

National Research Action Plan on Long COVID

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Preparation Notice

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Executive Summary

On April 5, 2022, President Biden issued the *Memorandum on Addressing the Long-Term Effects of COVID-19* outlining actions needed to support the American people in addressing the longer-term effects of COVID-19. The President charged the Secretary of Health and Human Services with coordinating a government-wide response to Long COVID. An element of that response was for the Department of Health and Human Services, in collaboration with federal partners, to develop two reports

- Services and Supports for Longer-Term Impacts of COVID-19 Report (Services Report)
- National Research Action Plan on Long COVID (the Plan).

The Services Report outlines federal services and mechanisms of support available to the American public in addressing the longer-term effects of COVID-19. The Plan provides the first U.S. government-wide national research agenda focused on advancing prevention, diagnosis, treatment, and provision of services and supports for individuals and families experiencing Long COVID.

The end of the COVID-19 public health emergency will not signal the end of the effects of the pandemic. These lingering effects may impact the health of the nation for years to come. Recovery from infection with SARS-CoV-2, the virus that causes COVID-19, can vary from person to person. Most individuals seem to recover quickly and completely. However, some report symptoms that persist or emerge weeks or even months after the initial phase of the infection has passed, even when the infection was asymptomatic. These sets of conditions are often referred to as “Long COVID.” This term was created and has been promulgated by patients and is used in this Plan. The Plan also recognizes the importance of two technical terms, Post-COVID-19 conditions, or PCC, broadly equivalent to Long COVID, and Post-acute Sequelae of SARS-CoV-2 infection, focused on the direct effects of the virus.

Research into the causes and consequences of Long COVID and associated conditions, the underlying biological mechanisms, the therapies that work, and services and supports needed for persons experiencing Long COVID are necessary to develop strategies to prevent, treat, and support those with Long COVID. The Plan was developed with four guiding principles: orienting research towards improving patient care and outcomes, health equity, accelerating and expanding existing research, and partner engagement. The Plan ensures an effective, comprehensive, and equitable research strategy to inform the national response to Long COVID’s impacts on individuals, families, communities, and all of society, inclusive of age, gender, race, ethnicity, geographic location, socioeconomic status, insurance coverage status, pregnancy status, and disability status. The actions in the plan will require federal investment. Action that can be taken with current funding are underway. Additional funding proposed in the President’s fiscal year 2023 budget and beyond will enable expansion the implementation of this Plan.

Partner Input

The Plan was developed with engagement from both public and private partners, including individuals experiencing Long COVID. Meaningful input is critical throughout the research process, as it can help guide research projects with attention to context and culture, thereby facilitating translation of research into effective policy and practice. We will continue facilitating these important conversations with our partners to gain feedback on the Plan, implement the Plan's strategies, and iterate the Plan moving forward.

Current U.S. Government Long COVID Research

The Plan builds on ongoing research supported or conducted by the U.S. government and aims to accelerate and expand it, in addition to calling for enhanced action by the private sector. The current Long COVID federal research portfolio, ongoing since 2020 and represented in over 100 published articles, demonstrates innovation and early achievements and highlights the importance of collaboration between the public and private sectors.

The current U.S. government portfolio is described in detail in this report and spans the following seven areas: **characterizing the full clinical spectrum of long COVID and diagnostic strategies; pathophysiology; surveillance and epidemiology; Long COVID and overall well-being; therapeutics and other health interventions; human services, supports, and interventions; and health services and health economics research.**

While the U.S. government continues to lead and make advancements in research, much more must be done to support persons experiencing Long COVID symptoms and to inform care and support for patients, their families, and caregivers. A national, U.S. government-wide coordinated, action-oriented approach is urgently needed. By infusing health equity considerations throughout the Plan, such as having inclusive and diverse participation in research activities, we are ensuring that our research and resulting policy and programmatic actions are effective and responsive to the needs of affected populations.

Accelerating Research and Innovation in Long COVID

Fully understanding the implications of Long COVID requires a comprehensive, multi-disciplinary, effective approach, leveraging the resources of the U.S. research enterprise and collaborative efforts across the federal government, coupled with strong public and private partnership. With these core tenets, the Plan includes steps to *Accelerate Research and Innovation in Long COVID*.

The Plan provides a detailed call to action across all sectors of research, both public and private, including academia, to accelerate the delivery of evidence and data. The Plan describes priorities across the **seven research areas**, as follows.

- 1. Characterizing the Full Clinical Spectrum of Long COVID and Diagnostic Strategies.**
Build on extensive ongoing research led by National Institutes of Health (NIH), Centers

for Disease Control and Prevention (CDC), the Department of Veterans Affairs (VA), and other agencies, for example the Researching COVID to Enhance Recovery (RECOVER) Initiative and Innovative Support for Patients with SARS-CoV-2 Infection (INSPIRE), to convene public and private partners to better align interim definitions of Long COVID for clinical care, surveillance, and research; lead further studies of the impact of SARS-CoV-2 infection on development and clinical course of new onset chronic disease states (e.g. diabetes); initiate research that disentangles the broader longer-term effects of the pandemic on physical and behavioral health (e.g., mental health and substance use challenges) from those of SARS-CoV-2 infection and re-infection; and further research to examine Long COVID and other post-infectious illnesses, including dysautonomia, and myalgic encephalomyelitis and chronic fatigue syndrome (ME/CFS), to identify commonalities and differences.

- 2. Pathophysiology.** Build on extensive ongoing research, for example the RECOVER Initiative led by NIH, to achieve a deeper understanding, from the molecular to system levels, of Long COVID within the broader context of post-infectious chronic conditions and other diseases that may have infectious origins, including dysautonomia and ME/CFS.
- 3. Surveillance and Epidemiology.** Build on extensive ongoing research, primarily led by CDC, such as INSPIRE Study, and the VA, to conduct additional studies of Long COVID risk factors, health trajectories and outcomes that are inclusive of age, gender, race, ethnicity, geographic location, socioeconomic status, insurance coverage status, pregnancy status, and disability status, enabled by new capabilities in data analytics; and lead studies that can rapidly adapt to examine risk and protective factors as they emerge (i.e., new variants, vaccinations, repeat infections, and therapies for COVID-19) on risk of Long COVID.
- 4. Long COVID and Overall Well-Being.** Conduct comprehensive studies of the effects of Long COVID on educational outcomes in children and youth, with a focus on vulnerable populations, including racial and ethnic minority groups, those who are economically disadvantaged, and those in rural communities; and lead research, including qualitative and mixed methods studies, to understand the impact of Long COVID on health-related quality of life, behavioral health, employment, disability determinations, education and development, and the impact on caregivers and family well-being, especially among disadvantaged groups, expanding upon initial work led by the VA, for example the COVID-19 Observational Research Collaboratory Long-term Outcomes Study (CORC-LTO), the Health Resources and Services Administration, for example National Survey of Children's Health Longitudinal Cohort Study (NSCH-LC), the Social Security Administration, and the Department of Labor.
- 5. Therapeutics and Other Health Interventions.** Expand the portfolio of studies, including the RECOVER Initiative and others, on the effectiveness of therapeutics to prevent and treat Long COVID to include antivirals, anti-inflammatory, immune modulators, and

other existing or new treatments; further studies to subtype Long COVID including characterization of distinct sub-entities with distinct set of risk factors and outcomes and evaluation of treatment strategies for these sub-types; and initiate studies of non-pharmacologic interventions to prevent and treat Long COVID.

- 6. Human Services, Supports, and Interventions.** Lead new work in identifying and evaluating optimal person-centered models of care for people with various forms of Long COVID; and lead comprehensive studies of human services and supports interventions, including disability services and caregiver supports, to ensure individuals living with Long COVID can fully participate in their communities, building on work by the Administration for Community Living (ACL), the Department of Defense (DOD), and the SSA.
- 7. Health Services and Health Economics Research.** Lead new studies, including systems research, to develop, implement, and evaluate models of care delivery that enable primary care providers to effectively manage Long COVID and associated conditions; lead new research to address barriers to effective care in underserved communities and models of care designed to address and eliminate health inequities; conduct rapid and ongoing synthesis of new evidence to distill existing research into actionable insights guiding care of people with Long COVID, including cost-effectiveness modeling of prevention and treatment strategies; and expand work, for example analyses led by the Office of the Assistant Secretary for Planning and Analysis, in impact of Long COVID on and economic costs of Long COVID to the health system, human services and supports programs, and society.

To lead and coordinate the work on Long COVID and in response to the April 5, 2022, Presidential Memo, *Memorandum on Addressing the Long-Term Effects of COVID-19*, HHS established a U.S. government-wide Long COVID Coordination Council (LCCC), chaired by the HHS Assistant Secretary for Health. HHS will continue the current approach of the Assistant Secretary of Health serving as the Long COVID coordinator and formalizing the responsibility through establishment of a new Office of Long COVID Research and Practice. The Assistant Secretary for Health, in a role as the Long COVID Coordinator, will implement the National Research Action Plan on Long COVID and coordinate efforts across the federal government through the Long COVID Coordination Council. The Coordinator will also establish the Secretary's Advisory Committee on Long COVID to continually engage non-governmental partners and develop and implement a strategic communications plan to share findings from Long COVID research. This new office, which will need resources and staffing, will ensure standardization and accountability for the Plan through implementation plans and annual progress reports.

HHS and federal partner agencies will also work with Congress and government leaders through continued investment in Long COVID coordination and research, to create and establish new structures to fulfill the calls to action, such as establishing and maintaining a framework for a multipronged approach to Long COVID surveillance; effective systems and strategies for rapid

implementation of Long COVID clinical trials; considering comprehensive approaches to fund interdisciplinary research on Long COVID; and engagement of federal agencies to contribute to a coordinated effort for a national real world evidence approach that would include Long COVID.

The best prevention of Long COVID and its related impacts remains to avoid infection and re-infection of SARS-CoV-2 by following basic interventions such as getting vaccinated and boosted, maintaining social distancing, wearing a mask, and handwashing. At the same time HHS will work diligently to advance research to prevent, diagnose, treat, and alleviate the impact of Long COVID for the nation. The Plan affirms the U.S. government's commitment to addressing the impacts of Long COVID with federal government resources, in collaboration with the private sector, and improving our Nation's health and well-being. The Plan, along with the accompanying Services Report, represent the federal government's response to ensure the acceleration of scientific progress and provide individuals with Long COVID the support and services they need.

Letter from the Secretary of Health and Human Services

Thank you, President Biden, for the opportunity to coordinate a U.S. government-wide effort to develop an interagency national research agenda, the *National Research Action Plan on Long COVID*.

The COVID-19 pandemic has been burdensome physically, psychologically, and socially. In May 2022, we marked one million American lives lost to COVID-19. The individuals lost represent loved ones who were taken from their families, friends, and communities.

The pandemic has disproportionately affected racial and ethnic minorities, with Black, Hispanic, American Indian, and Alaska Native populations experiencing higher rates of COVID-19 and death compared to White populations. Individuals with intellectual disabilities were also disproportionately affected and found to be six times more likely to die from COVID-19 than other members of the population. The challenges associated with COVID-19 exacerbated the existing health inequities in our country, highlighting social and racial injustices that impede equitable health outcomes.

As our nation continues to make advancements in addressing this pandemic through enhanced vaccine availability, research, testing, and treatment, we are also working to address the impact of Long COVID and associated conditions. For persons with Long COVID, symptoms like fatigue, shortness of breath, heart palpitations, and joint pain can persist for months, and new chronic conditions can prevent them from returning to their baseline state of health.

Conducting research in this area is critical to advancing our understanding of Long COVID and addressing the associated challenges of the pandemic. The U.S. government has been working on Long COVID research since 2020, with momentum building through 2021 and 2022. The *Memorandum on Addressing the Long-Term Effects of COVID-19* in April of 2022 highlighted the Administration's commitment to harness the full potential of the federal government and to coordinate with public- and private-sector partners to fully and effectively respond to the longer-term effects of COVID-19 by developing a National Research Action Plan. The Plan builds on the research already begun across the federal government to improve our understanding of the underlying biological causes, epidemiology, and impact of Long COVID; help us understand the burdens of those affected; foster development of new diagnostics and treatments; inform decisions related to support services and interventions; develop, implement, and scale innovative models of care delivery; improve data sharing and transparency among researchers; and explore the impacts of Long COVID on persons who are underserved by the health care system and public health infrastructure.

Principles guiding the Plan include a commitment to health equity, partner engagement, public-private collaboration, and prioritization of translational research to inform better health care delivery and human services.

The challenges posed by Long COVID and associated conditions require that we continue to work rapidly and share research findings as quickly as possible to drive delivery of effective health care and supports services. This Plan, along with the companion Services Report, represent the coordinated, action-oriented, federal government response to ensure the acceleration of scientific progress and to provide individuals with Long COVID the support and services they need.

Even as we endeavor to learn more about Long COVID, we already understand that the best prevention remains to avoid infection and reinfection by following basic prevention interventions such as getting vaccinated and boosted, maintaining social distancing, wearing a mask, and handwashing.

I want to thank the staff in the 14 departments and agencies who worked diligently to prepare this Plan. I also want to thank the Assistant Secretary for Health and the Assistant Secretary for Planning and Evaluation for their leadership in conceptualizing and driving the production of this report. Finally, I want to express my sincere gratitude to numerous organizations and individuals who contributed their time, resources, contacts, and invaluable conversations with us. This collaboration remains critically important in advancing the science and paving the way of progress. Those with lived experiences are central to these efforts.

Sincerely,

Xavier Becerra
Secretary of Health and Human Services

Chapter 1: Introduction

Recognizing Long COVID: A Brief Timeline

In April 2020, shortly after the beginning of the pandemic, anecdotal reports from patients started to emerge that previously healthy individuals were experiencing lingering symptoms and were not fully recovering from an infection with SARS-CoV-2.¹ These patients coalesced around each other and formed support groups, started to refer to themselves as “Long Haulers,” and coined the term “Long Covid.”^{2,3} They surveyed their membership and published the first landmark survey in May 2020 cataloguing the breadth of symptoms experienced by people with Long COVID.⁴ Controlled large-scale reports soon followed in early 2021 which provided a detailed systematic characterization of the condition.⁵ Studies detailing the breadth of organ dysfunction in people with Long COVID were published in late 2021 and early 2022.^{6,7} Overall, the early recognition by the patient community, their effort to organize, colloquially name the condition, and alert the world to study it, galvanized the research community to pursue research programs in this area, which in a short period of time resulted in substantial conceptual advances and significant breakthroughs in understanding the condition.⁸ The U.S. government has been conducting research on Long COVID since 2020 and providing care for individuals with Long COVID within federally supported healthcare systems such as the Veterans Health Administration, Federally Qualified Community Health Centers, Certified Community Behavioral Health Clinics, and the Indian Health Service. Milestones in the U.S. government response include a call for action on Long COVID in the Presidential Health Equity Task Force, Final Report and Recommendations, released in October 2021, announcement of the landmark RECOVER study in February 2021, and inclusion of Long COVID in the National COVID-19 Preparedness Plan in March 2022.

The Challenges of Long COVID: Public Health, Economic, and Societal Impacts

In August of 2022, it is now well understood that, amidst the many challenges of the pandemic are the persistent health effects some individuals face well after initial infection. Recovery from infection with SARS-CoV-2, the virus that causes COVID-19, can vary from person to person. Most individuals seem to recover quickly and completely. However, some report symptoms that persist or emerge weeks or even months after the initial phase of SARS-CoV-2 infection has passed. These sets of conditions are often referred to as “Long COVID.”³

Long COVID is a multifaceted disease that can affect nearly every organ system.^{5,6,9,10} In total, about 200 symptoms of Long COVID spanning nearly every organ system have been reported. Long COVID can manifest as new onset chronic disease, such as heart disease,¹¹ diabetes,¹² and

kidney disease;¹³ hematologic (blood) consequences; as well as mental and neurologic conditions.¹⁴ While estimates of the general risk of Long COVID vary between 5 and 30%, a recent large study by CDC suggested that one in five adult COVID-19 survivors aged 18 to 65 years and one in four survivors aged 65 years and over have a health condition related to their previous COVID-19 illness.¹⁰ Another recent CDC mathematical modeling study estimated that millions of U.S. adults have new long-term symptoms that limit their daily activities after infection with the virus that causes COVID-19 and that women may be disproportionately impacted.¹⁵ Finally, based on self-reported data from adults participating in the Census Bureau’s online Household Pulse Survey, more than a third of those who report having had COVID-19 reported ever having Long COVID symptoms and nearly one-fifth of those who have had COVID-19 reported currently having Long COVID symptoms.¹⁶ While estimates of burden of Long COVID vary across studies and settings, the breadth of symptoms and conditions that are manifestations of Long COVID and the potential scale are consistent throughout the scientific literature. It is evident that Long COVID is real, that it already impacts a substantial number of people, and that this number may continue to grow as new infections occur.

“I think it is a mistake to separate Long COVID and acute COVID. They work hand in hand. The conversation with health care providers needs to include ‘If you’ve been diagnosed with COVID-19, Long COVID symptoms may occur once you recover.’”

—Representative of a Mental Health Organization

Reduced health status and complications related to Long COVID are only a small portion of the consequences of the pandemic. Longer-term disease and disability will have ongoing economic and societal impacts.

- For example, in one survey, 44% percent of patients with Long COVID reported not being able to work at all, compared to their pre-COVID-19 work capacity, and 51% had reduced their working hours.¹⁷
- According to one estimate, roughly one million workers may be out of the workforce at any given time due to Long COVID. This figure equates to approximately \$50 billion dollars annually in lost salary.¹⁷

Health care cost burdens are also expected to increase for treatment of Long COVID as well as new chronic conditions, such as heart disease, diabetes, and kidney disease, that may be attributable to COVID-19.

As the United States continues to respond to COVID-19, it will be critical to address how Long COVID is impacting various communities and populations. While racial disparities in Long COVID are relatively unexplored, it is well understood that some racial and ethnic minority communities are disproportionately impacted by COVID-19. Of the 61.4 million COVID-19 cases recorded in the United States through early 2022, race and ethnicity were recorded for 65%.¹⁸ Among those cases, Hispanic persons had the largest number of cases, and Black persons

experienced higher COVID-19-related deaths, relative to their population share.¹⁸ When adjusted for age, the disparities are even more pronounced, with Hispanic persons being 2.4 times, American Indian or Alaskan Native persons being 3.2 times, and Black persons being 2.5 times more likely to be hospitalized with COVID-19 than their White counterparts.¹⁸ Other analyses also point to non-Hispanic American Indian or Alaska Native persons being at highest risk for COVID-19 hospitalization, and death.¹⁹

In addition to higher rates of COVID-19 in certain racial and ethnic minority groups, the higher burden of co-morbid chronic disease conditions seen in these communities can put people at a higher risk for severe illness and complications related to COVID-19, including Long COVID. Finally, outcomes associated with Long COVID are likely to be influenced by social determinants of health such as housing and income—likely driving even further an uneven distribution of the toll of Long COVID.²⁰ The health care and services communities will need to understand and engage with this new disease process and learn how to use culturally and linguistically effective services to provide the highest quality of care possible.

The consequences of Long COVID span individual health and the health care system, the economy, and society as a whole. Pandemics such as influenza and polio resulted in long-term consequences that persisted for decades. If history is any indicator, COVID-19 will also have long lasting effects that are only starting to be assessed and understood.²¹

Long COVID

Long COVID is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 or SARS-CoV-2 infection. The signs, symptoms, and conditions

- are present four weeks or more after the initial phase of infection;
- may be multisystemic;
- and may present with a relapsing–remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection.

Long COVID is not one condition. It represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes.

A Foundational Challenge: Understanding Long COVID and Associated Conditions

The medical, scientific, and public health communities have developed precise terms with agreed-upon, interim definitions of Long COVID, such as Post-COVID-19 conditions (PCC) and Post-acute Sequelae of SARS-CoV-2 infection (PASC), to use for communicating about clinical, research, and public health activities (see text box for an interim public facing definition of Long

COVID; see Appendix C for a detailed list of terms in use). This definition was developed by HHS in collaboration with other departments including with subject matter experts at HHS Office of the Secretary, CDC, and NIH. The first, Post-COVID-19 conditions, is equivalent to Long COVID, is broad to optimize sensitivity, and includes both direct and indirect effects of the virus. It is useful in various clinical setting, assessing the burden to the health care system, and surveillance. The second is Post-acute Sequelae of SARS-CoV-2 infection, which includes only the direct effects of the virus. It is used often in clinical contexts and critical to the medical research community aiming to understand the root causes of Long COVID. In diagnosing Long COVID, other illnesses need to be excluded. Additional research is underway to sufficiently separate the various forms and conditions of Long COVID, including from pre-existing ones. The differences and nuances among the definitions reflect the central challenge of defining, studying, and addressing the impact of Long COVID. In addition, some scientists and patient advocate communities point to the importance of conditions associated with Long COVID, drawing parallels in symptoms and underlying biology to other diseases, such as post-infectious conditions. The terminology of Long COVID and associated conditions leverages existing experience and knowledge to recognize commonalities to better treat and care for the many affected individuals, including the domains of disability and insurance coverage. Although the definitions will likely change as we learn more, using terms with commonly understood definitions helps research and public health communities compare findings across studies and facilitates turning surveillance and research findings into action to improve patient care.

While the Plan uses the term Long COVID throughout, it will be noted if and where specific research uses a more specific term (i.e., PCC and PASC). Also, it is emphasized that “Long COVID” is not just one condition, and the use of the term Long COVID in this report should not be construed as such.

The Need for a National Research Action Plan on Long COVID

Research into the causes and consequences of Long COVID and associated conditions, the underlying biological mechanisms, the therapies that work, and services and supports needed for persons experiencing Long COVID are necessary to develop strategies to prevent, treat, and support those with Long COVID. As described in detail in Chapter 3, federal agencies are currently studying the incidence, mechanism, duration, and severity of symptoms following SARS-CoV-2 infection, as well as risk factors associated with Long COVID. U.S. government has a leading role in Long COVID research through the work it conducts itself, including research in government-led health systems such as the VA and Indian Health Service; by funding private research; and by coordinating efforts across public and private entities. Some of U.S. government efforts include the Researching COVID to Enhance Recovery (RECOVER) Initiative, led by the NIH.²² This research initiative brings together patients, caregivers, clinicians, community leaders, and scientists from across the nation to understand, prevent and treat Long COVID. The RECOVER Initiative is focusing on enrolling individuals across all ages, genders, races, ethnicities, and socioeconomic statuses. Enrollment includes pregnant people,

individuals of reproductive age, individuals with disabilities, and those from the communities hardest hit by the pandemic. In addition, CDC is leading numerous studies, including the Innovative Support for Patients with SARS-CoV-2 Infections (INSPIRE) Study. It is following nearly 6,000 individuals at select sites across the country for up to 18 months and conducting other dedicated research in Tribal and other hard-hit, high-risk communities.²³ A final example are studies leveraging the Department of Veterans Affairs electronic health record data, which includes over 10 million Veterans, to understand different health impacts of Long COVID over time as well as evaluating models of care, which has resulted in important early findings about the clinical manifestations of Long COVID.²⁴

“I got COVID-19 and I was embarrassed that I continued to have symptoms after the 14-day quarantine. I am 70 years old. I doubted my own symptoms for so long. I was afraid to even go to my doctor because I thought they wouldn’t believe me.”

—Person with Long COVID

While the U.S. government continues to lead and make advancements in research, much more must be done to support persons experiencing Long COVID symptoms and to inform care and support for patients, their families, and caregivers. A national, U.S. government-wide coordinated, action-oriented approach is urgently needed. The National Research Action Plan on Long COVID ensures an effective, comprehensive, and equitable research strategy to inform our national response to Long COVID’s impacts on individuals, communities, and our entire society.

The Purpose of the National Research Action Plan on Long COVID

The purpose of the Plan is to advance progress in prevention, diagnosis, and treatment of Long COVID; and provision of services and supports for individuals, families, and communities experiencing Long COVID. This includes advancing our understanding of the health and socioeconomic burdens on individuals with Long COVID, including among subcategories of age, gender, race and ethnicity, rurality, insurance coverage, economic disadvantage, pregnancy status, and disability status. The research must identify and provide strategies to inform our national response to address the pandemic’s impact on these communities and populations.

While the Plan describes several U.S. government Long COVID research initiatives, meeting the challenge of Long COVID will require deep engagement by private partners including academia, pharmaceutical industry, professional organizations, and private research organizations, including the role of organizations that provide the patient data without which research cannot occur. The Plan also recognizes the centrality of persons affected by Long COVID and their role as active partners at the core of the research enterprise from initial inception until successful completion. As such, the U.S. government will lead the effort to convene various stakeholders

and partners and facilitate collaborations and partnerships among them to accelerate discovery and innovation in Long COVID.

Guiding Principles of the National Research Action Plan on Long COVID

Increasing and enhancing research efforts is imperative to inform and provide equitable prevention, care, and support to individuals, families, and communities with Long COVID. The Plan was developed and will be implemented with a coordinated government-wide approach (see Appendix B for a list of 13 Departments in addition to the Department of Health and Human Services that participated in the Plan development). The guiding principles of our coordinated efforts in addressing the impacts of Long COVID are

Orienting the Research Effort to Improve Patient Care and Outcomes. We will accelerate knowledge synthesis, dissemination, and implementation of research findings to promote coordinated, integrated care models and expand access to high-quality care in communities across the country and drive more effective public health action.

Health Equity. Issues of access and utilization of health care are critical barriers for both COVID-19 and Long COVID. To achieve our vision, the Plan is guided by health equity principles, building upon prioritized recommendations made by the Presidential COVID-19 Health Equity Task Force. These recommendations include, but are not limited to, understanding how racism, ableism, and discrimination along with provider bias are associated with health care access, symptom recognition, disease progression, and severity of Long COVID in communities that are disproportionately disadvantaged and other people who are underserved, as well as improving data collection, integration, and use so that data can be disaggregated for these populations who are at higher risk and used to inform equity-centered response decisions.²⁵⁻²⁷

Accelerating and Expanding Current Research. While research on Long COVID is underway both within and outside of the U.S. government, we must accelerate and broaden our efforts. The Plan calls for new research partners and data sharing, and new strategies to extract lessons sooner from existing investments in research. Acceleration will require rapid short-term trials designed to alleviate the symptoms of those now living with Long COVID and long-term research on topics such as natural history of disease and optimal treatments.

“We need to do everything we can now to learn about Long COVID and how to help people, because soon we’re going to have lots of people with this chronic condition.”

—Person with Chronic Fatigue Syndrome

Partner Engagement. We will continue to work with people living with Long COVID and other partners on building relationships with communities that are disproportionately impacted through transparent and ongoing meaningful engagement to ensure that these efforts address the highest priority needs of persons experiencing Long COVID.

This Plan is intended for U.S. government agencies and to inform Congress and researchers both public and private, including academia. This information is also relevant to other groups such as state policymakers, foundations and other funders of research, health care and service personnel, public health partners, Long COVID patients and advocacy groups, pharmaceutical companies, and the general public.

Development of the National Research Action Plan

Workgroup Formation and Report Development

In response to the April 5, 2022 publication of the *Memorandum on Addressing the Long-Term Effects of COVID-19*²⁸, a workgroup was created to draft this Plan. Representatives from agencies across the U.S. government were brought together. As part of the writing process, each agency's workgroup members inventoried current and planned Long COVID research, shared information about published research articles, and coalesced around future research topics and priorities.

Partner Engagement

An essential part of the Plan, as President Biden highlighted in his Memorandum, is the engagement of not only U.S. government agencies, but also nongovernmental experts, organizations, and partners. A coordinated effort within and outside of the U.S. government is required to adequately address the research challenges we face with Long COVID.

The Plan workgroup gathered relevant information and individual input from a variety of partners, including persons with Long COVID, through a series of listening sessions. Over a dozen sessions were held during the drafting on this Plan and the Services Report. Sessions will continue after publication of the reports.

Participants in these listening sessions included

- Long COVID patients and caregivers, as well as Long COVID advocacy groups
- Patients with disabilities and chronic illness and their caregivers, as well as disability and chronic illness advocacy groups
- Provider groups and organizations (health care organizations and systems, community health centers, behavioral health providers, and hospitals)

- Researchers, including patient researchers
- Public health partners
- Professional medical organizations and societies
- Mental health advocates
- Children’s advocates
- Organizations representing health and health care for people who are underserved, such as African Americans or Black persons, Latino persons, Asian and Pacific Islander persons, American Indian and Alaskan Native persons, and LGBTQIA+ persons.

We also invited participants to share resources and reviewed relevant plans, reports, and guidelines. These resources highlight the burden of Long COVID and of other post-infectious conditions, set out strategic goals and research priorities to address these conditions, and demonstrate skillful approaches to partner engagement.²⁹⁻³²

Concurrently, we sponsored non-governmental partners to conduct a human-centered research project, termed Health+, to better understand Long COVID. This approach works to co-create solutions with—not for—people impacted by Long COVID. By listening and learning from patients experiencing Long COVID and associated conditions, caregivers, frontline workers, and those with lived experience, we will accelerate understanding and breakthroughs together. Most importantly, the Health+ Long COVID cycle will generate insights with actionable opportunity areas to improve the quality of care and life.

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Chapter 2: Summary of Partner Input

The Long COVID National Research Action Plan was developed with engagement of individual public and private interested persons. The Department of Health and Human Services' Office of Intergovernmental and External Affairs hosted a series of interactive listening sessions to inform the development of the Plan. The sessions included a broad range of participants including persons with Long COVID, researchers, health care personnel, organizations representing health professionals, public health partners, and advocacy organizations.

Across listening sessions, some messages were consistently voiced. These messages influenced the development of the report and are reflected in the Plan.

Urgency

An overarching concern among Long COVID patients, health care personnel, researchers, and public health partners is the urgent need for information that can guide health care, programs, and services. Since the start of the pandemic, people with Long COVID and associated conditions have been in need of symptom relief, health care services, and financial assistance. Research represents hope for persons with Long COVID and those who care for them. To provide relief to those with Long COVID, legislatures and governmental and nongovernmental partners must recognize the urgency of this work and act accordingly.

Partner Engagement throughout the Research Enterprise

An integral way to address research gaps and provide the most insightful and effective results is to ensure that partners, particularly Long COVID patients are integrated into every stage of the

Summary of Recommendations as Reflected in the Plan

The Long COVID National Research Action Plan workgroup considered and incorporated many individual concerns and recommendations. The highest priority recommendations were

- Assuring patient engagement in all government-sponsored research throughout the research enterprise
- Inaugurating a central coordinating office for Long COVID research
- Accelerating therapeutic research
- Engaging researchers and harnessing prior research on other post-infectious conditions
- Ensuring transparency in communications about the research and findings.

Conversations will continue with a broad set of partners to gain individual feedback on the Plan, work to implement the Plan's strategies, and iterate the Plan moving forward.

research process. Existing studies and initiatives have engaged patients, but advocacy organizations indicated that these efforts need to be more robust and occur earlier in the planning process when research questions and study designs are planned. Long COVID patients' perspectives are critical to effective, meaningful research.

Research Coordination

Participants in the listening sessions called for cross-governmental coordination to maximize current and future federal research efforts. The government and private researchers, including those in academia are conducting a great deal of COVID-19 research. Coordination is required to ensure that the nation's research agenda is comprehensive, transparent, and effective.

Standard Definitions

Many inside and outside of government have highlighted an important, yet basic, action of moving towards a set of standard research, clinical, and surveillance definitions of Long COVID. Partners indicated a concern over insufficient clarity and consistency in the emerging terms and definitions, as they might affect the diagnosis of the condition. Others point to the critical importance of inclusion and the risks with moving too quickly to narrowly define a set of conditions as yet not sufficiently understood.

Research Gaps and Funding

Participants identified a number of knowledge gaps that should be addressed by research. Some topics recommended for future research include identification of innovative therapies, Long COVID in pediatric populations, the impact of reinfection on Long COVID, and the impact of medical bias on patients with Long COVID. It is particularly important to develop a portfolio of clinical trials to test as many therapeutics and models of care delivery as possible to enhance understanding of what works for Long COVID patients. All areas require further research and funding.

To expedite this research, academic researchers and patient-led research groups requested faster research funding mechanisms. Due to the highly dynamic nature of Long COVID, conventional funding mechanisms have limitations to addressing the urgent questions related to the condition. There was a call for the U.S. government to establish new funding mechanisms that can help dynamically resource researchers who are working on Long COVID.

Some partners expressed concerns about current governmental research projects, based on their personal participation in, or engagement with them. For example, patient advocates highlighted the need to integrate evidence and learnings from prior and current research on post-infectious conditions, including dysautonomia and myalgic encephalomyelitis

“A National Research Action Plan must be explicit and intentional about including, recruiting, and engaging a diverse research cohort.”

—Long COVID Researcher

and chronic fatigue syndrome (ME/CFS), into ongoing Long COVID research. Some also expressed concerns with studies that require a positive SARS-CoV-2 test result to be eligible for enrollment, which excludes persons who were not tested, had false negative results, or those who were asymptomatic during the initial infection. The importance of relevant control groups in studies of Long COVID was emphasized. One of the lessons learned from the Centers for Disease Control and Prevention's (CDC) longstanding ME/CFS program, echoed by some individual partners, is that ME/CFS-like illnesses are often unrecognized or overlooked. There is a need to distinguish the ME/CFS-like (medically unexplained) subgroup of Long COVID from subgroups with COVID-19-related well-established chronic conditions (such as heart disease, diabetes, and renal disease) and prioritize research on Long COVID ME/CFS-like illnesses. There are parallel observations for dysautonomia.

Chapter 3: The Current United States Government Long COVID Research Portfolio

The National Research Action Plan on Long COVID will build on ongoing efforts across the federal government. The current federal Long COVID research portfolio demonstrates innovation and early achievements, as evidenced by a growing body of published studies funded or conducted by the U.S. government. The portfolio highlights the importance of a collaboration between the public and private sectors in advancing progress in prevention, diagnosis, treatment and provision of health care, public health, and human services for individuals experiencing Long COVID. Ensuring broad representation in research activities of underrepresented groups remains a challenge, and attention and innovation are required to specifically address these challenges. The description of the federal research portfolio in this chapter is intended to be a summary with highlights, and it is not an exhaustive inventory of all U.S. government supported Long COVID research.

Organization of the Research Portfolio

The federal Long COVID research portfolio described in this chapter is organized into the following topic areas with subtopics:

1. Characterizing the Full Clinical Spectrum of Long COVID and Diagnostic Strategies
2. Pathophysiology
3. Surveillance and Epidemiology
4. Long COVID and Overall Well-Being
5. Therapeutics and Other Health Interventions
6. Human Services, Supports, and Interventions
7. Health Services and Health Economics Research.

Within each topic area there is a brief synopsis of research, with descriptions of a small number of the principal research initiatives. Studies may appear in more than one topic area; for example, a survey of patients with Long COVID can provide information about impacts of illness as well as access to health care.

Text boxes in each area highlight the core research questions, health equity considerations, and anticipated impacts of research. Appendix D, the U.S. government Long COVID Research Portfolio, complements this Chapter by providing an alphabetical list of studies with basic information and includes more studies than those mentioned here.

1. Characterizing the Full Clinical Spectrum of Long COVID and Diagnostic Strategies

It is a public health priority to identify, understand, and effectively diagnose conditions across the full clinical spectrum of Long COVID.* These are necessary first steps toward the development of optimal prevention and treatment strategies. Important research topics include clinical manifestations of Long COVID and associated conditions, how these may vary across the lifespan and across different demographic groups, how they may change over time, and how they may be affected by viral variants, reinfections, and various interventions such as vaccines.

The observed heterogeneity of Long COVID thus far strongly suggests that, rather than being a singular condition, Long COVID is likely multiple clinical conditions. Data being collected from longitudinal studies on Long COVID include a wide range of data from laboratory testing, imaging, functional studies, genomics, mobile health-wearable devices, participant surveys, electronic health records, demographic data, information on social determinants of health, and other data sources. In addition, the breadth and complexity of data being collected in current studies will necessitate advanced analytics, such as machine learning, artificial intelligence,

Core Research Questions

- What is the clinical spectrum of recovery from acute SARS-CoV-2 infection and how does it change over time?
- What are the clinical manifestations of Long COVID? Are there distinct subtypes (phenotypes) of Long COVID?
- What is the natural history of Long COVID? How do the clinical manifestations of Long COVID vary across the lifespan and different demographic groups? How do they change over time? How are they affected by various interventions, such as vaccines?
- Are there distinct phenotypes among those patients who do not fully recover or who develop new onset symptoms?
- What are the biologic causes of Long COVID and how can they be reversed?
- How does SARS-CoV-2 infection initiate or promote the pathogenesis of conditions or findings that evolve over time to cause organ dysfunction or increase the risk of developing other disorders?
- What are the clinical criteria for diagnosing Long COVID?
- What diagnostic tests and assays can be used to accurately and reliably diagnose Long COVID?

* Much of the research described in this section is specific to Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), but the term “Long COVID” used throughout the report includes PASC.

natural language processing, or deep learning to extract meaning and create the needed specialized tools for prediction, detection, prognosis, diagnosis, and monitoring treatment response for Long COVID.

Clinical Spectrum of Long COVID

Multiple U.S. government studies are currently underway investigating important factors of the clinical spectrum of Long COVID including understanding different presentations and symptom clusters; identifying factors that may modify Long COVID such as the impact of variants and severity of acute illness; determining the risks for development of other medical conditions (such as diabetes or cognitive impairment) after a SARS-CoV-2 infection; and understanding how Long COVID may impact pre-existing health conditions.

Many of these U.S. government studies are recruiting diverse adult and pediatric populations and focusing on specific populations, including Veterans, pregnant people and their infants, those with pre-existing health conditions, and persons from medically underserved populations.

Federal agencies and departments have formed strategic partnerships that leverage individual missions, resources, and capabilities to launch collaborative research efforts and strengthen areas of synergy. For example, Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) are working together on refining definitions; NIH and the Patient-Centered Outcomes Research Institute (PCORI) have worked together on patient-reported outcome measures; and CDC, the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Department of Health and Human Services (HHS) are engaged in governance of the Researching COVID to Enhance Recovery (RECOVER) Initiative.

Federal departments and agencies recognize that as the science of Long COVID evolves, discoveries will emerge and yield new avenues for pursuing research. Many of

NIH RECOVER Initiative: Principal Features

RECOVER is a multi-pronged, multi-disciplinary research effort of national scale to improve understanding of Post-Acute sequelae of SARS CoV-2 infection (PASC) and to inform the development of safe and effective diagnostic, treatment, and preventive strategies. Features include

- Clinical cohorts with thousands of diverse participants across the lifespan
- Patient involvement in all levels of the initiative
- Inclusive, diverse participation
- Community engagement
- Studies with access to tens of millions of de-identified electronic health records and mechanistic studies of pathogenesis
- Tissue pathology and autopsy studies of more than 50 tissue types
- Clinical trials of promising treatments

the large, U.S. government research initiatives are gathering comprehensive data and biospecimens with the intent to leverage these in the short and long term.

Principal Research Initiatives

A critical component of the U.S. government approach to researching the clinical spectrum of Long COVID is the RECOVER Initiative. NIH launched RECOVER to improve understanding of and ability to predict, treat, and prevent PASC. RECOVER is a multi-study, patient-centered initiative of national scale with diverse participation and community engagement. RECOVER has multiple scientific aims and seeks to understand the clinical spectrum and the biology underlying recovery over time, as well as define distinct subtypes of Long COVID. It includes multiple sub-studies, such as longitudinal observational clinical cohort studies with thousands of diverse participants across the lifespan; ancillary clinical studies leveraging cohort data and specimens; pathobiology studies; analyses of electronic health records; and clinical trials. RECOVER will also conduct clinical trials to test promising treatments in subsets of persons with Long COVID for their ability to reduce symptom burden and correct or prevent the abnormal biologic factors that give rise to the conditions.

Given the variety of organs in the body affected by Long COVID and the multitude of symptoms observed, RECOVER will examine a wide array of body systems. Assessments are tailored to different populations including adults, children and their caregivers, pregnant participants and their newborn infants, and people of reproductive age. The methodology helps capture different types of data including radiology, laboratory tests, surveys, immune assays, and genome analyses. These analyses will be complemented by electronic health record-based studies that collectively access de-identified health records of tens of millions of adult and pediatric patients accessible through the National COVID Cohort Collaborative (N3C), the National Pediatric-Centered Clinical Research Network (PCORnet) and PEDSnet (the Pediatric Learning Health System consortium of PCORnet). Attention is given to include participants who live in rural

NIH RECOVER Initiative: Research Questions

Goal: To understand, diagnose, treat, and prevent post-acute sequelae of SARS-CoV-2 infection (PASC)

- What are the various forms of PASC? Characterization of full clinical spectrum and phenotypes
- How long does PASC last? Can it have effects later in life? Does it alter the course of or risk for other diseases and conditions?
- What are the risk factors for developing PASC?
- What are the impacts of different variants and vaccination?
- What are the underlying biologic mechanisms responsible for PASC?
- What are the underlying mechanisms responsible for resilience and resistance to PASC?
- What are specific therapeutic targets for clinical interventions (treatment and prevention)?

areas, those who are medically underserved, and those who are non-English speaking. The surveys and research protocols for adults and children are available in multiple languages.

In addition to the RECOVER Initiative, NIH leads or funds additional prospective observational cohort studies that include adults and children with varying severities of underlying disease, which will help characterize the clinical sequelae of SARS-CoV-2 over time. Some studies are characterizing immune responses, while others are focused on specific populations, such as children and adults who developed diabetes mellitus after SARS-CoV-2 infection, individuals with dysautonomia, myalgic encephalomyelitis and chronic fatigue syndrome (ME/CFS), and children with multisystem inflammatory syndrome (MIS-C).

Additional NIH-supported studies are investigating the persistent neurological and cognitive symptoms experienced by many patients who have recovered from SARS-CoV-2 infection. These studies are recruiting across adult and pediatric populations and enrolling pregnant people and their infants, patients with other neurological diagnoses, and those from historically underserved backgrounds. The studies are gathering different types of information and biospecimens, such as performance on cognitive measures, Magnetic Resonance Imaging (MRI), cerebrospinal fluid (CSF), blood specimens, and autopsy tissue to better understand the neurological sequelae associated with Long COVID.

NIH-supported researchers have also been studying the mental health impacts of Long COVID. Researchers have developed a publicly available dataset of COVID-19 patients' firsthand accounts of their illness and recovery, including their anxiety about illness and its lasting effects on their mental and behavioral health.¹ In addition, researchers supported by RECOVER developed a machine learning model that uses electronic health record data to identify COVID-19 patients who experienced Long COVID. Thus far, this research has revealed that diagnosis features such as dyspnea, dyssomnia and other sleep disorders, and malaise are informative for recognizing potential Long COVID.² These conditions and other features of Long COVID can interact to exacerbate patients' experiences with new or pre-existing mental health conditions.

The Department of Veterans Affairs (VA) is conducting several collaborative studies as part of the Post COVID Collaborative Merit Program that focus on the clinical spectrum of Long COVID,

Anticipated Impacts of Research

- Evidence generated by research will inform researchers, guidelines developers, health care personnel, payers, patients, caregivers, and policy makers. Information will be disseminated through publications, professional scientific and medical society meetings, federal webpages, and webinars.
- Practitioners will be better able to diagnose, manage, and monitor Long COVID.
- The research will inform the development of new treatment and prevention strategies.

including cognitive impairment, mental health effects, persistent fatigue (as seen in ME/CFS), functional impairment, sleep disturbances, and recurrent pain symptoms.

CDC has completed and published several studies that have assessed clinical presentation of Long COVID through both survey and analyses of electronic health record data.³⁻⁵ Also, CDC's National Health Interview Survey (NHIS) contains questions in 2022 and will again in 2023 on ME/CFS and will provide data to examine the connections between ME/CFS, Long COVID, and other chronic conditions.

The Department of Defense (DOD) is conducting the Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) study, a prospective observational cohort study evaluating Long COVID chronic symptoms and health care encounters after SARS-CoV-2 infection. EPICC also includes machine learning approaches to identify Long COVID early symptom clusters, predict return to pre-illness health, and identify subtypes of Long COVID.

In conjunction with EPICC, the VA launched the Epidemiology, Immunology, and Clinical Characteristics of COVID-19 (EPIC³), which is following a cohort of Veterans after a positive or negative test result for the presence of SARS-CoV-2. The study will describe the clinical trajectory from acute to Long COVID over time, as well as examine the role of biomarkers influencing the risk for Long COVID. At completion of the respective studies (EPICC and EPIC³), researchers plan to compare findings from the two participant groups.

Furthermore, the NIH and the VA are partnering on a cohort study that aims to define risk factors for severe COVID-19, with a focus on the role of the immune system, inflammation, and tissue damage. This research will aid in our understanding of how the immune system affects whether an individual develops severe COVID-19. Results from these studies will complement evidence generated from other studies to build a more complete and comprehensive understanding of Long COVID.

Health Equity Considerations

- Inclusive and diverse participation in Long COVID research helps ensure that the results of the research are applicable to the wide range of populations affected
- Meaningful patient and community engagement is a guiding principle of RECOVER, which has intentionally engaged patients, caregivers, and individuals from communities most affected by SARS-CoV-2 at nearly all levels of the Initiative. RECOVER includes a National Community Engagement Group and, at the level of enrolling sites, collaborates with the NIH Community Engagement Alliance Against COVID-19 Disparities program
- Research methods must establish the validity of instruments in diverse populations that are the focus of the studies

Diagnosis of Long COVID

The heterogeneity of Long COVID, likely representing multiple clinical conditions, poses enormous challenges to development of diagnostic strategies for Long COVID. Different diagnostic tests may be required for different types of Long COVID. Research is just beginning to establish clinical criteria for diagnoses and to inform laboratory and other test development and other diagnostic strategies.

Principal Research Initiatives

The NIH RECOVER Initiative is collaborating with the NIH Rapid Acceleration of Diagnostics (RADx®) Radical (RADx-rad) program, which focuses on rapid detection devices and home-based testing technologies to address COVID-19 testing needs. The RADx-rad-RECOVER collaboration is leveraging the National COVID Cohort Collaborative (N3C) to support the development and validation of data-driven artificial intelligence, including machine learning and natural language processing (using deep learning software tools) to better understand the clinical, environmental, social, and behavioral risk factors for developing Long COVID and for Long COVID prognosis. In addition, a request for information on technologies and approaches that can identify individuals susceptible to PASC was published in 2021.

Several NIH-supported studies are also investigating specific symptoms. For example, the loss of smell (anosmia or hyposmia) and its occurrence in Long COVID is one such focus. These projects aim to develop a quick, inexpensive, self-administered smell tests to screen for COVID-19 at the individual level and assess prevalence in communities, especially those that have been traditionally underserved by the health care system and public health infrastructure. For those with Long COVID, the developed smell tests will facilitate recovery monitoring.

2. Pathophysiology

There is an urgent need to identify the pathological processes that underpin Long COVID. It is important to rapidly advance understanding at the molecular level of the mechanisms at the root of the clinical phenotypes and symptoms and other observed health effects and identify targets for preventive and therapeutic interventions. Multiple hypotheses currently exist regarding underlying biological processes, including persistence of SARS-CoV-2 or viral antigens, reactivation of other latent viruses (such as Epstein-Barr virus), dysregulated immunological or inflammatory responses, and central or peripheral neurological

Core Research Questions

- What are the pathophysiologic mechanisms of Long COVID?
- What potential role do the following play in the development of Long COVID: immune dysregulation (including autoimmunity), persistent SARS-CoV-2 virus, reactivation of endogenous viruses, and organ injury during acute infection?

damage (including autonomic dysfunction, and inflammation of blood vessels). As Long COVID is likely not one singular condition, there will likely be multiple underlying pathophysiologic mechanisms at play.

Principal Research Initiatives

Multiple studies across the U.S. government are examining a broad range of potential pathophysiological mechanisms of Long COVID in both adult and pediatric populations. The DOD’s EPICC study and the parallel VA EPIC³ study are focused on examining the pathophysiology of Long COVID, including the role of viral and inflammatory markers to inform the Military Health System clinical care and practice guidelines that aim to improve clinical care and management of those with COVID-19, as well as inform future disease prevention strategies. These studies are capturing clinical and laboratory data from patients with SARS-CoV-2 infection to better

understand the disease’s natural history, including the clinical, virologic, and immunologic determinants of severe disease. NIH’s RECOVER Initiative includes a broad suite of pathobiology studies to identify mechanisms underpinning clinical phenotypes and symptomatic manifestations, pathology in multiple organ systems that has led or will lead to clinically significant health problems, and potential therapeutic targets. RECOVER also includes tissue pathology studies conducted at five centers across the country that utilize a common protocol with standardized methodologies to analyze organs and tissue obtained at autopsy, including the brain. These studies will enable detailed identification of tissue injury in critical organs and systems due to SARS-CoV-2 infection, its sequelae, or both that lead or contribute to Long COVID.

Additional NIH studies seek to understand the underlying pathobiology of Long COVID. This includes studies of immunology of both severe and mild to moderate COVID-19, including longitudinal in-depth immunophenotyping. Longitudinal cohorts of both adult and pediatric populations with prior

Health Equity Considerations

Inclusive, representative, and diverse participation in pathophysiology research helps ensure that the results of the research are applicable to the wide range of populations affected. Ensuring that interventions for Long COVID are effective, acceptable, and accessible for diverse populations contributes to future uptake and effectiveness.

Anticipated Impacts of Research

The most important target audience for this information is other researchers.

Information will be shared primarily through publications and professional meetings.

These studies will contribute to our understanding of the causes of Long COVID, help identify biomarkers and enable risk stratification, contribute to the development of new therapeutic targets, and help inform Long COVID clinical trials.

Understanding Long COVID at the molecular level is critical to inform better diagnostics and targeted interventions for prevention and treatment.

SARS-CoV-2 infection include the assessments of immune responses and other investigations aimed at understanding the underlying biology of Long COVID. Further, an NIH-supported study aims to evaluate the effects of immunotherapies on patients experiencing persistent neurological symptoms following a mild to moderate SARS-CoV-2 infection.

NIH's RECOVER Initiative is also collaborating with the NIH *All of Us* research program, which is enabling precision medicine research using five major data types (biometrics, genomics, electronic health records, surveys, wearable devices) and biospecimens longitudinally obtained from participants across the United States, with a goal to enroll one million diverse participants. The collaboration will evaluate the use of biospecimens in potential ancillary studies to analyze features of the immune system and genomes to further our understanding of the biology that underpins Long COVID. The VA's Million Veterans Program genomic program includes over 40,000 patients with documented SARS-CoV-2 infection among 800,000 subjects with genomic and survey data; surveys are planned to examine the role of genomic markers in the development of Long COVID symptoms. A principal audience for this information is the broad community engaged in empirical research to improve the lives of persons living with Long COVID.

3. Surveillance and Epidemiology

Public health surveillance is the systematic and ongoing collection, analysis, interpretation, and dissemination of data linked to public health action.⁶ Surveillance tracks the occurrence and burden of Long COVID in the population and can provide insights into groups affected. The ultimate objectives of surveillance for Long COVID are to inform and guide the planning and implementation of private and public programs designed to reduce Long COVID and its complications, and to evaluate the effectiveness of public health interventions and policies.^{7,8}

Epidemiologic studies investigate the causes and risks of health-related events in populations and the application of new insights to control or mitigate health problems. The aims of epidemiologic studies are to provide estimates of the risk of Long COVID by demographic groups and identify potential risk or protective factors compared with groups without history of COVID-19. While surveillance of Long COVID tracks the burden in the population and can provide insights into groups impacted, epidemiologic studies provide estimates of the occurrence of Long COVID by demographic groups and potential risk or protective factors.

Core Research Questions

- What are the population-level incidence and prevalence of Long COVID and associated conditions?
- What are the population-level incidence and prevalence of activity limitation and disabilities associated with Long COVID and associated conditions?
- What are the factors associated with incidence and prevalence of Long COVID?

Characterizing the numbers of people living with Long COVID, tracking these numbers over time, and identifying protective and risk factors will require the use of multiple epidemiologic studies and surveillance approaches leveraging different sources of information.⁹ Federal agencies have implemented a diverse, layered, research and surveillance portfolio to answer questions.

There are several challenges in surveillance and epidemiologic research for Long COVID given the wide range of symptoms, effects, and spectrum of severity. These challenges lead to differing characterizations of Long COVID across studies. Studies vary greatly in how assessment and measurement are conducted. Studies to date have included patient-reported outcomes, clinical assessments, laboratory measures, and diagnoses of new conditions and symptoms. Some studies, but not all, have included measures of Long COVID severity, disability, and disruption in activities of daily living. Some have focused on hospitalized patients, others only on ambulatory patients, and others on persons with initial infections that were asymptomatic. Few studies have included children.

Because many of the individual symptoms and conditions that comprise Long COVID are common, the inclusion of a comparison group is vital to understand the excess burden of these symptoms and conditions among persons infected with SARS-CoV-2. Studies currently underway have approached this in multiple ways, some using participants who test negative but have COVID-like symptoms, others using historical (pre-pandemic) participants, and others using participants with no evidence of SARS-CoV-2 infection or COVID-like symptoms.

Diverse Research Portfolio Needed for Long-COVID Surveillance and Epidemiology

Prospective Cohort Studies: Assess how Long COVID progresses and measure short-term and longer-term impacts.

Cross Sectional Surveys: Provide point-in-time view of Long COVID in the population by demographic factors, underlying medical conditions, and other risk factors.

Medical Record Review: Provide insights into common conditions, symptoms, care, and treatment that patients are receiving in the medical setting.

Modeling studies: Provide population-level estimates of numbers of people affected by Long COVID when it is not feasible or practical to count all cases.

Electronic Health Care Data: Leverage large numbers of patients to provide estimates of the incidence of new conditions, symptoms, and health care utilization among persons who had COVID-19 compared with persons who did not.

Several federal interview surveys harmonize the Long COVID data collection, including the National Health Interview Survey, the Household Pulse Survey, and the Behavioral Risk Factor Surveillance System. Along with these self-reported interview data, data from complementary methods such as cross-sectional health surveys, cohort studies, analyses of electronic health record data, and sentinel surveillance are needed to fully characterize the natural history of post-COVID-19 conditions. More work needs to be done to align these efforts across the U.S. government. For all areas, published studies provide new and important findings that contribute to the evidence-base for Long COVID surveillance and epidemiology.

Population-Level Incidence and Prevalence

There is a growing body of research to provide measures of population-level incidence (the proportion of people with new occurrence of Long COVID among those at risk during a specific period of time) and prevalence (the proportion of persons with Long COVID at a specific point in time). Prospective observational cohort studies, electronic health care data analysis, and health surveys currently underway will provide estimates of the incidence and prevalence of Long COVID in the general population and in specific subpopulations. Building on the existing evidence-base, we will continue to learn more about estimates of population-level incidence and prevalence, for specific populations and by subpopulation. Studies from CDC, FDA, HRSA, NIH, VA, and their partners will help us fill in the gaps in our understanding of incidence and prevalence of Long COVID.

Principal Research Initiatives

CDC, the Department of Commerce (the Census), FDA, HRSA, NIH, and VA are leading several studies that will provide estimates of incidence and prevalence (see Appendix D). Select examples include CDC's National Health Interview Survey and Behavioral Risk Factor Surveillance System. Starting in January 2022, CDC's National Health Interview Survey (NHIS) added questions to identify the prevalence of Long COVID based on self-report (for adults) and parent-report (for children). Also, in 2022, CDC's Behavioral Risk Factor Surveillance System (BRFSS) added a question to collect information about symptoms of post-COVID-19 conditions to produce state and territorial-level estimates of burden among adults based on self-report.

Health Equity Considerations

The COVID-19 pandemic has had a disproportionate impact on some racial and ethnic communities, people with lower socio-economic status, and some people with disabilities. Understanding risks for Long COVID and the impact of the inequities that led to the disproportionate outcome in infection, hospitalization, and death are critical. Groups may be more at risk for Long COVID due to the inequities that put them at risk for COVID-19 or there may be other factors. Studies of Long COVID must examine race and ethnicity, socio-economic status, disability status and other factors impacted by health inequities and assess associations within groups, not just across groups.

Other examples include CDC’s multi-state Long COVID survey that surveyed adults who had a positive test result for SARS-CoV-2 for self-reported acute and post-COVID-19 symptoms lasting four weeks or more to estimate burden of post-COVID-19 conditions and identify demographic and disease-specific risk factors for developing post-COVID-19 conditions.

Starting in June 2022, questions were added to the Household Pulse to identify Long COVID in adults through self-report. Early results indicate a high level of respondents stating that they have symptoms of Long COVID.¹⁰ The Household Pulse Survey, led out of the Census Bureau, in partnership with CDC, is one of the first federal data systems to collect information on Long COVID and will be a valuable resource to understand disparities within the U.S. population.

The Health Resources and Services Administration (HRSA) is administering the National Survey of Children’s Health Longitudinal Cohort Study (NSCH-LC). By leveraging the large nationally- and state-representative sample of the NSCH, the NSCH-LC will be among the only national studies with pre- and post-pandemic information on children and youth, including racial and ethnic minority groups and children with special health care needs.

Individual-Level Incidence and Prevalence

Many of these same studies detailed above and in Appendix D also provide estimates of the individual-level risk of developing Long COVID. Many of these studies include persons without evidence of SARS-CoV-2 infection as a comparison group. Comparison of the incidence of Long COVID-19 conditions and symptoms between persons with and without COVID-19 provides an estimate of both relative and absolute risk. Although each research platform can provide estimates by subpopulations, the subpopulations included in each varies. The multiple studies across CDC, CMS, NIH and the VA capture a wide group of populations and subpopulations, while the longitudinal study at HRSA is focused on children and is expected to provide multiple independent estimates of the risk of Long COVID as well as risk disaggregated across multiple factors.

Anticipated Impacts of Research

Evidence generated by surveillance and epidemiology is useful for the public, patient groups, health care personnel, health care systems, patient groups, and policy makers.

Synthesized information on Long COVID is being analyzed and shared through peer-reviewed publications, news media, social media, webinars, professional associations, and websites aimed at professional and general audiences.

Evidence from surveillance and epidemiology studies is used by the public to understand individual risk and make informed decisions, by health care systems and service providers to project and plan for human, financial and infrastructure resources, and by policy makers to similarly plan for resources and to develop and promote effective programs and services.

Many of these studies will also measure whether COVID-19 can result in new disease states or exacerbate pre-existing disease. Studies from both the VA and CDC have already documented increased occurrence of many chronic diseases, such as heart disease, diabetes, and kidney disease.¹¹ Understanding the impact of Long COVID on behavioral health (mental health and substance use), quality of life, activities of daily living and any resulting disability is vital to understanding the overall impact on society, health care systems, and persons with Long COVID. Some studies are directly assessing the impact of Long COVID resulting in disabilities either through detailed abstraction of medical records, or through direct patient reported outcomes.

Principal Research Initiatives

The VA initiated the COVID-19 Observational Research Collaboratory Long-term Outcomes Study (CORC-LTO) to investigate outcomes up to 36 months after SARS-CoV-2 infection using a national cohort of over 200,000 COVID-infected Veterans along with matched controls to estimate the incidence of and risk factors for Long COVID and the impacts on specific health outcomes, including functional status and quality of life. The study used a combination of electronic health record (EHR) data and structured telephone surveys of subsamples from different time periods to document new diagnoses, symptoms, health-care related quality of life and health care utilization up to 36 months after infection.

The VA's Epidemiology, Immunology and Clinical Characteristics of COVID-19 [EPIC³] is a prospective controlled cohort study of SARS-CoV-2 infection among Veterans recruited from 16 VA medical centers, conducted in partnership with DOD. EPIC³ will describe the clinical trajectory from acute to Long COVID and examine clinical risk factors (including prior infection or vaccination) in influencing the risk for Long COVID.¹²

Several of CDC's studies using electronic health care data and patient databases have and will continue to provide estimates of incidence. For example, CDC is partnering with the American Board of Family Medicine to analyze electronic health record data from COVID-19 patients seen at approximately 700 primary care and family medicine practices to assess frequency of new symptoms and conditions among patients with COVID-19 diagnosis compared with patients with other respiratory diagnoses. CDC is also conducting analyses of several large health care data sources to provide estimates of new symptoms and conditions following COVID-19 diagnosis in outpatient and inpatient settings by patient demographic and clinical characteristics.

Another CDC study focusing on the Navajo and White Mountain Apache communities, COVID-19 within American Indian Communities at High Risk in the Southwest United States, follows people who are infected with SARS-CoV-2 for up to 12 months to assess the development and duration of symptoms, complications from infection, and the immune response to infection.

The DOD established a COVID-19 patient registry in 2020, as a pandemic response capability for clinical performance improvement in the DOD. Currently, the COVID Registry is capturing and analyzing data and information on Long COVID, conditions occurring after COVID-19 disease

and after vaccination. Current analyses will examine Long COVID diagnosis requiring a health care visit 30-180 days after COVID-19 or vaccination; number of individuals with a diagnosis associated with Long COVID; and number of individuals with each combination of Long COVID associated diagnosis (such as fatigue plus headache, plus loss of taste).

Risk Factors

Understanding what risk factors may be associated with occurrence of Long COVID is a critical research question. Both prospective cohort studies and those using electronic health care data include data on potential risk factors associated with Long COVID such as age, genders, race, ethnicity, and underlying medical conditions, including multiple co-morbidities. Those with more severe illness requiring hospitalization are at highest risk of developing Long COVID.^{13,14} Most people experiencing Long COVID were never hospitalized and so additional information on premorbid characteristics, genetics, education level, employment, and social determinants of health is necessary and is more likely to be captured in prospective cohort studies. A few electronic health care data sources can also provide residential and facility geographic information linked to measures of social deprivation or vulnerability or other measures of social determinants of health.

Important risk factors for the occurrence of Long COVID are the SARS-CoV-2 variant associated with the infection and the vaccination status of the individual. Studying how different SARS-CoV-2 variants may be related to Long COVID symptoms and conditions is important to our understanding of protective and risk factors. Because many of these studies are ongoing, they will include persons infected with SARS-CoV-2 at different waves of the COVID-19 pandemic and will capture infections with different variants. Vaccination has also been observed to decrease the risk of an individual developing Long COVID.¹⁵

“Like so many other health-related struggles in the pandemic, Long COVID illustrates the underlying, fundamental challenges with our health care system. More urgent attention and action to its reform is a priority for pandemic preparedness.”

—State Epidemiologist

Principal Research Initiatives

CDC’s Immune Response to SARS-CoV-2 among patients in Louisiana follows patients recovering from COVID-19 to assess longer term clinical and immunity related outcomes up to one year after the beginning of the illness. The study includes a subgroup of COVID-19 patients hospitalized for severe COVID-19 illness. Multiple virologic and immunologic specimens are collected during acute illness, and then patients are followed for one year to determine what acute factors are correlated with adverse longer-term outcomes.

The longitudinal observational studies of the NIH RECOVER Initiative provide a robust scientific platform and infrastructure for systematic and ongoing long-term assessments of Long COVID in highly diverse populations. With its national scale, standardized methodologies, biospecimen

collection, comprehensive data, and studies of molecular pathogenesis, RECOVER will be critical for understanding the risk factors for developing Long COVID and informing development of diagnostic, treatment, and preventative strategies. RECOVER's EHR-based studies, which leverage health records from tens of millions of diverse patients across the lifespan, including pre-exposure health records, are also ideally suited for identifying risk factors for Long COVID.

In association with CMS, the FDA is using Medicare claims data to study the frequency of possible Long COVID health outcomes and the risk factors associated with the occurrence of these outcomes among Medicare Beneficiaries who were discharged from a hospital with a COVID-19 diagnosis.

Protective Factors, Including Vaccination

Protective factors can help guide public health messaging and efforts to prevent Long COVID. Potential protective factors under investigation include pre-existing health status, COVID-19 treatments such as Paxlovid™ (nirmatrelvir 150 mg and ritonavir 100 mg), and vaccination.

Vaccination is perhaps the most prominent of protective factors currently under investigation. Evidence is emerging that vaccinated people who are subsequently infected with SARS-CoV-2 are about less likely to report symptoms of Long COVID than people who received one dose of COVID-19 vaccine or were unvaccinated in the short-term (four weeks after infection), medium-term (12 to 20 weeks after infection) and long-term (6 to 12 months after infection).^{11,15-18}

Vaccine effectiveness studies measure the effectiveness of the COVID-19 vaccine in preventing infectious, symptomatic illness, hospitalization and death, and the acute outcomes of SARS-CoV-2 infection.¹⁹ With the recognition of Long COVID as an outcome from SARS-CoV-2 infection, many of these studies are including longer follow-up of participants to estimate the effectiveness of prior COVID-19 vaccination in reducing Long COVID among persons infected with SARS-CoV-2. Most studies to date have focused on adults, with only a few including the adolescent population. In addition, studies have not reported results by subpopulations or underlying medical conditions or risk factors. In addition to vaccine effectiveness studies, many of the studies in Appendix D include collection of information on COVID-19 vaccinations and boosters. Some of this is through available electronic health data, other directly reported by the patient, and other with linkage to state vaccine information. Some studies will be able to examine if COVID vaccination prior to SARS-CoV-2 infection reduces the occurrence of Long COVID, and others if COVID-19 vaccination after SARS-CoV-2 infection reduces on-going Long COVID symptoms. Importantly, studies will also consider the impact of COVID-19 vaccine dose and boosters on Long COVID.

Principal Research Initiatives

The FDA is collaborating with the VA and CMS to study the safety and effectiveness of vaccines and Long COVID. The FDA and the VA are describing the main medical outcomes associated with Long COVID and their severity, estimating the incidence of Long COVID among U.S. Veterans, selecting among all potential Long COVID outcomes, those more likely to be

associated with prior COVID-19 than with other respiratory infection, and lastly, evaluating potential risk factors for Long COVID. CDC has developed multiple longitudinal cohort studies that will assess vaccine effectiveness in adults and children and has worked to incorporate specific objectives that will assess Long COVID outcomes (including ongoing symptoms, health status, disability, missed work, and missed school) in similar ways across these studies.

Validation of Operational Definitions of Long COVID in Real-World Data Sources

The validation of operational definitions of Long COVID, for different purposes, in real-world data sources considers that there are a wide range of physical and behavioral health consequences that can follow SARS-CoV-2 infection. To operationalize the definitions, many studies look for evidence of COVID-19 and SARS-CoV-2 infection determined through either medical record review or abstractions, confirmation of SARS-CoV-2 test results, or identification of cases in other electronic health care data, and then look for new or persistent symptoms or conditions to identify cases of Long COVID. One recent approach to operationalize a definition has included the use of machine learning using large electronic health care data to identify Long COVID clinic patients.²⁰ Since October 2021, there is an ICD-10 code (code U09.9, Post COVID-19 condition, unspecified) for classifying diagnoses and reason for visits in all health care settings. The ICD-10-CM code for Long COVID is gaining acceptance and also provides a method to assess and possibly validate Long COVID definitions.²¹ Further validation of operational definitions in real-world data sources will include linkage of patient reported outcomes with electronic health care data in prospective cohort studies.

4. Long COVID and Overall Well-Being

The persistent health effects of COVID-19 have broad ramifications. In addition to the discrete physiologic effects of Long COVID outlined previously, longer-term symptoms can have serious impacts on important aspects of life that are not captured in clinical diagnoses or self-report of individual symptoms. These include impacts on quality of life, education, employment, disability, mental health and substance use challenges, and caregiving. Persistent symptoms may affect quality of life, and patients experiencing severe fatigue or cognitive symptoms and impairment (also known as “brain fog”) may have trouble with schooling or employment and may require caregiving from a family member or professional. These effects in turn can have severe economic impacts on individuals with Long COVID and their families. Although outcomes of COVID-19 have been found to be less severe in young people and current data show that the prevalence of Long

Core Research Questions

- What are the impacts of Long COVID on
- Health related quality of life
 - Employment, insurance, disability, and socioeconomic status
 - Educational and developmental outcomes
 - Caregivers and families?

Why Is This Important?

The wider impacts of Long COVID are important to patients and families and to the local, state, and federal organizations responsible for supporting children's health and education, persons with disabilities, families and caregivers, and unemployed persons. Such information will be critical for developing policies regarding support for patients, students, and families with Long COVID and for planning programs to help patients recover and regain productive schooling or employment.

Information is developing rapidly on the medical effects of Long COVID, and large representative studies from the United States and other countries are beginning to allow for population-based estimates. With respect to effects on development, educational outcomes, employment and long-term disability, data from individual patients has documented the profound and prolonged effects for some children and adults, but at this time we lack representative data to inform guidelines or policies at this time.

COVID is low²², Long COVID can occur in children and may impact normal development; if not mitigated or otherwise addressed, these effects may have a long-lasting impact. The RECOVER Initiative is developing a cohort of children to study such issues. Family caregivers of people with Long COVID may be at risk for secondary effects, including psychological stress and economic impacts if they must reduce their paid work. From a societal level, it is important to capture the magnitude of these impacts, which may be as important as the direct health impacts for many individuals and their families. The COVID-19 pandemic and its burden of infection has already had detrimental effects on the physical and behavioral health and financial well-being of the population. Overall, the impact of Long COVID will likely compound these existing repercussions, reverberating in every dimension of our lives, as Long COVID does not only impact the health and well-being of those directly affected with this disease, but may have consequential ramifications on labor force participation, economic productivity, and societal well-being.

Efforts to address these questions take a variety of approaches. Some cohort studies of affected patients are adding questions related to employment, schooling, and income. Many federally sponsored national health surveys are beginning to include questions on past SARS-

CoV-2 infection. Relevant federal agencies are tracking change in outcomes, such as education and employment over the pandemic period. There are a few national databases for tracking child development, education, or employment. Some researchers are attempting to link these databases to clinical databases to learn more about these factors. Furthermore, policy research is important to enable and ensure alleviation of impacts based on traditional knowledge gained. Thus, while pandemic impacts on many of these outcomes have been reported, it can be difficult to separate out the direct effects of Long COVID from the disruption caused by COVID-19 or the indirect effects of pandemic disruption to child development, schooling, families, and employment. Detailed work in survey research is therefore critical.

Health-Related Quality of Life

Individual symptoms may not adequately capture the overall impact on patients of an illness like Long COVID, which may be accompanied by multiple symptoms affecting many activities.²³ Several federal research agencies are funding large, longitudinal cohorts involving either patients with new COVID-19 or patients meeting some diagnostic criteria for Long COVID. These include the RECOVER cohorts funded by NIH, the EPIC³ cohort of Veterans funded by the VA, the parallel DOD study of active-duty military, and multiple studies from CDC that use standardized instruments for collecting patient-reported outcomes. All three of these efforts are including validated self-reported quality of life outcomes in addition to other more specific outcome measures. Populations included in these studies include a broad range of geographic locations, racial and ethnic, and sociodemographic groups and settings.

Principal Research Initiatives

The VA has also launched the COVID-19 Observational Research Collaboratory Long-term Outcomes Study (CORC-LTO) to investigate the longer-term effects of SARS-CoV-2 infection in a nationally representative sample of SARS-CoV-2 infected Veterans and controls. Patient surveys will include quality of life measures along with more specific symptom scales. The methods for identifying the cohorts of persons with Long COVID vary somewhat by study, as does the presence and nature of any control population. Nonetheless, this portfolio of projects will provide estimates of health-related quality of life (HRQOL) in Long COVID for a proportion of the U.S. population in the near term.

Data are much more limited for children. The RECOVER Initiative has as its goal to enroll a pediatric cohort of approximately 19,000 children. The Pediatric COVID Outcomes Study (PECOS) led by the Children's National Hospital in collaboration with NIH's National Institute of Allergy and Infectious Diseases (NIAID) will examine the longer-term effects of COVID-19 and multisystem inflammatory syndrome in children (MIS-C), including health-related quality of life and social impacts for participants and families and caregivers. Finally, the Maternal and Child Health Bureau (MCHB) of the Health Resources and Services Administration (HRSA) is supporting the National Survey of Children's Health Longitudinal Cohort Study (NSCH-LC), which aims to produce publicly available data on the longer-term effects of the COVID-19 pandemic on children and families in the United States, including their quality of life. In 2023, MCHB will follow up with the parents and caregivers of approximately 60,000 children from birth through age 17 years, who were originally interviewed right before the pandemic in 2018 to 2019 for

Health Equity Considerations

Factors such as health care access and use, occupation, and gaps related to education, income, and wealth are associated with higher rates of COVID-19 infection, hospitalization, and death among racial and ethnic minority groups. Implications of Long COVID on such factors affecting health equity could further exacerbate disparities, particularly among racial and ethnic minority and socioeconomically disadvantaged communities who have been historically underserved.

the NSCH. As part of the 2023 data collection, the NSCH-LC will collect data on children’s mental health diagnoses and behavioral problems, impact of children’s health on their quality of life, children’s education and young adults’ employment outcomes, as well as family-level employment impacts. The NSCH-LC will also have information on children’s chronic conditions to assess the impact of Long COVID on children with prior chronic conditions.

Employment, Health Insurance, and Other Economic Impacts

Data on the effects of Long COVID on employment, health care coverage, medical costs, and loss of personal income are far more limited than data regarding the effects on health outcomes. Current efforts to assess these impacts include some population-based surveys of Veterans; a variety of study cohorts of individuals with Long COVID that include questions on one or more of these outcomes; and some employment datasets that are being augmented or linked to try to identify patients with Long COVID. Three Department of Labor (DOL) programs are trying to fill in gaps. Retaining Employment and Talent After Illness/Injury Network (RETAIN) anticipates enrolling 15,900 working age participants from health care settings with a work limiting illness or injury including Long COVID with an emphasis on individuals who are medically underserved. These data may help determine whether early coordinated services will improve employment outcomes for people experiencing work disabilities from Long COVID. The DOL Office of Workers Compensation Programs collects information on workers compensation claims, including for federal employees who contract COVID-19 as part of their duties. Another DOL Survey of Occupational Injuries and Illnesses (SOII) estimates nonfatal occupational injuries and illnesses across 200,000 employers in the private and public sectors (state and local government). Although data to date do not include a specific mention of Long COVID, trends may be inferred from COVID-related cases that require days away from work. Also, the NSCH-LC (previously mentioned) will collect data on the impact of children’s health on young adults’ employment outcomes, as well as family-level employment impacts. CDC is funding a study to evaluate Long COVID in U.S. state workers’ compensation systems. The study is focused on essential and public-facing workers (such as health care, public safety, retail industries) in a detailed population of workers for six states (California, Illinois, Michigan, Ohio, Washington, Wisconsin) and a broader sample of 27 states through the Workers Compensation Research Institute (WCRI) for up to a two-year period (January 2020 to 2022).

“People with Long COVID are experiencing mental health harm as the world returns to normalcy. It is difficult for children with Long COVID to return to schools that no longer have mask mandates. It is difficult for someone with Long COVID to return to a workplace that has removed accommodations like remote work or masking.”

—Public Health Administrator

Education and Development

The COVID-19 pandemic had profound impacts on education from pre-school through post-graduate education, due to suspension of in-person classes at the height of the pandemic, prolonged remote learning, disruptions among families with COVID-19, and illnesses among teachers and staff. Most of these effects are due to policies imposed because of the pandemic or to direct effects of illnesses. Little data currently exist on the specific effects of Long COVID on educational outcomes, with most coming from anecdotal reports from patients. Because the prevalence of Long COVID in school-age children and adolescents appears low,^{22,24} national surveys may have a hard time capturing this effect and distinguishing it from other pandemic-related disruptions.

Although Long COVID was first recognized in adults, cohort data and national survey data confirm that children and young people do experience post-COVID-19 conditions. Initial data indicate children may be less affected than adults, but data are limited.²⁵⁻²⁸ Attributing symptoms to Long COVID is complicated by the fact that COVID-19 in children may be missed due to milder or more general symptoms that could be overlooked. Studies have shown that Long COVID can have a negative effect on quality of life for children and adolescents by limiting physical activity and creating feelings of distress about symptoms, behavioral health challenges, and decreased school attendance and participation. Improved study design and methods are needed to better address these challenges.

Principal Research Initiatives

Two studies are expected to provide some data on developmental outcomes and impact on education. The National Survey of Children's Health Longitudinal Cohort Study (NSCH-LC) collects a wide range of outcomes from parents and caregivers of children who were ages 0 to 17 years from 2018 to 2019, including development, education, and behavioral concerns. The Pediatric COVID Outcomes Study (PECOS) will enroll up to 1,000 children and young adults in a study from Children's National Hospital in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) to examine the longer-term effects of COVID-19 and MIS-C after these patients have recovered from a COVID-19 infection. Outcomes assessed include social impacts for participants, families, and caregivers.²⁹

Disability

The Social Security Administration (SSA) Office of Disability Policy is collecting information on the effects of COVID-19 and resulting Long COVID through review of disability claims with reports of COVID-19 and Long COVID, and research on the effects of Long COVID, primarily through a contract with the National Academies of Science, Engineering, and Medicine (NASEM), Health and Medicine Division (HMD) to support a Consensus Committee on the Long-Term Functional Effects of COVID-19. This effort will examine the relationship between Long COVID and Social Security's definition of disability, convening a consensus committee to study Long COVID following an HMD workshop in March 2022. This workshop discussed disparate

impacts of the virus experienced by people facing barriers and the effects on work-related functioning due to Long COVID. The Consensus Committee will study and provide information about similar topics.

The National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) within the Administration for Community Living is supporting a five-year research grant examining employment among people with physical disabilities, including a small qualitative study of how Long COVID has affected return-to-work (RTW) efforts for people with disabilities. NIDILRR also supports a three-year project on

COVID-19 pandemic-related experiences of working-age adults with disabilities. Data collection launched May, 2022 and includes a newly developed supplement on Long-COVID.

"Although the pandemic has highlighted the importance of data, this is not a new issue. The solutions are not technically hard, but the administrative and political complexity and its resource intensive nature are formidable. Continued support for comprehensive, national, public health-driven data modernization efforts are needed."

—Hospital Chief Informatics Officer

Impact on Caregivers and Family Well-Being

Data are similarly limited on impacts of Long COVID on caregivers and family well-being. The two studies of children noted earlier, The National Survey of Children’s Health Longitudinal Cohort Study (NSCH-LC) and the Pediatric COVID Outcomes Study (PECOS), are collecting information on families and caregivers. The NSCH-LC will also collect family outcomes for parents of children with Long COVID, including food security, housing, employment, and mental health of caregivers, but at this time there are no other U.S. government studies focused on family and caregivers for affected adults.

The companion report to this Plan, the Services and Supports for Longer-Term Impacts of COVID-19, provides links to U.S. government programs currently available to support those impacted by Long COVID.

5. Therapeutics and Other Health Interventions

With potentially millions of Americans experiencing Long COVID, the development and testing of strategies to prevent and treat Long COVID are public health priorities. A challenge of Long COVID is that it is likely multiple conditions with a wide range of symptoms and health effects. Therefore, it is necessary to test and develop a range of intervention and prevention strategies to

Core Research Questions

- What treatments are safe and effective for persons diagnosed with Long COVID? For which persons are they effective?
- Which treatments are ineffective or unsafe?
- What strategies will effectively prevent Long COVID?

Health Equity Considerations

Inclusive and diverse participation in clinical trials, including those typically underrepresented in biomedical research and those disproportionately affected by SARS-CoV-2 infection, helps ensure that the results of the research are applicable to the wide range of populations affected.

Ensuring that interventions for Long COVID are effective and accessible for diverse populations enhances future uptake and effectiveness. This includes language access and culturally competent care.

management; and the other to solicit trial proposals to identify safe and effective treatments and preventive strategies for Long COVID in those ages 18 years and over. The research is anticipated to begin by the end of 2022. The focus and design of RECOVER clinical trials are being informed through a consultative process that engages patients, clinical practitioners, and experts from academia and industry regarding symptom clusters, outcome measures, and interventions. As is the case with RECOVER longitudinal observation studies, RECOVER clinical trials will include diverse communities and populations. As our understanding of the underlying mechanisms of Long COVID improves through basic and pre-clinical research, additional candidate interventions will be evaluated and prioritized for testing.

Two federal initiatives will provide opportunities to study interventions for Long COVID in real-world settings. The VA is in the process of establishing a Long COVID Practice

address the various symptom clusters and underlying mechanisms of pathobiology and improve functioning and quality of life for persons with Long COVID. It is critically important that clinical trials are well-designed and have the scale and power necessary to generate clear evidence regarding the safety and effectiveness of strategies for treating or preventing Long COVID. This will be especially challenging due to the various definitions of Long COVID in use and lack of agreed-upon outcome measures for assessing meaningful improvements.

Principal Research Initiatives

A major component of the U.S. government efforts in therapeutics research is the RECOVER Initiative. In April 2022, NIH issued two research opportunity announcements: one for a clinical trials data coordinating center to provide overall project coordination and support and comprehensive data

Anticipated Impacts of Research

Information from Long COVID clinical trials will be important for patients, caregivers, practitioners, third party insurers, clinical care guideline developers, and policy makers.

Information will be shared through publications and professional meetings, webinars, and government websites.

Interventions are needed to improve functioning and quality of life for persons experiencing Long COVID.

Evidence regarding effective therapies is needed to inform guidelines for health care and payers.

Based Research Network to coordinate research in the growing number of VA Long COVID clinics (currently 22 and growing). This will allow real-world examination of what interventions patients are undergoing (including self-administered treatments such as supplements) and whether there are any early signals of effectiveness on safety. In addition, DOD’s EPICC observational study aims to address numerous gaps in the current understanding of COVID-19 and support the development of treatment and prevention strategies that will benefit uniformed service personnel and civilian populations.

6. Human Services, Supports, and Interventions

Long COVID impacts a person's ability to participate fully in society and introduces complex needs and challenges beyond individual or community health. The accompanying Services Report outlines the services and supports available to individuals experiencing Long COVID, health care personnel who work with and treat individuals experiencing Long COVID, individuals experiencing longer-term impacts of COVID-19, including mental health conditions and substance use challenges, and individuals dealing with losing a family member or loved one to COVID-19. In addition to understanding the landscape of federally supported services and mechanisms, researchers must also lay the groundwork to systematically collect data on the human services, supports, and interventions to address the unmet needs of individuals with Long COVID. Conceptualizing disability in Long COVID is essential for this research agenda.

Health Equity Considerations

Individuals may have a disability due to Long COVID or have a pre-existing disability in addition to Long COVID.

Individuals from underserved populations may experience multifaceted systemic barriers to accessing human services, supports and interventions for Long COVID.

Core Research Questions

- What are the human services and supports needs of individuals with Long COVID?
- What are the service delivery gaps or barriers for individuals with Long COVID in existing human services?
- What interventions can be adapted or created to meet the needs of individuals with Long COVID to promote their full participation in society?

Disability and rehabilitation researchers and practitioners and individuals with lived experience are positioned to inform a research agenda and lead future research on the human services, supports, and interventions for Long COVID.

Principal Research Initiatives

Federal agencies have initiated data collection that may address some domains of the human services, supports, and interventions for Long COVID. The only published work thus far has been related to return to work needs for

individuals with Long COVID in a single small qualitative study of rehabilitation professionals on how Long COVID has affected return-to-work efforts for people with a disability, funded by the NIDILRR in the Administration for Community Living (ACL).³⁰ In the area of understanding the human services and supports need, several efforts are underway by ACL, DOL, and SSA. These will provide information from national survey data on the experiences of working-age adults with disabilities and Long COVID as well as information on participants in the RETAIN initiative.

The DOL is also conducting internal synthesized literature reviews of existing research on COVID-19 and Long COVID and developing resources for employers on interventions to meet the needs of persons with Long COVID including a forthcoming guide for employers to support individuals with Long COVID. Together this body of work will drive the emerging evidence-base on the impacts of Long COVID on an individual's ability to work, the needs and challenges relating to employment services and supports including disability benefits, and information on potential interventions to maintain employment. Multiple years are likely needed to produce and disseminate high-quality, rigorous research.

NIDILRR is funding two grantees collecting data on Long COVID as part of their larger data collection efforts. The Rehabilitation Research and Training Center (RRTC) on Employment for People with Physical Disabilities completed a small qualitative study with rehabilitation professionals on how Long COVID has affected return-to-work efforts for people with disabilities.³⁰ Research participants discussed challenges in working with “long-haulers” and recommendations included modifying workplace policies and providing individualized workplace accommodations. The University of Kansas Center for Research is administering another iteration of the National Survey on Health and Disability to document the COVID-19 pandemic-related experiences of working-age adults with disabilities. This survey includes a Long COVID supplement. Data are being collected from May to September 2022.

“Enrollment in Long COVID studies are often limited to English and Spanish speakers. Asian American, Native Hawaiian, and Pacific Islander communities speak over 100 different languages. We want to be involved too.”

—Person with Long COVID

Several agencies and programs within the DOL are collecting data on Long COVID through discretionary grants and other existing data collection mechanisms. The Office of Disability Employment Policy (ODEP) and the Employment and Training Administration in DOL and the SSA jointly administer the Retaining Employment and Talent after Injury/Illness Network (RETAIN) initiative. RETAIN programs in five states (Kansas, Kentucky, Minnesota, Ohio, Vermont) target individuals with work-related or non-work-related injuries and illnesses, including Long COVID, who are employed or, at a minimum, in the labor force when the injury or illness occurs. ODEP collects a comprehensive set of administrative data from each of the RETAIN states that includes information on individuals' primary and secondary injury/illness ICD-10-CM codes (including the ICD-10-CM code for post-COVID-19 conditions), demographics, socioeconomic indicators, program characteristics and employment outcomes. This data

collection is underway. Also, ODEP’s Employer Assistance and Resource Network on Disability Inclusion is conducting meta-analyses of existing research on COVID-19 and Long COVID and developing resources for employers on how to support individuals with these conditions.

As noted previously, the SSA sponsored the Health and Medicine Division of the National Academies of Sciences, Medicine, and Engineering (HMD/NASEM) to conduct a public workshop on the Long-Term Health Effects from COVID-19 and Implications for the SSA in March 2022. A proceeding of the presentations and discussions at the workshop will be prepared.

HHS’s Office of the Assistant Secretary for Health is sponsoring a human-centered research project to better understand Long COVID, termed Health+. The approach works directly with patients experiencing Long COVID and associated conditions, caregivers, frontline workers, and those with lived experience. The goal of Health+ Long COVID is to generate insights with actionable opportunity areas to improve the quality of care and life.

7. Health Services and Health Economics Research

As the world learns more about Long COVID and discovers ways to diagnose, treat, and manage its effects, it is also important to learn how best to provide person-centered health care for people living with Long COVID in the context of co-existing illness and risk factors including social risks. The science of how care is delivered and how care delivery can be improved is called health services research, including mathematical modeling. Health services research will help the nation improve the quality, safety, patient-centeredness, and value of Long COVID care. It will also allow us to understand if that care is accessible to all who need it and if not how to expand access and ensure equity.

Core Research Questions

- What is the current level of access to care for persons with Long COVID?
- What are the barriers to care for persons with Long COVID?
- How can the quality of care for persons with Long COVID be improved?
- What are the best models of care for Long COVID, and how can those models be more widely adopted?
- How do we leverage primary care to diagnose and manage the care of people with Long COVID in collaborative care models that provide effective access to needed specialty services?
- What are the impacts of Long COVID on health care utilization?
- What are the medical costs of Long COVID for individuals, families, communities, the health care system, states, and the nation?
- How can we improve the financing of Long COVID care in the United States.?
- What are the broader economic impacts of Long COVID?

For evidence-based health policy, decision makers must resolve outstanding questions including: which health services are needed, who receives Long COVID health care services, how the services will be financed, and the total cost of the care? Health economics research can help address these questions.

Access to Care, Models of Care, Quality of Care

The U.S. government will do more to examine access and barriers to care, models of care, and quality of care for persons with Long COVID. Health care services include access to acute care, outpatient services, behavioral health, and supportive services.

Principal Research Initiatives

The VA has led the nation in thinking systematically about how best to provide coordinated care for Veterans living with Long COVID, which is helping to inform how to treat the general public. The VA has conducted a baseline assessment of the Long COVID-19 care delivery models currently used in different regions and facilities across the country. Their initial and on-going evaluations of Long COVID care delivery models, including the use of Long COVID multispecialty clinics, may provide valuable lessons for the rest of the nation. With the establishment of a Long COVID Practice Based Research Network, the Veterans Health Administration (VHA) will begin to compare the outcomes of different care models within and between clinics.

CDC is funding the Long COVID and Fatiguing Illness Recovery Program, which aims to improve the health of patients in underserved communities who have Long COVID and other complex chronic conditions with similar symptoms, such as myalgic encephalomyelitis and chronic fatigue syndrome (ME/CFS) and other post-infectious fatiguing illnesses. Embedded in the program is a randomized trial of online educational interventions for primary care providers in a Federally Qualified Health Center, to support their management of long COVID and associated conditions. The Long COVID and Fatiguing Illness Recovery Program will provide guidance on how online participatory learning and mentoring can make primary care more effective in treating Long COVID and accelerate the delivery of evidence-based care

Health Equity Considerations

As in all forms of health research, it is critical to consider equity when working to understand health care access, barriers to care, effective models of care delivery, and the quality and safety of care. Analysis of health care use, medical costs, and broader economic costs must also consider domains of equity.

Individuals who are medically underserved and historically marginalized communities whose perspectives and needs must be included in health services and economics research include but are not limited to racial and ethnic minority groups, people living in rural areas, people with disabilities, people with limited English proficiency and LGBTQ+ people. In addition, research must consider Long COVID care for people of all age groups, people who are or who want to become pregnant, and all genders.

CDC is conducting an on-line needs assessment of health care professionals to identify information gaps around Long COVID. This information will be used to inform educational and outreach materials for health care professionals.

AHRQ, along with other HHS and other government agencies, is leveraging health information technology to collect real-world data to better understand the impact of Long COVID on health outcomes in diverse populations. AHRQ in partnership with NIDDK is developing and testing three open-source, Substitutable Medical Applications, Reusable Technologies (SMART®) on Fast Health care Interoperability Resources (FHIR®) electronic care (e-care) plan applications for clinicians, patients, and caregivers that include standardized data elements to study and manage Long COVID. AHRQ is also developing living clinical decision support to build the capacity to readily bring evolving evidence on Long COVID to the point of care. This living CDS will be freely available on AHRQ's CDS Connect web-based platform.

Testing and Laboratory Capability

Laboratory testing in clinical medicine (for diagnostic purposes) and public health (for example, needed for screening and surveillance) is critically important to render care to patients and to guide interventions to communities. As highlighted by the pandemic, testing outside of the laboratory in other clinical venues, pharmacies, and in homes complements laboratory-based testing by enhancing access, efficiency, and speed. Systems and operational

Anticipated Impacts of Research

- The results of health services research are relevant to health care professionals, public and private health care delivery organizations, payers, public health, and health services researchers
- Information from this research will be important for the growing number of individuals and caregivers seeking to make informed decisions about services
- Information will be shared through publications, professional meetings, professional associations, webinars, and government websites
- When implemented, the findings from health services research will guide the expansion of equitable access to effective, safe, high-quality, high-value, and patient- and family-centered Long COVID care
- Care will be inclusive of rehabilitation and therapies to ensure full participation in society. Tremendous potential exists for this research to prevent further marginalization and lead to more equitable outcomes and societal participation by individuals who experience Long COVID
- The findings from health economics research will allow local, state, and federal policy makers to make informed decisions about financing Long COVID care and ensuring effective support for individuals, families, and communities with Long COVID

research are needed to ensure testing is available in a timely fashion, that it generates accurate results based on sufficient and optimized test performance, and that it delivers those results primed to aid decision making for the patient and public health purposes. The pandemic highlighted some previously unanticipated systems research questions in manufacturing, supply chain, test performance (e.g., balancing test accuracy to diagnosis infection vs. the need to determine contagiousness), results reporting, and integration of data across systems.

“Where should you tell someone with Long COVID to go? What if they don’t have a doctor that they regularly see? What if they don’t have health insurance? Even when there is a Long COVID expert in the area, there is a wait time of at least four months to be seen.”

—Community Health Care Worker

Health Care Utilization, Medical Costs, Financing Models, and Broader Economic Impacts

Although there is ongoing research on the economic impacts of COVID-19, much work remains to examine health care use, medical costs, options for financing Long COVID care, and the broader economic impacts of Long COVID. As data and coding systems advance, many types of health economics research will become easier and more accurate.

Principal Research Initiatives

CMS, in partnership with the HHS Office of the Assistant Secretary for Planning and Evaluation are conducting analyses to document health services use by Medicare beneficiaries who have been diagnosed with COVID-19.

Prior to the pandemic, the Health Resources and Services Administration (HRSA) began a longitudinal, observational cohort study that enrolled approximately 60,000 children and their families. By collecting information on COVID-19 infections and the emergence of Long COVID in these families, along with information about health care use, health care expenses, and experience of care, this study may provide some important information on pediatric health care utilization for Long COVID, costs to families, and the accessibility and experience of Long COVID care for families.

The VA is conducting a large, population-based study of the longer-term impacts of COVID-19 using a group of matched cases and controls to examine a range of clinical outcomes, health care utilization, and health care costs. Although not focused on Long COVID, the study will permit comparison of a subset with longer-term symptoms to patients with resolved symptoms and controls who were never infected. VHA is also establishing a practice-based research network involving Long COVID clinics (currently 22 in the VA) that will collect data on the care received and costs of patients presenting with Long COVID symptoms.

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Chapter 4: Accelerating Research and Innovation in Long COVID

The end of the declared Public Health Emergency will not signal the end of the COVID-19 pandemic.¹ Long after the more immediate effects of the pandemic, the long-term impacts on the health of the nation will continue for years to come. The scale of Long COVID morbidity and the breadth of its clinical manifestations represent an unprecedented, but not insurmountable, challenge.

Federal agencies have already launched ambitious and significant research efforts to understand Long COVID and ameliorate its devastating impacts, as demonstrated in Chapter 3 and Appendix D. The current Long COVID research enterprise demonstrates solid scientific foundations, dedicated researchers, and sound partnerships. However, we acknowledge that conventional research endeavors are not sufficient to address the serious and urgent challenges posed by post-infectious illnesses of pandemic proportion. The current lag in research being translated into practice is simply not acceptable in the current environment. We must aggressively innovate how we do research and accelerate the pace of research to meet the challenge of the moment. We must collaborate with private research entities and the pharmaceutical industry to focus our efforts on the highest priority research questions. We need to rethink how we disseminate research and translate findings into practical solutions more quickly.

Long COVID demands a comprehensive, multi-disciplinary, effective approach, leveraging the resources of the U.S. research enterprise and collaborative efforts across the U.S. government coupled with strong public and private partnership. Beyond the U.S. research enterprise, the global health research community and international health organizations play an important role. This chapter is outlined in three sections. The first section, Research Priorities, describes priority research areas for both public and private research, including academia. The second section, Strategic Actions, describes actions that the U.S. government will take to not only drive public-sector research but also accelerate private-sector research, through funding, collaboration, and data sharing; disseminate research; and translate research into policy and program. The final section describes Implementation.

Research Priorities for Long COVID

The following are the research questions and topics that we deemed to be of highest importance and with the greatest potential to yield early, safe, and effective benefit for persons with Long COVID. This Plan is a call to action to enhance research efforts as well as to rapidly deliver evidence and data in these areas. Addressing the challenge of Long COVID and the most pressing research priorities will require an urgent and coordinated all-hands-on-deck whole-of-government approach, including robust public-private partnership. Research questions that can

be investigated with current funding are underway. Additional federal investment will be necessary in fiscal year 2023 and beyond as well as commitment from partners in the private sphere include academia, the pharmaceutical industry, private research organizations, public health entities, and medical professional organizations. To most efficiently and effectively accelerate research on Long COVID, it is particularly important to leverage knowledge and expertise (of affected individuals and researchers) gained from research of conditions with similarities to Long COVID including dysautonomia, myalgic encephalomyelitis and chronic fatigue syndrome (ME/CFS), and other post-infectious illnesses.

While this is a call to action to the U.S. research enterprise, this Plan also lays out the U.S. government commitment in these areas. Appendix E describes new and enhanced activities that the U.S. government intends to take within the areas, which will build on the portfolio of ongoing research described in Chapter 3 and Appendix D, and documented in over 100 published U.S. government Long COVID research articles.

1. Characterizing the Full Clinical Spectrum of Long COVID and Diagnostic Strategies

- a. Convening public and private partners to better align interim definitions of Long COVID for clinical, surveillance, and research
- b. Further study of the impact of SARS-CoV-2 infection on development and clinical course of new onset chronic disease states including diabetes mellitus, kidney disease, heart disease, gastrointestinal disease, neurologic disease, hematological (blood) illnesses, and other potential long-term consequences
- c. New research that disentangles the broader longer-term effects of the pandemic on physical and behavioral health (i.e., mental health and substance use challenges) from those of SARS-CoV-2 infection, for example, distinguishing the neurocognitive and behavioral effects on children and adolescents of infection with SARS-CoV-2 from the cumulative effects of loss of access to in-person early childhood education and learning environments
- d. Leveraging of existing research on post-infectious chronic illness to support identification of commonalities and differences with Long COVID, accelerate research and innovation, as well as prepare for the long-term consequences of future pandemics
- e. Further research to identify clinical screening tools and diagnostic tests and assays

2. Pathophysiology

- a. Deeper understanding, from the molecular to system levels, of Long COVID within the broader context of post-infectious chronic conditions and other diseases that may have infectious origins, including dysautonomia and ME/CFS

3. Surveillance and Epidemiology

- a. Coordinated and enhanced surveillance to characterize and understand Long COVID, the potential health impacts, and provide information for public health and health care planning
- b. Additional studies of Long COVID risk factors, health trajectories and outcomes that are inclusive of age, gender, race, ethnicity, geographic location, socioeconomic status, insurance coverage status, pregnancy status, and disability status, enabled by new capabilities in data analytics
- c. Studies that can rapidly adapt to examine risk and protective factors as they emerge, including new variants, vaccinations, repeat infections, and therapies for COVID-19 on risk of Long COVID

4. Long COVID and Overall Well-Being

- a. Comprehensive studies of the effects of Long COVID on educational outcomes in children and youth, with a focus on vulnerable populations, including racial and ethnic minority groups, those who are economically disadvantaged, and those in rural communities
- b. Research, including qualitative and mixed methods studies, to understand the impact of Long COVID on health-related quality of life, behavioral health, employment, disability determinations, education and development, and the impact on caregivers and family well-being, especially among disadvantaged groups

5. Therapeutics and Other Health Interventions

- a. Expanded and expansive portfolio of studies on the effectiveness of therapeutics to prevent and treat Long COVID to include antivirals, anti-inflammatory, immune modulators, and other existing or new treatments, based on molecular level understanding and disaggregated by age, gender, race, ethnicity, and pregnancy status
- b. Further studies to subtype Long COVID including characterization of distinct sub-entities with distinct set of risk factors and outcomes and evaluation of treatment strategies for these sub-types

- c. New studies of non-pharmacologic interventions to prevent and treat Long COVID

6. Human Services, Supports, and Interventions

- a. New work in identifying and evaluating optimal person-centered models of care for people with various forms of Long COVID in the context of co-existing illness, risk factors, and social and community circumstances
- b. Comprehensive studies of human services and supports interventions, including disability services and caregiver supports, to ensure individuals living with Long COVID can fully participate in their communities

7. Health Services and Health Economics Research

- a. New studies, including systems research, to develop, implement, and evaluate models of care delivery to enable primary care providers to effectively manage Long COVID and associated conditions in partnership with specialty care when needed and community service organizations
- b. Research to address barriers to effective care in underserved communities and models of care designed to address and eliminate health inequities
- c. New work in identifying and evaluating optimal models of care for people with various forms of Long COVID and associated conditions
- d. Rapid and ongoing synthesis of new evidence to distill existing research into actionable insights guiding care of people with Long COVID, including cost-effectiveness modeling of prevention and treatment strategies
- e. Expanded work in impact of Long COVID on and economic costs of Long COVID to the health system, human services and supports programs, and society

Strategic U.S. Government Actions for Long COVID Research

The following are the structures and processes to be created within the U.S. government specifically to drive the research described above. Innovation and comprehensive approaches will drive an accelerated and enhanced research portfolio. To address the urgency of this moment and the monumental challenges of Long COVID, HHS will need to work with private partners and with Congress to fund and support action on these items.

Establish the HHS Office of Long COVID Research and Practice to lead efforts across the U.S. government and with private partners. On the basis of the April 5, 2022 Memorandum, the HHS Secretary directed the Assistant Secretary for Health to lead a U.S. government response, who, in turn, formed a Long COVID Coordination Council with two workgroups. To formalize

and further the work, HHS will transition to more permanent high-level leadership by designating the Assistant Secretary as the Long COVID Coordinator to oversee the newly created HHS Office of Long COVID Research and Practice. The Office will be charged with the implementation of the National Research Action Plan on Long COVID and the Services and Supports for Longer-Term Impacts of COVID-19 Report. The Office will be responsible to update the Plan on a regular basis. To stand up and maintain the Office and ensure the needed long-term focus on Long COVID dedicated funding for permanent staff and operations will be necessary.

The Coordinator will maintain the Long COVID Coordination Council (established in May 2022 in response to the Presidential Memorandum on Addressing the Long-Term Effects of COVID-19) as a mechanism for coordination and communication across the government. The Coordinator will also establish the Secretary's Advisory Committee on Long COVID. The Coordinator and the Office will establish methods to ensure standardization and accountability across all U.S. government conducted or sponsored research, including the following

- **Harmonize an approach in U.S. government-sponsored Long COVID cohort research to include measurement of the broader impacts of the disease** (such as development, education, employment, disability, and health-related quality of life)
- **Incorporate the voices of patients and others with lived experience into research from inception to completion and including dissemination.** The Coordinator will comprehensively place the lived experiences of patients at the core of the research enterprise to inform development of research priorities, research design, execution, interpretation, and dissemination. Building on existing model patient engagement strategies, the Secretary's Advisory Committee on Long COVID will establish principles for patient and stakeholder inclusion in research and identify and implement strategies to address barriers to engagement of underrepresented groups and to prioritize the

Federal Government Efforts That Will Improve Identification of Long COVID and Connect Patients to Care

- Convene public and private partners to better align the definitions of Long COVID and develop agreed upon terminology for clinical care, surveillance, and research
- Develop comprehensive and equitable Long COVID diagnosis, care, and treatment guidance
- Make available tools to help individuals recognize symptoms of Long COVID and to discuss their symptoms with their health care providers
- Advance research that helps separate the broader effects of the pandemic on an individual's physical and mental health from those of the initial SARS-CoV-2 infection and re-infections
- Use findings from Health+ Long COVID patient-centered research to improve the way individuals access and receive health care and services.

voices of patients disproportionately affected by COVID-19 and Long COVID. The Coordinator will be responsible for implementation and monitoring of these strategies.

- **Implement strategies to measure and mitigate inequities in Long COVID.** This includes continuing efforts to collect detailed information on age, gender, race, ethnicity, rurality, economic disadvantage, insurance coverage, pregnancy status, and disability status in all U.S. government-conducted and sponsored research in Long COVID, in line with Office of Management and Budget (OMB) and other U.S. government policies, and ensuring diverse representation in all research activities including clinical trials, with focused efforts to identify and address barriers to participation. This also includes ensuring access to U.S. government-funded clinical trials and proposed Centers of Excellence.
- **Identify strategic collaborations between public and private entities needed to accelerate Long COVID diagnostic and therapeutic research and identify and address barriers to collaborations.** Host convenings of research partners, including government, public health, academia, pharmaceutical industry, national pharmacy chains, and health systems to initiate collaborations.
- **Further harmonization of and consensus on clinical care, surveillance, and research definitions of Long COVID, described above.** The definitions will evolve as our understanding of Long COVID progresses, and while multiple definitions for different purposes will be needed, developing consensus on evidence-based definitions will facilitate clinical care, surveillance, and research, including clinical trials, epidemiology, and health services research.
- **Translate research into evidence and guidance.** Work with partners to rapidly develop comprehensive and equitable Long COVID diagnosis, care, and treatment guidance, and compile existing guidance. Develop mechanisms to synthesize new data about therapies (such as innovative drugs, rehabilitation), models of care, and services and supports so that national guidelines can be developed and updated quickly.
- **Develop and implement a strategic communications plan to share findings from Long COVID research, including evidence-based guidelines, with the broader research community, including public and private research institutions, federal and state policy makers, health care, rehabilitation, payers, industry, patients, care givers, and advocates.** An accelerated phase of generating knowledge must be accompanied by an intentional strategy to share information in rapid fashion, combat misinformation, generate and maintain momentum in implementing a shared research agenda, promote stakeholder engagement, and facilitate translation of evidence into practice. The communications plan will include strategies to ensure materials are culturally and linguistically effective and include digital resources, such as a public reporting portal and website. Simultaneously, develop and implement a plan specifically for health care personnel, services and supports providers, and policy makers to drive adoption of

effective interventions. Implementation strategies may include expanding and tailoring existing state-of-the-art tele-mentoring and practice facilitation.

- **Broadly share U.S. government research on Long COVID.** Leverage existing platforms and resources for clinical trial, genetic data, and literature (e.g., ClinicalTrials.gov, GenBank, Sequence Read Archive, and PubMed Central) to provide broad access to information about U.S. Long COVID research and the results as a foundational component of the communications plan.

Establish a framework for a multipronged approach to Long COVID surveillance. Given the medical and public health complexity of Long COVID, surveillance is best achieved through integrated approaches leveraging other data modernization initiatives, which requires collaboration with public health, health care, and developers of data collection systems. The approach needs to build on established methods and approaches to implement sustainable surveillance to monitor incidence and prevalence. Progress will be parallel to other approaches depending on innovation in electronic health record surveillance and serve as a model for surveillance of post-infectious sequelae in future pandemics. In the interim, prompt analyses of varied estimates of incidence, prevalence, and risk factors (including vaccination status) in the overall U.S. population and in various demographic groups will provide up-to-date estimates of the burden of Long COVID that can be shared publicly to guide policy-making and resource allocation. Additional funding is being requested in FY23 to support these efforts.

Build on existing programs and infrastructure to improve systems and strategies for rapid implementation of clinical trials to test existing and new diagnostic tests and therapies for Long COVID. The U.S. government, in partnership with academia, patients, health care systems, and pharmaceutical companies, developed tests, vaccines, and therapeutics for COVID-19 in record time. Continue this level of urgency, ingenuity, and flexibility in developing therapies for Long COVID; testing whether existing therapeutic interventions (both pharmacologic and non-pharmacologic) can be repurposed; and developing new therapies. Long COVID may also be considered as an area of focus for the newly formed Advanced Research Projects Agency for Health (ARPA-H). Additional funding has been requested in FY23 to support these efforts.

Engage U.S. government agencies to contribute to a coordinated effort for a national real world evidence approach, which would include Long COVID. Engage private partners (such as industry, health care systems, payers, state governmental public health and other stakeholders) to develop a prompt data sharing and harmonization approaches to address urgent knowledge gaps in Long COVID. The COVID-19 pandemic demonstrated well that coordinated, real-time, real-world evidence collection

“Once there is agreement on evaluation tools and outcome measures, we need to create a model for linkages to care. This is a critical component of anything we do and the data we are collecting.”

—Long COVID Researcher

systems need to be in place and ready for major emerging issues. The standing up of a true real-world evidence center will require coordination of EHR Vendors and large health care systems, resources, and time. Long COVID should be part of broader efforts supported by the U.S. government. For example, this effort shall leverage the computing prowess and new computational mechanisms of the Department of Energy, CDC's Data Modernization Initiative, and engagement of biomedical, clinical, and social science researchers to analyze data and generate evidence. The strategic priorities will be to understand the longer-term health consequences of SARS-CoV-2 infection and accelerate the discovery of therapeutics of Long COVID.

Develop a network of Long COVID Centers of Excellence to integrate gold-standard patient-engaged care delivery and research. Establish and engage a network of Long COVID Centers of Excellence that will advance implementation research in care delivery models that include state-of-the-art and evidence-based rehabilitation services, behavioral health, and linkages to human services and supports programs and to primary care. Funding has been requested in FY23 to grow this network.

Establish primary care networks to develop, implement, evaluate, and scale person-centered models of care to enable primary care to prevent, diagnose, and manage Long COVID. These primary care networks will work in partnership with diverse communities to determine the most effective strategies for improving access, quality, equity, and outcomes of care for Long COVID, integrating behavioral health and primary care, implementing stepped care and collaborative models with specialty care and Long COVID clinics, and building linkages to public health. The Long COVID Centers of Excellence and primary care networks will collaborate to help assure that all persons with Long COVID receive the level of care they need in a timely fashion and make it easier to navigate the health system. Funding has been requested in FY23 to grow this network.

Continue to prioritize the recruitment and retention of investigators tackling interdisciplinary Long COVID research. Support a diverse body of researchers and research portfolios to solve the interdisciplinary challenges facing people with Long COVID.

Overall, we must build upon lessons learned in addressing other public health crises, such as HIV, to drive innovation in terms of how research is conceived, funded, conducted, and disseminated. Research should facilitate data integration, harmonization, and novel approaches of developing synthesized and linked data that safeguard privacy and facilitates rapid research. Improved methods to synthesize findings will assist in the rapid dissemination and implementation of important research.

Implementing the National Research Action Plan on Long COVID

The National Long COVID Coordinator, supported by the Long COVID Coordination Council and in consultation with the Secretary’s Advisory Committee on Long COVID, will be responsible for coordinating the implementation of this Plan. HHS will develop regular implementation plans, including performance and progress metrics, to execute the strategic priorities and coordinate the activities of federal agencies and private partners to expedite research on Long COVID (see Appendix E for an Interim Implementation Plan). Regular reports shall be produced documenting progress made and outlining any new strategic directions and priorities that should be incorporated into the strategic plan.

Implementation of this Plan will maintain focus on the principles set forth in this report, including a commitment to health equity, partner engagement, and orientation of the research effort to improve patient care and outcomes. Strategic plans and implementation plans must reflect the recommendations of, and contribute to, the overall U.S. government’s implementation of the Presidential COVID-19 Health Equity Task Force. These plans must push the needle in measuring and responding to health inequities in Long COVID.

While there is reason to be optimistic and an opportunity to seize the incredible momentum of the moment, there are important challenges to acknowledge and address. The COVID-19 pandemic is not over, and other threats to our nation’s health unrelated to SARS-CoV-2 continue to demand our attention. Challenges specific to Long COVID include various research approaches, complicated by distinct agency missions; the need to elevate the patient voice across the research portfolio; persistent challenges in engaging underrepresented groups into clinical research; and, most importantly, the challenge of implementing a comprehensive and coordinated research portfolio, from basic science all the way to services delivery, for a set of symptoms and conditions with emerging understanding. Nevertheless, with this Plan, the U.S. government affirms its commitment to leverage existing and future resources to implement the necessary steps to address the still-unfolding pandemic sequelae of SARS-CoV-2 infection.

References















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Appendix A: Report Abbreviations

ACL	Administration for Community Living, HHS
CDC	Centers for Disease Control and Prevention, HHS
CMS	Centers for Medicare & Medicaid Services, HHS
COCA	Clinician Outreach and Community Activity
CORC-LTO	COVID-19 Observational Research Collaboratory Long-term Outcomes
COVID-19	Coronavirus disease of 2019
CSF	Cerebrospinal fluid
DOD	Department of Defense
DOL	Department of Labor
EPIC ³	Epidemiology, Immunology, and Clinical Characteristics of COVID-19
EPICC	Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential
FDA	Food and Drug Administration, HHS
HHS	Department of Health and Human Services
HMD	Health and Medicine Division
HRQOL	Health-related quality of life
HRSA	Health Resources and Services Administration, HHS
ICD-10-CM	10th revision of the International Statistical Classification of Diseases and Related Health Problems
INSPIRE	Innovated Support for Patients with SARS-CoV-2 Infections
LGBTQI+	Lesbian, gay, bisexual, transgender, queer, intersex
MCHB	Maternal and Child Health Bureau, HRSA, HHS
ME/CFS	Myalgic encephalomyelitis and chronic fatigue syndrome
MIS-C	Multisystem Inflammatory Syndrome—Children

MMWR	Morbidity and Mortality Weekly Report
MRI	Magnetic resonance imaging
N3C	National COVID Cohort Collaborative
NASEM	National Academies of Science, Engineering, and Medicine
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases, NIH, HHS
NIDILRR	National Institute on Disability, Independent Living, and Rehabilitation Research, NIH, HHS
NIH	National Institutes of Health, HHS
NSCH-LC	National Survey of Children’s Health Longitudinal Cohort
ODEP	Office of Disability Employment Policy, DOL
PASC	Post-acute sequelae of SARS-CoV-2 infection
PCC	Post-COVID-19 Conditions
PCORnet	National Patient-Centered Clinical Research Network
PECOS	Pediatric COVID Outcomes Study
RECOVER	Researching COVID to Enhance Recovery (NIH Initiative)
RETAIN	Retaining Employment and Talent After Illness Injury Network
RRTC	Rehabilitation Research and Training
RTW	Return-to-work
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SOII	Survey of Occupational Injuries and Illnesses
SSA	Social Security Administration
VA	Department of Veterans Affairs
VHA	Veterans Health Administration, VA

Appendix B: Contributing U.S. Government Departments

Departments			
Department of Defense (DOD)		Department of Labor (DOL)	
Department of Education (ED)		Department of the Treasury (DOT)	
Department of Energy (DOE)		Department of Veterans Affairs (VA)	
Department of Health and Human Services (HHS)*		Equal Employment Opportunity Commission (EEOC)	
Department of Homeland Security (DHS) Federal Emergency Management Agency (FEMA)		National Council on Disability (NCD)	
Department of Housing and Urban Development (HUD)		Office of Personnel Management (OPM)	
Department of Justice (DOJ)		Social Security Administration (SSA)	

HHS Divisions*

Administration for Children and Families (ACF)
 Administration for Community Living (ACL)
 Agency for Healthcare Research and Quality (AHRQ)
 Centers for Disease Control and Prevention (CDC)
 Centers for Medicare & Medicaid Services (CMS)
 Food and Drug Administration (FDA)
 Health Resources and Services Administration (HRSA)
 Indian Health Service (IHS)
 National Institutes of Health (NIH)
 Office for Civil Rights (OCR)
 Office of Global Affairs (OGA)
 Office of Intergovernmental and External Affairs (IEA)

Office of the Assistant Secretary for Administration (ASA)
 Office of the Assistant Secretary for Health (OASH)
 Office of the Assistant Secretary for Planning and Evaluation (ASPE)
 Office of the Assistant Secretary for Preparedness and Response (ASPR)
 Office of the Secretary (IOS)
 Office of the Surgeon General (OSG)
 Substance Abuse and Mental Health Services Administration (SAMHSA)

Appendix C: Terminology and Definitions

“Long COVID” is the term used in the National Research Action Plan and reflects the voice of patients. Several terms for Long COVID exist, such as Post-COVID-19 Conditions (PCC), Post-Acute Sequelae of SARS-CoV-2 (PASC) infection, and persistent symptoms, or COVID-19 consequences. While there has been progress towards a common understanding of the two technical terms (i.e., PCC and PASC) differences in understanding and usage remain. The table below provides historic information regarding some terms used, the primary source for the term along with an online reference and definition. The list is not exhaustive but demonstrates the challenges with terminology for a new, emerging set of complex, inter-related conditions and the need to promote consensus for research, clinical care, and surveillance.

Source	Term	Definition	Reference
Patients and people with lived experience; patient-researchers	Long COVID	Can be broadly defined as signs, symptoms, and sequelae that continue or develop after acute COVID-19 or SARS-CoV-2 infection for any period of time; are generally multisystemic; might present with a relapsing–remitting pattern and a progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection	How and why patients made Long Covid, ScienceDirect
Centers for Disease Control and Prevention (CDC)	Post-COVID-19 conditions (plural)	Umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection; equivalent to the lay term, “Long COVID”	Long COVID or Post-COVID Conditions CDC
Department of Veterans Affairs (VA)	Post-COVID Conditions	Post-COVID conditions are symptoms that last or start weeks or months after a person was infected with the SARS-CoV-2 virus. This is the virus that causes COVID-19. This can happen even if you didn’t know you had the virus. You may hear these conditions called long COVID, post-acute COVID, chronic COVID, or other terms. The symptoms can include tiredness, headaches, loss of taste and smell, trouble breathing, and dizziness	About Post-COVID Conditions (Long COVID, Chronic COVID) Veterans Affairs (va.gov)

National Institutes of Health (NIH)	<i>Post-acute Sequelae of SARS CoV-2 infection</i>	Ongoing, relapsing, or new symptoms, or other health effects occurring after the acute phase of SARS-CoV-2 infection (i.e., present four or more weeks after the acute infection). The definition will be revised in an iterative manner based on existing and new data, medical literature, and feedback from the scientific community	Understanding the Long-term Impact of COVID-19 in Adults (recovercovid.org)
Food and Drug Administration (FDA)	<i>Post-COVID conditions (plural)</i>	While most people with COVID-19 have resolution of their symptoms within weeks of their illness, some people experience post-COVID conditions. Post-COVID conditions are new, returning, or ongoing health problems people can experience four or more weeks after initial infection with the SARS-CoV-2 virus. These conditions have also been termed long COVID, long-haul COVID, post-acute sequelae of COVID-19, long-term effects of COVID, or chronic COVID. Post-COVID conditions have been observed in people with mild to severe COVID-19 infection, and can present with localized and systemic symptoms impacting nearly all organ systems.	FDA CERSI Lecture on Long COVID: Risk factors, Symptomology and Patient Reported Outcomes Captured Through a Novel Digital Platform by Dr. Erica Spatz & Dr. Kelli O’Laughlin - 11/09/2021 - 11/09/2021 FDA
World Health Organization (WHO)	<i>Post-COVID-19 Condition (singular)</i>	Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis; common symptoms include fatigue, shortness of breath, and cognitive dysfunction, and generally have an impact on everyday functioning; symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness; symptoms might also fluctuate or relapse over time; a separate definition might be applicable for children; recognize “Long COVID”	A clinical case definition of post-COVID-19 condition by a Delphi consensus - The Lancet Infectious Diseases
Broader Research Community	<i>Persistent symptoms or COVID-19 consequences</i>	Persistent signs and symptoms that continue or develop after acute COVID-19 for any period of time	Persistent symptoms following SARS-CoV-2 infection amongst children and young people: A meta-analysis of controlled and uncontrolled studies - ScienceDirect

American Academy of Physical Medicine and Rehabilitation	Post-acute sequelae of SARS CoV-2 infection (equates it with Long COVID)	Post-Acute Sequelae of SARS-CoV-2 infection (PASC) or Long COVID is a condition that occurs in individuals who have had COVID-19 and report at least one persistent symptom after acute illness. Long COVID encompasses a constellation of varied and ongoing symptoms – even in the same patient across time – and may include neurological challenges, cognitive symptoms such as brain fog, cardiovascular and respiratory issues, fatigue, pain and mobility issues, among others.	PASC Guidance (aapmr.org)
American College of Cardiology	Post-acute sequelae of SARS-CoV-2 Infection	PASC encompasses a constellation of symptoms that emerge or persist weeks to months after recovery from COVID-19 [referencing CDC, WHO]. Although evidence guiding the care of these patients continues to evolve, there is a need to develop common taxonomies and approaches to care that can be updated iteratively as new data become available.	2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee Journal of the American College of Cardiology (jacc.org)
American Thoracic Society	Long COVID	The term that is often used to describe these persistent symptoms. You are considered to have ‘Long COVID’ when you are still having symptoms at least 4 weeks after the initial infection. Long COVID may also be referred to by other names such as post-COVID conditions, PASC (post-acute sequelae of SARS-CoV-2 infection) or long-haul COVID.	Long COVID Patient Fact Sheet (thoracic.org)
Humana Military	Long COVID	While most people with COVID-19 get better within weeks, some continue to have symptoms—or develop new ones—after their initial recovery. The technical term for this is post-acute sequelae of SARS-CoV-2 infection (PASC), or simply “long COVID.” People with long COVID are often called “longhaulers.” A person of any age who has had COVID-19 can later develop a post-virus condition.	Long COVID resource guide (humana.com)
Infectious Disease Society of America	Post-COVID-19 Conditions (plural)	References other definitions, Long COVID, CDC, and WHO	Post COVID Conditions (e.g., Long COVID) (idsociety.org)

Wikipedia	Long COVID	<p>Long COVID is a condition characterized by long-term consequences persisting or appearing after the typical convalescence period of COVID-19. It is also known as post-COVID-19 syndrome, post-COVID-19 condition, post-acute sequelae of SARS-CoV-2 infection (PASC), or chronic COVID syndrome (CCS). Long COVID can affect nearly every organ system, with sequelae including respiratory system disorders, nervous system and neurocognitive disorders, mental health disorders, metabolic disorders, cardiovascular disorders, gastrointestinal disorders, musculoskeletal pain, and anemia. A wide range of symptoms are commonly reported, including fatigue, malaise, headaches, shortness of breath, anosmia (loss of smell), parosmia (distorted smell), muscle weakness, low fever and cognitive dysfunction.</p>	Long COVID - Wikipedia
International Classification of Diseases (ICD)-10-CM code	U09.9 Post-COVID condition, unspecified	<p><i>No definition is given, but the following are noted:</i></p> <ul style="list-style-type: none"> • This code enables establishment of a link with COVID-19. • This code is not to be used in cases that are still presenting with active COVID-19. However, an exception is made in cases of reinfection with COVID-19, occurring with a condition related to prior COVID-19. • Post-acute sequelae of COVID-19 	2022 ICD-10-CM Diagnosis Code U09.9: Post COVID-19 condition, unspecified (icd10data.com)
National Institute for Health and Care Excellence (NICE)*	Ongoing symptomatic COVID-19	Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks	Guideline COVID-19 rapid guideline: managing the long-term effects of COVID-19 (nice.org.uk)
National Institute for Health and Care Excellence (NICE)**	Post-COVID-19 syndrome	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis; it usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body; post-COVID-19 syndrome might be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed	Guideline COVID-19 rapid guideline: managing the long-term effects of COVID-19 (nice.org.uk)

Note: Adapted from the Table titled, “Commonly used terminology in the research of COVID-19 sequelae” in Munblit D, O’Hara M, Akrami A et al. Long COVID: aiming for a consensus. *Lancet Respir Med.* 2022; S2213-2600(22)00135-7. <https://www.thelancet.com/action/showPdf?pii=S2213-2600%2822%2900135-7>. Accessed June 21, 2022.

*United Kingdom National Institute for Health and Care Excellence (NICE)

**NICE also states that: “In addition to the clinical case definitions, the term ‘long COVID’ is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).”

Appendix D: Highlights of Current U.S. Government Research Portfolio on Long COVID

The U.S. government is currently conducting and supporting many studies that will contribute to the successes of the National Research Action Plan. This table contains a comprehensive list of the most prominent projects in the Long COVID federal research portfolio, including the research described in Chapter 3. This is not an exhaustive list of all Long COVID research or U.S. government supported research. The list is in alphabetical order based on the study title. Agencies that are leading and collaborating in the research are also listed. Finally, for each research study, research areas corresponding to the topic areas highlighted in Chapter 3 of this report are listed.

Study Title	Agency*	Research Areas
Advancing the epidemiological and mechanistic understanding of the neurological complications of COVID-19	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Surveillance and Epidemiology
All of US Research Program	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology
Applied Research to Address the Coronavirus (COVID-19) Emerging Public Health Emergency	CDC	Surveillance and Epidemiology Long COVID and Overall Well-Being
Behavioral Risk Factor Surveillance System (BRFSS)	CDC	Surveillance and Epidemiology
Characterization of host immune responses to SARS-CoV-2	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology

Cognitive sequelae of the biological effects of COVID-19 on the nervous system in a health disparity population	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies
Cohort study of effects of SARS-CoV-2 infection, vaccination, and immunology on gut tissue and clinical symptoms	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology
COVID-19 Neuro Databank Biobank	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Surveillance and Epidemiology
COVID-19 Observational Research Collaboratory Long-term Outcomes Study (CORC-LTO)	VA	Impacts of Illness Surveillance and Epidemiology
COVID-19 patient registry	DOD	Clinical Spectrum of Long COVID and Diagnostic Strategies
COVID-19: Predictive Immune and Airway Monitoring in Healthcare workers and Hospitalized COVID-19 patients	NIH, VA	Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology Surveillance and Epidemiology
COVID–Standardized Evaluation of Long-term Effects (COVID-SELECT)	CDC	Surveillance and Epidemiology
COVID-19: Understanding the Post-Viral Phase (COVID-UPP)	CDC	Surveillance and Epidemiology Clinical Spectrum of Long COVID and Diagnostic Strategies
COVID-19 within American Indian Communities at High Risk in the Southwest U.S.	CDC	Surveillance and Epidemiology
CSP #2028 (Epidemiology, Immunology and Clinical Characteristics of COVID-19 [EPIC3])	VA	Surveillance and Epidemiology Clinical Spectrum of Long COVID and Diagnostic Strategies

Descriptive and Analytical Study of Post-acute Sequelae of COVID-19 (Long COVID) among U.S. Veterans	FDA, VA	Surveillance and Epidemiology
Effects of Long COVID on inflammatory processes in the central nervous system	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology
Effects of Long-COVID on Maintenance and Incidence of ME/CFS	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Surveillance and Epidemiology Pathophysiology
Effects of Long COVID on Topological Mapping of Immune, Microbiota, Metabolomic and Clinical Phenotypes to Reveal ME/CFS Disease	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies
Employer Assistance and Resource Network on Disability Inclusion	ODEP	Human Services, Supports, and Interventions
Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC)	DOD	Clinical Spectrum of Long COVID and Diagnostic Strategies
Exploratory Analysis of Long COVID service use among Medicare beneficiaries	CMS, ASPE	Health Services and Health Economics Research
FindCOVID	CDC	Clinical Spectrum of Long COVID and Diagnostic Strategies
Formative Evaluation of Long COVID care delivery models in the VA	VA	Health Services and Health Economics Research
Health+	HHS, OASH	Long COVID and Overall Well-Being

Household Pulse Survey	CDC, Commerce	Surveillance and Epidemiology
Identifying Long COVID algorithms to operationalize for use in the FDA Sentinel system and other administrative claims or electronic health records data sources.	FDA, CDER	Therapeutics
Immune Response to SARS-CoV-2 among patients in Louisiana	CDC	Surveillance and Epidemiology
Immunophenotyping in a COVID-19 Cohort (IMPACC)	NIH	Surveillance and Epidemiology Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology
Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2 (IN-PASC)	NIH	Pathophysiology Therapeutics
Impact of Long COVID on return-to-work efforts for people with disability	ACL	Human Services, Supports, and Interventions
Innovative Support for Patients With SARS-CoV-2 Infections (INSPIRE)	CDC	Clinical Spectrum of Long COVID and Diagnostic Strategies
Leveraging the power of VA data to understand Long COVID	VA	Surveillance and Epidemiology
Long COVID and Fatiguing Illness Recovery Program (LC&FIRP)	CDC	Surveillance and Epidemiology
Long COVID Needs Assessment of Health Professionals (2022 DocStyles Survey)	CDC	Health Services and Health Economics Research
Long COVID Practice Based Research Network	VA	Therapeutics
Long COVID supplement to the National Survey on Health and Disability	ACL	Health Services and Health Economics Research

Longitudinal Study of COVID-19 Antibody Response in Children in Seattle, WA	CDC	Surveillance and Epidemiology
Longitudinal At Home Smell Testing to Detect Infection by SARS-CoV-2	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies
Longitudinal Study of COVID-19 Sequelae and Immunity	NIH	Surveillance and Epidemiology Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology
Longitudinal study of immune memory in COVID-19 patients with mild to moderate symptoms	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology
Multi-site Study of Post-COVID Conditions (MPCC)	CDC	Surveillance and Epidemiology Clinical Spectrum of Long COVID and Diagnostic Strategies
Multi-state Long COVID Survey	CDC	Surveillance and Epidemiology
National COVID Cohort Collaborative (N3C)	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Surveillance and Epidemiology Long COVID and Overall Well-Being Pathophysiology Therapeutics and Other Health Interventions
National Health Interview Survey	CDC	Surveillance and Epidemiology

National Patient-Centered Clinical Research Network (PCORnet)	PCORI	Clinical Spectrum of Long COVID and Diagnostic Strategies Surveillance and Epidemiology Long COVID and Overall Well-Being Pathophysiology Therapeutics and Other Health Interventions
National Survey of Children’s Health Longitudinal Cohort Study (NSCH-LC)	HRSA,	Surveillance and Epidemiology Health Services and Health Economics Research
NIH Epidemiologic Study of Diabetes Incidence and Severity and Its Potential Association with COVID-19	NIH	Surveillance and Epidemiology
Occurrence of post-COVID-19 conditions and symptoms among adults seen in primary care practices by sociodemographic factors—American Board of Family Medicine PRIME Registry, American Family Cohort	CDC	Surveillance and Epidemiology
Office of Workers Compensation Program	DOL	Impacts of Illness
Pediatric COVID Outcomes Study (PECOS)	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Surveillance and Epidemiology Pathophysiology Impacts of Illness
Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM)	NIH	Surveillance and Epidemiology Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology

Pediatric Learning Health System consortium of PCORnet (PEDSnet consortium)	PCORI	Clinical Spectrum of Long COVID and Diagnostic Strategies Surveillance and Epidemiology Long COVID and Overall Well-Being Therapeutics and Other Health Interventions
Planning workshop: Long-Term Health Effects from COVID-19 and Implications for the SSA	SSA	Human Services, Supports, and Interventions
Population-based study of long-term impacts of COVID-19 infection (including subset of Veterans with Long COVID)	VA	Health Services and Health Economics Research
Post COVID Collaborative Merit Program	VA	Clinical Spectrum of Long COVID and Diagnostic Strategies
Project ECHO (Extension for Community Healthcare Outcomes)	AHRQ	Health Services and Health Economics Research
RADx Radical program	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies
Rapid olfactory tools for telemedicine-friendly COVID-19 screening and surveillance	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies
Researching COVID to Enhance Recovery (RECOVER)	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Surveillance and Epidemiology Long COVID and Overall Well-Being Pathophysiology Therapeutics and Other Health Interventions
Research on COVID Long-Term Illness, Effects, and Risk Factors (COVID-RELIEF)	CDC	Surveillance and Epidemiology
Retaining Employment and Talent After Illness/Injury Network (RETAIN)	DOL	Impacts of Illness

Risk Factor Assessment Study for Post-Acute Sequelae of COVID-19 (Long COVID) in the Medicare Population	FDA, CBER, CMS	Surveillance and Epidemiology
Risk of developing post-COVID-19 conditions among younger and older adult COVID-19 survivors—Cerner Real World Data	CDC	Surveillance and Epidemiology
SCENTinel: A Rapid Smell Test for COVID-19 Surveillance	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies
Survey of Occupational Injuries and Illnesses (SOII)	DOL	Impacts of Illness
TLC Trial (Treatment of Long COVID).	FDA, CDER, NIH, NCATS	Therapeutics and Other Health Interventions
Understanding the Pathophysiology and Clinical Course of New-Onset Diabetes Following COVID-19	NIH	Clinical Spectrum of Long COVID and Diagnostic Strategies Pathophysiology
VA COVID-19 Observational Research Collaboratory Long-term Outcomes Study (CORC-LTO)	VA	Surveillance and Epidemiology
Qualitative study Long COVID-19 impact on return-to-work efforts for people with disability	ACL	Human Services, Supports, and Interventions
COVID-19 pandemic-related experiences of working-age adults with disabilities	ACL	Human Services, Supports, and Interventions
Analysis of disability claims with report of Long COVID	SSA	Human Services, Supports, and Interventions

***Agency abbreviations, in alphabetical order**

ACL: Administration for Community Living

AHRQ: Agency for Healthcare Research and Quality

ASPE: Office of the Assistant Secretary for Planning and Evaluation

CBER: Center for Biologics Evaluation and Research

CDC: Centers for Disease Control and Prevention

CDER: Center for Drug Evaluation and Research
CMS: Centers for Medicare & Medicaid Services
DOD: Department of Defense
DOL: Department of Labor
FDA: Food and Drug Administration
HHS: Department of Health and Human Services
HRSA: Health Resources and Services Administration
NCATS: National Center for Advancing Translational Sciences
NIH: National Institutes of Health
OASH: Office of the Assistant Secretary for Health
ODEP: Office of Disability Employment Policy
PCORI: Patient-Centered Outcomes Research Institute
SSA: Social Security Administration
VA: Department of Veterans Affairs

Appendix E: U.S. Government Long COVID Research, Interim Implementation Plan

As the U.S. government is standing up the new Office of Long COVID Research and Practice, there is a need for an interim implementation plan. The following tables demonstrate the actions that the U.S. government will take over the next six months to implement the strategies and priorities of this Plan. At a high level, this interim plan will guide federal efforts until the Department of Health and Human Services develops the first annual implementation plan, including performance and progress metrics, to execute the strategic priorities and coordinate the activities of federal agencies and private partners. **Efforts described in these tables are new or enhanced activities, above and beyond the research described in Chapter 3 and Appendix D, almost all of which is ongoing.** These two tables correspond to the two main sections in Chapter 4. The first table below, U.S. Government Research Priorities for Long COVID, describes specific research that U.S. government will undertake to respond to the broad call to action described in Chapter 4 for the U.S. government as well as the private research community. The second table below, Strategic U.S. Government Actions, are the new structures and processes in U.S. government to drive the research.

U.S. Government Research Priorities for Long COVID

Characterizing the Full Clinical Spectrum of Long COVID and Diagnostic Strategies

Host a convening of public and private partners to better align interim definitions of Long COVID for clinical, surveillance, and research

Augment use of existing chronic disease initiatives (e.g., the Serological Sciences Network (SeroNet)) to better understand the increased risk of chronic disease and clinical course among persons with Long COVID

Surveillance and Epidemiology

Establish a framework for a multipronged approach to Long COVID surveillance to coordinate and enhance existing efforts in the context of broader data modernization efforts

Leverage existing research on post-infectious chronic illness to support identification of commonalities and differences with Long COVID, accelerate research and innovation, as well as prepare for the long-term consequences of future pandemics

Long COVID and Overall Well-Being

Publish findings from Health+ Long COVID patient-centered research, qualitative studies of patients experiencing Long COVID and associated conditions, caregivers, frontline workers, and those with lived experience

Assess existing cohort studies as well as studies conducting qualitative interviews with persons with Long COVID, to expand consideration of outcomes such as behavioral health, employment, education, caregiving, care utilization, and experience with care, especially among groups who are disproportionately affected

Therapeutics and Other Health Interventions

Implement additional strategies to accelerate and enhance enrollment into RECOVER studies

Human Services, Supports, and Interventions

Identify existing national surveys related to human services, supports and interventions that could be amended to include modules for data collection about Long COVID

Health Services and Health Economics Research

Build on current studies to evaluate the economic costs and outcomes of Long COVID, across the full range of economic costs and outcomes, and at all levels-- patient and family, health system, state, federal (including Medicare and Medicaid), and national

Strategic U.S. Government Actions

Establish an Office of Long COVID Research and Practice

Support ongoing meetings of the Long COVID Coordination Council

Develop first annual implementation plan

Establish the Secretary's Advisory Committee on Long COVID

Develop and contribute to best practices to collect detailed information on age, gender, race, ethnicity, rurality, economic disadvantage, insurance coverage, pregnancy status, and disability status in all USG-conducted and sponsored research on Long COVID, in line with OMB and other U.S. government policies

Facilitate development of comprehensive and equitable Long COVID diagnosis, care and treatment guidance and compile existing guidance

Develop and immediately begin implementation of a strategic communications plan to share findings from Long COVID research widely with partners and stakeholders to coordinate and enhance current efforts

Leverage existing platforms and resources for clinical trial, genetic data, and literature (e.g., [ClinicalTrials.gov](https://clinicaltrials.gov), GenBank, Sequence Read Archive, and PubMed Central) to provide broad access to information about U.S. Long COVID research and the results.

Host a convening of research partners, including government, academia, public health, pharmaceutical industry, national pharmacy chains, and health systems to initiate collaborations.
