

Forty-fifth ASPEN Presidential Address: Research in a pandemic—Why, what, how?

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I titled my presidential address “Research in a pandemic—Why, what, how?” First, I have no relevant disclosures to this talk, but I am a consultant for a number of companies that I have listed here, none of which will be relevant to what I discuss in this talk. Here is what I am hoping you will take away from the next ~40 min: I am going to try to characterize the research community’s response to the coronavirus disease 2019 (COVID-19) pandemic. We are going to talk about some of the cool innovation that has allowed research to be done during the pandemic and is undoubtedly going to carry forward into postpandemic research times. And then, I am going to outline why it is important to conduct rigorous research to guide treatment during a pandemic. In fact, I am going to start the talk with a lot of the “why research is important” in the middle of this pandemic.

Anything big happen in the last year? Any big medical news over the last 12 months? Anything that, you know, might have affected the world? Obviously, the biggest story of the last 12, really 18, months in the world (12 months in the United States) has been the SARS-CoV-2 pandemic, or COVID-19. The impact has been immense: >120 million people infected worldwide, almost 30 million infected in the United States alone, with >2.5 million deaths across the globe, and more than half a million people dead from COVID-19 in this country alone.¹ As impressive as that is, the bulk of this manuscript will detail the response to this pandemic.

Medical science took front and center stage. There definitely were some bad aspects, some mistakes, some areas we would like to do differently in future pandemics. Hopefully, we will not have future pandemics, but let us use the experience from the current pandemic to be better prepared. However, the medical response also had a lot of good, real innovation and some really important discoveries. Medical science

is responsible for where we are today, with some known effective treatments and numerous effective vaccines. Let me see if I can describe the view from a medical scientist in the belly of the beast of SARS-CoV-2 research over the past 12 months.

The US story starts in February or March 2020. As cases, hospitalizations, and, unfortunately, deaths were starting to increase, many of us in the medical profession were starting to get a pretty high level of anxiety. For us, this was a new disease; we did not know exactly what to expect. We had heard reports and we had read reports but we had not personally seen a lot of actual cases yet. We did not exactly know what we were getting into. And in fact, we labeled this a new disease, but then we argued, Is it truly a new disease?

In the critical care world alone, a number of publications argued back and forth: Was COVID-19 actually a new disease? Or was it just a new virus causing a disease we had seen before? Some argued that COVID-19 was typical acute respiratory distress syndrome (ARDS).^{2,3} Others argued it was different—maybe even high-altitude pulmonary edema and not ARDS at all.^{4,5} Still others rebutted that it is typical ARDS, and in fact, it was almost insulting to call it high-altitude pulmonary edema.⁶ Yours truly even jumped into the fray and said, “We should continue to do what we know are the best treatments for patients with typical ARDS and patients who are critically ill in general⁷—because that is what we know is best for our patients.” We should not waver from that treatment plan and either do things that are unknown or, in some cases, follow rash recommendations to do things that the medical community had previously studied and knew to be detrimental and harmful to our patients. But instead, we should continue to practice critical care medicine as best we could.⁷

Also, at this time, there were numerous questions about specific COVID-19–related treatments. Almost all of the treatments were based on anecdotal reports. There was no real, rigorous research during this time, no published randomized trials, no good treatment trials that had been published. The data that were emerging were mostly case series, cohort studies, and associations. And, having lived through and tried to practice medicine during the early part of the pandemic, I would best describe it as complete chaos. It was absolute chaos. Every day somebody would think that they came up with a new treatment. Maybe we should try it? I would get calls from lots of people saying, “Hey, have you thought of this?” “Hey, have you thought of that?” And it was complete chaos.

The treatment paradigm remained uncertain, with lots and lots and lots of theoretical and proposed treatments. But, at that time, none of the proposed treatments had really been rigorously studied. And we did not know whether any of these proposed treatments actually worked. We did not know whether any of these were good for patients, neutral to patients, or even harmful for patients. It was a very unsettling time to both practice medicine and try to conduct research.

The problem with the data that were available for these treatments was that they largely came from cohort studies. The data came from observational studies, which often find a relationship between an exposure and an outcome. However, trying to understand whether that relationship is causal or whether it is just coincidence is, at best, difficult and, many times, impossible when using observational studies. Determining causality is frequently (or almost always) not achievable through observational studies. Look at an example of this: alcohol and lung cancer. Many moons ago, we used to think that alcohol was related to lung cancer and that alcohol maybe even caused lung cancer. Then, we realized that there might be a confounder—specifically, smoking—in the relationship between alcohol and lung cancer. We know smoking causes lung cancer. And we know there is an association between alcohol and smoking. Patients who drink a fair amount of alcohol are more likely to be smokers. It turns out that this relationship that we thought we had understood and had found between alcohol and lung cancer was merely a coincidence, as smoking was really the causative factor. And though there was an association between alcohol and smoking, alcohol really did not play any role in lung cancer at all. Smoking was the confounder in the relationship between alcohol and lung cancer and the real cause of lung cancer.⁸

However, early in the pandemic, observational studies were all that were available. Therefore, observational studies represented the level of science available for all of these proposed treatments for COVID-19 during the early parts of the pandemic. The treatments were associated either with better outcomes or with not contracting the disease. However, that association was not necessarily causative. The studies demonstrated an association, but that did not equal evidence of cause and effect, and the association is likely to be affected by many confounders. What were needed in order to figure out causal relationships and effective treatments were more randomized controlled trials to answer these questions.

Without known effective treatments from randomized controlled trials, and only knowing treatments from numerous anecdotal reports

or confounded data from observational studies, the clinical care being provided to patients varied widely. To give you an idea, early unpublished data from >40 hospitals across the United States in the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network, funded by the National Heart, Lung, and Blood Institute (NHLBI), looked at treatment provided for ~15,000 hospitalized patients with COVID-19 from March 2020 through June 2020.⁹ Almost two-thirds of the patients got azithromycin as a treatment for their COVID-19. More than half received hydroxychloroquine as a treatment for their COVID-19. Steroids, which later became the first known effective treatment for COVID-19 through multiple randomized trials demonstrating benefit, were only given to about one of every five or six patients with COVID-19 at that time. Again, clinicians were trying to use the data that were available at that time to direct their treatments, but the data were largely associations, not from randomized trials, and not able to answer the question of whether these treatments caused improved outcomes.

What was understood at this time was there were different phases of the disease (Figure 1). Some patients who were infected were asymptomatic carriers of SARS-CoV-2 coronavirus. They transmit the virus and give it to other people and other patients. However, from a treatment and research perspective, the goal for not-yet-symptomatic patients infected with COVID-19 is to try to prevent symptoms and prevent transmission of the virus to others. The next phase is a mild phase during which people have symptoms but the symptoms are not severe enough that the patient needs to be in a hospital. At this point, the body is starting to see some viral tissue injury occurring, but not really an inflammatory injury—just early viral tissue replication and injury. This could occur in the gastrointestinal tract, causing nausea and diarrhea, but mostly occurs in the upper and lower respiratory tract, where angiotensin converting enzyme 2 (ACE-2) is largely found. This results in upper respiratory symptoms, cough, and some shortness of breath. From a research standpoint, the goal here would be to find therapies that improve symptoms and prevent people from progressing to needing to be in the hospital. Next, you have moderate COVID-19, in which patients get a little bit worse. They have some symptoms such as severe hypoxemia that requires oxygen. They need to be cared for in the hospital. In this phase, the body is experiencing some inflammatory injury, more than just the viral tissue injury. In fact, the virus may not even be actively replicating in the body anymore. The body may have cleared the virus, but now the inflammatory response is causing lung injury and other organ dysfunctions. The goal from a research standpoint in these patients with moderate COVID-19 is to try to find treatments that get these patients better faster and, if we cannot find treatments that get them better faster, at least find treatments that prevent them from progressing to more severe disease. Patients with more severe COVID-19 develop organ failures, especially respiratory failure. They are at an incredibly high risk of death and need care in the intensive care unit. In these patients who already have significant organ dysfunction, the research goal is to find therapies that prevent death and allow those organ failures to heal more quickly.

Early in the pandemic, such as in February, March, and April 2020, there were no known effective therapies for patients with COVID-19.

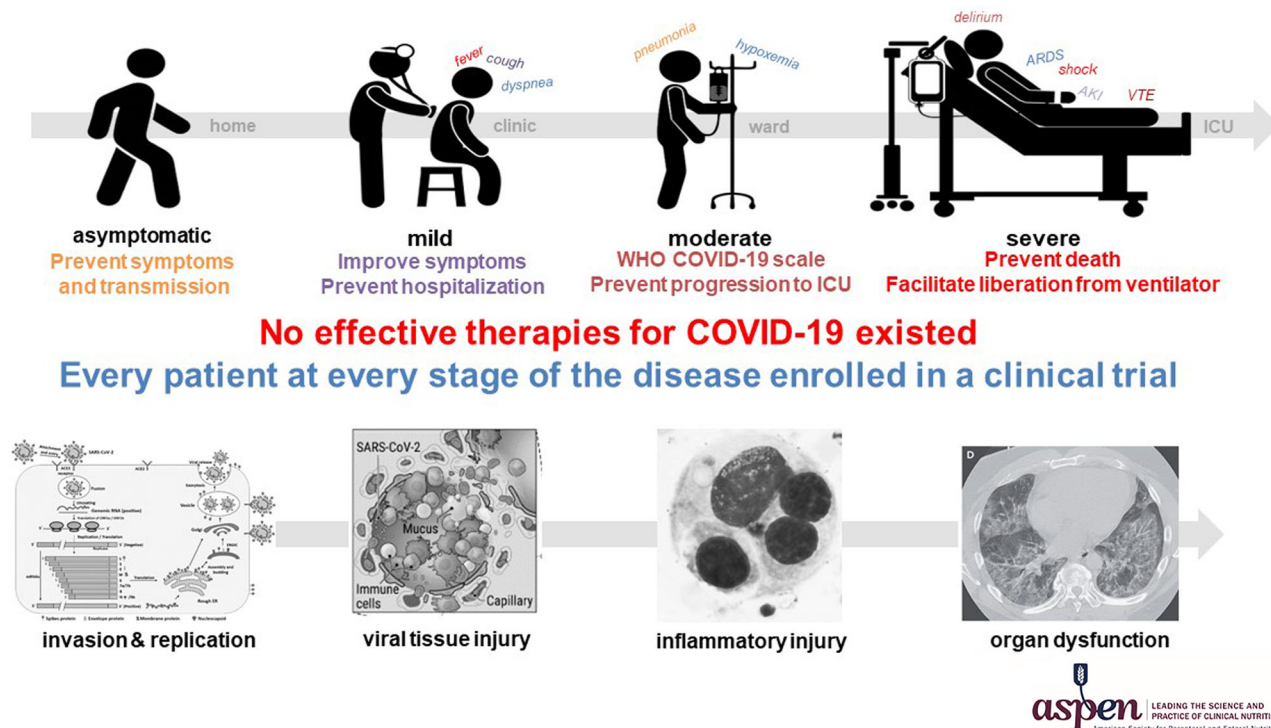


FIGURE 1 Different stages of COVID-19 infection. Patients infected with SARS-CoV-2 virus can have varying and progressive degrees of illness, starting with asymptomatic infection on the left and progressing to critical illness with multisystem organ failure and risk for death on the right. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICU, intensive care unit; VTE, venous thromboembolism; WHO, World Health Organization

None existed. And what we said in this kind of research world was that we should provide an opportunity for every patient, no matter what stage of disease that they are in, to be enrolled in a clinical trial so that we can better understand this disease and better treat patients. It does not matter whether that is preventing them from getting symptoms or preventing them from dying and helping them recover their failing organs faster. We want opportunities and trials in each of the above phases in order to understand this disease and improve patient outcomes.

What did research look like during this early February, March, and April 2020 time period? Well, dedicated funding for COVID-19 research was largely absent at that time. There really was not a lot of it around. The National Institutes of Health (NIH) did have programs that allowed researchers already funded by the NIH to submit ancillary submissions for a COVID-19 funded project, but the proposal needed to be added onto an already established and funded network or grant. Therefore, if you were not already an NIH-funded researcher or were not already part of an NIH-funded network, there really was not an opportunity for you to get large NIH funding to study COVID-19 during this early phase.

Many established, NIH-funded networks actually did submit ancillary proposals for COVID-19 early in the pandemic. I am part of the PETAL Network from NHLBI, who used ancillary funds to study hydroxychloroquine in hospitalized patients and ultimately demonstrated that hydroxychloroquine did not improve outcomes in these patients.¹⁰ It was the biggest question early in the pandemic. In vitro

data suggested that hydroxychloroquine might have some antiviral activity against the SARS-CoV-2 coronavirus, leading many to hypothesize that it might be an effective treatment for patients with COVID-19. In addition, numerous observational studies suggested it might be associated with improved outcomes.^{11–16} The PETAL Network utilized ancillary funding from NHLBI to study hydroxychloroquine in a blinded randomized controlled trial and demonstrated that it did not improve outcomes in patients hospitalized with COVID-19.¹⁰ Another NHLBI-funded network, Strategies to Innovate Emergency Care Clinical Trials Network (SIREN), is an emergency department network that received funding for evaluating convalescent plasma in outpatients with COVID-19.¹⁷ Another funding source early in the pandemic was the Biomedical Advanced Research and Development Authority (BARDA). BARDA also had some funding and was trying to fund some clinical trials, but honestly, it was a pretty archaic and slow process, and it was difficult to get funding through BARDA.

Another NIH agency, the National Institute of Allergy and Infectious Diseases (NIAID), also had funding early in the pandemic to study treatments for COVID-19. NIAID had already coordinated a number of their networks into a group called the Adaptive COVID-19 Treatment Trial (ACTT). ACTT was a platform trial that NIAID had already set up prior to the pandemic reaching the United States. Because it was already in place, the ACTT study seamlessly turned out to be the infrastructure for the NIH's first trial in patients with COVID-19, named ACTT-1. ACTT-1 enrolled >1000 patients from sites both in the United States and internationally, from February 21 through April 19,

2020, and demonstrated that remdesivir got patients better faster.¹⁸ Remdesivir shortened the time to resolution of symptoms and time to recovery, which really amounted to getting out of the hospital in patients who were hospitalized with COVID-19.

So this was big, because this was the first proven treatment for patients with COVID-19, and everybody sort of celebrated this treatment and was excited about the fact that finally, in April 2020, we had something that had demonstrated benefit and that was a treatment specific to patients with COVID-19. It turns out, as subsequent data came along, that maybe this was not the most effective treatment ever, but it still was sort of a morale booster for the research world because we had found something. And we had found something in just a few short months that we could at least use to treat patients who were hospitalized with COVID-19.

There were other sources of funding for research beyond governmental funding early in the pandemic. Industry provided some funding for research, although it was largely supporting their specific randomized trials of their products to see if they had a beneficial treatment effect in patients with COVID-19. Many institutions had institutional funds. They were not often huge amounts of money, but they would support small projects at their institution to look at specific aspects related to COVID-19. Institutional funds were almost never large enough to support randomized controlled trials of potential therapies. Finally, we would be remiss if we did not also mention the professional medical societies. Societies such as the American Society for Parenteral and Enteral Nutrition (ASPEN)—many through their research foundations—provided funding for research projects specific to COVID-19. For example, the ASPEN Rhoads Research Foundation developed a COVID-19 research fund and funded specific projects investigating COVID-19. Other societies did similar, and so there were other sources of funding. But the NIH funding opportunities, which represented the bulk of the funding, were pretty much tied to already being an NIH-funded investigator during these early pandemic times.

Some of you may have heard that there was even philanthropy that occurred during the early pandemic times. Dolly Parton, in my state of Tennessee, donated \$1 million of her own money to Vanderbilt University Medical Center to do COVID-19 research. It turns out that I was fortunate enough to get some of Dolly Parton's donated money to do a trial called Passive Immunity Trial of Nashville, or PassItON. PassItON was a trial of convalescent plasma that you will hear a lot about during this talk. This multicenter randomized controlled trial started with funding from Dolly Parton. The "PassItON" name was perfect for the mnemonic for the Passive Immunity Trial of Nashville, but it also kind of went back to Dolly. As some of you may not know, Dolly Parton, decades ago, developed and has continued to fund and support a philanthropic endeavor called the Imagination Library. The Imagination Library is an organization that Dolly has set up that sends children's books to every child in the state of Tennessee. I understand it has expanded past the state of Tennessee now, but it started in Tennessee from funding from Dolly Parton. One of the books that the Imagination Library actually sends to children in the state of Tennessee is a book by Sophy Henn called *Pass It On*. It kind of came back home with Dolly that we named our trial

PassItON because she funded the start of this trial and it is one of the books that she sends out through the Imagination Library.

A little later in the pandemic, starting in May 2020, Operation Warp Speed got funded and started operations. Many of you have probably heard about Operation Warp Speed. If you have not, here are some details. On May 15, 2020, the US government officially announced the creation of Operation Warp Speed, which would serve as the funding source for future discoveries in COVID-19.¹⁹ It was really designed in late April 2020, and many people knew about it before it was officially announced. But the government officially announced its existence on May 15, 2020. Operation Warp Speed was a public-private partnership between a number of government organizations that conduct research and private firms, mostly pharmaceutical companies. The goal was to pair government organizations and private pharmaceutical companies to expedite the task of discovering effective therapeutic and preventative strategies against COVID-19. The objective of Operation Warp Speed was to facilitate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. Operation Warp Speed spent a lot, a lot of money and time on vaccines. They also had a charge to discover therapeutics and diagnostics, but a big portion of the money and their expenditures went toward COVID-19 vaccines. Through the Coronavirus Aid, Relief, and Economic Security (CARES) Act passed by Congress, Operation Warp Speed was initially funded with \$10 billion, which was increased to \$18 billion in October 2020.

How did Operation Warp Speed spend their money? About \$12 billion of their \$18 billion in funding went toward vaccine development. They had two big objectives: produce and deliver 300 million doses of a safe and effective vaccine or multiple safe and effective vaccines, with the hope that the initial doses would be available for public use by January 2021. They also did something really important. They facilitated manufacturing of vaccine candidates while the vaccine remained in preapproved status during pre-final research. So what Operation Warp Speed did was contract with a number of the vaccine-producing companies (Pfizer, Moderna, Johnson & Johnson, AstraZeneca), and they said, "We are going to buy 100 million doses of your vaccine, whether it works or not. There is no risk for you to start producing it, so start mass producing it, even before the data show whether it is effective or not. If it works, great, we are going to buy it. And if it does not work, we will still buy those 100 million doses of a vaccine that does not work, just so that we do not have to wait for the research to get done to know that the vaccine is effective before we start mass producing these vaccines." This was a big reason why vaccines came to be used in the public in ~9 months or a little less than 9 months from the start of these trials. This was a huge advancement—a monetary and financial risk, but a big advance in speeding up the process to get an effective vaccine to the population.

Other Operation Warp Speed money was directed toward COVID-19 therapeutics and diagnostics, and this was pretty broad. There was funding for monoclonal antibody research. There was funding for other NIH projects and funding for the institutes within the NIH. The NHLBI of the NIH developed and funded a group called Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS), which is a group that now oversees all NHLBI

Passive Immunity Trial of Our Nation (PassITON)

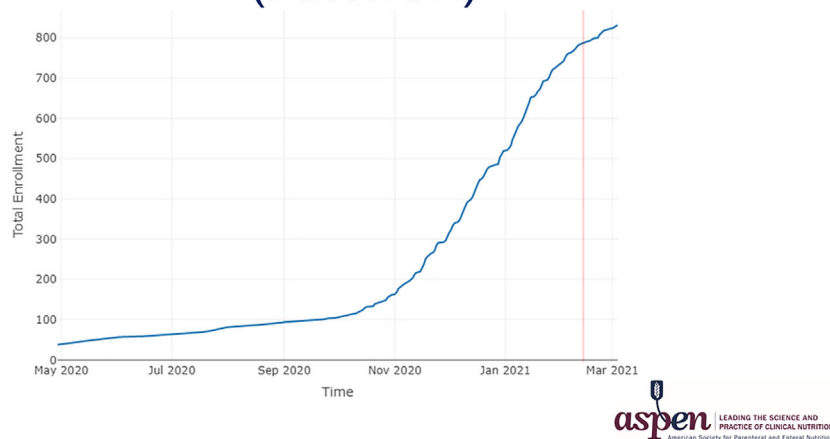


FIGURE 2 Enrollment in the Passive Immunity of Our Nation (PassITON) trial over time. Initially, the trial began as a single-center study funded by Dolly Parton’s COVID-19 Research Fund. In August 2020, National Center for Advancing Translational Sciences (NCATS) funding was obtained, and the project expanded to include >30 sites across the United States

COVID-19 research. It was developed from Operation Warp Speed funding around June or July 2020, and it is responsible for the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) platform, which is a therapeutic platform testing treatments for both inpatients and outpatients with COVID-19. The ACTIV platform contains many different treatment arms testing a wide variety of therapeutics. Operation Warp Speed took over funding the NIAID ACTT platform; so it took over funding of the platform that had developed and studied remdesivir. Through the National Center for Advancing Translational Sciences (NCATS), another institute in the NIH, Operation Warp Speed also funded clinical trials investigating convalescent plasma as a treatment for patients with COVID-19. We already had the infrastructure in place and a trial investigating convalescent plasma up and running, thanks to some of Dolly Parton’s donation. Lastly, additional funding from Operation Warp Speed went to the Centers for Disease Control and Prevention (CDC) to understand the COVID-19 disease process from an epidemiologic standpoint and to study vaccine effectiveness once the vaccines were available to the public.

Let us specifically look in more detail at the NCATS convalescent plasma study. I already mentioned that Dolly Parton had given money to Vanderbilt University Medical Center, and we were fortunate to get some of that money to start our PassITON trial of convalescent plasma. This was a randomized trial, convalescent plasma vs a placebo, which turned out to be a lactated ringer’s solution with multivitamin in it to make it the same color as plasma. The objective was to truly understand whether convalescent plasma was beneficial to hospitalized patients with COVID-19.²⁰ Using some of Dolly’s donation, we got this study up and running in May 2020. We actually got it enrolling, and as you can see, we were enrolling slowly in May, June, and July 2020, only enrolling hospitalized patients with COVID-19 at Vanderbilt as a single-center study (Figure 2). Throughout these months, we

had numerous discussions with NCATS to try to obtain funding to do a big, multicenter, nationwide study of convalescent plasma to quickly enroll a lot of patients and efficiently get an answer to the question of whether or not convalescent plasma was beneficial for hospitalized patients with COVID-19. We had lots of back and forth with NCATS, but ultimately NCATS told us, “Operation Warp Speed kind of controls the purse strings, and until they give us the money, we do not have the funding to give you to conduct a multicenter trial.” Talking back and forth, back and forth, back and forth, we suddenly get THE email. I know you are probably thinking, Well, what does that mean, Todd? What is THE email? So here is THE email: Friday, July 17, 2020, from Clare Schmitt, who is one of the program officers at NCATS, with the subject of “Urgent-Convalescent Plasma Trial Info Needed.” “Hello. When it rains it pours. This trial is now on many folks’ radar. The WH . . .” And as I read this I thought, the WH? Wait, that is the White House. “The WH and BARDA need a bit more information ASAP. I’d appreciate your responses as quickly as possible.” So it turns out that in the middle of July, the White House and the President of the United States were very interested in convalescent plasma and learning whether or not it worked to treat patients with COVID-19. Their interests led to pressure on Operation Warp Speed. After some discussion and consultation, Operation Warp Speed then provided funding to us to expand from a single-center trial just at Vanderbilt University Medical Center to a multicenter trial across the country with >30 different sites enrolling patients in this trial. And the name of the trial changed from Passive Immunity Trial of Our Nashville to Passive Immunity Trial of Our Nation.

This was definitely different than what any of us who had NIH funding before had ever seen. The purse strings were a little different. The way the money flowed was a little bit different. And this was, I guarantee you, the first and the only time I will receive an email that

says the White House is really interested in the research that you are conducting.

Figure 2 shows what happened after that. We got money for multicenter funding in August. We started opening multiple centers in September 2020. We actually started to see a surge in cases across the country during that time, too. And we went from kind of smoldering along with enrollments to a pretty steep slope of enrollments, and currently, we have a little less than 850 patients enrolled on our way to 1000 to try to truly answer the question of whether convalescent plasma is beneficial to patients hospitalized with COVID-19. That is just one personal anecdote demonstrating the chaotic research environment that occurred during the first ~9 months during COVID-19. It was chaotic. I am not sure it was great. It was disorganized. There were lots of people studying similar things and stepping on each other. However, despite all of the downsides, there were a number of positives that came from it. Lots of innovation has come from research in the last 9 months. Let us talk about some of this innovation.

The first and the biggest innovation obviously is the vaccines, and specifically the mRNA vaccines. mRNA is messenger RNA, the actual RNA that the cells within our body use to make proteins. It is the kind of script, the directions, the recipe for making the proteins within the cells. Although technically new technology, mRNA was actually isolated in the 1990s. The potential of mRNA was already known well before the start of this pandemic.²¹ It was already known that mRNA technology would allow us to manipulate a cell in the human body to make it produce a protein that we wanted it to make. But honestly, scientists had encountered significant difficulty getting mRNA inserted into human cells and being able to get the cells to actually make the coded protein. It turns out that when injecting naked mRNA by itself, some of it gets into cells, but the process is not very efficient and it does not really cause the cell to make a lot of the desired protein. In the 2010s, scientists discovered that if you put the mRNA in a lipid nanoparticle, the cell would actually take it up better. The cell would degrade the lipid nanoparticle, leaving the now naked encoded mRNA in the cell, and the cell would actually make the proteins coded for by the mRNA. This allowed for the development of mRNA vaccines—specifically, SARS-CoV-2 mRNA vaccines. The mRNA in the lipid nanoparticle gets taken up by the cell and the lipid nanoparticle degrades, leaving the naked mRNA in the cell for translation into protein. The ribosome in the cellular cytoplasm sees that mRNA and starts translating the message from that mRNA into a protein, which it then sends to the Golgi apparatus, which packages that protein up and presents it on the cell surface. In the case of this SARS-CoV-2 vaccine, the protein presented on the cell surface is the viral spike protein from SARS-CoV-2. The cell then displays that spike protein on its surface, and as it shows it on the surface of the cell, it actually will present it to the patient's immune system. The patient's immune system recognizes the protein as foreign and develops patient-derived antibodies from these proteins being presented on these cells. Then, those antibodies actually protect the patient when they are exposed to the SARS-CoV-2 virus, as they already have circulating antibodies against the spike protein.

Many of you already know that the spike protein is the protein on the virus that -it uses to attach to human cells in order to put its RNA into the cell to replicate within our cells. When that spike protein on the virus is blocked by an antibody, the virus cannot attach to the cells. It cannot transmit its instructions through its RNA into the cell. It cannot manipulate the cell to make the viral proteins, and the virus essentially cannot replicate. That is how viral replication works and how the vaccines prevent viral replication and essentially protect patients from getting infected with SARS-CoV-2.

However, prior to COVID-19, this mRNA and nanoparticle technology had never been used before in human vaccines. It had been used in animals; it had been used in chimpanzees; but it had never actually been used in humans before COVID-19. This is one of the reasons that the SARS-CoV-2 mRNA vaccine trials enrolled 30,000 people in them—to understand what this mRNA did in humans, what the body's response was, what the antibody response was, and what the immunogenetic response from humans was to this vaccine. And it turns out it is highly efficient. And that is why the vaccines are 95% effective at preventing people from getting infected, because the mRNA vaccines are really, really efficient at getting the body to produce its own antibodies against those proteins and, specifically, the spike protein in the case of COVID-19 mRNA vaccines. It also turns out that this innovation is groundbreaking, and it is going to lead to a lot of advances in medicine.

Some of my colleagues who conduct research in respiratory viral areas tell me that mRNA technology is likely going to lead to a vaccine against respiratory syncytial virus (RSV) in the near future. And they tell me that it will also probably lead to a vaccine against parainfluenza illness. In fact, many are hopeful that mRNA vaccine technology may largely eliminate childhood hospitalizations from respiratory viral illnesses that contribute a significant proportion of childhood hospital admissions because of the high level of efficacy of these mRNA vaccines. However, mRNA technology is not just going to revolutionize vaccines. It is also going to be relevant in cancer treatments. Instead of giving patients the mRNA for a protein on a virus, doctors will inject them with the mRNA of a protein that is specific to their cancer—not just their cancer type, but their specific cancer, specific to them. The mRNA prompts the cells to produce that protein, and the patient then creates antibodies against that specific protein of their own cancer. They will produce massive amounts of antibodies that actually go and fight that cancer and those malignant cells. In addition, the patient actually maintains those antibodies, or at least an immune response, to those proteins, so if their cancer tries to return as a metastasis someplace, the patient still has antibodies and an immune response, allowing the patient to fight that metastasis early on in the process of the cancer trying to metastasize. Another realm that mRNA technology has created optimism in is gene therapy, specifically for either diseases that lack a protein that the body needs or diseases in which a protein that is needed for normal functioning of the human body is malformed and/or malfunctioning. In these situations, this technology is used to give mRNA to patients to prompt their cells to make the actual functional protein and provide a potential treatment, or maybe even a cure, for patients with these missing or malfunctioning protein diseases. The mRNA technology is exciting technology for sure.

Another innovation from the pandemic is improved efficiency in conducting clinical research. Let me show you exactly what that means. Take two scenarios for conducting research. The first is sort of the old way of doing things. Imagine how this goes during an infectious disease outbreak. The outbreak occurs, clinical research endeavors start to get up and running, a public health response begins to develop, preclinical research response starts, and clinical research starts to run through its normal tracks. Somewhere way down the road, usually as the outbreak is kind of waning, the clinical research response actually gets fully up and running. What research realized in this pandemic was the ability to do multiple steps of this process simultaneously and move the whole clinical research response very far to the left, or very much earlier in the course of the pandemic. Although maybe clinical trials were not fully up and running exactly as the outbreak was starting, they certainly were during the early surges, which allowed the medical and scientific communities to have actual clinical research that was responsive to the pandemic. The scientific community could do this—have good research but do it efficiently and fast and get answers that might actually affect the outcome of patients during the pandemic and not just as a response to the pandemic near its end or once it is over.

What are some examples of this in action? One example is the Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among Inpatients With Symptomatic Disease (ORCHID) trial, which was conducted by the PETAL Network and funded by NHLBI.¹⁰ The network met on March 20, 2020, for the very first meeting of the study group to discuss potential treatments for hospitalized patients with COVID-19. At that first meeting, the obvious first question in any research project was discussed, namely, “What do we want to study?” At that point, it had not even been decided that hydroxychloroquine was going to be the first drug studied in patients hospitalized with COVID-19. That first meeting (all by video conferencing, of course) was a brainstorming discussion about what treatment the network would study first. On April 2, 2020, a mere 13 days after that first meeting, the network actually enrolled the first patient in the trial. That is <2 weeks between the very first planning meeting of the network and enrollment of the first patient. What happened during those 13 days? A protocol was written and sent to the US Food and Drug Administration (FDA). The FDA reviewed the protocol and agreed that the study could be done under FDA regulations—specifically, under an investigational new drug (IND) exemption. A consent form was developed, and the protocol and consent form were sent to an institutional review board (IRB) to review and approve. In addition, an electronic consent form was also developed so that consent could be obtained from patients remotely without needing research staff present in the hospital. We will look at the electronic consent (e-consent) process in more detail as another innovation in this era in a little bit. The statisticians developed a randomization scheme, and the pharmacy developed a matching placebo. The pharmacy at Vanderbilt developed a placebo in these 13 days to match the commercially available hydroxychloroquine, which enabled the network to conduct a randomized, BLINDED, placebo-controlled trial.²² That first enrollment on April 2, 2020, started trial enrollments, which totaled 479 patients enrolled over the course of ~2.5 months at 34 US hospitals. This randomized, placebo-controlled trial was decided

upon, designed, and approved with first enrollment in <2 weeks and full enrollment in <3 months—a process that, before COVID-19, would have taken 9 months and 3 years to complete, respectively. Although it turned out that hydroxychloroquine was not beneficial in the treatment of these patients, the PETAL Network ORCHID trial definitively answered the question of whether or not hydroxychloroquine benefited patients with COVID-19.

The first NIAID study in COVID-19, ACTT-1, which studied the effects of remdesivir in hospitalized patients with COVID-19, represents another great example of the times. ACTT-1 studied intravenous remdesivir, a brand-new antiviral medicine, compared with placebo in hospitalized patients with COVID-19.¹⁸ Unlike hydroxychloroquine, intravenous remdesivir was not a medicine that was already FDA approved. It was not a medicine that was already being used in the treatment of other diseases (hydroxychloroquine was already being used to treat lupus or malaria in clinical practice, for example). As such, remdesivir, unlike hydroxychloroquine, was not a medicine for which we already had lots of safety data. This was a brand-new drug, with a bunch of regulatory hoops to jump through in order to ensure safety in studying it. Despite this, the NIAID-sponsored ACTT-1 trial enrolled 1062 patients in <2 months (58 days, to be exact) at 133 trial sites in 10 different countries. And it was a fabulous thing. That is an unbelievable feat in its own right, with the last patient enrolled April 19, 2020. You may have seen Dr Fauci’s press conference from the White House on April 29, 2020, 10 days after the last patient was enrolled, announcing the results. Within 10 days of the last patient being enrolled, the data were available and analyzed, allowing Dr Fauci to announce from the White House that remdesivir shortened the time to recovery in these patients. This was followed by a *New England Journal of Medicine* publication—a preliminary publication, but still a publication in the *New England Journal of Medicine*—on May 22, 2020, essentially a little over a month after the last patient was enrolled. The efficiency in which this trial was designed, conducted, completed, and analyzed with the results publicly disseminated to clinicians caring for patients was truly remarkable and unbelievable.

I briefly mentioned “e-consent” a little bit ago. Let us revisit electronic consent. What about electronic consent during the pandemic was innovative? Not surprisingly, consent for research during this time was a bit chaotic. Personal protective equipment (PPE) to protect against contracting the virus was limited. Patients were in isolation, and families were at home, as hospital visitation was suspended. Most research personnel were also prohibited from being in the hospital because they were furloughed or were restricted to working from home. Given these limitations, how were research teams ever going to obtain consent from patients with COVID-19 for participation in research studies? Here is where innovation came in (Figure 3). First, the traditional paper-based consent process was adapted to accommodate the situation. A scanned copy of the consent form that the research team had already signed was sent to either the patient, if they were able to make their own decisions, or their surrogate decision makers, if the patient’s decision making was impaired. If the patients themselves were consenting, the research team gave patients a paper copy of the consent form in their rooms. If a surrogate was being consented, the

eConsent During COVID-19 Pandemic

Paper-based Approach

1. **Scanned copy of the signed consent form** emailed, faxed, or otherwise electronically **transferred to the patient** (institutional policy)
2. Research staff contacts the patient by telephone or videophone to have an informed consent conversation. *This step confirms patient identity.*
3. **Patient signs the consent form.**
4. **Photograph is taken of the signature page** of the consent form and uploaded to research staff. Using the patient's device (such as a patient's personal cellular phone), a REDCap survey link can be sent to their device. This survey link will allow direct upload of the image to REDCap.
6. The participant retains the consent form.

Electronic Approach

1. A **link for the electronic consent** is **sent** to the participant.
2. Research staff contacts the patient by telephone or videophone to have an informed consent conversation. *This step confirms participant identity.*
3. **Patient signs the consent form electronically.**
4. Copy of the **completed consent form is emailed** to participant



FIGURE 3 e-Consent during the coronavirus disease 2019 (COVID-19) pandemic. Because of a marked decreased or absent ability to physically interact with potential study participants in person, two different e-consenting approaches were developed to allow participants to provide informed consent for participation in research studies for COVID-19

research team sent a scanned copy of the consent form electronically to the surrogate, who was not at the hospital. This electronic delivery of the scanned consent form was operationalized in a way that was acceptable by different institutional policies. Some institutions allowed texts, some wanted delivery via email, others wanted delivery by tablet, etc. After the patient had received the paper consent form or the surrogate had received the scanned consent form, the research team either called the patient in their room (often times using the room landline phone) if they were able to consent for themselves or called their surrogate by either phone or videophone to walk them through the informed consent conversation. The patient then signed the paper consent form within their room (they are in isolation, remember) and took a picture of the signature page. In cases when the patient was not able to consent, the surrogate would print out the electronic copy, sign the copy, and take a picture of their wet signature on the consent form. The research team would then send either the patient or surrogate an electronic link where they could upload that picture of their signature. If the patient signed, they kept the paper consent form that they received in their isolation room to eliminate the risk of contamination with the consent form coming out of the room. Both of these methods resulted in a legally allowable consent form with the picture of their signature. If the research team was obtaining consent from the surrogate, the surrogate did not have to return any signed consent form but just electronically uploaded the picture of their signature, as the study team had continued access to the electronic scanned version of the consent form.

The second way that consent for research was obtained during the early part of the pandemic used a purely electronic approach. A link to an IRB-approved and study-specific wholly electronic consent form was sent to either the participant or the surrogate. Then, just like with the paper-based approach, the research team would contact the patient or surrogate by phone or videophone, walk them through the informed consent conversation, and have them sign the consent form

electronically on their phone or a tablet. After they signed the electronic consent form, the patient or surrogate would get a copy of the completed consent form emailed to them or sent to them by fax if they did not have an email address (the research team would get a fax number for them or a place that they could receive a fax so that they could get a copy of the consent). A copy of the signed consent was also kept in their electronic research file. This meant that the research team had a copy (electronic copy) of the consent form and the participant or surrogate also received a copy of the consent form, a consent process that was entirely done electronically. For people like me who were both conducting research and caring for patients early in the pandemic, we were actually able to merge these two consenting processes. I would obtain consent from the patients using an electronic approach in the patient's isolation room, where I, dressed in full PPE, would take a tablet, pull up the electronic consent form, walk the patient through the consent, and have them electronically sign the consent form. Then, the system would send an email to their email account with a copy of their signed consent form, and the electronic consent form would also be stored in the research database. Then, I would wipe down the tablet on my way out of the room to prevent contamination with anybody outside the room. This consenting process that was developed and utilized during the pandemic is not going to be specific or restricted to COVID-19—well, the contamination part might be. This electronic consent, as you are going to experience here shortly, is going to be used for lots of things outside of COVID-19 and is going to make research consent much more feasible, practicable, and easy than what was done prior to the pandemic. The FDA signed off on all of these approaches. They are all now formally endorsed by the FDA.²³

Another innovation resulting from the pandemic is touchless research. What is meant by the term “touchless research?” Well, let us look at an ongoing outpatient trial that was started during COVID-19 as an example to learn about this process. The trial, named

Trial of Early Therapies During Non-hospitalized Outpatient Window (TREAT NOW), is a multicenter, double-blind, placebo-controlled trial in patients with COVID-19 who are outpatients and not sick enough to need hospitalization. The trial enrolls nonhospitalized patients who have confirmed COVID-19 with <6 days of symptoms. To be eligible, patients need to have had a positive COVID-19 test and <6 days of symptoms. The intervention being studied is an old HIV antiviral drug. There are actually studies that have found that the drug does not benefit patients if treatment is started once they are sick enough with COVID-19 to need hospitalization, but many think because it is an antiviral, it may work better if given earlier—that is, before patients need hospitalization. The TREAT NOW study enrolls patients with COVID-19 in the disease phase before they are admitted to the hospital. The drug is compared with a blinded placebo, and both study drug and placebo are given to patients twice daily for 14 days. Therefore, patients are randomized to receive either the placebo or active drug. The goal is to enroll a sample size of 600 patients. How is this study actually being conducted? The study team gets lists of patients from the healthcare system, drug stores, or outpatient testing clinics of patients who have tested positive. Initially, these lists of patients only came from within the study institutions, but after a few months, we coordinated with drug stores and community testing centers to get lists from them also. The study also utilizes broad advertising through print, media, radio, TV, and billboard advertisements in the areas where centers are actively enrolling for the trial. These advertisements result in a considerable amount of self-referring patients who reach out to inquire about participating in the study. In addition, the study utilizes social media for advertisements, including Facebook and Google, which results in a number of patients seeing the ads and referring themselves from all over the country.

Once a participant who has tested positive for COVID-19 and met the study eligibility criteria is identified, either from the lists or from the advertisements, the study team contacts them by either phone or email to gauge their interest. If the patient says they are not interested in participating in the study, they are thanked for their time and apologized for any inconvenience. However, most patients express interest in at least hearing about a potential opportunity for them to participate in a trial. In these cases, the study team sends them a consent form, usually by email or some other electronic means. The patient reads the consent form, and the study team calls them and walks them through the details of the study. If they agree to participate in the study and sign the consent form, the patient is immediately randomized in the study to either the placebo arm or the intervention arm. Their randomization assignment is then sent to a pharmacy in Colorado for that pharmacy to deliver overnight either the active drug or the placebo (whichever arm the patient was randomized to) to the patient's home address. The patient receives the study medicine the next day and is instructed to start taking it twice a day once the medicine shows up. Just like that, and without any physical interaction with the study team, the patient is enrolled in the study and receives study medication. You may be thinking, Well, that is great, but you still have to get the study outcomes from them. How do you get study outcomes from them? The study outcomes are also collected in a "touchless" manner using newer technology. The

primary study outcome is daily symptoms, which the patient reports daily through an app called MyCap on their phone (projectmycap.org). This technology allows a person to fill out surveys on their phone. The patients are instructed to complete a survey as to what symptoms they are experiencing daily. Alternatively, the study also collects outcomes using a second method. The study database sends the patients a daily text or email (whichever the patient prefers) that allows the patient to just click on a link, which pulls up the survey for them to fill out what symptoms they are experiencing. The patients are essentially performing the data entry for their own symptoms. One of the study concerns and one of the outcomes that the study was very interested in collecting was whether the patients got hospitalized. If patients did get hospitalized, they simply checked a box on their daily symptom score survey documenting that they were hospitalized. Then, the study team reaches out and gets a release of information allowing access to the patient's medical records so the study can record how severe their symptoms were, what they were hospitalized for, etc. That is the data collection process for the study. If the patient fails to answer the daily text or email, the study team receives a notification and calls to remind them or ask them about their symptoms over the phone and records the data in the database for them. However, given that the patients are in quarantine with COVID-19, many with nothing better to do, most of the patients actually answer their texts and their emails. They fill out their own symptomatology in the study database.

You might be thinking, Well, that is kind of cool. I wonder if anybody else is doing this? Other studies are using similar methods. For example, Washington University in St Louis published their trial of fluvoxamine vs placebo in outpatients with COVID-19 in *JAMA* in November 2020.²⁴ This fully remote, double-blind, placebo-controlled clinical trial used "contactless" study methods very similar to those in TREAT NOW. Fluvoxamine is a selective serotonin reuptake inhibitor often used for depression but may have some activity in outpatient COVID-19. The research group sent study supplies to outpatients with COVID-19 who were self-quarantining. However, they actually increased it a little bit and upped the ante. They delivered study materials in a package that was left outside the patient's front door. That study package contained the patient's study medicine, an oxygen saturation monitor (or pulse oximeter), automated blood pressure monitor, and thermometer. This allowed the study to measure and collect vital signs from the patients with the technology that they were delivering to the patient's door. Outcomes of the study were collected similarly to those in TREAT NOW through twice-daily REDCap surveys that were sent via email so that patients could report their symptoms and whether or not they were hospitalized and for the direct download of data from the pulse oximeter and automated blood pressure monitor.

Like electronic consent, although developed during the pandemic, this "contactless" conduct of clinical trials in outpatients is not going to be exclusive to COVID-19 or the pandemic. This research methodology can be extrapolated to outpatient studies in patients with diabetes, hypertension, or other acute or chronic diseases. In fact, we were a little naive at the beginning and only started with enrolling patients in the communities surrounding one of the academic centers participating as an enrolling site. However, we quickly realized that because of the

remote nature of the methodology, enrollment could be expanded to patients almost anywhere. As long as we had access to a list of patients who had tested positive for COVID-19 or patients who tested positive self-referred through advertisements, we could enroll a patient in Montana. The study team could call them from Vanderbilt, get the e-consent, and get study medicine delivered to them overnight to their home in Montana, and they could record their symptoms or whether they were hospitalized remotely by the application or through their phone. Because of the remote methodology, these studies could have one or relatively few enrolling centers that could enroll patients from across the country with the right advertising and outreach.

The last innovation I will discuss is the concept of learning healthcare systems. Learning healthcare systems are not a concept that started during the pandemic, but instead were already taking shape before the pandemic and the pandemic just expedited people's understanding of their importance. If you know me, you probably already know that I practice and conduct research in this area, and I am really excited about the transformative ability of learning healthcare systems. Despite knowing that part of my work, you may not really understand what the learning healthcare system is. A learning healthcare system is a novel way of conducting clinical research. It is comparative effectiveness research within clinical practice. There are two ends of the research spectrum: traditional clinical efficacy trials, which are sort of at one end of the spectrum, and comparative effectiveness research within clinical practice, or a learning healthcare system, which is at the other end of the spectrum. In fact, the Institute of Medicine describes the learning healthcare system as a pragmatic comparative effectiveness clinical trial embedded within a real-world setting of clinical practice.²⁵ This means that learning healthcare system studies enroll a large, heterogeneous study population, with really broad inclusion criteria and few to no exclusion criteria. Outcomes of learning healthcare system studies are simple and hopefully already being collected within the medical record and clinical care. The study interventions are simple and can be done by the actual practicing clinician at the bedside. They do not need a special research team. They are frequently already a part of usual care and even maybe do not need strict compliance to be studied. Often times, learning healthcare system studies will test usual-care interventions or an intervention being implemented into practice compared with a usual-care arm already in practice.

Why is this important? Why is the learning healthcare system important? Well, it allows clinical research to be done within clinical practice. It uses clinical practice as the research infrastructure to understand the risks and benefits of usual practices.²⁶ Take an example in which a patient has a common condition and there are at least two available therapies: If evidence is available supporting one of those therapies, clinicians provide that therapy to the patient so that the patient receives the best available therapy. However, if evidence is lacking that one of the therapies is better, clinicians do not know which of the two therapies is better for their patients, and therefore, those therapies are distributed almost arbitrarily or haphazardly to patients. Patients actually still incur the benefits and the risks of those therapies, but arbitrary distribution in clinical practice makes it very diffi-

cult to gain knowledge as to which of the two therapies is superior as a treatment. Subsequently, it is hard to utilize the outcomes of clinical practice to actually improve the care of future patients because of this arbitrary distribution of therapies. However, if that arbitrary distribution is changed to a random distribution of the two therapies, through randomization in a learning healthcare system study, now there is a randomized trial, which allows the determination of cause-and-effect relationships between the therapies and outcomes. This allows knowledge gain and improvement in the care of future patients by better understanding the questions such as whether therapy A is better than therapy B, which is also being used in clinical practice, or whether therapy B is the better therapy for these patients and what are the risks of these two therapies that clinicians are already providing to patients. That is the concept of a learning healthcare system.

To show it to you in a different way, let us compare the traditional research environment, where clinical practice and enrollment in trials are separate, with a learning healthcare system, where they are combined. In the traditional research environment, clinicians care for patients separate from research studies. As patients receive their clinical care in the system, they receive either treatment A or treatment B, which is often decided arbitrarily at the sole discretion of their clinical team. They are incurring the risks and experiencing the benefits of those treatments. Separate from that, there may be a trial comparing treatments A and B. The actual randomization occurs via a dedicated research team. The clinical research study is occurring in a few of those patients, and the study is collecting outcomes from only a few of those patients. The learning healthcare system actually combines these and says, "Let us take common treatments for common conditions, and while they are being given to patients as treatments, let us randomize them and rigorously study them to understand the outcomes, the risks, and the benefits in order to better care for the patients who we are currently taking care of and also the patients who we will take care of in the future."

A learning healthcare system requires tons of people, patients, community members, clinicians, leaders, and biostatisticians. However, it represents a more efficient and more real-life way of doing research and understanding the true effectiveness of treatments for patients. The study results turn out to be immediately generalizable, representative, and personalized to the patient.

Learning healthcare systems were utilized to study treatments for COVID-19. At least three large groups utilized learning healthcare systems to rapidly and efficiently conduct clinical trials in patients with COVID-19: Solidarity, which is done by the World Health Organization (WHO)²⁷; Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), which is a multinational organization that was originally designed before the pandemic to study community-acquired pneumonia but had the ability to flex during the COVID-19 pandemic and study COVID-19 instead of community-acquired pneumonia²⁸; and the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Group, which is largely based in the United Kingdom.²⁹ As examples of their work, the Solidarity Trial Consortium published their 11,000-patient platform randomized controlled trial investigating remdesivir, hydroxychloroquine, lopinavir,

and interferon compared with placebo in the *New England Journal of Medicine*.³⁰ The REMAP-CAP consortium has numerous COVID-19 randomized trials published, but the most important one may have been their randomized platform trial evaluating the effect of interleukin 6 receptor antagonists in critically ill patients with COVID-19.³¹ The RECOVERY Group provided the first randomized data demonstrating the benefit of corticosteroids in hospitalized patients with COVID-19.³² The RECOVERY corticosteroids trial was the first to demonstrate that corticosteroids reduced mortality in patients with COVID-19. All three of these groups conducted highly efficient multinational studies during COVID-19 using similar learning healthcare system approaches. And although they all have made a huge impact on the care of patients with COVID-19, this talk is going to focus on the RECOVERY Group as the example to provide some details of what these groups actually did to in order to produce fast and efficient answers for the treatment of patients with COVID-19.

All three of the consortiums are randomized, platform-design, controlled trials, meaning they have multiple intervention arms compared with a common control arm. In all three, the control arm is an open-label arm with no research intervention added; patients just receive whatever represents the local standard of care. Some randomized platform trials may have a placebo-controlled arm, but none of these three large consortiums used placebos in their control arms. They all used standard of care, meaning all three tested the drugs in an open-label fashion compared with known standard of care. This is learning healthcare system methodology, meaning the bedside clinician is providing the interventions and recording the outcomes. The bedside clinician is placing the order for the drug in the intervention arm, or they are caring for the patient; however, they would normally be without any of the study drugs in the standard-of-care arm. In the RECOVERY Group, in order to facilitate this, bedside clinicians underwent a 5-min online research training course so that they could understand what they were supposed to do as the researcher. Five minutes—that is all it took for the clinician to become the researcher. And if you are familiar with the RECOVERY trial and their results, they have enrolled >20,000 patients with COVID-19 in trials. The vast majority of people in the United Kingdom who have been hospitalized with COVID-19 have been enrolled in one of the study arms of a RECOVERY trial. They are churning out answers using this learning healthcare system methodology.

As stated earlier, this is not entirely new with COVID-19. Pragmatic, learning healthcare system studies are occurring outside of COVID-19. In fact, these types of trials are happening in the nutrition world. The Effect of Higher Protein Dosing in Critically Ill Patients: A Multicenter Registry-based Randomized Trial—The EFFORT Trial is a large, pragmatic, randomized trial of high vs low protein in critically ill patients.³³ The EFFORT trial started in 2019 and is being conducted at >75 international sites. Like other learning healthcare system studies, the intervention and data entry are being done by the local clinicians. Sometimes it is a doctor as the bedside clinician conducting the study. Sometimes it is a registered dietitian. Sometimes it is the bedside nurse. But the interventions and the data entry are all being done by the local clinicians who are also caring for the patients. Enrollments are occurring in Latin America, North America, Europe, Asia, and the

Middle East, and the study is going quite well. The methodology is working. The treatment arms are different, and there is a difference in the amount of protein being administered in the two arms: almost 2 g per kilogram of body weight administered per day in the high-protein group compared with ~1 g per kilogram of body weight delivered per day in the low-protein group. Enrollment is going well, and trial results should be published in the next 12–15 months. This EFFORT trial represents a learning healthcare system-type trial being conducted in nutrition. Nutrition, with its variability in clinical practice and need for data on the effectiveness of some of the nutrition interventions currently used in practice, represents an area ripe for conducting these learning healthcare system trials.

Finally, I have talked to you a lot about research during this pandemic, but what about nutrition research in COVID-19? As you can see from a commentary that I wrote for the *Journal of Parenteral and Enteral Nutrition* for their COVID-19 research issue,³⁴ nutrition research has been largely absent from the COVID-19 research scene. Despite the fact that nutrition is a big component of COVID-19 care, research into the best way to provide this nutrition has largely been missing. Supplements and immunonutrition might be readily available and effective treatments for patients with COVID-19, but the research has been largely missing. Mechanick and colleagues published a scoping review of nutrition research in COVID-19 that found the paucity of randomized controlled trials in nutrition in patients with COVID-19 is particularly glaring.³⁵ Knowledge gaps were discovered for questions on pediatrics, micronutrients, bariatric surgery, transcultural factors, enteral nutrition, protein-energy requirements, glycemic control, home enteral and parenteral nutrition support, and many, many other areas of nutrition support and care. The conclusion of the scoping review found that “multiple critical areas for urgent nutrition research have been identified, particularly using a randomized controlled trial design, to improve nutrition care for patients before, during, and after COVID-19.”

Why has there been such a big gap in nutrition research during this pandemic? What do we need in nutrition research in order to fill that gap? I think we need a number of things. We need dedicated researchers. We need traditional science. We need innovation. Fortunately, we already have some of this. We may need more of this, but many of you already fit into one of these “needs,” and through you, we already have some of this in place. However, what is really lacking is the infrastructure. We lack the infrastructure for informatics and well-established networks. We lack funding specific for nutrition research. We need big-time funding dedicated to nutrition research. Currently, <5% of the NIH budget goes toward nutrition research. Dedicated funding is how big, multicenter studies are done and major discoveries are found. Ultimately, what we really need is THAT email—the email that I received from NCATS that got me funding for our multicenter convalescent plasma trial in patients with COVID-19. We need that sort of breakthrough-type email for nutrition research.

There is hope that the funding for nutrition research is coming. The NIH has a medical nutrition implementation working group³⁶ that ASPEN has been a big part of shaping, and in fact, the NIH reached out

to ASPEN by email last week. ASPEN has met with NIH leadership and is planning to meet with them again and help push forward increased funding for nutrition research from the NIH—real funding representing significant dollars that can support big projects and answer big, practice-changing research questions, fundamental questions that are foundational to understanding nutrition therapy in our patients.

With the pandemic and everything surrounding it, it has been an interesting year to be President of ASPEN. I certainly could not have done it without a number of supporting people. First, the ASPEN Board of Directors: I thank each and every one of you. You have been great and supportive the entire year. You have tolerated lots of videoconference meetings. Thank you all. And of course, the ASPEN staff have been amazing as they always are. Throughout the year, despite all that has been different, the staff have continued to be very supportive and able to adapt. They really are the foundation that all of this is based on, and the Board of Directors really could not do it without the ASPEN staff. And finally, thank you to all the members; thank you all for your time and attention. I hope we have a great meeting. I know we are going to. And I look forward to talking to you more tomorrow and throughout Tuesday.

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Todd W. Rice contributed to the conception and design of the research; Todd W. Rice contributed to the design of the research; Todd W. Rice contributed to the acquisition and analysis of the data; Todd W. Rice contributed to the interpretation of the data; and Todd W. Rice drafted the manuscript. Todd W. Rice critically revised the manuscript, agrees to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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