



MILKEN
INSTITUTE
FasterCures

LESSONS LEARNED FROM COVID-19:

Are There Silver Linings for Biomedical Innovation?

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ABOUT US

About the Milken Institute

The Milken Institute is a nonprofit, nonpartisan think tank. For the past three decades, the Milken Institute has served as a catalyst for practical, scalable solutions to global challenges by connecting human, financial, and educational resources to those who need them. Guided by a conviction that the best ideas, under-resourced, cannot succeed, we conduct research and analysis and convene top experts, innovators, and influencers from different backgrounds and competing viewpoints. We leverage this expertise and insight to construct programs and policy initiatives. These activities are designed to help people build meaningful lives in which they can experience health and well-being, pursue effective education and gainful employment, and access the resources required to create ever-expanding opportunities for themselves and their broader communities.

About FasterCures

FasterCures, a center of the Milken Institute, is working to build a system that is effective, efficient, and driven by a clear vision: patient needs above all else. We believe that transformative and life-saving science should be fully realized and deliver better treatments to the people who need them.

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Introduction by Michael Milken, Chairman, The Milken Institute

Despite enormous human, social, and economic devastation that will forever mark it as a year for the ages, 2020 was also a time of great advances in medical science and public health.

Our recent achievements are built on the solid base of previous support for science beginning with America's response to the 1957 Soviet launch of Sputnik. Recent advances in genomics, bioengineering, drug development, surgery, medical instrumentation, imaging, virology, and artificial intelligence have their roots in this period. The support given to America's biomedical infrastructure over the past half-century has increased our current understanding of cancer, rare diseases, cardiovascular conditions, the brain and—as we've seen with COVID-19—infectious diseases.

Accompanying these developments were effective programs to promote funding for basic, translational, and clinical research. My colleagues and I have worked for decades to help reduce the burden of suffering, disability, and premature death from disease. Since the 1970s, our efforts have helped to transform the process of medical research, raise funds to support studies by thousands of physicians and scientists, and lead programs by nonprofit groups calling for federal action to accelerate cures.

In response to COVID-19, research scientists, health-care providers, government officials, and major companies have thrown aside their parochial interests to cooperate. While the Manhattan Project, the Apollo Program, and the Human Genome Project had each taken years to plan and execute, the comparably ambitious COVID project came together in a matter of weeks. We believe this remarkable achievement signifies a permanent culture change.

All of the Milken Institute's centers have played a crucial role. We focused on six areas: education, testing, prevention, care, cures, and economic support. In March 2020, as part of the education focus, I initiated a series of podcasts featuring interviews with more than 125 global leaders in health, government, industry, and academia. Guests included physicians, Nobel laureates in science, philanthropists, military leaders, and CEOs of the major companies developing vaccines and advanced therapeutics. A list of selected health-related podcasts is in the Appendix of this paper.

FasterCures launched the COVID-19 Treatment and Vaccine Tracker to increase collaboration, minimize clinical trials duplication, and provide a clearer regulatory pathway for small research groups. The center created public policy recommendations and worked to minimize funding delays and other roadblocks. We collaborated with the Biomedical Advanced Research and Development Authority and several vaccine developers to facilitate the ramp-up of manufacturing.

In the following report, FasterCures has identified five broad opportunities for future focus:

- Formalize the unprecedented research collaboration that developed in response to the crisis.
- Make heavy investments in new product development.
- Expand on recent innovations in clinical trial design and execution.
- Accelerate the collection and use of real-world data and evidence.
- Seize this moment to reduce racial and ethnic disparities in health care and research.

Continued focus on these areas will help establish a more robust early warning system for emerging pandemic threats worldwide, expand support for the next generation of researchers, build vaccine manufacturing capacity before it's needed, and involve patients more completely in R&D.

The Milken Institute launched what became FasterCures in 1993 based on the concept that time equals lives. Now is the time to double down on what has worked well so we will never again face a pandemic unprepared. Just as America created the National Aeronautics and Space Administration and the Defense Advanced Research Projects Agency in response to Sputnik, the nation needs a permanent force to confront emerging health threats. COVID-19 is our new Sputnik moment. Let us use it to recommit to bioscience progress and preparedness on behalf of all the world's people.



Mike Milken
Chairman

TABLE OF CONTENTS

- Introduction** 1
 - Why Focus on “Silver Linings”? 1
 - What Lessons Have We Learned? 2
 - Key Takeaways and Opportunities for Future Focus 3
- Research Collaboration** 5
- Accelerating Product Development**..... 10
- Clinical Trial Design and Execution**..... 15
- Collection and Use of Real-World Data and Evidence** 20
- Racial and Ethnic Disparities in Health Care and Research**..... 24
- Conclusion** 28
- Appendix: Select Podcasts from Conversations with Mike Milken:**
- What Are the Lessons of COVID-19?** 29
- Endnotes** 32
- Acknowledgments: Leaders Interviewed**..... 37
- About the Authors**..... 38

INTRODUCTION

As the COVID-19 crisis has unfolded, and as policymakers, scientists, and companies have jumped into the fray to rapidly develop the tools needed to combat the virus, many fault lines have been exposed that FasterCures believes slow progress in biomedical R&D even in the best of times. We have also seen remarkable innovation in the R&D process born of necessity. FasterCures wants to ensure that the lessons of this crisis are not lost when the current urgency subsides—not only for combatting future infectious disease outbreaks but also for conducting every other aspect of biomedical R&D.

Through research and three dozen interviews with key opinion leaders from government, industry, academia, and the nonprofit sector (see Acknowledgments), we have identified promising policies and practices that have emerged from the COVID-19 crisis and should be preserved and enhanced. We have started to explore what must happen to realize those opportunities.

Our focus has centered on five broad areas: (1) research collaboration; (2) acceleration of product development; (3) clinical trial design and execution; (4) collection and use of real-world data and evidence; and (5) racial and ethnic disparities in health care and research.

Our intended audience is policymakers and other leaders across the biomedical R&D ecosystem. For private funders looking for opportunities to create more resilient health and research systems, the Milken Institute Center for Strategic Philanthropy is developing an additional resource, “Infrastructure, Readiness, and Resilience: Giving Smarter to Create a Long-Term, Biomedical Systems-Based Response to COVID-19.” This report will be released in early 2021.

Why Focus on “Silver Linings”?

FasterCures recognizes the crushing loss of lives and livelihoods due to COVID-19 across the globe. As of this writing, more than 1.6 million people have died worldwide, and hundreds of millions more have lost incomes, homes, food security, and more. We acknowledge that much of the COVID-19 response in the United States and around the world has been ineffective and inconsistent and has contributed to preventable harm. We, as a society, have not learned many of the lessons from past outbreaks.

Nonetheless, we are focused on the positive actions by some in the biomedical innovation ecosystem, in part because we believe it is more likely that we will collectively be willing to build on things we have done well or view as positive, as opposed to fixing all the mistakes or the negatives, which can feel like an overwhelming challenge. In our experience, culture change is more likely to occur if treated as a response to opportunity rather than to failure.

Other analysts will rightly focus on how we can better prepare for the next pandemic or infectious disease outbreak. In our view, many of these actions are also relevant to improving biomedical innovation for all diseases. Once a crisis passes, we tend to lose focus or support for implementing all the after-action recommendations. If we can focus on the recommendations with the greatest relevance for our ongoing work in biomedical R&D—emergency or not—perhaps more forward progress can be made.

What Lessons Have We Learned?

The importance of science to not only our health but also our economic well-being is now front and center in the public's and policymakers' attention. While the occasional messiness of scientific inquiry has been on display, the world is aware like never before of the critical importance of investments in biomedical innovation and public health. Science and scientists are held in high global esteem.¹ The number of students applying to medical school has soared.² The biopharmaceutical industry's reputation with the public improved significantly early in the pandemic.³ The UK highlighted the importance of R&D to swift social and economic recovery from COVID-19 in a new roadmap for science, research, and innovation that features a significant increase in investment.⁴

*"We've been running a series of experiments right now, and we need a systematic approach to figure this out. ... If we don't do the hard work right now of learning what we should have learned from COVID, it will be a moment in time where we lost an opportunity to learn."
-Interviewee*

The level of investment of financial and human resources will not continue once the crisis passes—but the mindset can. People in government agencies, biopharma companies, and research labs have been able to accelerate biomedical innovation in part by expending an enormous amount of money, time, and energy. And because this disease impacted the developed world and its economies so directly and so hard, the focus and commitment were unprecedented. But we have also seen some important shifts in mindset, that is, a greater willingness to reduce actions and requirements to the essentials, to bring a lot of creativity and speed to problem solving, and to set precedents to be built upon and improved.

Desirable behaviors will not magically remain in place. Some policies put in place by governments will officially expire when the public health emergency ends, and we need to advocate strongly for their institutionalization. Legislation or policies will not be sufficient in many cases. We need to identify resources, training, and incentives that are necessary to foster the behavior we desire within and among companies, government agencies, and the academic research establishment. Leaders in these sectors have to be persuaded of the benefits of making these changes permanent and commit themselves and their organizations to doing so.

COVID-19 accelerated the deployment of several innovative technologies and platforms that were already in development. The emergency gave people license and a sense of urgency to try new approaches. We are hopeful that these innovations will persist into the future because some stakeholders were already invested in them, and others have had an opportunity to see their value. The pandemic has clearly demonstrated the value of government, philanthropic, and private investments in shared platforms and enduring infrastructure.

Key Takeaways and Opportunities for Future Focus

The following sections on our five areas of focus summarize “the past” (the status quo in biomedical R&D), “the present” (what has changed during the pandemic), and “the future” (how we can work to keep “the good” for R&D across all conditions). In this section, we provide brief abstracts of the key takeaways and opportunities for future focus.

Research Collaboration

Although sometimes exhibiting a lack of coordination and “more talk than action,” domestic and international researchers, companies, and government entities have collaborated at unprecedented scale and speed to tackle the challenges presented by the novel coronavirus.

1. Repurpose infrastructure that has been created, such as the National Institutes of Health’s (NIH’s) ACTIV and RADx initiatives, to target other high-priority, unmet health needs. Dovetail these efforts with existing public-private partnerships to amplify impact.
2. Formalize and provide incentives to use successful efforts, such as the Reagan-Udall Foundation’s Evidence Accelerator.
3. Initiate a public dialogue about the future of scientific communication, specifically the nexus of peer-reviewed journals and pre-print servers.
4. Document, characterize, and, to the extent possible, quantify the benefits of collaboration during COVID-19.

Acceleration of Product Development

Faster R&D timelines are due not only to an extraordinary investment of financial and human capital but also to long-term investments in platform technologies and infrastructure, deployment of innovative research designs and approaches, and regulators’ speed and flexibility.

5. Invest in platform technologies, such as mRNA and prototype pathogens, and research infrastructure that can benefit many researchers and developers.
6. Capture and share the efficiencies of COVID-19 trial design and conduct, such as master protocols, seamless trials, and pragmatic trials. Update Food and Drug Administration (FDA) guidance as needed to give sponsors confidence to use these approaches after the pandemic.
7. Initiate a public dialogue about how regulation can become more agile based on need. Support FDA efforts to make guidance more rapid and iterative.
8. Consider how user fee negotiations and 21st Century Cures 2.0 legislation can provide support and authorization for priorities that are emerging from the pandemic experience.

Clinical Trial Design and Execution

Innovations such as master protocols, platform trials, and adaptive designs have shown their value

in bringing speed and efficiency to the trial process. The use of remote tools and decentralized approaches to maintain non-COVID trials has increased during the pandemic.

9. Keep COVID-19 trial infrastructure, including platform trials and networks such as the COVID-19 Prevention Trials Network, in place to streamline and incentivize research in areas of high unmet need.
10. Make more efficient and effective trial models such as master protocols and seamless trials the norm rather than the exception through public and private funding, incentives and policies, and regulatory guidance.
11. Support, expand, and link clinical trial networks. Develop a more pragmatic trial network to reach more participants through community-based settings and run larger, simpler trials.
12. Invest in making decentralized trials and the use of remote tools easier to adopt.

Collection and Use of Real-World Data and Evidence

Real progress has been made to integrate real-world data (RWD) from disparate sources in centralized platforms to enable faster learning, deploy RWD to drive hypotheses and improve care, and demonstrate the value of randomized real-world evidence (RWE) as a rapid, rigorous, knowledge-generation engine.

13. Sustain and deploy valuable RWD/RWE platforms and initiatives such as the Evidence Accelerator and the National COVID Cohort Collaborative (N3C) against other urgent public health questions.
14. Invest in pragmatic trials networks to rapidly generate RWD/RWE.
15. Integrate lessons learned into FDA's existing plans, frameworks, and guidance on RWE and technology modernization.

Racial and Ethnic Disparities in Health Care and Research

COVID-19 has elevated longstanding health inequities to public consciousness to an extent not seen before. Attention is not sufficient, but it is a critical prerequisite to action, and we must seize this moment to make real change.

16. Build relationships and trust with individuals and partner organizations in minority communities.
17. Bring leadership, resources, and cohesive plans to set priorities and create accountability across stakeholders.
18. Improve data collection and use.
19. Broaden eligibility criteria and change study designs to include more participants.
20. Bring trials to the communities you need to engage through site selection, creation of more robust trial networks, and use of remote tools.

RESEARCH COLLABORATION

“People want to pursue truth,” declared one of our interviewees, and they “have an itch to innovate, that is why they became scientists, to bring relief to the world,” said another. That desire to contribute has certainly been very apparent during COVID-19. Many observers have noted the unprecedented scale and speed of collaboration among researchers, companies, and government entities—domestically and internationally—to tackle the myriad challenges presented by the novel coronavirus.

The types of collaboration that emerged during 2020 range across a wide spectrum—from informal cooperation among individual researchers sharing information, knowledge, and sometimes data to large, formal multi-stakeholder collaborations, some of which existed before COVID-19 and were redirected. Our interviewees were highly enthusiastic about the possibility of “a completely new culture of doing research,”⁵ one in which easy opportunities exist to work together, bureaucracy is reduced to the bare minimum, and incentives are aligned around solving the problem at hand. As *The New York Times* reported in an April headline, “Covid-19 Changed How the World Does Science, Together.”⁶

However, several interviewees highlighted the need for less talk and more action: “the spirit is willing, but the flesh is still weak,” or “the signal-to-noise ratio is terrible, a lot of people just wanted to feel like they’re helping.” Many believed that all the collaboration would benefit from a bit more coordination. Few data currently exist to clarify the extent and outcomes of R&D collaboration during the pandemic, and the pull of the old ways of doing business will be strong once the emergency passes. But culture change can often be sparked by catalytic events, and COVID-19 may prove to be such an event for the biomedical innovation ecosystem.

THE PAST

Collaboration among researchers, institutions, sectors, and disciplines has long been a challenge in biomedical R&D, which lags behind many other scientific fields in this regard. Collaboration has been hindered by misaligned incentives and competitive pressures in academia and the private sector, insufficient investment in supporting infrastructure, and other factors. This landscape has evolved in recent years, as it has become clear that cracking our complex biological code will require engaging partners from diverse disciplines and with a range of skills. However, the pandemic provided significant impetus to remove barriers and work together and perhaps exposed the potential long-term benefits to various stakeholders, as well as their self-interest, in doing so.

THE PRESENT

The tone for rapid collaboration was set with the quick sequencing and sharing of the coronavirus genome in China on January 11. Researchers around the world sprang into action, individually and collectively, to understand how best to test for and treat COVID-19. Some of these were essentially “pop-ups” with little or no funding, using open-source research platforms such as Just One Giant

Lab and Slack channels to communicate and share work. In just one example, a Slack workspace called the “Wu-han Clan”—named for the hip-hop group the Wu-Tang Clan—convened experts to coordinate work on primate models of the coronavirus and to compare results.⁷

Scientists have also introduced an unusual level of transparency to their work by using “pre-print servers”⁸ at an unprecedented rate to share their findings in real time for review by a broad community of peers. Although this trend has not been without controversy, sometimes elevating premature or lower quality work, it demonstrates a strong desire by researchers to rapidly share learnings outside the usual constraints of the journal publication and academic promotion systems. These agile communications platforms have been an important enabler of and venue for scientific collaboration.

As a result, as one interviewee colorfully put it, scientific collaboration has produced “hellaciously good biology” in a very short time period. As just one example, key chemical building blocks for antiviral drugs were identified by collaborators operating at “breakneck speed” at the University of California, San Francisco’s Quantitative Bioscience Institute and two National Laboratories. They published their data directly online to contribute to other researchers’ efforts. What would have been a two-year timeline shrank to 10 weeks by a “philanthropic grant and the collaborative spirit.”⁹ As a result of this type of collaboration, we have learned much not only about the SARS-CoV-2 virus (and coronaviruses more broadly), but about the human immune system and response, its relationship with other systems such as the cardiovascular and nervous systems, and more.

In addition, governments, companies, and research institutions immediately joined together to identify products in the pipeline that could address the new threat. For example, the US National Institute of Allergy and Infectious Diseases (NIAID) and Moderna, which had been collaborating on a vaccine for another virus, immediately swapped in the SARS-CoV-2 RNA and sped toward a first manufactured batch of a vaccine candidate within 25 days of the release of the gene sequence.¹⁰ In the UK, researchers at the University of Oxford collaborated with the National Health System and more than 100 hospitals to fund and launch, within a matter of weeks, the multi-arm RECOVERY “master protocol” trial to rapidly test in parallel the efficacy of several existing and novel treatments for the disease. This trial has thus far yielded the greatest trove of definitive results.

Companies are sharing their knowledge, resources, and capabilities more openly than is their habit; the **Co-Vig Plasma Alliance**¹¹ is one example of normally competitive companies collaborating to accelerate the development and manufacturing of a convalescent plasma product for COVID patients. These companies are sharing preclinical information, study protocols, and patient-level control data. Other initiatives sprang up to enable companies to share resources, including compound libraries and expertise, such as **COVID R&D**,¹² The Bill & Melinda Gates Foundation-funded **COVID-19 Therapeutics Accelerator**,¹³ and the Biotechnology Innovation Organization’s **COVID Hub**.¹⁴ The speed of agreements has been noteworthy; for example, in less than one week, Eli Lilly and AbCellera entered into an agreement to use the latter’s screening platform to identify an antibody candidate that entered trials within three months.¹⁵

Federal agencies are coordinating among themselves and collaborating with other stakeholders in some exciting ways. Notable examples include the following:

- The **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)** public-private partnership brings together all the relevant US federal health agencies, the European Medicines Agency, and several biopharma companies, academic institutions, and philanthropies to “develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines.”¹⁶ Whereas previous NIH-driven collaborations such as those of the Accelerating Medicines Partnership (AMP)¹⁷ can take two years to negotiate, ACTIV took two weeks. Its working groups are harmonizing and sharing preclinical resources, setting up master protocol trials to test candidates efficiently, and maximizing existing trial infrastructure.
- The Reagan-Udall Foundation’s **COVID-19 Evidence Accelerator**, created in collaboration with Friends of Cancer Research, is providing “a unique venue for major data organizations, government and academic researchers, and health systems to gather and design quick-turn-around queries and share their results.”¹⁸ More than 100 organizations participate in weekly calls described by one participant as a “pick-up game,” allowing them to work through challenges with RWD standardization, interoperability, and methods in real time. The forum has been a breeding ground for new relationships and collaborations among participants.
- The NIH National Center for Accelerating Translational Sciences (NCATS) launched the **National COVID Cohort Collaborative (N3C)**, a partnership among the research institutions that are supported by NIH’s Clinical and Translational Science Awards program, enabling them to contribute and use their clinical data to answer critical questions related to the pandemic.¹⁹ N3C builds on NCATS’ multi-year work to provide a harmonized data platform for clinical research;²⁰ the pandemic provided the driving force to get 53 academic research centers to sign data transfer agreements, agree to use a single Institutional Review Board, and harmonize their data. As one interviewee commented, “Once you’ve done it for one thing, it’s easier to do it for the next.”
- NIH’s **Rapid Acceleration of Diagnostics (RADx)**²¹ initiative seeks to accelerate the development of innovative diagnostics, building on an existing academic infrastructure to vet technologies,²² and is working closely with FDA to set expectations for approval.

“Oftentimes the reason for having FDA at the table is so that you know what the regulators think. But this time [in the Evidence Accelerator], the regulators are at the table to build familiarity and muscle, with new capabilities, along with groups that have historically not come together. I call [the old way] ‘vendor thinking’—you’re over there, the vendor, being told what to do, as opposed to the two of us sitting down and saying ‘that’s an interesting problem, let’s see how we might solve it.’”
-Interviewee

THE FUTURE

Although we have seen a natural desire for scientists and other stakeholders—sometimes competing interests—to want to work together, building and sustaining collaborative ventures that stand the test of time will require us to address incentive systems, funding, infrastructure, and governance challenges.

“We have to sustain not just initiatives but communities and build a business model around it.” –Interviewee

1. Repurpose the infrastructure that has been created to target other high-priority, unmet health needs. Dovetail these efforts with existing public-private partnerships to amplify impact.

The leaders we interviewed shared a strong sentiment that platforms such as ACTIV and RADx should be directed toward other high-priority, unmet health needs. Having them in place for the next infectious disease outbreak would be beneficial. In the meantime, they could be deployed for specific priorities, such as researching other pathogens or the mechanism of action of new technologies. They might even serve as a platform for “**grand challenges**” posed by the government or other entities, which could provide not only funding but also access to other resources such as expertise and trial networks to solve important public health challenges. NIH has taken one step in this direction by committing to maintain ACTIV’s inventory of clinical trial capacity within NCATS for other research efforts. These initiatives and resources can complement existing public-private partnerships such as AMP to amplify their impact.

2. Formalize and provide incentives to use efforts that are working, such as the Reagan-Udall Foundation’s Evidence Accelerator.

Although important, personal relationships built in the crucible of COVID-19 will not be sufficient to carry productive collaborations into the future. Every effort should be made to codify and make sustainable the platforms and venues that are creating value. Temporary tools as simple as **online portals** for companies to submit solutions for consideration or to request feedback from federal agencies could be made permanent. Funders could create academic **research “sandboxes”** to encourage the kinds of collaborations that popped up during COVID-19. Successful **agreements** among companies, government agencies, and other stakeholders that were established during COVID should be evaluated to identify approaches to form future rapid collaborations.

Equally importantly, the **use of these platforms and tools must be incentivized**, whether with funding or with policies and requirements. Just because they exist does not mean they will be utilized. Congress and philanthropic funders need to invest in this important infrastructure.

3. Initiate a public dialogue about the future of scientific communication, specifically the nexus of peer-reviewed journals and pre-print servers.

COVID-19 has been an object lesson in two worlds colliding—the ossified system of traditional scientific journals and the “Wild West” of pre-print servers and other platforms for exchanging information and data. Journals have exhibited an ability to accelerate their processes to publish information in a more timely and freely available manner; some journals have even required posting of submissions on a pre-print server first. The open-access platforms recognize the need for more rigor and standards and are moving in that direction; they have concerns about their business model sustainability as well.

Although there have been endless dialogues about needed changes to the peer-review journal ecosystem, few fundamental changes have resulted. However, it appears as though the “yin” and “yang” are beginning to meet and merge in the middle in some ways. The time seems ripe for a renewed focus on the scientific publishing business model. The US government might consider adopting an approach advocated by “Plan S” in Europe, in which publicly funded research must be accessible in open-access journals or platforms *immediately*, rather than within the typical 12-month timeframe. The Howard Hughes Medical Institute—the largest private funder of biomedical research in the US—recently signed on to Plan S.

Why should speed and efficiency of knowledge sharing apply only to official public health emergencies and not to ongoing research on cancer, tuberculosis, heart disease, or other maladies that kill millions globally every year?

4. Document, characterize, and, to the extent possible, quantify the benefits of collaboration during COVID-19.

Many engaged in COVID-19 R&D have seen the benefits of collaboration and aligned problem solving among researchers, product developers, providers, and regulators—faster knowledge generation, pre-competitive understanding of disease biology, and progress toward innovative solutions. The massive amount of knowledge generated will lead to many peer-reviewed publications. Pre-competitive information sharing has accelerated competitive novel product development, and efforts to identify and repurpose existing compounds for COVID are increasing companies’ value.

The government agencies, companies, academic institutions, and philanthropies involved in COVID-19 R&D should **document, characterize, and, to the extent possible, quantify the benefits of pre-competitive collaboration** to demonstrate its value to all. To supplement the “carrot” of these benefits, NIH and other funders could apply some “sticks,” such as requiring participation in the N3C platform as a condition for an NIH Clinical and Translational Science Award.

“If the pandemic stopped tomorrow, we would spend the next couple of years rethinking the infrastructure of research, in particular scientific communication. It’s the whole issue of peer review and deciding what’s worth publishing and what needs modification, how to do that in a faster and more effective manner than we were doing. We’ve accepted sluggishness, and I think we’re learning we don’t need to.” –Interviewee

ACCELERATING PRODUCT DEVELOPMENT

Much of the acceleration of research and product development can be ascribed to what one interviewee called an exercise in “brute force, bringing money and materiel and logistical support and you name it. I don’t see that necessarily being recapitulated because that’s an emergency.” However, this shared experience has revealed a commitment to “getting it done,” a spirit we wish we could put in a bottle to be opened when we need a reminder of our common mission to save lives and improve health.

“We showed it can be done. We shouldn’t be satisfied with hearing these long timelines in the future.” –Interviewee

Some in this ecosystem, as well as the broader public, have expressed legitimate concerns about the potential trade-offs made to accelerate product development. The biopharmaceutical industry and some federal agencies have felt compelled to issue some extraordinary communications to shore up public trust in the products being developed and authorized.²³

Nevertheless, many interviewees agreed that lessons from this crisis could be applied in non-emergency R&D processes to benefit patients waiting for treatments for many diseases. For example, the rapid pace of COVID-19 R&D can be attributed to **long-term investments** in platform technologies and infrastructure, the deployment of **innovative research designs and approaches**, and the **FDA’s speed and flexibility**.

THE PAST

Embedded in FasterCures’ name and mission is the notion that biomedical R&D takes too long. The development of a new medicine or vaccine takes on average 10-15 years from discovery to approval. Several good reasons explain the long timelines and high risk of failure, most importantly, that science is difficult and unpredictable. However, other reasons, such as insufficient collaboration, misaligned incentives, and lack of the right kind of capital in the right place at the right time, can be addressed.

THE PRESENT

Listed below are a few indicators of the sheer volume of events and the speed at which they have unfolded during the COVID-19 pandemic:

- The time required for vaccine developers to advance from genetic sequence selection to first-in-human studies was 20 months for the 2003 SARS outbreak compared to three months for the SARS-CoV-2 pandemic.²⁴
- As of this writing, more than 550 treatments and vaccine candidates are being studied for COVID-19, a disease we did not know existed one year ago.²⁵
- Under its Coronavirus Treatment Acceleration Program, FDA had reviewed more than 390 trial protocols (not including vaccines) as of November 30—some of them in less than 24

hours.²⁶ The agency has issued almost 300 Emergency Use Authorizations (EUAs) for tests, along with 5 for therapeutics, and has approved one drug.²⁷ Amid all this activity, FDA has addressed other important business; as of August 26, FDA had already approved 37 New Molecular Entities, “a strong number for any year.”²⁸

Investments in scientific platforms and infrastructure are paying off. Some of the compressed COVID-19 R&D timelines are due to long-term investments made by government, philanthropy, and industry that made their debut or demonstrated proof of concept during this pandemic—including in some important **platform technologies**. For example, investments in novel mRNA technologies, along with the use of prototype pathogens to speed the development of vaccine candidates for a new virus,²⁹ allowed NIAID and Moderna to launch studies of an mRNA vaccine within weeks.

The federal government is already heavily invested in **trial networks**, which have been rapidly linked together and used to great effect during COVID-19,³⁰ and NIH has done a great service by surveying and mapping clinical trial capacity across the US.³¹

Innovative trial designs and approaches have been proliferating. The use of several innovative approaches to clinical trials greatly accelerated product development during COVID-19. These approaches are not new, but they had not been widely adopted because of unfamiliarity or concerns about their risk from a regulatory standpoint. The pandemic’s urgency pushed researchers to use these approaches more broadly, increasing familiarity and the potential for more routine use across therapeutic areas.

Master protocol trials for COVID-19 therapeutics have been springing up in numbers not seen in any other therapeutic area to date. RECOVERY³² in the UK was launched in a matter of weeks, demonstrating that complex trials do not require years to negotiate, as in the past, and that high-quality randomized studies can be run in the context of a fast-moving public health emergency. NIH’s five ACTIV master protocols were slower to launch than many of the other trials but encompass a broader range of therapeutics.³³ Existing master protocols such as REMAP-CAP³⁴ for pneumonia and I-SPY³⁵ for breast cancer pivoted to studying treatments for COVID, showing the value of enduring trial infrastructure.

Sponsors have also been utilizing “**seamless**” **trial designs** during the pandemic to move more rapidly through the phases of development, including Regeneron in its studies of an antibody cocktail therapeutic.³⁶ Again, this phenomenon is not new but has not been widely adopted in the past, especially outside of oncology.

Several interviewees also highlighted faster reviews by **Institutional Review Boards (IRBs)** as important. Some IRBs created COVID-specific subcommittees or split into smaller groups that met more frequently to attend to COVID-related as well as all other business.

FDA’s speed and flexibility have been unprecedented. One silver lining of the pandemic has been the widespread praise for the performance and responsiveness of FDA staff. As evidenced by the

data above, they have been dealing with a torrent of new work, and their responsibilities range from diagnostics to therapeutics and vaccines to manufacturing capacity. Almost all of the leaders we interviewed acknowledged that the 24/7 nature of the response could not be replicated outside of a public health emergency, and processes such as the EUA will be unavailable in non-emergency settings. However, they also believed that some of the ways in which the evaluation process was conducted to minimize timelines without sacrificing patient safety offer important lessons. As one interviewee noted, the crisis has focused people's minds on the most essential information and processes; for example, the length of applications required for some EUAs decreased by ten-fold. Although such a reduction may not be appropriate in every situation, a critical assessment of what information is essential and what information might be extraneous would be welcome.

Other leaders highlighted the rapidity and flexibility of FDA's **guidance development** as another bright spot during the pandemic. FDA released guidances within weeks, rather than the typical years; in some cases, it had to update guidance, but some leaders deemed this approach to be better in general. FDA "can be much more helpful with guidance by getting it out fast. And when you get it out fast, it's fresh," said one. FDA had already been working on "business process improvement" around guidance development before COVID hit, but once again, the emergency provided an opportunity for the community to see that improvement in action and realize that it can be done.

Many interviewees also appreciated the **enhanced interaction** among researchers and regulators, along with more regular use of rolling reviews, and hoped that these changes can be sustained in some fashion. FDA's existing accelerated review pathways³⁷ allow for greater interaction with sponsors. Still, some interviewees believed that even these options are too rigid, with prescribed timeframes and conditions for meetings that might not foster timely collaborative problem-solving as issues arise in high-priority programs.

Given the nature of COVID-19, regulators have needed to collaborate internally and externally with experts outside their usual disciplines; this disease does not sit neatly within the Division of Antivirals. In recent years, the FDA has recognized the need for a more **multidisciplinary approach to regulation** through its creation of Centers of Excellence in Oncology and Digital Health. COVID-19 provided another object lesson in the importance of rethinking traditional scientific silos.

THE FUTURE

While we cannot expect scientists and regulators to burn the candle at both ends indefinitely, we can conduct a rigorous examination of the factors that enabled accelerated product development during the pandemic and consider the application of those factors to R&D across all conditions.

"All of that can be hard to replicate in other conditions where there isn't such a magnitude of health and economic impact, but I think that there are lessons that can be learned. First of all, guidance from FDA matters in terms of providing some clarity about the steps for developing products, clinical trials networks help, and manufacturing capacity planning helps." - Interviewee

5. Invest in platform technologies, such as mRNA and prototype pathogens, and research infrastructure that can benefit many researchers and developers.

As one leader we interviewed noted, the COVID-19 experience “does provide some kind of window into how the federal government, if there is an urgent problem like Alzheimer’s disease that was really threatening society, that the federal government could lean in on that and provide much more support to *development* than it has up till now. They did the *basic science* part, but they aren’t really doing a lot of the development part.”

Government and philanthropic funding play a key role in “de-risking” novel **scientific platforms**—defined as an infrastructure designed to generate knowledge cost-effectively—from universal flu vaccines to diagnostic platforms that can accommodate several different specific tests and more. These investments help unleash private-sector innovation and move new insights into Phase I trials more quickly.

Trial networks supported by federal funding tend to be in high-cost and less accessible academic medical centers, creating barriers to trial participation for many patients and clinicians. Greater effort is needed to expand these networks and prepare them to plug efficiently into practical trials.

6. Capture and share the efficiencies of COVID-19 trial design and conduct, such as master protocols, seamless trials, and pragmatic trials. Update FDA guidance as needed to give sponsors confidence to use these approaches after the pandemic.

FasterCures has convened, along with the Clinical Trials Transformation Initiative (CTTI) and the Duke-Margolis Center for Health Policy, several investigators from COVID-19 master protocol trials to share information about their operations and experiences in the fast-paced pandemic environment. Analysis of the essential elements of the trials’ rapid start-ups—other than the urgency of COVID itself—could encourage adoption of such models by sponsors and researchers who have been reluctant to do so in the past.

Further, developers’ and regulators’ experience with seamless trials and other parallel R&D processes during COVID-19 should be analyzed, and the learnings integrated into updated FDA guidance to increase sponsors’ confidence in their value. In non-emergency settings, adaptive designs can benefit patients because trials can be conducted with shorter timelines and fewer participants.

COVID-19 has also engendered much discussion about making trials faster and easier to execute by simplifying their designs, endpoints, and data collection. Trial designs that are as lightweight as possible for clinicians to conduct, requiring only as much data collection as is necessary to answer the question at hand and simplifying (and digitizing) consent, would benefit the trial enterprise writ large.

Finally, IRBs should analyze how they accelerated their processes during the pandemic to identify approaches that can be carried forward to improve efficiency.

7. Initiate a public dialogue about how regulation can become more agile-based on need. Support FDA efforts to make guidance more rapid and iterative.

FDA has long been considered the world's "gold standard" organization for regulation of medical products. As one interviewee noted, "I don't think FDA timelines are really the big issue in routine product development," and in fact, over the past decade, the agency has introduced several different pathways to accelerate the development of high-priority products. However, we also heard a strong message in our interviews that the COVID-19 experience highlighted some ways in which the agency can accelerate its work while protecting the public's safety. Leaders discussed the importance of tailoring regulatory approaches based on need rather than following cookie-cutter approaches. As one leader asked, "What's the right balance between speed and safety and certainty, and how much does context matter? We should do a careful unpacking for what products and for what circumstances can some of the ways that we have accelerated become the new normal, and what things really need a special circumstance because of the risk, the cost, the uncertainty." Another leader stated, "We need to be applying really sophisticated, modern thinking around designs of clinical trials and around the concept of benefit-risk frameworks applied to data sets as they evolve over time, to understand the thresholds upon which we can supply innovation to patients."

"If you revisit the history of the FDA and other agencies, they've largely been put in to protect us from unsafe drugs rather than to guarantee that we get good ones. It's a relatively adversarial process at the moment. ... Certainly this area of accelerating development has dimensions that could be to the benefit of all of us if we have a very public conversation about what it means to approve a medicine, and are we comfortable with the prevailing view of what 'good' looks like, and did we all agree on these hurdles?"
-Interviewee

8. Consider how user fee negotiations and 21st Century Cures 2.0 legislation can provide support and authorization for priorities that are emerging from the pandemic experience.

FDA is already examining the practices it adopted during COVID-19 to determine which should continue. Some practices might require more resources and different authorities. Upcoming user fee negotiations and Cures 2.0 legislation³⁸ (a follow-on to the 21st Century Cures Act of 2016) may be opportunities to provide ongoing support (including additional staff) and authorization for some of these priorities. Policymakers should also support the FDA's continued business process improvements to quicken the pace of guidance development and iteration.

CLINICAL TRIAL DESIGN AND EXECUTION

Much of the **collaboration** and **acceleration** of R&D during the pandemic have occurred in the context of the clinical trials needed to demonstrate the safety and efficacy of potential treatments and vaccines for COVID-19. Collaborative trial platforms and networks have coalesced with incredible speed.

Unfortunately, federal officials report that 94 percent of the hundreds of individual studies underway may not yield meaningful evidence because they are too small or poorly designed.³⁹ Not unique to COVID trials, this challenge has plagued the biomedical R&D enterprise across the board.

However, relatively recent **design innovations** such as master protocols, platform trials, and adaptive designs have proven their ability to bring speed and efficiency to the trial process during COVID-19. **Networks of institutions and investigators** ready to conduct trials have been key, though with some limitations. In addition, the use of **remote tools and decentralized approaches** to maintain operations of non-COVID trials has proliferated, lighting a fire under a movement that has been much desired by sponsors but not widely adopted until becoming a necessity.

THE PAST

Clinical trials are a lengthy and expensive part of the product development process. Despite many efforts to spotlight and overcome these shortcomings (e.g., a new National Academies initiative on “Envisioning a Transformed Clinical Trials Enterprise for 2030”⁴⁰), little has fundamentally changed in terms of timelines or cost.

NIH has played a significant role in supporting trial infrastructure and has well-developed networks in HIV and oncology. Outside of academic medical centers, however, the US has few clinical trial networks. Efforts to create primary care research networks that would further reach underserved communities have met with insufficient government or industry commitment. Clinicians are not well supported to conduct research and, therefore, do not have the time or incentives to do so. Trials miss large swaths of the population because many require participants to travel to study sites, take off work, and incur out-of-pocket expenses.

Master protocols and other innovative trial designs have existed for years but have been slow to stand up, and sponsors have been reluctant to sign on. Similarly, the use of remote monitoring and other tools to decentralize trial conduct has been hindered not only by policy barriers such as cross-state licensing restrictions on physicians but also by inertia and risk-aversion among sponsors.

“We won’t go back to doing trials the way we did before.”

–Interviewee

“Our clinical trial academic community isn’t very efficient in terms of timetable from idea to enrollment. There’s a lot of wheel spinning that goes on. And the capacity of academic clinical research is tied up in trials that are too small to have much chance of giving meaningful results. We can’t afford to waste those resources on trials that have little chance of changing practice.”

–Interviewee

THE PRESENT

Innovative trial approaches are demonstrating their value to a wider audience. For example, **master protocol trials** have

been a relatively rare phenomenon, but in a matter of weeks, a remarkable number emerged to evaluate treatments for

COVID-19. RECOVERY in the UK has received the most attention because it launched rapidly and has produced some of the most notable results to date, both positive (e.g., dexamethasone) and negative (e.g., hydroxychloroquine). Some have ascribed much of RECOVERY's success to its embedding in the UK's National Health Service (NHS), a ready-made trial network that encompasses the entire country and provides access to patients' longitudinal health records. One leader we interviewed described RECOVERY as "the moral equivalent of the Defense Production Act for clinical trials"—that is, the NHS basically mandated an environment for efficient trials.

However, several leaders we interviewed attributed RECOVERY's success to its study design, which made participation in high-quality, randomized trials relatively easy for frontline providers. The design requires measurement of few endpoints and minimal data collection, and it streamlined and digitized consent for patients under uniquely difficult circumstances—factors that are not unique to the UK health system. In addition to being a platform for testing multiple therapies at once, it is a good example of a "large, simple trial," which is another model that researchers and sponsors have been slow to adopt.

Other notable COVID-19 master protocol trials include REMAP-CAP, I-SPY COVID, SOLIDARITY,⁴¹ AGILE-ACCORD,⁴² and ACTIV's suite of five master protocols. FasterCures, along with partners CTTI and the Duke-Margolis Center for Health Policy, convened a series of meetings of investigators from these trials to share their learnings, to coordinate on aspects such as endpoints and compound selection, and to expand the number and type of trial sites to which they have access. Other adaptive strategies such as **seamless trials** have also been deployed during COVID-19 to an extent not seen before.

Existing trial networks have partnered and pivoted to scale up COVID-19 studies. NIH has effectively knit together a number of existing **trial networks** (largely in HIV/AIDS) into the COVID-19 Prevention Network to test vaccine candidates. Other NIH-funded trial networks such as the Prevention and Early Treatment of Acute Lung Injury (PETAL) network⁴³ have been tapped to stand up treatment studies quickly. This trial infrastructure has been critical, though it is widely acknowledged that the large academic medical centers that comprise many of these networks do not reach many racial and ethnic minority communities that have been hardest hit by the virus.

Decentralized trials and remote tools have become a necessity, not a novelty. The pandemic has wreaked havoc on existing clinical trials, with some experts estimating that 80 percent of these trials have been impacted by participants' inability to visit clinical sites.⁴⁴ Enabled by the FDA's swift guidance, many trials adopted decentralized and remote approaches to maintain operations, including remote check-ins with participants (by phone or video), shipment of study products

"Properly conducted research is critical even in desperate situations." -Interviewee

directly to patients' homes, and use of mobile devices. As one interviewee noted, what was previously regarded as "risky" by sponsors all of a sudden became essential "risk mitigation." "There is really nothing in [FDA's guidance] that lowered the bar for anybody that we suddenly need to become the new normal. All the guidance says over and over again is, patient safety comes first, document what you're doing. There were never barriers to using telemedicine for visits or remote monitoring or home health before, they are simply encouraging you to use these strategies that exist." A movement that had been unfolding slowly before the pandemic received a jolt of energy.

The Centers for Medicare & Medicaid Services (CMS) has leveraged its clout as a payer to incentivize research participation and remote approaches. Early in the pandemic, CMS offered physicians incentives to participate in COVID-19 clinical research, in the form of credits in the Merit-based Incentive Payment System (MIPS). This was one among a barrage of flexibilities that CMS put in place during the pandemic, many of which have also enabled greater use of telehealth for routine care.⁴⁵

THE FUTURE

For too long, patients with cancer, heart disease, or a rare disease, for example, have been expected to be "patient" with the traditional and rigid clinical research process. COVID has put in high relief the reality that lost time means lost lives, livelihoods, productivity, and quality of life. We should not fail to seize the opportunities before us to improve our clinical trials ecosystem.

9. Keep COVID-19 trial infrastructure, including platform trials and networks such as the COVID-19 Prevention Trials Network, in place to streamline and incentivize research in areas of high unmet need.

This infrastructure could be deployed in service of "grand challenges" set out by leaders across sectors to address priority public health needs. As one leader we interviewed said, "The balance of clinical trial attention does not line up with what we know to be the patterns of scourge of disease or the patterns of biologic discovery. There needs to be more meta-strategy about what we're going to go after. Every single time you do something there is some trade-off that's happening, and those trade-offs should be seen as very precious decisions. I don't really think I would advance a point of view that says there should be somebody playing the czar for all the different trials out there, but there should be some more meta-thinking about this than we currently have in play."

"Post COVID-19 we need to start thinking about how we can let more people participate in clinical research by making clinical research simpler, leverage our technologies. You can do clinical trials in the community, but you have to make it so simple. ... [FDA] could probably be more forward-leaning in this pragmatic clinical trial area. There is tremendous inertia there." –Interviewee

10. Innovative, more efficient and effective trial models, such as master protocols and seamless trials, should become the norm rather than the exception.

As a reflection of FDA's interest in fostering greater adoption of master protocols,⁴⁶ CTTI has created a valuable set of tools and resources to capture emerging best practices and streamline the process of implementing them.⁴⁷ Marrying this work with an understanding of the factors that contributed to the speed of deployment of new and existing master protocols in COVID-19 could produce a powerful model for making them a more regular feature of the clinical trials enterprise. Government and philanthropic funders should prioritize platforms such as these. FDA needs to update its draft guidance from 2018⁴⁸ to reflect the COVID-19 experience.

FDA, sponsors, and other experts should also **analyze the use of seamless trials** during the pandemic to better understand their outcomes and utility and whether further FDA guidance is required to encourage wider adoption.

NIH should consider its role in **improving the quality of the trials it funds** and whether its review criteria do enough to ensure that the resources it invests in research result in actionable data. Other funders should do the same.

11. Support, expand, and link clinical trial networks. Develop a more pragmatic trial network to reach more participants through community-based settings and run larger, simpler trials.

Trial networks have proven to be critical infrastructure for research in this country and around the world. We need to support these networks and direct their efforts toward the highest-value R&D initiatives. We also need to make them as “interoperable” as possible to enable their ability to readily link together in networks of networks or to pivot to other areas with an urgent need for capacity.

Trial networks should be expanded to reach as many potential participants as possible. The COVID-19 pandemic has highlighted the inability of academic medical centers to serve many of the individuals we most need as research participants—whether in racial and ethnic minority communities, rural areas, or other underserved populations. A more “pragmatic” trial network must be crafted; the NHS is an excellent model, but it is an imperfect analogue to the fragmented US health-care system. As one interviewee summarized, “These larger, simpler trial networks I would view as complementary to the very detailed costly types of studies. There is another way to get good evidence, which is to go for numbers and randomization. Let’s try to get to simpler trials that can get maybe not all possible data, but all clinically relevant data reliably from electronic data systems, reduce the need for site-specific intrusions and burdens on medical practice because you are focusing on data clinicians are collecting anyway.” As we have learned during the COVID-19 pandemic, a pragmatic trial network is not a “nice-to-have.” It is “a must-have” to ensure a learning health-care system.

12. Invest in making decentralized trials and use of remote tools easier to adopt.

Much has been made of the move toward decentralized trials and use of remote tools during COVID-19—a move that many sponsors have long desired but are now more comfortable making. Sponsors should analyze what has and has not worked well as they have been accelerated into this new paradigm.

The fact is, however, that FDA's recent guidance on conduct of trials during COVID-19 will expire with the public health emergency because it is aimed at what sponsors can and should do in the context of this pandemic. **Sponsors need clarity from FDA** on two fronts: (1) how will FDA consider data and results from trials conducted under the cloud of COVID when new drug applications are submitted and (2) how will FDA apply these approaches in future research.

Specific actions will be required quickly to preserve the possibility of progress. For instance, CMS drove a movement to temporarily suspend state-level barriers to telehealth and remote trials such as requirements related to cross-state physician licensure and drug supply chain management. Complex workarounds to these barriers that have emerged over the years all of a sudden became unnecessary, but the CMS suspensions are due to expire, many of them imminently. **CMS should drive a dialogue with states** about streamlining these requirements on a permanent basis. CMS should also continue to **support appropriate levels of reimbursement** for telehealth services after the public health emergency expires, which will likely cause private payers to follow suit. Finally, CMS should continue payments and other incentives for physicians to participate in clinical trials, including through its quality rating program.

CTTI has compiled a wealth of tools and resources in the past related to decentralized trials⁴⁹ and sponsors' use of digital technologies⁵⁰ in trials. However, **more tools and resources are needed** to enable this evolution. As one interviewee explained, more contemporary endpoints⁵¹ for studies are needed, "a factory for endpoint validation." Technical standards are required as well as infrastructure for promoting their adoption. These types of resources present opportunities for philanthropic or other funders.

Sponsors also need to resource this work within their organizations properly; it cannot be a "hobby" for a handful of passionate advocates because investment in human capital is required to make it a priority.

Care must be taken to ensure that efforts to advance the use of decentralized trials and remote tools do not further disenfranchise already underserved communities. This movement presents an opportunity to engage more patients than has been possible in the traditional model, but it could freeze out patients who lack the technology required to benefit. **Building tools and systems with and for these communities will be critical.**

COLLECTION AND USE OF REAL-WORLD DATA AND EVIDENCE

The pandemic has demonstrated both the challenges to drawing sound conclusions from evidence not generated in a rigorous, randomized way, as well as the necessity of being able to learn as much and as quickly as we can about disease and treatments under real-world conditions and timeframes. We have seen “the good, the bad, and the ugly” of the use of RWD (i.e., health data collected routinely from a variety of sources outside the context of a clinical trial) and RWE during COVID-19. But we as an ecosystem have learned a tremendous amount about its utility and have brought together some remarkable initiatives to collaborate on standards and methods and improve the quality of both the data from real-world sources and the analytics.

“We saw a lot of progress in addressing the data challenges before the pandemic. ... I think what has come out of the pandemic is more understanding that there’s a sort of win-win for everybody if they ... agree to have some standard approaches and better established methods, thanks to all this work taking place.”
- Interviewee

THE PAST

Although randomized controlled trials (RCTs) are still considered the “gold standard” for new product evaluation and approval, recent years have seen growing recognition of their limitations in accurately capturing the likely performance of treatment approaches in actual practice and in specific populations. In addition, their complexity and requirements have created a wall between the systems of clinical research and clinical care in terms of data, personnel, and processes, driving up time and cost.

RCTs often do not capture a representative population of participants, given their limitations in terms of design and where and how they take place. This failing is not only ethically problematic but also an indicator that we might be getting the science wrong. RWE could be a better way to understand a more representative patient experience with disease and treatment.

FDA has used RWD/RWE for some time for post-market surveillance through its Sentinel Initiative. The 21st Century Cures Act and the Prescription Drug User Fee Act VI agreement pushed the agency to expand its use in new product or indication evaluations; FDA has been exploring the implications and issuing frameworks⁵² and guidances⁵³ about its treatment of evidence generated outside the context of RCTs in its deliberations.

THE PRESENT

Clinicians, product developers, and regulators had little choice but to learn from the events unfolding in real time as the novel coronavirus hit. Although rigorous trials were stood up in record time, doctors still had to treat patients with whatever therapeutics they had access to that seemed like they might help. Platforms and apps, such as CURE ID,⁵⁴ sprang up or were leveraged to enable providers to share and improve how they treated patients.

Several initiatives for aggregating and analyzing RWD data came together quickly and early in the pandemic. A key effort has been the Reagan-Udall Foundation's COVID-19 Evidence Accelerator. Based on a model developed by Friends of Cancer Research to better define parameters and conditions of the use of RWE in oncology, this unique platform does not aggregate data per se; rather, it serves as a forum in which dozens of participants from across the research and care ecosystem convene weekly to agree on a common set of core data elements, prioritize COVID-related research queries of their data, conduct parallel analyses, share and compare results, and improve methods. One interviewee noted that a significant value of the Accelerator has been having data and technology companies at the table as partners in problem-solving rather than as "vendors" told what to do after the fact. Participants believe this work will have a long-term impact on the conduct and integration of RWD/RWE in public health and R&D.

"Accelerating product development means being as smart as possible and using all the data that we've got to decide what to do, to do it well, and then we've got to really be balanced with what needs clinical trials and what doesn't. The dogma becomes a clinical trial for everything, which is not practical." -Interviewee

Other notable initiatives include:

- NCATS's N3C, in which more than 50 academic medical centers that are Clinical and Translational Science Awardees, signed on to share and harmonize their clinical data, an effort that had been in the works for years. "All of the really hard informatics work is now done," said one of our interviewees;
- FDA's collaboration with Aetion to learn from data generated by the health-care system;⁵⁵ and
- Datavant's COVID-19 Research Database, including medical and pharmacy claims data, electronic health record data, mortality data, and consumer data contributed by a number of private-sector partners, along with their analytics capacity and expertise.⁵⁶

The RECOVERY trial rates are mentioned here, once again, as an excellent example of the rigorous collection and use of RWD and RWE. Data in this multi-arm, randomized trial is being collected in clinical care through electronic health records.

THE FUTURE

We have seen the "good" of RWE in RECOVERY's findings on dexamethasone⁵⁷ and hydroxychloroquine,⁵⁸ we have seen the "bad" in the retraction of papers based on Surgisphere's data, and we have seen something in between in the mixed reviews of the way convalescent plasma evidence was generated.⁵⁹ The pandemic has presented a rare learning opportunity. We have a better understanding now of the limitations of RWE for causal inference—and of what it is good for. We need RWE to fill the gaps in our knowledge, understand disease progression, improve care, and determine which RCTs need to be conducted. Further, we have realized that a hard and fast dichotomy between randomized and observational research does not exist.

Although generally supportive of the importance of RWE, many of the leaders we interviewed stressed the need to focus on the level of quality and rigor of RWE to render it suitable for decision making of any type. Said one interviewee, “I won’t endorse that observational RWE has been a positive in COVID. Making RWE synonymous with observational research is not the way to go. We need to generate more randomized RWE [like the RECOVERY trial], not observational.” More bluntly, a second interviewee said, “RWE shouldn’t become synonymous with sloppy science” or with “anecdotal evidence and uncontrolled trials,” said a third.

13. Sustain and deploy valuable RWD/RWE platforms and initiatives such as the Evidence Accelerator and National COVID Cohort Collaborative (N3C) against other urgent public health questions.

Government and philanthropic funders play a key role in supporting enduring research infrastructure that benefits the entire ecosystem, and the same holds true here. As evidenced by the quotes above, more needs to be done to build confidence in the methodological rigor of RWE. The Evidence Accelerator should remain a forum for stakeholders to advance the science of RWD/RWE, working out difficult methodology and data collection issues in real time with real data around real-world, high-priority health challenges. It should be continued under the leadership of the Reagan-Udall Foundation, which was created to develop knowledge and tools to advance the FDA’s work and raise philanthropic support to do so.

Likewise, N3C, which is part of a broader NCATS initiative called the National Center for Data to Health (CD2H), has achieved an enviable level of integration of the clinical data from dozens of the most prominent academic research institutions in the US and made it ready for advanced analytics. Participation in this effort should be a requirement of continued funding under the CTSA program, which provides more than \$500 million to the universities and health-care institutions in the network; these institutions would need to sign a new protocol and transfer agreement. CD2H has run several “DREAM Challenges” in collaboration with Sage Bionetworks,⁶⁰ and this infrastructure should be deployed to help address other urgent public health questions.

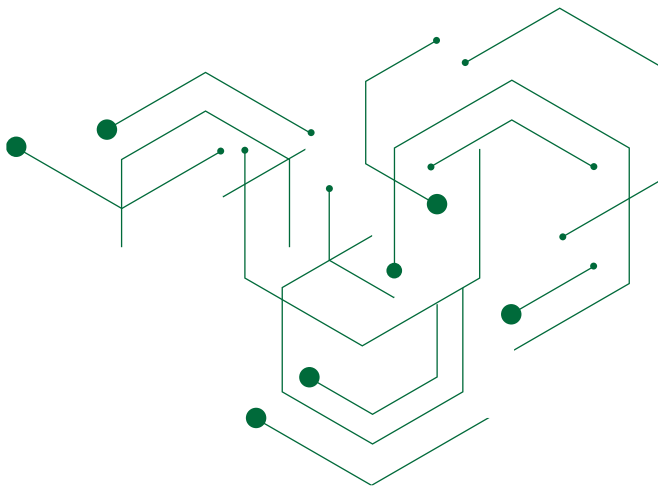
14. Invest in pragmatic trials networks to rapidly generate RWD/RWE.

The US has networks such as Sentinel,⁶¹ PCORnet,⁶² and others that generate RWD/RWE; efforts such as the NIH Collaboratory⁶³ provide a learning environment to support high-quality research in pragmatic settings. However, COVID-19 exposed a need for a more cohesive and widespread infrastructure for rapidly deploying studies and collecting and analyzing RWD. One leader we interviewed called for “better ways to collect data in simple protocols that could be stood up and operationalize quickly” that are lightweight for clinicians and take place where patients routinely get their care. The Duke-Margolis Center for Health Policy is working on a COVID-related effort to knit together such a network and then marry it with the REMAP-CAP and I-SPY master protocol trials for more rapid evidence generation about potential interventions across a broader swath of the country. Ultimately all these efforts could break down the wall and bring the worlds of data from and for research and care closer together.

15. Integrate lessons learned into FDA's existing plans, frameworks, and guidances on RWE and technology modernization.

COVID-19 has provided an opportunity to pressure-test the frameworks and plans that FDA has developed in recent years. Mistakes were made, and some decisions based on RWE had to be walked back. Although these realities are, to some extent, part of a learning system, lessons should be extracted regarding what level and type of evidence is enough for the agency to take action in a variety of scenarios. What role did observational studies play in the FDA's ability to evaluate product effectiveness in COVID-19? What is needed to improve researchers' ability to deliver what the agency needs? The FDA has been working to identify relevant standards and methodologies for collecting and analyzing RWD;⁶⁴ did the COVID experience advance this work, and what role can the Evidence Accelerator play in continuing progress?

FDA also released a Technology Modernization Plan in 2019, a precursor to a more detailed agenda to follow.⁶⁵ The plan addresses more than the basic information technology upgrades that have been an FDA focus in the past but takes a more comprehensive approach to FDA's access to and use of technology, data, and analytics, including RWE. Lessons learned from the COVID experience should be integrated into this effort as well.



RACIAL AND ETHNIC DISPARITIES IN HEALTH CARE AND RESEARCH

Coinciding as it did with a time of intense ferment around issues of racial injustice in the US, COVID-19 has focused the public's attention on racial and ethnic disparities in health outcomes, access to health care, and trust and participation in research to an extent probably never seen before. Black, Latinx, and Native Americans account for more than one-half of all reported cases⁶⁶ of COVID-19 in the US and are more than four times as likely to be hospitalized.⁶⁷

Unfortunately, these inequities are not surprising to anyone who has been paying attention. The reasons for them are no secret either, including social determinants of health that limit communities' access to quality care and result in higher rates of underlying health conditions that complicate COVID-19. There is also a lack of trust in medicine, particularly in the Black community, which has sadly been earned over many years.

These problems have been decades, if not centuries, in the making, and they have no quick or easy solutions. However, attention is a critical prerequisite to action, and we must seize this moment to make real change.

THE PAST

Black, Latinx, and Native Americans are more likely to suffer from chronic conditions such as diabetes, heart disease, and asthma and less likely to have private health insurance than white Americans. Although they would benefit disproportionately from advances in treatment for such conditions, they are under-represented in clinical research: almost 40 percent of the US population belongs to a racial or ethnic minority, yet clinical trial participation remains overwhelmingly white, in some cases 80 to 90 percent.⁶⁸

There are many reasons for this low participation rate. Many trials are conducted in academic medical centers that may not serve significant populations of minority patients. The costs of participation, including time off work, time to travel to sites, and out-of-pocket costs, can be a significant deterrent. Trials are designed with inclusion/exclusion criteria that can disproportionately exclude minorities.

And then there is the trust deficit.⁶⁹ The shorthand often used to explain this deficit is "Tuskegee," referring to the infamous experiment in which Black men with syphilis were studied and left untreated and uninformed for decades. However, Tuskegee is only one among many abuses, large

"If you really want to get to equality, there are things that you need to make a decades-long commitment to change. If there is a silver lining in this, it's to have us really realize the importance of disparities in health." -Interviewee

"This is a big, big, big wakeup call. We should have woken up to what is going on over the past few years with HIV. Forty-five percent of new infections are among African-Americans, there is a major disparity. COVID has told us about even more nuanced disparities." -Interviewee

and small over many decades, that has left a legacy of distrust within minority communities. Lack of consent for research, immigrant communities' interactions with government agencies, and the thousands of indignities encountered in the health-care system are among the abuses that must be overcome.

The 1993 NIH Revitalization Act mandated the inclusion of racial and ethnic minority participants in federally funded research, but more than 20 years later, Black and Latinx Americans still comprise only 6 percent of the research population despite being 30 percent of the US population. NIH has recently made a major investment in recruiting under-represented populations for its watershed *All of Us* Research Program, and as a result, more than one-half of current participants are members of minority groups.⁷⁰ NIH also made a symbolic but meaningful rapprochement with the family of Henrietta Lacks,⁷¹ whose cell line has been used for research for decades without her or her family's consent.

THE PRESENT

Of course, it is too soon for there to have been any meaningful progress in addressing these long-term challenges based on our learnings from this pandemic. However, attention is being paid, and some actions have been taken.

For example, Moderna recently slowed recruitment for its Phase III COVID-19 vaccine trial to ensure greater diversity in the study population.⁷² Bristol Myers Squibb announced that it will invest \$300 million over the next five years to improve its focus on diversity, including in hiring practices, clinical trial recruitment, raising disease awareness, and access to care.⁷³ Gilead is partnering with the Morehouse School of Medicine on a data resource to better understand and address minority health inequities.⁷⁴

"It's great to see the demand for diversity within trials. We've heard it in the vaccine space for years, and companies kind of try to figure it out, but they don't really work hard at figuring it out, not as much as they are now." - Interviewee

NIH is working through community partners engaged with its trial networks to share public health information and promote participation in COVID-19 therapeutic and vaccine trials.⁷⁵ One arm of the RADx program to accelerate innovation in COVID-19 diagnostics is specifically focused on understanding and addressing the needs of underserved populations.⁷⁶

Much has been made of the potential for telehealth and other remote tools to engage broader swaths of the population in research and improve care access. As one of our interviewees stated, "Decentralized trials fit at the intersection of COVID and racial justice. They're a key countermeasure." However, others warn that the rise in the use of remote technologies could actually widen racial and socioeconomic gaps if we are not careful⁷⁷—and we are already seeing that possibility play out.⁷⁸

THE FUTURE

There is no shortage of research and writing about the extent of health disparities in minority communities, the reasons for them, and the sources of low participation rates and mistrust in

research. Likewise, many solutions have been proposed, and some good models and promising approaches are in action. So why has progress been so elusive? In part because the solutions extend beyond the scope of the health-care and research systems and require addressing the consequences of systemic racism and socioeconomic disadvantage, from outright discrimination to lack of access to high-quality education, housing, jobs, environment, food, and more. However, the biomedical innovation enterprise has its part to play. And it should recognize its self-interest in doing so: In the words of the National Minority Quality Forum, “Underrepresentation of minorities in clinical trials has resulted in science that is inadequate to support recommendations of effectiveness for minorities. Powering clinical trials with sufficient minority participants may be the greatest challenge in determining what constitutes effective and safe care.”⁷⁹

“The solutions that are needed are beyond just saying, ‘I want to make sure that you’ve got the consent form in Spanish.’ We have to think differently about social structures within which people are living and working and moving through their lives ... and trying to understand what else is needed beyond consent forms and blood draws.” –Interviewee

16. Build relationships and trust with individuals and partner organizations in minority communities.

This is critical, long-term, difficult work without shortcuts. The *All of Us* Research Program has learned valuable lessons that it needs to share. The broader field and discipline of patient engagement has much to teach us about the unique expertise that patients bring to the R&D process with the lived experience of their conditions and treatments and the benefits of integrating them into planning and decision making at the earliest stages. Similarly, community-based participatory research is a growing discipline and network that is developing best practices for partnering with as-yet-unengaged populations in research.⁸⁰ These approaches take a fundamentally different view of patients as *participants* rather than *subjects* in research, with a comprehension of and respect for the value of their contributions.

Ready partners exist in minority communities. Examples include community-based organizations such as the National Black Church Initiative, which has led an effort to advocate for research education and clinical trial enrollment for some time; Historically Black Colleges and Universities such as Morehouse School of Medicine and Meharry Medical College; and policy organizations such as the National Minority Quality Forum.

17. Bring leadership, resources, and cohesive plans to set priorities and create accountability across stakeholders.

As noted above, many organizations are committing to change at the moment, and that matters. However, we also need cohesive plans and solid leadership to set priorities and to hold people accountable over the longer term. Government and philanthropy can inspire such commitments, collect data, and issue report cards on whether and how we are improving.

“Start by shutting up and listening.” –Interviewee

Within companies, it is an encouraging sign that new positions are being created to address diversity, equity, and inclusion—much as new “chief patient officer” positions created after FDA made clear its expectations for higher levels of patient engagement by sponsors. These leaders need to have resources and authorities within R&D decision-making, not just marketing and access.

18. Improve data collection and use.

We cannot improve what we do not measure, and we do not measure racial and ethnic disparities in health care and research all that well. For instance, early in the pandemic, many states were not reporting data on race/ethnicity with regard to COVID-19 cases or deaths. Now, most states are, but the data are incomplete.⁸¹ We need to identify where these gaps exist and address them in the collection process.

FDA does collect and share data about the racial and ethnic makeup of study populations in its excellent Drug Trials Snapshots.⁸² To what greater use could such data be put?

19. Broaden eligibility criteria and change study designs to include more participants.

In 2019 FDA released guidance on “Enhancing the Diversity of Clinical Trial Populations”—the result of requirements of the last round of user fee agreements—which lists specific recommendations to sponsors on eligibility criteria, enrollment practices, and trial designs.⁸³ For example, FDA recommends defining exclusion criteria as narrowly as possible and not automatically transferring Phase II exclusion criteria (which are often broader) to Phase III trials. In the new round of user fee agreements, can sponsors be made more accountable for engaging in these practices?

20. Bring trials to the communities you need to engage through site selection, building of more robust trial networks, and use of remote tools.

Bringing trials to patients means recruiting sites where they get their care, as well as using tools such as remote or mobile visits when appropriate and feasible. It also means recruiting providers from minority communities to participate in trials and giving them the resources and support they need to serve in that role.

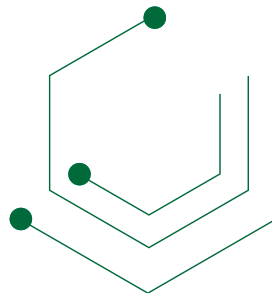
Diversity and inclusion is yet another objective that would be “enabled by large, simple trials deployed everywhere,” in the words of one of our interviewees.

“How do you make sure that you’re doing the trials in places where there’s a high likelihood of having enrollees from communities of color? Companies have to look internally and say, ‘Is it because I’m using my same, standard clinical trial networks that I always use?’ There’s a need to look at our clinical trial networks that are established and say, ‘Should there be a concerted effort to encourage physicians of all colors in communities of color to become trialists and make sure they have the resources they need to do so?’” -Interviewee

CONCLUSION

The COVID-19 pandemic has been a global tragedy that struck quickly and has only deepened its grip over the course of the year. Around the world, the number of cases and deaths shows no signs of slowing anytime soon despite the advent of authorized vaccines.

We are realizing ourselves bound together in a common experience, interdependent to a degree few appreciated, both in the spread of the disease as well as its resolution. In the biomedical R&D ecosystem, we have been reminded why we do this work—to help and to heal—and that we do it better when we do it together. We can see more clearly some of the man-made impediments we have put in our way, and many of the leaders we interviewed expressed a strong desire for a thoughtful examination of those barriers and how we might remove them. FasterCures is committed to continuing to highlight these lessons learned and to working with partners to preserve the “silver linings” and the creative solutions that are emerging from the crucible of COVID-19.



APPENDIX: Select Podcasts from Conversations with Mike Milken: What Are the Lessons of COVID-19?

Available at mikemilken.com

Big Science, with NIH's Francis Collins

Francis Collins, Director, National Institutes of Health

Grand Rounds, with Providence's Rod Hochman

Rod Hochman, President & CEO, Providence St. Joseph Health; Chair-Elect, American Hospital Association

An Unlikely Patient, with Allogene's Arie Beldegrun

Arie Beldegrun, Executive Chairman and Co-Founder, Allogene Therapeutics

Moonshot, with Johnson & Johnson's Alex Gorsky

Alex Gorsky, Chairman & CEO, Johnson & Johnson

Breaking the Code, with Nobel Laureate David Baltimore

David Baltimore, President Emeritus, Professor of Biology at Caltech; Nobel Laureate

Mobilization, with George Washington University's Lynn Goldman

Lynn Goldman, Dean, Milken Institute School of Public Health, George Washington University

Team Science, with MD Anderson's James Allison and Padmanee Sharma

James Allison, Regental Professor and Chair, Department of Immunology, The University of Texas MD Anderson Cancer Center; Nobel Laureate

Padmanee Sharma, Scientific Director, Immunotherapy Platform; Professor, Genitourinary Medical Oncology and Immunology, The University of Texas MD Anderson Cancer Center

Legacy, with former FDA Commissioner Andrew von Eschenbach

Andrew von Eschenbach, President, Samaritan Health Initiatives Inc.; former Commissioner, US Food and Drug Administration; former Director, National Cancer Institute

The Public Servant, with former FDA

Commissioner Margaret Hamburg

Margaret Hamburg, Foreign Secretary, National Academy of Medicine; former Commissioner, US Food and Drug Administration

Impatient, with Tempus/Groupon's Eric Lefkofsky

Eric Lefkofsky, Founder and CEO, Tempus

Renaissance Woman, with Sue Desmond-Hellmann

Sue Desmond-Hellmann, Former CEO, Bill & Melinda Gates Foundation; former Chancellor, UCSF; former President of Product Development, Genentech

The Record-Keeper, with Epic's Judy Faulkner

Judy Faulkner, Founder and CEO, Epic

The Translator, With PCF's Jonathan Simons

Jonathan Simons, President and CEO, Prostate Cancer Foundation

Ramping Up, with Novartis's Vasant Narasimhan

Vas Narasimhan, CEO, Novartis

Gaining Ground, with Amgen's Robert Bradway

Robert Bradway, Chairman and CEO, Amgen

The Right Thing, with Children's National Hospital's Kurt Newman

Kurt Newman, President and CEO, Children's National Hospital

Reaching Out, with Humana's Bruce Broussard

Bruce Broussard, President and CEO, Humana

Backstop, with the Veterans Health Administration's Richard Stone

Richard Stone, Executive in Charge, Veterans Health Administration

Sequencing, with Illumina's Francis deSouza
Francis deSouza, President and CEO, Illumina

Upside Down, with Vivek Ramaswamy
Vivek Ramaswamy, Founder and CEO, Roivant Sciences

The Pioneer, with The National Cancer Institute's Steven Rosenberg
Steven Rosenberg, Chief, Surgery Branch, National Cancer Institute

Disparities, with Freda Lewis-Hall
Freda Lewis-Hall, Former Executive Vice President & Chief Medical Officer, Pfizer, Inc.

Foresight, with WorldQuant Predictive's James Golden
James Golden, CEO, WorldQuant Predictive

Turning Point, with CEPI's Richard Hatchett
Richard Hatchett, CEO, Coalition for Epidemic Preparedness Innovations (CEPI)

The Virus and the Clock, with Moderna's Tal Zaks
Tal Zaks, Chief Medical Officer, Moderna

Unprecedented, with UCLA Health's John Mazziotta
John Mazziotta, Vice Chancellor, UCLA Health Sciences; CEO, UCLA Health

Time Equals Lives, with FasterCures' Esther Krofah
Esther Krofah, Executive Director, FasterCures

A Special Episode with PCF and FasterCures
Jonathan Simons, President & CEO, Prostate Cancer Foundation
Esther Krofah, Executive Director, FasterCures

In Translation, with NCATS' Christopher Austin
Christopher Austin, Director, National Center for Advancing Translational Sciences (NCATS)

Care for the Caregivers, with Cleveland Clinic's Tomislav Mihaljevic
Tomislav Mihaljevic, CEO and President, Cleveland Clinic

Healing, with Children's National Hospital's Joelle Simpson

Joelle Simpson, Medical Director for Emergency Preparedness, Children's National Hospital

Outcomes, with Helmsley Charitable Trust's David Panziner
David Panziner, Trustee, Helmsley Charitable Trust

Well-Being, with the Motsepe Foundation's Precious Moloi-Motsepe
Precious Moloi-Motsepe, Co-Founder and CEO, Motsepe Foundation

Compassionate Capitalism, with Biocon's Kiran Mazumdar-Shaw
Kiran Mazumdar-Shaw, Executive Chairperson, Biocon

Real Impact, with Jennifer Doudna
Jennifer Doudna, Nobel Laureate; University of California, Berkeley; Founder, Innovative Genomics Institute; Co-inventor of CRISPR technology

Transitions, with the Peter MacCallum Cancer Centre's Michael Hofman
Michael Hofman, Professor, Director, Prostate Cancer Theranostics and Imaging Centre of Excellence, Peter MacCallum Centre; University of Melbourne

On the Verge: Leaders in Bioscience Discuss the State of Vaccines and Treatments
George Yancopoulos, Co-founder and Chief Scientific Officer, Regeneron

Joseph Vinetz, Professor of Medicine, Yale University; Infectious Disease Physician
Tal Zaks, Chief Medical Officer, Moderna

No Silos, with Google Health's David Feinberg and FasterCures' Esther Krofah
David Feinberg, Vice President, Google Health; Advisory Board Member, FasterCures
Esther Krofah, Executive Director, FasterCures

Lessons Learned: The Intersection of Cancer Research and COVID Treatments

Himisha Beltran, Medical Oncologist, Dana-Farber Cancer Institute

Felix Feng, Radiation Oncologist and Vice Chair for Translational Research, UCSF Department of Radiation Oncology

Christopher Haiman, Genetic Epidemiologist and Professor of Preventive Medicine, Keck School of Medicine of USC

Deborah Scher, Executive Advisor to the Secretary, US Department of Veterans Affairs

Jonathan Simons, President and CEO, Prostate Cancer Foundation

Global Scale, with Leaders from Murdoch Children's Research Institute

Sarah Murdoch, Co-Chair, Murdoch Children's Research Institute

Kathryn North, Director, Murdoch Children's Research Institute; David Danks Professor of Child Health Research, University of Melbourne

Hamish Graham, Paediatrician and Senior Research Fellow, Murdoch Children's Research Institute; University of Melbourne; Royal Children's Hospital

Speed of Science, with Pfizer's Albert Bourla and Johnson & Johnson's Alex Gorsky

Albert Bourla, Chairman and CEO, Pfizer
Alex Gorsky, Chairman and CEO, Johnson & Johnson

"To Boldly Go," with Operation Warp Speed's Moncef Slaoui

Moncef Slaoui, Chief Science Advisor, Operation Warp Speed

Collaborating to Beat COVID: A Conversation with Leaders from Health and Bioscience

Sir Andrew Witty, President, UnitedHealth Group; CEO, Optum; Co-Leader, COVID-19 Vaccine Development, World Health Organization

George Yancopoulos, President and Chief Scientific Officer, Regeneron

Esther Krofah, Executive Director, FasterCures

New Heroes, with NIH's Francis Collins

Francis Collins, Director, National Institutes of Health

Revolutionary, with UC Berkeley's Jennifer Doudna

Jennifer Doudna, Biochemist, University of California, Berkeley; Founder, Innovative Genomics Institute; Co-inventor of CRISPR technology; Nobel Laureate (2020)

The Novelist and the Neurologist, with John Grisham and Neal Kassell

John Grisham, Author

Neal Kassell, Founder and Chairman, Focused Ultrasound Foundation

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