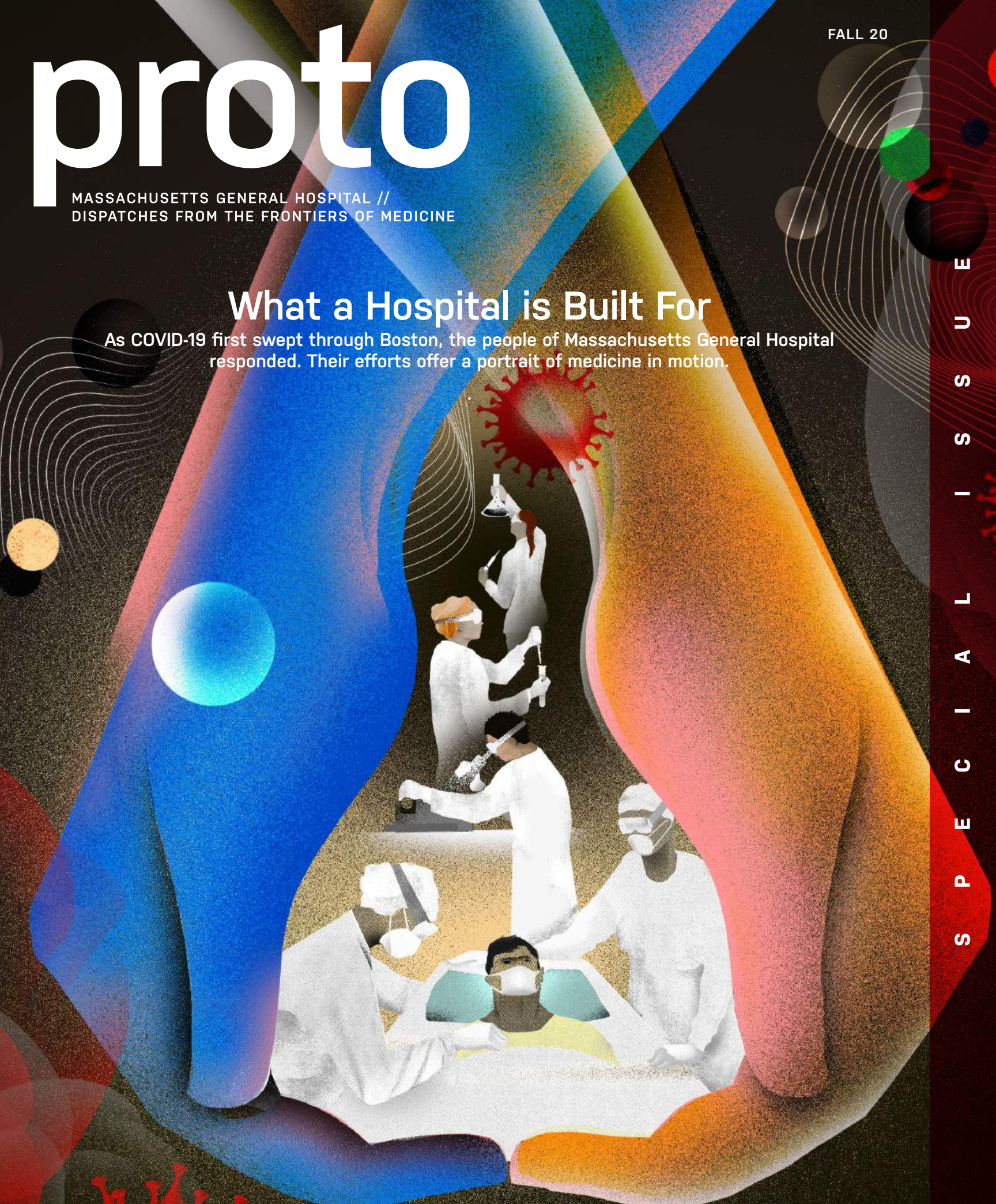
FALL 20

proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

What a Hospital is Built For

As COVID-19 first swept through Boston, the people of Massachusetts General Hospital responded. Their efforts offer a portrait of medicine in motion.



SPECIAL ISSUE

contents

FALL 2020

on the cover

The world remains unsettled by COVID-19 and the "new normal" that came with it. A close look at the first months of the pandemic shows how far the fight against the virus has come and what ground remains to be covered.

// Illustration by Brian Stauffer

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

proto

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Founded in 1811, Massachusetts General Hospital is a 1,000-bed academic medical center in Boston. It is a founding member of Mass General Brigham (formerly Partners HealthCare) and is the original and largest teaching affiliate of Harvard Medical School.

AS CASES OF COVID CONTINUE TO TICK UP at an alarming rate across the nation and around the world, the pandemic that has been omnipresent for nearly a year continues to shape the way we live and work and socialize and celebrate. The numbers alone, while sobering, provide some context and scope of the disease's reach, but to grasp the true magnitude of its human impact, we must turn to stories—stories of people, hope, grief, progress, frustration and joy. Inside hospitals, embracing each COVID patient has been an orbit of providers—physicians, nurses, respiratory therapists, social workers, chaplains and countless others—who have faced an unfamiliar and unpredictable viral foe, and with it, so much change.

There was the social worker, used to being at the bedside of cancer patients, who made telephone calls to learn something special about the COVID patients ventilated in the ICU, sedated and unable to communicate. There was the nurse who arrived for work one morning to learn that she would be taking care of a coworker who had been admitted to her own unit. There were the nonclinical employees whose regular jobs had been put on hold and who were redeployed to sit at patients' bedsides and listen for any signs of trouble with their ventilators. There were the clinicians, collaborating with researchers, who worked around the clock to figure out what drug, what strategy, what to try next time to give patients the best chance of recovery.

Spring was grueling; the grief, staggering. When, in July, the hospital hosted a day to thank staff, the mood throughout the hospital was relatively subdued without the usual flow of visitors, but there was a sense of relief that the surge was behind us and the hospital was returning to a new type of normal. COVID inpatient cases were way down, and staff could take a collective breath. And there was, finally, time to celebrate the triumphs: the more than 2,000 patients who were discharged back to home, the 75 healthy babies who were born to COVID-positive mothers.

Now, as we head into the winter—still masked and physically distanced—we do so with the benefit of experience, more data and a growing body of science that will inform our decisions and actions. The progress we have made—progress in therapies, prevention and our own workflows—has made us stronger as a community. Lauren DeMarco, the social worker who looked into the lives of ventilated patients, noted this spring that "joy runs faster than grief can walk." As we monitor the steadily rising number of COVID patients coming into our hospital, these hopeful words serve to remind us that this pandemic is truly a marathon, not a sprint. And we are distance runners.

EDWARD BOCHES

stat

FOCUS

A Boston man goes for a stroll down Commonwealth Avenue on day 60 of the pandemic. There's no saying whether his outfit is a statement or an overabundance of caution. Photographer Edward Boches captured this moment and others like it—the drive for safety coupled with the routines of normal life—in the early months of COVID-19.

The scientific understanding of SARS-CoV-2 transmission has evolved over the course of the year, shaping public health guidance. Initially suspicion fell on fomites, inanimate surfaces such as a door handle that carried the virus. Then the primary target became droplets, particles expelled with a sneeze or talking. In early October, the Centers for Disease Control and Prevention also described a third, less common way: aerosol spread, particles that can remain airborne for minutes or hours and cause a particular danger in enclosed, poorly ventilated spaces.

Each discovery about transmission has refined thinking on how to stay safe. While an outfit like this may protect the wearer from infection, face masks and observing distance guidelines will do the trick for most.

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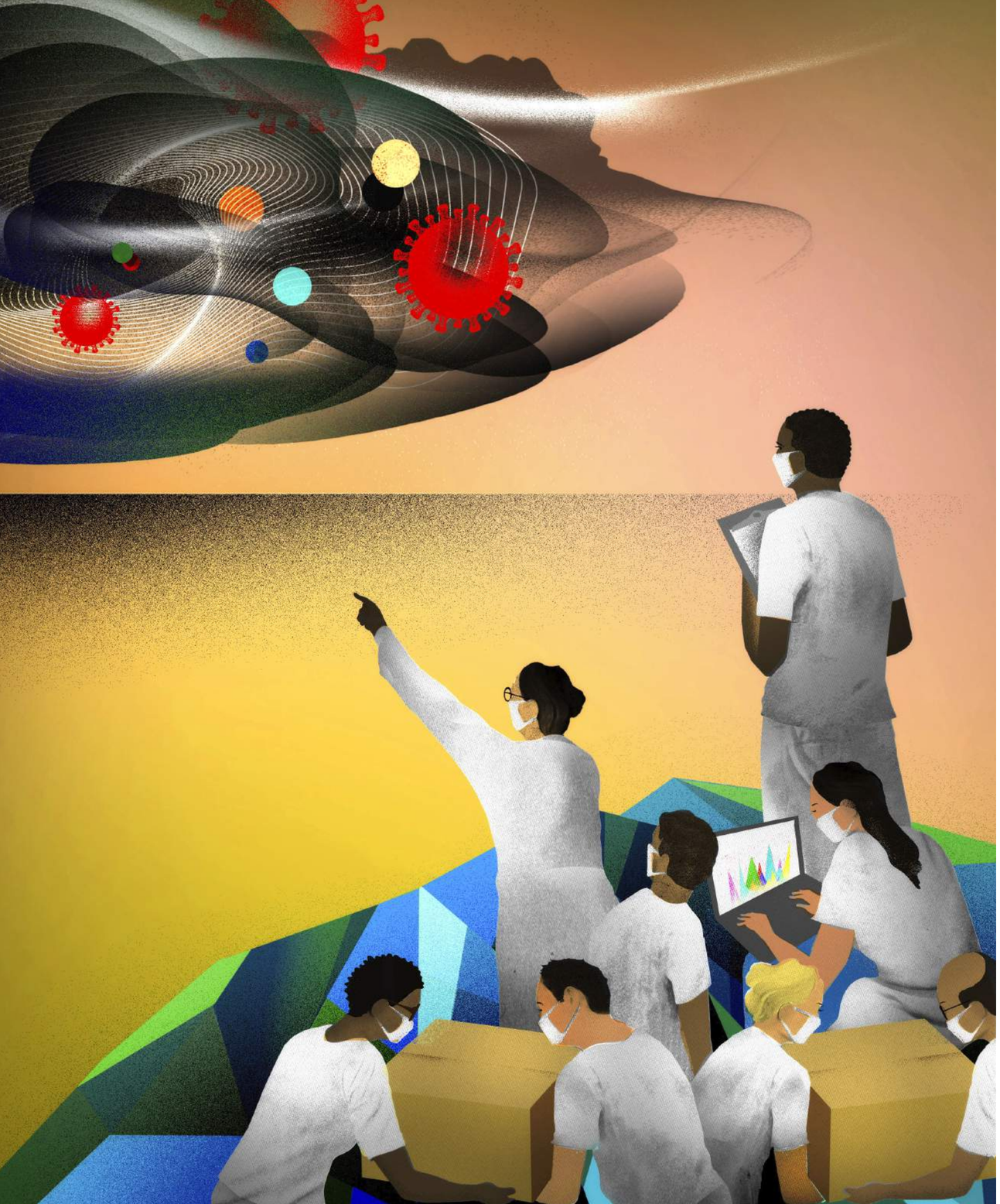


BRIAN STAUFFER

CHAPTER 1

IN THE PATH OF THE PANDEMIC

A novel coronavirus would come to affect every ward, clinician, researcher and patient at Massachusetts General Hospital.

After nearly a year living under a pandemic which has come to color every aspect of daily life, it's easy to forget that the whole thing arose rather quietly. In early January, news broke of an outbreak of pneumonia in Wuhan, China, and began to trickle out to an international audience. On January 11, Chinese authorities announced that a 61-year-old was the first person to die in the outbreak, which had been raging for at least a month. On the same day, Chinese researchers released a draft genome sequence of the pathogen they believed was causing those illnesses—a new coronavirus. By January 20, health authorities had determined it could pass from person to person and, like other coronaviruses, probably had been transmitted to a human by an animal. That same day, the Centers for Disease Control and Prevention confirmed the first known U.S. case, a resident of Washington state.

In Boston, physicians and other health care workers at Massachusetts General Hospital listened closely to every dispatch. Responding to a pandemic is a scenario hospitals both dread and are built for. MGH, with its 209-year history, had encountered them more than once, although the staff had no living memory of the local outbreak of smallpox in 1851 or the 1918 global flu pandemic. The hospital did, however, regularly conduct drills to prepare for mass disasters and emergencies—not only contagious diseases but also active shooters, bioterrorism events, train wrecks, chemical spills and hurricanes. The hours of preparation had served them well whenever patients flooded in, as they did after the Boston Marathon bombing of 2013, a grisly event in the hospital's history but one in which not a single admitted patient was lost.

Most hospitals drill for extreme scenarios in some way. But unlike most others, MGH had also been training for the previous five years to treat the world's most dangerous infectious diseases. Following the 2014 outbreak of the

BY TIM GOWER, LINDA KESLAR AND ANITA SLOMSKI

Ebola virus in West Africa, the U.S. government designated MGH as one of 10 regional Ebola and other special pathogen treatment centers. This meant the hospital had to piece together protocols for the isolation, evaluation and management of patients with rare and deadly infectious diseases and also develop a special pathogens unit. The latter would include, among other tools, negative-pressure rooms to contain potentially airborne infectious agents, specialized personal protective equipment (PPE) and a dedicated team, says Erica Shenoy, medical director of the MGH regional treatment unit and associate chief of the hospital's Infection Control Unit. In 2019, the hospital evaluated five suspected cases of Middle East respiratory syndrome (MERS). While this deadly coronovirus was ruled out in all five patients, no one suspected that it might be a dress rehearsal for the coming year.

Megan Macduff, Respiratory Therapist

We were facing so much uncertainty. Were we going to have enough PPE? Enough ventilators? What gave me courage were the staff relationships that had built up through the years. Every nurse, therapist, physician, radiologist, cleaning staff member—I knew where they stood. It was a camaraderie that got us through. Because what we were facing, we were facing together.

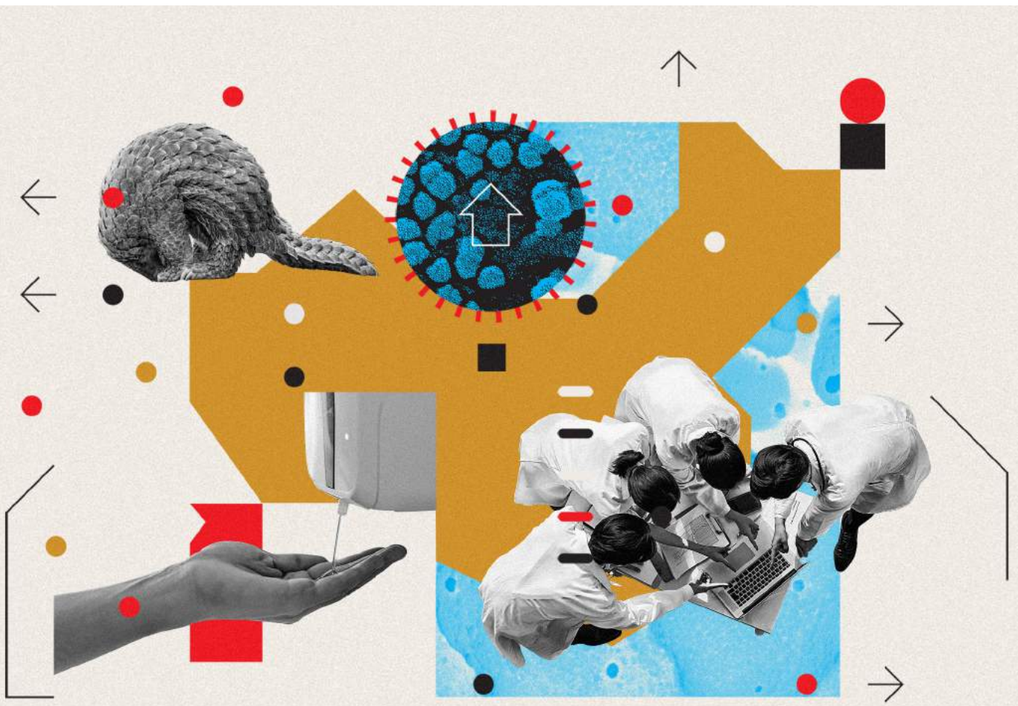
Well before the pathogens unit would be needed, however, other teams were springing into action. When the genome of the new virus was made public, Boston-area researchers at Beth Israel Deaconess Medical Center, the Ragon Institute of MGH, MIT and Harvard, Massachusetts Eye and Ear and MGH began creating candidates for vaccines. Other researchers and scientists at MGH sorted through the literature to come up with possible treatments, while those who worked in community health asked questions about how a coronavirus pandemic might affect the Boston area and began laying the groundwork for a local response.

All of these efforts came as a community of 27,000 employees began to imagine worst-case outcomes and how they might bring their own expertise to bear. On January 27, the hospital made the call to activate its Hospital Incident Command System (HICS)—an organizational streamlining, mirroring a strategy used by public safety agencies in times of crisis. It brought coordination and a military-style precision to decisions that would ultimately upend every aspect of the hospital's normal operations.

"At the start, we didn't have enough information," says Ann Prestipino, the HICS incident commander and an MGH senior vice president. Prestipino has spent her entire career at MGH, and previously was incident commander not only for the 2013 marathon bombing but also for the 2003 Station nightclub fire in West Warwick, R.I., which killed 100 people and injured more than 200, many of whom were rushed to MGH. This time, she says, "We were in active communication with colleagues around the world. We tried to learn as much as we could about how to keep our staff safe and to effectively take care of the wave of infected patients, who we knew were on the way." Data and guidance did begin to flood in from federal and state health departments, but recommendations changed constantly, forcing HICS leaders to convene again and again—in the stately conference room that serves as the HICS command center during disasters—to revise their plans. "Key decisions had a shelf life of less than a week," says Inga T. Lennes, senior vice president of Practice Improvement and Patient Experience at MGH.

During these early days, Katrina Armstrong, chair of the Department of Medicine and physician-in-chief at MGH, remembers sharing information in round-the-clock emails with her colleagues. One email stands out, a message from Bruce Walker, director of the Ragon Institute, who shared some of the frightening information coming from northern Italy. Walker was also talking with other Boston-area experts, including Harvard Medical School Dean George Daley, about how to jump-start collaboration across the local medical community, which included some of the most prominent research and biotech organizations in the world. He and an impressive cohort of health care leaders signed a letter to *The Boston Globe* on March 5, 2020, that stated: "No single institution is going to solve this problem."

They had just called a meeting at Harvard Medical School to launch what would soon



ISRAEL VARGAS; PHOTOS FROM MGH PHOTOGRAPHY AND GETTY IMAGES

COURTESY OF MGH ARCHIVES

200 Years of Preparation

Since its founding in 1811, MGH has both faced pandemics and learned from them.

1833 Isolation Wards

One of the greatest global outbreaks of cholera starts in 1831, and by 1833 it has spread to Quebec, Nova Scotia and New York. MGH doctors propose special wards to isolate patients with this and other contagious diseases. By 1849, construction begins on a standalone building—"The Brick."

1851 Vaccination of the Vulnerable

Boston sees an outbreak of smallpox. A vaccine has been available for more than 50 years, but despite compulsory vaccination in Massachusetts, many haven't received it. The trustees of the hospital vote that year that whenever a case occurs in the hospital, all patients should receive a fresh vaccination.

1918 A Disease Census

Accurate numbers of Spanish flu victims are critical for planning, especially on the war front in Europe. At Base Hospital No. 6, a hospital run by MGH in France, the staff epidemiologist takes a survey of troops in the area and produces daily reports on the presence of disease. This innovation gives commanders critical information that helps blunt outbreaks.

1961 The Respiratory Intensive Care Unit

During the polio outbreak of 1952 to 1955, MGH takes the unprecedented step of devoting an entire floor—the ninth floor of the White Building—to the disease. One of its hallmarks is the weakening of chest muscles, and many patients require an iron lung to breathe. Soon after, MGH creates the first unit dedicated to respiratory intensive care in the United States.

2015 Prepared for the Worst

The 2014 Ebola outbreak sees more than 11,000 deaths in Africa and a few cases make it to the United States. This highly infectious, deadly pathogen calls for a national response. MGH is designated one of only 10 regional emerging and special pathogens treatment centers in the United States, which entails a trained staff and a network of transmission protections.

be named the Massachusetts Consortium on Pathogen Readiness—Mass-CPR—made up of representatives from leading universities, academic hospitals, biotechnology and pharmaceutical firms, research institutes, foundations and the Massachusetts Department of Public Health. This decision to work together formally was perhaps the most telling sign that the new virus would leave a lasting mark on the medical community. Consortium members, including medical titans that were normally rivals for patents and discoveries, agreed to share their data and research on diagnostic tools, treatments and vaccines. That kind of precedent-shattering cooperation would be essential in fighting the new disease that the World Health Organization had named COVID-19.

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By the time of that March meeting, the virus was already roaring across Europe and overwhelming many hospitals, which found themselves desperately short of beds, ventilators and workers. At MGH, Peter Dunn, vice president of Perioperative Services and Healthcare Systems Engineering (HSE), was tasked with helping the hospital avoid the same fate. The first order of business was to estimate how many patients with COVID-19 might arrive at MGH, and when. At the pandemic's peak, what resources would be needed for general care and how many people would land in the ICU? How many ventilators would be enough?

The HSE team includes not only doctors but also mathematicians, who use advanced systems modeling to calculate better health care delivery. In less harried times, their focus had been to create more efficient flows of patients into and out of the hospital, as when the team applied machine learning techniques to assign scores to patients after surgery, helping predict when they would be ready to go home. This model, published in *JAMA Network* last year, could speed up discharges and free beds for new patients.

The forecasting tools they needed now, however, would have to apply to a wholly new contagion about which very little was known. They found one source of data in Italian hospitals, which had been devastated by COVID-19 in February and early March. "This provided enough data to give us a head start on planning new surge units," says Kyan Safavi, medical director of HSE and a critical care physician.

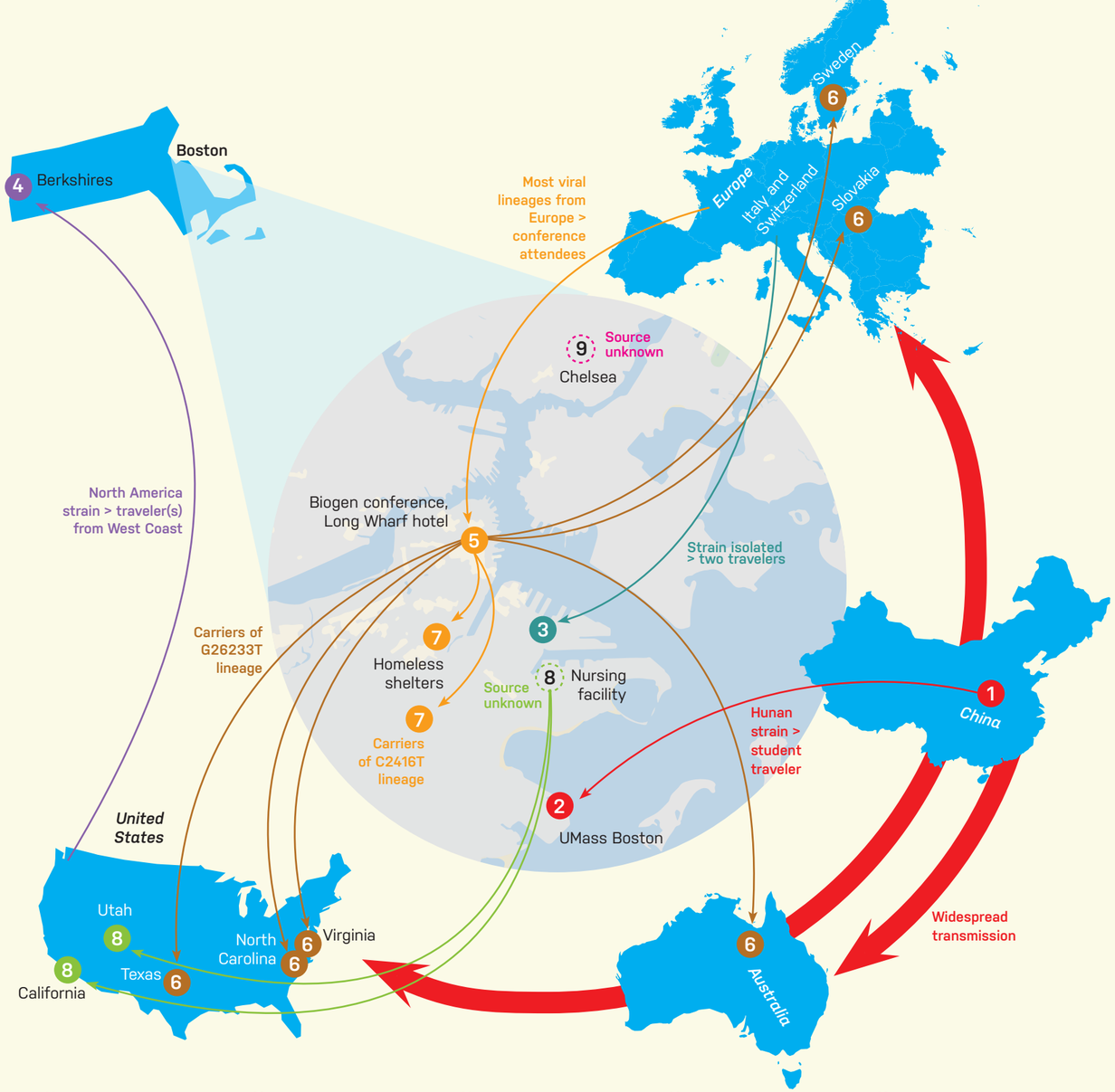
The bigger challenge was to determine when MGH and other hospitals in its network might hit their peak volume of COVID-19 patients—a number that would give them the upper target for beds and other resources. Safavi, Dunn and the rest of the HSE team adapted an epidemiologic model and applied different estimates for the virus's behavior and infection rate as well as the proportion of infected people who might need to be hospitalized. They also calculated how many COVID-19 patients might need treatment in the ICU and how long they would need to stay, all based on ever-changing information that became available to them.

In their worst-case scenario, the Mass General Brigham hospital system—of which MGH is a part—looked like it could need 1,000 ICU beds for COVID-19 patients and an additional 1,500 general-care beds. "These estimates set a planning exercise in motion to ensure that all hospitals were prepared for the capacity, providers, nurses and other resources they might need," Safavi says.

The incident command team saw that much of the hospital would have to be transformed on the fly. "Before COVID, I would have said you were out of your mind for even imagining that we could create 100 ICU beds in three weeks," says Kathryn Hibbert, director of the Medical Intensive Care Unit. Yet, through what Hibbert describes as an "incredible, herculean team effort by infection

How Did COVID-19 Get Here?

Massachusetts' first known case of SARS-CoV-2 arrived on January 29. The patient was a university student who had been traveling in Wuhan, China, and was quickly quarantined at home. Despite early vigilance, the disease had started to spread widely in the state by early March. In collaboration with the Broad Institute and the Massachusetts Department of Public Health, Jacob Lemieux, an infectious disease fellow at Massachusetts General Hospital, led a team of dozens of researchers trying to pin down the precise origin and spread of the virus. They performed whole genome sequencing of 772 virus samples from the Boston area, including nearly all cases confirmed during the first week of the epidemic. The data revealed more than 80 introductions into the Boston area, including events that spread the disease far and wide.



1
CHINA
November 2019
Infections first emerged in the Hubei province of China. SARS-CoV-2 was first identified in the context of a super-spreading event in the Huanan Seafood Market in the city of Wuhan.

2
ARRIVAL IN BOSTON
Jan. 29, 2020
A UMass student returned from his home in Wuhan, China, with the virus. No other infections resulted. Officials retraced the student's steps and disinfected every railing and doorknob he may have touched.

3
SECOND CASE
March 2, 2020
A recent traveler to Italy and Switzerland carried the virus, and a fellow passenger was the third case, but these strains were also successfully isolated.

4
OUTBREAK IN THE BERKSHIRES
March 3, 2020
Cases began to arrive at the Berkshire Medical Center, and soon totaled more than 500. Many had attended the same sporting event. The source was most likely a strain spreading along the West Coast of North America—a sign of widespread and uncontrolled transmission.

5
BIOGEN LEADERSHIP CONFERENCE
Feb. 26 to 28, 2020
An international business conference gathered 175 executives in Boston. The infection most likely came from Europe. By March 11, 77 of the 96 cases in the state were tied to the Biogen conference—the state's first super-spreading event.

6
GLOBAL SPREAD
March 2020
Two strains at the Biogen conference spread widely: G26233T and C2416T. G26233T was exported to several states as well as Australia, Sweden and Slovakia. C2416T has traveled internationally and accounted for 2.7% of U.S. sequenced lineages through May.

7
BOSTON HOMELESS SHELTERS
April 2020
Cases were detected at two Boston homeless shelters, Pine Street Inn and Southampton Street Shelter. Of 193 SARS-CoV-2 genomes, 105 were of lineages associated with the Biogen conference.

8
SKILLED NURSING FACILITY
April 2020
The virus was found in 85% of residents and 37% of staff at one institution. Most cases came from a single, recent source, though the history of that source remains unknown. Viruses were then exported to Utah and California.

9
CHELSEA
April 2020
By the second week of April, SARS-CoV-2 was disproportionately hitting dense, low-income areas. Chelsea become the local epicenter by April 9, with an infection rate almost four times that of the statewide average. The source of most infections is unknown.

MSJONESNYC

control, nursing, respiratory therapy, materials management and physicians working around the clock," MGH nearly doubled the hospital's existing 133 intensive care beds. Pediatric, burn and neurosurgery ICUs were commandeered for the COVID-19 effort, with some of the patients who would ordinarily be cared for in those units diverted to other hospitals. New ICUs were created in post-operative recovery rooms that were no longer needed for patients after elective surgeries, which had been canceled.

To staff these new units, the hospital recruited any physician with critical care experience. But one of the most pressing needs was for nurses. Associate chief nurse Theresa Gallivan estimated that an additional 600 full-time critical care nurses would be required to meet the increased demand for ICU beds. To get there, a partnership model was employed and supported by nurses throughout the hospital to spread current critical care nurses across all of the ICU units and reassign general care nurses to work alongside them. The hospital also brought in as many travel nurses as it could. "This crisis partnership model, while challenging for all involved, enabled us to care for the high number of critically ill patients," Gallivan says.

The new ICUs would be called into service on a just-in-time basis. "We didn't want to waste resources by opening them too soon," Dunn says. As COVID-19 cases rose, patients were admitted to the first additional ICU on March 14, with the other new facilities coming online as the patient count rose.

> **Addressing the coming shortages of personal protective equipment became a national riddle without good answers.**

With a pandemic looming, the problem of reducing infection risk for hospital workers was on everyone's mind—and addressing the coming shortages of personal protective equipment became a national riddle without good answers. "We were hearing about how deadly the virus was for health care workers, but we really didn't know the best approach for protecting them," Armstrong says.

It quickly became clear that one recommended measure—N95 respirators, face masks that filter out at least 95% of airborne particles—would be crucial. In mid-February, the hospital calculated that its cache of N95 masks and other PPE, meant to last two weeks, might be depleted even more quickly than that. New shipments from China, the main supplier of PPE, had slowed to a trickle, and 3M had stopped consistently shipping the hospital's regular order of masks.

N95 respirators have to seal precisely, and clinicians undergo an elaborate fit test each year. By February's end, however, the N95 inventory at MGH was depleted, and small sizes were becoming an acute supply issue. The hospital was able, with the help of other hospitals within Mass General Brigham, to procure additional N95s, but the newer models would require another 5,000 fit tests. More N95s would be needed as patient numbers went up.

BOSTON GLOBE/GETTY IMAGES

Rehabilitating Masks
The team at MGH found a novel way to decontaminate the N95 respirators that were in short supply. This allowed thousands more to be in circulation.

Finding more N95s fell to Ed Raeke, director of Materials Management at MGH, whose job is to see that supplies arrive at the right time and place. As shortages mounted, Raeke fielded hundreds of offers of N95s—mostly by email—from people who claimed to have a connection in China or to know someone who had access to the masks. When a legitimate offer could be locked down, the hospital might have to pay $4 to $8 a mask, compared with less than $1 pre-pandemic. Without a steady and reliable new source, the hospital would need to find a way to reuse the masks it had. The question was how to do this safely.

Scientists in the lab of Orhun Muratoglu, director of the Harris Orthopaedics Laboratory and the Technology Implementation Research Center at MGH, pivoted their research from developing hip joint implants to decontaminating used N95 respirators. That wasn't a huge leap, curiously, because it was related to a problem that Muratoglu encountered regularly. "There are many ways to sterilize an implant, and we threw all of them at the N95 masks," he says.

The first few approaches—discussed on daily Zoom calls with more than 100 participants around the world—degraded the fit of the respirator or deactivated the protective electrostatic charge on the mask filter. But Muratoglu's group soon hit on decontaminating the masks with hydrogen peroxide vapor. That met all of the criteria for preserving the integrity of the masks and killing the virus.

Successfully decontaminating one mask in the lab, however, was a far cry from decontaminating the thousands used every day. In mid-March, the researchers found a defense contractor, Battelle, that had developed a hydrogen peroxide vapor system as part of its bioterrorism research, and Massachusetts state officials chose the company as the vendor for a decontamination facility that was set up in a former Kmart. Starting on April 7, 50 people there would sort, label, package and deliver thousands of decontaminated N95 respirators daily, making sure that individual clinicians received their original masks back. "N95 decontamination was a game-changer," Raeke says.

That left the problem of a ventilator shortage. In severe cases, COVID-19 causes the air sacs in the lungs to fill with fluid, leaving patients gasping for air. Mechanical ventilation, in which a tube is inserted through the nose or mouth to push air into the lungs, may prevent further damage and restore oxygen to organs and tissues. But looking at the case projections in early February, it wasn't clear there would be enough ventilators to go around.

All told, the hospital had 150 ventilators. Robert Kacmarek, director of respiratory care, was ultimately able to buy, rent or borrow an additional 100, which would prove to be more than enough to provide care for the peak number of patients on ventilators—188, on April 19. But there was one complication. The ventilators that Kacmarek added for the surge weren't wired to the hospital's central monitoring system, which sounds an alarm if a ventilator malfunctions or a patient needs help. The solution was decidedly low-tech. More than 100 MGH employees, mostly researchers whose labs were closed during the pandemic, took shifts outside patients' rooms. They sat and listened, around the clock, for any problems the machines might encounter.

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Even as MGH raced to prepare for a flood of infected patients, hundreds of people at the hospital threw themselves into a different kind of effort. The Massachusetts General Research Institute (MGRI) is the country's largest research enterprise based at a hospital, and it normally oversees more than 1,900 simultaneous clinical trials, often collaborating with U.S. agencies, other research institutions and pharmaceutical companies. Now MGRI shifted its mammoth resources to investigate potential COVID-19 vaccines and therapies. "Research is in the DNA of what we do, and especially in a crisis like this, we

REMIE GEOFFROI

100,000 Animals

While most research slowed or stopped, someone had to care for the animals that made it possible.

Massachusetts General Hospital has more research going on under its roof than any other hospital. That means animals, and many of them. As the pandemic shut down most research operations, the question arose: How do you care for the more than 100,000 rabbits, pigs, primates, sheep, frogs, zebrafish and (many, many) rodents used in nonclinical and preclinical research?

The Massachusetts General Research Institute put its emergency response plan into action, activating a team of 100 "nurses"—trained technicians, seven veterinarians and two veterinary residents who rotated as animal care teams in 24/7 shifts across three campuses. They provided water and food, cleaned cages and monitored the well-being of their "patients" and their anxious human "guardians," who virtually interacted with care teams for real-time updates. Though wearing PPE is part of the job, the care teams took extra precautions in labs to limit any possibility of the COVID-19 infection passing among humans or between humans and animals. While most labs are now up and running, such safety measures continue as researchers and their animals get back to work.

knew we had to generate knowledge," says Paul Biddinger, director of MGH's Center for Disaster Medicine and chief of the MGH Division of Emergency Preparedness.

Researchers at the Ragon Institute were among the first to sound the alarm about the seriousness of what was to come. When the draft genome of the virus was released in early January, they noticed similarities to the genetic makeup of past coronaviruses as well as peculiar, worrying features. "It had the hallmarks of a virus that could spread substantially," says Dan Barouch, a group leader at the Ragon and director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center.

By Monday, January 13, after a frenzied weekend analyzing the genome, Barouch and his team had designed several prototypes for a human vaccine. They planned to test two delivery mechanisms. One would use DNA molecules to ferry in genetic materials to host cells; the other would use a deactivated common cold virus known as Ad26—adenovirus serotype 26. Either way, the genetic instructions from the vaccines would prompt the recipient's cells to start producing the virus's distinctive spike protein. This in turn would stimulate an immune response from the body, training it to make antibodies that could prevent further infection. Barouch had used the Ad26 virus approach in an experimental HIV vaccine and an experimental Zika vaccine, both of which are in human trials.

Researchers at the Ragon Institute were among the first to sound the alarm.

Animal studies in mice and monkeys began less than a month later. In a proof of concept study, monkeys were infected with COVID-19, then exposed to the virus a second time to see whether it was at all possible to generate a protective immune response against this virus. One reason it has been almost impossible to develop an HIV vaccine is that the virus doesn't generate what is known as natural protective immunity—the human body, exposed to HIV or to some form of the virus in a vaccine, doesn't develop antibodies that could fight off infection. Some scientists feared that COVID-19 might fall into the same category—"and if there was no sign of natural protective immunity, it was unlikely any vaccine would succeed," Barouch says.

Working at home on an early April afternoon, he received an email with the first study results—which showed that monkeys exposed to the new vaccines did indeed develop natural protective immunity. "I was very nervous before I opened the attached file because I knew the numbers from our studies would have profound implications not just on our vaccine, but also on all vaccine efforts globally," Barouch says. In May, the team released findings in two published studies, confirming that several versions of the prototype vaccine produced antibody responses in the test animals, preventing infection.

Meanwhile another team had also begun studying the COVID-19 genome that was posted online. Luk Vandenberghe, director of the Grousbeck Gene Therapy Center at Massachusetts Eye and Ear, and Wenlong Dai, a postdoctoral research fellow in Vandenberghe's lab, had come up with their own vaccine candidates within a few days.

Central to their model is another kind of well-established vector. The adeno-associated virus, or AAV, is commonly found in humans, doesn't cause disease and has been used successfully in experimental gene therapies, including in two drugs now approved by the Food and Drug Administration to treat rare diseases. In those therapies, AAV is efficient at transporting genetic material into cells, which could be an advantage in developing a vaccine that would operate in similar ways.

In this case, however, Vandenberghe was looking at a slightly different

ISRAEL VARGAS; PHOTOS FROM MGH PHOTOGRAPHY

REMIE GEOFFROI

Your New Job Is ...

The new normal meant new tasks to be done. Those jobs were often filled by very unconventional candidates.

Many of the core functions of the hospital shifted dramatically or went away during the first surge. Research and elective operations, for instance, were largely paused. But the pandemic response also came with fresh needs, and hundreds of existing MGH staff members did what they could to fill the gaps.

Many scheduled procedures were put on hold, so **Mitchel Harris, chief of Orthopaedic Surgery**, helped out where he could. At least once he took on the role of a medical scribe—the person who keys information into the computer so the primary providers can have their hands free. His two-fingered approach got the job done until more experienced typists could arrive.

Normally **Tatiana Sultzbach, director of International Services**, helps to coordinate foreign patients. But during the surge, she headed up an effort to cold-call 6,000 residents of Chelsea, a hard-hit city near Boston, to see whether they had COVID-19 symptoms. Callers also asked about supplies of food and masks, connecting households to local resources where they could.

The Gordon Center generally makes highly sophisticated radiopharmaceuticals for medical imaging. But when hand sanitizer became hard to find, **Georges El Fakhri, the center's director**, shifted its production. In two months the center made 800 liters of the stuff, which was distributed in thousands of plastic pump bottles purchased from a beauty supply company.

Many ventilators were new to the hospital. The alarms weren't connected to the central monitoring system. So **Pamela Parker, an MGH surgical technologist at North Shore Medical Center**, came to the main campus to serve as a "vent listener"—one of a dedicated corps of volunteers who sat near intubated patients for hours, on high alert for sounds of trouble.

AAV—AAVrh32.33, a hybrid combining two AAVs found in monkeys. He had created it 15 years earlier, as a graduate student in a lab led by James Wilson, director of the Gene Therapy Program at the University of Pennsylvania's Perelman School of Medicine, and it had shown early promise in HIV vaccines before ultimately being shelved. Now Vandenberghe wondered whether the rh32.33 hybrid might be a particularly effective delivery vehicle for fragments of the spike protein of COVID-19. Wilson endorsed the idea and eventually signed on as a collaborator, and by the end of February, 18 scientists in Vandenberghe's lab were working on the vaccine project full time.

The Biogen conference was one of the country's first major super-spreader events.

In early March, Vandenberghe began sharing data about the vaccine with Mason Freeman, director of MGH's Translational Research Center. Freeman and his Center had previously participated in AAV gene therapy studies and he was familiar with aspects of Vandenberghe's research. "I had never thought about AAV and vaccines," Freeman says. "But based on how well AAV works in gene therapies, this seemed like a really exciting, unique approach."

Freeman has led efforts to design clinical studies for AAVCOVID, the experimental vaccine, and in preclinical testing of two variations, it produced a robust immune response in mice and monkeys. Human trials are likely to follow, although first the FDA has to approve use of rh32.33, the engineered hybrid AAV vector, which doesn't occur naturally and hasn't yet been shown to be safe in humans. But if trials proceed and are successful, this vaccine might have an advantage over the dozens of others now under development. Only a miniscule amount would be needed for each dose, and one production run produces a million doses. "There are dozens of vaccines moving forward, but this one is eminently doable," Vandenberghe says.

ISRAEL VARGAS; PHOTOS FROM GETTY IMAGES

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On February 26, the biotech company Biogen welcomed about 175 executives from around the world to the Marriott Long Wharf hotel in Boston for a two-day conference. One week later, Biogen reported that two attendees who had flown home to Europe had tested positive for COVID-19—and on the same day, March 4, several local Biogen employees who had also attended the conference showed up at the MGH Emergency Department, asking to be tested for the virus.

The Biogen conference would later be recognized as one of the first major "super-spreader" events in the United States, responsible for many of the COVID-19 infections treated at MGH. But tracking down which attendees might be infected required testing for the virus, which in early March was available only through the state public health laboratory. MGH had to ask the Massachusetts Department of Public Health for permission to perform any COVID-19 test—and based on the CDC criteria at the time, only three of the five employees qualified for testing. Two days later, MGH had the results—all three Biogen employees had COVID-19. Later that morning, Erica Shenoy of the MGH Infection Control Unit had a conference call with the Department of Public Health, counterparts at Brigham and Women's Hospital and Biogen's medical director. It was agreed that the two hospitals would test Biogen conference attendees identified by the company as well as symptomatic household members—a total of approximately 270 people.

That night—two days ahead of its planned opening date—MGH launched a testing site it had constructed in an indoor ambulance bay adjacent to the ED. Although the space, which normally accommodates seven ambulances, couldn't be heated or cooled, it was spacious. Over the next three weeks, 2,667 people with COVID-19 symptoms were tested for the virus in the ambulance bay. "In March, we had no way of knowing that people without symptoms could be infected—the Department of Public Health had no capacity to test asymptomatic people," says David Hooper, chief of the MGH Infection Control Unit and associate chief of the Division of Infectious Diseases.

Dean Xerras, Medical Director, MGH Chelsea HealthCare Center

When Chelsea rose to the forefront of COVID cases, we asked: What is it about this city? There is something different going on here. Is it language? Is it poverty? Is it because so many essential workers live here and take public transportation to their jobs, where they're restocking shelves in grocery stores and facing more exposure to the virus? It turned out to be all of those things.

The shortage of testing was the most dangerous blind spot in tracking the early spread of the pandemic. "Even getting approval to test patients with clear symptoms had become extremely challenging, because the case definition that dictated whether or not testing was permitted was so restrictive," Shenoy says. So researchers at MGH became focused on inventing their own version of the test. The MGH pathology department's microbiology lab and the Center for Integrated Diagnostics set about creating an assay that could separate the infected from the uninfected.

Any test would have to use CDC protocols governing testing chemicals and equipment, which led to a scramble to assemble the needed components. And the testing platform also had to match CDC targets for its ability to detect minimal amounts of COVID-19. The team tested its first assays against swab samples from Biogen employees who had tested positive for COVID-19. Then it used the test to analyze biosamples from former patients who had been hospitalized for respiratory problems before the pandemic. "We needed to be 100% sure our test was specifically detecting SARS-CoV-2 and not other common cold viruses," says Jochen Lennerz, medical director of the MGH Center for Integrated Diagnostics.

In early March, just one week after work on the test began, it went live, and MGH became one of the first academic medical centers to gain FDA emergency use authorization for COVID-19 testing in the Boston area. The platform soon ramped up from 30 specimens a day to 150. It was another hurdle cleared, and with the testing, ventilator, mask and ICU conundrums on their way to solutions, the hospital was as prepared as it could be for the onslaught of COVID-19 patients to arrive. They were not long in coming.

DOSSIER

"Assessment of Community-Level Disparities in Coronavirus Disease 2019 (COVID-19) Infections and Deaths in Large US Metropolitan Areas," by Samrachana Adhikari et al., *JAMA Network Open*, July 2020. Poor and marginalized communities faced the worst of the early pandemic, according to the research letter.

"The Association Between Symptoms and COVID-19 Test Results among Healthcare Workers," by Chana Sacks et al., *Annals of Surgery*, Sept. 15, 2020. The study outlines how hospitals can keep workers safe with PPE and testing protocols.

MassGeneral.org/news/coronavirus/research. The page hosts the latest in diagnostics, treatments, trials and disease biology from researchers at the hospital.

BRIAN STAUFFER

CHAPTER 2

THE VIRTUES OF NECESSITY

As the first COVID-19 patients arrived, pressure mounted to discover how the disease worked and how it could be beaten back.

After the first COVID-19 cases from the Biogen conference arrived in the MGH Emergency Department, normal operations quickly came to a halt. Hundreds of infected patients soon flooded in, many struggling to catch their next breath. "We were seeing a relentless tide of critically ill COVID patients in respiratory failure," says David Brown, chair of the Department of Emergency Medicine. Where the ED might normally see two patients a day with lungs deteriorated enough to require a ventilator, physicians there were soon using the machines on some 20 patients a day.

Brown and the 480 clinicians in his department were the first to encounter this surge, and even as they sought to help frightened people suffering from a poorly understood new disease, Brown and his team also had to consider their own safety. "At the start, we weren't sure how transmissible COVID was, how dangerous it was to providers or whether our PPE would work," he says. "We're all used to taking care of horrendous injuries and devastating illnesses in emergency medicine. But that care doesn't normally endanger ourselves or our families."

Brown assumed he would soon be infected, and to avoid passing along the virus to his wife and adult children, one of whom was pregnant, he moved out of his home and into an apartment near the hospital. There he roused himself every day at 2 a.m., logged into the hospital system to see how many patients were in the ED and then called colleagues on the floor to find out how they were faring. At 5 a.m., he would check in again before heading to the hospital. His usual team had been swelled by orthopedists and other surgeons who, when elective procedures were sidelined by the crisis, had eagerly stepped forward to help.

In the ED, physicians barely had time to issue medical orders for one patient before moving on to the next. But Brown made time to visit the ICUs and COVID-only floors to look in on patients. "My department saw only acutely ill patients gasping for air," he says. "It was really important for staff morale to know that the vast majority of COVID patients at the hospital got better and went home."

Worse outcomes—protracted illness and death—were also in the cards, and preparing for those meant developing a deployment strategy for a team of palliative care physicians, whose goal was to understand a patient's suffering

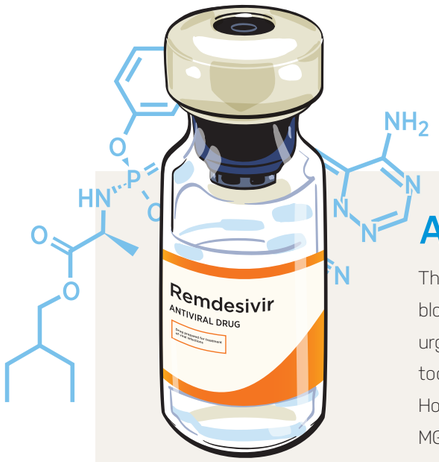
and reduce it if they could. “We were there to get to know them and understand their goals, to hold and support them and to be a conduit to families,” says Vicki Jackson, chief of Palliative Care and Geriatrics. One frequent task involved explaining to elderly patients what they could expect if they were intubated and admitted to the ICU—a job made especially challenging when dementia was involved. “They were confused, fearful and couldn’t be with someone they knew,” Jackson says. “It was so important for families to see that we were taking time to get to know their loved ones as we made our recommendations.”

As infections in the Boston area multiplied, Inga T. Lennes, senior vice president of Practice Improvement and Patience Experience, oversaw the opening of three additional COVID-19 testing sites. At one, in the hospital’s sports medicine clinic two blocks away, an ambulance stood ready to take people to the ED. “Within hours of being referred for testing by their doctors, some patients’ conditions had rapidly deteriorated and we needed to get them in quickly,” Lennes says. “We used that ambulance every day.”

Meanwhile, a new kind of treatment area—a respiratory illness clinic, or RIC—was created. RICs serve as an intermediate step between testing and possible hospitalization. At the MGH testing sites, some patients with COVID-19 symptoms who were considered at high risk of getting very sick were sent immediately to one of the new RICs. There, doctors performed chest radiographs and checked oxygen saturation levels to gauge whether infections were progressing dangerously. Patients then might be directed to the ED or sent home to recover. By mid-April, clinicians in the RICs, which freed ED staff to concentrate on caring for those who were already critically ill, were examining about 320 patients a day.

On April 5, the hospital had 201 COVID-19-positive patients, 82 of whom were in the ICUs. Infected patients ultimately filled 12 floors of the hospital, and the hospitalists—specialists who attend to hospitalized patients—and medical residents were stretched thin trying to take care of so many seriously ill people. So doctors from other specialties pitched in, and on COVID floors, a patient might be attended by a radiologist, a neurologist, a gastroenterologist, a general internist or a pediatrician. “At the peak, we had 30 teams taking care of COVID patients and only one-third of those were hospitalists and residents,” says Amber Moore, a hospitalist who led the deployment of physicians for COVID-19 patients. It was just one more example of the “all hands on deck” ethos that now prevailed throughout the hospital.

On April 5, the hospital had 201 COVID-19-positive patients, 82 of whom were in the intensive care units.



REMIE GEOFFROI

A Hope Emerges

The push to test remdesivir—a drug that blocks viral replication—was one of the first urgent clinical priorities of the pandemic. Trials took place across 50 sites, and Elizabeth Hohmann, the trial's principal investigator at MGH, says that "there were as many as 140 people on the weekly conference calls among sites." The drug's apparent success in April was followed by mixed news in October: preliminary findings from a large international study that suggested minimal benefits of the drug; and the full approval of remdesivir by the FDA.

Though much of MGH was transformed to respond to the crisis, there was no guarantee that the pandemic wouldn’t overwhelm every hospital in the Boston area. On March 31, retired Brigadier General John “Jack” Hammond got an urgent phone call from Massachusetts Gov. Charlie Baker asking whether he would oversee construction and management of a field hospital—1,000 new beds inside the Boston Convention and Exhibition Center equipped to host an overflow of post-acute COVID-19 patients. And also … could he get it built in a week?

Hammond is director of Home Base, a program run by the Red Sox Foundation and MGH for war veterans with mental health conditions and brain injuries. During his decades in the military, he led expeditionary missions in Afghanistan, Iraq and the United States. But this felt even more daunting. “In the Army, I learned that you can do pretty much anything as long as you have the right people and the right stuff,” Hammond says. “In the beginning, we didn’t have any people or any stuff.”

The field hospital, to be called Boston Hope, would be reserved for patients who no longer needed acute care but who were too sick to go home or were still infectious. Boston Hope would also provide treatment for members of the city’s homeless population who tested positive for the coronavirus.

Hammond quickly assembled a leadership team, which included Michael Allard, chief operating officer for Home Base, Jeanette Ives Erickson, chief nurse emerita at MGH, who agreed to co-direct clinical care and operations, and Giles Boland, president of the Brigham and Women’s Physician’s Organization. On April 1, the new team met with Hammond at the 516,000-square-foot convention center. Soon, construction crews were working around the clock, and in less than a week they had built and equipped all 1,000 patient rooms, including a six-bed rapid response unit for those whose conditions unexpectedly worsened. “Our goal was to deliver post-acute care, but when these patients crash, they crash quickly,” Hammond says.

Clinicians from Mass General Brigham—a health system that includes MGH, Brigham and Women’s and other area hospitals—volunteered to work shifts at the new facility, and many others came from the large pool of doctors, nurses and other health workers who had been furloughed from local hospitals and clinics during the pandemic. The U.S. Army Reserve sent an 80-person team to pitch in. More than 1,000 people ultimately worked shifts at Boston Hope, and they treated more than 700 patients during the nearly two months it was in operation.

Wherever COVID-19 spread, physicians and nurses labored at a constant disadvantage, handicapped by a lack of knowledge about the new virus and what therapies might be effective against it. Those became the most pressing scientific questions of the decade, and to fill that knowledge gap, hundreds of COVID-19 research trials were launched around the world. The Mass General

MGH PHOTOGRAPHY

The Hexapod Booth

A crisis in testing logistics leads to a breakthrough device.

Health care workers are problem solvers by nature, says internist and pediatrician Kristian Olson. "People who don't think of themselves as innovators have come up with remarkable solutions using totally unanticipated approaches," says Olson, who has worked overseas developing affordable medical technology. Olson also heads MGH's Springboard Studio, which looks for smart design ideas that arise from everyday interactions with health care.

One of those interactions—COVID-19 testing—was causing no end of headaches. A health care provider needed to interact safely with dozens or hundreds of individuals each day. In practice, this meant donning and doffing PPE frequently and sanitizing the entire testing area. When Mass General Brigham leadership asked Olson to devise a better approach, he looked at existing solutions and also drew on his own ingenuity.

Within nine days, Olson's team, with help from Healthcare Innovation Partners LLC, had built a prototype of a testing booth with arm ports that allowed a provider to stand inside while performing a nasal swab test on the patient outside. He asked nurses, infection control experts and housekeeping staff to test-drive it. One user suggested arm ports on three sides of the booth so the tester could quickly move to the next patient while the previous bay got cleaned. Another asked for elliptical ports to accommodate different heights of testers and patients. "Ergonomics is important when you're testing 200 patients per day," Olson says.

The "Hexapod" dramatically shortened testing times—46 seconds per patient compared with the previous 10 minutes per test. In the booth, testers wear only surgical masks, saving on N95 respirators and shields, and saving 27,082 gowns since the Hexapods were installed on April 16. There are now four Hexapods at MGH—testing 28,938 patients by October 1—as well as two other iterations. With the Oasis, the patient steps into the booth so a provider on the outside is protected while doing aerosol-generating procedures. Edele walls, the other innovation, are simpler plexiglass barriers with arm ports used in the emergency department to evaluate patients and collect other vital signs.

Olson has sent Hexapod blueprints to partners in Uganda, and the University of Alabama ordered a variation of the Hexapod, with other institutions expressing interest in receiving their own version. Its success confirms Olson's belief that "the best solutions come from people closest to the challenge."

Research Institute was inundated by proposals from academic researchers looking to put their ideas into practice at the hospital. "Everybody wanted to do a trial at MGH," says Maurizio Fava, chief of the Department of Psychiatry and director of the Division of Clinical Research of the MGRI.

On March 20, most non-COVID-19 research at MGRI was put on hold, and many of the scientists and physicians who had been working on other studies shifted to COVID-19, aiding a wide range of efforts to find vaccines and treatments.

These first clinical trials sponsored by the hospital were led by Lorenzo Berra, an anesthesiologist and medical director for respiratory care. Italian by birth and educated in Milan, Berra had heard from family members and colleagues about COVID-19's devastating impact in Italy. Many severe cases there led to a life-threatening lung condition called acute respiratory distress syndrome, or ARDS. Nitric oxide, which can improve lung oxygenation, is a Food and Drug Administration–approved treatment for ARDS, and studies during previous coronavirus outbreaks suggested that the inhaled gas has a virus-killing effect. In late March, the hospital began testing inhaled nitric oxide. Berra is leading three multicenter trials sponsored by MGH: one using the gas with very sick patients, another for those with mild to moderate symptoms and a third testing whether it can protect health care workers.

Terry Doherty, Intensive Care Unit Nurse

I remember thinking, is there going to be enough PPE? How contagious is COVID-19? Am I going to catch COVID-19? I've been an ICU nurse for a long time, but this was so different. There were no therapeutics. There was no vaccine. And everybody was scared. We watched and we waited. And I knew we had to do something.

Clinical trials of another possible treatment, remdesivir, were already underway in China, and in late February, the National Institute of Allergy and Infectious Diseases (NIAID) announced it was spearheading a test of the antiviral, which had been used during the 2018 Ebola outbreak in the Democratic Republic of Congo. MGH became the first site in New England to take part in the NIAID trial. Enrolled patients, who had COVID-19 and were experiencing lower respiratory tract infections, were randomized into treatment and placebo groups.

But as the hospital began recruiting patients for this and other trials, things were becoming chaotic on COVID-only patient floors. Nurses were already hard pressed to take care of so many sick and infectious patients, and now they also had to keep track of which ones were in what trials, each of which demanded a strict protocol. "It was clear we needed to organize a coordinated research response," says Katrina Armstrong, physician in chief and chair of the Department of Medicine at MGH.

On March 24, Armstrong called Keith Flaherty, director of Clinical Research at the Mass General Cancer Center and a colleague for three decades. She asked him to help create a system that could keep abreast of all new COVID-19 trial proposals and coordinate the initial four trials already in motion. Over the next two days, Flaherty reached out by email to invite dozens of investigators to participate in an enterprise that would be overseen by three committees—a steering group, another devoted to scientific review and a third looking at trial implementation. "I didn't know most of the people I contacted, but everybody said yes," Flaherty says. "I don't think they knew what they were getting into."

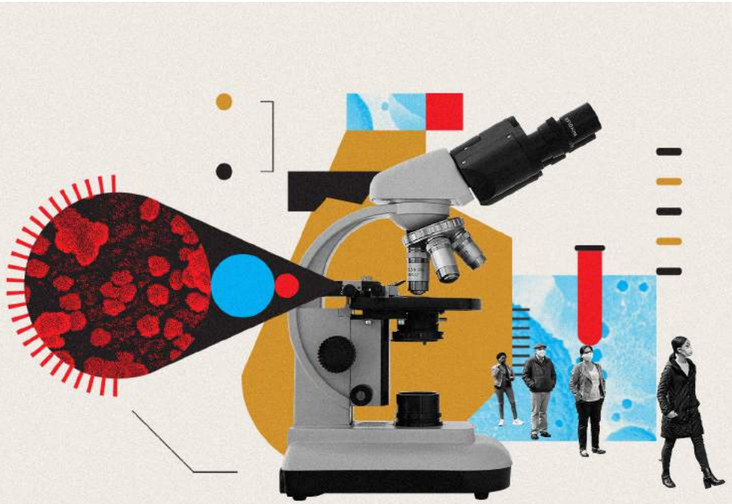
The steering committee inherited a deluge of proposals, with several more arriving every day. A randomized trial that would normally take a year or more to launch now needed to happen in weeks, even days. "We had to very quickly determine which studies might move the needle," Flaherty says. During the pandemic's first wave, the group seriously considered more than 100 proposals.

Most didn't make the grade, but one that did qualify was hydroxychloroquine, an antimalarial medication also used to treat lupus and rheumatoid arthritis. It was highly touted after several small studies in China and France suggested that it might help patients with COVID-19, and the FDA had issued emergency authorization to use the drug to treat hospitalized patients, despite known side effects that included heart irregularities and seizures. "It was a hot issue," Flaherty says.

Even as this study got started in mid-April, emerging research signaled that the drug might do more harm than good, and questions were raised about the validity of past studies. At MGH, only patients participating in the trial were given the drug, and in June the study was halted and the FDA emergency authorization withdrawn.

Studies were also taking a fresh look at tocilizumab, also known as Actemra, a rheumatoid arthritis drug, and in mid-April, MGH led a study looking at its effects on COVID-19-related systemic inflammation. The treatment was designed to mitigate the body's "cytokine storm," an overzealous immune response observed in many COVID-19 patients that can lead to pneumonia, blood clots, organ failure and often death. Other area hospitals also began enrolling patients, and the study eventually included almost 250 patients. "Most were very sick and eager to participate," says John Stone, director of Clinical Rheumatology at MGH and principal investigator in the trial. "We enrolled patients from early in the morning until late in the evening, and they typically received the drug within two hours of consent. Time was of the essence."

As these and other trials got under way, the trials network made changes to untangle the snarls they encountered in coordination and implementation. In early April, Flaherty appointed a team of three physicians to find and screen every COVID-19 patient for possible enrollment. "The teams organizing



ISRAEL VARGAS; CONTAINS PHOTOS BY GETTY IMAGES

AKIROMARU/GETTY IMAGES

For Some, ECMO

An intensive procedure helped patients breathe while their lungs healed.

In 1979, MGH ran the nation's first randomized controlled trial for a stunning new technology—extracorporeal membrane oxygenation, or ECMO. Patients whose lungs were in partial failure would be hooked up to a device that would siphon out their blood, fill it with oxygen and return it to the body.

ECMO offered hope for COVID-19 patients who couldn't breathe on their own, and it had been mobilized in past pandemics, including the outbreak of H1N1 influenza in 2009. The procedure comes with significant risks, however, including blood clots and infection. Not every patient could benefit from it, and mortality from ECMO is traditionally as high as 50%.

The choice of whether to try ECMO became one of the more wrenching calls at the bedside. Faced with a dying patient, it was exceedingly difficult for a physician to deny the patient any shot at survival—even when ECMO was likely to be futile. "Making the decision to offer ECMO or to withhold it from a patient can be devastating emotionally and psychologically," says Yuval Raz, medical director of Respiratory ECMO at MGH. To relieve that burden, Raz initiated a protocol that took that decision out of the single physician's hands. A committee of at least four ECMO experts evaluated each patient's likely outcome on ECMO and decided whether to administer. The team approach worked well enough that it will continue post-COVID-19, Raz says.

MGH had as many as 10 COVID-19 patients at a time on ECMO, which requires massive resources—labor as well as financial. One physician's full-time job was to keep track of hundreds of ICU patients to identify those who might benefit from ECMO. As of early September, 23 patients had been on the treatment and about 60% of them survived.

MGH leadership didn't suggest refusing ECMO referrals from other institutions, even though many patients were uninsured, Raz says. "MGH's willingness to try to help anyone we could, including on ECMO, meant so much to me and my team," he says.

individual trials weren't identifying anywhere near all of the infected patients," says Michael Dougan, a gastroenterologist and immunotherapy researcher who was part of the team. "In this situation, if a COVID patient is in the hospital and isn't offered a clinical trial, it's a failure in standard of care. Our system was designed not just to prevent these trials from bumping into each other, but also to prevent people from being missed."

Every morning, the team met to review patient medical records and generate a list of potential trial candidates. Team members had to consider an encyclopedic list of details governing each trial's criteria for inclusion and exclusion. "Some required a positive COVID test within 48 hours, others within 14 days," says Chana Sacks, an internist at MGH and another member of the team. "For one trial patients had to be intubated on a ventilator; for others, they couldn't be." Team members were in round-the-clock contact with trial researchers to let them know about possible new participants.

Initially, there were more eligible patients than trial slots, but that quickly changed as more trials got up and running. From April 9 to July 9, the team screened more than 1,300 patients and referred as many as it could to trials involving antivirals, immune modulation, anticoagulants and several respiratory treatment strategies.

Jonathan Alicea, Orthopaedic Staff Nurse

I was in the Army for 21 years, but when I was assigned to the proning team, I was almost as nervous as going into Iraq. It turned out to be incredible. We were glad to be a fresh set of arms for our tired colleagues; one time people clapped when we arrived. But what I appreciated most was the chance to help, having seen the impact of COVID on Latinos and on the city of Chelsea, where I grew up.

The job of putting the trial protocols into practice—charting patient data, collecting blood or other biospecimens and administering treatments—fell to Kathryn Hall, nurse director for the Translational and Clinical Research Centers, and her team, including more than two dozen research nurses and nurse practitioners. Hall and her colleagues saw some trial patients recover, while others succumbed. "There was nothing else to offer these patients except the clinical trials, and we saw people holding on to hope that they were receiving a drug that would help them," Hall says. "We didn't know whether someone was receiving the drug or the placebo, and we watched many patients deteriorate quickly, in much larger numbers than we were used to. It was very distressing to all of the providers."

At the end of April, early results from the remdesivir trials provided a sorely needed morale boost. The antiviral had helped some patients recover more quickly and appeared to improve survival as well. "The positive remdesivir results were a turning point," Flaherty says. "I think many of us felt relieved that everything we were doing wasn't futile."

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As the first wave of COVID-19 patients began filling beds at MGH in March, chief resident Aisha James and several other physicians-in-training realized that language barriers could be an issue. In the early stage of the pandemic, a large percentage of patients came from four communities north of Boston that have large Spanish-speaking populations: Chelsea, East Boston, Everett and Revere. "There were so many more patients from these cities than the hospital was used to seeing," James says.

No community in Massachusetts had been hit harder than Chelsea, a densely populated city of 40,000 where about one in five residents lives below the poverty line. Multiple generations often share small apartments, where the virus spread through respiratory droplets. Almost 80% of employed Chelsea residents were also deemed essential workers during the pandemic, and most relied on public transportation to get to their jobs.

All of those factors made Chelsea residents far more likely to be infected with COVID-19—and those who did get sick were also at increased risk for severe symptoms and complications. A large portion of residents have pre-existing conditions that include obesity, diabetes and heart disease, says Dean Xerras, medical director of MGH Chelsea HealthCare Center. The people of Chelsea, which is near Logan Airport and is clogged with heavy truck traffic, also have high rates of asthma and other respiratory illnesses. And many there who developed symptoms of COVID-19 may have delayed seeking care out of fear they would lose jobs or, in the case of undocumented immigrants, be reported to federal authorities, Xerras says. That could explain why a significant portion of COVID-19 patients arriving from Chelsea and neighboring communities were so sick on arrival.

As this data filtered up to the Hospital Incident Command System, it became clear that a coordinated effort in these neighborhoods would have to be a critical part of the hospital's response. Joan Quinlan, vice president of Community Health at MGH, joined with Joseph Betancourt, vice president and chief equity and inclusion officer at MGH, to create the Mass General Equity and Community Health COVID Response Team. "These places are on fire," Betancourt recalls thinking. "We had to figure out a way to stop the spread."

Betancourt, Quinlan and other MGH officials developed a plan. Their launch pad was the MGH Chelsea HealthCare Center, which had opened in 1971 and now serves 32,000

Read My Lips?

Universal masking put the hard of hearing at a disadvantage, but the adoption of clear masks helped some.

Facial coverings quickly became mandatory on every floor of MGH. This created a problem for some patients who weren't there for COVID-19, especially people with hearing disabilities who rely on lip reading. "Once you require everyone to wear one as part of PPE requirements, it becomes a big issue," says physiatrist Cheri Blauwet of Spaulding Rehabilitation Hospital in Boston.

Blauwet, who heads a Mass General Brigham–wide COVID-19 disability task force, addressed the problem by obtaining a supply of special surgical masks. They were embedded with transparent material overlaying the mouth and nose. Deaf patients weren't the only ones to benefit, she notes. "Most elderly people acquire hearing loss as they age, and many rely more on lip reading than they think," Blauwet says. Children also connect better with clinicians when they can see facial expressions. While the masks weren't approved for use with patients with respiratory conditions (including COVID-19), they opened an invaluable window between staff and many patients.

LEFT: REMIE GEOFFROI; RIGHT: PETER GRUNDINI

Learning Interrupted

A teaching hospital had to radically reinvent how it taught clinicians. Some got the lesson of a lifetime.

Education has been a victim of the pandemic on a national level, and the same holds true for teaching hospitals, where many types of clinician go to learn their crafts. With so many patients infected and contagious, educators had to either coordinate digital coursework or bring learners onto the floor in a crisis climate.

Students

Real clinical interactions are critical for nursing, medical, pharmacy and other students. During the March surge, however, most of these had to be sent off campus. Classroom learning continued online, with virtual encounters and simulations. In June, students began to return to the hospital.

Trainees

Residents and fellows—positions held by those with licenses but at the beginning of their careers—remained on campus. James Gordon, chief learning officer at MGH, says it has been a "remarkable experience" to work alongside them in an atmosphere of heightened risk and intimate teamwork.

Faculty and Staff

Health care professionals are lifelong learners. Most certification boards bent or suspended their requirements this year. Many of the faculty at MGH were also figuring out how to alter curricula and shift traditional classroom and conference learning environments to a digital setting.

Community

MGH also has a mission as an educational resource for the public and hosts visiting scholars. While most visitors will not be able to return until 2021, new virtual opportunities have opened up. These include a digital COVID-19 textbook, online panels of experts reviewing the latest research and recordings of conferences, lectures and classroom discussions.

patients a year. Converting one of its four floors to a respiratory illness clinic, or RIC, meant that COVID-19 tests and evaluations of symptoms could be given daily to as many as 300 people from Chelsea and neighboring East Boston, Everett and Revere. Patients who visited the RIC also received "care kits," which contained masks, hand sanitizer, cleaning materials and educational pamphlets in English and Spanish. Another 80,000 of the kits were handed out across the city. Radio spots in English and Spanish, as well as infographics for Instagram and Facebook, reinforced advice about mask wearing, social distancing and other protective measures. "If you can't change people's social conditions, at least you can mitigate spread by offering some basic tools," Betancourt says.

The biggest puzzle in the MGH response was to find a way to help people in the community who had been diagnosed with COVID-19 but whose symptoms were mild. Because they were still contagious, they risked infecting family members or roommates if they went home. "We started to get particularly concerned when we heard that people who had tested positive were being summarily thrown out of their apartments by roommates," says Chelsea City Manager Thomas Ambrosino.

The solution was a bold plan, worked out with the help of municipal officials, that transformed a 147-room Quality Inn off Route 1 in Revere into an isolation center for those who had COVID-19 and nowhere else to go. MGH took responsibility for delivering medical care, which was overseen by Dean Xerras and registered nurse Jacky Nally, program manager for the MGH Center for Disaster Medicine. Under their guidance, the hotel lobby became a nursing station and an intake area. Hand-washing stations and areas for removing PPE were set up throughout the hotel, which was staffed with doctors, nurses, medical assistants, nurse practitioners and social workers. Nally tried to make sure that at least half of the workers were multilingual.

When the isolation center opened on April 16, a clinical team in full PPE was there to check on residents' symptoms twice a day. "Sometimes we simply took their vital signs and asked a few questions to ensure that they were still improving," Nally says. "Sometimes it involved a lot more than that." Many patients had medical conditions other than COVID-19 that needed management. Social workers called patients twice daily to monitor their mental health.

The isolation center closed on June 9 after caring for 153 adults, children and infants. "I think we absolutely slowed the transmission of the coronavirus," Nally says. At the height of the spring surge, Chelsea recorded more than 80 new cases of COVID-19 per day, but that figure had dropped into the single digits by August, Ambrosino says. The percentage of people in Chelsea testing positive for the virus continues to be disproportionate, about three times as high as the state average at the end of October. "This is not over," Xerras says. "It's a marathon, not a sprint to the finish line."

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The sense of fighting back, together, against an implacable foe animated the staff at the hospital during those months, which day to day involved long and grueling hours and a fear that everyone's best efforts would not be enough. Sometimes an encouraging development would arise, as when it was reported that "proning"—rolling patients onto their stomachs—could ease the breathing and improve oxygenation of some COVID-19 patients on ventilators. But proning in practice turned out to be a delicate, complicated procedure, requiring six practitioners to turn a patient safely without dislodging the endotracheal tube or any of the other tubes, lines and drains. "If the procedure isn't done precisely, proning can destabilize patients, causing them to have a severe and sustained drop in blood pressure, and some can develop cardiac arrhythmias," says Robert Kacmarek, director of Respiratory Care at MGH.

So the hospital created five specially trained proning teams, made up of 95

ALL PHOTOS MGH PHOTOGRAPHY EXCEPT TOP CENTER: BOSTON GLOBE/GETTY IMAGES

A Roar in the Streets

Social unrest came on the coattails of the pandemic, and hospital workers rose to fight that battle, too.

By May 25, Americans were grieving the death of nearly 100,000 people from COVID-19. Yet another lost life—George Floyd, who died after a Minneapolis police officer knelt on his neck for more than eight minutes—brought a parallel tragedy to light. The injustice drove thousands to fill the streets and triggered outrage that rippled across the world.

Medicine did not stay silent, and 11 days after Floyd's death, several groups within MGH organized a "kneel-in" on the hospital's Bulfinch Lawn. The area was filled with people in scrubs, white coats and suits—masked and physically distanced—holding signs that read "Black Lives Matter" and "Racism is a Pandemic."

Top middle: Nesli Basgoz helps counter those protesting the lockdowns at the State House in Boston. All other images: The MGH community gathers on the Bulfinch Lawn to hold a vigil and kneel-in for George Floyd.

The parallels between the protests in the streets and the fight going on inside the hospital were only too clear. People of color had been disproportionately hit by COVID-19, according to Joseph Betancourt, vice president and chief equity and inclusion officer at MGH. This was in no small part because systemic racism gives rise to low wages and lack of access to health care, which in turn put communities of color at higher risk during the outbreak. "We know that a virus like this does not discriminate," Betancourt says, "but COVID-19 shone a bright light on these disparities and our inability to think about ourselves as a community."

Leaning on one bent knee, the wet grass soaking through her scrubs, Marie Borgella, nursing director of MGH's Bigelow 7 Medical Unit, fought back tears as she thought of the gesture's dual meaning. "As a leader and a woman of color, I had to take a knee to pray for a better America," she says. "The solidarity of people from every walk of life coming together was overwhelming."

This was not the only time workers were called into action outside the hospital's walls. On May 30, a crowd gathered outside the Massachusetts State House to protest the restrictions brought on by the pandemic. Infectious disease specialist Nesli Basgoz saw many people shouting and singing, while few wore masks or socially distanced. "I was concerned not only for their health, but for the health of their households and communities," says Basgoz, a founder of Physicians for Policy Action, a group at MGH that advocates for policies that promote health and science. Basgoz spoke with several protesters, and explained that masks and distancing have been proved to save lives. Some listened politely, but most argued or walked away.

operating room nurses, operating room assistants and physical therapists. Each team is supported by the patient's primary nurse and respiratory therapist. On April 9, the teams were deployed in MGH ICUs, led by Colleen Snydeman, executive director of nursing and patient care services in the Office of Quality, Safety and Practice. "I will never forget being greeted by the angels of the proning team—arriving en masse like the 82nd Airborne Division to expertly flip over intubated critically ill patients with hypoxemia," says Walter O'Donnell, clinical director of the Pulmonary/Critical Care Unit.

Another promising way to deliver more oxygen to patients on ventilators is extracorporeal membrane oxygenation (ECMO). Blood is pumped outside the body to a heart-lung machine that removes carbon dioxide and adds oxygen before sending the rewarmed blood back into the patient. ECMO gives the lungs a chance to rest and heal while antibiotics and other therapies do their work, and reports from China and Italy showed it was effective for some patients with COVID-19. But ECMO is by no means benign therapy; bleeding complications are common and can be fatal, and blood infections also occur. "Using ECMO on the wrong patients is harmful and will just prolong the dying process," says Yuval Raz, medical director of Respiratory ECMO at MGH.

Indeed, the dying process was a bitter constant. While death in a hospital is by no means a rare occurrence, the pandemic rules that limited exposure to the virus meant patients usually were alone in their last moments, far from family and even their caregivers. In more normal times, says Kerry Reynolds, clinical director of Inpatient Oncology Services, doctors would hold patients' hands and take their time when they had to deliver bad news. "But we couldn't do that with COVID patients," Reynolds says. Face shields and masks could blunt the empathy in clinicians' faces. "Patients having to be isolated was traumatic for all of us," Reynolds says. Adds Kathryn Hibbert, director of the Medical Intensive Care Unit, "Watching patients, some of them young, die alone without family were the darkest, saddest times for me."

> **Every time someone became well enough to leave the ICU, it was a cause for hope.**

Beginning in March, however, the rules were changed to allow one or two family members to visit dying patients in a special unit at the hospital. Todd Rinehart, social work director for the Division of Palliative Care and Geriatric Medicine, collaborated with nursing leadership for that policy shift. With palliative care physician Kathleen Doyle and chaplain Sarah Byrne-Martelli, he created a program they called No One Dies Lonely, which found ways to connect absent loved ones with patients to say goodbye. Rinehart also organized, in coordination with primary care physician Kerri Palamara McGrath and others, a memorial service for MGH workers to honor patients who had died, an event at which cellist Yo-Yo Ma performed.

Yet most patients survived, and every time one became well enough to leave the ICU, it was a vindication and a cause for hope. Staff members would line the hallways and cheer as another person they had helped through many difficult and desperate moments was wheeled out. "Seeing those successes helped keep everyone's spirits up," Hibbert says. Patients continued to leave the hospital, and on one day in April, a milestone was reached, with fewer than 100 patients on ventilators. On that day, 20 doctors, nurses and respiratory therapists had an impromptu celebration on a parking garage roof. "We were just so elated and relieved," Hibbert says.

ISRAEL VARGAS; CONTAINS PHOTOS BY MGH PHOTOGRAPHY

PETER GRUNDINI

DOSSIER

"Veno-venous Extracorporeal Membrane Oxygenation for Respiratory Failure in COVID-19 Patients," by Asishana Osho et al., *Annals of Surgery*, May 2020. The piece outlines the use of ECMO as a life-saving therapy for COVID-19 patients.

"The Experience of Emergency Department Providers With Embedded Palliative Care During COVID," by Emily Aaronson et al., *Journal of Pain Symptom Management*, August 2020. Palliative care in the ED has particular value during a mass emergency event.

"Improving Clinical Trial Enrollment – In the Covid-19 Era and Beyond," by Crystal M. North et al., *The New England Journal of Medicine*, July 2020. The overview shows MGH's clinical trial strategy during the surge.

To MGH, With Love

A wave of donations helped feed and support clinicians while they worked.

The Boston community sent its good wishes to the hospital. It also sent deliveries of pizza (more than 500 of them), flowers (hundreds of arrangements), shoes for sore feet (north of 1,000 pairs) and, once, a massive original canvas of surgical residents posing as Rosie the Riveter. "It was really everything you could think of," says Riley Orrell, the administrative fellow who coordinated donations as they came in.

To help direct this generosity, Orrell's team built an online portal. People could indicate what they wanted to donate, then Orrell would walk them through safety guidelines. Donated food was prepackaged and individually wrapped. Employees of the donating companies were asked to wear gloves and masks while preparing food and be regularly checked for COVID-19 symptoms. Food donations were being taken only from places with a grade A permit, and only new nonfood items were accepted—"so it was a polite 'no' to homemade baked goods or used items," Orrell says.

Gifts of the financial variety were also forthcoming. In the wake of the Boston Marathon bombing, the hospital had created a fund that could provide flexible resources in extraordinary circumstances. Among the early donors this year were singer James Taylor and his wife, Kim Taylor, with a gift of $1 million. Other donors included Biogen, whose employees received care at the beginning of the pandemic, with the company also donating medical equipment and testing supplies.

BRIAN STAUFFER

CHAPTER 3

THE FIGHT THAT LIES AHEAD

When the caseload began to ease, clinicians came to grips with the new normal as researchers set their sights on ending the pandemic for good.

After COVID-19 cases in Massachusetts peaked at the end of April, they fell to a low by July and then rose moderately through the summer and fall. At MGH, this easing of the pandemic meant respite for exhausted workers throughout the hospital. But most understood that the drop in new infections merely marked a new phase, and that the fall and winter might well bring a second wave as the virus continued to spread through the rest of the country and around the world. There was an urgent need to develop better testing, more effective treatments and successful vaccines, research frontiers now being explored even more aggressively at MGH and the Ragon Institute. And while COVID-19 patients no longer overwhelmed the emergency department, the toll of delayed diagnosis and treatment throughout the hospital was another reckoning to be faced.

The push to treat and contain COVID-19 had led, nationally, to the unintended neglect of other serious conditions. In March, as widespread stay-at-home orders took effect, people who needed care unrelated to the pandemic stayed away from hospitals in great numbers. U.S. emergency department visits declined by more than 40% during the early months of the pandemic, according to the CDC, and in the 10 weeks between March 15 and May 23, heart attack patients dropped by nearly a quarter and potential stroke victims dropped by a fifth, compared with the preceding 10 weeks. At MGH, similar patterns emerged. Patients needing treatment for stroke, heart attacks, appendicitis and brain hemorrhages were noticeably absent in April, says ED chair David Brown. "Our volume of acute medical emergencies dropped by 30%, but the incidence of those diseases didn't drop," Brown says. "People were waiting out those conditions at home because they were afraid of becoming infected. That's the hidden morbidity and mortality of this epidemic—most of those people could have been treated and survived pre-COVID. But by delaying time-sensitive treatment, some people died. Others were more acutely ill when they finally came to the ED and died as a result of that."

One area in which time is of the essence—cancer diagnosis and treatment—also experienced delays, as diagnostic

procedures and surgery were postponed. That could lead to an as-yet-unmeasured rise in new or more advanced cancers, suggests Daniel Haber, director of the Mass General Cancer Center. Indeed, in a United Kingdom study that modeled the potential impact of medical service delays, deaths from breast, colorectal, esophageal and lung cancers in the five years after diagnosis were expected to increase by 5%.

Addressing this backlog of care has become a priority at MGH and other hospitals. Yet even as the pandemic waned and with new precautions in place, many patients seemed reluctant to come back to the hospital or to local clinics. In the spring, MGH and other Boston medical centers came together with a television advertising campaign urging people not to delay care and emphasizing new safety measures. Since then, the ED and other parts of the hospital have seen the return of a more normal mix of patients.

This is an issue that will certainly reemerge, however, if there is a second COVID-19 wave. "Last winter, we cleared the decks and shut down much of our routine operations," says Inga T. Lennes, senior vice president of Practice Improvement and Patient Experience. "But if we're in the same position again, we know we won't want patients to put off urgent medical care, and we won't shut down as much as we did before." Still, she adds, "we know so much more about treating COVID-19 now. We'll call on what we've learned to innovate in a more complex environment."

Todd Rinehart, Social Work Director

It was difficult for family members to see their loved ones at the end of life; however, we found a way to keep them safe so they could say goodbye in person. We provided the family with a small ceramic heart that had been held by their loved one then placed in a small plastic bag. It was a transitional object to be taken home, knowing their loved ones wouldn't be returning.

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One way to avoid shutting down doctor-patient visits even at the height of an infectious disease outbreak is to make those connections happen virtually, and the widespread adoption of telemedicine during the COVID-19 crisis has led to a range of tantalizing possibilities, most of which have already been battle tested. "In eight weeks, Mass General Brigham went from having 400 physicians who regularly used telemedicine to 11,000 providers who needed to be enabled," says neurologist Lee Schwamm, director of the Center for TeleHealth at MGH and vice president of Digital Health Virtual Care at Mass General Brigham. "Volume went from 0.2% of ambulatory care delivered virtually to 62%, which translated to some 200,000 visits per month."

The advent of "virtual video intercoms" could have a lasting impact, letting patients see and speak with clinicians outside their rooms and often far from the hospital. As COVID-19 cases rose and infection risks multiplied, clinicians began to use tablet computers mounted on IV poles. These devices, equipped with auto-answering software, provided a technological link to nurses and physicians who didn't have to wear masks and shields. "It's very frightening and impersonal for patients to only see providers covered in PPE," Schwamm says. In addition to conserving PPE, virtual connections by video led to warmer, less rushed interactions, and also enabled remote monitoring of patients who may have been sleeping, sedated or confused. More than 1,500 of these intercom setups had been deployed at Mass General Brigham hospitals by the end of April, and that equipment stands ready to be moved back into patient rooms if there's a new surge of COVID-19 cases.

Other innovations have included "virtual rounds," in which clinicians in multiple locations can look in on patients and provide consultations—of particular value in treating complex COVID-19 cases, where there are few simple answers about the most effective therapy. And in some specialties, telemedicine has had a particularly profound impact. In hematology and oncology, for example, few specialists saw patients in virtual visits before the pandemic, says David Ryan, chief of Hematology/Oncology at MGH. But by the fall, 30% of oncology visits and 80% of initial outpatient hematology consultations were still happening via telemedicine.

"This has opened the way to major changes in how cancer care will be delivered from now on," Haber says. Many "surveillance" visits, in which oncologists and hematologists review scans and lab results, can now be conducted remotely, and providers can check in with patients virtually before and after chemotherapy sessions. "And many patients who normally would have to drive to Boston for those sessions and to see their oncologist now can choose virtual visits and go to a Mass General Brigham satellite near them for their treatments," Ryan says. "This erases geographic boundaries," adds Haber, who notes that telemedicine is extending the reach of MGH across the country by offering virtual consults with its specialists.

Schwamm estimates that up to 30% of ambulatory visits will remain virtual even when there are no restrictions on patients coming to hospital clinics. The cost and logistical complications of traveling to a doctor's office can be high, especially for patients who live far away or have conditions that make it hard to leave home. And in some cases virtual care may be better care, offering doctors a view of their patients that wasn't possible before. "A video visit with a patient at home may provide important clues about why that person isn't doing well, and family members can be there to answer questions," Schwamm says. Virtual visits also make it easy for patients who have returned to a distant home after a hospital stay to continue to see MGH specialists, which can be important for continuity of care. "Physicians who once told me that telemedicine would never work for them now understand how much of a benefit it can be and how big a role it will play in their practices," Schwamm says.

Still, not every patient is set up for telemedicine, and the next step is to make virtual care accessible to those who don't have broadband internet, are visually impaired or have limited

BOSTON GLOBE/GETTY IMAGES

ISRAEL VARGAS; CONTAINS PHOTOS BY GETTY IMAGES

The New Digital Distance

Telemedicine saw not only an expansion but a reinvention during the surge.

The threat of infection in the hospital caused a rethinking of all care, and not only on the floors focused on COVID-19. Some projects looked into how the normal operations of the hospital could be better conducted with digital technologies, and a few of these innovations will most likely stick around.

- **Virtual Rounds:** Daily consultations at the patient's bedside are generally attended by clinicians who are available and able to fit in the room. Moving rounds online not only lowered infection risks, but also opened the virtual door to more attendees—specialists, off-site physicians and students.

- **Virtual Intercom:** An iPad mounted on an IV pole may seem low-tech, but it allowed clinicians outside the room to perform unlimited patient visits without wasting protective equipment. Letting patients see providers unmasked also gave a much-needed human dimension to encounters.

- **Patient Connect:** Personal communications became logistically tough. By creating a secure video connection and offering digital devices, this program got patients face-to-face with interpreters, family members and staff to discuss critical topics, including end-of-life decisions.

- **Inpatient Remote Monitoring:** Most patients have extensive digital monitoring of their condition once they reach the ICU. This system was designed to monitor patients—both at MGH and potentially at field hospitals—at earlier stages of the disease and predict when an intervention would be needed.

English. "Finding ways to deliver care virtually to patients who don't have or can't use existing technology is an intense area of focus for us," Schwamm says.

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Research at MGH exploring possible COVID-19 treatments continued through the spring and summer. In October, *The New England Journal of Medicine* published final trial results for the antiviral remdesivir showing that the drug cut recovery time by nearly one-third and also reduced the length of the initial hospital stay. While preliminary results from a larger international trial cast doubt on its effectiveness, the FDA in October granted full approval for the drug.

By August, however, the number of hospitalized patients at MGH who were eligible for COVID-19 trials had dwindled to the single digits, and participation in many studies—which needed those patients as test subjects—had slowed. One such trial was investigating a monoclonal antibody, LY-CoV555, that was derived from the blood of a recovered COVID-19 patient during the March outbreak in Washington state. In early June, MGH was one of several sites for a phase 1 safety trial of the drug being developed by drugmaker Eli Lilly. Following expanded testing at other sites, Lilly released data in September showing that the medication had helped improve the elimination of the virus that causes COVID-19 and may have reduced the rate of hospitalizations.

Other treatments failed to live up to expectations. A study published in October found that tocilizumab—which lead investigators at MGH thought might ease the "cytokine storm" that can prove deadly in COVID-19 patients—in fact didn't reduce the need for breathing assistance or prevent deaths.

In the meantime, with a possible resurgence looming, Keith Flaherty, director of Clinical Research at the Mass General Cancer Center and leader of the COVID-19 clinical trials platform, says that he and his colleagues have six new treatment trials ready to launch. They are also prepared for additional studies of possible vaccines.

What's Coming Next?

COVID-19 cases are again on the rise. MGH incident commander Ann Prestipino reflects on the road traveled so far and which next steps are critical.

In the fall of 2019, Ann Prestipino was teaching a course on hospital operations at Harvard Medical School. She brought in guest lecturer Paul Biddinger, chief of the Emergency Preparedness Division at MGH, who had the class work through a then-unthinkable scenario: A deadly flu pandemic hits a small community, straining resources, staff and supply lines. What should a hospital do?

Prestipino has been asking those kinds of questions her entire professional life. She chairs the MGH Emergency Preparedness Committee, which means that when the pandemic hit, Prestipino became the hospital's chief incident commander, leading the nerve center through which critical decisions got made. Now that the first surge has subsided, her thoughts have turned to the coming winter.

Q: What scenarios are you mapping out for the months ahead?
A: Right now we are trying to balance three tricky variables: non-COVID-19 patients, COVID-19 patients and flu patients. Those are all unknowns. Our decision was to make models and ask: What if we get the same number of COVID-19 patients as the last go-round? What if we got 50% of that number, and what if we got 150%? Everybody in our system has taken those three scenarios and translated them into surge plans. The guess right now is that we'll end up somewhere between the 50% and 100% mark. But that's just a guess. Our experts have told me that two weeks in the future is about as far as we can accurately see, so we are preparing to move quickly if we see a second wave.

Q: If there's another surge of a similar size, what will happen differently?
A: There has been so much clinical innovation—the proning of patients, the treatments we know to use and in what sequence and so forth. We've learned a tremendous amount and we'll put that into play, which might make things easier in a second wave. We've also secured ventilators and PPE.

On other fronts, I'll say that we're very concerned about the mental health of our workforce. When you're dealing with a longitudinal situation like this—and we all know this pandemic isn't over yet—you really need ways to revitalize and refresh staff. This includes thinking about their childcare issues, and how will those become more complicated because of school closures. It includes thinking about the anxiety of working in an environment where exposure to the virus is a daily reality. We need to do everything we can to support staff and their ability to be healthy and well.

TONY LUONG FOR *PROTO*

Q: What about PPE supply, which was such a problem in the spring? Could it be worse if outbreaks are national or worldwide?
A: It was a problem, and as you probably know, the federal government didn't help us in any way. Again, this is a situation where modeling is the answer. We drew expert analysts from departments all over the hospital. They did an incredible job looking at what was ordered, what was allocated, what was actually being utilized. They projected how many people might need to go into a patient room and what that meant in terms of masks, gowns and our 14 or so critical supply items. When things started, we had about a two-week cache of these critical PPE supplies. Now, with additional kudos to our supply chain folks, we are working toward a four-week cache in addition to a more secure supply line.

Q: Will there be other changes?
A: MGH did see a disproportionate number of COVID-19 cases. As proud as we are of having taken care of these very sick patients, the exhaustion of our staff points to a need to balance that load across the system and ideally across the city. And better utilizing other hospitals would be good for the patients too. There are also a few kinks in testing still to be worked out. We learned the breadth and depth of our laboratory capabilities, and how you have to shift strategies depending on the availability of lab and testing supplies.

Q: What are your takeaways from the first surge?
A: We've learned the importance of muscle memory, meaning that both drills and experiences of past mass casualty events and other disasters are instrumental in creating a skilled and nimble staff. People here did and have always done an extraordinary job. My main takeaway, frankly, has been a great sense of pride in the institution's resiliency and our ability to respond to anything that comes our way.

But researchers have shifted some of their efforts to basic science, with work in the lab probing questions that include one of COVID-19's biggest mysteries—why some people who are infected get severely ill while others have mild symptoms or none at all. Age, underlying health conditions and genetics play a role in deadly complications, but how they do so remains unexplained. In one of the largest basic research efforts to date, Nir Hacohen, director of the MGH Center for Cancer Immunology, is co-leading a 30-person team conducting molecular analyses of COVID-19 blood proteins, blood cells and antibodies. That work is providing a high-resolution look inside human immune cells as a way to find what separates infected patients who manage to shrug off the disease from those who become extremely ill. "We're working to identify underlying cellular molecular causes of good and bad outcomes," Hacohen says.

Discovering genetic signatures associated with COVID-19 susceptibility could lead to drugs or combination therapies targeting specific kinds of cells in the blood, for example. This kind of precision medicine is a hallmark of cancer research, and COVID-19 studies could learn from the groundwork cancer has covered. Many cancer clinical trials now include multiple treatment arms or "baskets" that can help gauge the response to a range of drugs by patients with different genetic mutations or locations of cancer in their bodies. Flaherty, who has been a pioneer of such "adaptive" trials, now wants to do something similar with COVID-19 patients, testing whether particular treatments work in those who share specific genetic or nongenetic biomarkers.

John Herman, Associate Chief, Department of Psychiatry

The important psychological rule during a crisis is to never worry alone. We set up and staffed 100 resiliency and peer-support groups around the hospital, and we offered virtual same-day cognitive behavioral therapy and psychiatric treatment. People could share their experiences so they knew they weren't suffering alone, which is critically important in helping people cope during an intensely stressful time.

By summer's end, many disrupted, non-COVID-19 clinical trials at the Massachusetts General Research Institute were back on track, and new ones were actively recruiting patients, says Maurizio Fava, MGRI director of the Division of Clinical Research. But many protocols were different. Often, trial subjects were recruited virtually, and rather than being required to show up at the hospital for testing, procedures and data collection, patients in many cases were able to have home visits with nurses. Many of these changes, which may save time and money while promoting safety, could become permanent, Fava says.

In several other areas, too, alterations made during the pandemic are being embraced as better ways to do things even during more normal times. "We're working to pilot a continued palliative care presence in the Emergency Department, for example," says Vicki Jackson, chief of Palliative Care and Geriatrics. And in the ICU, determining which patients would benefit from extracorporeal membrane oxygenation (ECMO) will still be made by a group of at least four ECMO experts, rather than giving a single physician the responsibility of what is often a life-or-death decision, according to Yuval Raz, medical director of Respiratory ECMO.

If fall or winter leads to a second surge of COVID-19 patients at MGH, materials management head Ed Raeke, charged with having sufficient supplies on hand, will be prepared. The hospital is currently supplied with a four-month cache that includes more than 600 items, which in addition to PPE includes disposable thermometers, stethoscopes and arterial blood gas syringes.

ISRAEL VARGAS; CONTAINS PHOTOS BY MGH PHOTOGRAPHY AND GETTY IMAGES

"Every department has been asked to come up with a plan to manage a variety of future COVID scenarios," says David Brown. "So we'll be ready for whatever happens."

On September 25, the research team team of Dan Barouch, of Beth Israel Deaconess Hospital and the Ragon Institute, published results from the human trials of their vaccine effort that started the day the coronavirus genome was made public. Nearly 100% of the subjects had an immune response with only mild to moderate side effects, and of the vaccines to reach phase 3 trials, it is the first that could require only one dose. Barouch's team plans to enroll more than 60,000 volunteers, and some may come from the MGH satellite clinic in Chelsea, which is encouraging community members not only to get involved in vaccine trials but to get vaccines once the FDA has approved them.

This approach—research working hand-in-hand with clinicians and community efforts—will continue to be a cornerstone of the hospital's response. As cases rise nationally, everyone at MGH will continue to look for answers, remain prepared and hope.

DOSSIER

"The Art of Oncology: COVID-19 Era," Kerry Reynolds et al., *The Oncologist*, July 2020. An essay from nine staffers of the Mass General Cancer Center walks through the emotional and logistical difficulties of shifting focus during the COVID-19 surge.

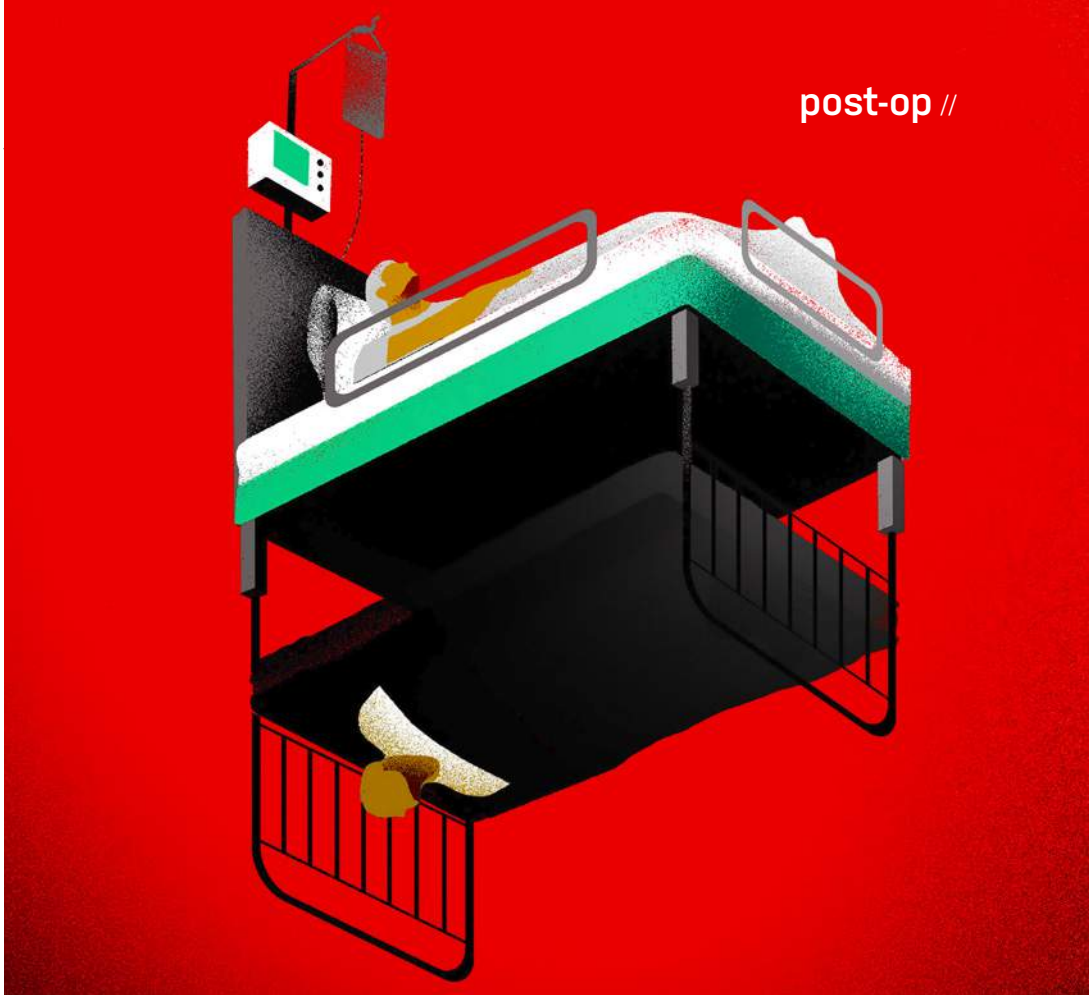
"A Digital Embrace to Blunt the Curve of COVID19 Pandemic," by Lee Schwamm et al., *npj Digital Medicine*, May 2020. The overview of virtual care innovations at MGH during the surge points to possibilities for enduring change in digital medicine.

"The Disproportionate Impact of Covid-19 on Communities of Color," by Thomas D. Sequist, *NEJM Catalyst*, July 2020. The chief patient experience and equity officer at Mass General Brigham explores how racism caused poor pandemic outcomes.

FIRST PERSON

100 Days of Loneliness

BY FRANK CUTITTA



I have no recollection of the 40 days I spent unconscious in the ICU. I know my family sent my caregivers playlists with Pavarotti and the Beach Boys. Those sounds, interspersed with the voices of my family, were supposed to connect me with my pre-comatose life. They were piped to me through earphones—a key factor, I believe, in my mental faculties staying sharp until I awoke.

When I finally came around, the first thing I realized was that my life would be remarkably different. I had no ability to stand or walk, compounded by massive lung damage I had sustained from the virus. There were dozens of adjustments to make in getting through my day-to-day life. But perhaps the biggest shift—the one not on any list of COVID-19 symptoms—was my emerging into a world of extreme isolation.

As with many COVID-19 patients, I had been sent to recover in a highly regulated environment, a space governed by quarantine rules and safety restrictions. I did have the occasional visit, but normal conversations with my providers were limited, since many of them were restricted on the time spent with us. As we know now, conversations are one way the virus spreads. Our interactions were, of necessity, mostly transactional—a medication dispensed, blood taken, vital signs checked.

In my normal "before" life I had been far from a social animal. But as the days wore on, I began to understand the perils of this kind of extreme isolation. My mind occasionally went to dark places, hungry for human contact and especially human faces.

I began to fixate on the masks, which added a dimension of anonymity to every interaction. In my 100 days of hospitalization, I saw the full faces of only three care providers. On two occasions my nurses removed them for a moment, saying they wanted me to recognize them if we ever met in my post-COVID-19 life. The third was a social worker. He understood my pain and showed me his face as a gift. The two of us would sit like that and talk about sports, food, politics—anything other than COVID-19 in the news.

At last I recognized my own pity party and how my mind was brooding on my circumstances. I began to speak with my doctors and nurses about the bigger problem, what I now refer to as the epidemic of institutionalized loneliness. From my own experience I began to think about how loneliness itself causes harm or, at minimum, prolongs recovery. In conversations, my clinicians agreed that it was a problem in this pandemic, and that loneliness needed to be treated as its own disease, in much the same way that chemotherapy is part of cancer care.

The topic began to occupy my thoughts. One weekend a resident said, "So you realized you're lonely. Have you ever thought about how lonely your doctors and nurses are?"

I hadn't. I began to learn how my caregivers' and hospital workers' lives also had changed. Many had lost friendships as a result of their exposure to COVID-19. Others spent weeks away from their families because of quarantine rules, faced with the financial alternative of giving up this job in a very risky employment market. They said, with some irony, that they missed the intimacy they had with cancer patients. The virus didn't only eat away at the lungs. It ate away at social bonds.

I've now been home for three months. Only last week I walked 2.5 miles and climbed a lighthouse at Woods Hole. But my mind still gravitates to that room and the thousands of new COVID-19 patients around the world who will be in a room like it.

I made a decision to devote my time to telling these patients that they are not alone. Where I can digitally reach people in isolation, I try to do that. I've also spoken with health care administrators about antidotes for loneliness, and how desperately we need them—for patients, for families and for the care providers who too often are lonely while protecting us from this pandemic.

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