DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases in Research to Address the COVID-19 Pandemic

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Madam Chair, Ranking Member Burr, and Members of the Committee:

Thank you for the opportunity to discuss the role of the National Institute of Allergy and Infectious Diseases (NIAID) in the research response to coronavirus disease 2019 (COVID-19) and its etiologic agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within the Department of Health and Human Services (HHS) and the National Institutes of Health (NIH), NIAID is responsible for conducting and supporting basic and clinical research on emerging and re-emerging infectious diseases, including COVID-19. As the Director of NIAID and the Chief Medical Advisor to the President, I am pleased to discuss NIAID's research addressing this pandemic.

COVID-19 is a once-in-a-lifetime global infectious disease pandemic requiring an unprecedented public-private research effort. NIAID plays a central and important role in the public health response to COVID-19. NIAID has capitalized on decades of investment in fundamental basic research, including groundbreaking structure-based vaccine design at the NIAID Vaccine Research Center (VRC); engaged domestic and international research infrastructure; and leveraged highly productive partnerships with industry and longstanding relationships with community partners. NIAID utilized its existing domestic and international clinical trials infrastructure, originally established to conduct research on HIV and influenza, and worked with partners in the public and private sectors to establish the COVID-19 Prevention Network (CoVPN). The CoVPN has supported multiple COVID-19 vaccine candidates to progress in record time from concept to authorization for emergency use by the U.S. Food and Drug Administration (FDA). NIAID also has built on its longstanding relationships with community partners to successfully conduct these crucial clinical trials. NIAID initiated clinical trials with creative and adaptive designs, allowing the evaluation of multiple new and existing therapeutics for use against COVID-19. Several of these trials provided evidence of safety and efficacy of COVID-19 therapeutics and helped support authorization by the FDA.

These successes have helped slow the progression of the pandemic in the United States. Currently, we are vaccinating approximately 2.5 million people per day, and we must continue to vaccinate as many people as we can as quickly as possible. FDA-authorized COVID-19 vaccines are safe and highly effective. The high levels of vaccine efficacy observed in the carefully controlled conditions of a clinical trial setting have been subsequently confirmed by their effectiveness in studies of vaccines administered to broad segments of the public. Vaccination and

adherence to public health measures are the fundamental tools that will help us head off another COVID-19 surge.

While we are cautiously optimistic about the future, we know that many challenges remain. One of the most concerning developments of the ongoing pandemic is the spread of genetic variants of SARS-CoV-2, some of which appear to be more transmissible than the original virus, more virulent, and/or less responsive to certain therapeutic agents and vaccine formulations. So far, scientific evidence suggests that the COVID-19 vaccines distributed in the United States under FDA Emergency Use Authorizations (EUA) continue to be effective against these variants, but we must remain vigilant. NIAID is rapidly conducting research to better understand these emerging variants of SARS-CoV-2, how they interact with the immune system, and their implications for COVID-19 therapeutic and vaccine formulations.

We also know that our fellow Americans in underserved and minority communities have been disproportionally affected by this pandemic. NIAID is committed to continuing to work directly with these communities, as well as partnering with other agencies in the federal government, and with industry and academia, to ensure that individuals in underserved and vulnerable communities are not left behind as we move forward towards defeating the COVID-19 pandemic. NIAID also recognizes that while many individuals with SARS-CoV-2 infection fully recover after a relatively short time period, some individuals suffer longer-term effects after the initial phase of illness and after the virus is cleared from the body. NIAID is supporting collaborative efforts to study outcomes in patients across all ages, genders, and co-morbid conditions, who have experienced a broad range of severity of original disease, to identify and characterize these post-acute sequelae of SARS-CoV-2 infection (PASC) and develop effective strategies to address them.

Developing Vaccines and Therapies to Prevent COVID-19

Sustained research investments by NIAID in the years prior to the emergence of SARS-CoV-2 enabled the unprecedented pace of COVID-19 vaccine candidate development. Two activities predate successful COVID-19 vaccines: the development of versatile vaccine platforms and the adaptation of structural biology tools to design agents (immunogens) that powerfully stimulate the immune system. Long before the pandemic, NIAID VRC scientists and their collaborators made the critical scientific discovery of how to stabilize in a highly immunogenic form viral proteins that are important for infection, including the spike protein of the Middle East

respiratory syndrome coronavirus (MERS-CoV), using a double mutation known as S2P. This key finding facilitated the design of vaccine candidates that generate robust immune responses against coronaviruses and other viruses of public health importance such as respiratory syncytial virus. As soon as the sequence of SARS-CoV-2 was made available in January 2020, 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 for coronaviruses has led to the development of safe and effective COVID-19 vaccine candidates across a range of vaccine platforms.

Five candidate COVID-19 vaccines have been assessed in large-scale Phase 3 clinical trials in the United States thus far, and three have received EUAs from the FDA. Clinical trials to test COVID-19 vaccine candidates in pediatric populations are ongoing. On December 11, 2020, based on data from a Pfizer-supported Phase 3 clinical trial, an investigational vaccine developed by Pfizer and BioNTech became the first to receive an EUA from the FDA for the prevention of COVID-19 in individuals 16 years of age and older. NIAID has helped to advance four additional COVID-19 vaccine candidates through support for research on the foundational biology underlying the vaccine concepts, as well as for clinical testing through the CoVPN. Two of these vaccine candidates, those from Moderna, Inc. and Johnson & Johnson/Janssen, have received EUAs.

Utilizing the CoVPN, NIAID is participating in the implementation of harmonized protocols to test investigational vaccines and preventive interventions against SARS-CoV-2. These protocols were developed in collaboration with the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership, vaccine manufacturers, and the Biomedical Advanced Research and Development Authority (BARDA). NIAID also supports the underlying critical infrastructure for these clinical trials, such as a common Data and Safety Monitoring Board (DSMB), an independent group that periodically reviews data from the ongoing trials to ensure the safety of study volunteers and to determine whether efficacy has been achieved. The CoVPN has enrolled thousands of volunteers across the United States and internationally in clinical trials testing multiple investigational vaccines and monoclonal antibodies intended to protect people from COVID-19. The CoVPN also has developed an extensive community engagement framework to reach out to the underserved and minority communities disproportionally affected by COVID-19; to better understand their interest in, and concerns about, research participation; and to partner with them to ensure that their vital input is reflected in the conduct of these clinical studies.

To further address the critical challenges of participation in clinical trials as well as vaccine acceptance and vaccine hesitancy, NIH established the Community Engagement Alliance Against COVID-19 Disparities (CEAL) initiative, led by the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities. CEAL brings together trusted community leaders to serve as champions who share information about the importance of participating in COVID-19 research and communicate data on the safety and efficacy of authorized COVID-19 vaccines.

mRNA-1273 (Moderna)

As part of a longstanding collaboration, the NIAID VRC worked with the biotechnology company Moderna to develop a vaccine candidate designated mRNA-1273, which uses a messenger RNA (mRNA) vaccine platform to express the stabilized SARS-CoV-2 spike protein. Early clinical trials demonstrated that mRNA-1273 was generally well tolerated and induced robust immune responses in healthy adults. NIAID and BARDA then began working with Moderna on a Phase 3 clinical trial through the CoVPN that showed that mRNA-1273 was 94.1 percent efficacious in preventing symptomatic COVID-19. On December 18, 2020, after a thorough review of comprehensive data on mRNA-1273, the FDA issued an EUA for the mRNA-1273 vaccine for prevention of COVID-19 in individuals 18 years of age and older. In subsequent observational studies under "real-world" conditions in broader segments of the population, mRNA-based vaccines continue to display a high level of effectiveness. In an article published in *Morbidity and Mortality Weekly Report (MMWR),* Centers for Disease Control and Prevention (CDC) researchers and their collaborators showed that among health care personnel, first responders, and other essential workers, the mRNA-1273 and the Pfizer-BioNTech mRNA vaccine were 90 percent effective against SARS-CoV-2 infections 14 or more days after receiving a second dose. In another *MMWR* article, these vaccines reduced the risk of COVID-19 hospitalization by 94 percent among people 65 years of age and older. Recently, NIAID scientists and their collaborators demonstrated that anti-SARS-CoV-2 antibodies persist for at least six months after the second dose of mRNA-1273.

Ad26.COV2.S (Johnson & Johnson/Janssen)

Decades of NIAID support for basic, preclinical, and clinical research on adenovirus (Ad)-based HIV vaccines underpin the development by Johnson & Johnson/Janssen of a coronavirus

vaccine candidate based on the Ad26-vector, known as Ad26.COV2.S or JNJ-78436735. NIAID is supporting a Phase 3 clinical trial of Ad26.COV2.S through the CoVPN and has provided immunological testing of the candidate using NIAID-funded core laboratory infrastructure. As reported in the *New England Journal of Medicine*, the one-dose vaccine candidate was 66 percent effective overall at preventing moderate to severe/critical COVID-19 occurring at least 28 days after vaccination and 85 percent effective overall in preventing severe/critical COVID-19 in the Phase 3 trial across several geographical regions, including areas where emerging viral variants predominate. In the United States, the efficacy against moderate to severe/critical disease 28 days after vaccination with Ad26.COV2.S was 72 percent. On February 27, 2021, the FDA issued an EUA for Ad26.COV2.S for prevention of COVID-19 in individuals 18 years of age and older. On April 13, 2021, out of an abundance of caution, the FDA and CDC released a joint statement recommending a pause in the use of Ad26.COV2.S in order to review extremely rare case reports of blood clots after vaccine administration. Medical and scientific teams at the FDA and CDC found that available data suggest such blood clots are very rare events. Following their thorough safety review – and in accordance with recommendations from the CDC's Advisory Committee on Immunization Practices – the FDA and CDC lifted the recommended pause on the use of Ad26.COV2.S on April 23, 2021.

Other COVID-19 Vaccine Candidates

NIAID, through the CoVPN, is supporting Phase 3 clinical trials of COVID-19 vaccine candidates from AstraZeneca (AZD1222) and Novavax (NVX-CoV2373). AstraZeneca's AZD1222 COVID-19 vaccine candidate uses a chimpanzee adenovirus-vectored vaccine approach developed by researchers at the University of Oxford in collaboration with scientists at NIAID's Rocky Mountain Laboratories. On March 25, 2021, AstraZeneca announced an updated interim analysis of AZD1222 reporting that the vaccine candidate was 76 percent effective at preventing symptomatic COVID-19, including 85 percent effective in participants aged 65 years and over. Importantly, the efficacy of AZD1222 against severe COVID-19 disease was reported to be 100 percent.

Clinical Trials of COVID-19 Vaccine Candidates in Special Populations

To effectively end the COVID-19 pandemic, it will be important to vaccinate as many people as possible, including those in special populations, such as pregnant and lactating women,

children, and people with immune deficiencies. Tens of thousands of pregnant and lactating women already have received the COVID-19 vaccines under FDA EUAs, and available data indicate that these vaccines are safe and effective in these populations. In addition, protective antibodies against SARS-CoV-2 have been detected in babies born to pregnant women who received mRNA COVID-19 vaccines. NIAID-supported investigators plan to continue to monitor the safety and further study the immune responses to these vaccine candidates in pregnant and lactating women. Efforts to evaluate COVID-19 vaccines in pediatric populations are ongoing. On March 16, 2021, Moderna, in collaboration with NIAID and BARDA, announced the launch of KidCOVE, a Phase 2/3 study to evaluate the safety and efficacy of mRNA-1273 in children ages 6 months to less than 12 years. This study is in addition to Moderna's ongoing TeenCOVE study of mRNA-1273 in adolescents between the ages of 12 and 17. Other vaccine developers also have begun, or are planning to begin, trials to test their vaccine candidates in children, adolescents, and other special populations. On April 23, 2021, NIAID launched an observational study at the NIH Clinical Center assessing how people with immune system deficiencies or dysregulations respond to COVID-19 vaccination. NIAID investigators also will gather information about COVID-19 illness in these individuals. This study will inform decision-making about COVID-19 vaccination in people with immune deficiencies and dysregulation conditions.

Monoclonal Antibodies to Prevent COVID-19

NIAID scientists, collaborating with Regeneron Pharmaceuticals and Eli Lilly and Company, also initiated two Phase 3 clinical trials to evaluate whether their investigational monoclonal antibodies, REGEN-COV and bamlanivimab alone and in combination with etesevimab respectively, can prevent infection or symptomatic disease in people at high risk of exposure due to their living or working conditions. Each company recently reported promising initial results. These studies have completed enrollment and further analysis of the data from the trials is ongoing. Due to the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab – when administered alone – the FDA revoked the EUA for bamlanivimab alone for the treatment of mild-to-moderate COVID-19 on April 16, 2021. In light of these concerns of variant resistance, the use of bamlanivimab alone is no longer being pursued for the prevention of COVID-19. The FDA now includes information on the susceptibility of SARS-CoV-2 variants in its fact sheets for health care providers for each of the monoclonal antibody therapies currently available through an EUA (REGEN-COV and bamlanivimab in combination with etesevimab). In

separate studies, NIAID-supported scientists and collaborators are evaluating the potential impact of emerging SARS-CoV-2 variants on the efficacy of monoclonal antibodies.

Identifying Therapeutics to Treat COVID-19

Safe and effective therapeutics are urgently needed to treat patients with COVID-19. NIAID 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. ACTT-1 examined the antiviral drug remdesivir for treatment of severe COVID-19 in hospitalized adults. Based on positive data from ACTT-1, the FDA approved the use of remdesivir for treatment in adults and children 12 years of age and older and weighing at least 40 kg hospitalized due to COVID-19. ACTT-2 evaluated the anti-inflammatory drug baricitinib in combination with remdesivir, and based on favorable data from ACTT-2, the FDA issued an EUA for the use of baricitinib in combination with remdesivir for treatment of adults and children older than 2 years hospitalized with COVID-19 and requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. ACTT-3 is currently evaluating treatment of hospitalized COVID-19 patients with remdesivir plus interferon beta-1a, which is used to treat individuals with multiple sclerosis. ACTT-4, a study assessing baricitinib plus remdesivir versus the glucocorticoid dexamethasone plus remdesivir in adults hospitalized with COVID-19, has closed to enrollment because the study met pre-defined futility criteria.

NIAID, in collaboration with other NIH Institutes, also launched two clinical trials as part of the ACTIV partnership, which utilizes master protocols allowing the addition of other investigational therapeutics as the trials continue. The two studies, ACTIV-2 and ACTIV-3, initially evaluated the use of the monoclonal antibody bamlanivimab to treat COVID-19 in outpatient and inpatient settings, respectively. ACTIV-2, which is focused on outpatients, has since been expanded to evaluate a combination monoclonal antibody therapy, BRII-196 and BRII-198, as well as four investigational therapeutics: SAB-185, a fully-human polyclonal antibody produced in cattle; SNG001, an inhalable beta interferon; AZD7442, an investigational long-acting antibody combination; and camostat mesilate, an orally administered drug that may block SARS-CoV-2 from entering cells. ACTIV-3 currently is evaluating the AZD7442 monoclonal antibody combination in hospitalized patients. On April 22, 2021, NIAID and NHLBI launched the ACTIV-3 Critical Care study to test Zyesami and remdesivir (alone and in combination), for their safety and efficacy in hospitalized COVID-19 patients who are experiencing acute respiratory

distress syndrome, a life-threatening condition. Zyesami is a synthetic version of vasoactive intestinal peptide, which is made naturally in the human body and appears to have lung-protective antiviral and anti-inflammatory effects.

On April 13, 2021, NIAID announced the launch of the COVID-19 anti-CD14 Treatment Trial (CaTT) to evaluate the use of a monoclonal antibody known as IC14 in adults hospitalized with COVID-19. IC14 works by binding to and blocking a human protein called CD14 that is associated with the development of severe inflammatory reactions in some COVID-19 patients. In addition, NIAID completed a Phase 3 trial called, "Inpatient Treatment with Anti-Coronavirus Immunoglobulin," or ITAC, to evaluate hyperimmune intravenous immunoglobulin (IVIG) for treatment of COVID-19 in hospitalized adults. The study demonstrated that IVIG plus remdesivir was not superior to remdesivir alone.

NIAID also launched the ACTIV-5/Big Effect Trial (BET), which is designed to streamline the identification of experimental COVID-19 therapeutics that demonstrate the most promise. BET, an adaptive Phase 2 clinical trial, compares different investigational therapies to a common control arm to identify treatments with relatively large effects as promising candidates for further study in large-scale trials. BET initially is evaluating two therapeutics: risankizumab, an immunomodulatory monoclonal antibody developed by Boehringer Ingelheim and AbbVie, which is FDA-approved for the treatment of severe plaque psoriasis; and lenzilumab, an investigational immunomodulatory monoclonal antibody developed by Humanigen.

The NIH also has established the COVID-19 Treatment Guidelines Panel to provide recommendations to health care providers regarding specific COVID-19 treatments based on the best available science. The Guidelines also address considerations for special populations, including pregnant women and children. Each Treatment Guidelines section is developed by a working group of Panel members with expertise in the area addressed in the specific section; these members conduct systematic, comprehensive reviews of relevant information and scientific literature. The Panel comprises representatives of NIH and five other federal agencies along with representatives of nine professional organizations, academic experts, and treating physicians including providers from high COVID-19 incidence areas, and community representatives. The Panel meets regularly to evaluate possible treatment options for COVID-19 and update the Treatment Guidelines as new clinical evidence emerges.

Responding to Emerging Variants of SARS-CoV-2

NIAID is fully engaged in efforts to mitigate the potential impact of emerging variants of SARS-CoV-2. NIH, including NIAID, participates in the HHS-established SARS-CoV-2 Interagency Group, along with CDC, FDA, BARDA, the Department of Defense (DOD), and the U.S. Department of Agriculture to address the potential impact of emerging variants on critical SARS-CoV-2 countermeasures. NIH, CDC, and DOD are assessing whether vaccine-induced immunity, or natural immunity from prior infection, can be effective in combating the variants. NIH, BARDA, and DOD also are determining the efficacy of certain authorized therapeutics against emerging variants in cell lines *in vitro* and in animal models.

NIAID is collaborating with vaccine manufacturers on key areas of research to investigate whether vaccines designed for the original strain of SARS-CoV-2 can maintain efficacy against emerging variants. NIAID also is conducting and supporting comprehensive studies to understand the ability of vaccine-induced antibodies to neutralize the variant viruses. NIAID researchers have analyzed the immune responses of individuals who recovered from COVID-19 prior to the emergence of variants and demonstrated that their T cells – a key component of the immune response to SARS-CoV-2 – also were capable of recognizing the three most widespread SARS-CoV-2 variants, B.1.1.7, B.1.351, and P1. These findings, published in *Open Forum Infectious Diseases*, shed new light on the role of T cells in the development of immunity to SARS-CoV-2 and suggest that these cells also may help protect against emerging variants of concern. On March 25, 2021, NIAID launched a Phase 1 clinical trial in healthy adults to assess the safety and immunogenicity of second-generation COVID-19 vaccine candidates developed by Gritstone Oncology, Inc. Gritstone's COVID-19 vaccine candidates utilize a strategy aimed at inducing both neutralizing antibodies and T cell responses to elicit a broad immune response. This approach could provide protection against emerging SARS-CoV-2 variants by targeting several viral antigens, all of which are highly conserved among viral strains.

NIAID also plans to test new vaccine formulations that may protect against certain variants that show early indications of reduced sensitivity to existing countermeasures. On March 31, 2021, NIAID launched a Phase 1 clinical trial of an investigational Moderna vaccine based on its FDA-authorized COVID-19 vaccine, designed specifically to target the B.1.351 SARS-CoV-2 variant first detected in South Africa. NIAID and Moderna are evaluating this vaccine candidate as a precautionary measure as we gain more data to confirm that current vaccines provide an adequate degree of protection against currently circulating SARS-CoV-2 variants.

NIAID, the National Human Genome Research Institute, and the National Library of Medicine are participating in the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance (SPHERES) initiative. SPHERES is a national genomics consortium led by CDC that helps to coordinate SARS-CoV-2 sequencing across the United States. NIAID is working with partners to identify, monitor, and calculate the frequency of current variations in the SARS-CoV-2 genome to help predict emerging variants. NIAID also facilitates the use of cutting-edge modeling and structural biology tools to understand how variants might affect interactions between the virus and the immune system or COVID-19 therapeutics. NIAID scientists are helping to inform our understanding of transmissibility of the variants by studying their stability in the environment of infected individuals and their ability to grow in human lung cells. These efforts add to a growing body of knowledge about SARS-CoV-2 variants and our ability to combat them.

Understanding the Immunology and Pathogenesis of COVID-19

NIH is supporting studies to understand the incidence of SARS-CoV-2 infection in specific populations, including children, as well as certain aspects of the clinical course of infection, including thromboses, strokes, heart attacks, and other sequelae of infection. NIAID is working with partners to delineate biological and immune pathways responsible for the varied manifestations of COVID-19. NIAID also will examine the quality and durability of the immune response to SARS-CoV-2; this information may be leveraged to develop novel SARS-CoV-2 therapeutics or vaccines and inform public health measures.

NIAID, along with FDA, is supporting a National Cancer Institute (NCI) effort to determine the sensitivity and specificity of certain SARS-CoV-2 serological tests, which can detect antibodies indicative of a prior exposure to SARS-CoV-2. NCI and NIAID also are working to establish a collaborative network to increase national capacity for high-quality serological testing with rapid return-of-results to subjects. These efforts include the use of serological testing to support clinical trials of convalescent serum and the establishment of registries for seroprotection studies. NIAID, NCI, the National Center for Advancing Translational Sciences, and the National Institute of Biomedical Imaging and Bioengineering are partnering on a study, called the Serological Sciences Network or SeroNet, to investigate whether adults in the United States without a confirmed history of SARS-CoV-2 infection have antibodies to the virus, thus indicating prior infection. The study is evaluating the durability of the immune response and aspects of the

immune response that contribute to protection against COVID-19.

NIAID scientists are participating in leadership of the COVID Human Genetic Effort, an international consortium of hospitals and genetic sequencing hubs that aim to discover genetic factors conferring resistance to SARS-CoV-2 infection or predisposing to severe COVID-19 disease. The consortium has identified a subgroup of patients with severe COVID-19 that have ineffective immune responses to SARS-CoV-2, some of whom have identifiable mutations in key immune pathways. NIAID also supports 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 hosted a virtual workshop on MIS-C with scientists and clinicians from academia, NIH, FDA, and industry, and a report of the workshop recommendations was published on November 2, 2020. NIAID also supports the Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM) to evaluate acute and long-term clinical and immunological effects of MIS-C and SARS-CoV-2 infection in children. In addition, NIAID is collaborating with Children's National Medical Center to follow 1,000 children with a history of SARS-CoV-2 infection, including those with MIS-C, to determine long-term effects of the illness. NIAID is participating in a trans-NIH effort to coordinate MIS-C research led by NHLBI and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. This centralized effort, the Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (CARING for Children with COVID), will permit data to be shared across studies to determine the spectrum of illness and predict long-term consequences of infection.

Monitoring the Long-term Effects of COVID-19

Many people who have had COVID-19 experience continued symptoms or other sequelae as they transition from the acute to post-acute phases of the disease, and we continue to learn more about the duration and manifestations of COVID-19 as we hear from these patients. In December 2020, NIAID hosted a Workshop on Post-Acute Sequelae of COVID-19 with clinicians, immunologists, virologists, and members of the patient community to present existing data, identify key knowledge gaps, and explore different perspectives on this heterogeneous condition. A report from this workshop highlighting the key scientific questions and knowledge gaps regarding PASC was recently published in the *Annals of Internal Medicine*. NIH has announced a trans-NIH effort to address PASC, including targeted funding for research in this critical area. The NIH PASC Initiative will complement ongoing NIAID studies to better understand the various

post-acute manifestations of COVID-19 in various populations.

NIAID intramural scientists initiated the Longitudinal Study of COVID-19 Sequelae and Immunity to better understand PASC and determine whether people who have recovered from acute SARS-CoV-2 infection develop an immune response to SARS-CoV-2 that provides protection against reinfection. NIAID-supported investigators also have established the Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC) to determine how immunological markers correspond to, or may even predict, the clinical severity of COVID-19. Since May 1, 2020, IMPACC researchers have collected detailed clinical data along with blood and respiratory samples from more than 1,200 hospitalized COVID-19 patients of diverse race and ethnicity at approximately 20 hospitals nationwide. The cohort will be followed during hospitalization and up to one year after discharge to assess their functional and immunologic recovery.

Conclusion

NIAID continues to expand efforts to elucidate the biology, pathogenesis, and clinical manifestations of SARS-CoV-2 infection, including emerging variants, and to employ this knowledge to develop safe and effective interventions to diagnose, treat, and prevent SARS-CoV-2 infection and COVID-19. NIAID is focused on developing safe and effective SARS-CoV-2 vaccines and therapeutics and sensitive, specific, rapid point-of-care molecular diagnostic and serological tests. NIAID also is conducting early-stage research on candidate vaccines that could protect against multiple strains of coronaviruses. All of these efforts will improve our response to the current pandemic and bolster our preparedness for the next, inevitable viral disease outbreak.