Biomedical Research COVID-19 Impact Assessment: Lessons Learned and Compelling Needs

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This discussion paper is part of the National Academy of Medicine's Emerging Stronger After COVID-19: Priorities for Health System Transformation initiative, which commissioned papers from experts on how 9 key sectors of the health, health care, and biomedical science fields responded to and can be transformed in the wake of the COVID-19 pandemic. The views presented in this discussion paper and others in the series are those of the authors and do not represent formal consensus positions of the NAM, the National Academies of Sciences, Engineering, and Medicine, or the authors' organizations.
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Introduction

The COVID-19 pandemic, a public health emergency of unprecedented scale and consequences, has revealed vulnerabilities in our health care system and public health infrastructure, yet also serves as a remarkable learning opportunity for transformational changes. Effects of the COVID-19 pandemic touch every aspect of life in ways not previously imagined—the biomedical and health research enterprises are no exception. Preexisting stresses in the research sector's workforce, processes, and organizations have been exacerbated in the sector's quest to effectively generate meaningful information in response to the pandemic and deliver research in new and innovative ways. The COVID-19 pandemic revealed the necessity to enhance the ability for researchers to share data through interoperable and customizable systems to enable rigor, reproducibility, and efficiency. This properly stewarded data essential for research is available and actionable, but trust remains a critical issue in establishing and maintaining data sharing entities [147].

Despite the rapid innovation occurring during the COVID-19 pandemic, longstanding problems remain. The disproportionate burden of COVID-19 cases and outcomes amongst lower-income populations and communities of color underscores the need to address the lack of diversity of clinical research participants as a top priority. The type of causal, clinical, and population-related intervention studies that may have a critical impact on outcomes in this pandemic necessitated the inclusion of a large, diverse pool of participants most adversely affected and traditionally underrepresented in research. Government funding focused on community engagement in research can certainly be a lever to promote diversity in study participation, as regulatory bodies seek to ensure the safety and efficacy of therapies across diverse populations [151]. This paper describes the current status of research and the challenges, lessons learned, and the potential, if the challenges are overcome, for a longer-term impact beyond the pandemic to enhance the resilience and diversity of the biomedical research workforce. These lessons learned can also be applied to help advance the rapid translation of research into practice (from basic science to clinical and population settings to applied public health), promote the sharing of data for delivering near real-time results in a clinical setting, and elevate community and participants as equal partners in research.

Overview of the Research Landscape

Within weeks of identifying a novel coronavirus known as SARS-CoV-2 and its disease manifestation, COVID-19, institutions, researchers, public research funding agencies, and the private sector pivoted to critical research efforts across a broad continuum of COVID-19-related issues. The earliest efforts focused on uncovering the disease's fundamental epidemiology (including public health surveillance studies to elucidate transmissibility) and analyzing data of new cases, hospitalizations, deaths, and demographic information (including age, race/ethnicity, and sex). Together with fundamental research of SARS-CoV-2 and COVID-19, clinical research priorities also quickly emerged.

Research discoveries generally aligned and emerged with the progression and priorities of the pandemic. During the initial weeks of the pandemic, clinical research began characterizing symptoms, clinical manifestations, outcomes, and risk factors for poor outcomes—an essential foundation for developing diagnostic and testing technologies, prevention (individual and social behaviors), and therapeutic approaches (e.g., pharmaceuticals). As the pandemic progressed, public-private collaborations for vaccine development and efforts in the private sector toward developing therapeutics and vaccines occurred at an unprecedented pace, enabled by a foundation of investment in basic science discoveries. In addition, health services and care delivery research efforts centered on necessary adaptations to health care. Underpinning these changes were the debates occurring in other areas of the research ecosystem.

With the intensified focus on racial injustice and structural racism throughout the United States, dissemination research and implementation science proved to be critical avenues for research focused on underserved populations and those at greatest risk for the most severe disease outcomes [51,157]. These discussions included best practices to engage participants and communities to build trust in the process of research and subsequent scientific outcomes. Remarkable progress on the virus and the disease emerged because of the rapid pivots necessitated by the pandemic. Decades of research, much of it in targeted fundamental science, the great majority of it publicly funded, enabled these pivots, as well as post-pivot progress.

Despite the many challenges, there were remarkable successes. Less than 11 months after SARS-CoV-2 was first discovered, at least two vaccines were developed, tested, and found to be more than 90 percent effective in pivotal trials [1]. Multiple large-scale treatment trials were completed, with some demonstrating therapeutic efficacy and others not. New large-scale diagnostic testing technologies were developed and launched. The success of vaccine research arguably exemplifies factors for success in biomedical research: prior basic science discoveries ready to be leveraged, existing infrastructure that can be repurposed when needed, and public-private partners who harmonize protocols, bring together existing networks, and share resources [1].

As the nation's largest public funder of biomedical research, the National Institutes of Health (NIH) leveraged existing infrastructure to establish a public-private framework for the goal of accelerating the development of therapeutic interventions, vaccines, and diagnostics through five strategies [2]:

1. Invest in NIH and NIH-funded researchers to increase fundamental and foundational knowledge of SARS-CoV-2 and COVID-19.
2. Speed innovation in COVID-19 testing technologies through NIH's recently launched Rapid Acceleration of Diagnostics (RADx) initiative, which aims to deliver rapid, widely accessible testing strategies to the public [3].
3. Participate in public-private partnerships, such as NIH's Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, and federal partnerships such as Operation Warp Speed (OWS) to forge approaches that would speed identification, development, evaluation, and manufacture of promising candidate therapeutics and vaccines [4].
4. Support studies on preventative treatments and behavioral and community prevention practices to identify and implement effective approaches for promoting individual and community safety.

5. Ensure that diagnosis, treatment, and prevention options are accessible and available for underserved and vulnerable populations that have been at the greatest risk for the most severe disease threats.

Similarly, the Centers for Disease Control and Prevention (CDC), at the forefront of the public health response to the COVID-19 pandemic, established *The Science Agenda for COVID-19* to guide the development of the evidence base needed for public health actions, guidance, and policy to curb the impact of SARS-CoV-2 and ultimately bring the COVID-19 pandemic to an end [5]. The agenda presents six priority areas:

1. COVID-19 disease detection, burden, and impact, especially as it relates to understanding disproportionate impacts on people at increased risk for health disparities and inequities;
2. transmission of SARS-CoV-2;
3. natural history of SARS-CoV-2 infection;
4. protection in health care and non-health care work settings;
5. prevention, mitigation, and intervention strategies; and
6. social, behavioral, and communication science.

Other research funders, including non-profit entities, created research agendas focused on their unique missions and opportunities to contribute to the pandemic response. The Patient-Centered Outcomes Research Institute (PCORI) established efforts focused on adaptations to health care delivery and vulnerable populations through its engagement, comparative clinical effectiveness research, and dissemination and implementation purview. PCORI also established the large-scale Healthcare Worker Exposure Response and Outcomes registry to understand the extensive impact of COVID-19 on the health and emotional well-being of both medical and nonmedical health care workers [149].

Medical specialty societies, such as the Infectious Disease Society of America, identified priorities for COVID-19 research more broadly and funded several research efforts. Other such organizations did the same in areas related to the intersection of COVID-19 with diseases as their mission.

The private sector mounted an expedited response for fundamental discovery related to SARS-CoV-2, the rapid development of diagnostics, preventive and therapeutic options, and vaccines [6]. The vast collaborative efforts with U.S. government agencies, nongovernmental entities, and the World Health Organization (WHO) drove the identification of the most pressing needs and independent and joint efforts for solutions. Despite these rapid efforts and the focus of research ecosystem leaders, experts, and entities to respond to the pandemic, the state of the research ecosystem before the pandemic and the devastating impacts of the pandemic on the research workforce raise concerns to address in the future.

The Research Workforce

Pre-Pandemic Concerns

Before the onset of the COVID-19 pandemic, the U.S. biomedical and health research workforce was under stress related to “hyper-competition,” inequality, lack of diversity, and loss of early and mid-career scientists, to name a few. This pressure on the research workforce is driven by the number of researchers competing for research awards, despite the shrinking pool of available funds to support the research enterprise. In the late 1990s and early 2000s, the U.S. government deliberately doubled public funding for biomedical and health research, leading to a period of enormous optimism [8]. U.S. institutions responded by erecting new research infrastructure and substantially increasing their graduate and post-doctoral student bodies [9]. As might have been expected, many more newly minted scientists entered the workforce within a few years, eager to set up their independent research operations.

In 2003, the budget doubling for publicly funded research ended. Over the next ten years, budgets remained nominally flat, with continuous low-level inflation eating away at real purchasing power [10,11]. For example, in fiscal year (FY) 2020, the biomedical research and price index increased by 2.5 percent, meaning that to maintain the same amount of purchasing power as the NIH did in FY 2019, the NIH would need to increase its budget by 2.5 percent [150]. Simultaneously, the workforce continued to increase in size, and institutions continued to act as if never-ending growth would be the norm [12,13]. At NIH, applicant numbers for research grants increased by nearly 50 percent, while the number of funded scientists barely changed [14].

Within a few years, the workforce faced a “payline crash” as the proportion of applications funded fell from over 30 percent to well under 20 percent [15]. Thought leaders entered a new reality of “hyper-competition,” with a surplus of scientists competing for fewer dollars and a wealth of postdoctoral researchers competing for fewer faculty positions [7,13]. The faculty positions were less attractive to potential career researchers, with far fewer being "tenure track" and more dependent on external funding for support [16,17]. In 2015, changes in the industry were also reported with reduced early-stage research support and focused support for medical devices, bioengineered drugs, and late-stage clinical trials [18]. Across public and private investments, health service research received only 5 percent of science funding, and U.S. government research funding declined from 57 percent (2004) to 50 percent (2012) of the global total [148].

Other stress-inducing forces have also been at play over the last 20–30 years. In the early 1990s, academic institutions ended mandatory retirement. Many successful scientists opted not to retire, leading to the aging of the research workforce greater than expected by demographic changes alone [19]. Early-career scientists found themselves crowded out by later-career scientists, who began receiving increasingly disproportionate funding shares over time. In the late 2000s, NIH instituted policies to ease competitive stresses on early-career scientists [20]. These policies mitigated the adverse trends described to funding tending toward late-career scientists, but in turn, led to new competitive stresses on mid-career scientists [21]. "Science of science" literature has shown that scientific advances occur uniformly throughout individual scientists' careers, meaning that under ideal circumstances, the research enterprise should enable early-, mid-, and late-career scientists to conduct their work, regardless of career stage [22,23].

Career-stage demographics were not the only sources of concern. Extensive literature has shown that women, Black, and Latinx/Hispanic scientists are underrepresented, despite representing increasing proportions of graduate school and early career cohorts of biomedical researchers [24]. Within academic medicine, women represent smaller proportions of the workforce as one moves up chains of leadership [25]. While women comprise over half of the medical students and nearly half of lecturers or instructors, the proportions fall dramatically as they progress throughout the hierarchy toward tenured professorships and institutional leadership roles and positions. Similar patterns have been observed for scientists from underrepresented groups, with disproportionately fewer represented in the highest academic ranks or securing independent research funding [26]. The root causes for the stresses facing women scientists and scientists from underrepresented groups are complex but likely to include cultural inertia in an enterprise dominated by well-funded older white men, issues related to family and childcare responsibilities, as well as outright harassment, discrimination, and family-unfriendly environments [27,28,29,30].

In summary, even before COVID-19, the biomedical research workforce faced several serious threats from increasing hyper-competition and inequality, with disproportionate stresses on early- and mid-career scientists and women and underrepresented minorities [13,20,21,24,31]. To address these issues, Congress; the National Academies of Sciences, Engineering, and Medicine; the NIH; and others have responded with reports and initiatives aiming to ease transitions for the "Next Generation" of researchers and increase diversity and inclusivity [20,32,33,34]. However, the COVID-19 pandemic negatively affected the morale and the capacity of researchers to respond to the pressing needs and vital importance of immense research agendas.

COVID-19 and Its Impact on the Biomedical Research Workforce

In March 2020, the COVID-19 pandemic created nearly instantaneous changes in the research environment, shutting down many of the sector's operations [35]. Public health officials worldwide initiated mitigation strategies mandating social distancing, which translated into an immediate inability of scientists and their staff to access their physical workspaces [36]. Universities canceled the remainder of the Spring 2020 academic terms, forcing students and faculty to stay at home despite their expectations to return within weeks. As the pandemic progressed, universities canceled successive terms and switched most, if not nearly all, academic operations to online platforms. While some operations (e.g., teaching basic chemistry or English literature) continued, others could not. Laboratories and clinical research activities requiring access to in-person space and use of tangible resources—cells, animals, human participants, specialized equipment, and physical clinics—were limited, substantially slowing down efforts as lab staff either changed or suspended their work. There were numerous other disruptions: canceled or transformed-to-virtual scientific meetings and conferences, interrupted supply chains, and suboptimal communications for day-to-day work. Cumulatively, these impacts had devastating consequences on the research ecosystem. From the inability to conduct non-COVID-19 scientific research to the reductions in collaboration and funding of other research because of the pandemic, research on other long-standing pressing issues was paused. The research ecosystem will experience implications of this pause long beyond when the pandemic recedes.

The pandemic made clear the interdependency of the biomedical research ecosystem on the health care and population health systems as hospitals prepared to care for patients affected with the most severe complications caused by COVID-19, and universities and academic health centers diverted efforts toward COVID-19-related needs such as research, testing, and academic planning and technology. With their priorities shifting away from their traditional operations because of the pandemic's urgency, universities shut down their revenue-generating operations, including providing patients with "elective" services and hosting students in dormitories and university housing for in-person training and learning [37]. As a result, academic hospitals reported up to $3 million per day in losses due to the emergence of COVID-19 as the sole priority of the health care and public health systems [38]. In academic and research institutions, financial stresses also led to furloughs and other resource cutbacks, including the culling of animal colonies and the dramatic reduction of clinical trial enrollments [39,40]. Many universities have announced freezes or substantial reductions in new hiring and promotions in addition to administrative staff layoffs [41]. One analysis found a 70 percent reduction in U.S. faculty job openings [42]. In addition, many clinicians were asked to cease research activities and focus entirely on patient care. The prolonged impact of the pandemic set back many ongoing research studies, further hampering broad research agendas.

Biomedical research rapidly shifted focus toward COVID-19, with laboratories and clinical research groups worldwide working furiously to advance scientific understanding of SARS-CoV-2 and develop and test candidate diagnostics, therapeutics, and vaccines. The scientific challenges were daunting, especially as the biology and pathophysiology of SARS-CoV-2 and COVID-19 were not well understood. For scientists already engaged in virus-related work, there was a new "boom" with billions of dollars of Congressionally allocated funding available to meet urgent public health needs. Nevertheless, scientists not engaged in COVID-19-related research confronted serious challenges, such as a lack of research career opportunities, funding, and crowding out due to the entire nation's focus on COVID-19-related activities [43].

There are concerns that financial and organizational shocks related to the COVID-19 pandemic have disproportionate effects on scientists already under stress [44]. These negative effects emerged because of the shifting priority of pandemic response and control over the activities of research entities, with no capacity, planning, or resources in mitigating research losses. Worldwide surveys have shown productivity falling among women, especially those faced with increased childcare and education responsibilities as schools and childcare facilities have closed. Data early in the pandemic indicate that women posted few preprints and published fewer papers, fueling concerns that previous progress on enhancing gender diversity in the scientific workforce may be lost [45]. As the pandemic entered into the final months of 2020, reports from academia and academic medicine suggest common and concerning trends, including mothers leaving the workforce and loss of women in leadership, with these adverse trends particularly severe among Black women [46,47]. These disparities indicate the need to better support researchers who may be supporting families and by association need to maintain stable wages.

The longer-term effects of COVID-19 on the research workforce are unclear, however, as the pandemic continues. Data collected from two large-scale NIH surveys, one of more than 200 institutional leaders and another of more than 45,000 researchers, confirm that researchers are concerned about the trajectory of their careers, research productivity, and mental health, especially in light of ongoing social and political stresses [50]. Leading correlates of researcher concerns included early career status, laboratory-based work, Asian ethnicity, resource constraints impeding the ability to write research grants, and caretaker responsibilities. Funders have responded by enabling extensions, sometimes funded, and increasing funding for investigators at early career stages [155]. Specifically related to mental health impacts, more than 65 percent of researcher respondents cited societal and political events along with physical and social isolation as adversely affecting their mental health and well-being. These concerns and stressors were particularly marked for early career investigators, caretakers for young children, and Black investigators who noted civil unrest tied to racism.

Interestingly, research funders continue to see increasing numbers of both COVID-19 and non-COVID-19 research grant applications, conduct grant peer review—entirely virtually—and issue new awards, even as the future of the scientific environment faces flux and uncertainty [49]. Emerging perspectives published in academic journals argue that the COVID-19 pandemic exacerbated existing systemic issues affecting research, a system that appears to cater to senior researchers, and has called for a "reset" with early-career scientists [52].

However, attention to the reset's specifics must reform the research ecosystem while preventing the unintended consequences of the 2003 NIH budget doubling. The pandemic is still not over: for biomedical research entities, funds continue to shift toward pandemic control, response, and therapeutics as many universities and K–12 schools keep their physical presences partially or wholly shuttered. As a result, the pandemic continues to prevent researchers from safely conducting experiments while halting the revenue-generating operations and activities that enable their research to be funded.

Health and Biomedical Research Approaches

Background

The health and biomedical research approaches invoked to address the COVID-19 pandemic span the comprehensive continuum of the research ecosystem, including:

- fundamental and mechanistic studies of SARS-CoV-2 and basic biology and pathophysiology of the virus and human response;
- public health surveillance studies focused on transmissibility and effective non-pharmaceutical prevention interventions as well as data of new cases, hospitalizations, deaths, and demographics;
- epidemiologic research to elucidate risk factors and outcomes for prediction, prevention, and treatment;
- diagnostic research and device studies aimed to develop testing technologies;
- clinical research focused on the characterization of clinical manifestations, emerging syndromes, and management of SARS-CoV-2 infection as well as other chronic conditions or comorbidities in the setting of COVID-19;
- clinical research providing insights on treatment outcomes and variation in treatment patterns;
- pharmacological studies identifying approaches for therapeutics and vaccine approaches for prevention;
- health services and care delivery research centered on necessary adaptations for care delivery, including telehealth for routine and chronic care management;
- health policy research examining different strategies emerging for mitigation and containment; and
- dissemination research and implementation science to move evidence to practice and application and attend to underserved populations and those at greatest risk for the most severe outcomes, including best approaches to engage participants and communities in research, building trust in science, and advancing health equity.

Research Initiatives during the COVID-19 Pandemic

Just as the COVID-19 pandemic led to sudden and possibly transformative effects on the biomedical research workforce, it also facilitated changes in the process of research and the establishment of unique research initiatives. Suddenly, the global community found itself facing a severe life-threatening novel infection, meaning that the human population was ill-equipped to address it on multiple levels: individual human immune systems, individual people with their worlds seemingly turned upside down, strained underresourced and knowledge-poor public health systems, and a scientific enterprise unable to produce immediate answers.

Instantly, the research sector's work increased in relevance and importance. The public looked to the scientific enterprise to deliver recommendations and action steps guided by rigorous evidence. Scientists and the research sector needed to explain the origins, nature, and magnitude of the pandemic, communicate effective non-pharmaceutical interventions and countermeasures, and develop safe and effective therapeutics and vaccines to halt the spread of the virus.

This response was in stark contrast to the pre-COVID-19 world. Before COVID-19, critics noted the biomedical research was highly inefficient, with the system requiring inordinate expense and time to develop new therapies for diseases like cancer, diabetes, Alzheimer's, dementia, and autism [54,55]. As scientists began to shift their attention toward COVID-19, the response from the sector lamented numerous fundamental problems: longstanding coronavirus threats had been ignored, research efforts were fragmented and chaotic, most COVID-19 clinical trials were too small or poorly designed to answer questions definitively, and science and public health were too vulnerable to political forces [56,57,58,59]. Despite progress in developing COVID-19 vaccines and testing potential therapeutics, the research sector's systemic problems will continue to reduce its performance and future sustainability unless lessons learned in the COVID-19 pandemic are used for sector transformation.

Against the tragic backdrop of record deaths and transmission of COVID-19, the research sector took unprecedented action to facilitate the testing, clinical, and therapeutic-based responses to the pandemic. These include the rapid installation and execution of public-private partnerships to develop testing technologies, treatments, and vaccines; the successful leveraging of existing clinical trial and research networks as well as standardized measurement protocols (e.g., the PhenX Toolkit); and the rapid increase in the rate of scientific communication [60]. In addition, the pandemic has borne witness to the potential of pharmaceutical and private companies as significant partners with the expertise and capital not just to develop vaccines and therapeutics but as entities that can scale up the manufacturing and distribution of these therapeutics. This section of the biomedical research sector assessment will review the research sector's attempts to rise to the pandemic's occasion, with attention to its unprecedented actions but also its necessity for systems transformation and reform to be sustainable and successful without the motivation of future crises.

Public-Private Partnerships during the COVID-19 Pandemic

Innovative public-private partnerships emerged during the COVID-19 pandemic to compensate for and move away from the nation's high morbidity and mortality from COVID-19. These partnerships were highly innovative and produced significant value, as they led to a vaccine being developed, tested, and approved in 11 months, an unprecedented achievement. They also provided valuable lessons learned to inform preparations for the next pandemic, as gaps still remained in executing a coordinated, cross-sectoral approach of the scale, scope, and complexity required to meet the escalating needs and trends.

OWS and ACTIV

With the passage of the CARES Act, Congress allocated nearly $10 billion in dedicated funds to develop COVID-19 countermeasures through an extensive private-public coalition called Operation Warp Speed (OWS) [61,62]. The allocation of OWS was to be coordinated through the Biomedical Advanced Research and Development Authority (BARDA) and the NIH. The OWS coalition included multiple government departments and agencies, including the Department of Defense, U.S. Food and Drug Administration, the Department of Health and Human Services, and the Department of Veterans Affairs, and private firms. The coalition planned to move research and implementation rapidly through fundamental changes in how biomedical interventions were traditionally developed and tested. These changes included coordinated development of protocols (instead of companies each developing their protocols) and manufacturing candidate vaccines and therapeutics at an industrial scale even before demonstrating safety and efficacy. To accomplish its work, OWS set itself to coordinate closely with other critical efforts, including ACTIV and RADx [3,4]. These efforts to produce therapeutics and vaccinations for COVID-19 were closely watched due to the nation's rapidly deteriorating public health situation.

In April 2020, NIH and private industry leaders announced the development of the ACTIV project, described as "an unprecedented partnership for unprecedented times [63]." The partnership developed a collaborative research framework that aimed to accelerate and streamline processes for prioritizing resources; identify candidates for study; design and execute master protocols; address safety and regulatory needs; and bring together multiple government agencies, nonprofit foundations, and private companies. The partnership was led by an executive committee consisting of leaders from the NIH, U.S. Food and Drug Administration (FDA), and private pharmaceutical companies. They rapidly convened four working groups to address the critical gaps in COVID-19 research and development:

1. **Preclinical,** responsible for increasing access to animal models and for identifying informative assays;
2. **Therapeutics clinical,** responsible for prioritizing and testing potential therapeutic agents as well as developing master protocols for clinical trials;
3. **Clinical trial capacity,** responsible for developing survey instruments, developing an inventory of clinical trial networks, and guiding the deployment of innovative solutions; and
4. **Vaccines,** responsible for accelerating the evaluation of vaccine candidates, identifying biomarkers to speed approval, and providing evidence to address safety concerns.

By July 2020, the OWS-ACTIV approach resulted in substantive national research infrastructure changes, enabling the design and execution of definitive therapeutics and vaccine trials. For example, the National Institute of Allergy and Infectious Diseases (NIAID) established the COVID-19 Prevention Trials Network (CoVPN) by merging four existing clinical trials networks: the HIV Vaccine Trials Network, the HIV Prevention Trials Network, the Infectious Diseases Clinical Research Consortium, and the AIDS Clinical Trials Group [64,65]. In addition to conducting vaccine and therapeutics trials, the CoVPN created a customized secure data collection platform to identify potential trial participants [65]. The PCORI-funded PCORnet, the National Patient-Centered Clinical Research Network, represents another national network leveraged to enroll participants in a streamlined fashion in one of the ACTIV protocols. These efforts also included other attempts by the nation's legislative branch to support research and development of diagnostics to support the control and mitigation of the pandemic's virulent impacts.

RADx

In April 2020, Congress also appropriated $1.5 billion to support research into and the eventual development of SARS-CoV-2 diagnostic tests that could be scaled up to widespread use within six months. Within days, NIH launched the RADx initiative with an ambitious goal: the ability to test 2 percent of the U.S. population (or 6 million persons) per day by December 2020 [3]. Public health authorities considered rapid, user-friendly, large-scale viral testing as a critical component to a successful systematic response that would enable the economy to "reopen" even as efforts to develop treatments and vaccines were ongoing.

The RADx effort had four components [66]:

1. **RADx-Tech,** aimed to identify, develop, and deploy testing technologies ready for use by Fall 2020. RADx-Tech rapidly implemented a novel approach, by which thousands of candidate technologies were rapidly screened, with promising approaches quickly advanced to Phase 1 (validation and risk review) and Phase 2 (clinical tests, regulatory approval, and scale-up) development over just a few months.
2. **RADx-Advanced Technology Platforms (or RADx-ATP),** aimed to scale up technologies already felt mature enough for rapid deployment.
3. **RADx-radical (or RADx-rad),** aimed to develop less mature, nontraditional technologies that might not be ready for scale-up and deployment until later.
4. **RADx-Underserved Populations,** aimed to establish community-engaged implementation projects targeted at underserved populations most vulnerable to COVID-19 disease.

By December 2020, the combined efforts of OWS, ACTIV, CoVPN, and RADx and their components could already claim several successes, including:

- Completion and publication of a definitive trial showing that an antiviral drug, remdesivir, generally improves health outcomes for patients hospitalized with COVID-19 [67].
- Completion of a definitive trial showing that the addition of baricitinib, an immunomodulator, to remdesivir, led to reduced recovery time and accelerated improvement in clinical status for patients hospitalized with COVID-19 [68].
- Launch of at least four large-scale definitive vaccine trials with realistic completion by the end of the calendar year 2020 or early calendar year 2021 [69]. As of December 2020, two trials of mRNA vaccines were completed, with each vaccine demonstrating more than 90 percent efficacy.
- Launch of several large-scale definitive trials to evaluate the possible benefits of monoclonal antibodies and anticoagulants [70,71].
- Identification of 16 varied diagnostic testing platforms considered ready for scale-up and manufacturing [72]. Some of these technologies may generate accurate and rapid point-of-care test results with relatively low maintenance requirements. Such technologies would be of particular value in remote and underserved communities.

RECOVERY Platform, the United Kingdom

Meanwhile, research networks worldwide realized some remarkable—and rapid—successes, synergizing with U.S. efforts to use science as a tool to combat the pandemic. Perhaps the most notable international contribution to the research sector was the United Kingdom's employment of a platform trial [73]. In this trial, a group of patients enrolled in a single clinical trial or platform are asked to answer multiple questions about a single disease. The platform, titled RECOVERY, tasked investigators with randomizing over 11,000 COVID-19 patients to four treatment groups (hydroxychloroquine, azithromycin, lopinavir-ritonavir, and dexamethasone) in addition to a usual care control [74]. This one control group was used for all four tested therapies in the trial. The investigators were able to enroll large numbers of patients and execute trials rapidly by leveraging close coordination, minimal data collection, robust national data registries, and public health infrastructure, and focus on hard clinical endpoints. One of the RECOVERY trials demonstrated that dexamethasone reduces mortality in patients requiring supplemental oxygen therapy or mechanical ventilation [75]. At the time of this writing, dexamethasone is the only therapy that has been shown to reduce COVID-19 mortality. The RECOVERY results were so striking and considered by many to be so robust that other steroid trials were halted [76]. Nonetheless, a meta-analysis including RECOVERY and other trials showed that steroid therapy reduces mortality among critically ill patients with COVID-19 [77].

Other platform trial programs included the United Kingdom's public-private Accelerating COVID-19 Research & Development (ACCORD) network, which developed a master protocol to run several candidates of therapeutic agents through Stage 1 and Stage 2 trials [79,80]. The WHO established the Solidarity network to conduct a large-scale clinical trial of remdesivir, hydroxychloroquine, interferon beta-1a, and lopinavir-ritonavir [81]. All four treatments were found to have no significant effect on mortality or disease course for patients hospitalized with COVID-19 [81].

While the dexamethasone finding can rightfully be considered a success, so can the RECOVERY trial "failures" be considered successes because their large samples and strong design allow for robust findings and can help guide clinicians away from interventions with limited or no efficacy in improving outcomes. For example, the RECOVERY investigators published their findings showing no benefit for the antiviral combination lopinavir-ritonavir [78]. This large-scale trial, with over 4,000 patients enrolled and over 1,000 endpoints, confirmed the findings of a previously published but much smaller trial.

Early Lessons for the Research Sector

Scientific Collaboration and Communications

The COVID-19 pandemic highlighted trends in the evolution of scientific communication and information sharing. Within a remarkably accelerated timeline, there was rapid sharing of SARS-CoV-2 sequence information online, signaling an important culture change during a time of crisis, demonstrating that research collaboration had positive public health benefits [152]. Data and technology were leveraged in health care systems and shared for real-time clinical information describing risks, outcomes, and variations in care patterns [153]. These approaches, driven by the willingness to collaborate and share, can be transformative for other research processes and initiatives if they are continued beyond the COVID-19 pandemic.

In scientific publishing, the COVID-19 pandemic realized the research sector's endeavors to reduce the publishing times of peer-reviewed results. There has been a longstanding frustration over how long it takes to publish peer-reviewed articles in mainstream biomedical journals [82]. Over the last 5–10 years, biomedical researchers are increasingly posting their findings in large-scale preprint servers; this practice has been encouraged by funders (including the NIH and private foundations) and permitted by journals [83,84,85]. Preprint servers have long been used by scientists in fields like physics, chemistry, astronomy, mathematics, and economics; only more recently have basic biomedical scientists also adopted this practice. Some sectors of clinical research remain resistant to preprints, perhaps because of concerns that unreviewed work might be prematurely praised and inappropriately translated into practice [86]. However, about 90 percent of the highest impact journals now allow preprints, and over the past couple of years, the *New England Journal of Medicine* allows authors to post preprints, as was done with the RECOVERY dexamethasone trial, which was posted as a preprint and then later published as a peer-reviewed manuscript [75,87,88,89]. Amidst the COVID-19 pandemic, the National Library of Medicine launched a preprint pilot by which preprints can be searchable in PubMed Central and discoverable in PubMed [90]. The pilot begins with preprints reporting on NIH-supported COVID-19 research and, in future phases, will progress to include other NIH-supported research in an effort to speed dissemination and enhance rigor.

There has also been an explosion of scientific communications related to COVID-19. According to one NIH-run communication tracking site, between March 2020 and October 2020, over 70,000 communications directly related to COVID-19 were posted, including over 56,000 peer-reviewed articles and 14,000 preprints, a challenging volume of information for researchers and policymakers [91]. One effort by Amedeo, a medical literature site, promotes and assembles abstracts of the ten most relevant COVID-19 research papers daily, enabling the dissemination of relevant information that has been compiled in a far more extensive, periodically updated 300-page "COVID Reference" and several associated chapters on topics such as comorbidities, epidemiology, and transmission [92].

The explosion of scientific activity and the apparent need to communicate results promptly has led to new challenges for biomedical journals and the scientific enterprise as a whole [93]. For example, the editors of *JAMA* note that they received 11,000 manuscripts over a few months in 2020; in the corresponding period in 2019, they received only 4,000 manuscripts, reflecting an almost tripling of submissions due to COVID-19 [94]. The journal has adapted its processes for considering manuscripts, including greater reliance on full-time editors, an internal review for certain types of papers, insistence on external review for papers thought likely to impact clinical practice, and, when appropriate, requests for additional data, data analyses, or confirmation of data accuracy. There are concerns that the rush to publish and a "fog of war" mentality may make the biomedical research publication system more vulnerable to disseminating questionable reports [95]. Indeed, early in the COVID-19 pandemic, two high-profile publications from Surgisphere, a little-known entity, had to be rapidly retracted when the authors were unable to reproduce the primary data [96].

Highlighted Challenges and Gaps

The COVID-19 pandemic has highlighted several inherent challenges in the conduct of modern biomedical research [97]. These include over-reliance on mathematical models, inaccurate data interpretations due to confirmation bias, and assessing the value of therapies using uncontrolled data (e.g., convalescent plasma [98]). Other problems noted by the authors include a lack of harmonization across research and development and clinical trial activities, costly replication efforts, and the overestimation of peer review's reliability. These gaps, along with other well-described problems in the scientific enterprise, stem in part from known human biases and heuristics and from difficulties linked to current systems of funding and publishing science [99].

Other key problems in the U.S. include fragmented data infrastructures, in part paralleling a fragmented health care system, and a long-standing disconnect between clinical care and clinical research: it has been pointed out, for example, that at best, only 4 percent of American COVID-19 patients have been enrolled in clinical trials [100,101]. COVID-19 demonstrates that the decades-old question, "Why not randomize the first patient?" remains as pertinent as ever [102]. Too much belief in observational studies or in small-scale trials may not only lead to erroneous conclusions but may also hinder our ability to get needed large-scale trials done [103]. To this point, a review of characteristics and expected strength of evidence of COVID-19 studies registered on ClinicalTrials.gov revealed few large multicenter trials had the potential to generate high-quality evidence and a large proportion of studies with an expected low level of evidence [104]. Caution was raised about the rapid dissemination of low-quality evidence due to potential harmful influence on public opinion, government actions, and clinical practice.

Foundational Strategies for Transforming Health and Biomedical Research

Transforming health and biomedical research beyond the COVID-19 pandemic requires incorporating lessons learned from the pandemic, facilitating emerging insights from cutting edge technologies, embracing partnerships and collaboration, advancing open science and data sharing, embedding a learning ethic throughout health care, and emphasizing patients and communities as full participants in the research enterprise to advance health equity.

Embracing the emergence of new technologies such as genetics and genomics, data science, including machine learning and artificial intelligence, and digital and precision health are critical for transforming health and biomedical research. It is critical to align these transformations with a health care and research landscape rapidly evolving toward precision medicine, an approach stating that moving toward the best available care for every individual requires care providers and researchers to access immense health and disease-related data sets linked to individual patients [146].

Genomics and other "-omics" have emerged as approaches for person-centered health care with the capability for risk stratification with deeper phenotyping and tailoring therapeutics with predictive responses. Technological advances are converting data from smartphones and wearable devices, search engines, claims, electronic health records (EHRs), public records, patient portals, aggregated research data, and other sources into actionable information in health care settings. Artificial intelligence and machine learning are being leveraged to enhance diagnosis and treatment. During the COVID-19 pandemic, rapid genetic sequencing of SARS-CoV-2 was a critical step in research response and testing, and vaccine development. Genomic studies of patients with COVID-19 focus on describing variability in susceptibility, infectivity, and disease severity [105]. Digital health with smartphone technology is emerging as a critical tool for surveillance, tracking, prediction of illness, and adverse event reporting for vaccine safety monitoring [106,107].

Incorporating lessons learned from public-private partnerships and collaborations such as OWS and ACTIV, the research enterprise can accelerate and streamline processes for prioritizing resources. The research sector can also coordinate and establish a cohesive approach for studies with shared priorities; convene multiple government agencies, nonprofit foundations, and private companies; and fundamentally enhance the infrastructure for research to enable synergistic and complementary approaches. While leaders from the government and the private sector rapidly assembled the ACTIV and RADx networks, the research enterprise will be better able to address ongoing and future threats to public health by having a robust research infrastructure in place [63,66]. Collaboration extends to data science approaches that advance data sharing within and across research and health sectors to accelerate evidence development, validation, and access to data sources in a pandemic and beyond.

While the benefits of increased collaboration and transparency were observed during the crisis, the competitive nature of academic and industrial science has made collaboration and transparency difficult to enact more broadly. There are legitimate concerns regarding academic career advancements as well as the protection of intellectual property (IP). However, improving sharing data and cross-sector partnerships has the potential to advance research more rapidly from the lab to the clinic and patients. Resolving IP concerns in sharing and using clinical data should also be explored. Although links between academia and industry have improved in recent decades, there are still too few examples of strong partnerships that emphasize advancing basic research to the application of knowledge and solutions.

This COVID-19 pandemic has revealed the long-term necessity for integrating clinical and research enterprises that create learning health environments. This integration must be adaptable in approaches to care delivery by leveraging clinical data for research to understand risks, outcomes, and variations in treatment; and embedding clinical trials and observational studies with the capture of clinical encounter data as outcomes.

While vital during the pandemic, science communications and information and data sharing across clinical communities will continue to prove essential for the future of a robust health and biomedical research enterprise. The pandemic also exposed the important interplay between the front-line clinician and the evidence generated and developed for rapid implementation and translation into practice. Further, the heightened focus on health equity has emphasized the imperative to address the social determinants of health and the urgency of combatting systemic racism as pathways to eliminate the marked disparities in risk, incidence, and outcomes in the COVID-19 pandemic and beyond. Public awareness and the centrality of research to end the COVID-19 pandemic, as well as an intensified recognition of the importance of health equity, have also emphasized the importance of communication strategies and the engagement of patients and the public as full research participants. Ensuring this participation will facilitate research that reflects the demographics of those affected and the trust of those who are the true consumers of the evidence produced. The trust of research participants, patients, and the broader public is a long-recognized challenge and one of the most important issues to address in the setting of the COVID-19 pandemic and the rising urgency of combatting health inequities fueled by racism and the social determinants of health.

Data Sharing

Background

Data sharing within and across research and health sectors holds the potential to advance processes that nimbly adapt to address the evidentiary needs in a pandemic and support rapid response and public health and clinical decision making. Before the COVID-19 pandemic, efforts to promote data sharing and build interoperability across data sets were gathering momentum, though challenged by technology, hesitancies regarding issues such as data misuse or competitive challenges to ongoing publication, and privacy concerns. Some report the lack of interoperability between clinical systems has impeded efforts to identify outbreaks, track mortality rates, and deliver efficient patient care amidst the COVID-19 pandemic [108]. The heightened urgency for data sharing and data sharing systems spurred by the COVID-19 pandemic provides a window to accelerate progress toward realizing principles exemplified in several research funders' data sharing policies and Open Science efforts [109,110]. Work to harmonize data collection will need to continue apace if the power of data science analytics and tools such as artificial intelligence and machine learning techniques are to be applied successfully across large data sets, which can be available broadly for research purposes. Currently, data is collected and stored from a wide array of sources and formats, hampering research efforts.

Data Sharing during COVID-19

Thoughtful approaches to data sharing have emerged during the COVID-19 pandemic, including a focus of efforts on data curation, de-identification, and inclusion of appropriate statistical expertise [111]. A recent comprehensive report with recommendations on data sharing in COVID-19 for four key research areas—clinical data, omics practices, epidemiology, and social sciences—offers best practices from the NIH, including the following [112]:

- The need to develop software and invest in information technology to support infrastructure for pandemic response and early publication and release of data outputs, aligned with FAIR (findable, accessible, interoperable, and reusable) principles and using a generally applicable metadata element set across sectors.
- Establishment of data governance that documents methodologies used to collect, define, and construct data, and establishes standards for "trustworthy" data repositories.
- Frameworks and standards for data cleaning, data imputation, and data provenance.
- Incorporation of legal and ethical considerations around participant and patient information tailored to this crisis. These considerations should promote the openness of individual participant data and trial documents as much as possible when balanced with protecting participant privacy and mitigation of risks related to data use or misuse.

The NIH has encouraged NIH-supported clinical research programs and researchers to adopt the standardized set of health care data classes, elements, and vocabulary specified in the United States Core Data for Interoperability (USCDI) to enable consistency in shared clinical research data [113]. The use of USCDI complements the HL7® Fast Healthcare Interoperability Resources® (FHIR®) standard and will facilitate the use of clinical data, such as EHR data, in research studies. The use of the USDCI standard will also promote structured clinical data for research with the potential to enhance collaboration, facilitate data aggregation and interoperability, and enhance discovery [114]. While encouraged broadly across all NIH-supported work, the USCDI standard provides a critical mechanism to bring coordination and collaboration to a broad set of COVID-19 research activities, including clinical trials, and to promote aggregation and validation of observational analyses using real-world data.

While these achievements are notable, data-sharing policies can be evaluated, strengthened, and improved with collaboration from experts to advance more robust data sharing based on the principles of FAIR data sharing [158].

Another example of improved data sharing is the National COVID Cohort Collaborative (N3C) Data Enclave, which creates an innovative analytics platform with a curated set of EHR data of people who were tested for COVID-19 or have had related conditions. The enclave serves as a centralized and secure data platform with a harmonized data set and analytics capabilities for an online query, visualization, and collaboration [115]. Given the ability to generate enormous, robust data sets, the approach taken by the N3C Data Enclave may be ideal for enabling machine learning and other rigorous statistical analyses across large and diverse patient populations to rapidly identify patterns relevant to clinical dilemmas.

In addition to these efforts, the NIH has funded the NIH Disaster Research Response (DR2) Program, a pilot program that aims to create a disaster research system including coordinated research data collection tools. Specific to COVID-19, several data collection tools (case report forms, instruments, surveys, questionnaires) are collated and each instrument's source is verified. While considering the significant expense, resources, and time involved, the program is also striving to provide access to study protocols, study designs, and data dictionaries to enhance timeliness for end users, as well as support data interoperability and harmonization. Another important resource is the PhenX Toolkit, which provides access to many of the COVID-19 instruments in the DR2 collection but is broken down into specific topic areas for improved ease of use [60,116].

While a centralized approach may facilitate coordination amongst disparate efforts, provide standards to facilitate data aggregation, support repositories for clinical trials data, and enable sufficient power to conduct nuanced clinical analyses, other approaches may facilitate the use of routinely collected EHR data for many different purposes. One such example of a data infrastructure leveraged for COVID-19 response is the PCORI-funded PCORnet, the National Patient-Centered Clinical Research Network established to improve the nation's capacity to conduct health research and to learn from the health care experiences of millions of Americans to enable large-scale research to be conducted with enhanced accuracy and efficiency. To position the PCORnet infrastructure to rapidly respond to the national need to answer critical patient-centered questions related to the novel coronavirus and COVID-19, PCORnet Network Partners are capturing complete, longitudinal health care data on their COVID-19-positive patient population, including EHR data from patient care in the delivery system, and claims information or other records representing care received outside the delivery system. This real-world data is transformed into a standardized format called the COVID-19 PCORnet Common Data Model (CDM) that is easily queried via a distributed network model. The distributed model is designed to promote patient data security. Research questions or queries obtain data and aggregate de-identified results before the data request is returned to the request's source. The entire process is performed locally at the network site. The data remains at the network site behind institutional firewalls, maintaining security.

This new COVID-19 CDM accelerates the traditional timeline of transforming new data into the CDM from months to days. The PCORnet Coordinating Center releases weekly queries to characterize this cohort of COVID-19-positive patients across all sites and provide detailed information on demographics, care settings, and pre-existing conditions. The PCORnet Network Partners are collaborating with the CDC to support COVID-19 surveillance efforts using this COVID-19 CDM infrastructure resource, the FDA-Reagan-Udall Foundation COVID-19 Evidence Accelerator initiative to examine therapeutics, and the NIH to create cohorts of emerging COVID-19 syndromes for natural history studies. Furthermore, the Patient-Centered Outcomes Research Trust Fund for data infrastructure administered through the Department of Health and Human Services will be focusing on data infrastructure issues related to building data capacity for research on patient outcomes associated with the COVID-19 pandemic.

Other efforts beyond PCORnet are facilitating the application of observational data to derive insights relative to the COVID-19 pandemic. For example, the Observational Health Data Sciences and Informatics (OHDSI) collaborative is a multi-stakeholder, interdisciplinary, open-science effort to promote data standards and harmonization. The collaborative pivoted to bring out the value of observational health data through large-scale analytics applied to understand COVID-19 outcomes from studies focused on deep phenotyping to the examination of risks and treatments [154]. Both PCORnet and OHDSI contributions to research during the COVID-19 pandemic underscore the critical nature of using clinical and patient-level data to ensure quality evidence is created, reviewed, and disseminated during times of crisis. Additionally, data acquisition and analytics for non-COVID-19-related health research is being supported through nonprofit organizations (e.g., Michael J. Fox Foundation) and for-profit entities (e.g., Blackfynn). Efforts encouraging the adoption of data sharing and harmonization platforms and practices across the research ecosystem, public, private, and nonprofit domains could produce a high return on investments, produce higher quality data, and accelerate research in times of crisis.

In addition to NIH efforts at the federal level, agencies such as the Office of the National Coordinator (ONC) for Health Information Technology published coding and guidance, relevant rules, regulations, and laws, and key interoperable data sets on their website. These resources helped facilitate the support of care, payment, research, and public reporting via the LOGICA platform, in addition to guidance on recording and reporting situational updates via the HL7 platform. The platform also helped advance research on the pandemic by using the COVID-19 Interoperability Alliance and its 600 data sets, enabling the use of interoperable and customizable data sets and platforms. Additionally, the ONC's response included publishing technical guidance on the adoption of other coding, record-keeping, and reporting mechanisms such as the SNOMED CT, LOINC, and the ICD. Finally, the website also published relevant guidelines per the CARES Act promoting compliance with HHS and its associated agencies, CDC, and the FDA [145].

As efforts such as these examples continue to build momentum, the research and broader health enterprise will be continuously challenged to find approaches to data sharing and create broadly accessible yet appropriately governed data platforms, interoperable solutions, and transparent reporting of analyses and results. Furthermore, a deeper understanding of participant choice and interest, as well as transparency around data sharing, will be critical for ongoing progress. Multiple purposes and applications will drive data sharing, and a variety of solutions are likely to be needed (e.g., centralized data repositories or federated data networks), particularly over time. The experience and momentum gained during this period of rapid innovation to address long-standing infrastructure and interoperability challenges, as well as policy issues related to incentivizing data sharing or promoting patient privacy and responsible data governance, should be capitalized upon to fuel future evolutions in scalable models able to meet specific research needs, knowledge, or outcomes desired, or accommodate other non-research-related factors.

Research Participants

Background

The transformation of the research workforce, research processes, and data sharing protocols, while essential to accelerating research results into practice, is not sufficient without the participation of many diverse participants and researchers in clinical studies and public health surveillance systems. Such a prospect necessitates the engagement of participants and communities as partners in research throughout the entire life cycle of clinical studies and translation into practice, from concept to implementation, with a focus on transparency throughout. Furthermore, such approaches build trust as a basis for participation in COVID-19-related clinical studies, including those who have been the most adversely affected by the COVID-19 pandemic, who are often also communities underrepresented in research and suffer marked health disparities.

Research Participants in the Setting of COVID-19

Despite remarkable progress in research and innovation and improvements in health over the decades, disparities are still clearly evident [117,118]. Nowhere is this more clearly elucidated than in observations of outcomes from the COVID-19 pandemic. COVID-19 death rates by age and race/ethnicity, aggregated from CDC data, are substantially higher for Hispanic/Latinx, Black, Asian, and Indigenous people: for these populations, the death rates from COVID-19 compared to White people are 2.3, 1.9, 1.0, and 2.4 times respectively [119]. Inequalities in COVID-19 infection and outcomes also exist for American Indian and Alaska Native populations, carrying 57 percent of cases while comprising only 9 percent of the total population in New Mexico [120]. However, these disproportionate impacts are not unexpected due to longstanding inequities in health and health care, social conditions, and income inequalities that promulgate crowded housing conditions and necessitate "essential" jobs, in addition to documented similar disparities in prior epidemics, including influenza [121,122,123].

Furthermore, the disparities witnessed in the COVID-19 pandemic by race/ethnicity are direct calls to action for the research community: to interrogate the social construct of race and intervene upon the complex multicomponent drivers of outcomes represented by the variable of race, including traditionally studied issues of geography and socioeconomic factors, as well as structural racism, discrimination, and bias and its biological and socioeconomic implications [124,125,126].

The research community's challenge is that COVID-19 necessitates research with the communities most adversely affected and distrustful of the biomedical enterprise. To flatten the curve or eradicate COVID-19, research and public health efforts will need to understand what makes for culturally appropriate and practical guidelines. For example, developing guidance for safety precautions in multigenerational homes or identifying approaches to mitigate risk when staying home is not a viable option for workers without sick leave or lack of flexibility in a work environment [122].

Meanwhile, vaccine trials require the recruitment of participants with high exposure rates, many with barriers to participation in research, and distrust of an enterprise that has historically marginalized, mistreated, and in some cases, actively harmed them. Making demonstrable progress necessitates educating and preparing the country for vaccines, addressing vaccine confidence, expanding surveillance and monitoring systems, and examining the determinants of vaccine response. With this devastating crisis comes a lesson and an opportunity to evolve research to engage traditionally marginalized communities to serve as equal partners in research.

To be successful in containing COVID-19, this is not optional. The COVID-19 pandemic presents a tremendous opportunity to engage the public around the rapidly evolving nature of science, ingrain the importance of behavioral and preventative non-pharmaceutical interventions such as physical distancing, quarantining, handwashing, and wearing masks in the setting of any infectious threat, and the ability of vaccines to eliminate such a threat, even beyond COVID-19.

Ensuring that historically marginalized communities serve as equal partners requires the research community to address the disproportionate burden for low-income and diverse individuals to participate in clinical trials [127]. Overcoming barriers such as distrust, lack of insurance, fear of medical costs, lack of sick leave, lack of information about the clinical trials process, language barriers, cultural and literacy competencies, and general time and resource constraints requires acknowledging, understanding, and addressing these issues in a tailored and specific way [128,129,130]. Meaningful engagement of both research participants and historically marginalized communities in research and application of findings from the development of a concept through study design, study conduct, and implementation can help bring long-existing problems and subsequent solutions to the fore. This meaningful engagement can serve as a pathway toward the diverse participation in trials that the COVID-19 pandemic necessitates [131].

Experience at PCORI has demonstrated that engagement is feasible and benefits those involved by generating enthusiasm for research, building trust, and enhancing successful recruitment and retention [131,132,133]. The NIH Community Engagement Alliance (CEAL) program provides trustworthy information through active community engagement and outreach to those most significantly affected by the COVID-19 pandemic, including African Americans, Hispanics/Latinos, and American Indians/Alaska Natives, with the goal of building long-lasting partnerships as well as improving diversity and inclusion in research related to COVID-19 [152]. Engaging communities as partners can build research capacity for short- and long-term impacts in diverse or underserved communities. Research entities should partner with stakeholders and individuals from hospital and clinical systems, as well as trusted voices in neighborhoods and communities – these individuals and groups could help build research capacity for short- and long-term impacts in diverse or underserved communities.

Public Engagement with Research

Background

Community, patient, and participant engagement in research begin with articulating the value and utility of research to the public and building trust among individuals, organizations, and broader communities. The COVID-19 pandemic presented an opportunity to implement these principles, as the imperative of science and research is currently being discussed in the media and in communities in the nation. Leveraging, learning from, and galvanizing awareness about research and its inextricable link to health and health care in the U.S. and globally is an opportunity for the research community to improve. Efforts to introduce fundamentals about research could go further now than ever before and facilitate essential efforts to engage the public as partners in the research process and disseminate key research findings. For example, PCORI recently released a new evidence-based learning package called *Research Fundamentals,* which uses plain language to provide foundational knowledge about the research process, patient-centered outcomes research, and how stakeholders may engage in research [134]. This package is a first step in further disseminating research and communicating its value to the broader public, a perennial challenge for the health system.

Public Engagement with COVID-19 Research

Helping all stakeholders, regardless of research experience, to feel included to participate in and shape research studies is more important now than ever. With the COVID-19 pandemic sparking increased interest in the research process, despite challenges to public confidence in science, researchers should take care to learn from study participants and communities by listening to their interests and needs, sharing decision-making power, and communicating effectively and honestly throughout the study's process. As the current pandemic requires at least 150,000 diverse research participants to enroll in vaccine clinical trials alone, the research enterprise must not miss the opportunity to enable broad public and patient engagement in research.

Aspects of a continuously learning health care system, including the transparent integration of research with clinical care and public health activities, the timely return of results to patients, and rapid dissemination of findings to clinical care, will be critical to overcoming barriers to participation in research. Moreover, diversifying the front line of research to reflect the communities most adversely affected by the COVID-19 pandemic will be critical to the success of treatment and vaccine trials. Polling data from February 2021 reveal that 61 percent of Black adults would be willing to receive the vaccine or had received at least one dose, compared to 69 percent of White adults [135]. That was up from 42 percent in November 2020. Research on engaging diverse communities in research has revealed that strategies to include Black and Latinx participants in trials require the research enterprise to acknowledge the challenges intrinsic to recruiting participants of diverse backgrounds, recognize the increased costs to address barriers to participation, and ensure successful implementation of an effective vaccine within the communities most affected [136,137]. Studies also documented that Black adults are more likely to participate in clinical research if the questions they ask are answered and if requests for additional time for consideration of receiving a vaccine are granted [138].

Now that vaccines have been developed, the research community's challenge is the implementation of strategies to vaccinate millions successfully and equitably. To rise to this occasion, an effective vaccine is first required. However, an effective vaccine must be guided by principles of health equity and aligned with the meticulous integration of lessons from implementation science on community engagement ahead of launching trials; testing strategies that leverage community leaders, health care extenders, and social and community pillars; and culturally and linguistically appropriate materials. In addition, scientists generally do not have the marketing or public relations expertise needed to begin to shift public opinion of science. The critical impact of basic and applied science in fighting the COVID crisis must be clearly highlighted moving forward to present why investing in science matters for society at large. These efforts underscore the importance of garnering and sustaining trust, ensuring access and availability of developed vaccines, and developing or leveraging relevant and culturally appropriate infrastructure to reach all Americans [130,139].

This task is a tall order for the biomedical, public health research enterprise, necessitating innovation, partnerships, and breaking from the tradition of research designed and implemented only in labs, hospitals, and academic centers. Stemming the tide of COVID-19 will require research that is patient-, participant-, community-, and public-centric. In addition, the application of lessons learned from research in this devastating pandemic is also required to create a long-term public health impact.

Health and Biomedical Research Leader Opportunities

As the health and biomedical research leadership reflects on the opportunities and responsibilities laid bare in the setting of the COVID-19 pandemic, development of research infrastructure, ongoing collaboration across and within the sector, and accessibility of science and engagement of the public in research have emerged as critical priorities.

Amidst a pandemic, research leaders in the public sector have the opportunity, in partnership, to develop priorities and timelines and promote coordination and collaboration across agencies, the private sector, and institutions. The research sector could also advance policies to enhance sharing of scientific and epidemiologic data and communication. In consideration of future pandemics and transformation of the research enterprise, public sector research leadership has the opportunity to leverage emerging technology for surveillance and event reporting; prospectively establish research infrastructure with public-private partnerships, clinical trial networks, and recruitment and implementation science as integral components to pandemic preparedness; and consider policies for accelerated emergency resourcing, funding, and decision-making. Maintaining the pipeline of researchers and research in an emergent setting is another priority for the future health of the biomedical and health research sector.

Research leaders in the private sector can continue, with scientific rigor at the forefront, to advance and invest in cross-industry collaboration, public-private partnerships, and sharing of information and resources that promote complementary efforts toward diagnostics, therapeutics, and vaccines.

Research leaders in institutions have critical opportunities to advance pathways for efficient and effective rapid scale-up of research operations for national priorities and emergencies. Research leaders can also leverage and promote opportunities after the pandemic to facilitate the integration of research and clinical practice to capture clinical data for outcomes assessment and enable a future where data is shared to hasten the speed of scientific discovery. Institutional leaders across the research sector are critical to the diversification and stability of the research workforce pipeline. With the challenges of the ecosystem evident, the need to double down efforts for diversification and retention of that pipeline has never been clearer.

Summary and Priorities

Assessing the Impact

The COVID-19 pandemic will have long-standing implications for the research enterprise, which may not return to pre-pandemic operations. A critical priority over the next 6–12 months will be to assess, in both quantitative and qualitative terms, the ongoing and longer-term impact of the pandemic, including opportunities for research to continue to help mitigate and overcome the pandemic, ensuring the future of the research enterprise is protected, and learning and transforming research to capitalize on lessons from the pandemic response. The Council on Governmental Relations posted a working paper in August 2020 describing a Research Impact Metric by which institutions can assess their operations. The working paper describes a new "Pandemic Normal" characterized by ongoing slow-downs, changes in operations (e.g., shift work, required protective equipment), supply challenges, core facility disruptions, slowed hiring and promotion, and perhaps above all, a great deal of uncertainty [36]. A recently published landscape review described some of the uncertainties: the trajectory of federal funds and policies, the role of charitable foundations, the impact of declines in non-research revenues on research operations, whether future shut-downs may be needed as the pandemic worsens, what the long-term effects on research collaborations (positive and negative) will be, how changes in rapid scientific communication and peer review will evolve, whether research will return to "normal" levels of productivity and on what timeline, and what will happen to the scientific workforce [140].

Research Workforce: The Path Forward

COVID-19 has exacerbated stressors on the research enterprise with disparate impacts on the workforce, particularly those underrepresented in science and early in their scientific careers. An essay published earlier this year noted that returning to normal may not be the desired goal since the previous normal was not ideal, bringing with it long-standing academic research challenges, including a complicated system that favors senior-level researchers [52]. As in many other areas, the pandemic offers opportunities for learning and transformation. Several priorities and considerations include:

- Focused attention on those underrepresented in science by overcoming systemic problems in building a research enterprise that includes scientists from diverse backgrounds through efforts that commit to racial/ethnic and gender equity in research processes and provides solutions to barriers for retention.
- Focused attention on those early in career by incorporating successful efforts to streamline application processes and policies piloted during the pandemic and extending advantages for investigators early in their careers. Actionable examples are research awards only for early-career scientists with less preliminary data at the time of application, revised application and review policies that are blind to career stage and focus on research topic and approach, and instructions to reviewers to disregard situations directly related to the COVID-19 pandemic, such as temporary declines in productivity [141,142,143].
- Focused attention on efforts overcoming any pandemic-related productivity losses and challenges, financial and otherwise, for scientists attempting to restart their research programs. These efforts should consider the potential of using multiple sources of funding from nonprofits, federal and state governments, the private sector, and individual donors. Funders could incorporate several approaches to expedite the case-by-case evaluation of challenges faced by applicants and awardees with the principle of being as flexible and accommodating as possible when responding to administrative and research delays during the pandemic. Three priorities for the research ecosystem are emerging with building anticipation of efforts to regenerate and restart research and training programs and enable future systems transformations. These priorities include:
    - Supporting early-career scientists and their research.
    - Rescuing meritorious and established investigators who are at risk for losing or unable to regain a substantial portion of their research funding.
    - Funding several high-priority clinical studies in which completion of minimum enrollment and follow-up thresholds are critical for study completion and methodological integrity.

Public-Private Collaboration and Communications

The pandemic also provided some initial guiding principles on best practices on PPPs and communications. These lessons should become more evident as future assessments of PPPs are undertaken.

- Internally, communication, coordination, and collaboration across researchers, clinicians, public and private sectors, and policymakers, such as the OWS-ACTIV approach of prioritizing and executing critical research.
- Externally, the translation and synthesis of research findings through various media mediums for broader public consumption and knowledge, especially to build and regain trust in the biomedical research ecosystem.

Research Processes and Data Sharing: Implications for a Longer-Term Impact

The enterprise has been challenged to rapidly establish clinical studies and associated infrastructure to translate research into practice, balance speed and rigor, promote the sharing of data and interoperability between platforms for delivering real-time results in clinical settings, and build public trust in validated research findings. Learnings in a pandemic provide opportunities for a longer-term impact. Priorities and considerations include the following:

- Coordination across efforts (e.g., federal, private, funders, and academic institutions) for coherence, efficiency, and increased effectiveness. An example of such efforts is an overarching set of research priorities across disciplines and methodologies with role delineation within the sector for activities and development of shared research infrastructure leveraging existing and new entities and networks for the implementation of research protocols.
- Clarity in implications of trials and studies based on design and limitations, including encouraging journals to publish negative studies to eliminate alternative clinical approaches to care that are not grounded in scientific evidence.
- Tailoring of study designs (observational or randomized) to specific questions with a shared understanding of strengths and limitations in addition to ensured reliability of data sources.
- Continued resolve and facilitation of requirements for researchers to share data sets and documentation for reanalysis and reuse consistent with, but not limited to, the NIH and PCORI data sharing policies.
    - Data governance requiring data sharing, infrastructure that supports sharing, and standards that promote interoperability as key to support these aims.
    - Governance that promotes the inclusion of stakeholders, specifically communities and patients, to generate solutions to concerns related to data misuse and privacy.

Research Participants and Public Participation in Research

This pandemic has created an imperative for communication, collaboration, and coordination across sectors that could not be stronger. Actions and considerations include the following:

- The establishment of meaningful partnerships and trust with affected communities as research partners is central to the path forward to combat high levels of distrust of scientists and researchers. Partnerships begin with the identification and involvement of community brokers and subsequently identified community entities in understanding the purpose of research studies, setting research priorities, and translating information to communities.
- Engagement of stakeholders, patients, and communities leveraging community brokers toward building trust and trustworthiness and enhancing diverse participation in research.
- Broad scientific communications enhance the value of research conveyed to the public and build trust among individuals, organizations, and broader communities.

In the face of unprecedented challenges and urgent necessity, the biomedical and health research enterprise has the potential to deliver the discovery, translation, and implementation science related to vaccines and therapeutics required to end the COVID-19 pandemic. To propel the entire sector toward a holistic approach, it is crucial that all components of the research ecosystem collaborate on a multifaceted transformation that enhances the resilience and diversity of the research workforce and innovates in funding processes and partnerships to maintain the viability of research efforts during a crisis. The research sector of the future accelerates the translation of knowledge to care and public health action, delivers on long-standing data sharing efforts, and coordinates across health and health care. Essential to the sector's efforts to innovate and achieve is the elevation of communities and participants as equal partners in research while engaging the public in science.

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