TESTIMONY

OF

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AN UPDATE ON THE ONGOING FEDERAL RESPONSE TO COVID-19; CURRENT STATUS AND FUTURE PLANNING

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Chairs McMorris Rodgers, Griffith, and Guthrie, Ranking Members Pallone, Castor, and Eshoo, and distinguished members of the Committee:

Thank you for the opportunity to discuss the role of the National Institutes of Health (NIH) in the response to emerging and re-emerging infectious diseases. NIH Institutes and Centers have played a central role in addressing coronavirus disease 2019 (COVID-19), and mpox (formerly known as monkeypox) by capitalizing on decades of basic, clinical, and applied research to facilitate the rapid development of vaccines, therapeutics, and diagnostics, which continue to be important tools to reduce the threat of these diseases. As the individual performing the duties of the NIH Director, I am pleased to discuss the ongoing and future NIH research to address COVID-19 and other critical public health threats.

For decades, NIH has been poised to quickly respond and develop medical countermeasures to combat these and many other emerging and re-emerging infectious diseases, including HIV/AIDS, SARS, influenza viruses with pandemic potential, and Zika. This requires researchers to think big. One such example is the President's Emergency Plan for AIDS Relief (PEPFAR). Led by President George W. Bush and launched 20 years ago, PEPFAR demonstrates what is possible when big ideas are pursued. Over 20 year later, PEPFAR programs are in more than 50 countries and have saved over 25 million lives. The work achieved by PEPFAR was instrumental in putting many communities on track for epidemic control and served as a platform to help combat recent disease outbreaks.

Leveraging the expertise of basic and clinical researchers allowed NIH to quickly address COVID-19 and mpox in a multifaceted manner, including through the evaluation of strategies for prevention and treatment.

Developing Vaccines to Prevent COVID-19

Sustained basic research investments by NIH over decades – prior to the emergence of SARS-CoV-2 – allowed the unprecedented pace of COVID-19 vaccine development. Longstanding National Institute of Allergy and Infectious Diseases (NIAID) support enabled the development of versatile vaccine platforms and the use of tools to visualize proteins including cryo-electron microscopy, and informed the design specific proteins—called immunogens—that powerfully stimulate the immune system. Prior to the COVID-19 pandemic, scientists at the NIAID Vaccine Research Center (VRC) and their collaborators made the critical scientific discovery of how to mutationally stabilize—in a highly immunogenic form—the spike

protein that coronaviruses use to infect human cells. This strategy facilitated the design of vaccine candidates that generate robust protective immune responses. As soon as the sequence of SARS-CoV-2 was made available in early January 2020, NIAID VRC researchers rapidly generated a stabilized SARS-CoV-2 spike protein for use in COVID-19 vaccine development. This crucial breakthrough in structure-based vaccine design led to the development of COVID-19 vaccine candidates, four of which are now authorized or approved by the U.S. Food and Drug Administration (FDA) for use in the United States, built upon a range of vaccine platforms including the highly successful mRNA platform. NIAID's pivotal clinical response enabled enrollment in the dose ranging study for the Moderna mRNA vaccine candidate within 60 days of antigen design.

Through fundamental research underlying the vaccine concepts and the establishment and utilization of an extensive and diverse clinical trials network, NIH helped advance the development of six candidate COVID-19 vaccines, including fulfilling the critical need for high-throughput validated testing of Phase 3 trial samples. As part of Operation Warp Speed, NIH supported the Phase 3 clinical trials for three of the vaccines that were made available for use in the United States: the mRNA-1273 vaccine, developed through a collaboration between the NIAID VRC and Moderna, Inc., the Ad26.COV2.S vaccine candidate from Johnson & Johnson/Janssen, and the NVX-CoV2373 vaccine candidate from Novavax. NIH also supported a Phase 3 clinical trial of the AZD1222 COVID-19 vaccine candidate from AstraZeneca. An NIH-supported Phase 3 clinical trial of the investigational SARS-CoV-2 adjuvanted recombinant protein vaccine from Sanofi/GSK is ongoing.

FDA-authorized and FDA-approved COVID-19 vaccines remain the most effective tools available to prevent COVID-19. However, we have seen that, with the continued emergence of new variants, protection against mild and moderate disease decreases over time following the primary vaccine series. NIH quickly established that boosting with the same vaccine that was used for the primary vaccine series could significantly increase levels of antibodies against variants, compared to levels in individuals who received the primary regimen alone. This "homologous" boosting has translated into increased protection against COVID-19. In addition, an NIH led study showed that boosting with a COVID-19 vaccine different than the one used for the primary vaccine series ("mix-and-match" or heterologous) was safe and prompted a robust immune response. Data from this study were evaluated by FDA in their decision-making to authorize the use of a mix-and-match approach to boosters for FDA-authorized or approved COVID-19 vaccines. NIH has

expanded the mix-and-match study to include evaluation of the Novavax COVID-19 vaccine as a heterologous booster vaccine, as well as to determine if the Moderna bivalent booster vaccine can elicit (and boost) mucosal antibody responses. Bivalent vaccines target two SARS-CoV-2 variants, in this case a component of the original SARS-CoV-2 strain and a component of the omicron strain.

Responding to Emerging Variants of SARS-CoV-2

To ensure patients receive effective vaccines and therapeutics, tracking the evolution of the SARS-CoV-2 virus and its impact on treatments is a critical need. Managed by the Foundation for the NIH, NIH was joined by its sibling agencies in the Department of Health and Human Services (HHS), including Biomedical Advanced Research and Development Authority (BARDA), Centers for Disease Control and Prevention (CDC), and FDA, as well as other government agencies to establish the public-private partnership Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV). At NIH, ACTIV is led by NIAID, the National Centers for Advancing Translational Sciences (NCATS), the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the Office of the Director (OD). ACTIV's Tracking Resistance and Coronavirus Evolution (TRACE) Working Group is tackling the challenge of tracking emerging SARS-CoV-2 variants. TRACE is following a multi-step approach to variant monitoring and data sharing which includes monitoring global emergence and circulation of SARS-CoV-2 mutations, charaterizing prioritized mutants, and rapidly sharing data with ACTIV and the scientific community.

The emergence of SARS-CoV-2 variants—some of which demonstrate increased transmissibility and an ability to partially evade the immune response from previous infection and/or vaccination—makes the authorized COVID-19 bivalent vaccines critical to help provide better protection. Relying on collaborative research to rapidly assess the effectiveness of vaccines, monoclonal antibodies, and antiviral drugs against SARS-CoV-2 variants, NIH continues to investigate ways to enhance protection afforded by COVID-19 vaccines and to understand the impact of SARS-CoV-2 variants on infection- and vaccine-induced immunity. NIH participates in the HHS-established SARS-CoV-2 Interagency Group (SIG) along with the CDC, FDA, BARDA, Department of Defense (DOD), and U.S. Department of Agriculture. The SIG tracks variants in real time to address the potential impact of emerging variants on critical SARS-CoV-2 countermeasures. NIH formed the SARS-CoV-2 Assessment of Viral Evolution (SAVE)

consortium in January 2021 as a critical data-generating component for the SIG and to facilitate rapid data-sharing with global partners and the scientific community. The SAVE program provides a comprehensive real-time risk assessment of emerging mutations in SARS-CoV-2 strains that could impact transmissibility, virulence, and infection- or vaccine-induced immunity. NIH remains on the cutting edge of science to end the pandemic. NIAID is currently supporting the development of next-generation COVID-19 vaccines that could provide broader protection against SARS-CoV-2 infection and disease caused by emerging SARS-CoV-2 variants.

Developing Diagnostics to Detect COVID-19

At the outset of the COVID-19 pandemic, there was an immediate need for diagnostic tests for SARS-CoV-2. Confronted with this challenge, NIH decided to take a novel large-scale collaborative approach to technology development. In April 2020, NIH launched the Rapid Acceleration of Diagnostics (RADx®) initiative. This was a call for scientists and engineers across the nation to bring innovative ideas to speed the development, validation, commercialization, and implementation of COVID-19 testing. At the forefront of this effort is the RADx® Tech program, which developed and deployed innovative COVID-19 testing technologies at an unprecedented speed and scale. RADx® Tech brought together over 900 experts from government, academic, and private industry to partner and produce over five billion tests and test products. Led by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), they leveraged and expanded its well-established Point-of-Care Technologies Research Network (POCTRN) to design and manage the RADx® Tech Program. In addition, RADx® established the Independent Test Assessment Program (ITAP) to accelerate regulatory review and availability of high-quality, accurate, and reliable at-home COVID-19 tests to the public. RADx® researchers have obtained 49 emergency use authorizations (EUAs) from the FDA, including seven at-home tests supported by ITAP and one point-of-care multiplex test for COVID-19 and influenza that is supported by ITAP. To date, RADx® and ITAP have produced around 5.8 billion tests and test products for COVID-19. ITAP will be utilized for other infectious diseases.

RADx® Tech is focusing on developing the next generation of COVID-19 tests with a major focus on accessibility. Recently, RADx® Tech solicitated applications for an initiative to improve accessibility of COVID-19 tests for people who are blind or have low vision, have motor skills challenges, developmental challenges, and other populations who may have difficulty using rapid tests that are currently authorized. The RADx® framework facilitated significant

productivity from the entrepreneurial-minded bioengineering community that NIBIB supports. Based on this success, NIBIB is partnering with other NIH Institutes, Centers, and offices to apply the RADx® funding model to accelerate solutions to other biomedical problems.

Identifying Therapeutics to Treat COVID-19

Safe and effective therapeutics were urgently needed at the onset of the pandemic to treat patients with COVID-19. In record time, NIH worked quickly to evaluate promising therapeutics for COVID-19 in rigorous, randomized, controlled clinical trials.

In February 2020, before many Americans had realized the magnitude of the pandemic, NIH launched a multicenter, randomized, placebo-controlled clinical trial—the Adaptive COVID-19 Treatment Trial (ACTT)—to evaluate the safety and efficacy of multiple investigational therapeutics for COVID-19. Data from ACTT were critical for FDA approval of the antiviral drug remdesivir and the anti-inflammatory drug baricitinib for treatment of COVID-19.

In April 2020, NIH established the public-private partnership ACTIV to harness the collective scientific power of both public and private sectors and develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines. ACTIV is focused on late-stage clinical trials investigating candidate drugs for outpatient and inpatient settings. ACTIV rigorously assessed data on more than 800 therapeutic agents and prioritized 33 of the most promising agents to be tested in randomized, placebo-controlled clinical trials. By developing and implementing multiple master protocols, which allow coordinated, efficient, and adaptive evaluation of potential therapeutic agents across multiple study sites, ACTIV has been able to nimbly test drug and biological candidates as they became available and to swiftly weed out those that do not demonstrate effectiveness. This work was aided by leveraging the existing Clinical and Translational Science (CTSA) Program clinical trial network led by NCATS. The CTSA Program showed the power of a nationwide clinical translational research network that could quickly develop and implement large, multisite trials testing potential treatments for COVID-19.

NIH also established the COVID-19 Treatment Guidelines Panel to provide recommendations to health care providers regarding specific COVID-19 treatments based on the best available scientific evidence. Each Treatment Guidelines section consists of recommendations developed by a working group of Panel members with expertise in the area addressed in the specific section. Each working group is responsible for identifying relevant information and

published scientific literature, and for conducting a systematic review of that information and literature. The Panel meets regularly to evaluate possible treatment options for COVID-19 and update the Treatment Guidelines as new clinical evidence emerges.

COVID-19 Going Forward

NIH continues to support research on COVID-19 vaccines in important at-risk populations, such as children and individuals who are pregnant or lactating or who are immunocompromised. NIH is engaged in efforts to understand the rare, but extremely serious, multisystem inflammatory syndrome in children (MIS-C) that has been associated with SARS-CoV-2 infection in children and adolescents. NIAID is supporting multiple studies to evaluate acute and long-term clinical and immunological aspects of MIS-C and SARS-CoV-2 infection in children. In addition, there is a trans-NIH effort to coordinate MIS-C research, the Collaboration to Assess Risk and Identify loNG-term outcomes for Children with COVID (CARING for Children with COVID). This effort supports data sharing across studies funded by multiple NIH Institutes to determine the spectrum of illness and predict long-term consequences of infection in children.

While most people recover quickly and fully from infection with SARS-CoV-2, some experience ongoing or new symptoms or other health effects after the acute infection has resolved; this syndrome is referred to as post-acute sequelae of SARS-CoV-2 infection (PASC) or Long COVID. In 2021, NIH launched the Researching COVID to Enhance Recovery (RECOVER) Initiative, a trans-NIH effort, co-led by NHLBI, the National Institute of Neurological Disorders and Stroke (NINDS), and NIAID, that includes targeted funding for research in this critical area. The wide scope of RECOVER is needed due to the complexity of Long COVID, as it leaves no tissue in the body untouched. At the heart of RECOVER is a longitudinal cohort study of children and adults, including pregnant individuals, at various stages of recovery from SARS-CoV-2 infection. This initiative is focused on ensuring a diverse patient population, with a particular focus on representing the communities hardest hit by COVID-19 in the clinical trials including rural communities. RECOVER is set to be the largest, most diverse, and deeply characterized cohort of Long COVID patients in the world. Clinical trials for all the cohorts are expected to launch in 2023. RECOVER has also focused on community and patient engagement since its inception. Patients have been involved at every step of the process, including the study designs and protocols to be used. RECOVER has the potential to enhance our basic knowledge of how humans recover from viral infections in general and is likely to improve our understanding of other

chronic post-viral syndromes and autoimmune diseases. This knowledge could help inform future pandemic preparedness.

In addition to the effects of Long COVID, there has been a significant impact on mental health during the COVID-19 pandemic. Research supported by the National Institute for Mental Health (NIMH) and others has confirmed much of what we knew based on prior research on disasters and epidemics. Through the course of the pandemic, the rates at which individuals report symptoms of depression, anxiety, substance use, and suicidal thoughts have all gone up. The demand for mental health services has also increased, especially amongst children. And the effects on our youth, though still not fully quantified, are substantial. These impacts have not been felt equally across American communities, with Black, Latinx, and other underserved communities as well as care practitioners and others on the front lines bearing the brunt of both the physical and mental health impacts of COVID-19.

Pandemic Preparedness Going Forward

Strategies for next-generation COVID-19 vaccines include targeting viral antigens that are highly conserved among SARS-CoV-2 strains, vaccinating with a broad array of viral antigens, and utilizing alternative routes of inoculation. In November 2022, NIAID held a workshop to explore the state of the science of SARS-CoV-2 mucosal immunity and the potential for the development of vaccines that induce mucosal immunity against SARS-CoV-2. Importantly, mucosal vaccine approaches target the site of SARS-CoV-2 infection and could potentially do a better job of preventing transmission of SARS-CoV-2. Although significant scientific gaps and challenges exist for mucosal vaccine development, multiple intranasal approaches are being pursued. Recent studies conducted by NIH scientists on two different nasal SARS-CoV-2 vaccine candidates showed encouraging results in animal models, suggesting intranasal approaches merit further study. NIH also is conducting research on pan-coronavirus vaccines designed to provide broad protective immunity against emerging SARS-CoV-2 variants as well as other coronaviruses with pandemic potential. Since 2021, NIAID has announced awards to seven academic institutions to conduct research to develop pan-coronavirus vaccines. One NIAID-supported vaccine candidate, which uses a nanoparticle-based approach, has been shown to induce broad neutralization of earlier SARS-CoV-2 variants and to protect animal models from multiple different SARS-related viruses.

The Administration's National Biodefense Strategy and Implementation Plan on

Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security establishes a bold series of targets for developing countermeasures against pandemic threats. NIH is playing a critical role in working towards those outcomes, including the ability to surge tens of thousands of diagnostics within 7 days, develop vaccines with 100 days, repurpose therapeutics within 90 days, and develop new therapeutics within 180 days of a future pandemic threat.

To achieve these goals, it is critical that we prepare for a range of viral threats that could cause future public health emergencies. There are 26 families of viruses that infect humans, many of which exhibit pandemic potential and for which we are far less prepared than coronaviruses and influenza. To support these goals, NIH's NIAID released a pandemic preparedness plan in 2021 to focus preparedness on two fronts. These efforts are designed to shorten timelines between pathogen emergence and authorization/approval of candidate products, such as vaccines and therapeutics. The first is to focus on prototype pathogens—viruses within viral families with the potential to cause significant human disease. This will be used as a framework for rapid research and product development for other viruses within that virus family should an outbreak occur. This was demonstrated by NIAID's earlier work on SARS-CoV-1 (the virus that caused the SARS outbreak in 2002) and MERS-CoV (the virus that caused the MERS outbreak, largely in the Middle East) that informed the rapid vaccine development for SARS-CoV-2. The plan's second focus is on priority pathogens—viruses already known to be capable of causing significant human illness (e.g., Zika virus) or death (e.g., Lassa virus).

In addition, NIH has already prioritized and accelerated the development of oral antivirals against potential pandemic pathogens by collaborating with BARDA to launch the Antiviral Program for Pandemics (APP). Within NIH, this effort is led by NIAID and NCATS. APP will accelerate the development of direct-acting antivirals targeting priority families of pandemic potential from discovery to early development. APP will focus on antivirals that directly act against viral targets, specifically for RNA viruses of pandemic potential such as *Coronaviridae* (including SARS-CoV-2), *Bunyavirales*, *Filoviridae*, *Flaviviridae*, *Paramyxoviridae*, *Picornaviridae,* and *Togaviridae.* A particular focus of APP is the discovery and development of drug candidates with suitable safety profiles for broad use in the outpatient setting, such as oral or intranasal administration at home. As part of APP, NIAID established nine multidisciplinary Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern with the goal of creating platforms that will target RNA viruses with pandemic potential, helping to better prepare

the nation for future viral threats. NIAID's pathogen approach to preparedness research was key in the development of a key countermeasure used against the mpox virus JYNNEOS™ (Imvamune or Imvanex). Mpox is part of the *Orthopoxvirus* genus, which includes the variola virus that causes smallpox. In the case of the mpox outbreak, basic research and countermeasures for a prototype pathogen within a given family of viruses were used to help treat and prevent a disease caused by closely related pathogens within that family.

In 2020, NIAID announced grants to establish the Centers for Research in Emerging Infectious Diseases (CREID) Network. The global, multidisciplinary network is focusing on emerging and re-emerging infectious diseases in high-risk regions. Research projects include surveillance studies to identify the animal sources or vectors of viral pathogens, and to determine what genetic or other changes make these pathogens capable of infecting humans. The breadth of research projects being carried out in the CREID Network will allow for study of disease spillover in multiple phases of the process, where pathogens first emerge from an animal host, where and when human-to-human transmission occurs, and how transmission is facilitated in urban areas. The work of the CREID Network has already shown to be critical with another emerging pathogen in 2022, mpox virus. CREID Network investigators are helping to strengthen mpox diagnostic capacity globally. Additionally, CREID Network scientists are developing a multiplex serological assay that will facilitate future mpox seroprevalence and surveillance studies of humans and animals in endemic regions. The CREID Network will enable early warnings of emerging diseases wherever they occur.

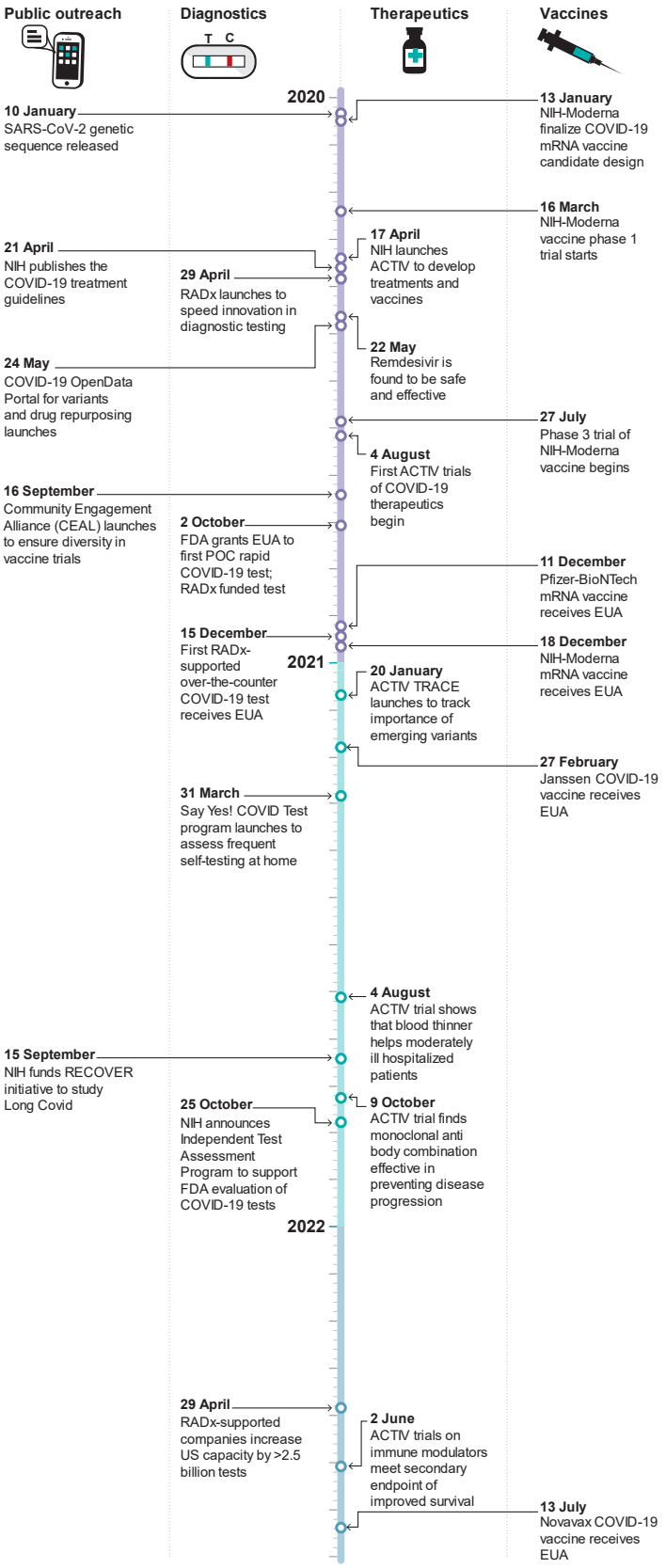
There are many lessons the global biomedical community, including NIH, have learned during past pandemics and the recent COVID-19 crisis. It is imperative that we take what has worked and apply it to other areas of research. One area that the COVID-19 response demonstrated weaknesses was that U.S. clinical trials should be better coordinated. We now have a good inventory of large-scale, well run, clinical trial networks to leverage for future health emergencies and public health needs. Through our ACTIV initiative, we found that having a consistent and connected infrastructure for clinical trials provides the foundation needed to respond quickly to any emerging disease. ACTIV benefited from the CTSA Program existing clinical trial network. In addition, NCATS developed the National COVID Cohort Collaborative (N3C), which was a secure data platform of harmonized, de-identified electronic health record data that was used to rapidly understand COVID-19. The importance of building partnerships and collaborations, using master protocols and harmonized data to ensure consistency, and a well-established clinical trial network

are strategies that NIH continues to expand to all areas of research to be better positioned to respond to the next pandemic.

We are already making significant progress on implementing this transformative agenda under the National Biodefense Strategy, which is so crucial to keep Americans safe from future biological threats from any source.

Conclusion

The more we know, the better positioned we will be to respond to the next pandemic. Sustained investment in NIH research, including basic biomedical science, has allowed the United States to respond to multiple public health emergencies. A robust understanding of the biology of infectious agents as well as a thorough understanding of immunology left the field well poised to move quickly. Additionally, the investments in enhancing infrastructure for clinical trials, developing master protocols, and establishing public-private partnerships have, and will continue to be, critical components of pandemic responsiveness. The ongoing work to begin to elucidate what the next viral threat may be will allow the biomedical community to quickly respond to the next emergent virus, in the same way that was done with COVID-19.



ACTIV, Accelerating COVID-19 Therapeutic Interventions and Vaccines; EUA, emergency use authorization; FDA, US Food and Drug Administration; NIH, National Institutes of Health; POC, point of care; RADx, Rapid Acceleration of Diagnostics; RECOVER, Researching COVID to Enhance Recovery; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TRACE, Tracking Resistance and Coronavirus Evolution.