research collaborator. Maldonado, who goes by Bonnie, is adept at meshing new data with knowledge built during decades fighting other vi-

ruses, including HIV, polio and measles, her colleagues said.

"Bonnie has stepped up to fill an undefined leadership role that only a crisis like this could demand," said Lloyd Minor, MD, dean of the School of Medicine. Maldonado has been a key player in shaping the response of Stanford's medical facilities and guiding its COVID-19 research efforts, and she has worked closely with infection control leaders at county, state and national levels to connect Stanford with the larger pandemic response. She also has been the university's primary scientific spokesperson, responding to hundreds of COVID-related media queries.

"Stanford Medicine's response to COVID-19 has been very much a team effort, with hundreds of individuals playing essential roles," Minor said. "But Bonnie has become an axis around which all of this spins."

### A PASSION FOR VIRUSES

**A**S SOUTHERN CALIFORNIA NATIVE and daughter of Mexican immigrants, Maldonado spent childhood summers with her paternal grandparents in the city of Chihuahua in northern Mexico.

Seeing the vast socioeconomic disparities between her own family living in Chihuahua and others there who were not so fortunate, she felt a duty to help, which planted the seed for a career in global health. Her parents, a butcher and a legal secretary, were frequent volunteers at community events such as food and clothing drives. They encouraged Maldonado and her sister — now a chemical engineer — to pursue both science and community engagement as the first members of their family to attend college.

After medical school at Stanford and further training in pediatrics and infectious disease at Johns Hopkins, Maldo-

nado spent two years in Berkeley, California, with the Centers for Disease Control and Prevention's Epidemic Intelligence Service program. Her first task upon arriving in 1986 was to find the source for what turned out to be the biggest U.S. malaria outbreak in more than 30 years. (She linked malarial mosquitoes in the ponds on a San Diego golf course with changes in Mexico's malaria control program and poor health care for undocumented immigrants who were crossing the U.S.-Mexico border.)

But AIDS is the disease that most shaped Maldonado's career. At the beginning of the AIDS crisis, she was the only epidemiologist in the Bay Area to study the disease in children, who can become infected during birth. "I was familiar with a horrible, virtually untreatable pandemic where we watched children die," she said.

Starting in 1987, while still at the CDC, Maldonado ran Northern California's HIV surveillance program, which she started a few weeks after her older daughter was born. She helped develop the criteria defining pediatric HIV, as well as treatments and strategies to prevent mother-to-child transmission, work that continued when she was hired at Stanford in 1988.

"The kids [with HIV/AIDS] were just horribly ill," she said. "By then, in the early 1990s, I had my oldest daughter and son as well. It was hard to see these little kids who were the same age as my children getting sick and dying."

Health care providers' fears were another challenge. HIV is not transmitted through casual contact, but many medical professionals were initially reluctant to treat HIV-positive children.

"I spent a lot of time teaching the nurses, doctors and other staff not to be afraid of the kids, to be willing to provide them with clinical care and not treat them like pariahs," Maldonado said.

Maldonado has also extensively studied such viral diseases as polio, measles and Ebola in developing countries. She's ad-

ept at tackling nitty-gritty problems that can leave research projects hamstrung, said Sarnquist. Once, her team ran out of dry ice for a study in Mexico, threatening their ability to keep doses of polio vaccine cold. "Bonnie said, 'How about the local Coca-Cola factory? They have dry ice. Can we buy some from them?'" Sarnquist recalled. (The idea to call the factory came from a team member in Mexico, Maldonado



#### **BONNIE MALDONADO'S**

leadership in shaping Stanford Medicine's pandemic response and explaining COVID-19 to the public is the culmination of a lifetime of learning.

said, adding, "If you listen to people in the community, they almost always have a good answer to a problem.")

#### **FULL-BORE COVID-19**

**I**N FEBRUARY, as it became clear that the novel coronavirus was spreading globally and Stanford Medicine leaders ramped up their response, Maldonado's expertise was in high demand.

"All of a sudden, I was on calls with her and others six or more hours a day," said Andra Blomkalns, MD, chair of Stanford's Department of Emergency Medicine. "And people were asking, over and over, 'Bonnie, what are your thoughts?'"

Norman Rizk, MD, then co-chair of the hospitals' joint clinical operations resource team, said, "Bonnie has been very involved in everything, from how we manage access to

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## THE VIRUS HUNTER BECOMES PREY

Renowned microbiologist's battle against the coronavirus gets personal

By Tracie White

ILLUSTRATION BY RICCARDO VECCHIO

**A**BOUT ONE WEEK after testing positive for COVID-19 in early April, famed virus hunter Peter Piot, MD, PhD, checked into the Royal London Hospital with a high fever, extreme exhaustion and mind-numbing headaches. He wasn't sure he would ever leave.

After years of tracking down dangerous and elusive viruses, including AIDS and Ebola, a new virus had finally tracked him down. "Revenge of the viruses," he thought to himself with grim humor. His wife, Heidi Larson, watched as they rolled Piot away from her and through the double doors to the isolation ward.

"It's a hard feeling when someone you love is very ill, and they're going to have to be alone," said Larson, PhD, an anthropologist, who traveled with her husband to Sierra Leone during the Ebola outbreak in 2014. The separation from her husband reminded her of what Ebola patients' families went through.

Piot was in the hospital, struggling for his life, for seven days and nights. Three other men with the same virus shared his hospital room. All three were diabetics and ethnic minorities, two categories known to increase the risk of COVID-19 complications in the United Kingdom. Because of his age, 71, Piot was also in a high risk category, but he had no pre-existing conditions, jogged regularly and was rarely ill. He hadn't taken a sick day in 10 years.

"I became a patient once the doors closed behind me," Piot said. "I wasn't trying to be a patient and a physician. I was so exhausted I couldn't think properly. At my darkest moments I thought, 'Maybe I won't get out.'"

Piot, who grew up in Belgium, has spent much of his career traveling to Africa and Asia to fight infectious dis-

ease. He was on an international team that discovered the Ebola virus in 1976 in northern Democratic Republic of the Congo (then referred to as Zaire). From 1991 to 1994, he was president of the International AIDS Society, then the first director of the U.N. Programme on HIV/AIDS, called UNAIDS. He said that he has great respect for viruses, but that he underestimated this one.

"When I first got sick, I thought, 'Oh, this is just a typical viral thing,'" he said. "It was clearly much, much worse than I imagined."

### TAKING PRECAUTIONS AGAINST THE VIRUS

**S**HORTLY AFTER THE World Health Organization declared the coronavirus a pandemic on March 11, Piot and Larson started isolating themselves physically from others, conducting business from their home in London. Britain went into lockdown on March 23, but it was already too late for Piot. He doesn't know where he caught the virus; it could have been so many places. As director of the London School of Hygiene & Tropical Medicine, Piot's duties keep him in the public eye. Prior to isolating, he was giving talks, attending meetings, chatting with students and, as a self-proclaimed foodie and wine lover, often eating out.

On the evening of March 19, Piot came down with a high fever, muscle aches, a sore throat and a splitting headache. He didn't have a cough, but, weirdly, his scalp burned when he touched it. He figured he had COVID-19.

At first, he continued to work. But that became harder every day. He lost his appetite. Getting out of bed in the morning was a struggle. The growing fatigue and the headaches consumed him. Yet, he couldn't easily get a test for the virus.



"It's extremely hard to get testing in London," he said. "I didn't meet the criteria because I didn't have a cough. So I went to a private clinic, and I tested positive. This lack of access to testing is really scandalous."

As the director of a university, Piot is responsible for overseeing the move to online teaching, so he refused to rest after testing positive. "We were in crisis," he said.

Eventually, though, working was no longer an option.

"It felt like this virus was in every single cell in my body. Maybe it was. We know today that it definitely affects other organs, rather than just the lungs."

When his fever spiked to 104 degrees, he and Larson finally took off in a taxi for the emergency room. X-rays of his lungs showed he had bacterial pneumonia. Even though he wasn't coughing and wasn't short of breath, his oxygen levels were frighteningly low. He was given oxygen through a mask, antibiotics for the pneumonia and blood thinners — a response to then-growing worries about blood clots causing strokes in coronavirus patients.

By the time he reached the hospital, he no longer tested positive for COVID-19 so he was relieved that he had previously been tested. It's not unusual for symptoms to linger after testing negative for the virus, he said.

While he was in the hospital, Piot was grateful that he could talk to his wife and grown children over FaceTime during the day. But the nights were long.

"I was really scared I'd have to go on a ventilator," he said. "I was still following the medical literature, and there was increasing evidence of high mortality for people on ventilators."

Fortunately, the high-flow oxygen was enough to keep him alive.

After he was released from the hospital, he took an above-ground train ride home. It was a nearly empty train and he was careful to wear his mask, he said. He wanted to soak in being outside and being alive.

**W**HEN PIOT WAS A medical student at Ghent University in Belgium, a professor warned him against a career in infectious disease, saying there was no future in the field. It was the 1970s, when many thought that antibiotics and vaccines would wipe out all infectious disease.

Piot ignored the advice and went on to earn his PhD in



clinical microbiology at the University of Antwerp. The era of infectious disease did not subside. Instead, antibiotics became less effective, an anti-vaccine movement grew and society became increasingly mobile, which combine to create prime conditions for infectious diseases to spread.

Meanwhile, Piot and others in his field began to predict that pandemics would strike.

"We've all predicted that one day something like this would happen," he said. "I gave speeches about it. I asked 'Are we ready for the pandemic?' The answer was no. I always thought, though, that it would be an influenza virus. Instead it turned out to be a coronavirus."

Early in his career, when Piot was a senior fellow at the

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## 'THESE PEOPLE ARE REALLY FRAGILE'

An intensive care team takes on COVID-19

By Tracie White

PHOTOGRAPHY BY STEVE FISCH

**T**HE FIRST CORONAVIRUS patients to arrive in the intensive care unit at Stanford Hospital were wheeled in on gurneys, sometimes struggling for breath, often with frighteningly low levels of oxygen circulating in their blood. They were pale and scared. Because visitors were barred to contain the spread of the virus, no family members were there to support them, and it was up to the ICU team to make life-or-death decisions fast.

This was early March, just before the World Health Organization declared the coronavirus outbreak a pandemic, and no one was sure how best to treat patients with this extremely infectious disease. No one on the ICU had cared for patients with this illness before. There were no standardized treatment guidelines, and very little reliable research existed. Mostly, there were just rampant rumors of high mortality rates and even higher levels of contagion. The ICU team had to start from scratch.

"It was nerve-wracking," said Dwayne Free, one of the frontline respiratory therapists, whose job is to help keep patients with infected lungs breathing. "There were so many questions around how the virus was spread. People were scared. Were there going to be enough ventilators? Enough personal protection equipment? Are we doing everything right?"

During the following months, the ICU team adapted daily to the ongoing crisis that has refused to subside. They've watched and learned from their patients while keeping up with an influx of new research from around the world. From the beginning, the ICU formed a task force, bringing in Stanford colleagues to debate and create guidelines for the care of people with COVID-19. The guidelines are posted online

and are continually updated in response to ever-changing news about the coronavirus.

It's been a grueling time for the health care workers, but not without rewards.

"For those first couple of patients who made it out of the ICU after 30 or 40 days, everyone — nurses, respiratory therapists and doctors — lined the hallway," said Maureen Fay, a registered nurse and director of clinical services for Stanford Health Care, who talks about the deeply felt camaraderie that has been forged among the ICU staff. "They were cheering. They were so proud."

### THE URGENCY OF COLLABORATION BECAME CLEAR

**C**HAIRIED BY ANGELA ROGERS, MD, the Stanford COVID-19 critical care task force met three times a week at first to hash out the best-practice guidelines. At its peak during those early days, staff members were caring for 10 to 15 patients and preparing for the possibility of a sudden increase along the lines of what hit New York and Boston.

"Right away we knew we had to work together as a team," said Rogers, an assistant professor of pulmonary and critical care medicine. "It quickly became evident that aspects of COVID-19 care were really different from anything we'd seen before. All voices needed to be heard. The respiratory therapists, nurses and pharmacists were crucial to the task force. They knew what could and couldn't be done, and what was safe to try."

This multidisciplinary team — composed of 50 health care workers, including physicians from a variety of specialties, nurses, respiratory therapists and a pulmonologist from Stanford Health Care – ValleyCare — met in the early morn-

ing. They reviewed and debated reams of research gathered through after-hours internet searches. Some called colleagues in New York or Italy, where hospitals were treating large numbers of COVID-19 patients, for advice. They shared what they knew from their own ICU experiences, and what they were learning from treating COVID-19 patients.

“We wanted a way to add some scientific rigor to the decision-making process,” said Javier Lorenzo, MD, a clinical assistant professor of anesthesiology.

At first, what little was known about severely ill patients came from China, where the outbreak began, said Norman Rizk, MD, who until mid-September served as medical director of Stanford Health Care’s intensive care unit. But the enormity of what they didn’t know kept the team up at night. How was the virus spread? What supplemental oxygen methods were best? Which medications would help keep their patients alive? What was the level of contagion risk for frontline health care workers? They needed to find answers, and do it quickly.

“Should we give steroids?” Rizk said as he listed some of the many questions debated, sometimes fiercely, during task force meetings. “Who belongs on ventilators? Do we put our own most vulnerable care workers at risk at the bedside?”

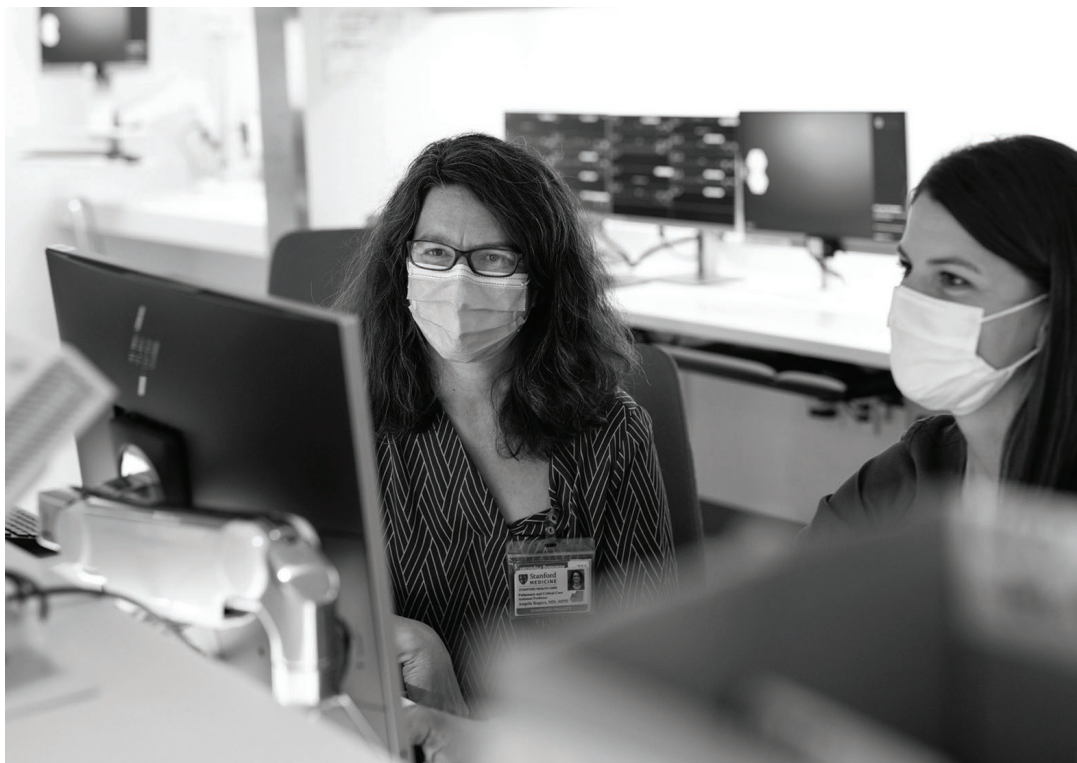
#### **SIMILARITIES WITH ACUTE RESPIRATORY DISTRESS SYNDROME**

**W**HILE A LOT WAS UNKNOWN about COVID-19, scientists did know it was caused by SARS-CoV-2, or severe acute respiratory syndrome coronavirus 2. They knew the virus attacked the lungs, causing inflammation and infection, and reducing oxygen to the rest of the body. But the details remained unclear.

“We knew this was very similar to another condition called ARDS — acute respiratory distress syndrome — something that has been studied for 50 years,” Rogers said. ARDS causes

fluid to collect in the lungs’ air sacs, depriving the body of oxygen. It, too, can be fatal.

“With ARDS, we often intubate and use ventilation to protect the lungs and allow them to heal,” she said. During intubation, a breathing tube is inserted through the patient’s mouth and into the airway. The tube is then attached to a mechanical ventilator that pumps air into the patients’ lungs,



**PULMONOLOGIST ANGELA ROGERS,**

left, with Jamie Kustudia, assistant nurse manager at Stanford Hospital Trauma Center, said, ‘It quickly became evident that aspects of COVID-19 care were really different from anything we’d seen before.’

basically breathing for them.

Because they knew COVID-19 could quickly progress to respiratory failure, the plan early on was to follow the advice from China and not delay intubation, but do it early, as they might with ARDS. As the weeks passed, though, they learned that there were many differences between these two diseases.

Firsthand experience showed it was better to postpone intubation and ventilation for as long as possible. They saw that COVID-19 patients produced thicker, more problematic secretions that blocked the airway and frequently needed to be suctioned out.

When these patients could no longer breathe for themselves and ventilation was needed, they often were on the machine for unusually long periods of time. With ARDS, a patient might be ventilated for four or five days, Rogers said.



‘I’VE SEEN A PATIENT WHO  
LOOKS FINE — THEY’RE SITTING UP ON THEIR PHONE  
TEXTING — THEN THREE HOURS LATER WE’RE

# INTUBATING

THEM TO KEEP THEM ALIVE.’

But COVID-19 patients were sometimes ventilated for weeks at a time. And, surprisingly, most often they still survived.

“Sometimes patients show progress, come off the ventilator, and then need to go back on,” said Jacqueline Hayes Albarran, a clinical specialist and respiratory therapist, who emphasized how difficult it can be to predict an outcome because this is a new disease. “I’ve seen a patient who looks fine — they’re sitting up on their phone texting — then three hours later we’re intubating them to keep them alive.”

Thousands of unvetted research studies quickly flooded the internet, sometimes helping the team make treatment decisions, sometimes generating more questions. Should they be using experimental drugs, like remdesivir or hydroxychloroquine, which was reportedly being used successfully in other countries? Because inflammation is common in COVID-19 patients, what about using more steroids to tamp down the immune system? Because blood clots are a serious concern, should higher doses of anticoagulation medication be considered?

“Among physicians, there is always a strong desire to do something rather than nothing,” Rogers said, especially when treating a patient who may be dying. Still, the best option is often to do less rather than more, she said. The goal became to wait for clear evidence, whenever possible, before changing practices.

“First, you do no harm,” she said. “As we start reaching for therapies, we have to remember these patients are really fragile.”

## FEW COVID-19 PATIENTS HOSPITALIZED

**A** SMALL PERCENTAGE — APPROXIMATELY 10% — OF CORONAVIRUS PATIENTS at Stanford ever see the inside of an ICU, Rogers said. Most at Stanford are treated on the wards and sent home to mend. Those who end up in the ICU are usually admitted because their organs are failing to the extent that they need round-the-clock expert care. The virus can cause multiple organs to fail, from the lungs and kidneys to heart or even brain. “It’s a crazy disease,” Rogers said.

Most ICU patients are given high levels of supplemental oxygen, which is supplied through a face mask or a tube inserted into the nose. If their condition continues to deteriorate,

they are placed on a ventilator through the mouth. In patients with prolonged respiratory failure, a breathing tube is inserted surgically into the neck because it’s more comfortable for the patient and requires less sedation.

The goal is to keep oxygen pumping into the body as long as it takes for the lungs to recover. Using a ventilator gives the body time to heal — to clear infection and inflammation — until the patient is strong enough to breathe independently.

“Part of the problem was that these coronavirus patients who showed up at the ICU often didn’t look as bad as they should with the extremely low oxygen levels they were showing,” Lorenzo said. That made it hard to know when a more invasive ventilation procedure was needed. “We are still learning how the virus affects the lungs, just how diffuse the inflammation is and how it affects the transfer of oxygen. It really just creeps up on people.”

Once the decision is made to put someone on a ventilator, health care workers follow a strict protocol to protect themselves.

Any time spent in the room of a COVID-19 patient puts staff at risk of exposure, Rogers said, so the goal is to keep that time to a minimum while still providing the best possible care. Caregivers are at risk, for example, if a patient coughs as the breathing tube for the ventilator is inserted, sending infectious droplets into the air, or if one of the circuits connecting the breathing tube to the ventilator comes loose, spraying air that’s been infected with the virus into the room.

Even touching a countertop is a risk. So the frontline workers must move cautiously, while also acting quickly to help a patient struggling to breathe and to minimize their own exposure.

Typically, three caregivers enter a patient’s room to insert a breathing tube: an anesthesiologist or critical care physician, a respiratory therapist, and a bedside nurse, each meticulously dressed in full protective gear — face mask, shield, gloves and gown, Free said.

They give the patients sedatives and paralytic agents to keep them calm and still, then a doctor slides a breathing tube down the windpipe into the lungs. The entire procedure normally takes about 15 minutes, but with the added

steps to prevent coronavirus exposure it can take up to an hour. A respiratory therapist at the bedside assists with the insertion of the breathing tube while also suctioning out lung secretions and checking that connections to the ventilator are safe and tight, Free said. The respiratory therapist and a nurse team up to reassure patients through what can be a frightening experience, he said.

“The hardest part for us is at the bedside,” he said. “You go in and see these patients in their most vulnerable state, really struggling to breathe, but right next door the same situation is happening. You try to keep them as comfortable and safe as possible. Then you have to just do your job, move on. I’d go home at night and talk about it with my wife. She’s a critical care nurse and could understand.”

After each of these 12-hour shifts, Free returned home to his wife and daughter, always first stripping down in the garage and throwing everything into the washing machine. Fear of infecting families is a continuing stressor for these caregivers, Fay said, but it was especially strong early in the pandemic.

“They’d say, ‘I signed up for this, but my family didn’t,’” she said.

As time has passed, Free said that he now feels safer at work than anywhere else outside of his home. The safety protocols set up by Stanford have helped the ICU COVID-19 team have confidence that they are not only keeping themselves safe but they’re doing the best they can for their patients, Rogers said. Today, many of those early fears have been replaced by moments of success.

“Caring for these patients is really hard,” Albarran said. “But there have also been some heartfelt moments, like getting to speak to a patient after the breathing tube is removed. Hearing those first words that my patient has spoken in months, and for those words to be, ‘Thank you for saving my life,’ brought tears to my eyes.”

As more rigorous science came to light — with new COVID-19 clinical trials reporting results and peer-reviewed journals reviewing them — treatment protocols for Stanford’s ICU patients began to change. After several large clinical trials showed positive results for the anti-viral remdesivir as a treatment for the virus, and there was a role for steroids in patients with more severe disease, clinicians adopted them as standard for care, Rogers said. When other studies showed that hydroxy-



#### **ANESTHESIOLOGIST JAVIER LORENZO**

said experience and input from others helped guide the ICU team’s treatment protocol for COVID-19 patients: “We learn from our mistakes. We refine our practices, try to make them a little bit more efficient.”

chloroquine didn’t harm patients but didn’t help them either, it was removed from the list of treatment options.

“We had a lot of meetings around these changes,” Rogers said. “In the early days, we were really flying blind, working hard to build a consensus based on our own team’s expertise and outside experts. It is exciting to see our standard of care continuing to advance in response to rigorous clinical trials. Every month of extra data helps.”

Now the ICU’s treatment guidelines recommend steroid use for severe respiratory failure. Similarly, protocol now calls for higher doses of anticoagulation medication for coronavirus patients to protect against blood clots that have been shown to cause strokes, Rogers said.

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## On George Floyd

THOUGHTS FROM A BLACK NEUROSURGEON WITH STRONG STANFORD TIES

By Samuel H. Cheshier, MD, PhD

**S**AMUEL H. CHESHER, MD, PHD, is a pediatric neurosurgeon, a cancer researcher and a Black man. A vital member of the Stanford Medicine community for decades — as an MD/PhD student, as a neurological surgery resident and as a neurosurgery faculty member — he recently moved to Utah, where he directs pediatric surgical neuro-oncology at the University of Utah School of Medicine.

Shortly after George Floyd was killed at the hands of police, Cheshier wrote a letter offering thoughts about anti-Black racism at Stanford and in the world beyond. The letter was sent to former colleague Irv Weissman, MD, director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, who had asked Cheshier for his perspective. With Cheshier's permission, we publish those thoughts here.

June 9, 2020

### THE HURT

**T**HE EVENTS OF THE PAST two weeks have, sadly, reinforced my perception of our country. Although I did not want to believe it's true, I believe that deep down we live in a racist country. We are a nation where a majority of white citizens are perfectly comfortable remaining uninvolved, allowing the worst things to happen to citizens of color.

As long as the atrocities are not witnessed, occur far away and do not directly affect the white majority, the oppressions/discriminations/killings are allowed to go unchecked.

On May 25, 2020, a Black man was dragged out of his car, restrained and then killed by a white police officer while three fellow officers casually watched, essentially guarding the murderer. These men knew they were being recorded, but

that fact did nothing to dissuade their actions and inactions. Every person of color knew what would happen next. The police would claim he had been resisting arrest or bring up the familiar narratives white Americans hold for



RICCARDO VECCHIO



Black men: He was threatening them. They were afraid for their lives. He has a criminal record.

The sad reality is that the system would have bought the police's defenses if not for the security camera footage, showing them dragging an unarmed, unresisting Black man from his car. They may have had to stand trial, but they would have had the best lawyers to defend them. Swaths of politicians would have been on their side. An entire information ecosystem would have supported their telling of the event while simultaneously denigrating the life of the victim: "This Black man got what was coming to him." "He deserved punishment." "He's one less criminal we have to protect you from."

Is spending a fake \$20 bill, using drugs or having an imperfect past grounds for capital punishment? It is if you are a Black man in the United States of America. Time and time again, we have all seen that the police need far less justification for killing or brutalizing a Black man or woman in the United States of America.

The killing of George Floyd has touched a nerve in this country and the world. It has been encouraging to see people of all races, colors and walks of life participating in massive peaceful protests against police brutality, racism and the structural inequalities baked into the very fabric of our nation. The video, the heavy-handed police tactics and the subsequent actions of our national and local leaders have all served as proof, leaving no doubt about the existence of institutionalized racism in our nation.

MANY OF US have watched the video of a Black man begging for his life, calling out to his dead mother, and then slumping, surrendering to death. If you watched, you could see yourself as one of seven people — five in the video, and

two not. Black people knew we were either Mr. Floyd or the person taking the video. Either someone has his knee on our neck, or we are witnessing the atrocity, powerless to do anything about it. White people may have realized they were one of the police. Either the cop with the knee on the neck or one of the three police officers who just let it happen. There is one other white person who I wish was in the video: the cop who would have pushed the knee off Mr. Floyd's neck. The cop who would not stand to let a person die unjustly under their watch.

White people, you need to ask yourself who you are. If you do nothing, you stand on the same side of the cop who has his knee on someone's neck. If you are the cop who would have pushed the knee off Mr. Floyd's neck, we thank you for your willingness to ally yourself with the cause by doing something.

These white people are the same who marched hand in hand with Dr. King in Selma, gave their lives in Mississippi so that Black people could have the right to vote, refused to move away when a Black family moved into the neighborhood, rented apartments to single Black mothers with teenage sons, and approved mortgages for Black families with a good income but a marginal credit score. We know who you are, and we appreciate your works.

However, what is hard to hear and harder to acknowledge is that many white individuals are the cops standing there, backs turned as a knee is on someone's neck. You are probably not a racist, but you are definitely not anti-racist. You will spend \$40,000 a year to send your child to private school but vote against a small tax increase meant to benefit schools in the poorer, darker areas of your community. You will post

on social media how horrible the Floyd incident was, but can't take the time to march in protest, to hand out masks or bottles of water. You will decry the violence of the protests, but not denounce the violence that led to the protests. You place Black Lives Matter signs in your front yard and call it a day.

You know who you are, and we are asking you to turn around, look at the knee on a human being's neck and please push it off. You can help.

#### THE HOPE

IN 1993, I CAME TO Stanford with a suitcase of clothes and another full of books. Those suitcases contained all of my possessions. I spent the next 25 years there as an MD/PhD student, a neurosurgery resident and faculty member. At every level, I encountered genuine discrimination. I had my fellow medical students tell me to my face that I got in only because of my race. I had a Stanford

sheriff run me down on my bike while riding home from the lab. Officers in the car identified themselves as police by turning the police lights on after I was already face down in the dirt. They quickly went back in their vehicle and rode off after I reached in my wallet and pulled out my Stanford ID card. I am

lucky they didn't think it was a gun.

I have had parents request the services of a different neurosurgeon for no apparent reason. I have had nurses mistake me for a food services employee and ask me to take out the food tray of a patient I had removed a brainstem tumor from a week earlier. I had a faculty colleague tell me that I didn't deserve to be a PI of a lab at Stanford. He didn't know I was instrumental in recruiting him to Stanford years earlier.

However, none of those negative experiences came close to the positive

You know  
who you are,  
and we  
are asking you  
to turn around,  
look at the  
knee on a human  
being's neck  
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push it off.  
You can help.

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# The cell whisperer

AN ENGINEER SWAYS TISSUE SAMPLES TO BEHAVE IN THE LAB LIKE THEY WOULD INSIDE US

By Laura Shields

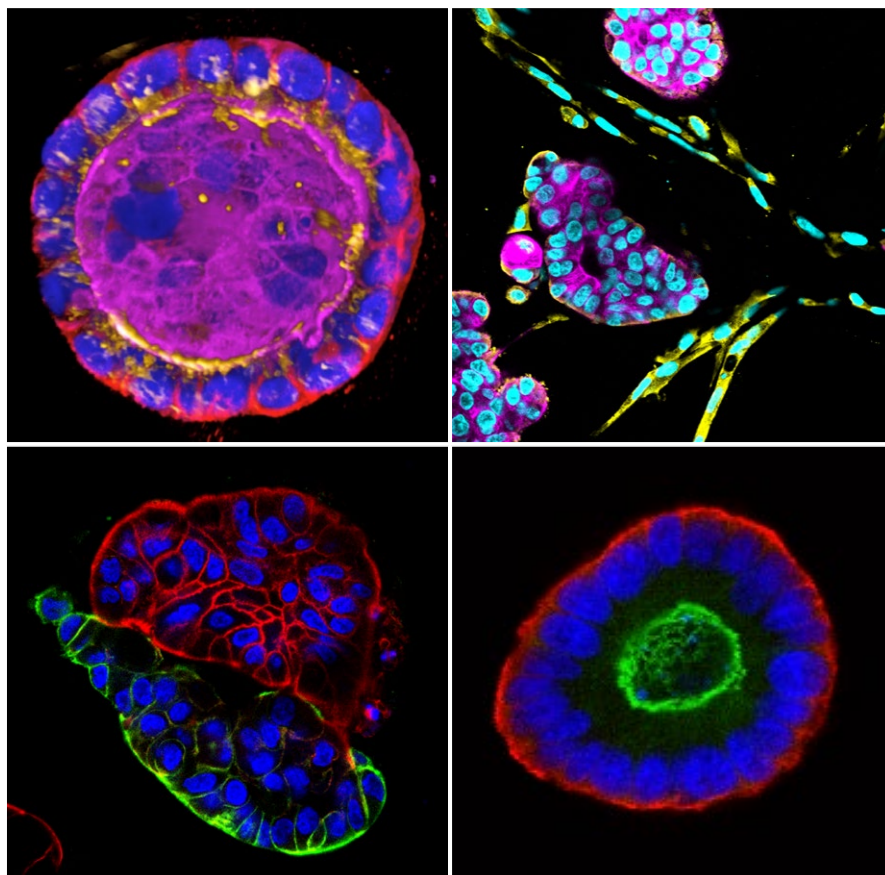
**T**O THE UNTRAINED EYE, THE GLOBS OF cells about the same size as a dust speck do not look like much, certainly not miniatures of the full-sized organs they represent. But these organoids are part of the latest revolution that could open up drug discovery and personalized medicine.

Until the 1950s, cell biologists struggled to keep human cells alive outside a person. But in 1951, Henrietta Lacks' aggressive cervical cancer cells, the first human cells that scientists were able to duplicate and grow in the lab, changed that. Researchers used these cells — named HeLa — to conduct some of modern medicine's landmark research studies and to learn how to immortalize many other types of cells.

Even with these advances, cell culture technology commonly used today remains inadequate for answering some important questions about the lives of cells. That's because the cells' habitats are largely two-dimensional.

"We culture them on a petri dish. It's just a flat dish," explained Sarah Heilshorn, PhD, associate professor of materials science and engineering, sketching a flat surface with her hands. "They're isolated little cells, and they're not doing anything like what they do in our bodies."

Biologists now want to coax cells into systems that more closely resemble human tissue to gain better insights into human development and disease. In the past decade, they have started growing cells in three-dimensional structures. Heilshorn, a 2009 National Institutes of Health New Innovator Award winner, is helping scientists build these structures to aid medical research at Stanford and elsewhere. Her specialty is developing new materials — known as scaffolds — to support the developing organoids. Though her work in the lab was on hold at the beginning of the COVID-19 pandemic, she restarted experiments in June.



CLOCKWISE FROM TOP LEFT: AN OVARIAN CANCER ORGANOID, HUMAN PANCREATIC CANCER ORGANOIDS (PINK) AND THEIR ASSOCIATED FIBROBLASTS (YELLOW), A HUMAN INTESTINAL ORGANOID, AND HUMAN PANCREATIC CANCER ORGANOIDS GROWN FROM PATIENT BIOPSIES.

## A RACE TO MODEL ORGANS

**I**N 2009, Calvin Kuo, MD, PhD, a professor of medicine at Stanford, and Hans Clevers, MD, PhD, at the Hubrecht Institute in Utrecht, the Netherlands, both reported that they successfully grew mouse intestine as organoids — a collection of cultured cells that emulate the natural architecture of the intestine within the body. The achievement kicked off a race to develop organoids that model other major organs, including the

liver, breast, eye and brain. Most laboratories grew organoids on a commercially available protein mixture called Matrigel, which is a gel derived from mouse tumors.

But Matrigel is not perfect. This stew contains 2,000 or so different compounds, and there's a lot of variability among batches, which creates problems, explained Ruby Dewi, a biology researcher in Heilshorn's group.

So a few researchers, including Heilshorn, have started developing artificial gels, called hydrogels. Importantly, they know exactly what they're putting into these hydrogels. "We try to make materials that in some way mimic those that are found in our own bodies," she explained.

Despite the broad range of disciplines in which she has worked — she began as a chemical engineer but went on to study chemistry, physics, bioengineering, and cell biology — Heilshorn sees herself as an engineer. Engineers, said Heilshorn, are "reductionists by nature."

"We want to make as simplified a model as possible to capture some biological phenomenon that we think is important," she said.

#### THE TRICKY BUSINESS OF GROWING STEM CELLS

**M**ANY MEDICAL researchers are especially interested in growing stem cells because their stemness — or ability to self-renew and form all different kinds of cells — makes them invaluable for understanding how tissues develop. But growing stem cells is tricky. Researchers want to culture stem cells in their undifferentiated, or unchanged, state. If the cells begin to differentiate into specialized cells, such as brain or lung cells, they lose their stemness, and scientists have difficulty coaxing them into other desired cell types.

University of Wisconsin-Madison researchers were the first, two decades

ago, to extract human embryonic stem cells that were kept alive in the laboratory. Scientific advances since have made it easier to maintain stemness in 2D cultures than in a 3D environment.

These 2D cultures, however, are quite different from the environment found inside the body where the stem cells would naturally differentiate, which means the cells inside those cultures will behave differently. The ability to develop 3D stem cell cultures, though difficult to achieve, would be a great advance for researchers.

#### FINE-TUNING GELS TO FINE-TUNE CELLS

**T**O BETTER UNDERSTAND how the properties of the 3D material influence cell stemness, Heilshorn and her collaborators designed a family of 3D hydrogels from proteins with tunable mechanical properties. In other words, the researchers could make small changes to the gel's properties — endowing them with more flexibility, for example — and then systematically test how the change affected a specific stem cell population.

Past studies had earmarked matrix stiffness — basically, the rigidity of the gel — as an important factor in maintaining cell stemness. But Heilshorn and her research collaborators found that varying degrees of stiffness had little effect on stemness for the neural stem cells they examined. Instead, cells tended to retain their stemness better in the gels that more easily break down and remodel. The team published their results in December 2017 in *Nature Materials*.

When working with biomaterials, changing one variable generally causes another property to change as well, making it difficult to observe the effects of a single variable's change. But

"We want to make as simplified a model as possible to capture some biological phenomenon that we think is important."

Heilshorn's approach allowed the team to independently study stiffness and matrix remodeling.

As it turns out, physical contact between the neural stem cells helps them retain stemness, explained Heilshorn. The researchers

found that the neural stem cells divided and made copies of themselves only after they could touch each other. If the properties of the gel prevented cell connections, the cells couldn't grow and divide as they normally do in the body.

"The engineering of the material allowed us to identify something about the biology," said Heilshorn.

#### NURTURING ORGANOID TO SPROUT AND GROW

**C**URIOSITY HAS driven Heilshorn since childhood. "I was one of those kids who'd ask 'Why?' like a thousand times every day," she said.

Collaborations with Stanford Medicine researchers allow her to satisfy her curiosity about a wide range of medical matters. Early research with Kuo, a pioneer in developing new organoid culture methods, sparked her interest in organoids. In their latest projects, they are growing intestinal organoids and cancer organoids, both from patient biopsies.

Organoids have typically been grown underneath the tissue culture scaffold, but Kuo uses an air-liquid interface that directly exposes the organoids to air. The technology allows him to grow larger fragments of tissues, which is helpful for studying diseased tissue. He's been using Heilshorn's artificial materials to find the conditions that allow the organoids to grow even better.

The organoid is the seed and the matrix is the soil, said Kuo. "You just



drop it in and it needs to sprout and grow — it's actually like a plant," he explained. "Sarah's trying to come up with better soil, basically."

Once you can grow the organoids, you can study them.

One area of great interest is growing tumor organoids from a patient biopsy and testing out potential drugs. "We are attempting to expose those tumor biopsies to many different treatments in the lab so that we can possibly suggest, or maybe even ultimately predict, to which treatments a patient's cancer would best respond," said Kuo. "That's personalized medicine."

Such work with organoids isn't limited to cancer. Kuo is looking at such genetic disorders as cystic fibrosis and such autoimmune conditions as celiac disease. "There's just any number of possibilities," he said.

#### TACKLING OVARIAN CANCER

ONE OF THOSE possibilities is taking shape elsewhere on campus, where Heilshorn is using her biomaterials expertise to tackle ovarian cancer in collaboration with Erinn Rankin, PhD, an assistant professor of radiation oncology and of obstetrics and gynecology, and Oliver Dorigo, MD, PhD, a surgeon and associate professor of obstetrics and gynecology.

Ovarian cancer is the fifth-leading cause of cancer-related deaths for American women, according to the American Cancer Society. The big problem, explained Rankin, is that by the time most women are diagnosed, the disease has already escalated.

"It's almost like a cottage cheese, spread throughout your abdomen," she said.

"That advanced disease has a 30% chance for survival compared with 90% survival in early stage disease," added Dorigo, who operates on women with ovarian cancer.

Most patients respond well to their first chemotherapy, but the disease recurs, said Rankin. And because their cancer is so advanced and widespread, it becomes resistant to subsequent rounds of treatment. Heilshorn's research goal is to help figure out why this happens.

With samples donated by Dorigo's patients, the team gets a snapshot of the different types of cells. Studying only the ovarian cancer cells, as is commonly done, is limiting, because the different cell types in tumor microenvironments communicate with each other.

For example, the cells surrounding a tumor respond to the tumor's cells by producing extra collagen, which becomes stiff and fibrous, said Heilshorn. Not only can her team characterize the material properties of the tissue, as well as its variety of cell types, they can also use that information to engineer 3D synthetic versions of the cancer matrix — their own ovarian cancer organoids — which they can study further.

Though the researchers are approaching the end of their two-year grant from Stanford Bio-X to pursue this line of inquiry, they plan to continue their collaboration, and they have new grant applications pending. Meanwhile, they are preparing to submit a manuscript for publication in a peer-reviewed journal. "We're really excited, because we've identified a new cellular component of the tumor microenvironment that promotes chemo resistance," said Rankin.

If they can figure out what makes the cancer cells become resistant, they can develop more effective therapies for women with ovarian cancer.

What's more, the models created by the team could be useful for identifying new biomarkers to aid early detection of the disease, said Dorigo.

"To me, the real beauty of being able to create a living sample of a patient's tumor is that you can study it from every different angle and in this exquisite detail that you couldn't if it were actually in the patient," said Heilshorn.

"My hope is that by doing that, we'll be able to really answer some more fundamental questions about the biology of cancer." **SM**

— Contact Laura Shields at [medmag@stanford.edu](mailto:medmag@stanford.edu)

*Portions of this article originally appeared in UC-Santa Cruz Science Notes in 2018.*

#### FEATURE

##### All together now

CONTINUED FROM PAGE 13

On May 4, after implementing a series of protocols to protect both patients and health care workers, Stanford Medicine resumed elective surgeries.

"Once we felt we met certain safety criteria, we started bringing back interventional care," Wald said. "We have tested our staff, and any patient who comes to the hospital is tested prior to their appointment. This ensures we are not bringing infected people into the hospital, which protects our staff and our patients."

Since then, the hospitals have steadily increased the number of procedures, and bed occupancy is up significantly as those who deferred their care return to Stanford Medicine.

"It is both a safe and a smart time to get needed care," Entwistle said, noting that the organizations have implemented a number of safety procedures and protocols and have tested thousands of patient-facing employees to monitor the health of the workforce. "We're confident we are providing a safe place for patients to receive their health care."

THE HARROWING, FRANTIC DAYS OF SPRING WERE AN IMPORTANT DRESS REHEARSAL FOR what many believe to be the main event yet to come. Infections have risen throughout the country as restrictions on gathering loosened and many people have been less willing than in the early days of the pandemic to take precautions to protect themselves and others.

"Where we are right now is disappointing," Kerr said. "There's no other word. There are so many measures that can be taken to limit the spread of this virus: hand washing, masking, social distancing. Science tells us these things work. But, for reasons that are unclear to me, they haven't been widely adopted."

But Stanford is ready.

"Now we have testing capacity, we have personal protective equipment and a

governance for this situation all in place,” Wald said. “We’re better informed about what constitutes a dangerous exposure and how to limit that for our health care workers. We can be more sophisticated in how we triage patients and be more nuanced in our responses.”

Arthofer agreed: “We know much more than before. We know all the next steps: how to get the beds, how to organize the physician teams, what the options are to handle various scenarios. It will be difficult, but if we had to do this, there is no place I’d rather be.” **SM**

— *Contact Krista Conger at  
kristac@stanford.edu*

## FEATURE The invader

CONTINUED FROM PAGE 19

of the hospital, speed recovery and reduce transmission.

If you don’t hate and respect viruses by now, maybe you haven’t been paying attention. But there’s more.

Viruses don’t always kill the cells they take hostage. Some sew their genes into the genome of the cells they’ve invaded, and those insertions add up. Viral DNA sequences make up 8% of our genome — in contrast with the mere 1% that codes for the proteins of which we’re largely made and that do most of the making.

“Our genome has been ‘invaded’ by previous encounters with retroviruses after infection of sperm or egg cells,” Carette told me. “Through evolution, these retroviruses’ genes have become inactive.”

But, as always, there’s an exception. As Carette said: “An ancient viral gene has been repurposed to play an essential role in embryogenesis,” the process by which an embryo forms and develops.

The protein this gene encodes enables the fusion of two kinds of cells in the developing fetus’s placenta, allowing nutrient and waste exchange between the developing embryo and the maternal blood supply. Without them, that is, there’d be no us. **SM**

— *Contact Bruce Goldman at  
goldmanb@stanford.edu*

## FEATURE

### Testing at the speed of COVID

CONTINUED FROM PAGE 23

Many more studies of all types are underway, including whether patient samples could be collected in less invasive ways than the long nasopharyngeal swab commonly used now. Researchers are studying whether people can collect their own samples, eliminating the need to travel to a health care facility and conserving PPE for health care workers.

Also, as of July 22, the Stanford clinical virology laboratory learned from the FDA that they can begin pooling samples from multiple testing subjects pending a final review by the agency. This will enable conservation of test resources and streamline routine testing. The method is likely to be critical for quickly identifying and suppressing outbreaks in communal living situations, including skilled nursing facilities, college dormitories and jails.

Meanwhile, researchers in Boyd’s laboratory and other Stanford labs are investigating whether long-term protection from the virus occurs after infection or vaccination and if so, how long it lasts. They’ve set up blocking assays to determine whether the antibodies detected by the serology assay are able to prevent the spike protein from binding to the human receptor protein, ACE2, or otherwise prevent the virus from infecting cells.

“Our tests, as well as others in non-human primates exposed to the virus, give some good experimental evidence to the idea that previously infected people will probably have at least some, possibly temporary, level of protection,” Boyd said. “Of course, the important thing will be to learn which antibody test results best correlate with the real protection of an actual person exposed to the virus in their environment, and then whether we can induce those antibody responses through vaccination.”

Answers to these questions are urgently needed as the number of cases in the Bay Area and across the country continue to rise and test components become scarce.

“It feels like we’re running in front of a huge tidal wave, trying to keep one step

ahead,” Kong said. “You’re always short something you never would have imagined. Right now, it’s pipette tips. But I’m confident we can handle this. COVID-19 is going to be with us for a while, and we’ve realized that we have to pace ourselves.” **SM**

— *Contact Krista Conger at  
kristac@stanford.edu*

## FEATURE

### Discovering our way out

CONTINUED FROM PAGE 29

COVID-19, even in people who have the virus but have no symptoms. In addition, the team plans to study whether the passive breathing test can detect who is at a higher risk for severe infection, based on readouts of lung function such as a constricted airway or tissue stiffness.

#### Using genetic clues to understand COVID-19 disease severity

**WHY IT MATTERS:** There is a huge range in disease severity in patients with COVID-19.

**TIMELINE:** *The work is underway, with early findings published online in a pre-print study.*

Although Euan Ashley is a geneticist and cardiologist by trade, he and a team of researchers are taking on perhaps the biggest conundrum facing virology today.

“From the earliest days of the pandemic, we’ve seen this unexplained range of responses to SARS-CoV-2, regardless of age,” said Ashley, professor of cardiovascular medicine, of genetics and of biomedical data sciences. For some people, the disease is lethal; some patients experience nothing more than a slight cough; and still others don’t even know they’re infected. “It’s a mystery that needs to be solved.”

Understanding who might be at a greater risk for severe illness is critical for individuals making decisions about their own health and for hospitals preparing for an influx of patients.

In collaboration with Chan Zuckerberg Biohub, Ashley, along with Carlos Bustamante, PhD, professor of biomedical data science and of genetics; Matthew

Wheeler, MD, assistant professor of medicine; Manuel Rivas, PhD, assistant professor of biomedical data science; and Victoria Parikh, MD, assistant professor of medicine, turned to what they know: genomic sequencing.

Their technique uses cells collected through a nasal swab from patients with COVID-19 and analyzes the DNA (from the human host) and RNA (from the virus). The goal is to provide a window into a few things: how patients' bodies respond on a molecular level to the viral attack; what, if anything, about their genetics might predispose them to a particular response to SARS-CoV-2; and how the virus interacts with human cells to incite damage.

"Understanding how the virus works on a basic level is a big part of being able to work out solutions," said Ashley. **SM**

— Contact Hanae Armitage at [harmitag@stanford.edu](mailto:harmitag@stanford.edu)

## FEATURE

### Sounding the mental health alarm

CONTINUED FROM PAGE 33

and skills for psychological recovery to counties' mental health staffers. Tailored to address pandemic-related stressors, this psychological training is intended for psychologists, psychiatrists, social workers, people who answer calls to crisis hotlines and anyone interacting with clients, including receptionists and clinic managers at county behavioral health clinics. The sessions began in September. "The staff are being equipped to do a basic stress and resilience intervention so they can treat their clients and communities," Carrion said.

Carrion also helps disseminate information for parents about how to look after themselves and their kids, and how to communicate with children on challenging subjects, such as the pandemic and racial injustice. He's been a key source for local and national media stories on the topic, and is conducting online seminars for a variety of audiences.

It's also important that people who already have mental health diagnoses continue receiving treatment during the pandemic, he said. Many mental health

providers have been able to transition to phone or videoconference appointments, though Carrion noted that barriers to treatment accessibility are far from over. (Pre-pandemic, two-thirds of the children in America who needed mental health services did not get them.)

And self-care is more important than ever, experts say, including getting enough sleep and exercise and eating well; moderating screen time; and engaging in restorative experiences such as meditating, praying or spending quiet time in nature.

"Many healthy ways of coping have been taken away," Jain said. "Things like support groups, Alcoholics Anonymous meetings, going to the gym for a workout: People really rely on those. And little organic opportunities for social interaction that lift up your day are no longer there."

In light of all this, Jain stressed the importance of being kind to yourself. In a phone call this spring, Jain's elderly mother was lamenting the cancellation of their family's summer plans and Jain gently reminded her to acknowledge what she had achieved: "I said, 'Mom, you've kept yourself alive, kept Dad alive, and neither of you has gotten sick. That's a huge accomplishment.'" **SM**

## Q & A

### How we can beat COVID-19 and face down future outbreaks

CONTINUED FROM PAGE 35

be vaccinated, particularly in this era of anti-vax and anti-science. We have a network of community workers who are being prepped for that outreach. You don't really want a lot of white guys in suits like me going into a mostly minority community and trying to convince them about something that they may be deeply skeptical of. You've got to get people the community trusts.

**MINOR:** If you could look at the scientific unknowns about this disease, what are the top ques-

tions to answer now so we will be much better off in the future?

**FAUCI:** The critical question is, will we get the body to induce a durable immune response that can protect us. No. 2: What about the long-term effects for people who recover? You're hearing about people who get sick, go to the hospital, come out, and then it takes weeks, if not months, for them to begin to even feel slightly normal. Another thing we want to know is, what is the full extent of the clinical manifestations? Finally, what about therapy? Are we going to be able to get a good antiviral that can shut it off completely?

**MINOR:** What would you say to the next generation of physicians, scientists and researchers?

**FAUCI:** If you're interested in scientific research, never before in history have the opportunities been so spectacular as they are right now. So much so that I often fantasize — I'd like to turn the clock back and be 25 years old, starting all over again. I am in awe at what's coming out from a scientific standpoint. **SM**

## FEATURE

### 'I've trained my whole life for this'

CONTINUED FROM PAGE 37

the hospital buildings, to what drugs we might use to treat the disorder, to whether it would be prudent to take in a lot of patients with COVID from other hospitals."

Maldonado began working 18 or more hours per day. As the chief of infection prevention and control at Stanford Children's Health, she consulted closely with her counterpart, Lucy Tompkins, MD, PhD, chief of infection prevention and control at Stanford Health Care, to ensure that infection control and pandemic response measures at the pediatric and adult hospitals were aligned.

She coordinated with Rizk and Sara Cody, MD, chief public health officer for Santa Clara County, to ensure that Stanford's resources — such as the virus test developed by Benjamin Pinsky, MD, PhD, in March — were available to

## WEB EXTRA

See the video of the Anthony Fauci conversation and the transcript at [stan.md/2WiFPBo](https://stan.md/2WiFPBo).



people in hard-hit parts of the county. And Maldonado was instrumental in securing funding from local philanthropists for some of the first pandemic-related research projects.

"She's able to distill a lot of information into what's immediately important for the conversation," said Blomkalns. "And she's not at all afraid to say things if she's in conflict with people in the room; she says what needs to be said."

These skills have helped guide common-sense decisions in an environment where things aren't perfect, Blomkalns said. Maldonado set policy for how to put contagious COVID-19 patients on respirators and for utilizing the limited number of negative-pressure rooms, which have ventilation systems that prevent unfiltered air from leaving the room. "We needed to innovate and create solutions for many possible situations. Bonnie was able to translate her scientific knowledge into what was most feasible given the constantly evolving situation," said Blomkalns.

For months, Maldonado was immersed in pandemic-related work without losing momentum. But when George Floyd, a Black man, was killed May 25 in Minneapolis by a white police officer kneeling on his neck, she says she hit a very low point.

"I just couldn't believe one more thing was happening in this world to make us less human," she said. "I had a hard time that week. As a person of color myself, I know this happens all the time. The fact that people thought this was new made me really sad; it hasn't ever gone away."

Maldonado, who is also the School of Medicine's senior associate dean for faculty development and diversity, helped organize online town hall meetings for the Stanford Medicine community that focused on the Black Lives Matter movement. Her team solicited and funded applications for grants that would address disparities around COVID-19, which has disproportionately affected people of color. They also assembled diversity-related resources from throughout the school. "I felt a need to keep going, to do something to support people who were feeling

vulnerable," she said. "I wanted to be out there protesting, but I realized my time is better spent here."

Maldonado has also been a key scientific spokesperson on all things COVID-19, communicating with the news media and the broader Stanford community.

"She can craft her message in a way that is understandable to each audience," said media relations specialist Lisa Kim, who has triaged media requests related to COVID-19 throughout the pandemic. Maldonado stays patient with reporters driven by breaking COVID developments, and she's available almost constantly, said Kim: "I've received emails from her as early as 5 a.m. and after midnight."

(Midway through reporting this story, I took a break to eat lunch and read the news. I opened a *New York Times* parenting story about letting kids use public restrooms during the pandemic — something I was vaguely worried about for my young kids. Maldonado was the first expert quoted, giving her usual sensible advice: "Most people aren't sitting in public bathrooms for hours and hours," her quote began. I burst out laughing.)

#### GENERATING NEW KNOWLEDGE

**E**ARLY IN the pandemic, several Stanford scientists began discussing how to study the novel coronavirus. So little was known about COVID-19, the disease it causes, that even the symptom list was incomplete.

"We recognized we would need to see COVID-positive patients in an outpatient setting because 80% of patients aren't admitted to the hospital, and we needed to figure out new medications and ways to manage the disease in patients with less severe illness," said infectious disease expert Upinder Singh, MD, professor of medicine.

The team also hoped to investigate the immune responses of these individuals, which could hold clues to why some people become much sicker than others.

"But bringing them into the main hospital or clinics for research was problematic for the safety of our other patients," Singh said. A member of Singh's

team had an idea: Why not set up tents to house research facilities? Researchers could see COVID-19 patients separately from uninfected people, and could easily keep everything clean and well-ventilated. Maldonado was among the first to support the plan.

"She got it," Singh said. Maldonado and Minor brought others on board and quickly assembled a funding proposal for a local donor who wanted to help.

Blomkalns helped the team plan research that compared COVID-19 test samples taken from the front of the nostril with those taken deep in the back of the nose, a step toward building self-testing for the disease.

Even in the teeth of a pandemic, the scientists were excited to be generating new knowledge. "It was really fun," Blomkalns said, sounding a little surprised at herself. "Bonnie's really good at encouraging her team."

Now, two tents house a COVID-19 clinical and translational research unit co-led by Singh and Maldonado. The tents are outfitted with air conditioning and heat, WiFi, electricity and research equipment, and they are close to the hospital's emergency department in case a COVID-19 patient participating in the trials is sick enough to need hospitalization. Other academic medical centers have struggled or failed to open similar research facilities, Singh said.

Maldonado is involved in two large epidemiological studies of the disease, as well as vaccine and treatment trials. Each Sunday, she sees participants in a placebo-controlled trial of a drug called favipiravir, an antiviral that researchers hope may reduce disease severity and make infected people less likely to spread the SARS-CoV-2 virus.

"I really love seeing patients because all the other stuff I'm doing takes a back seat and I can just focus on one person," Maldonado said. The experience reminds her of working with pregnant women in Zimbabwe, who often walked for hours to reach a clinic where they could get an HIV test and, if it was positive, medication to prevent viral transmission to their babies. "I really think it helps ground me. It's the

kind of thing that makes me really understand the meaning of what I'm doing."

It's an enormous workload, but Maldonado has some help. On weekdays, she's up between 5 and 6 to get ready for many hours of online meetings — a challenge because "anyone who knows me knows I am not a morning person," she said, laughing. She relies on assistants for scheduling and has become more efficient at everything: firing off emails during long meetings; using a 7-minute phone app workout to squeeze in exercise; and relying on her husband, Ramiro, a lawyer, to make dinner.

"I don't do this at all by myself. There are dozens and dozens of people who are working along with me," she said. "What I can do is bring people together. For every hour that I put in, I'm probably amplifying that by 100 hours of other people's work."

She gets a lift by walking or running on the Stanford campus, where she and her husband live. They both keep tabs on their three adult children — who visit occasionally — and her 87-year-old father, who lives in Los Angeles and whom they have seen only once since the pandemic began.

More than six months into the pandemic, her optimism has not waned. "I was always hopeful, and I still have hope," she said. "We can conquer this disease. We've conquered other diseases like this or worse."

"It's scary and horrifying that we have to learn about this virus through this living experiment that we are undergoing. But I really think that, in the end, I've learned more in the past seven months than I've learned about anything else over my lifetime. It's really moved very quickly." **SM**

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#### WEB EXTRA

What feeds  
Bonnie Maldonado's  
optimism?  
Tune in to our video  
and podcast: [http://  
stan.md/maldonado](http://stan.md/maldonado)

whom he considered a mentor. Falkow, a renowned microbiologist who later joined the Stanford faculty, discovered the molecular mechanisms of many infectious diseases.

"Stan told us to put yourself in the head of the microbe," Piot said. "Its purpose is to find

a living host — a plant, an animal or a human being — to infect. Viruses can only survive in a living cell. In other words, viruses will continue to try to infect more people all the time, otherwise they'll die."

This coronavirus has proven to be an expert at infecting people, easily jumping from one victim to the next, he said.

SARS, another coronavirus, enters the body and goes straight to the lungs. But the COVID-19 virus stays in the throat and nose longer, making it easier to spread. In addition, people infected with COVID-19 have been shown to be contagious for about two days before showing symptoms, an unusually long time. In addition, many people infected with the coronavirus remain asymptomatic, yet they are still able to spread the disease.

"This is a nightmare to control," Piot said. "If you only deal with people with symptoms, you're going to miss quite a few people."

#### STILL AN ENIGMA

**W**HILE THE WORLD struggles to control COVID-19, much about it remains unknown, Piot said. It's that uncertainty that's hardest for everyone, including scientists and world leaders, to manage.

After Piot returned home, he was still physically and emotionally fragile, and was easily fatigued. But his fever had gone and his oxygen levels were almost normal.

Then a new set of symptoms slapped him back down. His immune system went into overdrive, he said, and his oxygen levels started jumping around.

"We live in an old house with four floors," he said. "We're going up and down all the time." When that became a problem, he made an appointment at University College London Hospital for a second round of tests. That was April 19, a week

after he had been discharged.

"I was so scared that I might be admitted to the hospital again," he said. "They did the blood work and ran a CT scan. I saw the images of my lungs: They looked opaque, much worse than when I was admitted with the acute infection the first time."

Piot had what's called a hyper-inflammatory immune response. His heartbeat was irregular and he was diagnosed, this time, with interstitial pneumonia caused by inflammation in the lungs. Doctors put him on high levels of prednisolone — a steroid that dampens the immune response — and sent him home to rest.

His symptoms waxed and waned for two months. He worried the illness would become chronic, though he was relieved that, as a U.K. resident, his medical costs (except for that original coronavirus test) were covered by the National Health Service. Finally, he began to get better.

"It was so very frustrating," he said. "I couldn't do anything but be a patient and rest." During his recuperation, Piot was interviewed for a story that ran in a Belgian magazine describing how the famous virus hunter remained sick with the coronavirus after two months. *Science* and *The New York Times* ran similar stories, spreading the story wide.

Hundreds of messages flooded Piot's email box, many from people whose COVID-19 symptoms lingered for weeks, sometimes months. "We are going to see a whole generation of people coming out of this with chronic conditions. I've probably got a bit of lung fibrosis. Fortunately though, no kidney problems."

By the last day of June, Piot said, he was feeling 95% better and went for his first jog in months. He was gardening again, and enjoying wine. He joked that people who know him will understand how sick he was to go six weeks without it.

He was also working from home, though he still grew fatigued in the evenings. In addition to running a university, Piot works as a coronavirus adviser to European Commission President Ursula von der Leyen. World leaders in industry and politics also contact him for advice about how to protect against this virus.

#### FEATURE

##### The virus hunter becomes prey

CONTINUED FROM PAGE 39

University of Washington, he worked with Lucy Tompkins, MD, PhD, now a professor of infectious diseases at Stanford, and the late Stanley Falkow, MD,

His struggle to survive has given him a whole new set of insights, he said.

"I really think the personal story is absent from the conversation," he said. "In the U.K., at least, it's all about flattening the curve. It's almost an afterthought how to save people. This is about the people.

"It's really touched me personally how invasive this virus — one that I so underestimated — can be. I'm more dedicated than ever to fight this virus." **SM**

— *Contact Tracie White at*  
*traciew@stanford.edu*

## FEATURE

### 'These people are really fragile'

CONTINUED FROM PAGE 43

"We are still learning," she said. "We've seen enough patients to learn a lot from them, but it's too early to say these will always be the best treatments."

The team still meets once a week, with members spending their free time studying new scientific literature, sharing war stories with colleagues around the globe and learning from their patients at the bedside. The frontline caregivers still sweat under their protective gear while reassuring frightened patients. The recovery rate for their ICU patients has continued to hover around 80% throughout the pandemic, Rogers said. And no health care workers have contracted the virus while working in the ICU.

"We still have adequate PPE because of heroic efforts in our supply line," Rizk said in July.

By that time, the numbers of patients in the ICU had risen back to those highest levels seen early in May. A handful of state-mandated transfer patients from the Imperial Valley, where hospitals have been overwhelmed, are included in those numbers, but most are coming from the surrounding community. "We are prepared again to surge if required," Rizk said. "We have actually started a new ICU team that deals with just the COVID patients."

"In late July, we rose as high as 14 patients in ICU with seven on ventilators. By late August, as numbers in the region are falling again, the ICU numbers had similarly fallen to eight with five on

ventilators," Rogers said.

No one's sure why Stanford didn't see a steep initial surge; perhaps spread of the disease was limited by early stay-at-home orders in the San Francisco Bay Area, or the fact that the patients tend to come from areas with low population density. But patients with COVID-19 have not stopped coming, with some becoming severely ill and struggling to get better. So Stanford continues to prepare, responding to emerging data to provide the best care possible for each new patient, Rogers said.

"We learn from our mistakes," said Lorenzo. "We refine our practices, try to make them a little bit more efficient. We rest. We take care of ourselves and our loved ones. We realize now that this is probably not going to be a peak, but a trickle of patients for a long time to come." **SM**

— *Contact Tracie White at*  
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## PLUS

### On George Floyd

CONTINUED FROM PAGE 45

experiences I have had with the students, faculty and staff at Stanford. I can't tell you how many times a person at Stanford gave me a chance and took a chance on me. I can't tell you how many times at Stanford I heard, "Well, all things being equal, we are going to take the women and persons of color." I can't tell you how many times Stanford offered me opportunities to help others just like me.

Stanford is not a perfect place. Like the rest of our society, most there are content to turn their backs. There are even a few people who want their knee on someone's neck. However, Stanford's halls are filled with people, programs and institutions that are anti-racist. Over the next weeks, months and years, the Stanford community will respond to the tragedy of George Floyd's murder. There will be many responses — data-driven, compassionate and models for others to follow. For those of us who are Black, we must not give up, no matter how hard the struggle, because our surrender is victory to the cop with his knee on Mr. Floyd's neck. And to all

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our white colleagues, friends and family at Stanford who commit to a life of anti-racism, we thank you for your support because we cannot do this alone. Together we will stand; divided, we will fall.

Take care,  
Sam

— *Contact Samuel H. Chesbier at*  
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# THE DOCTOR IS IN — ON YOUR SMARTPHONE

## DURING A PANDEMIC, VIRTUAL HOUSE CALLS TAKE OFF

By mid-March, Bay Area residents were under shelter-in-place orders to avoid spreading the coronavirus, but Wendy Quivey couldn't stay home: She broke her leg badly doing the limbo at a wedding, had immediate surgery and needed follow-up care.

After the break, her doctor referred her to Stanford Health Care, where Michael Gardner, MD, professor of orthopaedic surgery, spent three hours on March 10 piecing together the 47-year-old's shattered tibia and ankle joint with the help of metal rods and screws. Quivey was in the hospital two nights before going home to San Mateo, California.

She had to return to Stanford for imaging to ensure her leg was healing properly, but other follow-up visits took place in her apartment, with her smartphone. After downloading an app that allowed her to talk with Gardner via video, she showed him and his team how well she could move her foot, discussed her pain medications and described her progress in physical therapy. She held the phone's camera over her leg so they could check her incision.



"It was so easy," said the pharmaceutical representative and mother of a 13-year-old and a 10-year-old. "It's so hard to find the time, being a mom with two kids and working. With a video visit, I can see my doctor on a break from work."

Back before COVID-19, Christopher Sharp, MD, chief medical information officer of Stanford Health Care, had been encouraging physicians, nurses and other providers to conduct online visits when patients didn't need tests or hands-on care. Progress was slow — in 2019, fewer than 2% of patient visits were conducted virtually — but that was expected. Legal, reimbursement and technological hurdles had to be sorted out, and some patients and clinicians were reluctant.

Then came the coronavirus. By mid-April, 70% of Stanford Health Care visits were virtual, with nearly 50,000 patients having their first online medical encounter. Visits at Stanford Children's Health exploded as well: "It's crazy how quickly it happened," said Natalie Pageler, MD, chief medical information officer at the children's hospital. In just a few weeks, online pediatric patient visits mushroomed from 35 a day to more than 500.

Other health care organizations have also seen a surge in online visits, though few are as dramatic as Stanford's: Based on insurance claim data from nonprofit FAIR Health, telemedicine across the nation grew from 0.38% of visits in February to 13% in April. Insurance companies and government agencies aided the transition by quickly changing their rules to reimburse online health care. "Everyone got comfortable with virtual visits overnight," Sharp said.

Once Stanford resumed non-emergency procedures and Bay Area counties started lifting shelter-in-place restrictions, the number of online encounters dropped. They currently make up about 40% of all visits at Stanford Health Care, and Sharp is confident they'll remain popular among patients and physicians.

"Telemedicine just makes sense for a lot of people," he said. "It's especially useful for working parents or people with transportation problems."

Sharp now hopes to push telemedicine to the next level, in which patients wear devices that measure heart rate, glucose levels, blood pressure and other indicators, then transmit that information to a health care team.

"We see a possibility for a change in paradigm, where the doctor-patient relationship becomes more of a continuous interaction, instead of a twice-yearly meeting," he said. "A lot of digital medicine is about building connections. It's a very patient-centric mode of contact." — BY MANDY ERICKSON

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# Game on

PUZZLE FIENDS SEEK TO OPTIMIZE A COVID-19 VACCINE

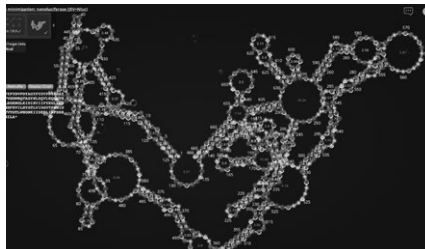
**Developing a vaccine formula that can protect people from COVID-19 is only the first step in beating the coronavirus that causes the disease.** That same vaccine also must retain its disease-prevention power during a global trek to reach the billions of people who will need it.

To create such a vaccine, Stanford biochemist Rhiju Das, PhD, has tapped the collective minds of video-game players through a project called the OpenVaccine challenge.

For the challenge, which is hosted on an interactive gaming platform that Das co-invented called Eterna, gamers from around the world are using their puzzle-solving skills to help design an RNA structure that protects the vaccine's potency by following a few video-game-like rules governing how the molecules fold.

Das studies how string-like RNA molecules, which encode the genetic information needed to make proteins, fold into three-dimensional shapes to carry out biological functions within a cell. RNA molecules are being investigated as potential vaccines for several diseases — including COVID-19 — although none has been approved for use in humans.

Each RNA molecule can assume many different conformations that vary in their resistance to degradation. Those conformations predicted to be the most resistant by the game's scoring system are tested in the labs of Das and geneticist Maria Barna, PhD.



Eterna was launched 10 years ago and has more than 250,000 players. Insights from the gamers — who don't need scientific training to play — have led to the publication of more than 20 scientific articles describing new configurations of the flexible RNA molecules.

"We're trying to recruit — potentially — millions of people to come play a video game," Das said in an interview for a pbs.org NOVA segment about decoding COVID-19. "The solutions they are providing very well could become a medicine that is injected into billions of people."

In the segment, during which Das was featured among a host of researchers, he discussed the urgency of COVID-19 vaccine research: "The advantage of RNA vaccines is that they are super fast to make, which is absolutely critical in the current pandemic situation." **SM** — KRISTA CONGER

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