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Francis Collins, MD, Ph.D.
Director
National Institutes of Health
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Dear Dr. Collins:

On behalf of the American Thoracic Society (ATS), thank you for your leadership during the COVID-19 pandemic. Under your leadership and that of Dr. Anthony Fauci, the NIH has led our nation's research response to this public health emergency and provided essential scientific and public health guidance to the American public. The ATS appreciates the opportunity to comment on the NIH-Wide Strategic Plan for COVID-19 Research. As physician-scientists treating individuals with COVID-19 and researching SARS-CoV-2 and COVID-19, we believe that the proposed plan provides a strong framework for guiding the NIH's ongoing and emerging research priorities for this respiratory disease. We have the following comments:

Priority 5: Prevent and Redress Poor COVID-19 Outcomes in Health Disparity and Vulnerable Populations

The ATS urges the NIH to elevate priority five, focused on health disparities in COVID-19 outcomes, to priority one in the revised NIH-Wide COVID-19 Research Strategic Plan. This a critically important area of study, as we have seen the disproportionate and devastating impact that SARS-CoV2 and COVID-19 have had on communities of color, Native American, low-income, rural and underserved communities, and vulnerable populations such as the elderly and those with chronic health conditions. We urge the NIH to expand research efforts in this area to address the ongoing needs in these communities as the pandemic continues and evolves.

Priority 1: Improve Fundamental Knowledge of SARS-CoV-2 and COVID-19

The ATS recommends broadening the scope of the fundamental research agenda to include study of the following:

Aerosol Transmission

Since the publication of the first NIH-wide Strategic Plan for COVID-19 Research, there has been recognition of the role of aerosol transmission of SARS-CoV-2. The ATS strongly recommends prioritizing the study of aerosol transmission in the next iteration of the Plan through research into strategies that investigate this mode of transmission, including aerosol sampling methods. The NIH should support studies to determine the optimal methods for monitoring and mitigating this mode of transmission through energy-efficient ventilation interventions and design that improve air exchanges, the use of

natural air circulation, HEPA filtration, and easily deployable technology in high-risk settings such as hospitals and clinics, large buildings, public transportation, indoor stadiums/concert halls, restaurants, retail, and other settings.

Differences in innate and acquired immunity in COVID-19

The ATS believes that studying anti-viral immune responses can pave the way for understanding the varied clinical development of host-directed and other therapies, as well as vaccination. This area of study should include identifying predictive biomarkers of disease progression or prognosis through bioinformatic and multiparameter immunoassay approaches, to determine how differences in innate immune and acquired T cell responses control infection and/or lead to progression of illness, and, in some cases, to the occurrence of a "cytokine storm." Research to improve our understanding of innate immune susceptibilities and how to correct them is also needed, including studies of the impact of SARS COV-2 infection on T cell numbers and subsets such as cytotoxic T cells and Th17 cells. In addition, we recommend that NIH support studies to improve our understanding of the kinetics of viral load and of cytokine profiles during treatment, particularly in long-term sufferers with clinical correlates. Many of the scientific and therapeutic breakthroughs achieved with study of HIV-1 infection may provide pathways to understanding and treating COVID-19. Studies of the antibody response to SARS COV-2 infection and vaccination will also be important in understanding the disease and viral clearance, including the generation of neutralizing antibodies.

Significant knowledge gaps remain in our understanding of how host innate responses contribute to the prevalence and severity of clinical illness in response to SARS-CoV-2 infection. Research efforts should include expanding our understanding of factors driving pediatric resistance and/or resilience. For instance, current data support the concept that altered or delayed activation of interferon pathways may increase the risk of severe illness in adults. However, the age-dependence, ontogeny, and cell type-specificity involved in this and other innate protective responses are undefined. The ATS recommends that the NIH expands fundamental and translational studies in this area, as they may identify key risk factors and/or novel interventions for critical illness.

Viral Inoculum and Route of Entry

Early in the pandemic, it was assumed, based on experience with other viruses such as influenza, that droplet and fomite transmission was responsible. However, current evidence does not support this, other than the fact that the virus survives on surfaces. It survives in the air, and further research is needed to understand the relative contribution of each mode of transmission, including dose-response studies. Moreover, we recommend studying the role of initial viral inoculum and route of entry, including respiratory tract, eye, gastrointestinal tract, and other organs. Cough aerosol sampling that measures the kinetics of aerosol survival and viral load in aerosols should be included in assessments of aerosol transmission. In addition, studies of reducing inoculum, finding means of blocking entry, and post-exposure prophylaxis are needed.

Vasculopathy and thrombosis

While studying immune responses in COVID-19 is crucial, there is considerable evidence of COVID-19 vasculopathy. As a significant target of SARS COV-2 infection, the vascular endothelium throughout the body is affected and may result in multi-organ system dysfunction. It appears that in many individuals, COVID-19 manifestations are related to this intersection of immune responses and vasculopathy. The pathogenesis apparently includes endothelial cell injury, leukocyte recruitment and activation, complement activation, dysfunctional angiogenesis, and extensive thrombosis. Although prophylactic

anticoagulation provides an overall mortality benefit in some patients, others suffer extensive thrombotic events and vascular injury with organ system consequences despite such treatment. There is a need to further understand the vascular pathogenesis, its intersection with the immune system, and to prevent and treat this significant dimension of COVID-19.

Objective 1.4: Understand COVID-19 disease progression, recovery, and psychosocial and behavioral health consequences

The ATS recommends a strategic prioritization of COVID-19 phenotyping. We have learned that COVID-19 does not affect all individuals in the same ways. Large epidemiologic studies of well-characterized subjects will allow better disease phenotyping that would help guide the strategic use of different treatment options and the implementation of interventions to address the long-term complications of COVID-19. Research efforts should include collection of standardized clinical information, viral load, profiling of immune and vascular biomarkers, and other parameters.

Comorbidities/Risk factors

We have learned that comorbidities -such as obesity, diabetes, hypertension, and some respiratory diseases- can predispose many individuals to severe COVID-19 and higher risk of death. In addition, it is not clear if smoking, drug abuse, and co-infections such as HIV-1 and tuberculosis are related to poorer outcomes in COVID-19 patients. Research into the mechanisms underlying susceptibility to SARS-CoV2 infection and progression to COVID-19, the results of which can be used to facilitate targeted patient interventions, should be prioritized as areas of study.

COVID-19 and ARDS

Determining common and unique features of acute lung injury in SARS-CoV2 infection will create crucial opportunities to target specific therapies for COVID-19 and identify generalizable opportunities to advance the science and improve the outcomes of all patients with acute respiratory distress syndrome (ARDS). Additionally, there are opportunities to expand therapeutic trials beyond pharmacologic agents to focus on best practices and processes of care.

Long-term health consequences of SARS CoV-2 infection

As the COVID-19 pandemic continues, patients that have been infected with SARS CoV-2 are currently at various stages of their recovery from the illness, whether they experienced mild symptoms or moderate to severe disease. Longitudinal research studies of patients recovering from COVID-19 are needed to document long-term outcomes of the disease (including pulmonary, cardiovascular, neurological, gastrointestinal effects) and whether new or repurposed therapies may be effective in ameliorating chronic conditions associated with COVID-19, such as organ fibrosis or neuropathy. Further research must also be done to identify specific subsets of patients recovering from COVID-19 who have increased susceptibility for development of chronic pathologic conditions. Similarly, research is needed to determine high- value approaches to care delivery for patients with protracted symptoms and/or functional impairment after COVID-19.

Psychosocial and Behavioral Health Consequences

Research to Determine the Most Effective Public Health Interventions and Communication Methods

The COVID-19 pandemic revealed serious challenges in the national public health response. Public uptake and acceptance of public health messages such as mask-wearing and social distancing has been quite challenging. The ATS recommends priority studies to evaluate and determine the most effective public health interventions and public education and communication strategies to be used during pandemics. This should include a review and assessment of the different strategies used in various

countries, to establish an evidence base for development of a comprehensive and effective national pandemic preparedness plan. Expanded public health authority to implement strategies to protect the vulnerable should be considered as part of a comprehensive strategy. Such research should include:

- Assessing and streamlining track-and-trace mechanisms, the use of software applications, and other digital strategies
- Dissemination of critical information such as hot spots, levels of shutdown and triggers to implement each level etc.
- Social science research to understand individual and community beliefs and health perceptions, including underserved communities in rural areas, communities of color, immigrant and non-English speaking communities, and low-income areas.

Priority 2: Advance Detection and Diagnosis of COVID-19

The lack of a national SARS-CoV2 testing strategy remains a serious challenge, with shortages of rapid tests continuing to occur throughout the country. A comprehensive testing strategy to mass-produce and distribute rapid sensitive diagnostic tests across specific populations must be a top priority in the U.S.'s pandemic preparedness plan. The ATS recommends the creation of an additional objective under priority 2 to focus on development and implementation of testing strategies for different settings, including inpatient and outpatient clinics, and congregate and other community settings. A comprehensive detection and diagnosis research priority will include study of variables including:

- Type of test, combinations of tests, time to diagnosis, frequency of testing, availability of testing, coupling with screening questions, home testing, role of wastewater testing and limitations, and assessment of false test results and their impact.
- Aerosol sampling and detection
- Testing modeling, artificial intelligence approaches, machine learning, and studies using actual data
- Implementation of testing strategies and assessment of their efficacy in different settings
- Understanding of patients' beliefs about testing and public education about testing, including different kinds of tests and the most effective for specific populations
- Creation of a national or international biobank for diagnostic and biomarker testing

Objective 2.1: Support research to develop and validate new diagnostic technologies

At-home sampling measures reduce contact with healthcare workers and reduce potential transmission from a positive symptomatic patient. Saliva is the ideal sample but there are currently difficulties in utilizing saliva, pointing to the need for more research to identify additional at-home sampling methods. We recommend modifying objective 2.1 as follows:

Objective 2.1: Support research to develop and validate new diagnostic technologies, including those that facilitate at-home sampling

Priority 3: Advance the Treatment of COVID-19

The ATS recommends a broadening of the scope of the research priority on COVID-19 treatment to support:

- Utilization of phenotyping to guide personalized treatment for the different phases of illnesses from mild to severe. Phenotyping can also be utilized within clinical trials to ensure a balanced approach across different phenotypes to assess the effects of different interventions in specific populations

- Development of host-directed therapies, including interferon and for those with innate immune defect, high viral load, or other indications
- Studies of agents that may block viral entry
- Studies of efficacy and implementation of best supportive care processes, including optimization of oxygen supplementation and approaches to mechanical ventilation
- Identification of therapies that address vasculopathy and clotting
- Establishing when treatments should be initiated and their duration
- Use of optimal type, dose, indications for dose escalation, and duration of anticoagulation or other treatments
- Treatment for children and adolescents with multi-inflammatory syndrome in children (MIS-C) and COVID-19
- Data science research that can examine treatment outcomes based on pre-existing conditions
- Expanded research into the long-term respiratory complications and outcomes following COVID-19 recovery
- Research into optimal delivery of palliative care for patients with high-risk of death
- Research on best delivery of care in times of resource limitation.

Priority 4: Improve Prevention of SARS-CoV-2 Infection

The ATS recommends initiation or expansion of the following research areas under the prevention priority to include:

- Utilization of precision medicine based on biomarkers to prevent infection, particularly in vulnerable populations such as individuals with chronic conditions, the elderly, and minority populations
- Agents that block viral entry or replication, such as nasal sprays, and other potential treatments
- Understanding people's health beliefs and the factors that influence them
- High-priority research that identifies the most effective public health communication strategies and messages, and educational or other interventions to improve acceptance of and adherence to public health measures to prevent transmission such as mask-wearing
- Utilizing group testing and isolation strategies to prevent further transmission
- Utilizing predictive models, artificial intelligence, and big data to identify communities at risk and the best strategies to prevent transmission in these communities, including assessment and utilization of effective models from other countries
- Study of the most effective ventilation strategies in different settings and building types to prevent airborne transmission

Priority 5: Prevent and Redress Poor COVID-19 Outcomes in Health Disparity and Vulnerable Populations

Objective 5.1: Understand and address COVID-19 as it relates to health disparities and COVID-19–vulnerable populations in the United States

Health disparities and income disparities often correlate. Thus, there is a need for vulnerable populations to be educated by health care professionals and/or social workers and provided with the tools to safeguard themselves and others, such as masks. The ATS recommends that objective 5.1 be modified as follows:

Objective 5.1: Understand and address COVID-19 as it relates to health disparities and COVID-19–vulnerable populations in the United States, with a focus on education

Objective 5.4: Address Global Health Research Needs From COVID-19

The ATS recommends that research to develop comprehensive pandemic preparedness strategies be a top global health priority. Robust communication and collaboration between all countries and international bodies such as the World Health Organization (WHO), including participation in global initiatives such as the COVAX vaccine initiative, are essential to effectively combat a global pandemic. Never again should the U.S.'s critical work with the WHO be permitted to be withdrawn or reduced during a global health emergency. The ATS urges the Trump Administration, the incoming Biden-Harris Administration, and the NIH to ensure that U.S. collaboration and leadership with the WHO and other international agencies in global pandemic preparedness, including U.S. participation in initiatives to develop and distribute diagnostics, treatments, and vaccines, is enshrined in our national pandemic preparedness strategy.

Environmental Factors Contributing to Pandemics

The ATS recommends expanded study of factors that contributed to the COVID-19 pandemic, such as the interactions between the environment and animal and human health and climate change. Recent studies have found an association between long term (years) exposure to air pollution with an 11% increase in mortality from COVID-19 infection for every 1 microgram/cubic meter increase in air pollution. [i] NIH should support research efforts to better understand the links between air pollution and other environmental exposures and COVID-19 susceptibility and COVID outcomes. Further, additional research is needed to better understand, monitor, and predict the transmission of viruses between species and between animals and humans. We recommend that this important objective include a strong focus on newly emerging viruses around the world, with research to develop and identify mechanisms, including through utilization of data science, of how viruses jump from animals to humans.

Identify the Most Effective Ventilation Strategies

We recommend an expansion of global health research to determine the most effective ventilation strategies in different settings and building types to prevent airborne SARS-CoV-2 transmission. This research and prevention strategy is especially critical in low-resource and developing countries and in densely populated areas.

Crosscutting Strategies

1. Partnering to promote collaborative science

COVID-19 presents as a set of symptoms affecting multiple organ systems, a rather unique way for a respiratory viral illness. Although NIH supports some large-and intermediate-scale collaborative teams and networks to identify and combat infectious diseases, there are needs and opportunities to establish new groups with expertise that matches diverse COVID-19 symptoms. The ATS recommends that the NIH invest to develop new collaborations that cut across multiple disciplines -virology, immunology, structural biology, computational biology, data science, epidemiology, statistics– and different organ systems, in order to understand and combat the acute and chronic effects of COVID-19. International collaborative efforts would also improve the efficiency and productivity of these programs. **The ATS recommends adding a fourth component to this cross-cutting strategy as follows: "Develop novel cross-NIH Institute collaborations, bringing together researchers from key areas (e.g., immunology, lung biology, epidemiology, statistics), to address the unique pathophysiology of COVID-19."**

2. Supporting the research workforce and infrastructure
The NIH has been instrumental in leading rapid dissemination of research through efforts such as LitCOVID, and resources such as BEI Resources and public databases with sequencing and clinical repositories. However, the availability of research tools developed by NIH-funded extramural researchers is delayed as funds are not necessarily set aside for the rapid dissemination of these tools. Additional resources from NIH that would assist the scientific and clinical workforce include:

- Support for rapid dissemination of extramurally developed digital tools
- Laboratory tools such as animal-adapted viruses
- Hospital-relevant tools such as equipment to decontaminate PPE for re-use
- Interest databases for intramural and extramural researchers to facilitate collaborations
- Development of a data science tool that mines COVID literature cross-referencing with PubMed to generate novel hypotheses as a basis for prior-mentioned collaborations

The ATS recommends that the "Provide research resources" focus be modified as follows:
Provide research resources including the rapid availability of newly developed tools and viral isolates, clinical tools and strategies for crisis prevention, and researcher databases for collaboration.

Restore Funding Flexibility to Support Research Program Staff
On October 1, 2020, the flexibility policy for NIH grant recipients to continue charging salaries and benefits to active NIH awards when no work is being performed due to local pandemic restrictions was ended. This emergency policy allowed research programs and institutions to retain grant-funded individuals during the COVID-19 pandemic. We understand that the current policy states that NIH institutes and centers will review such funding requests on a case-by-case basis, however, this stipulation is not allaying uncertainty and concern. The ending of this funding support for researchers, as COVID is again surging and causing work shutdowns at academic institutions, may cause some NIH funded investigators and research programs to lay off essential support staff, causing interruptions and delays in important biomedical research. It may also force some researchers and institutions to attempt to keep some research activities operating at a time of great risk to patients and staff. **The ATS urges the NIH to extend the policy permitting NIH grantees to charge research program support staff salaries and benefits to active NIH grant awards through August 2021.**

The ATS appreciates the opportunity to comment. Please contact Nuala S. Moore, Director of Government Relations, with any questions at Nmoore@thoracic.org.

Sincerely,

Juan C. Celedón, MD, DrPH
President
American Thoracic Society

[i] *Science Advances* 04 Nov 2020:Vol. 6, no. 45, eabd4049. DOI: 10.1126/sciadv.abd4049.