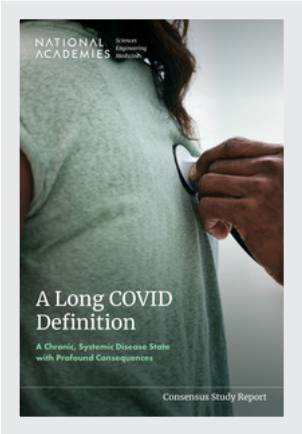


# A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences (2024)



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# A Long COVID Definition

## A Chronic, Systemic Disease State with Profound Consequences

Harvey V. Fineberg, Lisa Brown, Tequam Worku, and Ilana Goldowitz, *Editors*

Committee on Examining the Working Definition for Long COVID

Board on Health Sciences Policy

Board on Global Health

Health and Medicine Division

Consensus Study Report

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report, nor did they see the final draft before its release. The review of this report was overseen by **ENRIQUETA C. BOND,** Burroughs Wellcome Fund, and **SUSAN J. CURRY,** The University of Iowa. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

# Contents

**ACRONYMS AND ABBREVIATIONS** xiii

**PREFACE** xvii

**SUMMARY** 1

**1 INTRODUCTION** **15**
Prevalence of Long COVID Globally and in the United States, 15
Need for a Clear Definition, 17
Charge to the Committee, 20
Study Approach, 20

**2024 NASEM LONG COVID DEFINITION** **28**

**2 DEFINING LONG COVID** **31**
A Definition Designed to Evolve as New Evidence and Understanding Emerge, 31
Evidence Supporting Key Elements of the Definition, 35
Considerations for Implementation and Different Uses, 71
A Working Definition and Research Agenda, 82
Shortcomings in the Available Evidence, 85
Limitation and Unintended Consequences of the Definition, 86
Concluding Remarks and Recommendations, 88
References, 90

**APPENDIXES**

A DETAILED DESCRIPTION OF COMMITTEE'S APPROACH AND STUDY METHODS 105
B MEASURES OF DIAGNOSTIC PERFORMANCE: SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUE 145
C BIOGRAPHICAL SKETCHES 151

# Boxes, Figures, and Tables

## BOXES

S-1 2024 NASEM Long COVID Definition, 2

1 Selected Existing Long COVID Definitions and Descriptions, 18
2 Statement of Task, 21

## FIGURES

S-1 Definition figure: 2024 NASEM Long COVID definition, 4

1 Process map for the multi-phase activity of examining the working definition for Long COVID, 22
2 National Long COVID programs and initiatives, 25
3 Definition figure: 2024 NASEM Long COVID definition, 29
4 Frequencies of new onset symptoms, 46
5 Hypothesized mechanisms of Long COVID pathogenesis, 65

## TABLES

1 Possible Key Elements of a Disease Definition, 36
2 2024 NASEM Long COVID Definition Implementation Checklist for Clinicians, 75

3 Study Design Considerations for Application of the 2024 NASEM Long COVID Definition, 80
4 Public Health Surveillance Approaches for Long COVID, 83

# Acronyms and Abbreviations

| | |
|---|---|
| AIDS | acquired immunodeficiency syndrome |
| ASPR | Administration for Strategic Preparedness and Response |
| CDC | U.S. Centers for Disease Control and Prevention |
| CI | confidence interval |
| COVID-19 | coronavirus disease 2019 |
| CSTE | Council of State and Territorial Epidemiologists |
| DLCO | diffusing capacity of the lungs for carbon monoxide |
| EBV | Epstein–Barr virus |
| ECR | electronic case reporting |
| EHR | electronic health record |
| FDA | U.S. Food and Drug Administration |
| FEV1 | forced expiratory volume in one second |
| GI | gastrointestinal |
| HHS | Department of Health and Human Services |
| HHV-6 | human herpesvirus 6 |
| HIE | health information exchange |
| HIV | human immunodeficiency virus |
| HPO | Human Phenotype Ontology |
| HPV | human papilloma virus |

| | |
|---|---|
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| IACC | infection-associated chronic condition |
| ICD-10 | International Classification of Diseases, 10th revision |
| ICU | intensive care unit |
| IOM | Institute of Medicine |
| LC | Long COVID |
| ME/CFS | myalgic encephalomyelitis/chronic fatigue syndrome |
| MERS | Middle East respiratory syndrome |
| MIS-C | multisystem inflammatory syndrome in children |
| NAAT | nucleic acid amplification test |
| NICE | National Institute for Health and Care Excellence |
| NIH | National Institutes of Health |
| OASH | Office of the Assistant Secretary for Health |
| OR | odds ratio |
| PASC | post-acute sequelae of COVID-19 |
| PCR | polymerase chain reaction |
| PECO | population, exposure, comparator, outcome |
| PICS | post-intensive care syndrome |
| POTS | postural orthostatic tachycardia syndrome |
| QALY | quality-adjusted life year |
| RCGP | Royal College of General Practitioners |
| RECOVER | Researching COVID to Enhance Recovery |
| RNA | ribonucleic acid |
| RT-PCR | real-time polymerase chain reaction |
| SARS | severe acute respiratory syndrome |
| SARS-CoV-2 | severe acute respiratory syndrome-related coronavirus |
| SD | standard deviation |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SSA | U.S. Department of Social Security Administration |
| TLC | total lung capacity |
| USG | U.S. Government |
| WHO | World Health Organization |
| WSAS | Work and Social Adjustment Scale |

# Acknowledgments

This Consensus Study Report would not have been possible without the many experts—especially those with Long COVID—who generously contributed their time and expertise to inform the development of this report. The committee sincerely thanks EnSpark Consulting who led the engagement efforts and all those who participated in these efforts, as well as the speakers listed in Appendix A for their timely participation and expert contributions to the public workshops.

The committee would also like to thank the sponsor of this study, the Administration for Strategic Preparedness and Response (ASPR) and the Office of Assistant Secretary for Health (OASH). The committee also extends their gratitude to the group of interagency federal experts, including those at the National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC), for informing the committee's charge.

Many others within the National Academies supported this project. The committee thanks the staff of the Health and Medicine Division (HMD) Executive Office, Office of Communications, Office of Governmental Affairs, and Research Center. The committee is grateful to Ilana Goldowitz for her invaluable contributions to report writing. Finally, Robert Pool is to be credited for his editorial assistance in preparing this report.

Lastly, we are deeply grateful to the members of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats who planned and conducted three scoping and information-gathering meetings that helped to inform and shape this effort.

# Preface

Defining a widespread, poorly understood medical condition, such as Long COVID, is a freighted task. Patient groups, clinicians and researchers, government agencies, and international organizations have used different terms to name the condition and diverse descriptions to determine what fits the term. No well-documented, pathophysiological cascade nor any sufficiently discriminating biomarker can today definitively diagnose Long COVID. While most people infected with SARS-CoV-2 fully recover, tens of millions worldwide experience persistent symptoms and organ damage as well as other consequences for months to years after acute infection. As a result, patients can remain unacknowledged, in a kind of diagnostic limbo.

Inconsistent disease terminology and meaning can confound clinicians; limit the generalizability of research findings; and inhibit patients from obtaining the recognition, care, and support they need. Concerns about the adequacy and acceptability of existing definitions of Long COVID led units within the U.S. Department of Health and Human Services to ask the National Academies of Sciences, Engineering, and Medicine (the National Academies) to put forth a new definition for Long COVID. This report conveys the National Academies' response: the 2024 NASEM Long COVID Definition.

The approach and conclusions of the committee that prepared this report differ from the usual process and product of the National Academies in a couple ways. First, most committees rely mainly on a range of technical experts to craft a report, sometimes obtaining input from others. This

committee adopted a systematic and multi-phase information-gathering process that relied strongly on the insights of patients and other members of the public in addition to extensive literature and knowledge across a range of disciplines. The committee benefited from having some individual members who, whatever else their qualifications, brought personal experience with Long COVID and other infection-associated chronic conditions (IACCs). The report and an appendix explain in detail the array of evidence and input used by the committee.

Second, most committees of the National Academies aim for their conclusions to be the final word on a topic. By contrast, this committee anticipates, indeed recommends, that its definition be reviewed and revised in light of emerging knowledge and deeper understanding of Long COVID, including pathways of pathobiology and possible recognition of reliable and accurate biomarkers. Words have a way of evolving from their original meaning: nice originally meant silly or foolish, and silly originally referred to things worthy or blessed. While Long COVID is unlikely to endure such an extreme lexical conversion, its meaning can and should evolve to match the state of knowledge.

On behalf of the committee and the project staff, I extend my sincere thanks to the many individuals who shared their time and expertise to support the committee's work and inform its deliberations. The study was sponsored by the Administration for Strategic Preparedness and Response and the Office of the Assistant Secretary for Health, and we thank Rear Admiral Michael Iademarco, Allison O'Donnell, and Margaret Sloane for their guidance and support. We also thank the many experts who freely contributed their views. The committee especially appreciates the perspectives provided by people living with Long COVID who took the time and made the effort to contribute to our deliberations. This project began under the aegis of the National Academies Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats, and we owe every member of the standing committee a debt for helping to shape the earliest stages of this work.

It has been a privilege and joy to work with the Academies staff who so ably supported this project. Special recognition goes to Lisa Brown, staff director, and to Tequam Worku, Shalini Singaravelu, Matthew Masiello, Rayane Silva-Curran, Margaret McCarthy, and Burgess Manobah, along with National Academy of Medicine fellows Paule Joseph and Ben Watson and intern Jackie Brenner. Ilana Goldowitz provided research and writing assistance. The committee extends our gratitude also to Clare Stroud, senior board director of the Board on Health Sciences Policy.

Finally, I would like to thank my fellow committee members who so generously volunteered to take up this task. The committee's steadfast

engagement, active and energetic exchange of ideas, and cooperative spirit made preparing this report not only possible, but a highly rewarding experience. We hope it proves useful and is also a source of gratification to the many patients, family members, clinicians, researchers, officials, and others who contributed.

Harvey V. Fineberg, *Chair*
Committee on Examining the Working Definition for Long COVID
Standing Committee on Emerging Infectious Diseases
and 21st Century Health Threats

# Summary[1]

Individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), can experience ongoing symptoms after acute infection. This complex and lingering disease state known as Long COVID has profound medical, social, and economic consequences worldwide. Long COVID prevalence estimates vary widely, and some estimates of the percentage of those infected with COVID-19 who develop Long COVID range from 10 to 35 percent or higher. For example, a U.S. Census Bureau and the National Center for Health Statistics Household Pulse Survey showed, as of March 5 to April 1, 2024, about 17.6 percent of all U.S. adults have "ever experienced with Long COVID" and 6.9 percent of all U.S. adults are "currently experiencing Long COVID."[2]

Several working definitions that describe Long COVID exist currently. However, no common definition for Long COVID has yet been agreed upon. In August 2022, the Office of the Assistant Secretary for Health (OASH) published an interim working definition for Long COVID based on collaboration among several government agencies and outside subject matter experts, including medical societies and patients. Other major health organizations in the United States and internationally have also published various definitions of Long COVID and related terms. Furthermore,

[1] This summary does not include references. Citations for the discussion presented in the summary appear in the subsequent report chapters.

[2] The Pulse Survey defined Long COVID as "any symptoms lasting 3 months or longer that [they] did not have prior to having coronavirus or COVID-19."

several journal articles have proposed different ways in which Long COVID could be defined. The lack of a consensus definition presents challenges for patients, clinicians, public health practitioners, researchers, and policy makers. The diversity of Long COVID patient presentations, the overlap with other conditions, and the difficulty of ascribing symptoms to an earlier infection make defining Long COVID particularly challenging. For patients, challenges associated with the diversity of clinical presentations that can accompany a diagnosis of Long COVID may lead to difficulties accessing medical care and obtaining support; skepticism and dismissal of their experiences by medical professionals, peers, family members, and employers; delayed or denied treatment; and social stigma.

Recognizing the need for broad input and careful consideration of an improved definition, the Administration for Strategic Preparedness and Response (ASPR) and OASH asked the National Academies of Sciences, Engineering and Medicine (National Academies) Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats to take up the issue of defining Long COVID. To accomplish this complex task, a separate

**BOX S-1**
**2024 NASEM Long COVID Definition**

**Long COVID (LC) is an infection-associated chronic condition (IACC) that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.**

**LC manifests in multiple ways.** A complete enumeration of possible signs, symptoms, and diagnosable conditions of LC would have hundreds of entries. Any organ system can be involved, and LC patients can present with

- **single or multiple symptoms, such as** shortness of breath, cough, persistent fatigue, post-exertional malaise, difficulty concentrating, memory changes, recurring headache, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation, and diarrhea.
- **single or multiple diagnosable conditions, such as** interstitial lung disease and hypoxemia, cardiovascular disease and arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), fibromyalgia, connective tissue diseases,

expert committee, the Committee on Examining the Working Definition of Long COVID, was established. The committee consisted of experts in the fields of health research and policy, research related to Long COVID and chronic multi-symptom illness, clinical practice and guidelines, infectious diseases, public health and epidemiology practice, social and behavioral sciences, patients and lived experience, and community engagement and health equity.

To define Long COVID, the committee employed a systematic approach implemented through a multi-phase process with activities engaging more than 1,300 participants, with a focus on the patient perspective and interdisciplinary dialogue. The committee also assembled and analyzed reviews and primary literature on Long COVID and examined existing Long COVID definitions. In developing the definition, the committee considered the following criteria: precision, feasibility, acceptability, accessibility, balancing benefits and harms, potential impact on health equity, and unintended consequences.

hyperlipidemia, diabetes, and autoimmune disorders such as lupus, rheumatoid arthritis, and Sjogren's syndrome.

**Important Features of LC:**

- LC can follow asymptomatic, mild, or severe SARS-CoV-2 infection. Previous infections may have been recognized or unrecognized.
- LC can be continuous from the time of acute SARS-CoV-2 infection or can be delayed in onset for weeks or months following what had appeared to be full recovery from acute infection.
- LC can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, gender, sexual orientation, race, ethnicity, or geographic location.
- LC can exacerbate pre-existing health conditions or present as new conditions.
- LC can range from mild to severe. It can resolve over a period of months or can persist for months or years.
- LC can be diagnosed on clinical grounds. No biomarker currently available demonstrates conclusively the presence of LC.
- LC can impair individuals' ability to work, attend school, take care of family, and care for themselves. It can have a profound emotional and physical impact on patients and their families and caregivers.

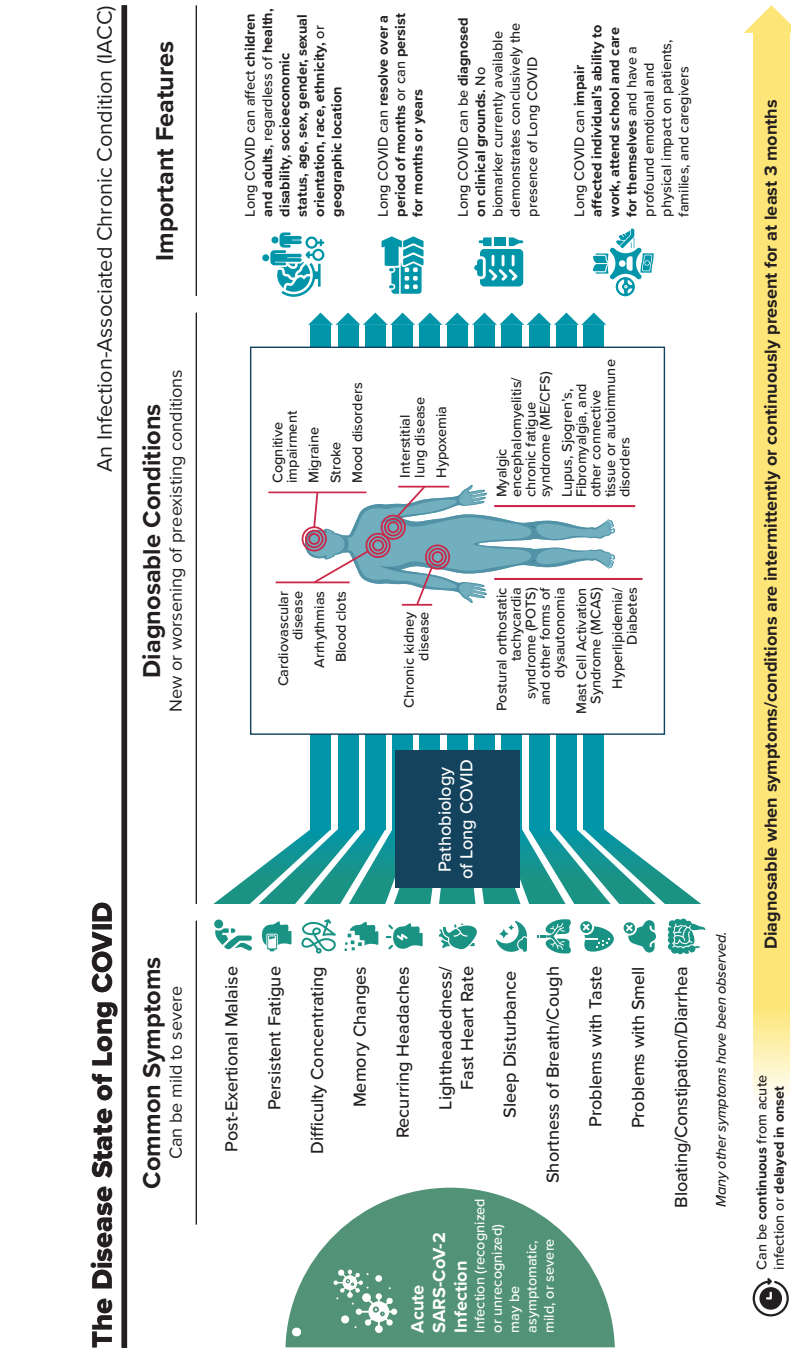


Figure S-1 Definition figure: 2024 NASEM Long COVID definition.

## 2024 NASEM LONG COVID DEFINITION

Relying on findings reported in the literature as well as input from engagement activities, the committee proposes the 2024 NASEM Long COVID Definition (see Box S-1 and Figure S-1). The 2024 NASEM Long COVID Definition consists of a core component in bold font, plus a set of illustrative symptoms and diagnosable conditions, followed by seven important features that elaborate on the core component. The committee chose to put forth a single definition for Long COVID. This definition is intended to cover most, if not all patients who experience Long COVID. The committee recognizes that eligible subsets who fit within the overall definition would need to be specified for particular purposes, such as research or surveillance.

The committee intends its definition to be applied to many purposes. These may include clinical care and diagnosis; eligibility for health services, insurance coverage, disability benefits, and school or workplace accommodations; public health; social services; policy making; epidemiology and surveillance; private and public research; and public awareness and education, especially for patients and their families and caregivers. In all these situations, the committee intends its Long COVID definition to interface with existing practices and policies without worsening health disparities or other problems.

In its report, the committee specifically offers ways in which the 2024 NASEM Long COVID Definition may be applied for clinical, research, and public health surveillance purposes and provides considerations as well as illustrative examples. Furthermore, the committee believes all stakeholders involved in social safety net programs, including but not limited to payers, workplaces and employers, academic institutions and educators, and support services and government, need to be aware of Long COVID to properly support patients, and their families and caregivers in need. In this regard, the committee refers the reader to the National Academies report, *Long-Term Health Effects Stemming from COVID-19 and Implications for Social Security Administration*.

The committee hopes that the 2024 NASEM Long COVID Definition will aid clinicians in the consistent diagnosis, documentation, and treatment of Long COVID; encourage further research into the pathophysiology, diagnosis, prognosis, consequences, and treatment of Long COVID; enhance patient access to appropriate care, treatment, services, and benefits; and harmonize research and surveillance efforts on Long COVID, while providing researchers flexibility in the design of studies on Long COVID; and raise awareness and educate the public about Long COVID.

## KEY ELEMENTS OF THE DEFINITION

The committee found no published, standardized guidelines for developing disease definitions. The committee gleaned lessons from the process of developing disease definitions for other multi-symptom conditions and took advantage of existing definitions for Long COVID, adopting elements when appropriate. The committee articulated several possible key elements of a disease definition: attribution, time, clinical features, equity, functional impairment, exclusions and alternative diagnoses, biomarkers and laboratory criteria, and risk factors. Below is a description of how the committee approached each key element of the definition.

The 2024 NASEM Long COVID Definition includes a few notable features and specifically introduces a few new features that existing definitions lack. It provides explicit examples of common symptoms and conditions that are characteristic of Long COVID. The definition requires symptoms or conditions to be present for a duration of 3 months or more. Notably, while symptoms need to be present for at least 3 months, the timing of those 3 months is unspecified. The definition also firmly acknowledges the profound impact of Long COVID on function and the ability of patients to work, attend school, take care of family, and care of themselves. The new definition also introduces an equity statement—"Long COVID can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, gender, or sexual orientation, race, ethnicity, or geographic location"—recognizing that social determinants and structural inequalities intersect to create health disparities and to discourage stereotypical assumptions and biases that could deflect patients, clinicians, public health practitioners, researchers, and policy makers from recognizing all those who experience Long COVID. The definition does not require laboratory confirmation or other proof of initial SARS-CoV-2 infection, recognizing that the initial infection may or may not have been recognized due to various factors, including the lack of availability of and limited access to tests early in the pandemic, limited sensitivity of some SARS-CoV-2 tests and the potential for false negatives, as well as financial barriers to testing even when tests were more widely available.

### Terminology Considerations

Using consistent terminology is as important as using a consistent definition. In medicine, the word "illness" often refers to the "innately human experience of symptoms and suffering," while the term "disease" often refers to an "alteration in biological structure or functioning." To stress the systemic reality of Long COVID, while acknowledging uncertainty about etiology, this report adopts the term "disease state" when referring to Long COVID. In addition to using "disease state" when referring to Long COVID,

the committee uses the terms "condition," "medical condition," or "chronic condition." Similarly, when referring to the unhealthy state related to any prior infection, the committee uses the term "infection-associated chronic condition." The term "infection-associated chronic condition" (IACC) applies to a variety of chronic conditions that can be triggered by viruses, bacteria, fungi, or parasites. Use of this term highlights the ongoing nature of the medical condition and its association with a triggering infection without conveying any unwarranted conclusions about pathobiological mechanisms.

Over the course of the COVID-19 pandemic, various terms have been applied to what this report terms "Long COVID." These include "long-haul COVID," "post-COVID conditions," "post-COVID syndrome," "post-acute COVID-19 syndrome," "chronic COVID," and "post-acute sequelae of SARS-CoV-2 infection (PASC)." All these terms pertain to the same broad clinical condition. The committee intentionally adopted the patient-developed term "Long COVID" because its simplicity and familiarity can facilitate communication within and between the scientific community and the public. Long COVID is also consistent with World Health Organization recommendations to adopt unbiased, neutral, non-stigmatizing descriptive terms when the cause, mechanism, or pathology of a new condition have not yet been established.

### Attribution to Infection

The 2024 NASEM Long COVID Definition states that Long COVID occurs after acute SARS-CoV-2 infection but does not require laboratory confirmation or other proof of initial infection. The definition emphasizes that Long COVID can follow infections of any severity (including asymptomatic infections), whether they were initially recognized or not. Because no test for SARS-CoV-2 infection has perfect sensitivity and because the rates of false negatives from antigen and PCR tests vary with time and other factors, some infected individuals will receive negative test results. Antibody testing can sometimes indicate a past SARS-CoV-2 infection, but antibody levels can fluctuate or wane over time. Vaccination against COVID-19 also complicates antibody testing as it can cause positive results on some antibody tests. Additionally, some individuals were not tested or could not access testing during a suspected acute SARS-CoV-2 infection. Individuals experiencing an asymptomatic infection may not be tested for SARS-CoV-2, yet a variety of post-acute sequelae can occur after asymptomatic or mild infections.

### Onset and Duration

The 2024 NASEM Long COVID Definition specifies 3 months as the minimum duration of symptoms, which means that 3 months after infection, whether consistent or relapsing and remitting, is the earliest that symptoms can be designated as Long COVID. Although the definition specifies a minimum duration of 3 months to qualify as Long COVID, a clinician should recognize, acknowledge, and monitor concerning symptoms before the 3-month mark. These symptoms should be assessed and treated appropriately, and the ICD-10 code U09.9 (post COVID-19 condition, unspecified) may be used even before establishing a Long COVID diagnosis. Most patients with acute SARS-CoV-2 infection recover after a period of days to weeks. A 3-month cutoff will likely provide enough time for most patients to recover from acute manifestations of COVID-19. The choice of a 3-month minimum duration may allow for the resolution of temporary symptoms that are due to non-medical circumstances (e.g., overwork, stressful situations, medication side effects) and may allow for evaluation and treatment for alternative conditions with similar initial presentations.

Because there is still ambiguity regarding the relationship between the timing of SARS-CoV-2 infection relative to Long COVID onset, the committee chose not to include a maximum latency period. Although this action may lead to an increase in the number of people diagnosed with Long COVID, any maximum latency chosen would be speculation without the backing of scientific evidence. Furthermore, such a move might exclude people who develop delayed onset Long COVID, did not recognize they might be affected by Long COVID until later in its course, or were not able to access care due to the availability or restrictive criteria of some Long COVID clinics.

At the same time, none of the symptoms or conditions associated with Long COVID are unique to that condition. As the number of cases of acute SARS-CoV-2 infection declines, an increasing fraction of patients with symptoms compatible with Long COVID will have their condition due to a different origin. The report suggests that by 2025, it will be prudent for the clinician considering a diagnosis of Long COVID to seek evidence of prior acute SARS-CoV-2 infection. Over time, if and as the time horizon for Long COVID following acute infection becomes more sharply defined, this will be an important aid to clinical judgment.

### Symptoms, Temporal Pattern and Duration of Symptoms, and Symptom Severity

The 2024 NASEM Long COVID Definition does not list any symptoms or conditions as being required and does not list any symptoms or

conditions as being exclusionary; this may have the effect of lessening the specificity while increasing the sensitivity of the diagnosis. The committee offered some examples of how Long COVID could manifest, including some symptoms and conditions, and how Long COVID could present as a new condition or an exacerbation of pre-existing conditions. This list is not meant to be exhaustive or to dismiss the significance of other symptoms or conditions. Studies estimate the prevalence of over 200 symptoms in multiple organ systems, and these symptoms can occur at varying frequencies. Another notable feature of Long COVID is the variable temporal pattern and duration of symptoms. The committee also recognizes that the severity of Long COVID symptoms can range from mild to severe.

### Equity

Equity needs to be considered at multiple steps in a Long COVID patient's journey to obtain care and services. Findings from the engagement process emphasized the need to address equity in the definition, with one participant saying, "*It could be helpful to include a specific statement around health equity in a Long COVID definition. That would maybe be a little unusual to include in a definition, but it is important, if not in the definition, somewhere else.*" The 2024 NASEM Long COVID Definition acknowledges that a Long COVID diagnosis may be considered regardless of health status, vaccination history, or demographics. This definition applies to both adult and pediatric patients. Socioeconomic factors, inequality, discrimination (based on race and gender, among others), bias, and stigma affect whether patients can receive a diagnosis and benefit from Long COVID-targeted health care or services. These factors include but are not limited to access to COVID-19 testing during acute illness, access to evaluation for possible Long COVID, willingness of physicians to diagnose a particular patient, access to insurance benefits, and patients' fears of stigmatization that could result from having a Long COVID diagnosis. No existing Long COVID definitions include references to equity.

### Functional Impairment

The 2024 NASEM Long COVID Definition emphasizes that some individuals with Long COVID are severely affected and can have a variety of activity limitations. This can profoundly affect patients' and caregivers' lives and is an important feature of Long COVID. In the evidence review, the committee found publications documenting a range of mild to severe functional impairments, activity limitations, and quality of life impacts in individuals with Long COVID.

### Alternative Diagnosis, Biomarkers, and Risk Factors

Consideration of alternative diagnoses is not directly addressed in the 2024 NASEM Long COVID Definition, and risk factors are not included. As an important consideration, the definition notes that no definitive biomarkers currently exist to determine the presence of Long COVID. The committee elected not to include a statement regarding exclusions or alternative diagnoses in the 2024 NASEM Long COVID Definition. There is no scientific evidence that any medical condition precludes the diagnose of or cannot exist alongside Long COVID. The 2024 NASEM Long COVID Definition does note myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS), among others, as examples of diagnosable conditions that can be part of the picture of Long COVID. These and other potentially overlapping conditions are compatible with a diagnosis of Long COVID. While risk factors, such as underlying comorbid conditions, may influence the probability and presentation of COVID-19 and of Long COVID, the proposed definition does not directly consider the potential for differential risk according to patient characteristics.

## A WORKING DEFINITION AND RESEARCH AGENDA

The committee believes that the 2024 NASEM Long COVID Definition should be revised as new evidence emerges and our understanding of Long COVID continues to evolve. This is in line with lessons from defining other diseases such as HIV/AIDS, which took years and multiple iterations to refine. Given the current pace of research, it is possible that the definition may need to be updated in no more than 3 years' time and will continue to require a multidisciplinary effort. Other triggers for updating the 2024 NASEM Long COVID Definition could include the emergence of new treatments with clear benefits for patients identified as a subset of people with Long COVID, the development of a new test, new evidence on prognosis, or other opportunities to improve the clarity or precision of the definition.

Looking ahead, it may also be valuable to have mechanisms in place for gauging how the 2024 NASEM Long COVID Definition is understood, how it is being used, what other elements need to be added, and whether it is being applied in a consistent and standardized way (e.g., assessment tools). A research agenda centered around improving the definition could focus on the key definition elements articulated in the report: attribution to infection, time, clinical features, equity, functional impairment, exclusions and alternative diagnoses, biomarkers and laboratory criteria, and risk factors.

New evidence of the following may play a role in decisions to reconsider the definition:

- Improved testing to identify those who have been infected, even when tested weeks, months and years later. However, a large proportion of the population has been infected with COVID-19 at this point, and, as a result, finding uninfected control groups will become an increasing challenge in conducting research.
- Symptoms and organ damage that distinguish Long COVID from healthy people and other medical conditions.
- Onset and duration, including delayed onset of Long COVID after an ostensible period of recovery from acute infection.
- Recovery trajectory and natural history over longer periods of time.
- Presence and prevalence of co-morbid conditions.
- Biomarker(s) to diagnose Long COVID.
- Risk factors for Long COVID.
- Prevalence and outcomes of Long COVID by sex, gender, race, ethnicity, socioeconomic status, and other factors.
- Patterns in Long COVID among special populations such as older adults; children and adolescents; pregnant, lactating, and postpartum persons; people with disabilities; people experiencing homelessness; tribal communities; and imprisoned populations; among others.
- Longitudinal consequences (e.g., risk and development of other diseases, disability, hospitalization, and death).
- Effects on functionality and daily living, overall well-being, and caregivers and families.
- Social sciences research aimed at understanding the social and economic consequences of Long COVID.
- New treatment and management options that could potentially affect the sensitivity threshold and elements of the definition.

## CONCLUDING REMARKS AND RECOMMENDATIONS

The committee confronted many difficulties in its efforts to define Long COVID—most prominently the challenge of balancing risks of false negative and false positive classification. By putting forth the 2024 NASEM Long COVID Definition, the committee hopes patients, clinicians, public health practitioners, researchers, and policy makers will be better equipped to cope with this continually unfolding health crisis. The committee also hopes to foster greater awareness, understanding, and support for those with Long COVID. To conclude, the committee recommends three actions about the adoption, implementation, and updating of the 2024 NASEM Long COVID Definition (Box S-2).

**BOX S-2**
**Recommendations**

**RECOMMENDATION 1. Adopt and Implement the 2024 NASEM Long COVID Definition.**
**The federal government, state, tribal, local, and territorial health authorities; clinical societies and associations; public health practitioners; clinicians; payers; researchers; drug industry; employers; educators; international organizations; and patients should adopt the 2024 NASEM Long COVID Definition and should use the term Long COVID. The 2024 NASEM Long COVID Definition is intended to be applied to many purposes, but the committee notes that there is flexibility within the broad definition, for example, to restrict research eligibility to a subset of Long COVID patients.**

**RECOMMENDATION 2. Promulgate and Monitor the Implementation of the 2024 NASEM Long COVID Definition.**
**The Office of the Assistant Secretary for Health's Office of Long COVID Research and Practice and the Long COVID Coordination Council should lead the coordination and collaboration efforts across federal, state, tribal, local, and territorial agencies and other relevant entities, including international organizations, in the wide dissemination and implementation of the 2024 NASEM Long COVID Definition. Such implementation efforts should:**

- **Give special attention to the definition's equity implications to maximize appropriate inclusion.**
- **Develop standardized communication for key stakeholders and the public about the revised definition and understanding of Long COVID.**
- **Empirically test the 2024 NASEM Long COVID Definition; monitor, evaluate, and identify barriers to implementation and adoption of the definition in research and in practice (including supporting**

**an individual's ability to apply for and receive Social Security disability benefits) that may be improved in future revisions.**

- **Develop a standard protocol for screening and diagnosing patients with Long COVID in clinical settings and enhance clinical education and training on infection-associated chronic conditions.**
- **Catalogue and summarize the application of the definition in research settings and identify sub-phenotypes of Long COVID that inform the need for further investigation across the translational research spectrum from discovery to delivery science.**
- **Take advantage of a unique opportunity to learn from epidemiologic surveillance of an infection-associated chronic condition and support, for example, improved data infrastructure, technologic and legal support for more efficient cross-jurisdictional information-sharing, and improved test types and access to testing.**

**RECOMMENDATION 3. Update the 2024 NASEM Long COVID Definition. In no more than 3 years or when triggered by the emergence of relevant new knowledge, the Office of the Assistant Secretary for Health's Office of Long COVID Research and Practice should convene a multidisciplinary group, including individuals with lived experience, to reexamine and update the 2024 NASEM Long COVID Definition set forth in this report. The Office of the Assistant Secretary for Health's Office of Long COVID Research and Practice should put into place the necessary infrastructure, policies, and mechanisms to support and prepare for future updates to the 2024 NASEM Long COVID Definition, including a process to track and assess new scientific knowledge that may inform the definition**.

# 1

# Introduction

Since the onset of the coronavirus disease 2019 pandemic, millions of individuals across the globe have experienced ongoing symptoms following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The long-term health effects of COVID-19, known as Long COVID, are profound. This complex and lingering medical condition has exposed shortcomings in public health messaging and education, clinical care, research, and social support services. It has also illustrated the need to better understand infection-associated chronic conditions (IACCs) more broadly, both to improve care for those who currently live with IACCs and to prepare for and respond to future pandemics (Al-Aly and Topol, 2024; CDC Foundation, 2024). Research results and available information on Long COVID have varied, in part because of the heterogeneous definitions used in research and clinical practice. A uniform, core definition could help patients, clinicians, public health practitioners, researchers, and policy makers understand and navigate Long COVID more effectively.

## PREVALENCE OF LONG COVID GLOBALLY AND IN THE UNITED STATES

Long COVID is a serious global issue with medical, social, and economic impacts. Prevalence estimates vary widely. One reason for this variation is the absence of a clear-cut diagnostic biomarker or other definitive diagnostic criterion that would distinguish those with Long COVID from those whose condition is due to other reasons. In the wake of the pandemic,

Long COVID has likely been underdiagnosed and misdiagnosed (Walker et al. 2021), with Long COVID patients reporting not being believed in clinical settings (Ireson et al. 2022). Variation in prevalence estimates is compounded by the absence of a consistent definition for Long COVID and variety of terminologies to label the medical condition. Estimates of prevalence depend on how Long COVID is defined in terms of presence, timing, severity of symptoms, laboratory and imaging results, documentation of prior SARS-CoV-2 infection, and background frequency of common symptoms, among other factors (O'Mahoney et al., 2023; Pagen et al., 2023; Woodrow et al., 2023).

Estimates of the percentage of those infected with SARS-CoV-2 who develop Long COVID range from 10 to 35 percent or higher (Huerne et al., 2023; Pavli et al., 2021). Based on a prevalence of 10 percent of those infected, Davis and colleagues conservatively estimate that at least 65 million people worldwide have experienced Long COVID (Davis et al., 2023). A U.S. Census Bureau and the National Center for Health Statistics Household Pulse Survey showed, as of March 5 to April 1, 2024, about 17.6 percent of all U.S. adults have "ever experienced with Long COVID" and 6.9 percent of all U.S. adults are "currently experiencing Long COVID" (CDC, 2024). The Pulse Survey defined Long COVID as "any symptoms lasting 3 months or longer that [they] did not have prior to having coronavirus or COVID-19" (CDC, 2024a).[1] Another recent publication in *Morbidity and Mortality Weekly Report* reported that the prevalence of Long COVID varied among the states and territories, ranging from 1.9 percent in the Virgin Islands to 10.6 percent in West Virginia (Ford et al., 2024).

In the United States, according to death certificate data in the National Vital Statistics System (NVSS), Long COVID (or related terms) was an "underlying or contributing cause" of 3,544 deaths between January 2020 and June 2022 (Ahmad et al., 2022). With the addition of preliminary data from 2023, estimates now suggest over 5,000 deaths have been attributed to Long COVID since the start of the pandemic (Rapaport, 2024).[2] The age-adjusted death rate was higher among men (7.3 per million) than women (5.5 per million), higher among those 85 years and older (117.1 per million) than among younger age groups, and higher among American Indian and Alaska Native (AIAN) people (14.8 per million) than among other racial and ethnic groups (Ahmad et al., 2022). Long COVID as an underlying or contributing cause of death is likely to be underestimated in the references

[1] Limitations of the Household Pulse Survey: only accounted for people 18 and above, based on self-report, only counts COVID-19 cases if participant received a positive test or was told by a health care provider that they had COVID-19, and does not include people who have a worsening of existing conditions following SARS-CoV-2 infection.

[2] These sentences were modified after release of the prepublication version of the report to be more consistent with the cited references.

studies as an ICD-10 code did not exist earlier in the pandemic and it has been underused (Wander et al., 2023).

## NEED FOR A CLEAR DEFINITION

Defining Long COVID is challenging because of the heterogeneous nature of long-term sequelae of COVID-19, which include a wide array of symptoms and conditions with potentially variable etiologies and potential overlap with other causes (Hayes et al., 2021; Malone et al., 2022). Adding to the challenge, the clinical and scientific understanding of Long COVID is evolving as new evidence emerges on the presentations, durations, and pathogenesis of Long COVID and on its relationships to other conditions.

The complexities of Long COVID and the methodologic problems associated with studying Long COVID indicate the need for a comprehensive approach to evaluating and defining this disease state. Despite Long COVID's relatively recent emergence, numerous definitions and descriptions of Long COVID have already been published (Box 1). However, a review of 295 research studies on Long COVID, all published before October 26, 2022, found high heterogeneity in existing definitions; this heterogeneity limits opportunities to compare interventions and accumulate evidence on Long COVID (Chaichana et al., 2023). Currently, the field does not conform to a single definition of Long COVID and does not evaluate the disease state in a consistent way (Rando et al., 2021).

The lack of a generally accepted and consistent definition for Long COVID presents challenges for clinical management and treatment, research, surveillance, and support services (Al-Aly et al., 2023; Saydah et al., 2022). For patients, challenges associated with the lack of a clear, consistent definition of Long COVID and the diversity of the range of clinical presentations and poor understanding of Long COVID can lead to: difficulties accessing medical care; skepticism and dismissal of patients' experiences by medical professionals, peers (Au et al., 2022), family members, and employers; delay or denial of treatment; stigma; and difficulty obtaining support (Callard and Perego, 2021). An improved definition can help with raising awareness—according to a Pew Research Center survey conducted among 10,133 adults in February 2024, 22 percent of Americans say they haven't heard of Long COVID, and 50 percent of Americans think that it is extremely or very important for researchers and clinicians to understand and treat Long COVID (Tyson and Pasquini, 2024).

In August 2022, OASH published an interim working definition for Long COVID based on collaboration among several government agencies and outside subject matter experts, including medical societies and patients

**BOX 1**
**Selected Existing Long COVID Definitions and Descriptions**

**Office of Assistant Secretary for Health (OASH)**
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 4 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 (HHS, 2022).

**Centers for Disease Control and Prevention (CDC)**
CDC references the OASH Long COVID definition, but also says: Long COVID is a wide range of new, returning, or ongoing health problems that people experience after being infected with the virus that causes COVID-19. Most people with COVID-19 get better within a few days to a few weeks after infection, so at least 4 weeks after infection is the start of when Long COVID could first be identified. Anyone who was infected can experience Long COVID. Most people with Long COVID experienced symptoms days after first learning they had COVID-19, but some people who later experienced Long COVID did not know when they got infected (CDC, 2023b). (Note that this is not a formal definition but rather a description on the CDC website.)

**National Institutes of Health (NIH)**
Recovery from infection with SARS-CoV-2, the virus that causes COVID-19, can vary from person to person. Most patients seem to recover quickly and completely, while others report symptoms that persist for weeks or even months after the acute phase of illness has passed (a condition often referred to as “Long COVID”). In other cases, new symptoms and findings emerge after the acute infection, including when the acute phase was asymptomatic. Collectively, these long-term effects of the virus are called post-acute sequelae of SARS-CoV-2 infection (PASC) (NIH, 2024). (Note that this is not a formal definition but rather a description on the NIH RECOVER website.)

**World Health Organization (WHO)—Adults**
Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include, but are not limited to, fatigue, shortness of breath, and cognitive dysfunction and generally have an impact on everyday functioning. Symptoms might be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms might also fluctuate or relapse over time (Soriano et al., 2022).

**World Health Organization (WHO)—Pediatrics**
Post COVID-19 condition in children and adolescents occurs in individuals with a history of confirmed or probable SARS-CoV-2 infection, when experiencing symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19. Current evidence suggests that symptoms more frequently reported in children and adolescents with post-COVID-19 condition compared with controls are fatigue, altered smell (anosmia), and anxiety. Other symptoms have also been reported. Symptoms generally have an impact on everyday functioning such as changes in eating habits, physical activity, behavior, academic performance, social functions (interactions with friends, peers, family) and developmental milestones. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. They may also fluctuate or relapse over time. Workup may reveal additional diagnoses, but this does not exclude the diagnosis of post COVID-19 condition (WHO, 2023).

**National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), and Royal College of General Practitioners (RCGP)**
Ongoing symptomatic COVID-19: Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks. 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 may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed. 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) (NICE et al., 2022).

**Global List of Long COVID Definitions**
In addition to the above definitions, many organizations and governments across the globe have developed definitions for Long COVID and related terms. In March 2023, a list of Long COVID definitions was crowdsourced from members of the EpiCore network around the world (EpiCore, 2023).

**Reimbursement Codes**
In addition to Long COVID definitions, reimbursement codes have been developed. In the United States, ICD-10 code U09.9 designates "post-COVID-19 condition, unspecified" and became available in October 2021 (Pfaff et al., 2023). In the UK, the National Health Service (NHS) has developed codes that align with the NICE/SIGN/RCGP definition (NICE et al., 2022)

(HHS, 2022). Other major health organizations in the United States and internationally have also published various definitions of Long COVID and related terms, and these can be useful starting points (Box 1). Furthermore, several journal articles have proposed different ways in which Long COVID could be defined (Alwan and Johnson, 2021; Baig, 2021; Chaichana et al., 2023; Fernández-de-Las-Peñas, 2022; Fernandez-de-Las-Peñas et al., 2021a; Haslam et al., 2023; Lippi et al., 2023; Monika et al., 2023; Pan and Pareek, 2023; Rando et al., 2021; Raveendran, 2021). In developing its definition, the committee took advantage of these existing definitions by reviewing definitions in the context of the literature and available data and then adopting elements where appropriate.

## CHARGE TO THE COMMITTEE

Recognizing the desirability of broad input and careful consideration of an improved definition, the Administration for Strategic Preparedness and Response (ASPR) and the Office of the Assistant Secretary for Health (OASH) asked the National Academies of Sciences, Engineering and Medicine Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats[3] (standing committee) to take up the issue of defining Long COVID. To accomplish this complex task (see Box 2), a separate expert committee, the Committee on Examining the Working Definition of Long COVID (committee), was established. Members and their backgrounds are described in Appendix C.

## STUDY APPROACH

The committee's charge was to recommend a new definition for Long COVID. To this end, the committee employed a systematic approach implemented through a multi-phase process (see Figure 1). Appendix A provides a detailed methodology of the committee's approach, including details on the engagement process, evidence review, and public meetings.

In the 2-month scoping phase, the standing committee held three information-gathering meetings to discuss the key issues and identify the areas of expertise and stakeholders to engage in this effort.

In Phase I, the committee, along with National Academies staff and a team of consultants, engaged patients and individuals across multiple sectors to solicit input from a wide range of interested and affected parties through a series of focus group discussions and an online questionnaire;

[3] To learn more about the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats, please visit https://www.nationalacademies.org/our-work/standing-committee-on-emerging-infectious-diseases-and-21st-century-health-threats.

**BOX 2**
**Statement of Task**

A National Academies of Sciences, Engineering, and Medicine committee will conduct a series of public workshops to examine the current U.S. government (USG) working definition for Long COVID and related technical terms. The workshop series will consist of several sessions designed to:

- Explore literature on definitions for Long COVID in the United States, including but not limited to, definitions that are currently used for clinical care, research, surveillance, and health communication;
- Learn about challenges and barriers due to currently available definitions for Long COVID; and
- Seek input from various stakeholder groups relating to refinement, dissemination, and implementation of a definition for Long COVID.

The workshop series will conclude with a 2-day workshop discussing potential considerations for refined Long COVID definitions, terminology, and harmonizing efforts for patient engagement, clinical care, research, surveillance, across USG and relevant stakeholders. The committee will define the specific topics to be addressed, develop the workshop agendas, and select and invite speakers and other participants.

Building on the workshop series, the committee will integrate and synthesize information from the stakeholder engagement and information gathering and produce a letter report that will:

- Review additional evidence for definitions of Long COVID;
- Consider efforts that have already been completed on this topic area;
- Recommend new definitions for Long COVID and related technical terms, with descriptions of the circumstances under which these new definitions and terminology should be adopted.

The committee will make recommendations to establish considerations for maintaining an up-to-date definition for Long COVID and related technical terms.


FIGURE 1 Process map for the multi-phase activity of examining the working definition for Long COVID.

both activities were offered in English and Spanish. More than 1,300 people participated in these activities, including patients and caregivers, public health and health care professionals, researchers, policy and advocacy professionals, payors, health care business professionals, and members of the public. One consistent theme throughout the engagement process was that the National Academies committee should listen and learn from those with lived experiences of Long COVID, including patients and their families and caregivers, and those who diagnose, treat, and study Long COVID. For example, one participant said, "*Listen to the people who have been experiencing the disease, but also to people who will need to use the definition in their work*."

Details on who participated in these activities (demographics and sector/group affiliation) and the key findings are published in a publicly available report titled *What We Heard: Engagement Report on the Working Definition for Long COVID*.[4] Engagement activities were publicly promoted through various mechanisms and networks, and the committee made focused efforts to identify an equitable list of participants that covered the full spectrum of impacted and interested people, geographies, and demographics. Demographic data was only formally collected for questionnaire respondents, and of those respondents who answered the demographic questions, they were overwhelmingly white, female, highly educated, living in urban or mostly urban areas of the United States, and had a total household income of at least $100,000. The committee notes this limited presence of underrepresented groups in its engagement efforts and emphasizes the importance of attention to recruitment methods and broader access in future efforts.

During Phase I, the committee also organized three information-gathering virtual meetings, created an online public portal to receive public comments, and held a 2-day hybrid symposium to review and discuss input gathered. Recognizing the limited presence of underrepresented groups in its structured engagement efforts, the committee made a special effort, including direct outreach to organizations that serve underrepresented populations, to engage with these groups in its information-gathering meetings and symposium.

In Phase II, the committee undertook activities to further build, prioritize, and synthesize the evidence to help inform development of the refined definition. A scoping review consisting of 116 reviews pertinent to the diagnosis of Long COVID was carried out along with an examination of

[4] Available on the study webpage https://www.nationalacademies.org/our-work/examining-the-working-definition-for-long-covid (accessed March 11, 2024).

the primary literature. The committee also held four additional committee meetings, three in closed session and one public meeting.

The committee developed its definition based on the best evidence to date and all of the above-listed sources of information. While responsive to outside needs, concerns, and preferences, the committee recognized that different groups have varied desires and interests and examined ideas and suggestions in the context of the available scientific evidence.

### Stakeholders in the Long COVID Community and Report Audiences

As mentioned previously, central to the committee's approach was soliciting input from a wide range of sources and groups in developing the refined definition. The audience for this report includes federal agencies such as the U.S. Department of Health and Human Services (HHS) agencies and offices, National Institute of Health (NIH), Centers for Disease Control and Prevention (CDC), and the U.S. Department of Social Security Administration (SSA); Long COVID patients, organizations, and groups; medical institutions and health care providers; public health agencies and practitioners; academic institutions, researchers, and educators; payers and health care business professionals; employers and human resource professionals; and international agencies. This report includes guidance for clinicians, researchers, and public health practitioners in applying the proposed definition. The committee hopes this refined definition will prove useful to ongoing federal programs and initiatives on Long COVID (see Figure 2).

### Study Scope

As specified in the statement of task for this study (see Box 2), the committee was asked to develop a definition for Long COVID. The committee recognizes the many conditions that are infection-associated in addition to Long COVID, but the committee was not asked to define or address the challenges in identifying, researching, or treating these other conditions.

The committee worked to identify the best available evidence and information to refine the definition for Long COVID. The report offers a framework for applying the definition in specific use cases, including for clinical care, research, and public health, recognizing that it may be advantageous to apply additional criteria to identify a subpopulation within the definition who are best suited to the particular purpose.

### A Note on Terminology

Using consistent terminology is as important as using a consistent definition. In medicine, the word "illness" often refers to the "innately

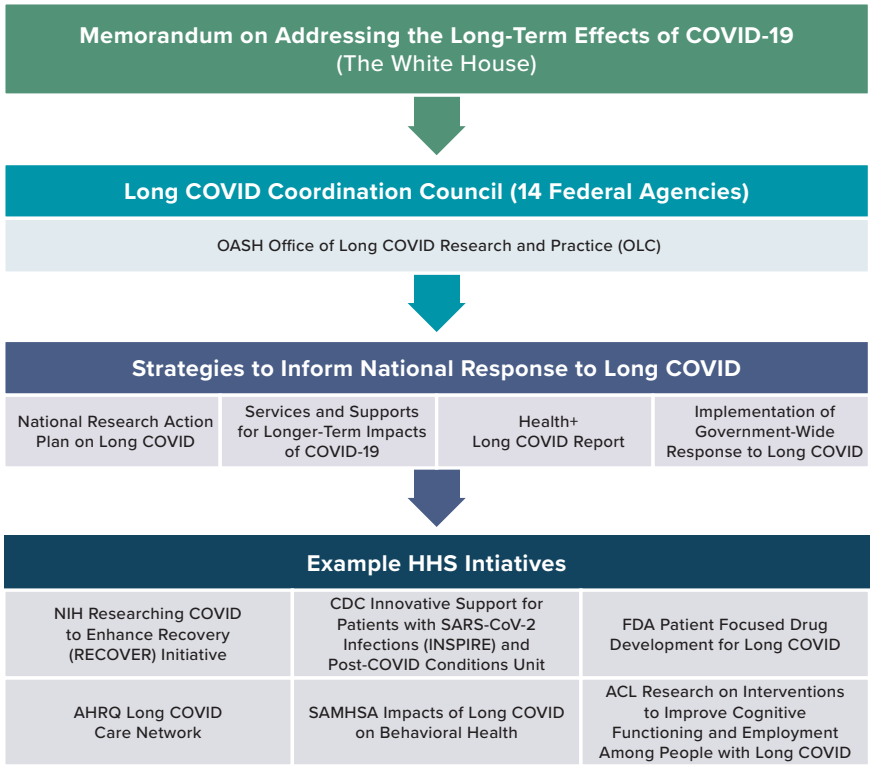


**FIGURE 2** National Long COVID programs and initiatives.

human experience of symptoms and suffering," while the term "disease" often refers to an "alteration in biological structure or functioning" (Kleinman, 1988). To stress the systemic reality of Long COVID, while acknowledging uncertainty about etiology, this report adopts the term "disease state" when referring to Long COVID.

The words "illness" and "medical condition" both refer to an unhealthy state. To some, the word "illness" may connote a more established and serious experience of ill health. To others, including many experiencing Long COVID, "condition" or "medical condition" connotes a more lasting and serious unhealthy state. In addition to using "disease state" when referring to Long COVID, the committee uses the terms "condition," "medical condition," or "chronic condition." Similarly, when referring to the unhealthy state related to any prior infection, the committee uses the term "infection-associated chronic condition."

The term "infection-associated chronic condition" (IACC) applies to a

variety of chronic conditions that can be triggered by viruses, bacteria, fungi, or parasites (CDC Foundation, 2024). While this term may be somewhat new, the conditions are not. Millions of Americans were living with IACCs prior to the COVID-19 pandemic. Use of this term highlights the ongoing nature of the medical condition and its association with a triggering infection without conveying any unwarranted conclusions about pathobiological mechanisms. Furthermore, the use of this collective term can promote alignment across diverse disease groups and patient organizations—allowing for the identification of common objectives, challenges, opportunities, and actionable steps.

IACCs include conditions triggered by infections such as Epstein-Barr, influenza, chikungunya, West Nile, Ebola, SARS, HIV, HPV, and MERS viruses (Choutka et al., 2022; Rando et al., 2021; Vivaldi et al., 2023). Conditions with a proposed non-viral infectious trigger include Q fever fatigue syndrome, tick- and vector-borne IACCs such as Lyme-associated chronic illnesses, and multiple chronic symptoms following *Giardia* infection (Choutka et al., 2022). Although there are variations linked to the particular infectious agent, many of these conditions share common symptoms such as fatigue, exertion intolerance, cognitive impairment, musculoskeletal pain, dysautonomia, and sleep problems, which can appear in a relapsing/remitting pattern and can resemble or overlap with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Choutka et al., 2022). Other researchers are considering possible similarities with chronic inflammation and immune activation seen in people living with HIV, where the persistence of the virus or viral components may be a contributing factor (Bonilla et al., 2023). Recognizing Long COVID as one of a group of IACCs could potentially facilitate research and the development of clinical indicators for better diagnosis (Kim et al., 2023). None of the pre-existing definitions the committee reviewed mention IACCs.

Over the course of the COVID-19 pandemic, various terms have also been applied to what this report terms "Long COVID." These include "long-haul COVID," "post-COVID conditions," "post-COVID syndrome," "post-acute COVID-19 syndrome," "chronic COVID," and "post-acute sequelae of SARS-CoV-2 infection (PASC)." All these terms pertain to the same broad clinical condition (Turner et al., 2023). The committee intentionally adopted the patient-developed term, "Long COVID," because its simplicity and familiarity can facilitate communication within and between the scientific community and the public. One participant said, "*Patients need to be able to understand it and see themselves in the definition, because they may need to advocate for themselves or their loved ones for initial care (or continued care or recognition)*."

The use of the term "Long COVID" is also consistent with WHO

recommendations to adopt unbiased, neutral, non-stigmatizing descriptive terms when cause, mechanism, and pathology of a new condition have not yet been established (WHO, 2015). While similarly neutral, the term PASC can imply a sharper virologic or symptomatic differentiation between "acute" and "post-acute" stages than is often the case (Munblit et al., 2022).

### Report Structure

The report is organized to reflect the study's approach and key priority areas for refining and implementing the working definition of Long COVID, as identified by the committee and statement of task. The report contains seven sections, the first of which is the above introduction and discussion of the background for the study (1). This is followed by a section and figure outlining the refined definition developed by the committee (2). The definition has a core component in bold font, plus a set of illustrative symptoms and diagnosable conditions, followed by seven important features that elaborate on the core component. The next section summarizes evidence supporting key elements and features of the definition (3), including such aspects as balancing errors of inclusion and exclusion, attribution to infection, onset and duration, symptoms and clinical expression, functional impact, considerations of equity, alternative diagnoses, biomarkers, and risk factors. The implementation use-cases section (4) outlines frameworks for applying the definition for multiple purposes, specifically clinical care, research, and public health surveillance applications. This is followed by a section discussing the need and parameters for updating the definition as evidence accumulates and understanding evolves (5). This section also identifies priority areas for future research to improve the definition. The report goes on to describe key limitations, prominently including limitations imposed by the available knowledge about and understanding of Long COVID (6). The final section (7) includes the committee's concluding remarks and three recommendations.

## 2024 NASEM LONG COVID DEFINITION

**Long COVID (LC) is an infection-associated chronic condition (IACC) that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.**

**LC manifests in multiple ways.** A complete enumeration of possible signs, symptoms, and diagnosable conditions of LC would have hundreds of entries. Any organ system can be involved, and LC patients can present with

- **single or multiple symptoms, such as** shortness of breath, cough, persistent fatigue, post-exertional malaise, difficulty concentrating, memory changes, recurring headache, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation, and diarrhea.
- **single or multiple diagnosable conditions, such as** interstitial lung disease and hypoxemia, cardiovascular disease and arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), fibromyalgia, connective tissue disorders, hyperlipidemia, diabetes, and autoimmune disorders such as lupus, rheumatoid arthritis, and Sjogren's syndrome.

**Important Features of LC:**

- LC can follow asymptomatic, mild, or severe SARS-CoV-2 infection. Previous infections may have been recognized or unrecognized.
- LC can be continuous from the time of acute SARS-CoV-2 infection or can be delayed in onset for weeks or months following what had appeared to be full recovery from acute infection.
- LC can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, gender, sexual orientation, race, ethnicity, or geographic location.
- LC can exacerbate pre-existing health conditions or present as new conditions.
- LC can range from mild to severe. It can resolve over a period of months or can persist for months or years.
- LC can be diagnosed on clinical grounds. No biomarker currently available demonstrates conclusively the presence of LC.
- LC can impair individuals' ability to work, attend school, take care of family, and care for themselves. It can have a profound emotional and physical impact on patients and their families and caregivers.

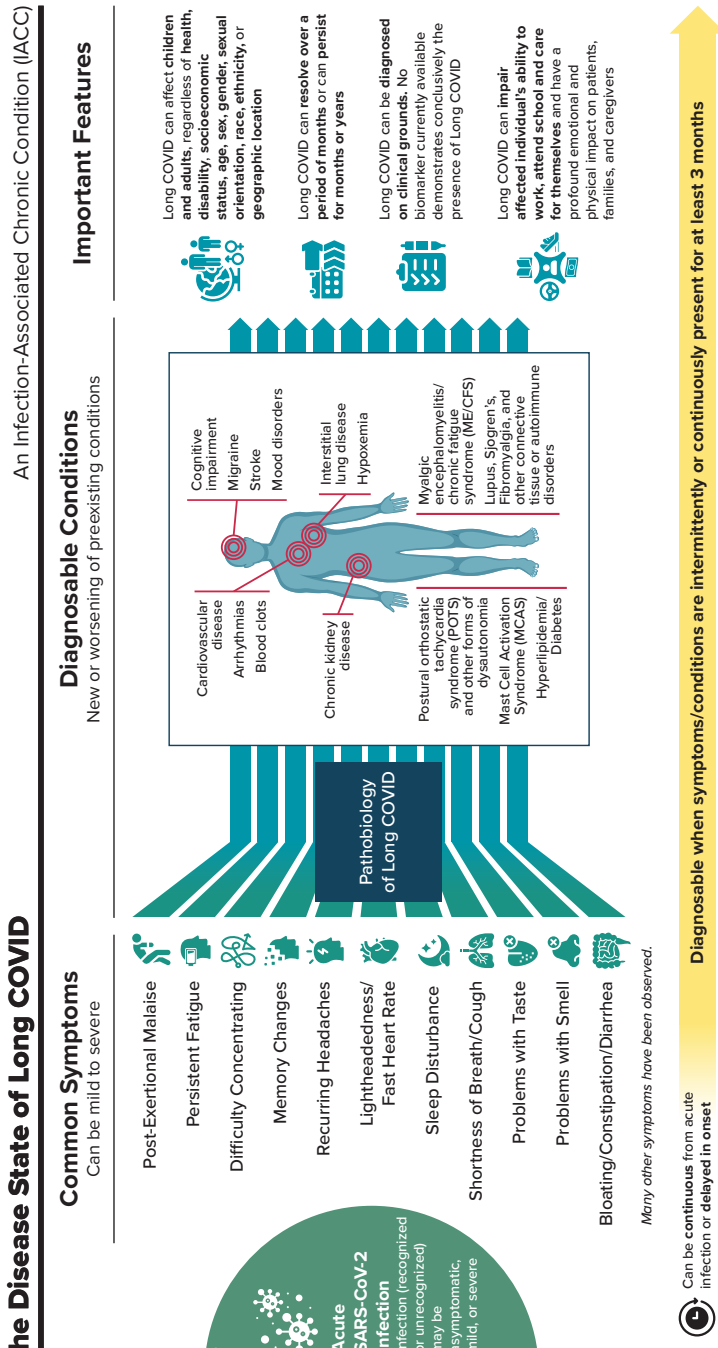


FIGURE 3 Definition figure: 2024 NASEM Long COVID definition.

# 2

# Defining Long COVID

## A DEFINITION DESIGNED TO EVOLVE AS NEW EVIDENCE AND UNDERSTANDING EMERGE

Evidence on the different presentations of Long COVID continues to emerge as the clinical and scientific understandings of Long COVID deepen. Because of this dynamic, the definition of Long COVID is expected to evolve, and the version described should be considered the "2024 NASEM Long COVID Definition." At this stage of understanding Long COVID, no definition can ensure that every affected individual will be correctly classified and that no others will be wrongly included. The 2024 NASEM Long COVID definition can only go as far as current science and evidence permit. With new evidence and better scientific understanding accumulating over time, the definition of Long COVID can and should be improved.

Relying on findings reported in the literature as well as on the engagement process, the committee proposed the 2024 NASEM Long COVID Definition. This definition identifies Long COVID as an infection-associated chronic condition (IACC), specifies a minimum duration of 3 months, and expressly incorporates common symptoms and diagnosable conditions characteristic of Long COVID. The bolded "Core Definition" is designed to be accurate and inclusive; the "Important Features" provide context and highlight notable aspects of Long COVID.

The committee hopes that this definition will:

- Aid clinicians in the consistent diagnosis, documentation, and treatment of Long COVID.
- Encourage further research into the pathophysiology, diagnosis, prognosis, consequences, and treatment of Long COVID.
- Enhance patient access to appropriate care, treatment, services, and benefits.
- Harmonize research and surveillance efforts on Long COVID, while providing researchers flexibility in the design of studies on Long COVID.
- Raise awareness and educate the public and policy makers about Long COVID.

### Balancing Risks of False Negative and False Positive Classification

Throughout its deliberations, the committee grappled with two contending objectives: to ensure that patients who experience Long COVID will be included in the definition and to avoid wrongly including patients whose conditions are not related to prior SARS-CoV-2 infection. This is a familiar dilemma in any diagnostic challenge, to balance the risks of false negative and false positive classification. The 2024 NASEM Long COVID Definition is intentionally inclusive, to satisfy the first objective. The committee acknowledges the potential for false positives with the definition. The committee believes the patient's treating clinician is best poised to strike the right balance between avoiding a false positive and a false negative classification.

All the symptoms and concomitant diagnosable conditions that are characteristic of Long COVID existed before the COVID-19 pandemic, and none are specific to Long COVID. What makes the case for association between symptoms and Long COVID is the temporal relation to the SARS-CoV-2 pandemic that may be documented as clinical findings or through patient self-report. The lack of biomarkers with high sensitivity and specificity for Long COVID is a major knowledge gap. As discussed later in this report, studies are underway to examine possible biomarkers for Long COVID, though none is yet dispositive for the disease state. Biomarkers may reinforce, or help exclude, a diagnosis of Long COVID, reducing the risk of false positives. Also discussed later is evidence for risk factors for developing Long COVID. As with any diagnosis, risk factors can be helpful in the clinical assessment of the probability of disease in any individual patient.

The definition does not require documentation of prior infection. Based on antibody surveys, more than three quarters of adult Americans had evidence of SARS-CoV-2 infection by the end of 2022, and it is reasonable to

estimate that 80–90 percent of all adult Americans were infected at least once between 2020 and the end of 2023 (CDC, 2024b).

In assessing a patient's condition and reaching a diagnosis, the clinician must take account of all aspects of a patient's history, symptoms, and signs, and test findings against the background of different disease probabilities. A clinician may need to overcome language, cultural, or educational barriers, and it may be difficult to elicit a complete and reliable history in patients who have experienced medical trauma or have cognitive impairment. It is incumbent on the clinician to consider alternative explanations of a patient's presentation and to balance the risks of false inclusion and of false exclusion in reaching any possible diagnosis.

A later section elaborates on applying the definition in clinical care, along with applications for research and for public health surveillance, and Appendix B defines key terms in the measurement of diagnostic performance.

## A Single Definition

The committee chose to put forth one broad definition for Long COVID that could apply to adults and children. Findings from the committee's engagement process indicate a desire for consistency between how Long COVID is defined in adults and children. An inclusive definition that sets appropriate boundary conditions (such as the minimum duration of symptoms) is designed to promote coordination among different audiences and purposes. For example, the results of research are more relevant when the study participants involved are like those identified in clinical practice. Public surveillance data can better inform disability policy when subjects of the former are defined similarly to those attempting to access benefits. Such a definition also helps ensure that compensation programs for loss of work or disability reflect the entirety of those affected by this chronic medical condition.

The committee sought to find balance between a single definition and the need to operationalize it for different purposes. Findings from the committee's engagement emphasize that the definition should encompass most, if not all, patients who are affected. More broadly, the committee sought to craft a definition usable in a variety of ways and for a range of purposes. In the final section of this report, the committee discusses how the definition can be applied to specific use cases. For example, as research and surveillance strive to answer many of the unknowns surrounding Long COVID, specific inclusion or exclusion criteria may be necessary to achieve the purposes of the particular study or surveillance.

## The Value Proposition for this Definition

The committee's central charge was to put forth a refined definition for Long COVID that lays the foundation for increased scientific understanding of the disease state and for better diagnosis and treatment of patients. The definition presented here includes a few notable features and specifically introduces a few new features that existing definitions lack.

The new definition provides explicit examples of common symptoms and conditions that are characteristic of Long COVID. Educating clinicians about common symptoms can improve the accuracy and speed of Long COVID diagnosis. Recognizing diagnosable conditions allows for the treatment of the specific conditions and communicates that these disorders are part of Long COVID. The definition reinforces divergent course patterns by describing the ongoing disease state as continuous, relapsing and remitting, or progressive.

The 2024 NASEM Long COVID Definition requires symptoms or conditions to be present for a duration of 3 months or longer. Notably, while symptoms need to be present for at least 3 months, the timing of those 3 months is unspecified. In particular, it is not necessary for symptoms to be experienced continuously from the time of the acute infection. The committee notes that this 3-month period allows for the spontaneous resolution of symptoms, evaluation for other diagnoses that might explain symptoms, and possible therapeutic trials to clarify the diagnosis. Although the definition specifies a minimum duration of 3 months to qualify as Long COVID, a clinician should recognize, acknowledge, and monitor concerning symptoms before the 3-month mark. These symptoms should be assessed and treated appropriately, and the ICD-10 code U09.9 (post COVID-19 condition, unspecified) may be used even before establishing a Long COVID diagnosis.

The committee developed this definition with equity in mind to recognize that social determinants and structural inequalities intersect to create health disparities (HHS, 2020) and to discourage stereotypical assumptions and biases that could prevent patients, clinicians, public health practitioners, researchers, and policy makers from recognizing all those who experience Long COVID. For example, a stereotypical assumption about conditions like Long COVID, which often present with more symptoms than definitive clinical signs, is that they are more common among affluent, highly educated white women. Such assumptions might deflect clinicians from recognizing that persons of color or young men might potentially have Long COVID. Considering this, one of the definition's important features is "Long COVID can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, gender, sexual orientation, race, ethnicity, or geographic location." Risk factors, per se, do not play a direct

part in the 2024 NASEM Long COVID Definition, though they are relevant to differential diagnosis, and a later section of this report summarizes current evidence about risk factors.

The definition does not require laboratory confirmation or other proof of initial infection. The initial infection may or may not have been recognized, in part due to the lack of availability of and limited access to tests early in the pandemic, limited sensitivity of some SARS-CoV-2 tests and the potential for false negatives, and an overall decline in testing rates later in the pandemic. However, the symptoms and diagnosable conditions characteristic of Long COVID can have alternative origins. If and as the background frequency of acute SARS-CoV-2 infection diminishes, as discussed earlier, other sources will likely become responsible for a growing proportion of cases. The probability that a particular clinical case is attributable to SARS-CoV-2 will be increased when there is evidence of prior, acute infection, or multiple infections, with that virus.

The definition firmly acknowledges the profound impact of Long COVID on function, and this has serious implications for the provision of services, accommodations, and benefits to patients.

## EVIDENCE SUPPORTING KEY ELEMENTS OF THE DEFINITION

The committee found no published, standardized guidelines for the development of disease definitions (Doust et al., 2017). The committee gleaned lessons from the process of developing and modifying definitions for other multi-symptom conditions such as ME/CFS and Gulf War Syndrome (IOM, 2014, 2015). As a first step in the committee's process, the committee articulated several possible key elements of a disease definition (Table 1). These key elements served as a framework for the committee as it developed and refined the definition of Long COVID. In the following section, the committee describes how the 2024 NASEM Long COVID Definition approaches each key element and provides a summary of the evidence from the scoping review and primary literature and also provides a summary of the findings from the engagement of multiple groups in support of its decisions.

In addition to the above key elements, the committee considered other foundational criteria in its deliberations. These foundational criteria are multi-factorial, layered, and interacting, and they were informed by many different frameworks and checklists (Doust et al., 2017; Moberg et al., 2018; NASEM, 2020). Those foundational criteria were:

**TABLE 1** Possible Key Elements of a Disease Definition

| Element | Description |
|---|---|
| Attribution | Source responsible for causing the disease |
| Time | Onset of disease |
| Clinical Features | Symptoms, symptom course and duration, and symptom severity of the disease to be defined |
| Equity | Identify persons affected and consider equity implications |
| Functional Impairment | Effect of the disease on daily activities |
| Exclusions/Alternative Diagnoses | Consideration of alternative diagnoses |
| Biomarkers and Laboratory Criteria | Objective tests (e.g., blood tests, neuroimaging, cognitive batteries) that help identify the disease |
| Risk Factors | Characteristics associated with a higher probability of disease or adverse outcome |

- **Precision:** A precise definition should be repeatable (agree in identical conditions), reproducible (agree across comparable conditions), and accurate (specific and sensitive).
- **Feasibility:** The definition must be reliably translated into operational terms for multiple different purposes and should be adaptable to a range of possible circumstances. The definition should consider the impact on resource usage.
- **Acceptability:** The definition should take account of stakeholders' values and preferences.
- **Accessibility:** The definition must be easily and equally well understood and applied by diverse stakeholders.
- **Balancing benefits and harms:** The definition should be guided by a balanced assessment of the anticipated benefits and harms, using the best available evidence, and considering both the individual and societal level.
- **Potential impact on health equity:** The definition should be equitable and should not perpetuate discrimination or inequities. The definition should also be perceived as equitable by socioeconomically, racially, culturally, and educationally minoritized groups and by those who have distinct historical experiences with the health system.
- **Unintended consequences:** The definition should consider potential for misuse, effect on measured incidence, changes to the apparent natural history of disease, suboptimal treatment of patients, psychological and financial consequences, and other adverse effects on individuals and society.

**How Does the Definition Address Attribution to Infection?**

**Definition**
occurs after SARS-CoV-2 infection

**Important Features**
LC can follow asymptomatic, mild, or severe SARS-CoV-2 infection. Previous infections may have been recognized or unrecognized.

Linking symptoms to a confirmed or suspected SARS-CoV-2 infection may be desirable in a Long COVID definition to reduce the risk of misdiagnosis of other conditions as Long COVID. However, the reality is that some, if not many, SARS-CoV-2 infections have gone unrecognized throughout the COVID-19 pandemic. Therefore, the 2024 NASEM Long COVID Definition states that Long COVID occurs after acute SARS-CoV-2 infection but does not require laboratory confirmation or other proof of initial infection. The definition emphasizes that Long COVID can follow infections of any severity (including asymptomatic infections), whether they were initially recognized or not.

Findings from both the engagement process and the evidence review highlighted the large number of SARS-CoV-2 infections, both throughout the pandemic and currently, that are not captured by testing and/or are not recorded in patients' medical records. Combined with the lack of a specific and sensitive test that can detect a past SARS-CoV-2 infection (e.g. antibody testing), this supports the committee's decision not to require laboratory evidence or formal diagnosis of an initial SARS-CoV-2 infection as part of the definition of Long COVID. Requiring such evidence would likely lead to underdiagnosis and raises equity issues. This aspect of the NASEM 2024 Long COVID definition is in accord with prior definitions the committee reviewed, none of which require laboratory evidence or formal diagnosis of infection. The evidence review also highlighted the challenges of attributing research study participants' symptoms and manifestations to SARS-CoV-2 infection; this task is likely to become more difficult as the population of never-infected individuals available for control groups decreases.

### *Findings from the Evidence Review*

Because no test for SARS-CoV-2 infection has perfect sensitivity and because the rates of false negatives on antigen and polymerase chain reaction (PCR) tests vary with time and other factors, some infected individuals will receive negative test results. For example, median real-time PCR

(RT-PCR) false negative rates vary from 38 percent on the first day of symptoms to 20 percent at day 3 after symptom onset and to 66 percent on day 21 (Davis et al., 2021; Dinnes et al., 2022; Kucirka et al., 2020). In addition to the possibility of false negatives on testing, some individuals were not tested or could not access testing during a suspected acute SARS-CoV-2 infection. Individuals experiencing an asymptomatic infection may not be tested for SARS-CoV-2, yet a variety of sequelae can occur after asymptomatic infections (Ma et al., 2023) or mild infections (Malkova et al., 2021). Individuals with an unrecognized or unconfirmed initial infection (including, potentially, those with a false negative test) can still develop Long COVID. A team at Northwestern Medicine investigated 61 patients with neurological symptoms linked to a suspected post-viral condition. They found no substantial difference in the average number of symptoms or the subjective perception of recovery between those who had a positive test for SARS-CoV-2 (n=32) and those without a positive SARS-CoV-2 test but who were found to have evidence of humoral or cellular SARS-CoV-2-specific immune responses during investigation (n=12) (Orban et al., 2023).

Because of these limitations, some clinicians and researchers have sought other ways to link ongoing symptoms to a possible past infection. Antibody testing can sometimes indicate a past SARS-CoV-2 infection, but antibody levels can fluctuate or wane over time. Vaccination against COVID-19 complicates antibody testing as it can cause positive results on some antibody tests (Fogh et al., 2022). Furthermore, the trajectories of antibody concentrations over time appear to differ between women and men after SARS-CoV-2 infection, and some research suggests that the sensitivity of antibody testing may be lower in women and may differ among age groups (Korte et al., 2021; Vashisht et al., 2021).

Attributing symptoms to a previous SARS-CoV-2 infection in a research study is a separate issue from attributing a particular patient's symptoms to a previous infection in clinical care. However, over time, the former may inform the latter. Sensitivity may be prioritized in diagnosis, while specificity may be prioritized in research. The inclusion of an uninfected control group in studies can be helpful in distinguishing manifestations specifically related to COVID-19 from those resulting from other causes. For example, one systematic review and meta-analysis with seven observational studies, including studies in adult and pediatric populations, found an increased risk of newly diagnosed diabetes mellitus in individuals with a past SARS-CoV-2 infection compared with uninfected individuals and compared with those with a past severity-matched influenza infection (Banerjee et al., 2022). Another systematic review and meta-analysis with over 20 million patients found an increased risk of acute myocarditis in individuals in their first year after confirmed SARS-CoV-2 infection compared with control subjects (Zuin et al., 2022).

A 2022 systematic review and meta-analysis of studies on Long COVID in children and adolescents (<19 years of age) by Behnood and colleagues highlights the need for high-quality data. Based on their analysis of five controlled studies, the only symptoms significantly more prevalent in cases than in controls were loss of smell (8 percent more), headaches (5 percent), cognitive difficulties (3 percent), sore throat (2 percent), and sore eyes (2 percent). Meanwhile, reported symptom prevalence was much higher in the 17 uncontrolled studies, and higher study quality was associated with lower prevalence of symptoms, except for smell loss and cognitive problems. The authors point out that including control or comparison groups in studies can help researchers distinguish symptoms resulting from SARS-CoV-2 infection from those resulting from other factors, such as background symptoms and concurrent social changes during the pandemic (Behnood et al., 2022). But control group comparisons also have limitations in knowing for certain that those in control groups do not have unrecognized prior SARS-CoV-2 infections. An evidence-mapping study based on a search conducted in November 2021 found that only 15 percent of 565 included studies on Long COVID had a control group; this may be a limitation of the current evidence base (Franco et al., 2022). Researchers may face rising challenges in including control or comparison groups in studies as the percentage of the U.S. and global populations with no history of SARS-CoV-2 infection continues to shrink.

### *Findings from the Engagement Process*

Participants suggested that requiring laboratory confirmation of SARS-CoV-2 infection would be too exclusive and observed that numerous individuals never received a laboratory confirmation of SARS-CoV-2 from a medical professional. Therefore, requiring a laboratory confirmation of a SARS-CoV-2 infection may result in barriers to health coverage or benefits. Regarding access to testing, a focus group participant said, "*A lot of marginalized people didn't have access to testing, and a lot of people in city centers got infected very early in the pandemic when testing was not available. That includes some of our poorest citizens.*" Phrases such as "probable COVID-19" or "suspected COVID-19" were supported in the definition to foster inclusivity. Some suggested that a patient-centered definition that attributes infection according to the patient's lived experience would be more appropriate.

### *Lessons from Existing Definitions*

The existing Long COVID definitions considered in this report do not mention whether a patient ever had a positive COVID-19 test. The WHO

Adult and WHO Pediatric definitions state that Long COVID may follow "probable" or "confirmed" SARS-CoV-2 infection, and the NICE definition uses the phrase "during or after an infection consistent with COVID-19." The CDC and NIH definitions acknowledge the possibility of Long COVID developing after an asymptomatic or unrecognized acute infection.

**How Does the Definition Address Onset and Duration?**

**Definition**
is present for at least 3 months

**Important Features**
LC can be continuous from the time of acute SARS-CoV-2 infection or can be delayed in onset for weeks or months following what had appeared to be full recovery from acute infection.

One of the most important elements that the committee wanted to clarify is the timeframe used in a definition for Long COVID. A Long COVID definition may address the minimum or maximum time after the onset of initial COVID symptoms that a medical condition can be designated as Long COVID as well as the minimum duration of symptoms needed to qualify for a Long COVID diagnosis. Precision with time course and duration may be an opportunity to create a more meaningful, specific definition of Long COVID that can prevent the misdiagnosis of patients who have continuing symptoms from a pre-existing illness or symptoms from a new-onset, unrelated illness. Decisions regarding duration and latency time can also affect eligibility for care, reimbursement, or benefits.

From the engagement process, the committee determined that 4 weeks of symptoms was likely too short to be defined as Long COVID, because in many cases, SARS-CoV-2-related symptoms that persist for 4 weeks will resolve shortly thereafter. The current evidence base regarding symptom resolution trajectories has limitations, but the literature review generally suggests many people have symptoms that resolve in a matter of weeks, while the smaller group of individuals with symptoms that last at least 3 months have a higher chance of persistent symptoms to at least 1 year. Both the evidence review and the engagement process highlighted that some individuals have onset of symptoms that is delayed by weeks or months after an apparent recovery from initial infection, although the frequency of delayed onset is unclear. Because there is still ambiguity regarding the relationship between the timing of SARS-CoV-2 infection relative to Long COVID onset, the committee chose not to include a maximum latency

period. Although this action may lead to an increase in the number of people diagnosed with Long COVID, any maximum latency chosen would be speculation without the backing of scientific evidence. Furthermore, such a move might exclude people who develop delayed onset Long COVID, did not recognize they might be affected by Long COVID until later in its course, or were not able to access care due to the availability or restrictive criteria of some Long COVID clinics. Additionally, research into delayed onset Long COVID or the long-term consequences of Long COVID might be discouraged were an artificial cut-off time established. The committee anticipates that as more knowledge is gained about Long COVID, methods (e.g. biomarkers for Long COVID) will emerge to help distinguish Long COVID from other conditions regardless of latency time.

The 2024 NASEM Long COVID Definition specifies 3 months as the minimum duration of symptoms, which means that 3 months after infection, whether consistent or relapsing and remitting, is the earliest that symptoms can be designated as Long COVID. In cases with delayed onset, the minimum 3-month duration would still apply but could begin at any time. Some individuals may present with persistent symptoms linked to COVID-19 before 3 months have elapsed; the ICD general code U09.9 (post COVID-19 condition, unspecified) is available for these patients. The committee would like to emphasize that individual symptoms or diagnosable conditions should be recognized and treated regardless of whether 3 months have elapsed.

### *Findings from the Evidence Review*

Most patients with acute SARS-CoV-2 infection recover after a period of days to weeks. A 3-month cutoff will likely provide enough time for most patients to recover from acute manifestations of COVID-19. The Global Burden of Disease Long COVID Collaborators conducted an observational analysis of 1.2 million people in 22 countries, using data from 54 studies plus two medical record databases. Considering three Long COVID symptom clusters (persistent fatigue with bodily pain or mood swings, ongoing respiratory problems, cognitive problems), the authors estimated that 6.2 percent of individuals with a history of symptomatic SARS-CoV-2 infection had one or more of these symptom clusters at 3 months post-infection (Wulf Hanson et al., 2022). Among 10 studies analyzed within a systematic review on Long COVID prevalence and manifestations, the prevalence of failure to recover full health and fitness by 12 weeks after infection ranged from 8 percent to 70 percent, with a pooled estimate of 34.5 percent (prediction interval, 4.3–85.9 percent) (Woodrow et al., 2023). The choice of a 3-month minimum duration may allow for the resolution of temporary symptoms that are due to non-medical circumstances (e.g., overwork,

stressful situations, medication side effects) or due to medical conditions other than COVID-19. A 3-month cutoff may also allow for evaluation and treatment for alternative conditions with similar initial presentations.

Another factor that influenced the committee's decision to choose a 3-month duration is that several primary studies suggest that people who have symptoms that persist for several months may have a high chance of still having symptoms at 1 year after infection. Among a cohort of unvaccinated adults randomly sampled from all confirmed wild-type SARS-CoV-2 infections in Zurich, Switzerland (which had mandatory reporting) (n=1,106), 72.9 percent of the infected reported that they had recovered fully within 3 months, including 55.3 percent within 1 month and 17.6 percent between 1 and 3 months post-infection. Meanwhile, 27.1 percent, 22.9 percent, and 18.5 percent of the infected individuals said they had not fully recovered at 3, 6, and 12 months, respectively, meaning that 4.2 percent of patients experienced recovery between 3 and 6 months and 4.4 percent between 6 and 12 months (Ballouz et al., 2023). An analysis of the ComPaRe Long COVID cohort found that 85 percent of patients who were experiencing symptoms at 2 months were still experiencing symptoms at 12 months after infection. The limitations of this study include the lack of an uninfected comparison group and the possibility that patients with more symptoms were recruited (Tran et al., 2022).

Delayed onset of Long COVID symptoms after apparent recovery from acute COVID-19 has been reported. In a survey-based, 7-month international study of individuals with confirmed or suspected Long COVID, some respondents reported recovery from symptoms within the first 4 weeks to 2 months of their initial illness followed by a relapse or the appearance of new symptoms in months 3, 4, or 5. However, this pattern was uncommon within the study population (Davis et al., 2021).

### *Findings from the Engagement Process*

Participants indicated that the disease's onset should be included in the definition; however, there were varying opinions on the specific approach to include such information. One participant said, *"The time frame is critical. I think 4 weeks is too short. WHO uses 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation. I think this is much better."* Furthermore, participants raised the duration of Long COVID as an important but ambiguous topic that should be addressed in the definition. Many noted that Long COVID may manifest in different ways and last different lengths of times, and yet

it is unknown whether Long COVID symptoms will persist indefinitely. Participants emphasized the importance of including the relapsing and remitting nature of Long COVID symptoms. One participant said, "*There are people for whom acute symptoms fade, and they have a period of wellness and then their long-term symptoms arise several months after the original acute infection. It's not the most common pattern, but it is common enough that we keep seeing it, and I am not sure that the current timelines accommodate that.*"

### *Lessons from Existing Definitions*

The WHO Adult definition states that Long COVID symptoms usually appear 3 months after initial infection, and the WHO Pediatrics definition includes a maximum latency time, stating that Long COVID symptoms initially occur "within 3 months of acute COVID-19." Both the WHO Adult and the WHO Pediatric definitions state that symptoms must last "at least 2 months" to be designated Long COVID. By contrast, the 2024 NASEM Long COVID Definition requires symptoms or manifestations to persist for at least 3 months and does not give a maximum latency time, instead recognizing that Long COVID can first appear weeks or months after an apparent recovery.

The U.S. definitions either reference 4 weeks (OASH and CDC) after infection as the earliest that Long COVID can be identified or do not give a specific earliest time point (NIH).

Patients experiencing symptoms 3–6 weeks or 4–12 weeks after infection may or may not develop illness that persists beyond that point. It may be desirable to accommodate patients seeking treatment before 3 months have elapsed while acknowledging the uncertainty over individual patients' future course of symptoms. Of the existing definitions covered here, only the NICE definition separates patients into two temporal subsets: signs and symptoms occurring between 4 and 12 weeks are "ongoing symptomatic COVID-19," and signs and symptoms that last beyond 12 weeks are "post-COVID-19 syndrome." According to NICE, both subsets can be considered Long COVID. The NICE definition also states, "Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed."

**How Does the Definition Address Symptoms, Temporal Pattern and Duration of Symptoms, and Symptom Severity?**

**Definition**
continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.

**LC manifests in multiple ways.** A complete enumeration of possible signs, symptoms, and diagnosable conditions of LC would have hundreds of entries. Any organ system can be involved, and LC patients can present with

- **single or multiple symptoms, such as** shortness of breath, cough, persistent fatigue, post-exertional malaise, difficulty concentrating, memory changes, recurring headache, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation, and diarrhea.
- **single or multiple diagnosable conditions, such as** interstitial lung disease and hypoxemia, cardiovascular disease and arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), fibromyalgia, connective tissue diseases, hyperlipidemia, diabetes, and autoimmune disorders such as lupus, rheumatoid arthritis, and Sjogren's syndrome.

**Important Features**
LC can range from mild to severe. It can resolve over a period of months or can persist for months or years.

LC can exacerbate pre-existing health conditions or present as a new condition.

The 2024 NASEM Long COVID Definition does not list any symptoms or conditions as required and does not list any symptoms or conditions as exclusionary; this may have the effect of lessening the specificity while increasing the sensitivity of the diagnosis. The symptoms and conditions listed in the definition are chosen to be representative of the hundreds of symptoms currently identified in the Long COVID population to date, but the intent was not to downgrade other symptoms. A complete enumeration

of signs, symptoms, and diagnosable conditions of Long COVID would have more than 200 entries. For example, one study estimated the prevalence of 203 symptoms in multiple organ systems (systemic, neuropsychiatric, reproductive, cardiovascular, musculoskeletal, immunological, head/ear/eye/nose/throat, pulmonary, gastrointestinal, and dermatologic) (Davis et al., 2021). Furthermore, Long COVID may present differently in different individuals, and a single set of illustrative symptoms cannot precisely capture all presentations of Long COVID.

Not every delayed consequence of acute SARS-CoV-2 will satisfy the definition of Long COVID. For example, chronic impairment of cardiac function could satisfy the definition's criterion of persistence for at least 3 months. However, an elevated incidence of acute myocardial infarction in the year following acute SARS-CoV-2 infection, as reported by Xie et al., 2022, would not meet the 3-month persistence criterion. Such delayed, acute events, although attributable to prior SARS-CoV-2 infection, would not in themselves qualify as Long COVID in accordance with the proposed definition.

In reviewing the evidence for Long COVID symptoms, the committee reviewed a large and diverse evidence base describing and investigating new symptoms and manifestations of Long COVID in different organ systems. The committee also reviewed studies indicating exacerbation of pre-existing conditions. The process of narrowing down a list of hundreds of reported signs, symptoms, and diagnosable conditions identified in the evidence review was challenging. In selecting the illustrative symptoms and diagnosable conditions, the committee considered prevalence data from the evidence and the engagement process. In future iterations of the Long COVID definition, it may be desirable to enlist specific inclusion criteria for the illustrative symptoms, such as a threshold frequency of their occurrence among patients and specificity to Long COVID. Multiple studies reported variable severity and variable time courses of symptoms among individuals with Long COVID, including examples of fluctuating, worsening, new-onset, improving, resolving, and stable courses for individual symptoms. Participants in the engagement process favored inclusion of a non-exhaustive list of possible symptoms and conditions in the definition, and there was strong support for including language around the fluctuating time course of some individuals' symptoms. Some of the previously developed Long COVID definitions do give examples of common symptoms, and some mention relapsing-remitting and other possible time courses of symptoms, while others do not discuss these aspects. The committee elected to include both aspects in the 2024 NASEM Long COVID definition.

*Findings from the Evidence Review*

**Signs, Symptoms, and Conditions:** Disease definitions may or may not include listings of specific signs, symptoms, or symptom clusters; some definitions include required symptoms or symptom clusters. These choices can affect the balance between specificity and inclusivity of a definition. The 2024 NASEM Long COVID Definition includes a non-exhaustive list of possible manifestations but does not require any specific manifestation.

Several studies and reviews have examined the most common or most specific symptoms and manifestations of Long COVID. For example, a RECOVER Initiative prospective cohort study (Figure 4) with 9,764 U.S. adults identified symptoms that were more frequent in individuals at a study visit 6 months or more after a positive SARS-CoV-2 test result than in individuals with no known infection history. The authors developed a Long COVID (post-acute sequelae of COVID-19, or PASC) score based on 12 symptoms; among these symptoms, there was a 15 percent or greater absolute difference between infected and uninfected individuals in frequencies

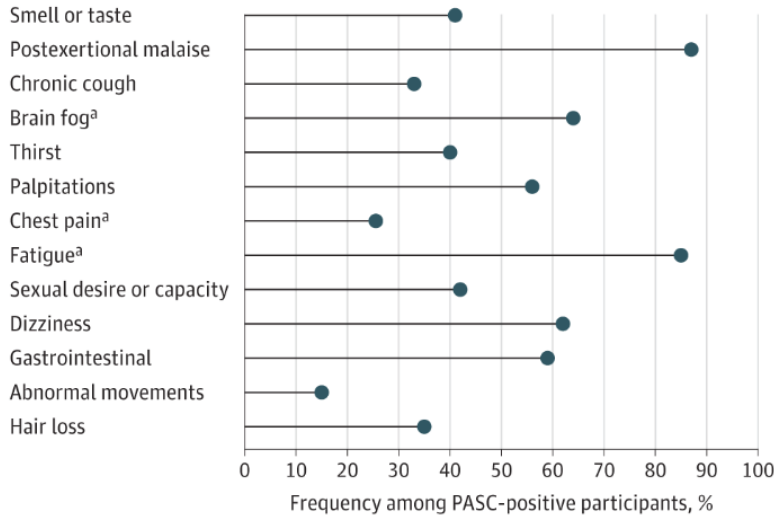


**FIGURE 4** Frequencies of new onset symptoms.
NOTE: Among participants with Long COVID, the most common symptoms were post-exertional malaise (87 percent), fatigue (85 percent), brain fog (64 percent), dizziness or lightheadedness (62 percent), GI (59 percent), and palpitations (57 percent).
SOURCE: Thaweethai et al., 2023.

of post-exertional malaise, fatigue, brain fog, dizziness, and gastrointestinal (GI) symptoms. Several other symptoms, such as shortness of breath, were common but were not included in the score because they were correlated with included symptoms (Thaweethai et al., 2023). Woodrow and colleagues conducted a systematic review of studies on Long COVID prevalence and manifestations that were published in 2020 and 2021. They found that fatigue, breathing problems, sleep problems, tingling or itching, and joint or muscle pain were among the most commonly reported Long COVID symptoms (Woodrow, 2023).

In a 2021 analysis, Deer and colleagues used the Human Phenotype Ontology (HPO) standardized vocabulary to integrate data from 81 cohorts of patients who were at least 3 weeks post SARS-CoV-2 infection. The use of HPO vocabulary allowed the authors to combine data from cohorts based on patient reports, clinical examinations, and electronic health record (EHR) data pulls, helping overcome the challenge of heterogeneity in how patients and clinicians describe the same symptoms. The authors identified 287 phenotypic abnormalities; 155 of these abnormalities were reported in two or more cohorts and 25 were reported in 12 or more cohorts (Deer et al., 2021).

Numerous primary studies and systematic reviews have investigated sequelae of SARS-CoV-2 infection in specific body systems. A non-exhaustive sampling from this large literature base is presented here.

*Cardiovascular and Pulmonary Symptoms and Conditions* Many research teams have documented cardiovascular and pulmonary sequelae of SARS-CoV-2, including interstitial lung disease and other lung abnormalities (Bazdar et al., 2023; Woodrow et al., 2023); a new or increased requirement for supplemental oxygen (Admon et al., 2023); platelet pathology and thromboembolic disorders (Pretorius et al., 2022; Shah et al., 2023; Turner et al., 2023); and arrhythmias and tachycardia (Mohammad et al., 2022).

*Autonomic Symptoms and Conditions* Multiple research teams have investigated autonomic symptoms and conditions following SARS-CoV-2 infection. A Stanford-based, international study that recruited mainly through social media and in COVID-19 and Long COVID support groups surveyed adults with a history of test-confirmed or test-unconfirmed SARS-CoV-2 infection. Of 2,314 surveyed adults (87.3% female) who had symptoms persisting beyond 30 days, 66% had median scores of 20 or greater on the Composite Autonomic Symptom 31 (COMPASS-31) assessment, indicating moderate to severe autonomic dysfunction (Larsen et al., 2022). Among 42 patients with moderate to severe post-COVID-19 fatigue and exertion intolerance who were evaluated by a medical team in Berlin, 32 patients also had COMPASS-31 scores above 20 (Kedor et al., 2022). An

Australian team evaluated 33 adults with PASC who either presented to a cardiology clinic or were recruited from a Long COVID support group. These participants had a median total COMPASS-31 score of 38, and 79 percent met the criteria for postural orthostatic tachycardia syndrome (POTS) (Seeley et al., 2023).

A systematic review of the literature as of April 2022 examined cases of new-onset autonomic dysfunction affecting the cardiovascular system within 6 weeks of confirmed SARS-CoV-2 infection. In the acute phase, reflex syncope was the most common form of autonomic dysfunction affecting the cardiovascular system, while in the chronic phase (>4 weeks after infection), POTS was the most common form. Patients with autonomic dysfunction >4 weeks after infection were mostly female and younger; only 15 percent of these patients experienced a full recovery during the follow-up period (19 ± 16 weeks) (Reis Carneiro et al., 2023).

*Neurological and Psychiatric Symptoms and Conditions* Multiple authors have investigated neurological and psychiatric complications and symptoms following SARS-CoV-2 infection, including stroke, migraine, smell and taste problems, cognitive impairment, difficulty concentrating, anxiety, and mood disorders (Crivelli et al., 2022; Nuzzo et al., 2021; Ong et al., 2023; Park et al., 2022; Premraj et al., 2022; Wingrove et al., 2023; Xu et al., 2022). A weighted analysis of a large Department of Veterans Affairs dataset, based on electronic health records, showed increased risk of epilepsy and seizures (hazard ratio 1.80), of cognition problems (hazard ratio 1.80), and of other neurologic sequelae in patients 12 months post SARS-CoV-2 infection compared with uninfected controls (Xu et al., 2022). To investigate sleep disturbances following COVID-19, Linh and colleagues conducted a systematic review and meta-analysis of worldwide studies focusing on adults at least 1 month following a SARS-CoV-2 infection. In the subset of studies with an uninfected or pre-infection control group, the authors found an increased prevalence of sleep disturbances in post-COVID-19 patients, with an odds ratio of 2.00 (1.28, 3.14) (Linh et al., 2023). A large community-based study in the United Kingdom (112,964 participants aged 18 or older) used a computerized cognitive test battery to evaluate cognitive functioning in individuals who had recovered from COVID-19 within 4, 4–12, or >12 weeks; individuals who reported unresolved persistent symptoms and were at least 12 weeks post-infection; and individuals who had no history of COVID-19. Results showed that participants whose COVID-19 symptoms had resolved had small deficits in cognitive performance (approximately –0.2 standard deviation on average) compared with those with no history of infection. Those with unresolved

symptoms beyond 12 weeks after infection had greater deficits in performance on cognitive tasks (approximately –0.4 SD on average), particularly in memory, reasoning, and planning tasks. Having had a more severe acute infection and having been infected during earlier periods in the pandemic were each associated with higher probabilities of cognitive impairment (Hampshire et al., 2024). It is important to note that some studies have not confirmed cognitive impairment in cohorts of Long COVID patients. In a narrative literature review by Garmoe and colleagues, most studies supported the occurrence of cognitive impairment in some individuals after SARS-CoV-2 infection, but a subset of three small studies (n=49–189 patients) failed to demonstrate cognitive dysfunction attributable to COVID-19 up to 6 months after infection (Garmoe et al., 2024).

*Systemic, Musculoskeletal, Rheumatic, and Immune-Related Symptoms and Conditions* Multiple research teams have documented post-COVID-19 systemic, musculoskeletal, rheumatic, and immune-related complications, including new-onset lupus, rheumatoid arthritis, and Sjogren's syndrome (Chang at al., 2023; Ciaffi et al., 2023; Kioi et al., 2023). Studies have also reported hyperlipidemia (Xu et al., 2023) and new-onset diabetes (Qeadan, et al., 2022). For example, a retrospective analysis of data from 27 million U.S. patients found that having a diagnosed SARS-CoV-2 infection was associated with significantly increased risk of new-onset type 1 diabetes mellitus compared with individuals with no history of SARS-CoV-2 infection, and this risk was disproportionately higher among American Indian/Alaska Native, Asian/Pacific Islander, and Black participants (Qeadan et al., 2022). Additionally, other teams have investigated similarities and possible overlap between Long COVID mast cell activation syndrome (MCAS) (Szukiewicz et al., 2022), fibromyalgia (Clauw and Calabrese, 2024; Gavrilova et al., 2022; Savin et al., 2023), and connective tissue disorders like Ehlers-Danlos syndrome (EDS) (Lim et al., 2023; Pollack et al., 2023). The RECOVER Initiative and several studies have documented that up to 40 percent of patients with clusters of persistent symptoms meet the diagnostic criteria for ME/CFS following SARS-CoV-2 infection (Bonilla et al., 2023; Kedor et al., 2022; Mancini et al., 2021; Sherif et al., 2023). Persistent fatigue following SARS-CoV-2 infection is well-documented (Sherif et al., 2023; Zhao et al., 2023).

*Exacerbation of Pre-Existing Conditions* Long COVID can present as a new condition that develops after SARS-CoV-2 infection. It can also worsen pre-existing health conditions, as shown in several studies. Among individuals with pre-existing type 1 diabetes, a history of SARS-CoV-2 infection was associated with an increased risk of experiencing diabetic

ketoacidosis (Qeadan et al., 2022). The American Diabetes Association's Standards of Care in Diabetes—2024 guideline provides information on the occurrence of new-onset diabetes after SARS-CoV-2 infection and includes a recommendation that individuals with underlying diabetes who have had COVID-19 should receive follow-up to assess possible complications and symptoms (American Diabetes Association Professional Practice Committee, 2024). Among patients with POTS evaluated at a University of Toledo center, 68 percent (28/41) of those infected with SARS-CoV-2 had a worsening of their baseline POTS symptoms that persisted more than 1 month post-infection, and 29 percent had persistent, exacerbated symptoms despite escalation of therapy (Meenakshisundaram et al., 2024).

**Temporal Pattern and Duration of Symptoms:** Another notable feature of Long COVID is the variable course of symptoms. An international survey distributed primarily to participants in COVID-19 support and advocacy groups found that 85.9 percent of respondents who had experienced COVID-19-related illness for at least 28 days reported that they had experienced relapses of symptoms during the survey period (which spanned up to 7 months) (Davis et al., 2021). In the ComPaRe Long COVID cohort (968 patients), part of a prospective study in France, 33.3 percent of 150 participants who reported full symptom remission later experienced a relapse (Tran et al., 2022). Other studies provide evidence that neurocognitive symptoms can worsen over time and that new manifestations, such as cognitive symptoms, post-exertional malaise, paresthesia, and parosmia, commonly appear for the first time months after the initial infection (Apple et al., 2022; Davis et al., 2021; Tran et al., 2022). In a ComPaRe Long COVID cohort study, the prevalence of individual symptoms decreased (e.g., cough, change/loss of taste), increased (e.g. paresthesia, back/neck pain), or remained stable (e.g., dyspnea, word finding problems) between 2 months and 1 year after infection (Tran et al., 2022). Similarly, in a systematic review and meta-analysis based on 63 articles published worldwide in September 2021 or earlier, Alkodaymi and colleagues found that certain symptoms (cough, loss of taste, loss of smell, headache) were most commonly reported during the 6- to <9-months follow-up interval, while other symptoms (fatigue, myalgia, dyspnea, and sleep disorder) were most common in the >12-month follow-up period (Alkodaymi et al., 2022).

In an integrated model for overall symptom trajectory proposed by Fernández-de-las-Peñas and coauthors, post-COVID-19 symptoms are divided into "new-onset" (symptoms that first appeared after infection with COVID-19) and "exacerbated" (pre-existing symptoms that worsened after infection with COVID-19); symptoms can be further labeled as

"fluctuating," "progressive," and "continuous." (Fernandez-de-las-Penas et al., 2021a).

Several studies provide data on the overall durations of symptoms among patients. Among 1,106 randomly sampled adults with wild-type SARS-CoV-2 infections from Zurich, Switzerland (which had mandatory reporting), 27.1 percent, 22.9 percent, and 18.5 percent of infected individuals said they had not fully recovered at 3, 6, and 12 months after infection, respectively (Ballouz et al., 2023). The ComPaRe Long COVID cohort study found that, of patients experiencing symptoms at 2 months post-infection, 85 percent still had symptoms at 12 months after infection (Tran et al., 2022). Symptoms and conditions associated with Long COVID can persist for multiple years. For example, a large Department of Veterans Affairs cohort study found that 2 years after infection, participants who had not been hospitalized during their acute infection still had an increased risk for 24 of 77 sequelae analyzed, including sequelae affecting the neurologic, musculoskeletal, and gastrointestinal systems. Meanwhile, participants who had been hospitalized during the acute phase had an increased risk of 50 of 77 sequelae at 2 years, including those affecting every organ system (Bowe et al., 2023).

**Severity of Symptoms:** Long COVID symptoms can range from mild to severe. In the RECOVER Initiative study by Thaweethai and colleagues in which the authors developed a PASC score based on 12 symptoms, patients who met the authors' criteria for PASC had responses on the Patient-Reported Outcomes Measurement Information System (PROMIS) Global 10 scale ranging from "not at all" to "completely" for ability to carry out every day physical activities, and responses ranging from "poor" to "excellent" on both quality of life and general physical health. Higher PASC score was associated with worse responses on PROMIS Global 10 (Thaweethai et al., 2023). As of 2023, estimates suggest that over 5,000 U.S. death certificates have attributed Long COVID (or related terms) as an underlying or contributing cause of death (Ahmad et al., 2022; Rapaport, 2024).[1] A large Department of Veterans Affairs cohort study found that veterans who had been hospitalized with COVID-19 had an elevated risk of death that persisted throughout the 2-year follow-up period, compared with a control group of veterans with no known SARS-CoV-2 infection. Compared with the control group, veterans who were not hospitalized during their acute COVID-19 illness were at increased risk of death during days 91–180 and at increased risk of hospitalization during days 361–540 following their acute infection (Bowe et al., 2023).

[1] This sentence was modified after release of the prepublication version of the report to be more consistent with the cited references.

*Findings from the Engagement Process*

Participants noted that many people will understand Long COVID through symptoms. Including a list of possible symptoms and conditions associated with Long COVID could help participants understand the breadth and severity of Long COVID. Participants emphasized inclusion of the most common symptoms: *"I do think that listing the three or four major symptoms that most studies are showing—brain fog, fatigue, shortness of breath—should be part of the definition";* another proposed, "C*ognitive dysfunction is as important to include as physical symptoms, especially since cognitive dysfunction is highly stigmatized*." Participants also emphasized the relapsing and remitting nature of symptoms. Some mentioned that these recurring symptoms hindered access to proper care, as some physicians lacked an understanding or were skeptical of this pattern. For instance, one participant said, *"Many of my patients, when we would talk about the definition, would find it validating that the definition itself from the WHO said that the symptoms were intermittent. I think that's a key part of the definition, because the patients have often experienced medical gaslighting. A lot of that is due to the inconsistency of the symptoms. I liked having that phrase in the definition that I can tell my patients, 'Look, that's part of this condition, and this is what you could show your employer and your family.' I like that."*

*Lessons from Existing Definitions*

The OASH and CDC definitions acknowledge the heterogeneity of presentations by including wording like "multisystemic" and "wide range" without listing specific symptoms. The NICE definition also mentions "clusters of symptoms" but does not list specific symptoms and acknowledges that symptoms may be multisystemic and heterogeneous. By contrast, the WHO Adults and Pediatrics definitions give specific common symptoms, while stating that other symptoms may appear. It is useful to consider whether any symptom or cluster of symptoms could be considered a hallmark or cardinal symptom of Long COVID. However, considering the heterogeneity of Long COVID manifestations, a definition that does not require any specific symptom or symptom cluster has the advantage of reducing false negative classifications. A definition that provides a non-exhaustive list of common symptoms may help balance the goals of specificity and inclusivity. The OASH definition includes the phrase "with the possibility of severe and life-threatening events even months or years after infection." The other existing definitions considered here do not directly mention severity, though both WHO definitions state that symptoms generally impact everyday functioning. A sound definition asserts what a term means rather than stating

what it does not mean; hence the 2024 NASEM Definition avoids stating, for example, that Long COVID is not one condition.

### How Does the Definition Address Equity?

**Important Features**
LC can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, gender, sexual orientation, race, ethnicity, or geographic location.

The 2024 NASEM Long COVID Definition does not exclude patients based on demographic factors, preexisting conditions, vaccination status, or history of antiviral use. This definition applies to both adult and pediatric patients.

Equity needs to be considered at multiple steps in a Long COVID patient's journey to obtain care and services. Socioeconomic factors, inequality, discrimination (based on race and gender, among others), bias, and stigma affect whether patients can receive a diagnosis and benefit from Long COVID-targeted health care or services. These factors include but are not limited to access to COVID-19 testing during acute illness, access to evaluation for possible Long COVID, the willingness of physicians to diagnose a particular patient, access to insurance benefits, and patients' fears of stigmatization that could result from having a Long COVID diagnosis (Bergmans et al., 2023; HHS and OASH, 2022; Kim et al., 2023; Kromydas et al., 2023).

Among participants in the engagement process, there was support for recognition of the impact of social determinants of health on the risk of Long COVID, the impact of cultural factors on decisions to seek health care, and the impact of Long COVID itself on financial status, especially among those with fewer economic resources. In the evidence review, the committee encountered data gaps, highlighting the possibility that underdiagnosis of Long COVID in communities with less healthcare access and under-representation of or under-reporting on some non-white groups in Long COVID research is influencing the Long COVID research base. However, the committee found evidence suggesting that Long COVID more frequently affects women, and some research supporting differences in Long COVID prevalence or manifestations among different age groups, among different racial and ethnic groups, or based on vaccination status. While the committee recognizes such differences in risk factors, the 2024 NASEM Long COVID Definition emphasizes that a Long COVID diagnosis may be considered regardless of health status, vaccination history, or demographics.

*Findings from the Evidence Review*

Social, economic, and environmental factors may affect individuals' risk for and burden of Long COVID as well as their access to health care for diagnosis and management of Long COVID. Among non-hospitalized individuals who experienced acute SARS-CoV-2 infection, one study found an 11 percent increased risk (HR 1.11, 95% CI 1.07–1.16) of COVID-19 symptom persistence among people in the most socioeconomically deprived versus the least deprived category (Subramanian et al., 2022). Researchers analyzing zip code and electronic health record data from two large clinical research networks found that among people with COVID-19, exposure to disadvantaged environmental characteristics (including certain air pollutants, limited food access, and overall neighborhood deprivation) was associated with increased risk for Long COVID (Zhang et al., 2023).

Numerous studies indicate that Long COVID is more frequently diagnosed and reported among women (Government of Canada, 2023; M. M. Jacobs et al., 2023; Sylvester et al., 2022). The U.S. Census Bureau and the National Center for Health Statistics' Household Pulse survey data from March 5 to April 1, 2024, which is based on self-reports, estimates that 21.1 percent of adult women and 13.9 percent of adult men in the United States have ever experienced Long COVID-19 symptoms that lasted 3 months or longer (CDC, 2024a). In the pediatric population as well, girls may be at greater risk for Long COVID (Zheng et al., 2023). The frequencies of specific Long COVID symptoms and manifestations may differ between women and men, and there is some evidence for sex-specific differences in immunological responses during Long COVID (Jiang et al., 2023; Silva et al., 2024; Sylvester et al., 2022). Additional evidence regarding sex- and gender-related risk factors for Long COVID is discussed below in the section "How Does the Definition Address Risk Factors?"

Results of some analyses suggest that the risk of Long COVID after an acute infection may differ among racial and ethnic groups in the United States, with most studies indicating a higher risk for Hispanic and Black individuals and a lower risk for Asian individuals compared with non-Hispanic White individuals (CDC, 2024a; Cohen and van der Meulen Rodgers, 2023; M. M. Jacobs et al., 2023; Louie and Wu, 2023). Members of other racial and ethnic groups, such as American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and multiracial individuals, are not tracked separately in most studies. The risk of Long COVID among these groups is currently a data gap.

In the U.S. Census Bureau and National Center for Health Statistics' Household Pulse survey data from March 1 to April 1, 2024, 21.2 percent of adult Hispanic or Latino respondents, 17.7 percent of non-Hispanic White respondents, 12.9 percent of non-Hispanic Black respondents, 12.1

percent of non-Hispanic Asian respondents, and 20.7 percent of non-Hispanic members of other races and multiple races reported having ever experienced Long COVID-19 symptoms that lasted 3 months or longer (CDC, 2024a). A two-stage modeling analysis based on Household Pulse data (four releases between June 1, 2022, and October 17, 2022) by Jacobs and colleagues (2023) that considered only participants who had COVID-19 found a comparatively higher risk of Long COVID among Hispanic participants and a slightly higher, statistically significant risk of Long COVID among Black participants (M. M. Jacobs et al., 2023). Several studies suggest that the frequency of specific symptoms and manifestations of Long COVID may differ among racial and ethnic groups (Khullar et al., 2023; Xie et al., 2021).

In a series of interviews by Bergmans and colleagues, multiple Black participants with Long COVID described their experiences of being treated dismissively by doctors or being sent home with COVID-19 or Long COVID symptoms (Bergmans et al. 2022). In another report by Bergmans and colleagues, based on a series of interviews with Black Americans who have Long COVID, participants described challenges in receiving care (including racial bias in medical treatment, health care costs, insurance coverage, and others) as well as impacts of social determinants of health on individuals' ability to manage their symptoms (including housing quality, neighborhood socioeconomic status, and access to healthy food). Black Americans are also underrepresented in Long COVID research (Bergmans et al., 2023).

Existing gaps in access to health care for the diagnosis of Long COVID could in turn affect research on Long COVID. As part of the RECOVER initiative, Hill and colleagues conducted a retrospective case–control study based on EHR data from 31 health systems; though the study was designed to identify risk factors for Long COVID, the authors also found that living in a county with a greater number of physicians per capita was associated with higher likelihood of Long COVID diagnosis or care at a Long COVID clinic. This suggests that underdiagnosis may be occurring among people with less access to health care. The authors point out that studies relying on EHR data may be influenced by existing biases and disparities in health care access (Hill et al., 2023). Ensuring the inclusion of all ethnic and racial groups in future research will be critical to improving the Long COVID research base and informing patient care (Bergmans et al., 2023; Khullar et al., 2023).

Long COVID can occur in the pediatric population and in adults of any age (SeyedAlinaghi et al., 2023). As in adults, Long COVID in children and adolescents can manifest with symptoms and conditions affecting a wide range of body systems or as an exacerbation of underlying conditions, or both (Rao et al., 2024).

*Findings from the Engagement Process*

Participants agreed that the definition should apply equitably to all people with Long COVID and that it is important to recognize that different people have different symptoms and experiences. Participants also emphasized the importance of a definition that supports access to services for people with Long COVID, thereby advancing equity. Many participants also deemed it significant to include the financial challenges posed by Long COVID to individuals of low socio-economic status; a majority indicated a desire to acknowledge the social determinants of health that can influence the likelihood of developing Long COVID, such as poverty, race, and geographic location. Comments were also shared about explicitly linking the definition for Long COVID to equity considerations due to the impact that COVID-19 and Long COVID have had at an individual level and also within communities that have less access to care or to economic resources. A participant said, "*It could be helpful to include a specific statement around health equity in a Long COVID definition. That would maybe be a little unusual to include in a definition, but it is important, if not in the definition, somewhere else.*" Participants also suggested that the definition reflect cultural humility and sensitivity. For example, one participant commented, "*Then there is also a cultural aspect in some communities where if you literally are not dropping [to the floor], you are fine to go to work. That is really problematic with a condition like Long COVID where your prognosis is significantly negatively affected when you try to do something like push through.*"

*Lessons from Existing Definitions*

While existing definitions of Long COVID exhibit an overarching aim towards inclusivity, a specific mention of equity considerations is notably absent from all definitions. All definitions approach Long COVID primarily from a clinical standpoint, largely overlooking the socioeconomic and demographic factors that could markedly influence Long COVID's distribution, severity, and patient outcomes.

In 2022, a group of stakeholders informed by data from the CLoCK Study of Long COVID in children and young people and by patients' experiences developed a research definition for Long COVID in children and young people using a modified Delphi process to achieve consensus (Stephenson et al., 2022). In 2023, the WHO released a separate Pediatric definition for Long COVID.

## How Does the Definition Address Functional Impairment?

**Important Features**
LC can impair individuals' ability to work, attend school, take care of family, and care for themselves. It can have a profound emotional and physical impact on patients and their families and caregivers.

A definition for Long COVID may or may not address its potential effects on functionality and daily living or its effects on overall well-being (e.g., financial, employment, quality-adjusted life-years [QALYs]). The 2024 NASEM Long COVID Definition emphasizes that some individuals with Long COVID are severely affected and can have a variety of activity limitations. This can profoundly affect patients' and caregivers' lives and is an important feature of Long COVID.

In the evidence review, the committee found publications documenting a range of mild to severe functional impairments, activity limitations, and quality of life impacts in individuals with Long COVID. It is also important to note that Long COVID symptoms may affect functionality in different domains. For example, individuals may be impaired in daily home functioning, working capacity, or both (Ford et al., 2023). Participants in the engagement process noted that impairments in Long COVID can be invisible to others and supported inclusion of functional impairment in the definition of Long COVID.

### *Findings from the Evidence Review*

Many primary studies and systematic reviews have highlighted the potential impact of Long COVID on activities of daily living. The authors of a systematic review based on a literature search of articles published in July 2021 or earlier investigated the range of activity limitations, physical function limitations, and health-related quality of life (HRQoL) impacts in COVID-19 survivors, many of whom had been hospitalized (de Oliveira Almeida et al., 2023). Participants were evaluated during time spans ranging from the day of admission to rehabilitation after acute care to 7 months after discharge from the hospital. The analysis revealed impaired performance among the COVID-19 survivors on pulmonary function and muscle strength tests, physical tests such as the 6-minute walk test, and daily living activities scales such as the Lawton scale (de Oliveira Almeida et al., 2023; Piquet et al., 2021). A systematic review by Figuereido and colleagues focused on HRQoL after discharge among patients who had been

hospitalized with COVID-19 (Figueiredo et al., 2022). Among six included studies that compared people hospitalized for COVID-19 with either the general population or matched controls, all found lower scores on HRQoL instruments (SF-36, 15D, St. George's Respiratory Questionnaire, or Short Form-12) for the post-COVID-19 individuals at time points ranging up to 3 months post-discharge. The authors write that although lower HRQoL can persist for months after hospitalization for COVID-19, partial improvements in HRQoL are often observed soon after hospitalization (Figueiredo et al., 2022).

As reported in the U.S. Census Bureau and the National Center for Health Statistics' Household Pulse Survey data (March 5 to April 1, 2024), 23.8 percent of U.S. adults currently experiencing Long COVID were estimated to have significant activity limitations and 78.7 percent were estimated to have any activity limitation from Long COVID (CDC, 2024a). In a UK study, patients receiving care at post-COVID-19 clinics were evaluated using the Work and Social Adjustment Scale (WSAS), a patient-reported measure of functional impairment. Of the participants, 53 percent scored over 20, indicating "moderately severe" impairment; impacts were observed across all five domains of the WSAS (Walker, 2023). That study also found a large impact on quality of life for many patients, with a median score of 0.60 (IQR 0.41 to 0.71) on the EQ-5d, a measure of HRQoL (Walker, 2023). In the LONG-COVID-EXP-CM study, a multicenter cohort study in Spain, 1,593 patients who were hospitalized during the first wave of the pandemic were later interviewed regarding their self-perceived functional status and limitations in comparison with their status before their COVID-19 illness. Interviews took place at T1 (mean 8.4 months after discharge) and T2 (mean 13.2 months after discharge). The percentages of patients reporting limitations at T1 and T2, respectively, were 20.9 percent and 12.8 percent for occupational activities, 30.1 percent and 20.8 percent for leisure/social activities, 27.1 percent and 18.1 percent for instrumental activities, and 19.9 percent and 13.7 percent for basic activities (Fernández-de-Las-Peñas et al., 2022c).

Long COVID can have serious impacts on employment. An analysis of the University of Southern California's longitudinal survey, Understanding America Study, found that 25.9 percent of "long haulers" in mid-2021 reported that their symptoms affected their employment or work hours; these affected individuals worked 50 percent fewer hours compared to people who had never had COVID-19 (Federal Reserve Bank of Minneapolis, 2022). Among patients in Long COVID support groups who were surveyed in the fall of 2020, 45.2 percent said they required reduced work hours, and an additional 22.3 percent said they were not working due to their symptoms (Bowe et al., 2023). Based on estimates of Long COVID prevalence rates, impairment rates, and labor impacts, economist David

Cutler estimated that Long COVID has caused 3.5 million people to leave the labor force as of 2022. With the assumption that Long COVID cases last an average of 5 years with no change in severity, Cutler estimated that the cost of Long COVID would amount to $3.7 trillion (including the costs of lost QALYs, lost earnings, and increased medical spending) (Cutler, 2022). An April 2024 analysis by Economist Impact found that Long Covid symptoms have prompted some individuals to leave the workforce (estimated 953.6 million hours lost), others take time off work (estimated 363.3 million hours lost) or reduce their work hours due to symptoms (estimated 177.5 million hours lost)—resulting in 1.5 billion work hours lost in 2024 and a potential cost of more than $152.6 billion (Economist Impact, 2024).

Although there is little available published data regarding the impact of Long COVID on caregivers and families of patients, anecdotal reports indicate that caregivers are experiencing a wide range of impacts including financial and logistical challenges, impacts to employment, and impacts to their own health, among others (McGowan, 2023; Olsen, 2021). While caregiver burdens and impacts have been documented in other chronic illnesses (Strang et al., 2018), caregiver and family burdens in the context of Long COVID appear to be a research gap that merits further attention.

### *Findings from the Engagement Process*

Participants consistently called for the concept of impairment to be included in the definition of Long COVID, as many patients find that their symptoms interfere with daily functioning (such as socially, occupationally, mentally, and other aspects of daily life). The inclusion of a statement on impairment could affect degrees of access to disability and services accommodations. For example, one participant noted, "*What we need to be able to do with the definition, or a subset of it, is determine a degree of impairment because so many people are disabled.*" Another underlined the importance of including impairment in the definition, because many of the symptoms are invisible: "*When I think about Long COVID, it's about the symptoms that are causing functional impairment that you do not see.*"

### *Lessons from Existing Definitions*

Only one of the existing definitions, that of the USG, directly discusses Long COVID severity. The USG stands out for its acknowledgment of Long COVID's potential severity, noting that Long COVID "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." This characterization underscores the broad spectrum of severity that Long COVID can encompass, hinting at its substantial

implications for patient health and quality of life. Although this description hints at the variable severity and potential for significant health consequences, it stops short of explicitly discussing "functional impairment." Additionally, a Long COVID definition may need to include people with different current levels of severity or impairment. On the other hand, the WHO Adult and WHO Pediatric definitions directly address the functional consequences of Long COVID. The WHO Adult definition mentions that symptoms "generally have an impact on everyday functioning," including issues like fatigue, difficulty breathing, and cognitive challenges. The WHO Pediatric definition broadens this perspective, noting that symptoms "generally have an impact on everyday functioning" and can influence various aspects of a child's life, including eating habits, physical activity levels, behavior, academic achievements, and social interactions. These insights from the WHO underscore the critical need to consider functional impairment and the spectrum of severity when fully understanding Long COVID's effects on individuals' lives.

### How Does the Definition Address Alternative Diagnoses?

The 2024 NASEM Long COVID Definition does not include mention of alternative diagnoses.

Many diseases, like Long COVID, can share symptoms or characteristics with other conditions, leading to overlap and confusion in diagnosis. A disease definition could list exclusionary conditions or indicate the consideration of exploring alternative diagnoses (Lim and Son, 2020). For example, the Ramsay definition of ME/CFS considers depression and anxiety to be exclusionary conditions. In contrast, the IOM ME/CFS definition does not list exclusionary conditions (Lim and Son, 2020).

The committee elected not to include a statement regarding exclusions or alternative diagnoses in the 2024 NASEM Long COVID Definition. First, there is no scientific evidence that any medical condition prevents or cannot exist alongside Long COVID. Second, the history of a similarly debilitating medical condition, ME/CFS, illustrates that such requirements can lead to a denied or delayed diagnosis. Patients have reported that clinicians were reluctant to diagnose them with ME/CFS if any other co-morbidity—like reactive depression—was present that could partially explain their symptoms even as aspects of their presentation—like a post-acute-infectious onset or post-exertional malaise—were not typical for mood disorders. Conversely, clinicians have voiced hesitation to diagnose ME/CFS because

they were not confident they had eliminated enough alternative conditions when the disease was framed as a diagnosis of exclusion.

The 2024 NASEM Long COVID Definition does include ME/CFS and POTS, among others, as examples of diagnosable conditions that can be part of the picture of Long COVID. These and other potentially overlapping conditions are compatible with a diagnosis of Long COVID. To the contrary, evidence exists these conditions may be more common among Long COVID patients than the general population, and that they might share some common physiological pathways (Komoraff and Lipkin 2023). For example, patients may be diagnosed with Long COVID and POTS or Long COVID and ME/CFS. In addition, patients may be diagnosed with Long COVID and new-onset diabetes, Long COVID and new-onset rheumatoid arthritis, etc. Long COVID is thus an umbrella term and can be diagnosed alongside associated conditions. This is in accord with the WHO-Pediatrics definition for Long COVID, which states that other diagnoses do not exclude a diagnosis of Long COVID but is in contrast to the WHO-Adults definition and the NICE definition, which specify that Long COVID symptoms must not be "explained by an alternative diagnosis." Lack of language concerning alternative diagnoses does not absolve health care professionals of their clinical responsibilities, which include generating a reasonable differential diagnosis, testing for other causes of a patients' symptoms, re-considering initial impressions, and monitoring patients with uncertain diagnoses regularly and carefully. Despite not including this element in the definition, the committee articulates relevant findings below.

### *Findings from the Evidence Review*

When discussing the long-term ramifications of acute SARS-CoV-2 infection, it is useful to consider another well-described condition called the post-intensive care syndrome (PICS). PICS is an intense form of suffering that persists during the months and years following treatment in medical and surgical intensive care unit (ICUs), which of course includes survivors of acute SARS-CoV-2 infection (Nanwani-Nanwani et al., 2022; Weidman et al., 2022). There are hundreds of thousands of people around the world who—after prolonged hospital courses on mechanical ventilation and dialysis during acute SARS-CoV-2 infection—are now experiencing cognitive, mental health, and physical disabilities (Hägglöf et al., 2023; Heesakkers et al., 2022; Jackson et al., 2010; Neville et al., 2022; Roedl et al., 2022; Sevin and Ely, 2022). These hospital survivors are struggling to recover from a constellation of symptoms and conditions that often include both PICS and Long COVID. These two conditions have a tremendous amount of overlap, and it is important to acknowledge that some patients have both PICS and Long COVID.

There are some relevant distinctions. Both PICS and Long COVID involve structural and functional organ dysfunction of the brain, heart, lungs, kidneys, muscles, and nerves. The mechanisms of PICS and Long COVID likely vary (e.g., immune dysregulation, mitochondrial disease). PICS, unlike Long COVID, can include non-infectious triggers (pancreatitis) as well as infectious triggers (including infections unrelated to SARS-CoV-2). Clinically, both often leave patients with troublesome cognitive impairment that meets the criteria for mild to moderate dementia. While there is early evidence to indicate that PICS patients may find improvements in memory and executive function after cognitive rehabilitation, Long COVID patients anecdotally report that "brain exercises" or even simply reading causes them days of mental worsening. Similarly, while fatigue and neuromyopathy are common in PICS, post-exertional malaise that Long COVID patients experience is often more unpredictable and refractory than that seen in PICS (Jackson et al., 2012). It can be challenging clinically to differentiate within an individual patient between PICS and Long COVID related symptoms, thus clinicians and patients must work together to decipher what therapies help versus which exacerbate symptoms.

In summary, PICS can follow treatment in intensive care, and Long COVID can follow acute SARS-CoV-2 infection. While different in etiology, the two conditions overlap in symptoms of cognitive impairment and profound fatigue. When patients with Long COVID have also been treated with intensive care, either the infection or the experience of treatment, or both, could be contributing factors to their condition. Further research will be needed to understand better the pathophysiology of both PICS and Long COVID and to determine whether similar or different treatment regimens will provide the best care for patients.

Similarly, a notable proportion of individuals presenting with symptoms consistent with Long COVID also meet the diagnostic criteria for or exhibit symptoms of other diagnosable conditions such as POTS or other forms of dysautonomia (Larsen et al., 2022; Kedor et al., 2022; Seeley et al., 2023), or ME/CFS (Goldenberg, 2023; Morrow et al., 2022), although most ME/CFS criteria require at least 6 months of symptoms in contrast to the 3 months of symptoms required by the 2024 NASEM Long COVID Definition. POTS is a clinical syndrome often triggered by infection that can include symptoms associated with a dysfunctional vasomotor and sympathetic nervous system (e.g., lightheadedness, palpitations, and headache) (Diekman and Chung, 2023; Morrow et al., 2022). ME/CFS is characterized by persistent fatigue, post-exertional malaise, unrefreshing sleep, orthostatic intolerance, and cognitive impairment; many but not all cases are reported to occur following an infectious or infectious-like illness (Goldenberg, 2023; Vivaldi et al., 2023). Long COVID may be considered alongside dysautonomia presentations other than POTS, mast cell

activation syndrome (MCAS), or a range of other diagnoses (Diekman and Chung, 2023; Larsen et al., 2022; Morrow et al., 2022). Long COVID can be diagnosed alongside these and other conditions.

*Findings from the Engagement Process*

Most participants did not feel that the definition required language about excluding alternative diagnoses or considering Long COVID a diagnosis of exclusion. However, one participant noted that when symptoms are solely attributed to Long COVID, there have been instances of missed diagnoses, like lung cancer, when patients await care at Long COVID clinics.

*Lessons from Existing Definitions*

The WHO Pediatrics definition acknowledges the potential for additional diagnoses coexisting with Long COVID in children and adolescents, allowing for a broad diagnostic scope: "Workup may reveal additional diagnoses, but this does not exclude the diagnosis of post COVID-19 condition." The WHO Adults definition and the NICE definition specify that Long COVID symptoms must not be "explained by an alternative diagnosis."

**How Does the Definition Address Biomarkers?**

**Important Features**
LC can be diagnosed on clinical grounds. No biomarker currently available demonstrates conclusively the presence of LC.

Although Long COVID is defined as a chronic condition that occurs following a SARS-CoV-2 infection, the current evidence base does not indicate a clear pathobiology that is universal among patients. Long COVID symptoms appear to arise from pathobiological changes that span many different organ systems and tissues (Deer et al., 2021), and no definitive biomarker for Long COVID has yet been identified. It may be that no single or small number of biomarkers will explain the vast complexity of Long COVID (Al-Aly and Topol, 2024).

From the evidence review and engagement process, the committee determined that the research and medical communities have not yet identified any diagnostic tests that are well documented to have high specificity and sensitivity for Long COVID. Therefore, the 2024 NASEM Long COVID Definition does not include any requirements for biomarker testing that must be performed before diagnosing Long COVID.

However, numerous studies and reviews have identified pathobiological abnormalities (e.g., immune dysfunction and coagulation abnormalities) in patients experiencing Long COVID (Figure 5) (Davis et al., 2023; Mohandas et al., 2023; Turner et al., 2023). These findings, elaborated on below, make it clear that Long COVID is a physical health condition. These findings also raise the possibility that further discoveries will enable biomarkers to be incorporated in a revised, future Long COVID definition.

*Findings from the Evidence Review*

Over 200 potential biomarkers for Long COVID are currently under investigation, often in connection with hypotheses regarding pathobiology. However, more research is needed to overcome the limitations of the data, and candidate biomarkers need validation in larger studies, including clinical studies (Espin et al., 2023; Lai et al., 2023). In a systematic review of biomarkers in Long COVID published in January 2023, Lai and colleagues discussed 113 biomarkers that have been significantly associated with Long COVID in 28 eligible studies (Lai et al., 2023). These biomarkers include 38 cytokine/chemokines, 24 biochemical markers, 20 vascular markers, 6 neurological markers, 5 acute phase proteins, and 20 others. Of these, the authors state that upregulated interleukin 6, C-reactive protein, and tumor necrosis factor alpha could potentially be used to support Long COVID diagnosis or clinical management. In addition, increased levels of neurofilament light chain and glial fibrillary acidic protein could potentially serve as biomarkers for Long COVID with neurological manifestations, while increased transforming growth factor beta could potentially serve as a biomarker for Long COVID with pulmonary manifestations (Lai et al., 2023). A scoping review by Espín and colleagues published in May 2023 identified a longer list of 239 candidate biomarkers from 23 cohort studies; these include cellular biomarkers (e.g. T regulatory cells), immunoglobulins, cytokines/chemokines, and others. Some of the reviewed studies aimed to develop biomarkers for Long COVID risk prediction during acute illness, while others investigated potential biomarkers for specific Long COVID symptoms or manifestations (Espin et al., 2023).

Several research groups have investigated the persistence of SARS-CoV-2 RNA or proteins after a SARS-CoV-2 infection. For example, one small study found S1 protein in the plasma of 64 percent of 22 people with Long COVID and in 35 percent of a control group of 17 people who had had COVID-19 but did not develop Long COVID; none of these participants had been vaccinated against COVID-19 (Schultheiss et al., 2023). Another research team used the Simoa (Quanterix) single molecule array detection platform to analyze the presence of SARS-CoV-2 spike, S1, and nucleocapsid antigens in 660 plasma specimens collected from 171 adults

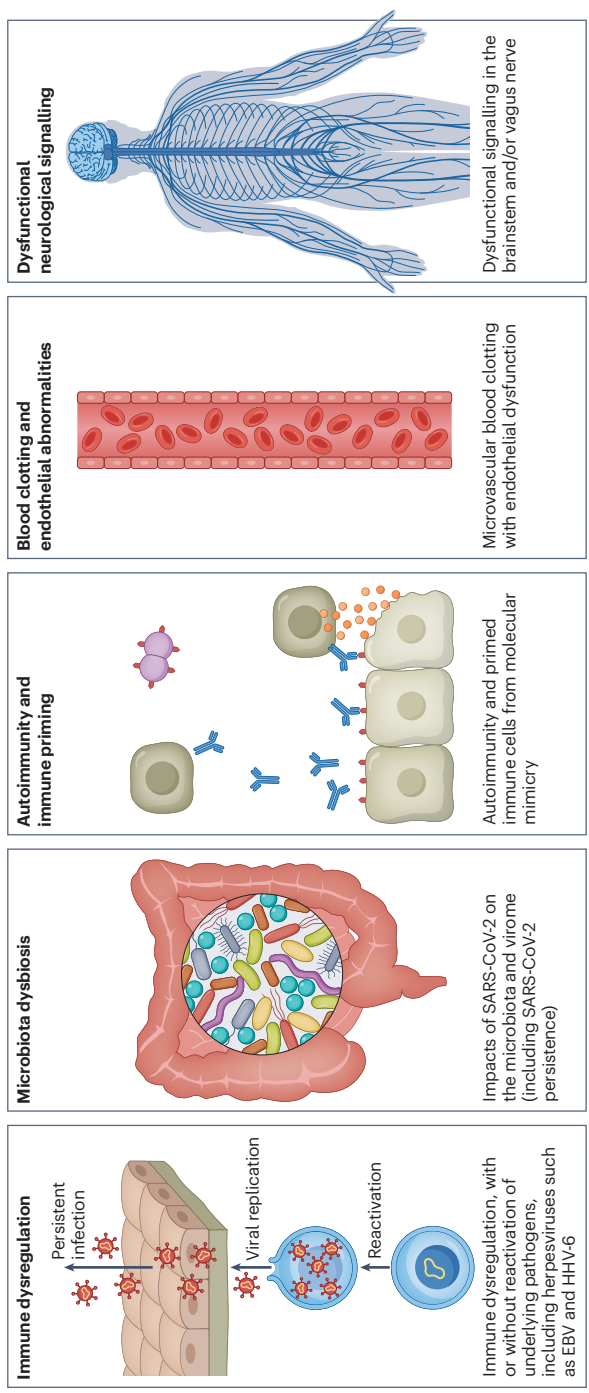


**FIGURE 5** Hypothesized mechanisms of Long COVID pathogenesis.
NOTES: There are several hypothesized mechanisms for long COVID pathogenesis, including but not limited to immune dysregulation, microbiota disruption, autoimmunity, clotting and endothelial abnormality, and dysfunctional neurological signaling. EBV = Epstein–Barr virus; HHV-6 = human herpesvirus 6; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
SOURCE: Davis et al., 2023.

during the 14 months following their RNA-confirmed SARS-CoV-2 infections. They found at least one detectable SARS-CoV-2 antigen in 9.2 percent of the specimens, including those from 25 percent of the participants, compared to a 2 percent positivity rate for plasma specimens collected from 250 adults before 2022 (Peluso et al. 2024b).

Evidence of SARS-CoV-2 persistence, including partial viral fragments, complete virus and viral RNA, have been identified months to years after acute infection in tissue biopsy studies and tissue autopsy studies, including in lymph nodes, central nervous system, lung tissue and many other tissue types (Proal et al., 2023).

Multiple research groups have investigated immune dysfunction in Long COVID. According to the authors of a review published as part of the NIH-funded Researching COVID to Enhance Recovery (RECOVER) initiative, both innate and adaptive immune dysregulation may play a role, but many research questions remain open in this area (Mohandas et al., 2023). Potential immune-related contributors to Long COVID that are under investigation include persistent activation of inflammatory pathways in macrophages; transcriptional changes in monocytes, lymphocytes, or dendritic cells; activation of mast cells; and involvement of neutrophils, T cells, or B cells (Altmann et al., 2023; Mohandas et al., 2023; Peluso et al., 2024a). A cross-sectional immune phenotyping study by Klein and colleagues compared participants with a Long COVID diagnosis to matched control individuals who either had no history of SARS-CoV-2 infection or had fully recovered after COVID-19. The participants with Long COVID had significant alterations in circulating myeloid and lymphocyte populations and showed exaggerated humoral responses against both SARS-CoV-2 and herpesviruses (Klein et al., 2023). In an analysis based on the DigiHero cohort study in Germany, both individuals with Long COVID (median of 8 months post infection) and individuals without Long COVID (median of 7.5 months post infection) had markedly elevated levels of monocyte/macrophage-related soluble factors, including pro-inflammatory and pro-fibrotic cytokines, compared with people with no COVID-19 history (Schultheiss et al., 2023). In a pre-print study of unvaccinated individuals 8 months post-acute COVID-19, those experiencing Long COVID symptoms (n=27) showed mis-coordination between humoral and cellular responses, signatures of inflammation, and T-cell perturbations suggestive of an ongoing immune response; these changes were not seen in those without Long COVID (n=16) (Yin et al., 2023). Multiple research studies have suggested that SARS-CoV-2 infection, particularly severe infection, can induce autoantibodies. This phenomenon has also been noted with influenza infection, though to a lesser extent (Altmann et al., 2023; Proal et al., 2023). Other researchers have proposed that reactivation of latent Epstein-Barr virus (EBV) or other herpesviruses during SARS-CoV-2 infection could lead to

the production of autoantibodies (Altmann et al., 2023; Mohandas et al., 2023).

Autoimmunity induced by SARS-CoV-2 infection has also been investigated in multisystem inflammatory syndrome in children (MIS-C) and severe COVID-19 disease (Altmann et al., 2023; Mohandas et al., 2023).

Several research groups have investigated the possibility that interactions between the effects of SARS-CoV-2 infection and pre-existing infections (e.g. HIV) or reactivated, latent viruses (e.g. EBV) could contribute to the development of Long COVID through immune-mediated or other mechanisms (Chen et al., 2023; Peluso et al., 2022).

Pointing to future research directions, an international scientific conference on Long COVID, held by the Keystone Symposia in August 2023, highlighted research on potential pathogenesis and mechanisms of Long COVID, connections to other post-infection complications, diagnosis and biomarkers, disease management, and potential treatment directions (Durstenfeld et al., 2024).

### *Findings from the Engagement Process*

Although there were varying views, overall participants emphasized that adding biomarkers at this time will not improve the definition. One participant said, "*We don't have good biomarkers, and I anticipate in a few years' time, we probably will have more in the way of biomarkers. I think it's good to acknowledge that we anticipate the evolution of the definition.*"

### *Lessons from Existing Definitions*

No existing Long COVID definitions include explicit mention of specific biomarkers, but the USG definition includes an overarching statement that states, "Long COVID represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes."

## How Does the Definition Address Risk Factors?

The 2024 NASEM Long COVID Definition does not explicitly include risk factors.

Various risk factors, such as underlying comorbid conditions, may influence the risk and presentation of COVID-19 and Long COVID in a particular individual and may be useful in assessing individual patients or

populations at risk. However, as risk factors do not in themselves define a disease, the committee chose not to include risk factors in the 2024 NASEM Long COVID Definition.

Some participants in the engagement process supported including risk factors in the Long COVID definition. In the evidence review, the committee found studies and systematic reviews that support possible risk factors for Long COVID, including female sex, certain health conditions, greater severity of initial COVID-19 illness, reinfection, and others. However, much of the data on Long COVID risk factors has limitations (e.g. some relies on EHR data, which is influenced by existing health care disparities) and some risk factors are difficult to disentangle from one another based on current data (e.g. certain SARS-CoV-2 strains encountered an increasingly vaccinated population; certain health conditions could increase Long COVID risk directly or through increased risk of severe acute illness). The committee's decision not to include risk factors in the 2024 NASEM Long COVID Definition is in accord with the previous Long COVID definitions, which do not give risk factors.

*Findings from the Evidence Review*

Several systematic reviews have examined risk factors for Long COVID. A review and meta-analysis by Tsampasian and colleagues included 41 studies and over 860,000 patients. The authors found evidence in support of several risk factors for Long COVID, including female sex, age above 40, obesity, smoking status, history of hospitalization or ICU admission during acute COVID-19, and several pre-existing conditions (anxiety and/or depression, asthma, chronic obstructive pulmonary disease, diabetes, immunosuppression, ischemic heart disease) (Tsampasian et al., 2023). The authors note that it is unclear whether obesity and smoking increase the risk for Long COVID directly or through an increased risk for severe COVID-19. In addition, the association between hospitalization/ICU admission and Long COVID may be influenced by overlap with post-intensive care syndrome (Tsampasian et al., 2023). Some evidence suggests that individuals in middle age groups may be at highest risk for Long COVID. For example, a retrospective case–control study based on data from 31 health systems found that individuals from 40 to 69 years were more likely than adults in other age groups to be diagnosed with Long COVID or to visit a Long COVID clinic (odds ratio [OR] ranging from 2.32 to 2.58). This study also identified female sex, greater severity of acute infection, obesity, chronic lung disease, depression, and metastatic cancer as risk factors. The authors note that the reliance on EHR data is a limitation of this study because such data may be influenced by existing biases and disparities in health care access (Hill et al., 2023). An analysis of data from the

LONG-COVID-EXP-CM study, a multicenter cohort study in Spain, found that female sex was associated with greater odds of reporting ≥3 post-COVID symptoms at a mean of 8.4 months post-discharge (adjusted OR 2.54, 95% CI 1.671–3.865, p < 0.001) among 1,969 individuals who had been hospitalized with COVID-19 (Fernandez-de-Las-Peñas et al., 2022b).

Among children and adolescents, a review and meta-analysis with 40 studies identified possible risk factors for Long COVID including older age; female sex; and history of severe COVID-19, multisystemic inflammatory disease, or hospitalization for COVID-19 (Zheng et al., 2023).

Multiple studies support an association between greater severity of initial COVID-19 illness and higher risk for Long COVID. For example, Xie and colleagues investigated the impact of the severity of acute illness among 181,384 veterans (average age, 67.13; 90.47 percent male) using data in the U.S. Department of Veterans Affairs database. After adjustment for age, race, sex, comorbidities, and other factors, and after subtraction of background symptoms using a comparison group of uninfected veterans, the authors calculated the burden of Long COVID (defined as the number of individuals per 1,000 who had at least one of 33 specific SARS-CoV-2-attributed sequelae). They found that the adjusted burden of Long COVID at 6 months was 44.51 for non-hospitalized patients, 217.08 for hospitalized patients, and 360.16 for patients who had been in intensive care (Xie et al., 2021). As part of the LONG-COVID-EXP-CM study, 1,969 patients who were hospitalized with COVID-19 between February and May 2020 were interviewed a mean of 8.4 months post discharge. The number of symptoms at hospital admission (OR 1.309, 95% CI 1.15–1.49) and the number of days at the hospital (OR 1.01, 95% CI 1.007–1.017) were each associated (p<0.001) with greater number of post-COVID-19 symptoms at the time of the interview (Fernandez-de-Las-Peñas et al., 2022b). In addition to differences in risk for Long COVID, some analyses support differences between hospitalized and non-hospitalized patients in the prevalence of specific post-COVID-19 symptoms (Fernandez-de-Las-Peñas et al., 2021b, 2023). Despite these associations, because non-severe COVID-19 cases have been far more prevalent than severe cases, most Long COVID cases occur in individuals who did not have severe initial disease (Al-Aly and Topol, 2024).

In support of the suggestion that SARS-CoV-2 reinfections are a risk factor for Long COVID or for increased severity of Long COVID, or both, an analysis of the U.S. Department of Veterans Affairs national health care database found that individuals with one or more reinfections (n=40,947), compared with those with a single infection (n=443,588), had increased risks of hospitalization, all-cause mortality, and sequelae affecting the pulmonary and multiple extra-pulmonary organ systems, in both the acute (0–30 days) and post-acute (30–180 days) phases after the reinfection. During the post-acute phase, these risks gradually decreased, but elevated risks

of death, hospitalization, and having at least one sequela persisted until 6 months after reinfection. In this study, reinfections were recorded between June 2020 and June 2022, when pre-Delta, Delta, and Omicron were the dominant variants (Bowe et al., 2022). There is some evidence to suggest that vaccination against SARS-CoV-2 may lower the risk of Long COVID. In the meta-analysis by Tsampasian and colleagues described above, among four high-quality studies that investigated the effect of vaccination (over 249,000 patients), individuals who had received two vaccine doses had a lower risk of Long COVID (OR 0.57; 95% CI 0.43–0.76) (Tsampasian et al., 2023). Another analysis of the Veterans Affairs database found that people with breakthrough SARS-CoV-2 infection (infection that occurs after vaccination) had a higher risk of post-acute sequelae at 6 months compared with uninfected controls (HR = 1.50, 95% CI: 1.46, 1.54), but a lower risk of post-acute sequelae compared with unvaccinated people infected with SARS-CoV-2 (HR = 0.85, 95% CI 0.82, 0.89) (Al-Aly et al. 2022). A staggered cohort study based on health records from the United Kingdom, Spain, and Estonia investigated whether vaccination reduces the overall risk of developing Long COVID (defined as having at least one of 25 Long COVID-associated, new symptoms >90 days after a SARS-CoV-2 infection), whether through effects on the risk of infection or through effects on the risk of developing Long COVID after an infection. The analysis included >10 million unvaccinated and >10 million vaccinated individuals. After weighting to reduce confounding, the authors found that vaccination consistently reduced the risk of Long COVID; hazard ratios for a first dose varied from 0.48 to 0.71 depending on the database (Català et al., 2024).

Some reports suggests that infection with SARS-CoV-2 strains circulating earlier in the pandemic may be associated with higher risks for Long COVID (Hedberg et al., 2024; Antonelli et al., 2022). However, it can be difficult to disentangle the effects of the SARS-CoV-2 strain from the effects of concurrent changes in vaccination status, reinfection status, social circumstances, and other confounders (Fernandez-de-Las-Peñas et al., 2022a). The authors of an observational cohort study in Italy used a multivariable logistic regression model to investigate the risk of Long COVID (defined in this study as persistent symptoms more than 4 weeks after SARS-CoV-2 infection) according to patients' vaccination status and timing of infection. All participants in this study were health care workers and received their first and second vaccine doses in January–February 2021 and a booster dose in November–December 2021. Among 739 non-hospitalized adults with SARS-CoV-2 infection, Long COVID prevalence was 48.1 percent of those infected during wave 1 (February–September 2020, wild-type variant), 35.9 percent in wave 2 (October 2020–July 2021, Alpha variant) and 16.5 percent in wave 3 (August 2021–March 2022, Delta and Omicron variants). However, in the same study, Long COVID prevalence varied from

41.8 percent among unvaccinated participants to 16.0 percent among those with three vaccine doses before infection (Azzolini et al., 2022). In the second report from the Canadian COVID-19 Antibody and Health Surveys, a series of self-report surveys based on random sampling of Canadian adults, the percentage of those infected who said they had persistent symptoms varied over time (27.3 percent of those infected in 2020, 26.7 percent of those infected from January 2021 to June 2021, 14.5 percent of those infected between July 2021 and Nov 2021, 12.7 percent of those infected between December 2021 and May 2022). However, these results may be affected by changes in both the predominant virus variant and changes in the percentage of vaccinated adults over time, as 72.1 percent of Canadian adults received their first vaccine dose by June 2021, and 86.7 percent had completed the primary vaccination series by December 2021. In the same survey, 25.0 percent of participants who were unvaccinated at the time of their initial infection reported persistent symptoms, compared with 13.2 percent of those who received two vaccine doses and 12.2 percent of those who received three vaccine doses (Government of Canada, 2023).

### *Findings from the Engagement Process*

Participants underscored the importance of including specific risk factors in the definition, citing them as key considerations for underserved and minority populations.

### *Lessons from Existing Definitions*

No existing Long COVID definitions include explicit mention of specific risk factors, but the USG definition includes an overarching statement that "Long COVID represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes."

## CONSIDERATIONS FOR IMPLEMENTATION AND DIFFERENT USES

Participants highlighted the need to develop a definition that is both operational for varied uses and widely acceptable to all users of the definition, with one participant noting, "*It is important to consider the different 'needs' of the definition. For example, researchers want reproducibility; clinicians and patients want to help people get treatment.*" The committee intends its definition to be applied to many purposes. These may include clinical care and diagnosis; eligibility for health services, insurance coverage, disability benefits, and school or workplace accommodations; public health; social services; policy making; epidemiology and surveillance; private and

public research; and public awareness and education, especially for patients and their families and caregivers (Pan and Pareek, 2023; Soriano et al., 2022). In all these situations, an ideal Long COVID definition will likely need to interface with existing practices and policies without worsening health disparities or other problems.

This section describes ways in which the 2024 NASEM Long COVID Definition may be applied for different purposes (clinical, research, and public health surveillance) and provides considerations as well as illustrative examples. The committee also recognizes the need to adopt the definition for policy and service uses and refers the reader to the National Academies report, *Long-Term Health Effects Stemming from COVID-19 and Implications for Social Security Administration* (NASEM, 2024), to the HHS *Guidance on "Long COVID" as a Disability Under the ADA, Section 504, and Section 1557* (HHS, 2021), and to the Social Security Administration's guidance *Long COVID: A Guide for Health Professionals on Providing Medical Evidence for Social Security Disability Claims* (SSA, 2023) for key considerations and resources. Long COVID qualifies as a disability under Titles II (state and local government) and III (public accommodations) of the Americans with Disabilities Act (ADA),[2] Section 504 of the Rehabilitation Act of 1973 (Section 504),[3] and Section 1557 of the Patient Protection and Affordable Care Act (Section 1557).[4] The 2024 NASEM Long COVID Definition includes a key feature on functional impairment, but does not address when Long COVID may meet the legal definition of disability. All stakeholders involved in social safety net programs, including payers, workplaces and employers, academic institutions and educators, and support services and government officials, need to be aware of Long COVID to properly support patients, and their families and caregivers in need.

### How Can Clinicians Apply the Definition?

By implementing the 2024 NASEM Long COVID Definition, clinicians can enhance their ability to identify, diagnose, and manage Long COVID effectively. As previously stated, the goal of the definition is to aid clinicians in the consistent diagnosis of Long COVID. The definition is meant to be inclusive and should lead the clinician to provide comprehensive care for individuals experiencing Long COVID. This should also improve patients' understanding of Long COVID and enhance access to care and effective treatment.

[2] 42 U.S.C. §§ 12101-12103, 12131-12189.
[3] 29 U.S.C. § 794.
[4] 42 U.S.C. § 18116.

Because of issues concerning COVID-19 test sensitivity, availability, access, and reporting, the 2024 NASEM Long COVID definition does not require a positive COVID-19 test to qualify for a Long COVID diagnosis. For those patients without a positive test, health care professionals will need to use their clinical judgement to decide whether the patients' clinical picture fits a Long COVID diagnosis. For example, a history of contact with someone with a confirmed SARS-CoV-2 infection, persistence of symptoms from the time of an acute infection, and/or presence of symptoms like anosmia or post-exertional malaise, which are not common features of other medical conditions, would point towards Long COVID. On the other hand, a long intervening period between acute SARS-CoV-2 infection and occurrence of new symptoms, recurrence of symptom similar to a patient's pre-COVID co-morbidities, or a diagnosis that better explains the patient's presentation would not favor a Long COVID diagnosis.

The minimum 3-month duration criterion ensures that patients with persistent symptoms are not overlooked, allowing clinicians to distinguish Long COVID from acute viral effects. This 3-month period can occur anytime: the committee chose not to specify that duration be counted from the instigating acute SARS-CoV-2 infection because studies have shown Long COVID symptoms can appear after a period of seemingly normal health. In cases of unconfirmed, asymptomatic SARS-CoV-2 infections, 3 months can be counted from the initial appearance of the patients' symptoms. Overdiagnosis of Long COVID can be mitigated by assessing whether a patient's set of symptoms are consistent with Long COVID and whether another diagnosis could better account for their symptoms.

While conducting their differential diagnosis, clinicians should recognize any concerning symptoms before the 3-month mark to provide appropriate clinical care and avoid missing other unrelated conditions. The broad spectrum of symptoms and associated diagnosable conditions outlined in (but not limited to) the definition provide clinicians with a framework to recognize the diverse manifestations of Long COVID, ranging from respiratory issues to neurological and autoimmune conditions. It is also imperative to recognize that following an acute SARS-CoV-2 infection, an existing diagnosis may notably deteriorate or exacerbate, necessitating clinicians to incorporate this into patient care and align it with the definition of Long COVID. For instance, complications such as controlled asthma escalating to severe asthma with frequent exacerbations exemplify this phenomenon.

Moreover, the definition promotes a holistic approach to patient assessment by encouraging the clinician to consider the various symptoms, organ system dysfunctions, and conditions that may be present in a person with Long COVID. The definition also encourages interdisciplinary collaboration among health care specialists. Clinicians should form collaborative teams of relevant experts to address the multi-organ impact of Long COVID.

A multi-disciplinary approach that is team-based will facilitate a more nuanced understanding of Long COVID and allow for tailored diagnostic and treatment strategies based on the specific organ systems affected. This approach aligns with the evolving understanding of Long COVID as a complex and heterogenous disease state, requiring a nuanced and collaborative health care response. Clinicians should be strongly encouraged to conduct thorough evaluations when presented with any symptomatology suggestive of Long COVID, prioritizing testing for potentially serious sequalae.

Clinicians are encouraged to use the ICD-10 code for Long COVID of U09.9 as well as to participate in research collaborations to contribute valuable insights to the growing body of evidence around Long COVID. Clinicians should stay actively engaged in learning about Long COVID to drive continuous improvement in the understanding and management of Long COVID.

Clinician goals include (1) improving patients' and caregivers' understanding of Long COVID, (2) effectively assessing and documenting Long COVID, and (3) considering this diagnosis in any patient (inclusive of children and adults of all ages) who presents with persistent symptoms after SARS-CoV-2 infection. Table 2 provides considerations for the clinician who is implementing the 2024 NASEM Long COVID Definition.

### How Can Researchers Apply the Definition?

The 2024 NASEM Long COVID Definition is by design inclusive and overarching, with many possible areas of use and application; this allows researchers flexibility in designing studies that are consistent with the definition while also sufficiently specific to meet the study objectives. The committee recognizes that most research studies are designed to answer a small number of very focused questions and that this will require identifying a subset of patients who satisfy the overarching definition and also satisfy more restrictive eligibility criteria for the study. Researchers may consider additional criteria to select the subset of Long COVID patients suited to the research project's aims and hypothesis. The study investigators should specify the following elements:

- Documentation of SARS-CoV-2 infection: Whether and how the initial SARS-CoV-2 infection is documented (e.g., suspected, probable, or confirmed SARS-CoV-2 infection) or based on self-reported symptoms. Some studies may also include a group of participants with no history of COVID-19 and negative tests for SARS-CoV-2.
- Time period of infection and/or study (e.g., month, year): May be associated with different dominant SARS-CoV-2 variants.

**TABLE 2** 2024 NASEM Long COVID Definition Implementation Checklist for Clinicians

| Steps in the Process | Key Considerations |
|---|---|
| Initial Assessment | • Consider Long COVID as a possible diagnosis when patients with a 3 months or more prior history of SARS-CoV-2 infection have persistent symptoms affecting one or more organ systems.<br>• Assess patients for a history of asymptomatic, mild, moderate, or severe SARS-CoV-2 infection (or suspected infection), including reinfections.<br>• Assess the duration of symptoms. |
| Comprehensive Medical Evaluation | • Obtain and document a detailed clinical history with attention to the onset and course of symptoms, recognizing that they can be continuous, intermittent, or delayed in onset.<br>• Consider the use of a comprehensive symptom inventory to capture the wide range of manifestations of Long COVID, including post-exertional malaise.<br>• Recognize that Long COVID can present as single or multiple symptoms and that severity may vary among individuals and even fluctuate for an individual.<br>• Document the presence and measure the severity of all symptoms reported. Common symptoms include shortness of breath, persistent fatigue, post-exertional malaise, difficulty concentrating, memory changes, recurring headache, dizziness, fast heart rate, sleep disturbance, and problems with taste or smell.<br>• Document and measure reported limitations and assess function, to see if and how symptoms and conditions are affecting an individual's life (i.e., activities of daily living, work, and quality of life).<br>• Most people affected by Long COVID can be diagnosed clinically based on history, physical examination, and/or symptom-directed diagnostic testing; yet thorough evaluations must be done. Testing for potential serious sequelae of SARS-CoV-2 should be prioritized. While certain symptoms like palpitations or shortness of breath are prevalent among individuals with Long COVID, it is crucial to recognize that in a minority of cases, they may signify underlying conditions requiring more acute medical intervention.<br>• Eliminate common and uncommon causes for each individual's symptoms. If, after a diagnosis of Long COVID, new symptoms appear or pre-existing symptoms worsen, consider re-evaluating these symptoms instead of automatically attributing them to Long COVID. |
| Diagnosis of Specific Conditions | • Identify specific diagnosable conditions associated with Long COVID.<br>• Recognize that some conditions may not be diagnosable at the initial visit.<br>• Assess comorbidities. |

*continued*

**TABLE 2** Continued

| Steps in the Process | Key Considerations |
|---|---|
| Diagnostics | • Order appropriate diagnostic tests and imaging studies based on the suspected organ system involvement. Clinicians must ensure comprehensive imaging, functional, and physiological testing is done to exclude overt organ pathology necessitating immediate medical attention.<br>• Consider relevant investigations to confirm specific Long COVID–related conditions including pulmonary function tests, cardiovascular assessments, autonomic testing, neuropsychological testing, relevant imaging, and labs.<br>• Use both standard vital signs and pulse oximetry for patients with fatigue or respiratory or cardiac symptoms; abnormal blood pressure and heart rate findings should be evaluated using a 10-minute active standing test for those with orthostatic intolerance or other autonomic symptoms. Beyond this, patients with ongoing orthostatic symptoms with a normal active stand test should be referred for further autonomic testing.<br>• Understand that many routine tests will be normal, and there is currently no diagnostic biomarker for Long COVID.<br>• Carefully monitor and follow up with patients who continue to be sick 4–12 weeks after SARS-CoV-2 infection; clinicians might choose to take a conservative diagnostic approach prior to the 3-month time frame following the SARS-CoV-2 infection, but appropriate diagnostics should not be delayed when there are signs and symptoms of urgent/life threatening clinical conditions. |
| Treatment | • While some diagnosable conditions that fall within the definition of Long COVID, such as an increased frequency of diabetes, are treatable, other manifestations of Long COVID have no FDA-approved treatment. And no biomarker exists to clearly ascribe symptoms and diagnosable conditions to Long COVID rather than to other causes. Treat a diagnosable condition related to Long COVID (e.g., diabetes, hypertension, POTS, Sjogren's syndrome), based on standard, evidence-based guidelines.<br>• Symptom management for single or multiple symptoms should be holistic and should use a multidisciplinary, patient-centered approach.<br>• Treatments for Long COVID or related conditions with minimal potential for harm can be trialed while the patient is being evaluated or awaiting a diagnosis of Long COVID. For example, educating patients about how to conserve/manage their energy (also known as pacing) and suggesting compression stockings for lightheadedness are relatively benign measures.<br>• Treatments for possible alternative diagnoses (e.g., sleep hygiene for chronic fatigue) can also be trialed. Complete or substantial resolution of a patients' symptoms would argue against a Long COVID diagnosis. |

**TABLE 2** Continued

| Steps in the Process | Key Considerations |
|---|---|
| Monitoring and Follow-Up | • Recognize that patients may require multiple visits over time to capture the course of Long COVID's clinical fluctuations and to allow various diagnostic entities to manifest clearly.<br>• Recognize that subspecialty clinic referrals are frequently beneficial, particularly for patients with multisystem disorders like Long COVID, although access to such follow-up care may be a privilege within the health care system. Clear communication between the primary Long COVID clinician and the subspecialist can avoid poor coordination of care, conflicting guidance to the patient, and drug–drug interaction. |
| Patient and Provider Education | • Educate patients and caregivers about Long COVID and its systemic, long-term impacts.<br>• Provide informational resources as well as resources for accessing social services and support groups.<br>• Thoroughly document symptoms, function, diagnostic findings, and treatment plans in the medical records for both clinical care and appropriate reimbursement. Careful documentation also assists patients in obtaining work/school accommodation and, if needed, disability benefits.<br>• Use the ICD-10 code for Long COVID, U09.9, and codes for any diagnosable condition related to Long COVID that may be present, such as ME/CFS (G93.32), POTS (G90.A), disorder of the autonomic nervous system, unspecified (G90.9), or MCAS (D89.42).<br>• Pay attention to new developments surrounding COVID-19 and LC. In particular, we anticipated the definition of LC will evolve in the future as we learn more about this medical condition. |
| Patient-Centered Collaborative Care | • Use a patient-centered approach that works toward "structural competency" by employing "cultural and epistemic humility" and active listening strategies.<br>• Understand that certain marginalized populations have experienced a higher burden of COVID-19, which has led to higher numbers of persons from these groups being affected by Long COVID, including racial and ethnic minority populations, persons with disabilities, and persons without access to health care.<br>• Recognize the complexity of Long COVID and facilitate a coordinated, multidisciplinary approach that may include primary care clinicians, subspecialty clinicians, nurses, social workers/case managers, pharmacists, physical and occupational therapists, behavioral health professionals, and others from relevant fields.<br>• Be aware that many individuals with Long COVID face stigma, and their symptoms and conditions have been misattributed to psychiatric causes alone. Though there are psychiatric manifestations of Long COVID, a comprehensive work up should be done. |

- Predominant Long COVID sub-phenotypes: Long COVID may present as a single symptom, symptom cluster (e.g., neurocognitive, sleep disturbance), or conditions (e.g., postural orthostatic tachycardia syndrome [POTS], myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS]). Where multiple symptoms are present, describe the predominant Long COVID sub-phenotypes that are the focus of study eligibility, if any. Temporal pattern of symptoms: fluctuating, increasing, new onset, persistent, relapsing/remitting, improving, or another pattern.
- Minimum duration of symptoms: e.g., 3 months, 6 months, 12 months.
- Time of onset of symptoms after infection: e.g., 0, 3, 6 months after SARS-CoV-2 infection.
- Severity of illness at the time of SARS-CoV-2 infection: e.g., WHO Clinical Progression Scale: uninfected, ambulatory mild disease, hospitalized moderate, hospitalized severe (Marshall et al., 2020).
- Co-morbid diagnoses: if relevant to the study's purpose, analysis, or application. Assessment of specific co-morbidities using standardized and validated instruments is recommended and is dependent on the research question.
- Exclusionary criteria: particular conditions (e.g., diagnosis of venous thromboembolism or interstitial lung disease prior to COVID-19).
- Equity in research: Equity must be considered, with additional awareness of and attention to the stigma and under-reporting that often occur with Long COVID. Consider access to and use of tests for SARS-CoV-2 and access to research studies. Consider populations that may be disproportionately affected by SARS-CoV-2 illness (e.g., rural and medically underserved populations; marginalized or minority populations; populations experiencing more severe disease).
- Choice of comparison group: For randomized clinical trials or observational studies, defining the comparison group is critical to interpreting results. The selection of the comparison group depends on the research question and should be justified scientifically.
- Additional design considerations including:
    - Treatment goals (e.g., mitigation of symptoms, cure, prevention)
    - Issues relevant in pediatric research, including children's ability to communicate their experience and parent stigma/under-reporting
    - The utility of including comparison groups with other IACCs
    - The implications of re-infections and co-infections
    - The value of long-term follow-up to understand the impact on conditions that may be slow to develop (e.g., cancer, Alzheimer's disease)

Research studies can include observational studies and clinical trials. Observational studies are designed to gather data on the prevalence, risk factors, or natural history of Long COVID symptoms. Study investigators do not assign participants to different treatments in an observational study. Clinical trials are studies designed to test different treatments, with the goal of identifying treatments that are both safe and effective.

Studies may need to deviate from the 2024 NASEM Long COVID Definition based on the underlying data sources that will be used or the specific study objective(s), as illustrated below for three hypothetical studies: (1) an observational study of MIS-C, (2) an observational study of neurologic sequelae in adults, and (3) a clinical trial of therapies for older adults with sleep disturbances (Table 3).

When the study inclusion criteria differ from the 2024 NASEM Long COVID Definition, the investigators are encouraged to (1) explain the rationale for adopting more restrictive or more expansive study inclusion criteria and (2) explain how the use of alternate study-specific inclusion criteria may affect the generalizability or interpretation of study findings.

### How Can Public Health Practitioners Apply the Definition?

The surveillance of conditions of public health significance is important for consistent tracking of trends within and across jurisdictions and over time. Federal, state, tribal, local, and territorial public health agencies have a long history of performing surveillance in a variety of ways to better understand and address health issues. Surveillance definitions will differ depending on a project's purpose, the availability of resources, and the need to make comparisons among different groups. Public health surveillance provides critical information to understand the epidemiology of a newly emerging pathogen and to assess for the impact of a novel infection on society. Public health surveillance goals include:

- Understanding the natural history and impact, e.g., the spectrum of physical, social, and mental illness that results from infection.
- Identifying the epidemiologic characteristics of affected persons, e.g., demographics, underlying health conditions, occupational risk, geography.
- Conducting risk assessments, e.g., probability, consequence.
- Comparing incidence and prevalence estimates among jurisdictions and nationwide.
- Monitoring trends, e.g., incidence, prevalence, impact, epidemiology of affected persons.
- Identifying opportunities for interventions, e.g., primary, secondary, tertiary prevention.

**TABLE 3** Study Design Considerations for Application of the 2024 NASEM Long COVID Definition

| | *Three studies as examples* | | |
|---|---|---|---|
| Study Type | 1. Observational study: retrospective study of multisystem inflammatory syndrome in children (MIS-C) | 2. Observational study: prospective cohort study of neurological sequelae in adults | 3. Randomized clinical trial in older adults with sleep disturbances |
| **Study Goal** | Identify risk factors | Characterize natural history | Evaluate and compare potential therapies |
| **Data Source** | Electronic health records (EHRs) | Participant questionnaires | Participant questionnaires and polysomnography |
| **Target Population** | Children with laboratory-confirmed SARS-CoV-2 infection with and without diagnosis of MIS-C | Patients at community medical centers serving racial/ethnic minorities | Age at least 65 years meeting eligibility criteria |
| **Analytic Strategy** | Logistic regression | Mixed-effects longitudinal models | Analysis of covariance |
| **Long COVID Definition Elements and Important Features** | | | |
| Documentation of SARS-CoV-2 infection | Confirmed infection with positive NAAT test in EHR | Self-report of illness | Suspected, probable, or confirmed SARS-CoV-2 infection |
| Time period of infection | March 1, 2020–February 28, 2021 | Any | Any |
| Predominant Long COVID phenotype | MIS-C | Neurocognitive | Sleep disturbance |
| Temporal pattern of symptoms | Any | Relapsing/remitting | Persistent |
| Minimum duration of symptoms | Any | 6 months | 3 months |
| Minimum time of symptom onset after infection | 0 months | 3 months | 3 months |
| Severity of illness at time of SARS-CoV-2 infection (WHO Clinical Progression Scale) | Ambulatory mild to hospitalized severe | Mild to moderate/never hospitalized | Hospitalized moderate to severe |

NOTE: NAAT = nucleic acid amplification test.

It is important that uniform criteria, also known as a case definition, are agreed upon to enable the above activities. As with any other health condition, each jurisdiction must determine, in accordance with its laws and regulations, whether to require the reporting of Long COVID as a condition of public health significance. The authority for implementing disease reporting from health care providers to public health authorities can rest with state, tribal, territorial, and some local governments (CDC, 2023a).[5] While no jurisdictions have made Long COVID reportable on an individual basis to public health authorities, many health departments have or may consider in the future conducting special surveillance or epidemiologic assessments of Long COVID in their jurisdiction. The 2024 NASEM definition of Long COVID will allow for implementation of a standard definition to be used for these purposes.

Early in the evolution of an epidemic or pandemic, especially if outcomes include severe illness, hospitalization, and death, it is important for public health surveillance to include all potential cases of a new disease to prevent further spread by enacting appropriate control measures. This inclusiveness, or high sensitivity, helps to ensure that the full range of possible presentations of a given condition is captured. However, like all conditions, this must be balanced with specificity to avoid diluting our understanding of a new condition by being too broad and including cases that do not truly belong.

For public health purposes, a case definition should be easy to apply consistently. The 2024 NASEM Long COVID Definition as proposed does not currently include a requirement for laboratory test evidence. This is due in part to known limitations in access to early testing that could have impacted some populations ability to access diagnostics, especially those with pre-existing difficulties accessing care. However, laboratory testing criteria might be added to the 2024 NASEM Long COVID Definition in implementation by researchers as previously discussed. And while it could potentially serve to augment surveillance, it is not necessarily required for all forms of surveillance activities.

Public health surveillance approaches to Long COVID should focus on monitoring trends, understanding the epidemiology of this condition (including identifying populations at risk), and assessing physical, mental, and social impact over time. Various methodologies, other than individual case reporting, have been used including cross sectional surveys, leveraging existing health care and administrative data sources (e.g., all payer

[5] For example, the current COVID-19 case definition as passed by CSTE and accepted by CDC can be found at https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-covid-19/ (accessed March 6, 2024).

databases, health information exchanges), modeling, sentinel surveillance, syndromic surveillance, or a combination of these approaches.

Jurisdictions may not have all the resources needed to completely implement all these surveillance activities. However, they may elect to still benefit from the consistency that the 2024 NASEM Long COVID Definition offers and begin to implement some, if not all, of these options. Considerations for jurisdictions seeking to implement the 2024 NASEM Long COVID Definition include the following:

- **Legal landscape:** Does the jurisdiction have the authority to require (or simply encourage/ask for) reporting?
- **Technical landscape:** Does the jurisdiction have the technical infrastructure necessary to implement surveys, electronic case reporting (ECR), health information exchange (HIE) extraction or message sharing, syndromic surveillance, sentinel surveillance, and modeling/forecasting?
- **Educational landscape:** What is the level of awareness and understanding of Long COVID among key stakeholders (e.g., the health care sector, public/community members, and/or elected officials)?
- **Capacity landscape:** Does the jurisdiction have funding support for the systems and personnel required to perform surveillance activities? If not, consider the cost of new systems (e.g., the Electronic Surveillance System for the Early Notification of Community-Based Epidemics, HIE) or the maintenance of existing systems. Also consider necessary support for training personnel to monitor and manage systems and results (e.g., control measures, action steps, etc.)

Table 4 provides examples of approaches that governmental public health jurisdictions may choose to employ to perform surveillance for Long COVID. Each of the activities below can be considered at the national, state, tribal, local, or territorial level depending on resource availability and needs.

## A WORKING DEFINITION AND RESEARCH AGENDA

The committee expects that the 2024 NASEM Long COVID Definition will evolve as new evidence emerges and our understanding of Long COVID continues to mature. The committee sought to be clear about the current understanding of Long COVID, and as one engagement participant commented, "*Use this as an opportunity to be transparent about what we know and what we don't know.*" This is in line with lessons from defining other diseases such as HIV/AIDS, which took years and multiple iterations to define. Given the current pace of research, it is possible that the definition

**TABLE 4** Public Health Surveillance Approaches for Long COVID

| Method | Description | Key Stakeholders |
|---|---|---|
| Survey | Any population-level survey design (e.g., cross-sectional, retrospective, etc.) delivered through the secure platform of a jurisdiction's choosing (e.g., Red Cap, Qualtrics) that uses the 2024 NASEM Long COVID Definition to better understand trends in a given population. | Public health officials, community members/residents/patients, community organizations, health care payers/providers, elected officials, media |
| Syndromic Surveillance | Use of key symptoms and/or billing codes (e.g., ICD codes) in an outpatient or inpatient setting that can be evaluated with the 2024 NASEM Long COVID Definition and integrated into current state and national surveillance systems. | Public health officials, hospitals, health care payers/providers, elected officials |
| Medical record review (electronic case reporting) | Review of medical records to extract symptoms and/or billing codes evaluated for agreement with the 2024 NASEM Long COVID Definition. Some jurisdictions may consider feasibility of automated processes for electronic case reporting depending on software capabilities and associated resources. | Public health officials, hospitals, health care payers/providers, elected officials |
| Sentinel Surveillance | Jurisdictions unable to broadly implement ECR due to resource limitations may consider identifying representative geographic or demographic groups to focus surveillance efforts on (e.g., one county, one hospital, one month of patient visits, etc.). | Public health officials, hospitals, health care payers/providers, elected officials |
| Prospective modeling/ forecasting | The 2024 NASEM Long COVID Definition can be applied to the emerging body of forecasting and modeling efforts to provide potential estimates of burden based on circulating SARS-CoV-2 infections for a given jurisdiction (e.g., assess potential future economic, health care, school, and work needs/impacts). | Public health officials, academic institutions, hospitals, health care payers/providers, elected officials, media |

*continued*

**TABLE 4** Continued

| Method | Description | Key Stakeholders |
|---|---|---|
| Education and Care Coordination | The 2024 NASEM Long COVID Definition can be shared widely with individuals and groups to provide greater understanding and recognition of Long COVID in our communities. | Public health officials, community members/residents/patients, community organizations, health care payers/providers, elected officials, media |
| Patient Registry | Voluntary patient registries can be facilitated by governmental public health the local, state, or federal levels together with health care providers and academic institutions to provide a method for monitoring and supporting persons with Long COVID over time. Such cohorts can also serve as key cohorts for new treatments and technology as it arises. | Public health officials, community members/residents/patients, community organizations, academic institutions, health care payers/providers. |

SOURCE: Adapted from CSTE, 2023.

may need to be updated in no more than 3 years, and the reconsideration may benefit from a multidisciplinary approach. Other triggers for updating the 2024 NASEM Long COVID Definition could include the emergence of new treatments with clear benefits for patients identified by a refined definition of disease, the development of a new test, new evidence on prognosis, or the need to improve the clarity or precision of the definition (Doust et al., 2017).

Findings from the committee's engagement process indicate the need to pair any new definition with a dissemination and education campaign to inform the public and key stakeholders. Furthermore, going forward, it may be valuable to have mechanisms in place for gauging how the 2024 NASEM Long COVID Definition is understood, how it is being used, what other elements need to be added, and whether it is being applied in a consistent and standardized way (e.g., assessment tools). A research agenda to improve the definition could focus on the key elements articulated earlier: attribution to infection, time, clinical features, equity, functional impairment, exclusions and alternative diagnoses, biomarkers and laboratory criteria, and risk factors. New evidence of the following may affect decisions to reconsider the definition:

- Improved testing to identify those who have been infected, even when tested weeks, months and years later. However, a large proportion of the population has been infected with COVID-19 at

this point, and, as a result, finding control groups will become an increasing challenge in conducting research.
- Symptoms and organ damage that distinguish Long COVID from healthy people and other medical conditions.
- Onset and duration, including delayed onset of Long COVID after an ostensible period of recovery from acute infection.
- Recovery trajectory and natural history over longer periods of time.
- Presence and prevalence of co-morbid conditions.
- Biomarker(s) to diagnose Long COVID.
- Risk factors for Long COVID.
- Prevalence and outcomes of Long COVID by sex, gender, race, ethnicity, socioeconomic status, and other factors.
- Patterns in Long COVID among special populations such as older adults; children and adolescents; pregnant, lactating, and postpartum persons; people with disabilities; people experiencing homelessness; tribal communities; and imprisoned populations; among others.
- Longitudinal consequences (e.g., risk and development of other diseases, disability, hospitalization, and death).
- Effects on functionality and daily living, overall well-being, and caregivers and families.
- Social sciences research aimed at understanding the social and economic consequences of Long COVID.
- New treatment and management options that could potentially affect the sensitivity threshold and elements of the definition.

Ongoing and new research should lead to a more complete understanding of the natural history, etiology, therapy, and clinical management of Long COVID, and this enriched knowledge may prompt reconsideration of the definition of Long COVID.

## SHORTCOMINGS IN THE AVAILABLE EVIDENCE

Research on Long COVID has been complicated due to heterogeneous study methods and lack of common data elements (e.g., different terms to describe the same symptom or condition) (Deer et al., 2021). Currently, most studies are among people with documented evidence of SARS-CoV-2 infection, which omits some who have been infected but have gone untested or had a false negative result. Differences in test availability and access could have affected the populations selected for these investigations. Time factors in studies were quite heterogenous—for example, how long people had to be sick before being included in a study, when they were assessed during a study, and the total follow-up period—which made it difficult to

synthesize data. Furthermore, when the vast majority of people have been infected with SARS-CoV-2, it is difficult to create a valid, uninfected control group.

Additionally, it seems few studies were adjusted for duration of illness when analyzing or interpreting results. Some studies lasted years, some only followed up for months to 1 year, and it was not clear if those who may have "recovered" were still followed to see if they had relapsed. Scientific studies take time and often confirm patterns that patients and clinicians may already be aware of. On the other hand, patient and clinician reports are usually not systematically gathered, and what appear to be common or prominent findings may appear different after more data are collected. Because the very nature of Long COVID requires evaluation over time, additional information and knowledge will continue to emerge, as will opportunities to document and understand the natural history of Long COVID.

## LIMITATIONS AND UNINTENDED CONSEQUENCES OF THE DEFINITION

The committee confronted many difficulties in its efforts to define Long COVID including:

- Varying working definitions and terminology used in studies that attempt to characterize Long COVID.
- The tradeoffs of a broad definition and effects of this broad definition on the IACC field.
- A lack of confirmatory tests for SARS-CoV-2 infection.
- Tests with limited performance characteristics (i.e., sensitivity, specificity).
- Changes in test types (e.g., shift from PCR to antigen tests, especially to those self-administered at home and not typically reported to public health authorities).
- Varying levels of access to diagnostic tests across the population at different times in the pandemic response.
- The social and cultural factors that can impact individuals' ability and decisions to seek health care and therefore ultimately impact who is diagnosed, managed and studied for acute infections as well as Long COVID (e.g., cost, economic ability to sustain a work absence, family care obligations, etc.).
- The inescapable circularity of relying on symptoms to define Long COVID and using the definition to indicate what symptoms are attributable to Long COVID.

- Striking the right balance between recognizing wide susceptibility to Long COVID while also acknowledging evidence of differential host risk factors (such as higher risk for women, those with multiple previous infections, or more severe prior infection).
- Understanding that for certain purposes (such as many research projects or public health surveillance), selection criteria that are more restrictive than the overall definition will be needed to characterize the target population.
- The reality of the unknown pathophysiologic mechanisms that are inherent to any new condition and that will ideally be further elucidated as more time passes.
- Limitations in the evidence base, as described above.

Disease definition is an essential tool in health care that aids diagnosis, treatment, and research; it also has implications for access to supportive services post diagnosis. Throughout its deliberations, the committee sought to define Long COVID while simultaneously recognizing that there is more to learn and understand about it, and this means acknowledging inherent limitations and anticipating that changes will be made as the science advances. Particularly, the absence of an independent diagnostic standard for Long COVID, such as a definitive biomarker, is a noteworthy limitation. In any current effort to define Long COVID, there is an unavoidable circularity in using symptoms to define Long COVID and then relying on the definition to recognize characteristic symptoms. If SARS-CoV-2 had infected just one-tenth of one percent of the population, there could be the same proportional increase in Long COVID, but it would likely never have been recognized as such, lost in the background noise of similar IACCs with uncertain etiology. The present exercise to develop a definition is feasible because SARS-CoV-2 infected such a large number of persons and was followed by an upsurge in multiple chronic symptoms among those who had experienced infection. This strong temporal association lends confidence to the pathobiological, clinical, personal, and social reality of Long COVID. However, in the absence of a highly sensitive and perfectly specific biomarker, the edges of inclusion and exclusion remain fuzzy: patients with a newly developed condition, such as diabetes, may have it attributed, rightly or wrongly, to Long COVID, while other patients with a single, persisting symptom, such as headache, that is due to Long COVID may fail to be properly diagnosed because there are many other possible causes of that symptom. Over time, with growing knowledge of the epidemiology and etiology of Long COVID and especially with the advent of one or more definitive biomarkers, the probability of both erroneous exclusion and erroneous inclusion will diminish.

## CONCLUDING REMARKS AND RECOMMENDATIONS

The committee hopes the 2024 NASEM Long COVID Definition will, first and foremost, benefit the Long COVID community by creating a shared understanding of what Long COVID is and that it will lend added recognition to IACCs within the medical community and society at large. The 2024 NASEM Long COVID Definition reflects and promotes a more holistic and integrated approach to understanding disease. Such an approach reflects a broader recognition of the complexities inherent in human health, including health disparities, social determinants of health, and the importance of including patient experience and knowledge in decision making. Furthermore, the 2024 NASEM Long COVID Definition recognizes the heterogeneity and complexity of Long COVID presentations and how Long COVID can affect individuals in multiple and profound ways.

Through a synthesis of current research, multidisciplinary clinical insights, and patient perspectives, the committee attempted to unravel the complexities of Long COVID and to define Long COVID in a way that can serve a range of needs. In support of its definition, the committee puts forth three recommendations about the adoption, implementation, and updating of the 2024 NASEM Long COVID Definition.

### Recommendations

**RECOMMENDATION 1. Adopt and Implement the 2024 NASEM Long COVID Definition.**

**The federal government, state, tribal, local, and territorial health authorities; clinical societies and associations; public health practitioners; clinicians; payers; researchers; drug industry; employers; educators; international organizations; and patients should adopt the 2024 NASEM Long COVID Definition and should use the term Long COVID. The 2024 NASEM Long COVID Definition is intended to be applied to many purposes, but the committee notes that there is flexibility within the broad definition, for example, to restrict research eligibility to a subset of Long COVID patients.**

**RECOMMENDATION 2. Promulgate and Monitor the Implementation of the 2024 NASEM Long COVID Definition.**

**The Office of the Assistant Secretary for Health's Office of Long COVID Research and Practice and the Long COVID Coordination Council should lead the coordination and collaboration efforts across federal, state, tribal, local, and territorial agencies and other relevant entities, including international organizations, in the wide dissemination and implementation of**

**the 2024 NASEM Long COVID Definition. Such implementation efforts should:**

- **Give special attention to the definition's equity implications to maximize appropriate inclusion.**
- **Develop standardized communication for key stakeholders and the public about the revised definition and understanding of Long COVID.**
- **Empirically test the 2024 NASEM Long COVID Definition; monitor, evaluate, and identify barriers to implementation and adoption of the definition in research and in practice (including supporting an individual's ability to apply for and receive Social Security disability benefits) that may be improved in future revisions.**
- **Develop a standard protocol for screening and diagnosing patients with Long COVID in clinical settings and enhance clinical education and training on infection-associated chronic conditions.**
- **Catalogue and summarize the application of the definition in research settings and identify sub-phenotypes of Long COVID that inform the need for further investigation across the translational research spectrum from discovery to delivery science.**
- **Take advantage of a unique opportunity to learn from epidemiologic surveillance of an infection-associated chronic condition and support, for example, improved data infrastructure, technologic and legal support for more efficient cross-jurisdictional information-sharing, and improved test types and access to testing.**
- **Continue to listen to and collaborate with the Long COVID community to learn from lived experience.**

**RECOMMENDATION 3. Update the 2024 NASEM Long COVID Definition. In no more than 3 years or when triggered by the emergence of relevant new knowledge, the Office of the Assistant Secretary for Health's Office of Long COVID Research and Practice should convene a multi-disciplinary group, including individuals with lived experience, to reexamine and update the 2024 NASEM Long COVID Definition set forth in this report. The Office of the Assistant Secretary for Health's Office of Long COVID Research and Practice should put into place the necessary infrastructure, policies, and mechanisms to support and prepare for future updates to the 2024 NASEM Long COVID Definition, including a process to track and assess new scientific knowledge that may inform the definition.**

## REFERENCES


Admon, A. J., T. J. Iwashyna, L. A. Kamphuis, S. J. Gundel, S. K. Sahetya, I. D. Peltan, S. Y. Chang, J. H. Han, K. C. Vranas, K. P. Mayer, A. A. Hope, S. E. Jolley, E. Caldwell, M. L. Monahan, K. Hauschildt, S. M. Brown, N. R. Aggarwal, B. T. Thompson, and C. L. Hough. 2023. Assessment of symptom, disability, and financial trajectories in patients hospitalized for COVID-19 at 6 months. *JAMA Network Open* 6(2):e2255795.

Ahmad, F. B., R. N. Anderson, J. A. Cisewski, and P. D. Sutton. 2022. Identification of deaths with post-acute sequelae of COVID-19 from death certificate literal text: United States, January 1, 2020–June 30, 2022. *NVSS Vital Statistics Rapid Release*, no. 25. https://stacks.cdc.gov/view/cdc/121968 (accessed March 30, 2024).

Al-Aly, Z., and E. Topol. 2024. Solving the puzzle of long COVID. *Science* 383(6685):830–832.

Al-Aly, Z., A. Agarwal, N. Alwan, and V. A. Luyckx. 2023. Long COVID: Long-term health outcomes and implications for policy and research. *Nature Reviews Nephrology* 19(1):1–2.

Al-Aly, Z., B. Bowe, and Y. Xie. 2022. Long COVID After Breakthrough SARS-CoV-2 Infection. *Nat Med* 28(7): 1461-1467.

Alkodaymi, M. S., O. A. Omrani, N. A. Fawzy, B. A. Shaar, R. Almamlouk, M. Riaz, M. Obeidat, Y. Obeidat, D. Gerberi, R. M. Taha, Z. Kashour, T. Kashour, E. F. Berbari, K. Alkattan, and I. M. Tleyjeh. 2022. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: A systematic review and meta-analysis. *Clinical Microbiology and Infection* 28(5):657–666.

Altmann, D. M., E. M. Whettlock, S. Liu, D. J. Arachchillage, and R. J. Boyton. 2023. The immunology of long COVID. *Nature Reviews Immunology* 23(10):618–634.

Alwan, N. A., and L. Johnson. 2021. Defining long COVID: Going back to the start. *Med* 2(5):501–504.

American Diabetes Association Professional Practice Committee. 2024. Comprehensive medical evaluation and assessment of comorbidities: Standards of care in diabetes–2024. *Diabetes Care* 47:S52–S76.

Antonelli, M., J. C. Pujol, T. D. Spector, S. Ourselin, and C. J. Steves. 2022. Risk of Long COVID associated with Delta versus Omicron variants of SARS-CoV-2. *Lancet (London, England) 399*(10343), 2263–2264.

Apple, A. C., A. Oddi, M. J. Peluso, B. M. Asken, T. J. Henrich, J. D. Kelly, S. J. Pleasure, S. G. Deeks, I. E. Allen, J. N. Martin, L. C. Ndhlovu, B. L. Miller, M. L. Stephens, and J. Hellmuth. 2022. Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19. *Annals of Clinical and Translational Neurology* 9(2):221–226.

Au, L., C. Capotescu, G. Eyal, and G. Finestone. 2022. Long COVID and medical gaslighting: Dismissal, delayed diagnosis, and deferred treatment. *SSM—Qualitative Research in Health* 2:100167.

Azzolini E., R. Levi, R. Sarti, C. Pozzi, M. Mollura, A. Mantovani, and M. Rescigno. 2022. Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers. *JAMA* 328(7):676–678.

Baig, A. M. 2021. Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers. *Journal of Medical Virology* 93(5):2555–2556.

Ballouz, T., D. Menges, A. Anagnostopoulos, A. Domenghino, H. E. Aschmann, A. Frei, J. S. Fehr, and M. A. Puhan. 2023. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: Population-based, longitudinal cohort study. *BMJ* 381:e074425.

Banerjee, M., R. Pal, and S. Dutta. 2022. Risk of incident diabetes post-COVID-19: A systematic review and meta-analysis. *Primary Care Diabetes* 16(4):591–593.

Bazdar, S., A. K. A. L. Kwee, L. Houweling, Y. de Wit-van Wijck, F. A. A. Mohamed Hoesein, G. S. Downward, E. J. Nossent, and A. H. Maitland-van der Zee. 2023. A systematic review of chest imaging findings in long COVID patients. *Journal of Personalized Medicine* 13(2):282.

Behnood, S. A., R. Shafran, S. D. Bennett, A. X. D. Zhang, L. L. O'Mahoney, T. J. Stephenson, S. N. Ladhani, B. L. De Stavola, R. M. Viner, and O. V. Swann. 2022. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: A meta-analysis of controlled and uncontrolled studies. *Journal of Infection* 84(2):158–170.

Bergmans, R. S., K. Chambers-Peeple, C. Yu, L. Z. Xiao, R. Wegryn-Jones, A. Martin, S. Dell'Imperio, D. Aboul-Hassan, D. A. Williams, D. J. Clauw, and M. DeJonckheere. 2023. "I'm still here, I'm alive and breathing": The experience of Black Americans with long COVID. *Journal of Clinical Nursing* 33(1):162–177.

Bonilla, H., M. J. Peluso, K. Rodgers, J. A. Aberg, T. F. Patterson, R. Tamburro, L. Baizer, J. D. Goldman, N. Rouphael, A. Deitchman, J. Fine, P. Fontelo, A. Y. Kim, G. Shaw, J. Stratford, P. Ceger, M. M. Costantine, L. Fisher, L. O'Brien, C. Maughan, J. G. Quigley, V. Gabbay, S. Mohandas, D. Williams, and G. A. McComsey. 2023. Therapeutic trials for long COVID-19: A call to action from the interventions taskforce of the recover initiative. *Frontiers in Immunology* 14:1129459.

Bowe, B., Y. Xie, and Z. Al-Aly. 2022. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nature Medicine* 28:2398–2405.

Bowe, B., Y. Xie, and Z. Al-Aly. 2023. Postacute sequelae of COVID-19 at 2 years. *Nature Medicine* 29(9):2347–2357.

Callard, F., and E. Perego. 2021. How and why patients made long COVID. *Social Science & Medicine* 268:113426.

Català, M., N. Mercadé-Besora, R. Kolde, N. T. H. Trinh, E. Roel, E. Burn, T. Rathod-Mistry, K. Kostka, W. Y. Man, A. Delmestri, H. M. E. Nordeng, A. Uusküla, T. Duarte-Salles, D. Prieto-Alhambra, and A. M. Jödicke. 2024. The effectiveness of COVID-19 vaccines to prevent long COVID symptoms: Staggered cohort study of data from the UK, Spain, and Estonia. *The Lancet Respiratory Medicine* 12(3):225–236.

CDC (Centers for Disease Control and Prevention). 2023a. *National Notifiable Disease Surveillance System (NNDS): What is case surveillance?* https://www.cdc.gov/nndss/about/index.html (accessed March 6, 2024).

CDC. 2023b. *Long COVID or Post-COVID Conditions*. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#:~:text=Some%20people%2C%20especially%20those%20who,kidney%2C%20skin%2C%20and%20brain. (accessed April 23, 2024).

CDC. 2024a. *Long COVID: Household Pulse Survey*. https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm (accessed March 30, 2024).

CDC. 2024b. 2022-2023 Nationwide COVID-19 infection- and vaccination-induced antibody seroprevalence (blood donations). https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence-2022 (accessed April 23, 2024).

CDC Foundation. 2024. *Infection-associated chronic conditions: Opportunities for action*. https://solvecfs.org/wp-content/uploads/2024/02/ICUEPublicReport.pdf (accessed March 30, 2024).

Chaichana, U., K. K. C. Man, A. Chen, I. C. K. Wong, J. George, P. Wilson, and L. Wei. 2023. Definition of post–COVID-19 condition among published research studies. *JAMA Network Open* 6(4):e235856.

Chang, R., T. Y.-T. Chen, S.-I. Wang, Y.-M. Hung, H.-Y. Chen, and C.-C. J. Wei. 2023. Risk of autoimmune diseases in patients with COVID-19: A retrospective cohort study. *EClinicalMedicine* 56:101783.

Chen, B., B. Julg, S. Mohandas, S. B. Bradfute, and RECOVER Mechanistic Pathways Task Force. 2023. Viral persistence, reactivation, and mechanisms of Long COVID. *eLife* 12:e86015.

Choutka, J., V. Jansari, M. Hornig, and A. Iwasaki. 2022. Unexplained post-acute infection syndromes. *Nature Medicine* 28(5):911–923.

Ciaffi, J., E. Vanni, L. Mancarella, V. Brusi, L. Lisi, F. Pignatti, S. Naldi, E. Assirelli, S. Neri, M. Reta, C. Faldini, and F. Ursini. 2023. Post-acute COVID-19 joint pain and new onset of rheumatic musculoskeletal diseases: A systematic review. *Diagnostics* 13(1):1850.

Clauw, D. J., and L. Calabrese. 2024. Rheumatology and Long COVID: Lessons from the study of fibromyalgia. *Annals of the Rheumatic Diseases* 2024;83:136-138.

Cohen, J., and Y. van der Meulen Rodgers. 2023. An intersectional analysis of long COVID prevalence. *International Journal for Equity in Health* 22(1):261.

Crivelli, L., K. Palmer, I. Calandri, A. Guekht, E. Beghi, W. Carroll, J. Frontera, D. García-Azorín, E. Westenberg, A. S. Winkler, F. Mangialasche, R. F. Allegri, and M. Kivipelto. 2022. Changes in cognitive functioning after COVID-19: A systematic review and meta-analysis. *Alzheimer's & Dementia* 18(5):1047–1066.

CSTE (Council of State and Territorial Epidemiologists). 2023. *State, tribal, local, and territorial public health agency approaches to long COVID-19/post COVID-19 condition surveillance: Lessons learned, gaps, and needs*. https://preparedness.cste.org/wp-content/uploads/2023/09/CSTE-STLT-Long-COVID-Surveillance-August-2023.pdf (accessed April 1, 2024).

Cutler, D. M. 2022. The economic cost of long COVID: An update. *Harvard University*. https://scholar.harvard.edu/files/cutler/files/long_covid_update_7-22.pdf (accessed April 4, 2024).

Davis, H. E., G. S. Assaf, L. McCorkell, H. Wei, R. J. Low, Y. Re'em, S. Redfield, J. P. Austin, and A. Akrami. 2021. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 38:101019.

Davis, H. E., L. McCorkell, J. M. Vogel, and E. J. Topol. 2023. Long COVID: Major findings, mechanisms and recommendations. *Nature Reviews Microbiology* 21(3):133–146.

de Oliveira Almeida, K., I. G. Nogueira Alves, R. S. de Queiroz, M. R. de Castro, V. A. Gomes, F. C. Santos Fontoura, C. Brites, and M. G. Neto. 2023. A systematic review on physical function, activities of daily living and health-related quality of life in COVID-19 survivors. *Chronic Illness* 19(2):279–303.

Deer, R. R., M. A. Rock, N. Vasilevsky, L. Carmody, H. Rando, A. J. Anzalone, M. D. Basson, T. D. Bennett, T. Bergquist, E. A. Boudreau, C. T. Bramante, J. B. Byrd, T. J. Callahan, L. E. Chan, H. Chu, C. G. Chute, B. D. Coleman, H. E. Davis, J. Gagnier, C. S. Greene, W. B. Hillegass, R. Kavuluru, W. D. Kimble, F. M. Koraishy, S. Kohler, C. Liang, F. Liu, H. Liu, V. Madhira, C. R. Madlock-Brown, N. Matentzoglu, D. R. Mazzotti, J. A. McMurry, D. S. McNair, R. A. Moffitt, T. S. Monteith, A. M. Parker, M. A. Perry, E. Pfaff, J. T. Reese, J. Saltz, R. A. Schuff, A. E. Solomonides, J. Solway, H. Spratt, G. S. Stein, A. A. Sule, U. Topaloglu, G. D. Vavougios, L. Wang, M. A. Haendel, and P. N. Robinson. 2021. Characterizing long COVID: Deep phenotype of a complex condition. *EBioMedicine* 74:103722.

Diekman, S., and T. Chung. 2023. Post-acute sequelae of SARS-CoV-2 syndrome presenting as postural orthostatic tachycardia syndrome. *Clinical and Experimental Emergency Medicine* 10(1):18–25.

Dinnes, J., P. Sharma, S. Berhane, S. S. van Wyk, N. Nyaaba, J. Domen, M. Taylor, J. Cunningham, C. Davenport, S. Dittrich, D. Emperador, L. Hooft, M. M. G. Leeflang, M. D. F. McInnes, R. Spijker, J. Y. Verbakel, Y. Takwoingi, S. Taylor-Phillips, A. Van den Bruel, and J. J. Deeks. 2022. Rapid, point-of-care antigen tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database of Systematic Reviews* 7(7):CD013705.

Doust, J., P. O. Vandvik, A. Qaseem, R. A. Mustafa, A. R. Horvath, A. Frances, L. Al-Ansary, P. Bossuyt, R. L. Ward, I. Kopp, L. Gollogly, H. Schunemann, P. Glasziou, and Guidelines International Network Preventing Overdiagnosis Working Group. 2017. Guidance for modifying the definition of diseases: A checklist. *JAMA Internal Medicine* 177(7):1020–1025.

Durstenfeld, M. S., S. Weiman, M. Holtzman, C. Blish, R. Pretorius, and S. G. Deeks. 2024. Long COVID and post-acute sequelae of SARS-CoV-2 pathogenesis and treatment: A keystone symposia report. *Annals of the New York Academy of Sciences*. https://doi.org/10.1111/nyas.15132.

Economist Impact. 2024. An incomplete picture: understanding the burden of Long Covid. https://impact.economist.com/perspectives/sites/default/files/download/ei264_-_an_incomplete_picture_understanding_the_burden_of_long_covid_v8.pdf. (accessed May 3, 2024).

EpiCore. 2023. Obtaining Long COVID definition through EpiCore. *EpiCore Long COVID definitions*. https://endingpandemics.org/wp-content/uploads/2023/03/EPICORE-Long-Covid-Definitions-NASEM-2023-4.pdf (accessed April 19, 2024).

Espin, E., C. Yang, C. P. Shannon, S. Assadian, D. He, and S. J. Tebbutt. 2023. Cellular and molecular biomarkers of long COVID: A scoping review. *EBioMedicine* 91:104552.

Federal Reserve Bank of Minneapolis. 2022. *Long-haulers and labor market outcomes*. Available at https://www.minneapolisfed.org/research/institute-working-papers/long-haulers-and-labor-market-outcomes (accessed April 1, 2024).

Fernández-de-Las-Peñas, C. 2022. Long COVID: Current definition. *Infection* 50(1):285–286.

Fernández-de-Las-Peñas, C., D. Palacios-Cena, V. Gomez-Mayordomo, M. L. Cuadrado, and L. L. Florencio. 2021a. Defining post-COVID symptoms (post-acute COVID, long COVID, persistent post-COVID): An integrative classification. *International Journal of Environmental Research and Public Health* 18(5):1–9.

Fernández-de-las-Peñas, C., L. L. Florencio, V. Gomez-Mayordomo, M. L. Cuadrado, D. Palacios-Cena, and A. V. Raveendran. 2021a. Proposed integrative model for post-COVID symptoms. *Diabetes & Metabolic Syndrome* 15(4):102159.

Fernández-de-las-Peñas, C., D. Palacios-Cena, V. Gomez-Mayordomo, L. L. Florencio, M. L. Cuadrado, G. Plaza-Manzano, and M. Navarro-Santana. 2021b. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *European Journal of Internal Medicine* 92:55–70.

Fernández-de-Las-Peñas, C., K. I. Notarte, P. J. Peligro, J. V. Velasco, M. J. Ocampo, B. M. Henry, L. Arendt-Nielsen, J. Torres-Macho, and G. Plaza-Manzano. 2022a. Long-COVID symptoms in individuals infected with different SARS-CoV-2 variants of concern: A systematic review of the literature. *Viruses* 14(12):2629.

Fernández-de-Las-Peñas, C., O. J. Pellicer-Valero, E. Navarro-Pardo, D. Palacios-Cena, L. L. Florencio, C. Guijarro, and J. D. Martin-Guerrero. 2022b. Symptoms experienced at the acute phase of SARS-CoV-2 infection as risk factor of long-term post-COVID symptoms: The long-COVID-exp-cm multicenter study. *Int J Infect Dis* 116:241–244.

Fernández-de-Las-Peñas, C., J. D. Martín-Guerrero, I. Cancela-Cilleruelo, P. Moro-López-Menchero, J. Rodríguez-Jiménez, E. Navarro-Pardo, and O. J. Pellicer-Valero. 2022c. Exploring the recovery curves for long-term post-COVID functional limitations on daily living activities: The LONG-COVID-EXP-CM multicenter study. *Journal of Infection* 84(5):722–746.

Fernández-de-Las-Peñas, C., J. D. Martin-Guerrero, L. L. Florencio, E. Navarro-Pardo, J. Rodriguez-Jimenez, J. Torres-Macho, and O. J. Pellicer-Valero. 2023. Clustering analysis reveals different profiles associating long-term post-COVID symptoms, COVID-19 symptoms at hospital admission and previous medical co-morbidities in previously hospitalized COVID-19 survivors. *Infection* 51(1):61–69.

Figueiredo, E. A. B., W. T. Silva, S. P. Tsopanoglou, D. F. M. Vitorino, L. F. L. Oliveira, K. L. S. Silva, H. D. H. Luz, M. R. Ávila, L. F. F. Oliveira, A. C. R. Lacerda, V. A. Mendonça, V. P. Lima, M. F. F. Mediano, P. H. S. Figueiredo, M. O. C. Rocha, and H. S. Costa. 2022. The health-related quality of life in patients with post-COVID-19 after hospitalization: A systematic review. *Revista de Sociedade Brasileira de Medicina Tropical* 55:e0741.

Fogh, K., T. G. Larsen, C. B. Hansen, R. B. Hasselbalch, A. R. R. Eriksen, H. Bundgaard, R. Frikke-Schmidt, L. M. Hilsted, L. Østergaard, I. S. Johansen, I. Hageman, P. Garred, and K. Iversen. 2022. Self-reported long COVID and its association with the presence of SARS-CoV-2 antibodies in a Danish cohort up to 12 months after infection. *Microbiology Spectrum* 10(6):e02537–e02522.

Ford, N. D., D. Slaughter, D. Edwards, A. Dalton, C. Perrine, A. Vahratian, and S. Saydah. 2023. Long COVID and significant activity limitation among adults, by age—United States, June 1–13, 2022, to June 7–19, 2023. *Morbidity and Mortality Weekly Report* 72(32):866–870.

Ford, N., A. Agedew, A. F. Dalton, J. Singleton, C. G. Perrine, and S. Saydah. 2024. Notes from the field: Long COVID prevalence among adults—United States, 2022. *Morbidity and Mortality Weekly Report* 73(6):135–136.

Franco, J. V. A., L. I. Garegnani, G. V. Oltra, M. I. Metzendorf, L. F. Trivisonno, N. Sgarbossa, D. Ducks, K. Heldt, R. Mumm, B. Barnes, and C. Scheidt-Nave. 2022. Long-term health symptoms and sequelae following SARS-CoV-2 infection: An evidence map. *International Journal of Environmental Research and Public Health* 19(1):9915.

Garmoe, W., K. Rao, B. Gorter, and R. Kantor. 2024. Neurocognitive impairment in post-COVID-19 condition in adults: Narrative review of the current literature. *Archives of Clinical Neuropsychology* acae017.

Gavrilova, N., L. Soprun, M. Lukashenko, V. Ryabkova, T. V. Fedotkina, L. P. Churilov, and Y. Shoenfeld. 2022. New clinical phenotype of the post-COVID syndrome: Fibromyalgia and joint hypermobility condition. *Pathophysiology* 29(1):24-29. https://doi.org/10.3390/pathophysiology29010003.

Goldenberg, D. L. 2023. Applying lessons from rheumatology to better understand long COVID. *Arthritis Care & Research (Hoboken)* 76(1):49–56.

Government of Canada. 2023. *Second report: Spring 2023*. https://health-infobase.canada.ca/covid-19/post-covid-condition/spring-2023-report.html (accessed March 3, 2024).

Hägglöf, E., M. Bell, E. Zettersten, L. Engerström, and E. Larsson. 2023. Long-term survival after intensive care for COVID-19: A nationwide cohort study of more than 8000 patients. *Annals of Intensive Care* 13(1):76.

Hampshire, A., A. Azor, C. Atchison, W. Trender, P. J. Hellyer, V. Giunchiglia, M. Husain, G. S. Cooke, E. Cooper, A. Lound, C. A. Donnelly, M. Chadeau-Hyam, H. Ward, and P. Elliott. 2024. Cognition and memory after COVID-19 in a large community sample. *New England Journal of Medicine* 390(9):806–818.

Haslam, A., T. Olivier, and V. Prasad. 2023. The definition of long COVID used in interventional studies. *European Journal of Clinical Investigations* 53(8):e13989.

Hayes, L. D., J. Ingram, and N. F. Sculthorpe. 2021. More than 100 persistent symptoms of SARS-CoV-2 (long COVID): A scoping review. *Frontiers in Medicine (Lausanne)* 8:750378.

Hedberg, P., and P. Nauclér. 2024. Post-COVID-19 condition after SARS-CoV-2 infections during the Omicron surge vs the Delta, Alpha, and Wild type periods in Stockholm, Sweden. *The Journal of Infectious Diseases* 229(1):133–136.

Heesakkers, H., J. G. van der Hoeven, S. Corsten, I. Janssen, E. Ewalds, K. S. Simons, B. Westerhof, T. C. D. Rettig, C. Jacobs, S. van Santen, A. J. C. Slooter, M. C. E. van der Woude, M. van den Boogaard, and M. Zegers. 2022. Clinical outcomes among patients with 1-year survival following intensive care unit treatment for COVID-19. *JAMA* 327(6):559–565.

HHS (U.S. Department of Health and Human Services). 2020. *Health equity in Healthy People 2030*. https://health.gov/healthypeople/priority-areas/health-equity-healthy-people-2030 (accessed March 31, 2024).

HHS. 2021. *Guidance on "Long COVID" as a disability under the ADA section 504, and section 1557*. https://www.hhs.gov/civil-rights/for-providers/civil-rights-covid19/guidance-long-covid-disability/index.html (accessed April 24, 2024).

HHS/OASH (Department of Health and Human Services and Office of the Assistant Secretary for Health). 2022. *HHS releases Long COVID report providing insights and opportunities to support patient community*. https://www.hhs.gov/about/news/2022/11/21/hhs-releases-long-covid-report-providing-insights-and-opportunities-support.html (accessed April 1, 2024).

HHS. 2022. *National Research Action Plan on Long COVID*. https://www.covid.gov/sites/default/files/documents/National-Research-Action-Plan-on-Long-COVID-08012022.pdf (accessed April 4, 2024).

Hill, E. L., H. B. Mehta, S. Sharma, K. Mane, S. K. Singh, C. Xie, E. Cathey, J. Loomba, S. Russell, H. Spratt, P. E. DeWitt, N. Ammar, C. Madlock-Brown, D. Brown, J. A. McMurry, C. G. Chute, M. A. Haendel, R. Moffitt, E. R. Pfaff, and T. D. Bennett. 2023. Risk factors associated with post-acute sequelae of SARS-CoV-2: An N3C and NIH RECOVER study. *BMC Public Health* 23(1):2103.

Huerne, K., K. B. Filion, R. Grad, P. Ernst, A. S. Gershon, and M. J. Eisenberg. 2023. Epidemiological and clinical perspectives of long COVID syndrome. *American Journal of Medicine Open* 9:100033.

IOM (Institute of Medicine). 2014. *Chronic multisymptom illness in Gulf War veterans: Case definitions reexamined*. Washington, DC: The National Academies Press.

IOM. 2015. *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness*. Washington, DC: The National Academies Press.

Ireson, J., A. Taylor, E. Richardson, B. Greenfield, and G. Jones. 2022. Exploring invisibility and epistemic injustice in Long COVID—A citizen science qualitative analysis of patient stories from an online COVID community. *Health Expectations* 25(4):1753-1765.

Jackson, J. C., J. Clune, H. Hoenig, M. Morey, V. Anderson, L. Denne, N. Williams, C. Seibert, R. Torres, D. R. Janz, B. Levine, B. Pun, K. Archer, E. Schiro, J. Jones, J. Zoz, J. Thompson, and E. W. Ely. 2010. The Returning to Everyday Tasks Utilizing Rehabilitation Networks (RETURN) trial: A pilot, feasibility trial including in-home cognitive rehabilitation of ICU survivors. *American Journal of Respiratory and Critical Care Medicine* 181:A5359.

Jackson, J. C., E. W. Ely, M. C. Morey, V. M. Anderson, L. B. Denne, J. Clune, C. S. Seibert, K. R. Archer, R. Torres, D. Janz, E. Schiro, J. Jones, A. K. Shintani, B. Levine, B. T. Pun, J. L. Thompson, N. E. Brummel, and H. Hoenig. 2012. Cognitive and physical rehabilitation of intensive care unit survivors: Results of the RETURN randomized controlled pilot investigation. *Critical Care Medicine* 40(4):1088-1097.

Jacobs, E. T., C. J. Catalfamo, P. M. Colombo, S. M. Khan, E. Austhof, F. Cordova-Marks, K. C. Ernst, L. V. Farland, and K. Pogreba-Brown. 2023. Pre-existing conditions associated with post-acute sequelae of COVID-19. *Journal of Autoimmunity* 135:102991.

Jacobs, M. M., E. Evans, and C. Ellis. 2023. Racial, ethnic, and sex disparities in the incidence and cognitive symptomology of long COVID-19. *Journal of the National Medical Association* 115(2):233–243.

Jiang, L., X. Li, J. Nie, K. Tang, and Z. A. Bhutta. 2023. A systematic review of persistent clinical features after SARS-CoV-2 in the pediatric population. *Pediatrics* 152(2):e2022060351.

Kedor, C., H. Freitag, L. Meyer-Arndt, K. Wittke, L. G. Hanitsch, T. Zoller, F. Steinbeis, M. Haffke, G. Rudolf, B. Heidecker, T. Bobbert, J. Spranger, H. D. Volk, C. Skurk, F. Konietschke, F. Paul, U. Behrends, J. Bellmann-Strobl, and C. Scheibenbogen. 2022. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. *Nature Communications* 13(1):5104.

Khullar, D., Y. Zhang, C. Zang, Z. Xu, F. Wang, M. G. Weiner, T. W. Carton, R. L. Rothman, J. P. Block, and R. Kaushal. 2023. Racial/ethnic disparities in post-acute sequelae of SARS-CoV-2 infection in New York: An EHR-based cohort study from the recover program. *Journal of General Internal Medicine* 38(5):1127–1136.

Kim, C., B. Chen, S. Mohandas, J. Rehman, Z. A. Sherif, K. Coombs, RECOVER Mechanistic Pathways Task Force, and RECOVER Initiative. 2023. The importance of patient-partnered research in addressing long COVID: Takeaways for biomedical research study design from the RECOVER Initiative's Mechanistic Pathways taskforce. *Elife* 12:e86043.

Kioi, Y., H. Yorifuji, Y. Higami, and Y. Katada. 2023. Serositis and lymphopenia are common features of systemic lupus erythematosus following SARS-CoV-2 infection: A case report and literature review. *International Journal of Rheumatic Diseases* 26(11):2267–2271.

Klein, J., J. Wood, J. Jaycox, R. M. Dhodapkar, P. Lu, J. R. Gehlhausen, A. Tabachnikova, K. Greene, L. Tabacof, A. A. Malik, V. Silva Monteiro, J. Silva, K. Kamath, M. Zhang, A. Dhal, I. M. Ott, G. Valle, M. Pena-Hernandez, T. Mao, B. Bhattacharjee, T. Takahashi, C. Lucas, E. Song, D. McCarthy, E. Breyman, J. Tosto-Mancuso, Y. Dai, E. Perotti, K. Akduman, T. J. Tzeng, L. Xu, A. C. Geraghty, M. Monje, I. Yildirim, J. Shon, R. Medzhitov, D. Lutchmansingh, J. D. Possick, N. Kaminski, S. B. Omer, H. M. Krumholz, L. Guan, C. S. Dela Cruz, D. van Dijk, A. M. Ring, D. Putrino, and A. Iwasaki. 2023. Distinguishing features of long COVID identified through immune profiling. *Nature* 623(7985):139–148.

Kleinman, A. 1988. *The illness narratives: Suffering, healing and the human condition*. New York: Basic Books.

Komaroff, A. L., and W. I. Lipkin. 2023. ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature. *Frontiers in medicine*, *10*, 1187163.

Korte, W., M. Buljan, M. Rösslein, P. Wick, V. Golubov, J. Jentsch, M. Reut, K. Peier, B. Nohynek, A. Fischer, R. Stolz, M. Cettuzzi, O. Nolte. 2021. SARS-CoV-2 IgG and IgA antibody response is gender dependent; and IgG antibodies rapidly decline early on. *Journal of Infection* 82(1):e11–e14.

Kromydas, T., E. Demou, R. Edge, M. Gittins, S. V. Katikireddi, N. Pearce, M. van Tongeren, J. Wilkinson, and S. Rhodes. 2023. Occupational differences in the prevalence and severity of long-COVID: Analysis of the coronavirus (COVID-19) infection survey. *Occupational and Environmental Medicine* 80(10):545–552.

Kucirka, L. M., S. A. Lauer, O. Laeyendecker, D. Boon, and J. Lessler. 2020. Variations in false-negative rate of reverse transcriptase polymerase chain reaction based SARS-CoV-2 tests by time since exposure. *Annals of Internal Medicine* 173(4):262–267.

Lai, Y. J., S. H. Liu, S. Manachevakul, T. A. Lee, C. T. Kuo, and D. Bello. 2023. Biomarkers in long COVID-19: A systematic review. *Frontiers in Medicine* 10:1085988.

Larsen, N. W., L. E. Stiles, R. Shaik, L. Schneider, S. Muppidi, C. T. Tsui, L. N. Geng, H. Bonilla, and M. G. Miglis. 2022. Characterization of autonomic symptom burden in Long COVID: A global survey of 2,314 adults. *Frontiers in Neurology* 13:1012668.

Lim, E. J., and C. G. Son. 2020. Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Journal of Translational Medicine* 18(1):289.

Lim, S. H., H. J. Ju, J. H. Han, J. H. Lee, W.-S. Lee, J. M. Bae, and S. Lee. 2023. Autoimmune and autoinflammatory connective tissue disorders Following COVID-19. *JAMA Netw Open* 6(10):e2336120. https://doi.org/10.1001/jamanetworkopen.2023.36120.

Linh, T. T. D., D. K. N. Ho, N. N. Nguyen, C. J. Hu, C. H. Yang, and D. Wu. 2023. Global prevalence of post-COVID-19 sleep disturbances in adults at different follow-up time points: A systematic review and meta-analysis. *Sleep Medicine Reviews* 71:101833.

Lippi, G., B. M. Henry, J. Favresse, and M. Plebani. 2023. Addressing standardized definitions of post-COVID and long-COVID. *Clinical Chemistry and Laboratory Medicine (CCLM)* 61(8):1361–1362.

Louie, P., and C. Wu. 2023. Race, socioeconomic status, and long COVID. *Social Currents* https://doi.org/10.1177/23294965231215081.

Ma, Y., J. Deng, Q. Liu, M. Du, M. Liu, and J. Liu. 2023. Long-term consequences of asymptomatic SARS-CoV-2 infection: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health* 20(2):1613.

Malkova, A., I. Kudryavtsev, A. Starshinova, D. Kudlay, Y. Zinchenko, A. Glushkova, P. Yablonskiy, and Y. Shoenfeld. 2021. Post COVID-19 syndrome in patients with asymptomatic/mild form. *Pathogens* 10(11):1408.

Malone, L. A., A. Morrow, Y. Chen, D. Curtis, S. D. de Ferranti, M. Desai, T. K. Fleming, T. M. Giglia, T. A. Hall, E. Henning, S. Jadhav, A. M. Johnston, D. R. C. Kathirithamby, C. Kokorelis, C. Lachenauer, L. Li, H. C. Lin, T. Locke, C. MacArthur, M. Mann, S. A. McGrath-Morrow, R. Ng, L. Ohlms, S. Risen, S. C. Sadreameli, S. Sampsel, S. K. S. Tejtel, J. K. Silver, T. Simoneau, R. Srouji, S. Swami, S. Torbey, M. V. Gutierrez, C. N. Williams, L. A. Zimmerman, and L. E. Vaz. 2022. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of postacute sequelae of SARS-CoV-2 infection (PASC) in children and adolescents. *PM&R* 14(10):1241–1269.

Mancini, D. M., D. L. Brunjes, A. Lala, M. G. Trivieri, J. P. Contreras, and B. H. Natelson. 2021. Use of cardiopulmonary stress testing for patients with unexplained dyspnea post-coronavirus disease. *JACC Heart Fail* Dec;9(12):927-937. https://doi.org/10.1016/j.jchf.2021.10.002.

Marshall, J. C., S. Murthy, J. Diaz, N. K. Adhikari, D. C. Angus, Y. M. Arabi, K. Baillie, M. Bauer, S. Berry, B. Blackwood, M. Bonten, F. Bozza, F. Brunkhorst, A. Cheng, M. Clarke, V. Q. Dat, M. de Jong, J. Denholm, L. Derde, J. Dunning, X. Feng, T. Fletcher, N. Foster, R. Fowler, N. Gobat, C. Gomersall, A. Gordon, T. Glueck, M. Harhay, C. Hodgson, P. Horby, Y. Kim, R. Kojan, B. Kumar, J. Laffey, D. Malvey, I. Martin-Loeches, C. McArthur, D. McAuley, S. McBride, S. McGuinness, L. Merson, S. Morpeth, D. Needham, M. Netea, M.-D. Oh, S. Phyu, S. Piva, R. Qiu, H. Salisu-Kabara, L. Shi, N. Shimizu, J. Sinclair, S. Tong, A. Turgeon, T. Uyeki, F. van de Veerdonk, S. Webb, P. Williamson, T. Wolf, and J. Zhang. 2020. A minimal common outcome measure set for COVID-19 clinical research. *The Lancet Infectious Diseases* 20(8):e192–e197.

McGowan, K. 2023. Family caregiver of people with Long COVID bear an extra burden. *National Public Radio*, February 6. https://www.npr.org/sections/health-shots/2023/02/06/1153800857/family-caregivers-of-people-with-long-covid-bear-an-extra-burden (accessed April 19, 2024).

Meenakshisundaram, C., A. Moustafa, M. Ranabothu, A. Maraey, and B. Grubb. 2024. Impact of COVID-19 infection on baseline autonomic symptoms in patients with preexisting postural tachycardia syndrome and orthostatic intolerance: A retrospective study. *American Journal of the Medical Sciences* 367(5):P323-P327. https://doi.org/10.1016/j.amjms.2023.12.011.

Moberg, J., A. D. Oxman, S. Rosenbaum, H. J. Schünemann, G. Guyatt, S. Flottorp, C. Glenton, S. Lewin, A. Morelli, G. Rada, P. Alonso-Coello, J. Moberg, A. Oxman, P. A. Coello, H. Schünemann, G. Guyatt, S. Rosenbaum, A. Morelli, E. Akl, C. Glenton, M. Gulmezoglu, S. Flottorp, S. Lewin, R. A. Mustafa, G. Rada, J. Singh, E. von Elm, J. Vogel, J. Watine, and P. Alonso-Coello for the GRADE Working Group. 2018. The GRADE evidence to decision (EtD) framework for health system and public health decisions. *Health Research Policy and Systems* 16(1):45.

Mohammad, K. O., A. Lin, and J. B. C. Rodriguez. 2022. Cardiac manifestations of post-acute COVID-19 infection. *Current Cardiology Reports* 24(12):1775–1783.

Mohandas, S., P. Jagannathan, T. J. Henrich, Z. A. Sherif, C. Bime, E. Quinlan, M. A. Portman, M. Gennaro, J. Rehman, and R. M. P. T. Force. 2023. Immune mechanisms underlying COVID-19 pathology and post-acute sequelae of SARS-CoV-2 infection (PASC). *Elife* 12:e86014.

Monika, M., T. D. Andrew, P. H. Jacqueline, H. Chuan, H. Yuk-Lam, T. Vidisha, W. C. Alicia, P. Vidul Ayakulangara, W. Xuan, G. Z. Harrison, Y. Doris, S. Malarkodi Jebathilagam, M. Michele, V. Shyam, R. B.-J. Brendin, B. R. Rachel, M. Sumitra, J. G. Michael, P. L. Katherine, X. Zongqi, A. B. Gabriel, C. Tianxi, and C. Kelly. 2023. Characterization of long COVID definitions and clinical coding practices. *medRxiv* 2023.2010.2004.23296301.

Morrow, A. K., L. A. Malone, C. Kokorelis, L. S. Petracek, E. F. Eastin, K. L. Lobner, L. Neuendorff, and P. C. Rowe. 2022. Long-term COVID 19 sequelae in adolescents: The overlap with orthostatic intolerance and ME/CFS. *Current Pediatrics Reports* 10(2):31–44.

Munblit, D., M. E. O'Hara, A. Akrami, E. Perego, P. Olliaro, and D. M. Needham. 2022. Long COVID: Aiming for a consensus. *Lancet Respiratory Medicine* 10(7):632–634.

Nanwani-Nanwani, K., L. López-Pérez, C. Giménez-Esparza, I. Ruiz-Barranco, E. Carrillo, M. S. Arellano, D. Díaz-Díaz, B. Hurtado, A. García-Muñoz, M. Relucio, M. Quintana-Díaz, M. R. Úrbez, A. Saravia, M. V. Bonan, F. García-Río, M. L. Testillano, J. Villar, A. García de Lorenzo, and J. M. Añón. 2022. Prevalence of post-intensive care syndrome in mechanically ventilated patients with COVID-19. *Science Reports* 12(1):7977.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2020. *Framework for equitable allocation of COVID-19 vaccine*. Washington, DC: The National Academies Press.

NASEM. 2024. *Long-term health effects stemming from COVID-19 and implications for social security administration*. https://www.nationalacademies.org/our-work/long-term-health-effects-stemming-from-covid-19-and-implications-for-the-social-security-administration (accessed April 24, 2024).

NIH (National Institutes of Health). 2024. *What is Long COVID? Building our understanding about recovery*. https://recovercovid.org/long-covid (accessed April 19, 2024).

Neville, T. H., R. D. Hays, C. H. Tseng, C. A. Gonzalez, L. Chen, A. Hong, M. Yamamoto, L. Santoso, A. Kung, K. Schwab, S. Y. Chang, N. Qadir, T. Wang, and N. S. Wenger. 2022. Survival after severe COVID-19: Long-term outcomes of patients admitted to an intensive care unit. *Journal of Intensive Care Medicine* 37(8):1019–1028.

NICE (Institute for Health and Care Excellence). 2022. *COVID-19 rapid guideline: Managing the longterm effects of COVID-19*. https://www.nice.org.uk/guidance/ng188/chapter/5-Management (accessed March 30, 2024).

Nuzzo, D., S. Vasto, L. Scalisi, S. Cottone, G. Cambula, M. Rizzo, D. Giacomazza, and P. Picone. 2021. Post-acute COVID-19 neurological syndrome: A new medical challenge. *Journal of Clinical Medicine* 10(9).

Olsen, J. 2021. Caregivers are missing for the Long COVID conversation. *STAT*, February 18. https://www.statnews.com/2021/02/18/caregivers-missing-long-covid-conversation/ (accessed April 19, 2024).

O'Mahoney, L. L., A. Routen, C. Gillies, W. Ekezie, A. Welford, A. Zhang, U. Karamchandani, N. Simms-Williams, S. Cassambai, A. Ardavani, T. J. Wilkinson, G. Hawthorne, F. Curtis, A. P. Kingsnorth, A. Almaqhawi, T. Ward, D. Ayoubkhani, A. Banerjee, M. Calvert, R. Shafran, T. Stephenson, J. Sterne, H. Ward, R. A. Evans, F. Zaccardi, S. Wright, and K. Khunti. 2023. The prevalence and long-term health effects of Long COVID among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine* 55:101762.

Ong, I. Z., D. L. Kolson, and M. K. Schindler. 2023. Mechanisms, effects, and management of neurological complications of post-acute sequelae of COVID-19 (NC-PASC). *Biomedicines* 11(2):377.

Orban, Z. S., L. Visvabharathy, G. S. Perez Giraldo, M. Jimenez, and I. J. Koralnik. 2023. SARS-CoV-2-specific immune responses in patients with postviral syndrome after suspected COVID-19. *Neurology, Neuroimmunology, & Neuroinflammation* 10(6):e200159.

Pagen, D. M. E., C. J. A. van Bilsen, S. Brinkhues, M. Van Herck, K. Konings, C. D. J. den Heijer, H. L. G. ter Waarbeek, M. A. Spruit, C. J. P. A. Hoebe, and N. H. T. M. Dukers-Muijrers. 2023. Prevalence of long-term symptoms varies when using different post-COVID-19 definitions in positively and negatively tested adults: The PRIME post-COVID study. *Open Forum Infectious Diseases* 10(10):ofad471.

Pan, D., and M. Pareek. 2023. Toward a universal definition of post–COVID-19 condition—How do we proceed? *JAMA Network Open* 6(4):e235779.

Park, J. W., X. Wang, and R.-H. Xu. 2022. Revealing the mystery of persistent smell loss in long COVID patients. *International Journal of Biological Sciences* 18(12):4795–4808.

Pavli, A., M. Theodoridou, and H. C. Maltezou. 2021. Post-COVID syndrome: Incidence, clinical spectrum, and challenges for primary healthcare professionals. *Archives of Medical Research*: 52(6):575-581.

Peluso, M. J., T. M. Deveau, Munter, S. E., D. Ryder, A. Buck, G. Beck-Engeser, F. Chan, S. Lu, S. A. Goldberg, R. Hoh, V. Tai, L. Torres, N. S. Iyer, M. Deswal, L. H. Ngo, M. Buitrago, A. Rodriguez, J. Y. Chen, B. C. Yee, A. Chenna, J. W. Winslow, C. J. Petropoulos, A. N. Deitchman, J. Hellmuth, M. A. Spinelli, M. S. Durstenfeld, P. Y. Hsue, J. D. Kelly, J. N. Martin, S. G. Deeks, P. W. Hunt, and T. J. Henrich. 2022. Impact of pre-existing chronic viral infection and reactivation on the development of Long COVID. *medRxiv* 06.21.22276660.

Peluso, M. J., M. Abdel-Mohsen, T. J. Henrich, and N. R. Roan. 2024a. Systems analysis of innate and adaptive immunity in long COVID. *Seminars in Immunology* 72:101873.

Peluso, M. J., Z. N. Swank, S. A. Goldberg, S. Lu, T. Dalhuisen, E. Borberg, Y. Senussi, M. A. Luna, C. Chang Song, A. Clark, A. Zamora, M. Lew, B. Viswanathan, B. Huang, K. Anglin, R. Hoh, P. Y. Hsue, M. S. Durstenfeld, M. A. Spinelli, D. V. Glidden, T. J. Henrich, J. D. Kelly, S. G. Deeks, D. R. Walt, and J. N. Martin. 2024b. Plasma-based antigen persistence in the post-acute phase of COVID-19. *The Lancet Infectious Diseases* S1473-3099(24)00211-1.

Pfaff, E. R., C. Madlock-Brown, J. M. Baratta, A. Bhatia, H. Davis, A. Girvin, E. Hill, E. Kelly, K. Kostka, J. Loomba, J. A. McMurry, R. Wong, T. D. Bennett, R. Moffitt, C. G. Chute, M. Haendel, N. C. Consortium, and R. Consortium. 2023. Coding long COVID: Characterizing a new disease through an ICD-10 lens. *BMC Medicine* 21(1):58.

Piquet, V., C. Luczak, F. Seiler, J. Monaury, A. Martini, A. B. Ward, J.-M. Gracies, and D. Motavasseli, on behalf of the COVID Rehabilitation Study Group. 2021. Do patients with COVID-19 benefit from rehabilitation? Functional outcomes of the first 100 patients in a COVID-19 rehabilitation unit. *Archives of Physical Medicine and Rehabilitation* 102:1067–1074.

Premraj, L., N. V. Kannapadi, J. Briggs, S. M. Seal, D. Battaglini, J. Fanning, J. Suen, C. Robba, J. Fraser, and S.-M. Cho. 2022. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis. *Journal of the Neurological Sciences* 434:120162.

Pretorius, E., C. Venter, G. J. Laubscher, M. J. Kotze, S. O. Oladejo, L. R. Watson, K. Rajaratnam, B. W. Watson, and D. B. Kell. 2022. Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with long COVID/post-acute sequelae of COVID-19 (PASC). *Cardiovascular Diabetology* 21(1):148.

Pollack, B., E. von Saltza, L. McCorkell, L. Santos, A. Hultman, A. K. Cohen, and L. Soares. 2023. Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. *Front Rehabil Sci* Apr 28(4):1122673. https://doi.org/10.3389/fresc.2023.1122673.

Proal, A. D., M. B. VanElzakker, S. Aleman, K. Bach, B. P. Boribong, M. Buggert, S. Cherry, D. S. Chertow, H. E. Davies, and C. L. Dupont. 2023. SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC). *Nature Immunology* 24:1616–1627.

Qeadan, F., B. Tingey, J. Egbert, M. G. Pezzolesi, M. R. Burge, K. A. Peterson, and T. Honda. 2022. The associations between COVID-19 diagnosis, type 1 diabetes, and the risk of diabetic ketoacidosis: A nationwide cohort from the U.S. using the Cerner Real-World Data. *PLOS One* 17(4):e0266809.

Rando, H. M., T. D. Bennett, J. B. Byrd, C. Bramante, T. J. Callahan, C. G. Chute, H. E. Davis, R. Deer, J. Gagnier, F. M. Koraishy, F. Liu, J. A. McMurry, R. A. Moffitt, E. R. Pfaff, J. T. Reese, R. Relevo, P. N. Robinson, J. H. Saltz, A. Solomonides, A. Sule, U. Topaloglu, and M. A. Haendel. 2021. Challenges in defining long COVID: Striking differences across literature, electronic health records, and patient-reported information. *medRxiv* Mar 26:2021.03.20.21253896.

Rao, S., R. S. Gross, S. Mohandas, C. R. Stein, A. Case, B. Dreyer, N. M. Pajor, H. T. Bunnell, D. Warburton, E. Berg, J. B. Overdevest, M. Gorelik, J. Milner, S. Saxena, R. Jhaveri, J. C. Wood, K. E. Rhee, R. Letts, C. Maughan, N. Guthe, L. Castro-Baucom, and M. S. Stockwell. 2024. Postacute sequelae of SARS-CoV-2 in children. *Pediatrics* 153(3):e2023062570.

Rapaport, L. 2024. Long COVID has caused thousands of U.S. deaths: New CDC data. *Medscape*, January 3. https://www.medscape.com/viewarticle/long-covid-has-caused-thousands-us-deaths-new-cdc-data-2024a100006l?form=fpf (accessed February 29, 2024).

Raveendran, A. V. 2021. Long COVID-19: Challenges in the diagnosis and proposed diagnostic criteria. *Diabetes & Metabolic Syndrome* 15(1):145–146.

Reis Carneiro, D., I. Rocha, M. Habek, R. Helbok, J. Sellner, W. Struhal, G. Wenning, and A. Fanciulli. 2023. Clinical presentation and management strategies of cardiovascular autonomic dysfunction following a COVID-19 infection—A systematic review. *European Journal of Neurology* 30(5):1528–1539.

Roedl, K., D. Jarczak, O. Boenisch, G. de Heer, C. Burdelski, D. Frings, B. Sensen, A. Nierhaus, S. Kluge, and D. Wichmann. 2022. Chronic critical illness in patients with COVID-19: Characteristics and outcome of prolonged intensive care therapy. *Journal of Clinical Medicine* 11(4):1049.

Savin, E., G. Rosenn, A. M. Tsur, O. Hen, S. Ehrenberg, O. Gendelman, D. Buskila, G. Halpert, D. Amital, and H. Amital. 2023. The possible onset of fibromyalgia following acute COVID-19 infection. *PLoS One* 18(2):e0281593. https://doi.org/10.1371/journal.pone.0281593.

Saydah, S. H., J. T. Brooks, and B. R. Jackson. 2022. Surveillance for post-COVID conditions is necessary: Addressing the challenges with multiple approaches. *Journal of General Internal Medicine* 37(7):1786–1788.

Schultheiss, C., E. Willscher, L. Paschold, C. Gottschick, B. Klee, L. Bosurgi, J. Dutzmann, D. Sedding, T. Frese, M. Girndt, J. I. Holl, M. Gekle, R. Mikolajczyk, and M. Binder, 2023. Liquid biomarkers of macrophage dysregulation and circulating spike protein illustrate the biological heterogeneity in patients with post-acute sequelae of COVID-19. *J Med Virol* 95(1):e28364.

Seeley, M. C., C. Gallagher, E. Ong, A. Langdon, J. Chieng, D. Bailey, A. Page, H. S. Lim, and D. H. Lau. 2023. High incidence of autonomic dysfunction and postural orthostatic tachycardia syndrome in patients with Long COVID: Implications for management and health care planning. *The American Journal of Medicine* S0002-9343(23)00402-3.

Sevin, C. M., and E. W. Ely. 2022. Outcomes among patients with 1-year survival after intensive care unit treatment for COVID-19. *JAMA* 327(21):2149–2150.

SeyedAlinaghi, S., A. Bagheri, A. Razi, P. Mojdeganlou, H. Mojdeganlou, A. M. Afsahi, A. Afzalian, P. Paranjkhoo, R. Shahidi, P. Mirzapour, Z. Pashaei, M. A. Habibi, P. Shahbazi, S. Nooralioghli Parikhani, N. S. Farizani Gohari, Y. Popoola, E. Mehraeen, and D. Hackett. 2023. Late complications of COVID-19: An umbrella review on current systematic reviews. *Archives of Academic Emergency Medicine* 11(1):e28.

Shah, B., M. N. Ahmad, M. Khalid, A. Minhas, R. Ali, Z. Sarfraz, and A. Sarfraz. 2023. Long COVID and wavering incidence of pulmonary embolism: A systematic review. *Journal of Community Hospital Internal Medicine Perspectives* 13(5):23–31.

Sherif, Z. A., C. R. Gomez, T. J. Connors, T. J. Henrich, W. B. Reeves, and RECOVER Mechanistic Pathway Task Force. 2023. Pathogenic mechanisms of post-acute sequelae of SARS-CoV-2 infection (PASC). *Elife* 12:e86002.

Silva, J., T. Takahashi, J. Wood, P. Lu, S. Tabachnikova, J. Gehlhausen, K. Greene, B. Bhattacharjee, V. Silva Monteiro, C. Lucas, R. Dhodapkar, L. Tabacof, M. Pena-Hernandez, K. Kamath, T. Mao, D. Mccarthy, R. Medzhitov, D. van Dijk, H. Krumholz, L. Guan, D. Putrino, and A. Iwasaki. 2024. Sex differences in symptomatology and immune profiles of long COVID. *medRxiv*. https://doi.org/10.1101/2024.02.29.24303568.

SSA (Social Security Administration). 2023. Long COVID: A guide for health professionals on providing medical evidence for social security disability claims. https://www.ssa.gov/disability/professionals/documents/EN-64-128.pdf. (accessed May 3, 2024).

Soriano, J. B., S. Murthy, J. C. Marshall, P. Relan, J. V. Diaz, and WHO Clinical Case Working Group on Post-COVID-19 Condition. 2022. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infectious Diseases* 22(4):e102–e107.

Stephenson, T., B. Allin, M. D. Nugawela, N. Rojas, E. Dalrymple, S. Pinto Pereira, M. Soni, M. Knight, E. Y. Cheung, I. Heyman, and R. Shafran. 2022. Long COVID (post-COVID-19 condition) in children: A modified Delphi process. *Archives of Disease in Childhood* 107(7):674–680.

Strang, S., M. Osmanovic, C. Hallberg, and P. Strang. 2018. Family caregivers' heavy and overloaded burden in advanced chronic obstructive pulmonary disease. *Journal of Palliative Medicine* 21(12):1768–1772.

Subramanian, A., K. Nirantharakumar, S. Hughes, P. Myles, T. Williams, K. M. Gokhale, T. Taverner, J. S. Chandan, K. Brown, N. Simms-Williams, A. D. Shah, M. Singh, F. Kidy, K. Okoth, R. Hotham, N. Bashir, N. Cockburn, S. I. Lee, G. M. Turner, G. V. Gkoutos, O. L. Aiyegbusi, C. McMullan, A. K. Denniston, E. Sapey, J. M. Lord, D. C. Wraith, E. Leggett, C. Iles, T. Marshall, M. J. Price, S. Marwaha, E. H. Davies, L. J. Jackson, K. L. Matthews, J. Camaradou, M. Calvert, and S. Haroon. 2022. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nature Medicine* 28(8):1706–1714.

Sylvester, S. V., R. Rusu, B. Chan, M. Bellows, C. O'Keefe, and S. Nicholson. 2022. Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: A review. *Current Medical Research and Opinion* 38(8):1391–1399.

Szukiewicz, D., P. Wojdasiewicz, M. Watroba, and G. Szewczyk. 2022. Mast cell activation syndrome in COVID-19 and female reproductive function: Theoretical background vs. accumulating clinical evidence. *Journal of Immunological Research* 9534163.

Thaweethai, T., S. E. Jolley, E. W. Karlson, E. B. Levitan, B. Levy, G. A. McComsey, L. McCorkell, G. N. Nadkarni, S. Parthasarathy, U. Singh, T. A. Walker, C. A. Selvaggi, D. J. Shinnick, C. C. M. Schulte, R. Atchley-Challenner, G. A. Alba, R. Alicic, N. Altman, K. Anglin, U. Argueta, H. Ashktorab, G. Baslet, I. V. Bassett, L. Bateman, B. Bedi, S. Bhattacharyya, M. A. Bind, A. L. Blomkalns, H. Bonilla, P. A. Bush, M. Castro, J. Chan, A. W. Charney, P. Chen, L. B. Chibnik, H. Y. Chu, R. G. Clifton, M. M. Costantine, S. K. Cribbs, S. I. Davila Nieves, S. G. Deeks, A. Duven, I. F. Emery, N. Erdmann, K. M. Erlandson, K. C. Ernst, R. Farah-Abraham, C. E. Farner, E. M. Feuerriegel, J. Fleurimont, V. Fonseca, N. Franko, V. Gainer, J. C. Gander, E. M. Gardner, L. N. Geng, K. S. Gibson, M. Go, J. D. Goldman, H. Grebe, F. L. Greenway, M. Habli, J. Hafner, J. E. Han, K. A. Hanson, J. Heath, C. Hernandez, R. Hess, S. L. Hodder, M. K. Hoffman, S. E. Hoover, B. Huang, B. L. Hughes, P. Jagannathan, J. John, M. R. Jordan, S. D. Katz, E. S. Kaufman, J. D. Kelly, S. W. Kelly, M. M. Kemp, J. P. Kirwan, J. D. Klein, K. S. Knox, J. A. Krishnan, A. Kumar, A. O. Laiyemo, A. A. Lambert, M. Lanca, J. K. Lee-Iannotti, B. P. Logarbo, M. T. Longo,

C. A. Luciano, K. Lutrick, J. H. Maley, J. G. Marathe, V. Marconi, G. D. Marshall, C. F. Martin, Y. Matusov, A. Mehari, H. Mendez-Figueroa, R. Mermelstein, T. D. Metz, R. Morse, J. Mosier, C. Mouchati, J. Mullington, S. N. Murphy, R. B. Neuman, J. Z. Nikolich, I. Ofotokun, E. Ojemakinde, A. Palatnik, K. Palomares, T. Parimon, S. Parry, J. E. Patterson, T. F. Patterson, R. E. Patzer, M. J. Peluso, P. Pemu, C. M. Pettker, B. A. Plunkett, K. Pogreba-Brown, A. Poppas, J. G. Quigley, U. Reddy, R. Reece, H. Reeder, W. B. Reeves, E. M. Reiman, F. Rischard, J. Rosand, D. J. Rouse, A. Ruff, G. Saade, G. J. Sandoval, S. M. Schlater, F. Shepherd, Z. A. Sherif, H. Simhan, N. G. Singer, D. W. Skupski, A. Sowles, J. A. Sparks, F. I. Sukhera, B. S. Taylor, L. Teunis, R. J. Thomas, J. M. Thorp, P. Thuluvath, A. Ticotsky, A. T. Tita, K. R. Tuttle, A. E. Urdaneta, D. Valdivieso, T. M. VanWagoner, A. Vasey, M. Verduzco-Gutierrez, Z. S. Wallace, H. D. Ward, D. E. Warren, S. J. Weiner, S. Welch, S. W. Whiteheart, Z. Wiley, J. P. Wisnivesky, L. M. Yee, S. Zisis, L. I. Horwitz, A. S. Foulkes, and R. Consortium. 2023. Development of a definition of postacute sequelae of SARS-CoV-2 infection. *JAMA* 329(22):1934–1946.

Tran, V. T., R. Porcher, I. Pane, and P. Ravaud. 2022. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. *Nature Communications* 13(1):1812.

Tsampasian, V., H. Elghazaly, R. Chattopadhyay, M. Debski, T. K. P. Naing, P. Garg, A. Clark, E. Ntatsaki, and V. S. Vassiliou. 2023. Risk factors associated with post-COVID-19 condition: Asystematic review and meta-analysis. *JAMA Internal Medicine* 183(6):ioi230017.

Turner, S., M. A. Khan, D. Putrino, A. Woodcock, D. B. Kell, and E. Pretorius. 2023. Long COVID: Pathophysiological factors and abnormalities of coagulation. *Trends in Endocrinology & Metabolism* 34(6):321–344.

Tyson, A. and G. Pasquini. 2024. How Americans View the Coronavirus, COVID-19 Vaccines Amid Declining Levels of Concern. https://www.pewresearch.org/science/2024/03/07/how-americans-view-the-coronavirus-covid-19-vaccines-amid-declining-levels-of-concern/ (accessed March 30, 2024).

Vashisht, R., A. Patel, and B. O. Crews. 2021. Age- and sex-associated variations in the sensitivity of serological tests among individuals infected with SARS-CoV-2. *JAMA Network Open* 4(2):e210337.

Vivaldi, G., P. E. Pfeffer, M. Talaei, T. J. Basera, S. O. Shaheen, and A. R. Martineau. 2023. Long-term symptom profiles after COVID-19 vs other acute respiratory infections: An analysis of data from the COVIDENCE UK study. *EClinicalMedicine* Oct 6:65:102251.

Vu, Q. M., A. L. Fitzpatrick, J. R. Cope, J. Bertolli, N. Sotoodehnia, T. E. West, and E. R. Unger. 2024. Estimates of incidence and predictors of fatiguing illness after SARS-CoV-2 infection. *Emerging Infectious Diseases 30*(3):539-547.

Walker, A. J., B. MacKenna, P. Inglesby, L. Tomlinson, C. T. Rentsch, H. J. Curtis, C. E. Morton, J. Morley, A. Mehrkar, S. Bacon, G. Hickman, C. Bates, R. Croker, D. Evans, T. Ward, J. Cockburn, S. Davy, K. Bhaskaran, A. Schultze, E. J. Williamson, W. J. Hulme, H. I. McDonald, R. Mathur, R. M. Eggo, K. Wing, A. Y. S. Wong, H. Forbes, J. Tazare, J. Parry, F. Hester, S. Harper, S. O'Hanlon, A. Eavis, R. Jarvis, D. Avramov, P. Griffiths, A. Fowles, N. Parkes. I. J. Douglas, S. J. W. Evans, L. Smeeth, and B. Goldacre. 2021. Clinical coding of Long COVID in English primary care: A federated analysis of 58 million patient records *in situ* using OpenSAFELY. *British Journal of General Practice* 71(712):e806-e814.

Walker, S., H. Goodfellow, P. Pookarnjanamorakot, E. Murray, J. Bindman, A. Blandford, K. Bradbury, B. Cooper, F. L. Hamilton, J. R. Hurst, H. Hylton, S. Linke, P. Pfeffer, W. Ricketts, C. Robson, F. A. Stevenson, D. Sunkersing, J. Wang, G. Gomes, W. Henley, and the Living With COVID Recovery Collaboration. 2023. Impact of fatigue as the primary determinant of functional limitations among patients with post-COVID-19 syndrome: A cross-sectional observational study. *British Medical Journal Open* 13(6):e069217.

Wander, P. L., A. Baraff, A. Fox, K. Cho, M. Maripuri, J. P. Honerlaw, Y. Ho, A. T. Dey, A. M. O'Hare, A. S. B. Bohnert, E. J. Boyko, M. L. Maciejewski, E. Viglianti, T. J. Iwashyna, D. M. Hynes, T. F. Osborne, and G. N. Ioannou. 2023. Rates of *ICD-10* Code U09.9 documentation and clinical characteristics of VA patients with post–COVID-19 Condition. *Journal of American Medical Association* 6(12):e2346783.

Weidman, K., E. LaFond, K. L. Hoffman, P. Goyal, C. N. Parkhurst, H. Derry-Vick, E. Schenck, and L. Lief. 2022. Post-intensive care unit syndrome in a cohort of COVID-19 survivors in New York City. *Annals of the American Thoracic Society* 19(7):1158–1168.

WHO (World Health Organization). 2015. *World Health Organization best practices for the naming of new human infectious diseases*. https://www.who.int/publications/i/item/WHO-HSE-FOS-15.1

WHO. 2023. *A clinical case definition for post-COVID-19 condition in children and adolescents by expert consensus*. WHO/2019-nCoV/Post_COVID-19_condition/CA/Clinical_case_definition/2023.1

Wingrove, J., J. Makaronidis, F. Prados, B. Kanber, M. C. Yiannakas, C. Magee, G. Castellazzi, L. Grandjean, X. Golay, C. Tur, O. Ciccarelli, E. D'Angelo, C. A. M. Gandini Wheeler-Kingshott, and R. L. Batterham. 2023. Aberrant olfactory network functional connectivity in people with olfactory dysfunction following COVID-19 infection: An exploratory, observational study. *EClinicalMedicine* 58:101883.

Woodrow, M., C. Carey, N. Ziauddeen, R. Thomas, A. Akrami, V. Lutje, D. C. Greenwood, and N. A. Alwan. 2023. Systematic review of the prevalence of Long COVID. *Open Forum Infectious Diseases* 10(7):ofad233.

Wulf Hanson, S., C. Abbafati, J. G. Aerts, Z. Al-Aly, C. Ashbaugh, T. Ballouz, O. Blyuss, P. Bobkova, G. Bonsel, S. Borzakova, D. Buonsenso, D. Butnaru, A. Carter, H. Chu, C. De Rose, M. M. Diab, E. Ekbom, M. El Tantawi, V. Fomin, R. Frithiof, A. Gamirova, P. V. Glybochko, J. A. Haagsma, S. Haghjooy Javanmard, E. B. Hamilton, G. Harris, M. H. Heijenbrok-Kal, R. Helbok, M. E. Hellemons, D. Hillus, S. M. Huijts, M. Hultström, W. Jassat, F. Kurth, I. M. Larsson, M. Lipcsey, C. Liu, C. D. Loflin, A. Malinovschi, W. Mao, L. Mazankova, D. McCulloch, D. Menges, N. Mohammadifard, D. Munblit, N. A. Nekliudov, O. Ogbuoji, I. M. Osmanov, J. L. Peñalvo, M. S. Petersen, M. A. Puhan, M. Rahman, V. Rass, N. Reinig, G. M. Ribbers, A. Ricchiuto, S. Rubertsson, E. Samitova, N. Sarrafzadegan, A. Shikhaleva, K. E. Simpson, D. Sinatti, J. B. Soriano, E. Spiridonova, F. Steinbeis, A. A. Svistunov, P. Valentini, B. J. van de Water, R. van den Berg-Emons, E. Wallin, M. Witzenrath, Y. Wu, H. Xu, T. Zoller, C. Adolph, J. Albright, J. O. Amlag, A. Y. Aravkin, B. L. Bang-Jensen, C. Bisignano, R. Castellano, E. Castro, S. Chakrabarti, J. K. Collins, X. Dai, F. Daoud, C. Dapper, A. Deen, B. B. Duncan, M. Erickson, S. B. Ewald, A. J. Ferrari, A. D. Flaxman, N. Fullman, A. Gamkrelidze, J. R. Giles, G. Guo, S. I. Hay, J. He, M. Helak, E. N. Hulland, M. Kereselidze, K. J. Krohn, A. Lazzar-Atwood, A. Lindstrom, R. Lozano, D. C. Malta, J. Månsson, A. M. Mantilla Herrera, A. H. Mokdad, L. Monasta, S. Nomura, M. Pasovic, D. M. Pigott, R. C. Reiner, Jr., G. Reinke, A. L. P. Ribeiro, D. F. Santomauro, A. Sholokhov, E. E. Spurlock, R. Walcott, A. Walker, C. S. Wiysonge, P. Zheng, J. P. Bettger, C. J. L. Murray, and T. Vos. 2022. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. *JAMA* 328(1):1604–1615.

Xie, Y., B. Bowe, and Z. Al-Aly. 2021. Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status. *Nature Communications* 12(1):6571.

Xie, Y., E. Xu, B. Bowe, and Z. Al-Aly. 2022. Long-term cardiovascular outcomes of COVID-19. *Nature Medicine* 28(3):583–590.

Xu, E., Y. Xie, and Z. Al-Aly. 2022. Long-term neurologic outcomes of COVID-19. *Nature Medicine* 28(11):2406–2415.

Xu, E., Y. Xie, and Z. Al-Aly. 2023. Risks and burdens of incident dyslipidaemia in long COVID: a cohort study. *Lancet Diabetes Endocrinol* Feb;11(2):120-128. https://doi.org/10.1016/S2213-8587(22)00355-2.

Yin, K., M. J. Peluso, X. Luo, R. Thomas, M. G. Shin, J. Neidleman, A. Andrew, K. Young, T. Ma, R. Hoh, K. Anglin, B. Huang, U. Argueta, M. Lopez, D. Valdivieso, K. Asare, T. M. Deveau, S. E. Munter, R. Ibrahim, L. Standker, S. Lu, S. A. Goldberg, S. A. Lee, K. L. Lynch, J. D. Kelly, J. N. Martin, J. Munch, S. G. Deeks, T. J. Henrich, and N. R. Roan. 2023. Long COVID Manifests with T cell dysregulation, inflammation, and an uncoordinated adaptive immune response to SARS-CoV-2. *bioRxiv* https://doi.org/10.1101/2023.02.09.527892.

Zhang, Y., H. Hu, V. Fokaidis, C. Lewis V, J. Xu, C. Zang, Z. Xu, F. Wang, M. Koropsak, J. Bian, J. Hall, R. L. Rothman, E. A. Shenkman, W. Q. Wei, M. G. Weiner, T. W. Carton, and R. Kaushal. 2023. Identifying environmental risk factors for post-acute sequelae of SARS-CoV-2 infection: An EHR-based cohort study from the RECOVER Program. *Environmental Advances* 11:100352.

Zhao, S., S. Toniolo, A. Hampshire, and M. Husain. 2023. Effects of COVID-19 on Cognition and Brain Health. *Trends in Cognitive Science* 27(11):1053-1067.

Zheng, Y.-B., N. Zeng, K. Yuan, S.-S. Tian, Y.-B. Yang, N. Gao, X. Chen, A.-Y. Zhang, A. L. Kondratiuk, P.-P. Shi, F. Zhang, J. Sun, J.-L. Yue, X. Lin, L. Shi, A. Lalvani, J. Shi, Y.-P. Bao, and L. Lu. 2023. Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review. *Journal of Infection and Public Health* 16(5):660–672.

Zuin, M., G. Rigatelli, V. Battisti, G. Costola, L. Roncon, and C. Bilato. 2022. Increased risk of acute myocardial infarction after COVID-19 recovery: A systematic review and meta-analysis. *International Journal of Cardiology* 372:138–143.

# Appendix A

# Detailed Description of the Committee's Approach and Study Methods

At the request of the Administration for Strategic Preparedness and Response (ASPR) and the Office of the Assistant Secretary for Health (OASH), the National Academies of Sciences, Engineering, and Medicine (National Academies) was asked to examine the definition for Long COVID. In response to this request, the National Academies convened the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats[1] to scope and better understand the issue. To respond to this new charge on Long COVID, the National Academies convened the Committee on Examining the Working Definition for Long COVID consisting of experts in the fields of health research and policy; research related to Long COVID and chronic multi-symptom illness; clinical practice and guidelines; infectious diseases; public health and epidemiology practice; social and behavioral health and decision science; patients and lived experience; and community engagement and health equity.

[1] The Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats was convened in March 2020 in response to the COVID-19 pandemic to help inform the federal government, and specifically ASPR, on critical science and policy issues related to emerging infectious diseases and other 21st century health threats. It comprises 27 members with expertise in emerging infectious diseases, public health, public health preparedness and response, biological sciences, clinical care and crisis standards of care, risk communications, epidemiology, regulatory issues, veterinary science, One Health, ethics, social science, and community engagement.

## MULTI-PHASE EFFORT

This study was a multi-phase activity that began with the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats convening a series of scoping meetings to initiate information gathering and identify key issues, areas of expertise, and stakeholders to engage in the effort. In the next phase (Phase I), an ad hoc committee was appointed, the Committee on Examining the Working Definition for Long COVID. The committee conducted engagement activities and hosted a symposium. The committee also integrated and synthesized information from the engagement efforts and reviewed relevant literature and information gathered through the workshop. In Phase II, the committee was asked by the sponsor to produce a report to review additional evidence for definitions of Long COVID, consider efforts that have already been completed on this topic area, and put forth new definitions and related technical terms, with descriptions of the circumstances under which these new definitions and terminology should be adopted.

### Scoping Phase

In the initial Scoping Phase of the study, the standing committee deliberated over a period of 2 months. The activities included three information-gathering scoping meetings to discuss the key issues and identify the areas of expertise and stakeholders to engage in this effort.

- The first scoping meeting featured a discussion on the request from OASH and ASPR, followed by a panel of federal and non-federal experts, including those with international perspectives and front-line community perspectives, examining lessons learned from other processes and experiences for developing disease definitions and diagnostic criteria. The meeting also featured a session where the standing committee took part in an initial stakeholder mapping activity.
- Building on the first scoping meeting, the second meeting featured a panel with experts, including those with lived experience, particularly focusing on lessons learned and best practices from engagement efforts for defining diseases and setting research priorities. The standing committee also had an opportunity to review and provide input on the first draft of the engagement plan focusing on the purpose, objectives, and the list of stakeholders.

- The final scoping meeting provided the standing committee with an opportunity to provide feedback and continue discussions on the revised engagement plan and the list of identified stakeholders.

### Phase I and Phase II

In Phase I and Phase II, the committee used various engagement activities and evidence-building activities to gather, prioritize, synthesize, and evaluate evidence and information to help inform the refinement of Long COVID definitions and related terminology and put forth a report with recommendations. The detailed methodology for the engagement process and evidence review are described below. The committee also hosted an online Public Comment Portal (April 10–June 12, 2023) on the project website for the public to provide comments and submit resources about the current working definition.

## ENGAGEMENT PROCESS

Engagement—of all those potentially affected by the definitions for Long COVID, including those with lived experience—was critical to ensuring that the right issues were addressed and to improve the transparency, accuracy, relevancy, usefulness, and acceptability of the definition. The committee worked with a consultant to engage patients and individuals across multiple sectors to solicit input from a wide variety of interested and affected stakeholders, including the general public, specific underserved communities, health professionals, government agencies, and relevant sectors of the economy.

The multi-perspective engagement process enabled the committee to solicit input from patients, caregivers, researchers, practitioners, health agencies, health policy and advocacy organizations, payors, and health industry businesses. A total of 1,315 participants were involved in engagement activities. Three key principles guided the engagement process:

- Commitment to inclusion to ensure that a wide set of perspectives were heard.
- Development of a fair and equitable process to ensure all participants had the information they needed to fully participate as well as accommodations necessary to enable their participation.
- Transparency in the process and in the documentation of findings from the engagement.

Two key engagement opportunities were hosted by the committee:

- **Questionnaire (April 19–May 12, 2023):** An online questionnaire was sent to interested and affected people and organizations. It was also publicly shared by invited participants. Respondents had the opportunity to provide specific feedback on key issues, concerns, and areas of improvement of the current working definition. The questionnaire was created using Qualtrics, and completed questionnaires were stored in Qualtrics's secure servers online. The questionnaire contained 37 questions, none of which were required to be answered. Twenty-five questions were about Long COVID, and 11 were demographic questions.
- **Virtual Focus Groups (April 26–May 8, 2023):** Seven facilitated virtual focus groups were held with invited people and organizations to deepen the shared understanding of the concerns and areas of improvement of the current working definition. Seven facilitated virtual focus groups were held with invited individuals and organizations to explore concerns and areas for the improvement of the current Long COVID definitions:
    - Researchers (April 26): For those who conduct research and report results to the scientific or medical community.
    - Practitioners (April 28): For those who provide health care and for professional associations who provide clinical guidance.
    - Patients, Caregivers, and Patient Organizations (April 29): For those who are living with Long COVID or supporting someone affected and for groups who advocate on behalf of Long COVID patients.
    - Health Agencies (May 2): For those who lead or deliver programs that provide public health or community services.
    - Health Policy and Health Advocacy Organizations (May 4): For organizations that advance health care and health policy through data analysis, funding research, advocacy, supporting initiatives, or making recommendations.
    - Payors and Health Businesses (May 5): For businesses that provide health insurance as well as businesses that produce drugs, tests, devices, procedures, etc. related to Long COVID.
    - All Categories (May 8): For those unable to attend the session for their sector.

Each online focus group session was 2.5 hours long. Most of each session was spent in small group discussion to ensure that participants were able to share their views and hear from others. Key discussion questions for the focus groups were:

- How might you use a definition of Long COVID?
- What feedback do you have about the USG's working definition, or other definitions, of Long COVID?
- What challenges might there be in using the current USG definition, or other definitions?
- What might address those challenges?
- What should the National Academies' committee keep in mind to make sure the definition does not unintentionally make it harder for people with Long COVID to get health care, workplace support, or other things they need?
- What advice do you have for the National Academies' committee charged with reviewing the USG's definition of Long COVID?

Further details on the methodology and analysis, the description of who participated in the questionnaire and focus groups, and the results and findings can be found in the publicly available report *What We Heard: Engagement Report on the Working Definition for Long COVID*.[2] Findings from the engagement process were integrated throughout the committee's report.

## EVIDENCE REVIEW

Given the rapidly emerging scientific literature on Long COVID and the time constraints on the study, the committee conducted a scoping review that first identified recently published reviews (2020 through November 2023), including systematic, qualitative, and comprehensive scoping reviews. This scoping review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was conducted with the help of a librarian and PICO Portal methodologists. This section describes in detail the scoping review methodology.

Importantly, the scoping review was supplemented with primary research. The primary research was identified through a secondary search, reference mining, forward citation searching, and committee suggestions.

### Scoping Review Search Strategy

Literature was identified through a systematic search as well as "snowballing" and reference mining to identify additional published and pre-print articles. Electronic databases used for the literature search include PubMed, Embase, Medline, Cochrane Library, Google, Scopus, COVID-specific

[2] *What We Heard: Engagement Report on the Working Definition for Long COVID*. Available on the study webpage https://www.nationalacademies.org/our-work/examining-the-working-definition-for-long-covid (accessed March 11, 2024).

databases including Lit COVID and the Centers for Disease Control and Prevention (CDC) COVID-19 Publications Database, and preprint databases. Literature was searched systematically and according to specific search criteria to identify signs, symptoms, and conditions experienced by individuals with Long COVID. The search was guided by the Population, Exposure, Comparator, Outcome (PECO) framework that supports the investigation of exposures with health outcomes. The PECO criteria for this review were:

- **Population:** Adults and children with ongoing symptomatic COVID-19 and Long COVID (i.e., post-acute sequelae of COVID-19, Post-COVID Conditions, Post-COVID-19 Syndrome).
- **Exposure:** Confirmed, probable, or suspected infection with SARS-CoV-2 or COVID-19 assessed by any diagnostic method or self-reported.
- **Comparator:** Any comparison.
- **Outcomes:**
  - Any health outcome (signs, symptoms, and conditions both patient-reported and clinical investigations).
  - Outcomes specific to adult versus pediatric populations.
  - Outcomes specific to other vulnerable populations.
  - Nature of health outcomes.
  - Clinical, laboratory, or other methods to assess health outcomes.
  - Onset of health outcomes following acute COVID-19 illness.
  - Short-term, long-term, and lifelong duration of health outcomes.
  - Impact of health outcomes on daily activities.
  - Common comorbid conditions (e.g., health conditions that commonly occur with Long COVID).
  - Severity of health outcomes.
  - Frequency of health outcomes.
  - Any symptoms, symptom constructs, clusters, or categories (e.g., autonomic manifestations, immune manifestations, fatigue, neurocognitive manifestations, neuroendocrine manifestations, post-exertional malaise, pain, etc.).
  - Disabilities and impairment.
  - Methods of assessment for health outcomes (e.g., clinical, imaging, questionnaire, etc.).

Studies were determined for inclusion in the review or exclusion, based on the criteria in Table A-1.

The initial search was conducted in May 2023, with subsequent, updated searches conducted in July 2023 and November 2023.

**TABLE A-1** Inclusion and Exclusion Criteria

| Category | Inclusion | Exclusion |
|---|---|---|
| Date | • Studies from 2020 to present day | • Studies before 2020 |
| Location | • Sources in English<br>• International literature | • Sources not in English |
| Study Design | • Systematic reviews, comprehensive scoping reviews, qualitative reviews, and meta-analyses of any study designs<br>• Reviews and meta-analyses of literature describing Long COVID signs, symptoms, and conditions in humans<br>• Reviews and meta-analyses of literature describing methods to assess Long COVID signs, symptoms, and conditions in humans | • Article types that are narrative or literature reviews with no methodologies, or article types that describe individual research studies<br>• Reviews focused on acute COVID-19<br>• Reviews and meta-analyses of experimental studies, including studies that compare the effects of a single or multiple treatments on the study populations<br>• Reviews and meta-analyses of animal studies or including both animal and human studies |
| Publication Types | • Reviews and meta-analyses | • Peer-reviewed journal articles that are not reviews/meta-analyses or grey literature<br>• Abstract-only articles<br>• Conference abstracts |

### Scoping Review Screening

Results were collated and imported to the PICO Portal. After removing duplicates from the multiple databases, all titles and abstracts were with a single reviewer (National Academies staff). During title–abstract screening, all records were tagged according to characteristics of the study including methods (e.g., systematic review, narrative review, scoping review, meta-analysis) and health conditions and symptoms (e.g., systemic manifestations, neurologic, genetic and biological markers, etc.). For full-text screening, articles prioritized were tagged as systematic reviews and all health conditions. After screening those records, the remaining records were screened without prioritization. All eligibility criteria were applied equally to potentially eligible records. All full-text records were screened in duplicate with independent methodologists from PICO Portal, and a National Academies staff member resolved all discrepancies.

**Scoping Review Quality Assessment**

Following established protocols, all records included at full-text screening were assessed for their reliability. The reliability was assessed with two independent PICO Portal methodologists, and all discrepancies were resolved with a third, senior methodologist. Data were extracted only from studies that were considered to be "reliable."

"Reliability" is an assessment of how transparent and reliable the methods used in a systematic review are for searching and synthesizing. There are many tools to assess the quality or risk of bias in systematic reviews, including Risk of Bias in Systematic Reviews (ROBIS), Assessment of Multiple Systematic Reviews (AMSTAR), Critical Appraisal Skills Checklist (CASP). These tools are valuable, but they are detailed and difficult to apply on a large scale. To aid their work and partnerships with clinical organizations and guideline development, Cochrane Eyes and Vision developed a method of assessing the presence of key elements to ascertain whether systematic reviews met the minimum criteria for being considered "reliable" enough to inform practice. This assessment takes common elements from the other, longer, tools and distills the minimum criteria to five questions, all of which must be answered yes for a systematic review to be reliable.

1. Does the systematic review provide the eligibility criteria for inclusion in the review?
2. Does the systematic review conduct a comprehensive search of the literature?
3. Does the systematic review assess the risk of bias/quality of the included studies using any relevant tool?
4. If there are quantitative analyses, are the methods (and the meta-analysis) appropriate?
5. Do the review's conclusions align with the results that it actually found?

*Explanation And Rational for Individual Items*

**Item 1 –** This item is a simple "Yes" or "No" based on what has been reported in the paper or in an associated and accessible registry or protocol. If a systematic review does not report the criteria used to determine eligibility, it is not reproducible, and the reasons for including certain articles but not others cannot be determined.

**Item 2 –** This item requires some degree of consideration since a "comprehensive" search can be difficult to assess if one does not have expertise in searching. As a general rule of thumb, a search CAN be comprehensive if it meets the following minimum criteria: (1) searches at least two

**Table A-2** Criteria for Assessing the Reliability of Systematic Reviews

| Criterion | Definition Applied to Systematic Review Reports |
|---|---|
| 1. Defined Eligibility Criteria | Described inclusion or exclusion criteria, or both, for eligible studies. |
| 2. Conducted Comprehensive Literature Search | Review authors (1) described an electronic search of two or more bibliographic databases, (2) used a search strategy comprising a mixture of controlled vocabulary and keywords, and (3) reported using at least one other method of searching, such as searching of conference abstracts, identifying ongoing trials, complemented electronic searching by hand-search methods (e.g., checking reference lists) and contacting included study authors or experts. |
| 3. Assessed Risk of Bias of Included Studies | Used any method (e.g., scales, checklists, or domain-based evaluation) designed to assess methodologic rigor of included studies. |
| 4. Used Appropriate Methods for Meta-Analysis (*if applicable*) | Used quantitative methods that (1) were appropriate for the study design analyzed (e.g., maintained the randomized nature of trials, used adjusted estimates from observational studies) and (2) correctly computed the weight for included studies. |
| 5. Observed Concordance Between Review Findings and Conclusions | Authors' reported conclusions were consistent with findings, provided a balanced consideration of benefits and harms, and did not favor a specific intervention if evidence was lacking. |

bibliographic databases (note: for this assessment, PubMed/MEDLINE counts as a single database), (2) uses a combination of keywords and database-specific controlled vocabulary (e.g., MeSH, EMTREE, etc.), (3) uses at least one other additional source of studies (e.g., grey literature, conference/hand searching, references of included studies, asking experts in the field, government databases, etc.), and (4) does not inappropriately restrict the search based on time, language, etc. These are important aspects to consider in the search, but just because a review has all of these in the search does not mean that it is comprehensive. For example, a review can have a search strategy that uses keywords and controlled vocabulary that is poorly put together and does not capture all the relevant articles. An additional consideration is the number of records that are retrieved in the search. If the systematic reviewers are searching for multiple databases and only find less than a couple hundred records for title abstract screening, it is suspicious, and most likely the search is not comprehensive. Without a comprehensive search, a systematic review cannot make the basic claim that it has synthesized "all" the available evidence for a clinical question.

**Item 3 –** This item is also a simple "Yes" or "No" based on what the reviewers have reported about their methodology. It can be reported in the paper itself or in the registration or protocol. Systematic reviewers can use any method to assess the quality or risk of bias of the included studies; there are many different tools for the same study designs and many different study designs. This is critical for systematic reviews since a qualitative synthesis requires consideration of the respective qualities of the studies. If a study includes studies of different designs and different qualities but gives them all equal weight in informing conclusions, the overall conclusions will not be appropriate.

**Item 4 –** This item also needs some statistical and epidemiological consideration. If there is no meta-analysis, then it does not apply, and a review must meet the other four criteria to be considered reliable. If there is a meta-analysis, then the methodologist assessing reliability needs to consider the following:

- Is it fair to combine the studies given the clinical/methodological/statistical heterogeneity? THIS SHOULD BE "YES": if they should not have combined them, then the analysis is inappropriate.
- Did they combine studies of different designs? THIS SHOULD BE "NO": if they combined randomized controlled trials and observational designs (e.g., non-randomized trials, cohort studies, etc.), then the analysis is inappropriate UNLESS they did an individual participant data meta-analysis.
- Did they include any study arms in the analyses that were inappropriate (e.g., multiple intervention arms from the same trial with the same control arm in each comparison, so that the control subjects are double counted in a single analysis)? THIS SHOULD BE "NO": if they have inappropriate arms in the analysis, it is inappropriate. *NOTE: For this project, given that the overall objective is a scoping review of associations, most reviews will include multiple different study designs in meta-analyses for estimating prevalence and proportions. Where these analyses would typically be considered inappropriate in the context of clinical care and intervention reviews (e.g., meta-analyzing measures of association such as risk ratios and odds ratios), more lenient criteria were applied so that any meta-analyses that combined different study designs for proportions were accepted.*

**Item 5 –** This item requires some consideration in terms of the review's results and main conclusions/recommendations. The main consideration for this item is to check for any spinning of the results or any extrapolation that one thinks is inappropriate. For example, if the review did not assess harms

but the authors concluded that the intervention was "safe" or "well tolerated" or did not have any harms, that is inappropriate. Similarly, if there were meta-analyses or the majority of studies were finding no difference in effects for the intervention, but the reviewers concluded that there was evidence the intervention was effective or made any strong recommendations based on weak evidence, that was inappropriate. This is the one criterion that requires the most judgement on behalf of the assessor. Methodologists should make their best judgement in terms of whether they would make the same conclusion given the evidence that is presented in the review.

### Scoping Review Data Extraction

Data were extracted from the reliable systematic reviews with one PICO Portal methodologist, and the data were verified by a second methodologist. Changes were checked by the verifier with a senior methodologist (PICO Portal and National Academies staff) during data cleaning to ensure accuracy and completeness of the data. Because of the study's shortened timeline, this single extraction with verification was a revised approach from the originally intended double-independent extraction. Data extraction variables included standard elements such as research question, year of publication of earliest and latest published articles, primary article setting, article types, total number of studies in review, total number of study participants, population, etc. Data extraction variables also included elements specific to a Long COVID definition, including acute COVID-19 confirmation methods, time since acute COVID-19 symptom onset, acute COVID-19 symptom severity, populations hospitalized with acute COVID-19, Long COVID symptom duration and severity, description of Long COVID symptoms, comorbidities, frequency and time frame of health outcomes, impacts of health outcomes on daily activities, reinfection description, etc.

### Scoping Review Results and Narrative Synthesis

After searching, a total of 1,590 records were imported for consideration in the review. These records were sourced from various databases, including 596 from Embase, 302 from NLM, 686 from MEDLINE, one from the Cochrane database, and five from other sources. Before screening, 47 records were removed as duplicates (n=46) or supplemental records (n=1). During the abstract screening phase, 1,543 records were assessed for eligibility with a single reviewer, excluding 702 as not relevant and an additional one as a duplicate. All 840 reports included at full-text screening were retrieved and screened, with priority given to those tagged as systematic reviews and/or meta-analyses. All full-text records were screened in duplicate with PICO Portal methodologists, and discrepancies were

resolved by National Academies Staff. Of these 840, 601 reports were excluded for various reasons: 575 were not systematic reviews, 28 did not include a population with Long COVID, 75 were excluded for other reasons, 21 focused on treatment rather than the review topic, and 2 more were excluded as duplicates. After the full-text review, 239 reports were deemed eligible and were included for reliability assessment. During reliability assessment/data extraction, one more article was removed because the scope did not fall within the question, and three more duplicates were identified (pre-prints for which the final publications were also included).

The reliability was of all 235 records was assessed according to five criteria, and 116 were judged to be reliable and continued with data extraction. The 116 included studies are listed below.

For the 119 studies deemed not reliable, 66 failed on a single criterion, 38 failed to meet two criteria, and 6 missed three criteria. The most common reason for being found not reliable was not having a risk of bias or quality assessment for the included studies (n=71), followed by not having a comprehensive search (n=65). These are also the most common reasons for unreliability in other fields and were expected for this set of reviews.

The committee reviewed the extracted data and synthesized the results narratively throughout the report where appropriate.

### Included Reviews

1. Aiyegbusi, O. L., S. E. Hughes, G. Turner, S. C. Rivera, C. McMullan, J. S. Chandan, S. Haroon, G. Price, E. H. Davies, K. Nirantharakumar, E. Sapey, and M. J. Calvert. 2021. Symptoms, complications and management of long COVID: a review. *Journal of the Royal Society of Medicine* 114(9):428-442.
2. Akbari, A., A. Hadizadeh, M. Islampanah, E. Salavati Nik, S. L. Atkin, and A. Sahebkar. 2023. COVID-19, G protein-coupled receptor, and renin-angiotensin system autoantibodies: Systematic review and meta-analysis. *Autoimmunity Reviews* 22(9):103402.
3. Alkodaymi, M. S., O. A. Omrani, N. A. Fawzy, B. A. Shaar, R. Almamlouk, M. Riaz, M. Obeidat, Y, Obeidat, D. Gerberi, R. M. Taha, Z. Kashour, T. Kashour, E. F. Berbari, K. Alkattan, and I. M. Tleyjeh. 2022. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: A systematic review and meta-analysis. *Clinical Microbiology and Infection* 28(5):657–666.
4. Almas, T., J. Malik, A. K. Alsubai, S. M. Jawad Zaidi, R. Iqbal, K. Khan, M. Ali, U. Ishaq, M. Alsufyani, S. Hadeed, R. Alsufyani, R. Ahmed, T. Thakur, H. Huang, M. Antony, I. Antony, A. Bhullar, F. Kotait, and L. Al-Ani. 2022. Post-acute COVID-19 syndrome and its prolonged effects: An updated systematic review. *Annals of Medicine and Surgery* 80:103995.
5. Ashton, R. E., B. E. Philips, and M. Faghy. 2023. The acute and chronic implications of the COVID-19 virus on the cardiovascular system in adults: A systematic review. *Progress in Cardiovascular Diseases* 76:31–37.

6. Badenoch, J. B., E. R. Rengasamy, C. Watson, K. Jansen, S. Chakraborty, R. D. Sundaram, D. Hafeez, E. Burchill, A. Saini, L. Thomas, B. Cross, C. K. Hunt, I. Conti, S. Ralovska, Z. Hussain, M. Butler, T. A. Pollak, I. Koychev, B. D. Michael, H. Holling, T. R. Nicholson, J. P. Rogers, and A G. Rooney. 2022. Persistent neuropsychiatric symptoms after COVID-19: A systematic review and meta-analysis. *Brain Communications* 4(1):fcab297.
7. Banerjee, M., R. Pal, and S. Dutta, S. 2022. Risk of incident diabetes post-COVID-19: A systematic review and meta-analysis. *Primary Care Diabetes* 16(4):591–593. https://doi.org/10.1016/j.pcd.2022.05.009.
8. Behnood, S. A., R. Shafran, S. D. Bennett, A. X. D. Zhang, L. L. O'Mahoney, T. J. Stephenson, S. N. Ladhani, B. L. De Stavola, R. M. Viner, and Swann, O. V. 2022. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: A meta-analysis of controlled and uncontrolled studies. *Journal of Infection* 84(2):158–170.
9. Bertuccelli, M., L. Ciringione, M. Rubega, P. Bisiacchi, S. Masiero, and A. Del Felice. 2022. Cognitive impairment in people with previous COVID-19 infection: A scoping review. *Cortex* 154:212–230.
10. Bocchino, M., G. Rea, L Capitelli, R. Lieto, and D. Bruzzese. 2023. Chest CT lung abnormalities 1 year after COVID-19: A systematic review and meta-analysis. *Radiology* 308(1):e230535.
11. Bourmistrova, N. W., T. Solomon, P. Braude, R. Strawbridge, and B. Carter. 2022. Long-term effects of COVID-19 on mental health: A systematic review. *Journal of Affective Disorders* 299:118–125.
12. Cabrera Martimbianco, A. L., R. L. Pacheco, A. M. Bagattini, and R. Riera, R. 2021. Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. *International Journal of Clinical Practice* 75(10):e14357.
13. Cares-Marambio, K., Y. Montenegro-Jiménez, R. Torres-Castro, R. Vera-Uribe, Y. Torralba, X. Alsina-Restoy, L. Vasconcello-Castillo, and J. Vilaró. 2021. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chronic Respiratory Disease* 18:14799731211002240.
14. Ceban, F., S. Ling, L. M. W. Lui, Y. Lee, H. Gill, K. M. Teopiz, N. B. Rodrigues, M. Subramaniapillai, J. D. Di Vincenzo, B. Cao, K. Lin, R. B. Mansur, R. C. Ho, J. D. Rosenblat, K. W. Miskowiak, M. Vinberg, V. Maletic, and R. S. McIntyre. 2022. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain, Behavior, and Immunity* 101:93–135.
15. Chen, C., S. R. Haupert, L. Zimmermann, X. Shi, L. G. Fritsche, and B. Mukherjee. 2021. Global prevalence of post-acute sequelae of COVID-19 (PASC) or long COVID: A meta-analysis and systematic review. *medRxiv*. https://doi.org/10.1101/2021.11.15.21266377.
16. Chinvararak, C., and T. Chalder. 2023. Prevalence of sleep disturbances in patients with long COVID assessed by standardised questionnaires and diagnostic criteria: A systematic review and meta-analysis. *Journal of Psychosomatic Research* 175:111535.
17. Choudhury, A., R. Tariq, A. Jena, E. K. Vesely, S. Singh, S. Khanna, and V. Sharma. 2022. Gastrointestinal manifestations of long COVID: A systematic review and meta-analysis. *Therapeutic Advances in Gastroenterology* Aug 19:15:17562848221118403.
18. Ciaffi, J., E. Vanni, L. Mancarella, V. Brusi, L. Lisi, F. Pignatti, S. Naldi, E. Assirelli, S. Neri, M. Reta, C. Faldini, and F. Ursini. 2023. Post-acute COVID-19 joint pain and new onset of rheumatic musculoskeletal diseases: A systematic review. *Diagnostics* 13(1):1850.

19. de Oliveira Almeida, K., I. G. Nogueira Alves, R. S. de Queiroz, M. R. de Castro, V. A. Gomes, F. C. Santos Fontoura, C. Brites, and M. G. Neto. 2023. A systematic review on physical function, activities of daily living and health-related quality of life in COVID-19 survivors. *Chronic Illness* 19(2):279–303.
20. Di Gennaro, F., A. Belati, O. Tulone, L. Diella, D. Fiore Bavaro, R. Bonica, V. Genna, L. Smith, M Trott, O. Bruyere, L. Mirarchi, C. Cusumano, L. J. Dominguez, A. Saracino, N. Veronese, and M. Barbagallo. 2022. Incidence of long COVID-19 in people with previous SARS-Cov2 infection: A systematic review and meta-analysis of 120,970 patients. *Internal and Emergency Medicine* 18(5):1573-1581.
21. Di Stefano, G., P. Falco, E. Galosi, G. Di Pietro, C. Leone, and A. Truini. 2023. A systematic review and meta-analysis of neuropathic pain associated with coronavirus disease 2019. *European Journal of Pain (United Kingdom)* 27(1):44–53.
22. Dirican, E., and T. Bal. 2022. COVID-19 disease severity to predict persistent symptoms: A systematic review and meta-analysis. *Primary Health Care Research & Development* 23:e69.
23. Du, M., Y. Ma, J. Deng, M. Liu, and J. Liu. 2022. Comparison of long COVID-19 caused by different SARS-CoV-2 strains: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health* 19(2):16010.
24. Durstenfeld, M. S., K. Sun, P. Tahir, M. J. Peluso, S. G. Deeks, M. A. Aras, D. J. Grandis, C. S. Long, A. Beatty, and P. Y. Hsue. 2022. Use of cardiopulmonary exercise testing to evaluate long COVID-19 symptoms in adults: A systematic review and meta-analysis. *JAMA Network Open* 5(1):e2236057.
25. Espin, E., C. Yang, C. P. Shannon, S. Assadian, D. He, and S. J. Tebbutt. 2023. Cellular and molecular biomarkers of long COVID: a scoping review. *EBioMedicine* 91:104552.
26. Espinoza, C., and D. Martella. 2023. Cognitive functions in COVID-19 survivors, approaches strategies, and impact on health systems: A qualitative systematic review. *European Archives of Psychiatry and Clinical Neuroscience*. https://doi.org/10.1007/s00406-023-01662-2 [Epub ahead of print].
27. Fernández-de-las-Peñas, C., M. Navarro-Santana, V. Gomez-Mayordomo, M. L. Cuadrado, D. Garcia-Azorin, L. Arendt-Nielsen, and G. Plaza-Manzano. 2021. Headache as an acute and post-COVID-19 symptom in COVID-19 survivors: A meta-analysis of the current literature. *European Journal of Neurology* 28(1):3820–3825.
28. Fernández-de-las-Peñas, C., D. Palacios-Cena, V. Gomez-Mayordomo, L. L. Florencio, M. L. Cuadrado, G. Plaza-Manzano, and M. Navarro-Santana. 2021. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *European Journal of Internal Medicine* 92:55–70.
29. Figueiredo, E. A. B., W. T. Silva, S. P. Tsopanoglou, D. F. M. Vitorino, L. F. L. Oliveira, K. L. S. Silva, H. D. H. Luz, M. R. Ávila, L. F. F. Oliveira, A. C. R. Lacerda, V. A. Mendonça, V. P. Lima, M. F. F. Mediano, P. H. S. Figueiredo, M. O. C. Rocha, and H. S. Costa. 2022. The health-related quality of life in patients with post-COVID-19 after hospitalization: A systematic review. *Revista da Sociedade Brasileira de Medicina Tropical* 55:e0741.
30. Franco, J. V. A., L. I. Garegnani, G. V. Oltra, M.-I. Metzendorf, L. F. Trivisonno, N. Sgarbossa, D. Ducks, K. Heldt, R. Mumm, B. Barnes, and C. Scheidt-Nave. 2022. Short and long-term wellbeing of children following SARS-CoV-2 infection: A systematic review. *International Journal of Environmental Research and Public Health* 19(2):14392.
31. Franco, J. V. A., L. I. Garegnani, G. V. Oltra, M. I. Metzendorf, L. F. Trivisonno, N. Sgarbossa, D. Ducks, K. Heldt, R. Mumm, B. Barnes, and C. Scheidt-Nave. 2022. Long-term health symptoms and sequelae following SARS-CoV-2 infection: An evidence map. *International Journal of Environmental Research and Public Health* 19(1):9915.

32. Guinto, E., F. V. Gerayeli, R. L. Eddy, H. Lee, S. Milne, and D. D. Sin. 2023. Post-COVID-19 dyspnoea and pulmonary imaging: A systematic review and meta-analysis. *European Respiratory Review* 32(1):220253.
33. Guo, B., C. Zhao, M. Z. He, C. Senter, Z. Zhou, J. Peng, S. Li, A. L. Fitzpatrick, S. Lindstrom, R. C. Stebbins, G. A. Noppert, and C. Li. 2023. Long-term cardiac symptoms following COVID-19: A systematic review and meta-analysis. *medRxiv.* https://doi.org/10.1101/2023.01.16.23284620.
34. Han, Q., B. Zheng, L. Daines, and A. Sheikh. 2022. Long-term sequelae of COVID-19: A systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. *Pathogens* 11(2):269.
35. Hanson, S. W., C. Abbafati, J. G. Aerts, Z. Al-Aly, C. Ashbaugh, T. Ballouz, O. Blyuss, P. Bobkova, G. Bonsel, S. Borzakova, D. Buonsenso, D. Butnaru, A. Carter, H. Chu, C. De Rose, M. M. Diab, E. Ekbom, M. El Tantawi, V. Fomin, . . . and T. Vos. 2022. A global systematic analysis of the occurrence, severity, and recovery pattern of long COVID in 2020 and 2021. *medRxiv*. https://doi.org/10.1101/2022.05.26.22275532.
36. Harding, J. L., S. A. Oviedo, M. K. Ali, I. Ofotokun, J. C. Gander, S. A. Patel, D. J. Magliano, and R. E. Patzer. 2023. The bidirectional association between diabetes and long-COVID-19: A systematic review. *Diabetes Research and Clinical Practice* 195:110202.
37. Hawkings, M. J., N. M. Vaselli, D. Charalampopoulos, L. Brierley, A. J. Elliot, I. Buchan, and D. Hungerford. 2023. A systematic review of the prevalence of persistent gastrointestinal symptoms and incidence of new gastrointestinal illness after acute SARS-CoV-2 infection. *Viruses* 15(8):1625.
38. Healey, Q., A. Sheikh, L. Daines, and E. Vasileiou. 2022. Symptoms and signs of long COVID: A rapid review and meta-analysis. *Journal of Global Health* 12:05014.
39. Hirt, J., P. Janiaud, V. Gloy, S. Schandelmaier, T. V. Pereira, D. G. Contopoulos-Ioannidis, S. N. Goodman, J. P. A. Ioannidis, K. Munkholm, and L. G. Hemkens. 2022. Validity of reported post-acute health outcomes in children with SARS-CoV-2 infection: A systematic review. *medRxiv.* https://doi.org/10.1101/2022.03.18.22272582.
40. Houben, S., and B. Bonnechere. 2022. The impact of COVID-19 infection on cognitive function and the implication for rehabilitation: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health* 19(1):7748.
41. Huang, Q., M. Jia, Y. Sun, B. Jiang, D. Cui, L. Feng, and W. Yang. 2022. One-year temporal changes in long COVID prevalence and characteristics: A systematic review and meta-analysis. *Value in Health* 26(6):934–942.
42. Hussain, N., P. Agarwala, K. Iqbal, H. M. S. Omar, G. Jangid, V. Patel, S. S. Rathore, C. Kumari, F. Velasquez-Botero, G. A. B. López, Y. Vishwakarma, A. P. Nipu, and N. K. Ahmed. 2022. A systematic review of acute telogen effluvium, a harrowing post-COVID-19 manifestation. *Journal of Medical Virology* 94(4):1391–1401.
43. Jennings, G., A. Monaghan, F. Xue, D. Mockler, and R. Romero-Ortuno. 2021. A systematic review of persistent symptoms and residual abnormal functioning following acute COVID-19: Ongoing symptomatic phase vs. post-COVID-19 syndrome. *Journal of Clinical Medicine* 10(2):5913.
44. Jiang, L., X. Li, J. Nie, K. Tang, and Z. A. Bhutta. 2023. A systematic review of persistent clinical features after SARS-CoV-2 in the pediatric population. *Pediatrics* 152(2):e2022060351.
45. Joli, J., P. Buck, S. Zipfel, and A. Stengel. 2022. Post-COVID-19 fatigue: A systematic review. *Frontiers in Psychiatry* 13:947973.
46. Kaszuba, M., N. Madej, R. Pilinski, and A. Sliwka. 2023. Post-COVID-19 symptoms in adults with asthma—Systematic review. *Biomedicines* 11(8):2268.

47. Kelly, J. D., T. Curteis, A. Rawal, M. Murton, L. J. Clark, Z. Jafry, R. Shah-Gupta, M. Berry, A. Espinueva, L. Chen, M. Abdelghany, D. A. Sweeney, and J. K. Quint. 2023. SARS-CoV-2 post-acute sequelae in previously hospitalised patients: Systematic literature review and meta-analysis. *European Respiratory Review* 32(169):220254.
48. Kiyak, C., O. A. Ijezie, J. A. Ackah, M. Armstrong, J. Cowen, D. Cetinkaya, H. Burianová, and T. N. Akudjedu. 2023. Topographical distribution of neuroanatomical abnormalities following COVID-19 invasion: A systematic literature review. *Clinical Neuroradiology* 34(1):13–31.
49. Kuodi, P., Y. Gorelik, B. Gausi, T. Bernstine, and M. Edelstein. 2023. Characterisation of post-COVID syndromes by symptom cluster and time period up to 12 months post-infection: A systematic review and meta-analysis. *International Journal of Infectious Diseases* 134:1–7.
50. Lai, H., M. Yang, M. Sun, B. Pan, Q. Wang, J. Wang, J. Tian, G. Ding, K. Yang, X. Song, and L. Ge. 2022. Risk of incident diabetes after COVID-19 infection: A systematic review and meta-analysis. *Metabolism: Clinical and Experimental* 137:155330.
51. Lai, Y. J., S. H. Liu, S. Manachevakul, T. A. Lee, C. T. Kuo, and D. Bello. 2023. Biomarkers in long COVID-19: A systematic review. *Frontiers in Medicine* 10:1085988.
52. Lee, J. H., J.-J. Yim, and J. Park. 2022. Pulmonary function and chest computed tomography abnormalities 6–12 months after recovery from COVID-19: A systematic review and meta-analysis. *Respiratory Research* 23(1):233.
53. Lemes, I. R., F. I. Smaira, W. J. D. Ribeiro, N. K. Favero, L. D. N. J. Matos, A. L. S. Pinto, E. Dolan, and B. Gualano. 2022. Acute and post-acute COVID-19 presentations in athletes: A systematic review and meta-analysis. *British Journal of Sports Medicine* 56(1):941–947.
54. Lin, C. W., Y. H. Wang, Y. E. Li, T. Y. Chiang, L. W. Chiu, H. C. Lin, and C. T. Chang. 2023. COVID-related dysphonia and persistent long-COVID voice sequelae: A systematic review and meta-analysis. *American Journal of Otolaryngology* 44(5):103950.
55. Linh, T. T. D., D. K. N. Ho, N. N. Nguyen, C. J. Hu, C. H. Yang, and D. Wu. 2023. Global prevalence of post-COVID-19 sleep disturbances in adults at different follow-up time points: A systematic review and meta-analysis. *Sleep Medicine Reviews* 71:101833.
56. Long, Q., J. Li, X. Hu, Y. Bai, Y. Zheng, and Z. Gao. 2021. Follow-ups on persistent symptoms and pulmonary function among post-acute COVID-19 patients: A systematic review and meta-analysis. *Frontiers in Medicine* 8:702635.
57. Lopez-Leon, S., T. Wegman-Ostrosky, N. C. Ayuzo Del Valle, C. Perelman, R. Sepulveda, P. A. Rebolledo, A. Cuapio, and S. Villapol. 2022. Long-COVID in children and adolescents: A systematic review and meta-analyses. *Science Reports 12*(1):9950.
58. Lopez-Leon, S., T. Wegman-Ostrosky, C. Perelman, R. Sepulveda, P. A. Rebolledo, A. Cuapio, and S. Villapol. 2021. More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. *Scientific Reports* 11(1):16144.
59. Maglietta, G., F. Diodati, M. Puntoni, S. Lazzarelli, B. Marcomini, L. Patrizi, and C. Caminiti. 2022. Prognostic factors for post-COVID-19 syndrome: A systematic review and meta-analysis. *Journal of Clinical Medicine* 11(6):1541.
60. Marasco, G., M. Maida, C. Cremon, M. R. Barbaro, V. Stanghellini, and G. Barbara. 2023. Meta-analysis: Post-COVID-19 functional dyspepsia and irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics* 58(1):6–15.
61. Marchi, M., P. Grenzi, V. Serafini, F. Capoccia, F. Rossi, P. Marrino, L. Pingani, G. M. Galeazzi, and S. Ferrari. 2023. Psychiatric symptoms in Long-COVID patients: A systematic review. *Frontiers in Psychiatry* 14:1138389.
62. Mat Hassan, N., H. S. Salim, S. Amaran, N. I. Yunus, N. A. Yusof, N. Daud, and D. Fry. 2023. Prevalence of mental health problems among children with long COVID: A systematic review and meta-analysis. *PLOS One* 18(5):e0282538.

63. Michelen, M., L. Manoharan, N. Elkheir, V. Cheng, A. Dagens, C. Hastie, M. O'Hara, J. Suett, D. Dahmash, P. Bugaeva, I. Rigby, D. Munblit, E. Harriss, A. Burls, C. Foote, J. Scott, G. Carson, P. Olliaro, L. Sigfrid, and C. Stavropoulou. 2021. Characterising long COVID: A living systematic review. *BMJ Global Health* 6(9). https://doi.org/10.1136/bmjgh-2021-005427.
64. Molero, P., G. Reina, J. D. Blom, M. Martínez-González, A. Reinken, E. R. de Kloet, and M. L. Molendijk. 2023. COVID-19 risk, course and outcome in people with mental disorders: A systematic review and meta-analyses. *Epidemiology and Psychiatric Sciences* 32:e61.
65. Mudgal, S. K., R. Gaur, S. Rulaniya, L. T, R. Agarwal, S. Kumar, S. Varshney, S. Sharma, S. Bhattacharya, and V. Kalyani. 2023. Pooled prevalence of long COVID-19 symptoms at 12 months and above follow-up period: A systematic review and meta-analysis. *Cureus* 15(3):e36325.
66. Müller, S. A., L. Isaaka, R. Mumm, C. Scheidt-Nave, K. Heldt, A. Schuster, M. Abdulaziz, C. El Bcheraoui, J. Hanefeld, and A. Agweyu. 2023. Prevalence and risk factors for long COVID and post-COVID-19 condition in Africa: A systematic review. *Lancet Global Health* 11(1):e1713–e1724.
67. Muthuka, J. K., C. M. Mutua, J. M. Nzioki, R. Nabaweesi, K. J. Oluoch, and M. K. Kiptoo. 2023. Event rate and predictors of post-acute COVID-19 sequalae and the average time to diagnosis in general population. *medRxiv.* https://doi.org/10.1101/2023.02.23.23286336.
68. Nguyen, N. N., V. T. Hoang, T. L. Dao, P. Dudouet, C. Eldin, and P. Gautret. 2022. Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: A systematic review. *European Journal of Clinical Microbiology & Infectious Diseases* 41(4):515–545.
69. Nittas, V., M. Gao, E. A. West, T. Ballouz, D. Menges, S. Wulf Hanson, and M. A. Puhan. 2022. Long COVID through a public health lens: An umbrella review. *Public Health Reviews* 43:1604501.
70. Notarte, K. I., J. A. Catahay, J. V. Velasco, A. Pastrana, A. T. Ver, F. C. Pangilinan, P. J. Peligro, M. Casimiro, J. J. Guerrero, M. M. L. Gellaco, G. Lippi, B. M. Henry, and C. Fernández-de-Las-Peñas. 2022. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. *EClinicalMedicine* 53:101624.
71. Nyasulu, P. S., J. L. Tamuzi, and R. T. Erasmus. 2023. Burden, causation, and particularities of long-COVID in African populations: A rapid systematic review. *medRxiv.* https://doi.org/10.1101/2023.01.13.23284305.
72. Paterson, C., D. Davis, M. Roche, B. Bissett, C. Roberts, M. Turner, E. Baldock, and I. Mitchell. 2022. What are the long-term holistic health consequences of COVID-19 among survivors? An umbrella systematic review. *Journal of Medical Virology* 94(1):5653–5668.
73. Pierce, J. D., Q. Shen, S. A. Cintron, and J. B. Hiebert. 2022. Post-COVID-19 syndrome. *Nursing Research* 71(2):164–174.
74. Premraj, L., N. V. Kannapadi, J. Briggs, S. M. Seal, D. Battaglini, J., Fanning, J. Suen, C. Robba, J. Fraser, and S.-M. Cho. 2022. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis. *Journal of the Neurological Sciences* 434:120162.
75. Rahmati, M., A. Koyanagi, E. Banitalebi, D. K. Yon, S. W. Lee, J. Il Shin, and L. Smith. 2023. The effect of SARS-CoV-2 infection on cardiac function in post-COVID-19 survivors: A systematic review and meta-analysis. *Journal of Medical Virology* 95(1):e28325.

76. Rahmati, M., R. Udeh, D. K. Yon, S. W. Lee, X. Dolja-Gore, E. M. McEVoy, T. Kenna, L. Jacob, G. F. López Sánchez, A.Koyanagi, J. I. Shin, and L. Smith. 2023. A systematic review and meta-analysis of long-term sequelae of COVID-19 2-year after SARS-CoV-2 infection: A call to action for neurological, physical, and psychological sciences. *Journal of Medical Virology* 95(6):e28852.
77. Rahmati, M., D. K. Yon, S. W. Lee, P. Soysal, A. Koyanagi, L. Jacob, Y. Li, J. M. Park, Y. W. Kim, J. I. Shin, and L. Smith. 2023. New-onset neurodegenerative diseases as long-term sequelae of SARS-CoV-2 infection: A systematic review and meta-analysis. *Journal of Medical Virology* 95(7):e28909.
78. Rahmati, M., D. K. Yon, S. W. Lee, R. Udeh, E. M. McEVoy, M. S. Kim, R. M. Gyasi, H. Oh, G. F. López Sánchez, L. Jacob, Y. Li, A. Koyanagi, J. I. Shin, and L. Smith. 2023. New-onset type 1 diabetes in children and adolescents as postacute sequelae of SARS-CoV-2 infection: A systematic review and meta-analysis of cohort studies. *Journal of Medical Virology* 95(6):e28833.
79. Ramadan, M. S., L. Bertolino, R. Zampino, E. Durante-Mangoni, D. Iossa, M. P. Ursi, F. D'Amico, A. Karruli, M. Ramadan, R. Andini, M. Bernardo, G. Ruocco, G. Dialetto, F. E. Covino, S. Manduca, A. Della Corte, M. De Feo, S. De Vivo, M. L. De Rimini, and N. Galdieri. 2021. Cardiac sequelae after coronavirus disease 2019 recovery: A systematic review. *Clinical Microbiology and Infection* 27(9):1250–1261.
80. Rao, S., T. Benzouak, S. Gunpat, R. J. Burns, T. A. Tahir, S. Jolles, and S. Kisely. 2022. Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients: A systematic review and meta-analysis. *Annals of Behavioral Medicine* 56(3):219–234.
81. Reis Carneiro, D., I Rocha, M. Habek, R. Helbok, J. Sellner, W. Struhal, G. Wenning, and A. Fanciulli. 2023. Clinical presentation and management strategies of cardiovascular autonomic dysfunction following a COVID-19 infection—A systematic review. *European Journal of Neurology* 30(5):1528–1539.
82. Rochmawati, E., A. C. Iskandar, and F. Kamilah. 2022. Persistent symptoms among post-COVID-19 survivors: A systematic review and meta-analysis. *Journal of Clinical Nursing* 33(1):29–39.
83. Rungjirajittranon, T., W. Owattanapanich, N. Leelakanok, N. Sasijareonrat, B. Suwanawiboon, Y. Chinthammitr, and T. Ruchutrakool. 2021. Thrombotic and hemorrhagic incidences in patients after discharge from COVID-19 infection: A systematic review and meta-analysis. *Clinical and Applied Thrombosis/Hemostasis* 27:10760296211069082.
84. Salamanna, F., F. Veronesi, L. Martini, M. P. Landini, and M. Fini. 2021. Post-COVID-19 syndrome: The persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. *Frontiers in Medicine* 8:653516.
85. Salari, N., Y. Khodayari, A. Hosseinian-Far, H. Zarei, S. Rasoulpoor, H. Akbari, and M. Mohammadi. 2022. Global prevalence of chronic fatigue syndrome among long COVID-19 patients: A systematic review and meta-analysis. *BioPsychoSocial Medicine* 16(1):21.
86. Sanchez-Ramirez, D. C., K. Normand, Y. Zhaoyun, and R. Torres-Castro. 2021. Long-term impact of COVID-19: A systematic review of the literature and meta-analysis. *Biomedicines* 9(8):900.
87. Sarfraz, Z., A. Sarfraz, A. Barrios, R. Garimella, A. Dominari, M. Kc, K. Pandav, J. C. Pantoja, V. Retnakumar, and I. Cherrez-Ojeda. 2021. Cardio-pulmonary sequelae in recovered COVID-19 patients: Considerations for primary care. *Journal of Primary Care & Community Health* 12:21501327211023726.

88. SeyedAlinaghi, S., A. Bagheri, A. Razi, P. Mojdeganlou, H. Mojdeganlou, A. M. Afsahi, A. Afzalian, P. Paranjkhoo, R. Shahidi, P. Mirzapour, Z. Pashaei, M. A. Habibi, P. Shahbazi, S. Nooralioghli Parikhani, N. S. Farizani Gohari, Y. Popoola, E. Mehraeen, and D. Hackett. 2023. Late complications of COVID-19: An umbrella review on current systematic reviews. *Archives of Academic Emergency Medicine* 11(1):e28.
89. Seyedmirzaei, H., M. Faramarzpour, A. Saghazadeh, A. L. Teixeira, and N. Rezaei. 2023. Post-COVID-19 depression and serum interleukin 6 levels: A systematic review and meta-analysis of COVID-19 convalescents with and without depression. *World Journal of Biological Psychiatry* 24(9):811–821.
90. Suh, H. W., C. Y. Kwon, and B. Lee. 2023. Long-term impact of COVID-19 on heart rate variability: A systematic review of observational studies. *Healthcare (Basel)* 11(8):1095.
91. Tan, B. K. J., R. Han, J. J. Zhao, N. K. W. Tan, E. S. H. Quah, C. J. Tan, Y. H. Chan, N. W. Y. Teo, T. C. Charn, A. See, S. Xu, N. Chapurin, R. K. Chandra, N. Chowdhury, R. Butowt, C. S. von Bartheld, B. N. Kumar, C. Hopkins, and S. T. Toh. 2022. Prognosis and persistence of smell and taste dysfunction in patients with COVID-19: Meta-analysis with parametric cure modelling of recovery curves. *BMJ* 378:e069503.
92. Torres-Castro, R., L. Vasconcello-Castillo, X. Alsina-Restoy, L. Solis-Navarro, F. Burgos, H. Puppo, and J. Vilaró. 2021. Respiratory function in patients post-infection by COVID-19: A systematic review and meta-analysis. *Pulmonology* 27(4):328–337.
93. Trott, M., R. Driscoll, and S. Pardhan. 2022. The prevalence of sensory changes in post-COVID syndrome: A systematic review and meta-analysis. *Frontiers in Medicin*e 9:980253.
94. Tsampasian, V., H. Elghazaly, R. Chattopadhyay, M. Debski, T. K. P. Naing, P. Garg, A. Clark, E. Ntatsaki, and V. S. Vassiliou. 2023. Risk factors associated with post-COVID-19 condition: A systematic review and meta-analysis. *JAMA Internal Medicine* 183(6):ioi230017.
95. Udeh, R., A. Utrero-Rico, X. Dolja-Gore, M. Rahmati, E. M. McEVoy, and T. Kenna. 2023. Lactate dehydrogenase contribution to symptom persistence in long COVID: A pooled analysis. *Reviews of Medical Virology* 33(6):e2477.
96. van Kessel, S. A. M., T. C. Olde Hartman, P. Lucassen, and C. H. M. van Jaarsveld. 2022. Post-acute and long-COVID-19 symptoms in patients with mild diseases: A systematic review. *Family Practice* 39(1):159–167.
97. Vandersteen, C., A. Plonka, V. Manera, K. Sawchuk, C. Lafontaine, K. Galery, O. Rouaud, N. Bengaied, C. Launay, O. Guérin, P. Robert, G. Allali, O. Beauchet, and A. Gros. 2023. Alzheimer's early detection in post-acute COVID-19 syndrome: A systematic review and expert consensus on preclinical assessments. *Frontiers in Aging Neuroscience* 15:1206123.
98. Velichkovsky, B. B., A. Y. Razvaliaeva, A. A. Khlebnikova, P. A. Manukyan, V. N. Kasatkin, and A. V. Barmin. 2023. Systematic review and meta-analysis of clinically relevant executive functions tests performance after COVID-19. *Behavioural Neurology* 2023:1094267.
99. Watanabe, A., M. Iwagami, J. Yasuhara, H. Takagi, and T. Kuno. 2023. Protective effect of COVID-19 vaccination against long COVID syndrome: A systematic review and meta-analysis. *Vaccine* 41(1):1783–1790.
100. Wildwing, T., and N. Holt. 2021. The neurological symptoms of COVID-19: A systematic overview of systematic reviews, comparison with other neurological conditions and implications for healthcare services. *Therapeutic Advances in Chronic Disease* 12:2040622320976979.

101. Wolff, D., K. P. Drewitz, A. Ulrich, D. Siegels, S. Deckert, A. A. Sprenger, P. R. Kuper, J. Schmitt, D. Munblit, and C. Apfelbacher. 2023. Allergic diseases as risk factors for Long-COVID symptoms: Systematic review of prospective cohort studies. *Clinical & Experimental Allergy* 53(11):1162–1176.
102. Woodrow, M., C. Carey, N. Ziauddeen, R. Thomas, A. Akrami, V. Lutje, D. C. Greenwood, and N. A. Alwan. 2022. Systematic review of the prevalence of Long Covid. *medRxiv.* https://doi.org/10.1101/2022.11.06.22281979.
103. Wulf Hanson, S., C. Abbafati, J. G. Aerts, Z. Al-Aly, C. Ashbaugh, T. Ballouz, O. Blyuss, P. Bobkova, G. Bonsel, S. Borzakova, D. Buonsenso, D. Butnaru, A. Carter, H. Chu, C. De Rose, M. M. Diab, E. Ekbom, M. El Tantawi, V. Fomin, R. Frithiof, A. Gamirova, P. V. Glybochko, J. A. Haagsma, S. Haghjooy Javanmard, E. B. Hamilton, G. Harris, M. H. Heijenbrok-Kal, R. Helbok, M. E. Hellemons, D. Hillus, S. M. Huijts, M. Hultström, W. Jassat, F. Kurth, I. M. Larsson, M. Lipcsey, C. Liu, C. D. Loflin, A. Malinovschi, W. Mao, L. Mazankova, D. McCulloch, D. Menges, N. Mohammadifard, D. Munblit, N. A. Nekliudov, O. Ogbuoji, I. M. Osmanov, J. L. Peñalvo, M. S. Petersen, M. A. Puhan, M. Rahman, V. Rass, N. Reinig, G. M. Ribbers, A. Ricchiuto, S. Rubertsson, E. Samitova, N. Sarrafzadegan, A. Shikhaleva, K. E. Simpson, D. Sinatti, J. B. Soriano, E. Spiridonova, F. Steinbeis, A. A. Svistunov, P. Valentini, B. J. van de Water, R. van den Berg-Emons, E. Wallin, M. Witzenrath, Y. Wu, H. Xu, T. Zoller, C. Adolph, J. Albright, J. O. Amlag, A. Y. Aravkin, B. L. Bang-Jensen, C. Bisignano, R. Castellano, E. Castro, S. Chakrabarti, J. K. Collins, X. Dai, F. Daoud, C. Dapper, A. Deen, B. B. Duncan, M. Erickson, S. B. Ewald, A. J. Ferrari, A. D. Flaxman, N. Fullman, A. Gamkrelidze, J. R. Giles, G. Guo, S. I. Hay, J. He, M. Helak, E. N. Hulland, M. Kereselidze, K. J. Krohn, A. Lazzar-Atwood, A. Lindstrom, R. Lozano, D. C. Malta, J. Månsson, A. M. Mantilla Herrera, A. H. Mokdad, L. Monasta, S. Nomura, M. Pasovic, D. M. Pigott, R. C. Reiner, Jr., G. Reinke, A. L. P. Ribeiro, D. F. Santomauro, A. Sholokhov, E. E. Spurlock, R. Walcott, A. Walker, C. S. Wiysonge, P. Zheng, J. P. Bettger, C. J. L. Murray, and T. Vos. 2022. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. *JAMA* 328(1):1604–1615.
104. Yang, T., M. Z. Yan, X. Li, and E. H. Y. Lau. 2022. Sequelae of COVID-19 among previously hospitalized patients up to 1 year after discharge: A systematic review and meta-analysis. *Infection* 50(5):1067–1109.
105. Yin, J.-X., Y. L. Agbana, Z.-S. Sun, S.-W. Fei, H.-Q. Zhao, X.-N. Zhou, J.-H. Chen, and K. Kassegne. 2023. Increased interleukin-6 is associated with long COVID-19: A systematic review and meta-analysis. *Infectious Diseases of Poverty* 12(1):43.
106. Yong, S. J., A Halim, M. Halim, S. Liu, M. Aljeldah, B. R. Al Shammari, S. Alwarthan, M. Alhajri, A. Alawfi, A. Alshengeti, F. Khamis, J. Alsalman, A. N. Alshukairi, N. A. Abukhamis, F. S. Almaghrabi, S. A. Almuthree, A. M. Alsulaiman, B. M. Alshehail, A. H. Alfaraj, . . . and A. A. Rabaan. 2023. Inflammatory and vascular biomarkers in post-COVID-19 syndrome: A systematic review and meta-analysis of over 20 biomarkers. *Reviews in Medical Virology* 33(2):e2424.
107. Yuan, N., Z. H. Lv, C. R. Sun, Y. Y. Wen, T. Y. Tao, D. Qian, F. P. Tao, and J. H. Yu. 2023. Post-acute COVID-19 symptom risk in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Frontiers in Public Health* 11:1112383.
108. Zakia, H., K. Pradana, and S. Iskandar. 2023. Risk factors for psychiatric symptoms in patients with long COVID: A systematic review. *PLOS One* 18(4):e0284075.

109. Zeng, N., Y.-M. Zhao, W. Yan, C. Li, Q.-D. Lu, L. Liu, S.-Y. Ni, H. Mei, K. Yuan, L. Shi, P. Li, T.-T. Fan, J.-L. Yuan, M. V. Vitiello, T. Kosten, A. L. Kondratiuk, H.-Q. Sun, X.-D. Tang, M.-Y. Liu, A, Lalvani, J. Shi, and L. Lu. 2023. A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: Call for research priority and action. *Molecular Psychiatry* 28(1):423–433.
110. Zheng, X., M. Qian, X. Ye, M. Zhang, C. Zhan, H. Li, and T. Luo. 2022. Implications for long COVID: A systematic review and meta-aggregation of experience of patients diagnosed with COVID-19. *Journal of Clinical Nursing* 33(1):40–57.
111. Zheng, Y.-B., N. Zeng, K. Yuan, S.-S. Tian, Y.-B. Yang, N. Gao, X. Chen, A.-Y. Zhang, A. L. Kondratiuk, P.-P. Shi, F. Zhang, J. Sun, J.-L. Yue, X. Lin, L. Shi, A. Lalvani, J. Shi, Y.-P. Bao, and L. Lu. 2023. Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review. *Journal of Infection and Public Health* 16(5):660–672.
112. Zuin, M., M. Mazzitelli, G. Rigatelli, C. Bilato, and A. M. Cattelan. 2023. Risk of ischemic stroke in patients recovered from COVID-19 infection: A systematic review and meta-analysis. *European Stroke Journal* 8(4):915–922.
113. Zuin, M., G. Rigatelli, V. Battisti, G. Costola, L. Roncon, and C. Bilato. 2022. Increased risk of acute myocardial infarction after COVID-19 recovery: A systematic review and meta-analysis. *International Journal of Cardiology* 372:138–143.
114. Zuin, M., G. Rigatelli, C. Bilato, G. Pasquetto, and A. Mazza. 2023. Risk of incident new-onset arterial hypertension after COVID-19 recovery: A systematic review and meta-analysis. *High Blood Pressure and Cardiovascular Prevention* 30(3):227–233.
115. Zuin, M., G. Rigatelli, C. Bilato, A. Porcari, M. Merlo, L. Roncon, and G. Sinagra. 2023. One-year risk of myocarditis after COVID-19 infection: A systematic review and meta-analysis. *Canadian Journal of Cardiology* 39(6):839–844.
116. Zurcher, S. J., C. Banzer, C. Adamus, A. I. Lehmann, D. Richter, and P. Kerksieck. 2022. Post-viral mental health sequelae in infected persons associated with COVID-19 and previous epidemics and pandemics: Systematic review and meta-analysis of prevalence estimates. *Journal of Infection and Public Health* 15(5):599–608.

## PUBLIC AGENDAS

The committee held eight committee meetings from March 2023 to February 2024, and portions of four meetings were open to the public. Furthermore, the committee held a 2-day public symposium in June 2023. The agendas for these public sessions are included in this appendix.

1. The committee's first meeting in March 2023 included a public session where the sponsors of the study provided their perspectives on the charge to the committee.
2. The committee's second meeting in April 2023 included a public session where colleagues from the National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) provided additional background information and context for the study.

3. The May 2023 meeting included a public session where the committee heard from additional federal colleagues on ongoing efforts related to Long COVID and from researchers, practitioners, and patients about defining Long COVID.
4. Supplementing the evidence-building activities and the implementation of the engagement strategy, the committee convened a 2-day symposium in June 2023 to discuss potential considerations for refined Long COVID definitions and terminology, and for harmonizing efforts for patient engagement, clinical care, research, and surveillance across the federal government and relevant stakeholders. The committee heard from dozens of experts and examined the evidence supporting different elements of a Long COVID definition. The committee also explored emerging evidence, gaps, and key considerations for updating and modifying the definition in the future and considered how the definition might need to be adapted for different purposes, including but not limited to clinical research, epidemiologic and surveillance, policy, and advocacy and education.
5. The January 2024 meeting included a public session where the committee engaged with additional experts to learn about relevant research and implementation considerations.

## MEETING 1 AGENDA

### Friday, March 31, 2023

**Purpose**

- Hold an open session to hear from sponsoring agencies on their perspectives of the statement of task.

### OPEN SESSION

**Sponsor Briefing: Discussion of the Committee's Charge**

4:00 p.m. **Welcome**
HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

4:05 p.m. **Sponsor Perspective on Charge to the Committee**
D. CHRISTIAN HASSELL
Deputy Assistant Secretary Senior Science Advisor
Administration for Strategic Preparedness and Response

ALLISON O'DONNELL
Deputy Director, Long COVID Office of the
Assistant Secretary for Health (OASH)

4:20 p.m. **Discussion with Committee**

5:00 p.m. **ADJOURN OPEN SESSION**

**MEETING 2 AGENDA**

**Friday, April 14, 2023**

**Purpose**

- Hold an open session to hear from federal agencies on ongoing efforts to define Long COVID.

**OPEN SESSION**

1:00 p.m. **Welcome and Introductions**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

1:05 p.m. **Lessons Learned from Long COVID Efforts Currently Underway and Discussion of Key Issues and Barriers to Defining Long COVID**

CLINTON WRIGHT
Associate Director
Director, Division of Clinical Research
National Institute of Neurological Disorders and Stroke

1:30 p.m. PRITI PATEL
Senior Advisor for Post-Covid Conditions
Centers for Disease Control and Prevention

1:55 p.m. **Concluding Remarks**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

2:00 p.m. **ADJOURN OPEN SESSION – BREAK**

## MEETING 3 AGENDA

**Friday, May 12, 2023**

**Purpose**

- Hold an open session to hear from federal, state, and local agencies on ongoing efforts on Long COVID.
- Hear perspectives from researchers, practitioners, and patients about defining Long COVID.

## OPEN SESSION

**SESSION Information Gathering to Inform Effort to Define Long COVID**

10:30 a.m. **Welcome and Introductions**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

10:35 a.m. **Federal Efforts to Establish an Understanding of Long COVID**

- Discuss insights into Long COVID through Infectious Disease Clinical Research Program studies

SIMON POLLETT
Infectious Disease Clinical Research Program
Department of Preventive Medicine and Biostatistics
Uniformed Services University of the Health Sciences
The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

BRIAN AGAN
Infectious Disease Clinical Research Program
Department of Preventive Medicine and Biostatistics
Uniformed Services University of the Health Sciences
The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

COL. ROBERT O'CONNELL
Infectious Disease Clinical Research Program
Department of Preventive Medicine and Biostatistics
Uniformed Services University of the Health Sciences

10:55 a.m. **Discussion with Panelists**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

11:15 a.m. **State, Local and Territories Perspective on Surveillance and Epidemiology of Long COVID**

- Discuss state, local, and territorial agency efforts to establish an understanding of Long COVID; epidemiological and surveillance considerations

RACHEL HERLIHY
State Epidemiologist
Colorado Department of Public Health and Environment

CHANIS MARI MERCADO OLAVARRIA
Diseases Intervention Specialist
Departamento de Salud de Puerto Rico

MARCUS PLESCIA
Chief Medical Officer
Association of State and Territorial Health Officials

11:45 a.m. **Discussion with Panelists**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

12:00 p.m. **BREAK (30 minutes)**

12:30 p.m. **Frontline Perspective on Long COVID**

- Discuss use of a definition; signs and symptoms of Long COVID; elements to include or not include in a definition; diagnostic criteria; barriers to providing care and support; and treatment for patients with Long COVID

DAVID PUTRINO
Director of Rehabilitation Innovation, Mt. Sinai Health System
Assistant Professor of Rehabilitation Medicine, Icahn School of Medicine at Mt. Sinai

NICOLE GENTILE
Co-Director
UW Post-COVID Rehabilitation and Recovery Clinic
Assistant Professor, Department of Family Medicine, Department of Laboratory Medicine and Pathology
University of Washington, Seattle, WA
Co-Investigator, Innovative Support for Patients with SARS-CoV2 Infections (INSPIRE) Registry

LINDA GENG
Clinical Assistant Professor, Stanford University
Co-Director, Stanford Post-Acute COVID-19 Syndrome Clinic

1:00 p.m. **Discussion with Panelists**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

1:15 p.m. **Research Perspective on Long COVID**

- Discuss pathogenesis of Long COVID; inclusion and exclusion criteria for Long COVID studies; and biomarkers

DAVID WALT
Hansjörg Wyss Professor of Biologically Inspired Engineering, Harvard Medical School
Professor of Pathology, Department of Pathology, Brigham and Women's Hospital
Core Faculty, Wyss Institute for Bioinspired Engineering, Harvard University
Howard Hughes Medical Institute Professor

MICHAEL PELUSO
Assistant Professor, Medicine
University of California, San Francisco, School of Medicine

ELIZABETH KARLSON
Scientific Director, Mass General Brigham Personalized Medicine
Professor of Medicine, Harvard Medical School
Associate Physician, Brigham and Women's Hospital

NANCY KLIMAS
Director, Institute for Neuro-Immune Medicine, Nova Southeastern University
Director, Clinical Immunology Research, Miami Veterans Administration Medical Center
Chair and Professor of Medicine, Department of Clinical Immunology,
College of Osteopathic Medicine, Nova Southeastern University
Professor Emerita, University of Miami, School of Medicine

1:45 p.m. **Discussion with Panelists**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

2:00 p.m. **Patient Perspective on Defining Long COVID**

- Learn from patients' experiencing Long COVID and associated conditions and those with lived experience to identify opportunity areas to improve the quality of care and life through the Long COVID Definition. In particular, discuss barriers to using a definition and key considerations for developing an inclusive definition.

HANNAH DAVIS LONG
COVID Researcher
Founding Member of the Patient-Led Research Collaborative

ELISA PEREGO
Honorary Research Associate
University College London
Long COVID Advocate

CHARLIE MCCONE
Long COVID Advocate

2:30 p.m. **Discussion with Panelists**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

2:45 p.m. **Q&A with OASH about the USG Long COVID Definition**

MICHAEL IADEMARCO
Rear Admiral and Assistant Surgeon General,
U. S. Public Health Service Deputy
Assistant Secretary for Science and Medicine
Office of the Assistant Secretary of Health

3:00 p.m. **ADJOURN OPEN SESSION**

## PUBLIC SYMPOSIUM AGENDA (DAY 1)

### Thursday, June 22, 2023

**Purpose**

- Discuss the approaches employed by the committee to solicit broad feedback about the U.S. government working definition for Long COVID.
- Examine the evidence supporting different elements of a Long COVID definition.
- Based on the evidence and stakeholder input, discuss the necessary elements of a definition for Long COVID.
- Explore emerging evidence, gaps, and key considerations for updating and modifying the definition in the future.
- Understand industry and payer perspectives on the definition for Long COVID, and consider how the definition might need to be adapted for different purposes, including but not limited to clinical research, epidemiologic and surveillance, policy, and advocacy and education.

## SESSION I DAY 1 OPENING SESSION

1:00 p.m. **Welcome and Project Reel: A Multi-Phase and Collaborative Approach**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

1:10 p.m. **Opening Remarks**

VICTOR DZAU *virtual*
President National Academy of Medicine

1:20 p.m. **Keynote Presentation – Long COVID: From Policy to Action**

SARAH BOATENG
Principal Deputy Assistant Secretary for Health
Department of Health and Human Services

## SESSION II PLENARY SESSION: LESSONS LEARNED FROM INFECTION-ASSOCIATED CHRONIC CONDITIONS

1:35 p.m. **Lessons Learned from Lyme Disease**

ABIGAIL DUMES, *Committee Member, virtual*
Assistant Professor Department of Women's and Gender Studies University of Michigan

1:45 p.m. **Fireside Chat with Patient Organization Leaders**

- Karyn Bishof in conversation with key patient organization leaders about challenges faced by people living with Long COVID and associated conditions and implications for defining Long COVID

KARYN BISHOF, *Moderator, Committee Member*

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President and Chief Executive Officer
Solve ME

LAUREN STILES
President Dysautonomia International
Research Assistant Professor of Neurology
Stony Brook University Renaissance School of Medicine

LISA MCCORKELL
Co-Founder
Patient-Led Research Collaborative

**SESSION III IMPACTS OF LONG COVID ON OVERALL WELL-BEING**

2:15 p.m. **Impacts of Long COVID on Health and Socioeconomic Well-Being and Implications for Defining Long COVID**

MONICA VERDUZCO GUTIERREZ, *Moderator, Committee Member*

**Patient Perspective on Long COVID and Health-Related Quality of Life**

KELLY SEALEY
Long COVID Patient Advocate

**Research and Perspectives from Patients on Employment, Disability, Socioeconomic Status, Educational, and Developmental Outcomes**

NETIA MCCRAY
Executive Director
Mbadika
Long COVID Patient Advocate

**Racial and Ethnic Disparities**

YONGKANG ZHANG
Assistant Professor
Department of Population Health Sciences
Weill Cornell Medical College

**Association of Post COVID-19 Condition Symptoms and Employment**

ROY PERLIS
Ronald I. Dozoretz, M.D. Endowed Chair
Associate Chief for Research
Department of Psychiatry
Director of the Center for Quantitative Health
Massachusetts General Hospital

**Long COVID and Impairments**

TAE CHUNG
Director
Johns Hopkins Postural Orthostatic Tachycardia Syndrome
Program Assistant Professor of Physical Medicine and Rehabilitation and Neurology
Johns Hopkins Medicine

**CDC INSPIRE**

MICHAEL GOTTLIEB *virtual*
Associate Professor and Vice Chair
Department of Emergency Medicine
Rush University Medical Center

**Q&A**

3:30 p.m. **30-MINUTE BREAK**

**SESSION IV RESEARCH ON THE CLINICAL MANIFESTATIONS, EPIDEMIOLOGIC CHARACTERISTICS, AND UNDERLYING MECHANISMS OF LONG COVID**

4:00 p.m. **Clinical Manifestations and Epidemiologic Characteristics of Long COVID – Signs and Symptom, Onset and Duration, Attribution to Infection**

JERRY KRISHNAN, *Moderator, Committee Member*

**Development of a Definition of PASC Infection**

TANAYOTT THAWEETHAI, *Co-Presenter*
Associate Director, Biostatistics Research and Engagement
Massachusetts General Hospital
Instructor in Medicine, Harvard Medical School

Leora Horwitz, *Co-Presenter*
Professor
NYU Langone

**Identification of SARS-CoV-2 Sub-Phenotypes**

MARK WEINER
Professor of Clinical Population Health Sciences and Medicine
Weill Cornell Medical College

**Recovery and Symptom Trajectories up to 2 Years After SARS-CoV-2 Infection**

MILO PUHAN *virtual*
Professor
Epidemiology, Biostatistics and Prevention Institute
University of Zurich

**Epidemiology, Immunology, and Clinical Characteristics of COVID-19 (EPIC3)**

JENNIFER ROSS *virtual*
Assistant Professor of Medicine
University of Washington
Attending physician in Infectious Diseases
Department of Veterans Affairs Puget Sound Health Care System
Co-Principal Investigator/Study Chair
Epidemiology, Immunology, and Clinical Characteristics of COVID-19
Department of Veterans Affairs

**Epidemiologic Characteristics of Long COVID**

SHARON SAYDAH
Post-COVID Conditions and Long-Term Sequelae Team Lead
Epidemiology Branch
Coronavirus and Other Respiratory Viruses Division
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

**Q&A**

5:00 p.m. **Biomarkers and Underlying Mechanisms of Long COVID**

ANDREA TROXEL, *Moderator, Committee Member*

**Immune Mechanisms Underlying COVID-19 Pathology and PASC**

SINDHU MOHANDAS
Assistant Professor of Clinical Pediatrics
Division of Infectious Diseases
Children's Hospital Los Angeles
Keck School of Medicine
University of Southern California, Los Angeles

**Multiple Early Factors Anticipate PASC**

JAMES HEATH *virtual*
President and Professor
Institute for Systems Biology in Seattle

**The Neurobiology of Long COVID**

MICHELLE MONJE *virtual*
Professor of Neurology
Howard Hughes Medical Institute Investigator
Stanford University

**Biomarkers and Underlying Mechanisms of Infection-Associated Chronic Illnesses**

TIM COETZEE *virtual*
Chief Advocacy, Services and Science Officer
National MS Society
Co-Chair, Toward a Common Research Agenda in Infection-Associated
Chronic Illnesses: A Workshop to Examine Common, Overlapping Clinical and Biological Factors

**Q&A**

**SESSION V DAY 1 CLOSING REMARKS**

5:45 p.m. **Chair's Reflection**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

6:00 p.m. **End Day 1**

**PUBLIC SYMPOSIUM AGENDA (DAY 2)**

**Friday, June 23, 2023**

**SESSION VI WELCOME TO DAY 2**

8:30 a.m. **Welcome and Recap of Day 1**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

8:35 a.m. **Keynote Presentation – The Therapeutic Validation of Long COVID**

JEREMY FAUST
Physician Division of Health
Policy and Public Health

Brigham and Women's Hospital
Harvard Medical School
Editor-in-Chief Medpage Today

8:50 a.m. **Fireside Chat – Untangling the Concept and Terminology of a "Definition"**

- Dr. Harvey Fineberg in conversation with Dr. Jim Curran about concepts related to defining a disease or syndrome, implications for defining Long COVID, and lessons learned from HIV/AIDS.

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

JAMES CURRAN
Dean Emeritus Rollins School of Public Health
Emory University

**SESSION VII LESS STUDIED LONG COVID SYMPTOMS AND EVIDENCE GAPS**

9:15 a.m. **Less Studied Long COVID Symptoms and Gaps in Evidence**

LINDA SPRAGUE MARTINEZ, *Moderator, Committee Member*

**Perspective on Considerations for Definitions from the ME/CFS Program at CDC**

JEANNE BERTOLLI *virtual*
Deputy Chief
Chronic Viral Diseases Branch
Division of High Consequence Pathogens and Pathology
National Center for Zoonotic and Emerging Infectious Diseases
Centers for Disease Control and Prevention

**Prevalence of ME/CFS-like Illness Following COVID-19 in a Large Integrated Health System**

JACEK SKARBINSKI *virtual*
Physician
Assistant Program Director
Kaiser Permanente Northern California HIV Fellowship
Research Scientist
Kaiser Permanent Northern California

**Gastrointestinal System and Long COVID**

SAURABH MEHANDRU
Physician Scientist
Professor and Vice Chair of Research
Icahn School of Medicine at Mount Sinai

**Reproductive Health Conditions, Connective Tissue Disorders, and Spinal Pathologies in Long COVID and Associated Illnesses**

BETH POLLACK *virtual*
Research Scientist
Department of Biological Engineering
Massachusetts Institute of Technology

**Post-Exertional Malaise, Sleep Disturbances, Cognitive Issues, and Dysautonomia and Long COVID**

TAE CHUNG
Director, Johns Hopkins Postural Orthostatic Tachycardia Syndrome
Program
Assistant Professor of Physical Medicine and Rehabilitation
Johns Hopkins Medicine

**Autonomic Symptoms, Mechanisms, and Pathology in Long COVID**

LAUREN STILES
President
Dysautonomia International
Research Assistant Professor of Neurology
Stony Brook University Renaissance School of Medicine

**Pediatric Long COVID**

LAURA MALONE
Co-Director, Pediatric Post-COVID19 Rehabilitation Clinic
Kennedy Krieger Institute
Assistant Professor of Neurology and Physical Medicine and Rehabilitation
Johns Hopkins University School of Medicine

**Q&A**

10:30 a.m. **30-MINUTE BREAK**

**SESSION VIII MULTI-SECTORAL PERSPECTIVE ON THE DEFINTION FOR LONG COVID**

11:00 a.m. **Drug Developers, Payer, and Health Plan Perspectives on Long COVID Definition**

PETER PALESE, *Moderator, Committee Member*

**Drug Developers**

PHYLLIS ARTHUR
Vice President
Infectious Diseases and Diagnostics
BIO

**Health Insurance Plans**

WINNIE CHI
Director of Population Research
Elevance Health

**Q&A**

11:30 a.m. **Updating and Disseminating a Definition – Policy, Communications, and Training and Education Considerations for a Long COVID Definition**

WES ELY, *Moderator, Committee Member*

**Coding ICD-10: Characterizing a New Disease Through an ICD-10 Lens**

EMILY PFAFF
Assistant Professor
University of North Carolina, Chapel Hill, School of Medicine

**PCP and Reimbursement Perspective**

JULIE WOOD
Family Physician
Senior Vice President
Research, Science, and Health of the Public
American Academy of Family Physicians

**CDC Long COVID and fatiguing illness recovery program**

CHRISTIAN RAMERS *virtual*
Chief, Population Health
Family Health Centers of San Diego

**Disability Perspective**

REBECCA VALLAS *virtual*
Senior Fellow, The Century Foundation
Senior Adviser, Disability Economic Justice Collaborative

**Applied Governmental Public Health Perspective**

LEISHA NOLEN *virtual*
State Epidemiologist
Utah Department of Health

**Q&A**

**SESSION IX DAY 2 CLOSING REMARKS**

12:30 p.m. **Final Words from the Sponsors**

MICHAEL IADEMARCO
Rear Admiral and Assistant Surgeon General,
U. S. Public Health Service Deputy

Assistant Secretary for Science and Medicine
Office of the Assistant Secretary of Health

D. CHRISTIAN HASSELL
Deputy Assistant Secretary
Senior Science Advisor
Administration for Strategic Preparedness and Response

12:45 p.m. **Symposium Closing Remarks**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

1:00 p.m. **Adjourn Symposium**

## MEETING 7 AGENDA

**Thursday, January 18, 2024**

Purpose

- Hear from experts about additional perspectives on defining Long COVID and implementation considerations for Long COVID definitions.

### SESSION I WELCOME AND INTRODUCTIONS

12:00 p.m. **Welcome and Introductions**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

12:05 p.m. **Long COVID Definition Considerations**

RAVINDRA GANESH
Internist Assistant Professor of Medicine
Mayo Clinic–Rochester

RYAN HURT
Internist
Vice Chair of Practice and Vice Chair of Research
Mayo Clinic-Rochester

12:20 p.m. **Implementation Considerations for Long COVID Definition**

EMILY MENDENHALL
Medical Anthropologist
Professor in the Science, Technology, and International Affairs
Georgetown University

12:30 p.m. **Discussion with Panelists**

HARVEY FINEBERG, *Committee Chair*
President
Gordon and Betty Moore Foundation

1:00 p.m. **Adjourn Open Session**

# Appendix B

# Measures of Diagnostic Performance: Sensitivity, Specificity, and Predictive Value

## SENSITIVITY

Sensitivity is a measure of the ability of a diagnostic test, or the application of diagnostic criteria, to correctly detect disease when the disease is present. More technically, Sensitivity is the probability a test is positive when the disease is present. Until there is an external reference standard (e.g., biomarker) for Long COVID (or sub-phenotypes), the diagnosis of Long COVID is based on the patient-reported symptoms as per the 2024 NASEM definition. It is therefore not possible to calculate the sensitivity of the 2024 NASEM definition.

Se represents the diagnostic measure of sensitivity.

D+ represents the presence of disease.

T+ represents a positive test result, or equivalently, that a set of diagnostic criteria, represented by T, are satisfied, as represented by T+.

P[T+|D+] is the probability a test is positive when the disease is present. Equivalently, this is the probability a set of diagnostic criteria are satisfied when the disease is present.

By definition, Se = P[T+|D+].

## SPECIFICITY

Specificity is a measure of the ability of a diagnostic test, or the application of diagnostic criteria, to correctly rule out disease when the disease is absent. More technically, specificity is the probability a test is negative when the disease is absent. Similar to sensitivity, it is not possible to calculate the specificity of the 2024 Long COVID NASEM Definition until an external reference standard is identified.

Sp represents the diagnostic measure of specificity.

D- represents the absence of disease.

T- represents a negative test result, or equivalently, that a set of diagnostic criteria, represented by T, are not satisfied, as represented by T-.

P[T-|D-] is the probability a test is negative when the disease is absent. Equivalently, this is the probability a set of diagnostic criteria are not satisfied when the disease is absent.

By definition, Sp = P[T-|D-].

Importantly, the ability to measure sensitivity and specificity depends on an independent truth standard for the presence or absence of the disease in question. When there is no independent truth standard, such as pathology or a definitive biomarker, there is no definitive way to measure sensitivity and specificity. This is the case currently with Long COVID. Given state of knowledge at the time of writing this report, the sensitivity and specificity of the 2024 NASEM Long COVID Definition is unknown.

## PREDICTIVE VALUE

Predictive value is a measure of the ability of a diagnostic test, or the application of a set of diagnostic criteria, to correctly detect disease (Positive Predictive Value) or to correctly rule out disease (Negative Predictive Value) when the presence or absence of disease is uncertain. More technically, Positive Predictive Value is the probability the disease is present when a test is positive, and Negative Predictive Value is the probability a disease is absent when a test is negative.

PPV represents Positive Predictive Value.

P[D+|T+] is the probability the disease is present when the test is positive. Equivalently, this is the probability the disease is present when the set of diagnostic criteria are satisfied.

By definition, PPV = P[D+|T+].

NPV represents Negative Predictive Value.

P[D-|T-] is the probability the disease is absent when the test is negative. Equivalently, this is the probability the disease is absent when the set of diagnostic criteria are not satisfied.

By definition, NPV = P[D-|T-].

When applying a diagnostic test, or set of diagnostic criteria, to a group of individuals, the predictive value of the test or set of diagnostic criteria depends on the prior probability of the disease in the group who are tested as well as on the sensitivity and specificity of the test.

P[D+] represents the prior probability of disease in a group who are tested for the disease. This could be considered the background frequency or prevalence of the disease.

P[D-] represents the prior probability of the absence of disease in a group who are tested for the disease. Because a disease is either present or absent, the sum of the probabilities P[D+] plus P[D-] equals 1.0. P[D-] can be represented as (1-P[D+]).

The mathematical relationship between predictive value and the prior probability of disease, test sensitivity, and test specificity is given by Bayes Formula.

Bayes Formula for Positive Predictive Value is:

$$P[D^+|T^+] = \frac{Se\ x\ P[D^+]}{(Se\ x\ P[D^+]) + (1 - Sp)\ x\ (1 - P[D^+])}$$

Similarly, Bayes Formula for Negative Predictive Value is:

$$P[D^-|T^-] = \frac{Sp\ x\ (1 - P[D^+])}{Sp\ x\ (1 - P[D^+]) + (1 - Se)\ x\ P[D^+]}$$

It may be easier to see the relationships among sensitivity, specificity, disease prevalence, positive predictive value and negative predictive value in the form of a 2×2 table.

| | **Disease Present** | **Disease Absent** | |
|---|---|---|---|
| **Test Positive** | A<br>True Positive | B<br>False Positive | A + B<br>Total Test Positive |
| **Test Negative** | C<br>False Negative | D<br>True Negative | C + D<br>Total Test Negative |
| | A + C<br>Total Disease Present | B + D<br>Total Disease Absent | A + B + C + D<br>Total Population |

$$Se = \frac{A}{A+C} = P[T^+|D^+]$$

$$Sp = \frac{D}{B+D} = P[T^-|D^-]$$

$$P[D^+] = \frac{A+C}{A+B+C+D}$$

$$P[D^-] = \frac{B+D}{A+B+C+D}$$

$$P[D^-] = 1 - P[D^+] = 1 - \frac{A+C}{A+B+C+D} = \frac{A+B+C+D}{A+B+C+D} - \frac{A+C}{A+B+C+D} = \frac{B+D}{A+B+C+D}$$

The PPV is the fraction of true positives (A) among all positives (A+B), or $\frac{A}{A+B}$ as may be seen directly from the table. The equivalence to the previously given formula can be shown in terms of sensitivity, specificity, and prevalence (that is, the prior probability of disease), as follows:

$$PPV = \frac{Se\ x\ P[D^+]}{(Se\ x\ P[D^+]) + (1-Sp)\ x\ (1-P[D^+])} =$$

$$\frac{\frac{A}{A+C}\ x\ \frac{A+C}{A+B+C+D}}{\left(\frac{A}{A+C}\ x\ \frac{A+C}{A+B+C+D}\right) + \left(1-\frac{D}{B+D}\right)\ x\ \left(1-\frac{A+C}{A+B+C+D}\right)} =$$

$$\frac{\frac{A}{A+B+C+D}}{\left(\frac{A}{A+B+C+D}\right) + \left(\frac{B}{B+D}\right)\ x\ \left(\frac{B+D}{A+B+C+D}\right)} = \frac{\frac{A}{A+B+C+D}}{\frac{A+B}{A+b+C+D}} = \frac{A}{A+B}$$

It may similarly be shown that the previously given formula for negative predictive value in terms of sensitivity, specificity, and prevalence (or prior probability of disease) equals the fraction of true negatives among all who test negative, or $\frac{D}{C+D}$, as represented in the table.

The prior probability of disease strongly influences the predictive value of a diagnostic test or the predictive value of a set of diagnostic criteria. For example, consider a highly inclusive set of diagnostic criteria, that is sensitivity = 0.98, with only middling ability to rule out the disease in question, that is specificity = 0.75. Consider two test populations of 10,000 persons, population A with a very high prior probability of the disease or condition in question, P[D+] = 0.6, and population B with a much lower prior probability of the disease or condition in question, P[D+] = 0.05. The results of applying this identical set of diagnostic criteria in each population would be as follows:

**Population A:**
Se = 0.98

Sp = 0.75

P[D+] = 0.6

| | Disease Present | Disease Absent | |
|---|---|---|---|
| Test Positive | 5,880 | 1,000 | 6,880 |
| Test Negative | 120 | 3,000 | 3,120 |
| | 6,000 | 4,000 | 10,000 |

PPV = 5,880/6,880 ~ 0.85

NPV = 3,000/3,120 ~ 0.96

In this case approximately five of six who test positive and 24 of 25 who test negative will be correctly classified with respect to the presence or absence of the disease.

**Population B:**

Se = 0.98

Sp = 0.75

P[D+] = 0.05

| | Disease Present | Disease Absent | |
|---|---|---|---|
| **Test Positive** | 490 | 2,375 | 2,865 |
| **Test Negative** | 10 | 7,125 | 7,135 |
| | 500 | 9,500 | 10,000 |

PPV = 490/2,865 ~ 0.34

NPV = 7,125/7,135 ~ 0.99+

In this case, a positive test will correctly classify a patient only in about one third of those with the disease or condition in question, while a negative test will virtually rule out the condition.

One implication is that the application of the same diagnostic criteria when many patients have recently had acute SARS-CoV-2 infection will produce a higher positive predictive value than will result after the acute infection declines in frequency, which means that patients with the same symptoms have a lower prior probability of the symptoms being related to COVID.

# Appendix C

# Biographical Sketches

## COMMITTEE MEMBERS

**Harvey V. Fineberg, M.D., PH.D.** (*Chair*), is president of the Gordon and Betty Moore Foundation. He previously served as president of the Institute of Medicine (now National Academy of Medicine) from 2002 to 2014 and as provost of Harvard University from 1997 to 2001, following 13 years as dean of the Harvard Chan School of Public Health. Dr. Fineberg devoted most of his academic career to the fields of health policy and medical decision making. His past research has focused on the process of policy development and implementation, assessment of medical technology, evaluation and use of vaccines, and dissemination of medical innovations. Dr. Fineberg serves as a trustee of the China Medical Board. He helped found and served as president of the Society for Medical Decision Making and previously chaired the boards of the William and Flora Hewlett Foundation and the Carnegie Endowment for International Peace. He chaired the committee to review the performance of the World Health Organization and the functioning of the International Health Regulations (2005) during the 2009 H1N1 influenza pandemic. Dr. Fineberg is co-author of the books *Clinical Decision Analysis*, *Innovators in Physician Education*, and *The Epidemic That Never Was*, an analysis of the controversial federal immunization program against swine flu in 1976. He has co-edited several books on such diverse topics as AIDS prevention, vaccine safety, understanding risk in society, and global health. He has also authored numerous articles published in professional journals. Dr. Fineberg chaired the National Academies committee that produced the 2019 report on Reproducibility and Replicability in

Science and chairs the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats. He earned his bachelor's and doctoral degrees at Harvard and is the recipient of several honorary degrees.

**Kevin M. Alexander, M.D.,** is an advanced heart failure and transplant cardiologist and an assistant professor of medicine at Stanford University. He completed internal medicine residency training at Johns Hopkins Hospital and a cardiology fellowship at Brigham and Women's Hospital. He then completed an advanced heart failure fellowship at Stanford Hospital. Dr. Alexander's clinical and research interests include heart failure, cardiac amyloidosis, and heart transplantation. His primary interest lies in cardiac amyloidosis, in particular unraveling the molecular determinants of transthyretin amyloid cardiomyopathy to improve diagnosis and treatment. He has co-authored many publications on cardiac amyloidosis and has received research grants from the National Institutes of Health and the American Heart Association. During the COVID-19 pandemic, he developed an interest in the interaction between cardiovascular disease and COVID-19 infection. He published several articles on the effect of COVID-19 on heart transplants and left ventricular assist patients (Trans-Co-V registry) as well as serving as a member of the Association of Black Cardiologists COVID Task Force. Dr. Alexander serves on an ongoing advisory board for Arbor Biotechnologies and in the past served as consultant for Alnylam, Bristol Myers Squibb, Eidos, Ionis, Novo Nordisk, and Pfizer.

**Donald Berwick, M.D., M.P.P., FRCP, KBE,** is president emeritus and a senior fellow at the Institute for Healthcare Improvement (IHI), an organization he co-founded and led as president and chief executive officer for 19 years. He is one of the nation's leading authorities on health care quality and improvement. In July 2010, President Obama appointed Dr. Berwick to the position of administrator of the Centers for Medicare & Medicaid Services, which he held until December 2011. A pediatrician by background, Dr. Berwick has served as a clinical professor of pediatrics and health care policy at the Harvard Medical School, professor of health policy and management at the Harvard School of Public Health, and as a member of the staff of Boston's Children's Hospital Medical Center, Massachusetts General Hospital, and the Brigham and Women's Hospital. He has also served as vice chair of the U.S. Preventive Services Task Force, the first "independent member" of the board of trustees of the American Hospital Association, and chair of the National Advisory Council of the Agency for Healthcare Research and Quality. He is an elected member of the American Philosophical Society, the American Academy of Arts and Sciences, and the National Academy of Medicine (NAM, formerly the Institute of Medicine, or IOM). Dr. Berwick served two terms on the IOM's governing

council, was a member of the IOM's Global Health Board, and currently chairs the NAM Board on Health Care Services. He served on President Clinton's Advisory Commission on Consumer Protection and Quality in the Healthcare Industry. His numerous awards include the 2007 William B. Graham Prize for Health Services Research, the 2006 John M. Eisenberg Patient Safety and Quality Award, and the 2007 Heinz Award for Public Policy. In 2005, he was appointed Honorary Knight Commander of the British Empire by Her Majesty Queen Elizabeth II, the highest honor in the United Kingdom for non-U.K. citizens. He is the author or co-author of over 200 scientific articles and six books. He also serves now as a lecturer in the Department of Health Care Policy at Harvard Medical School. Dr. Berwick is a member of the board of directors of LumiraDx and has been a member of the advisory group to the COVID Patient Recovery Alliance organized by Leavitt Partners, which has been considering the consequences of Long COVID and has made several public statements and drafted a bill.

**Karyn Bishof, B.S.,** is the founder and president of the COVID-19 Longhauler Advocacy Project (C19LAP), a nonprofit whose mission is to advance the understanding of Long COVID and expedite assistance and solutions to Longhaulers and their families through advocacy, education, research, and support. Ms. Bishof retired from her work as firefighter/paramedic due to Long COVID and associated conditions (LCAC) and currently serves on the National Institutes of Health's RECOVER Initiative Ancillary Studies Committee and sits on the executive committee of the Long COVID Alliance. In 2022, she received the Amelia Moore Sparkle Award for Compassionate Advocacy from Dysautonomia International. She holds a bachelor of science in exercise science and health promotion.

**Lily Chu, M.D., M.S.H.S.,** is the vice president of the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. She has a background in internal medicine, geriatric medicine, and health services research. Her career took a detour in 2006 when she became ill with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Since then, she has investigated various aspects of ME/CFS, including its epidemiology and the unusual symptom of post-exertional malaise. During 2014–2015, she served as a member of the National Academy of Medicine's Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, which created new, evidence-based criteria. From 2012 to 2021, she was a member of the community advisory board for the Stanford University ME/CFS Initiative. She has also collaborated with the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration, National Institutes of Health, and Cochrane. Dr. Chu hopes to bring her perspectives as a patient, physician, and researcher to this project.

**Betty Diamond, M.D.,** received her M.D. from Harvard Medical School, performed a residency in internal medicine at Columbia Presbyterian Medical Center, and then trained in immunology at the Albert Einstein College of Medicine. Her research has focused on the induction and pathogenicity of autoantibodies in systemic lupus erythematosus (SLE), especially in the brain. Most recently, she has become interested in the anti-inflammatory effects of C1q. In recent years, she has also become involved in clinical trials in SLE and has led several clinical trials of novel therapeutics. She has received the outstanding investigator and the mentoring awards of American College of Rheumatology. She is a member of the National Academy of Medicine and the National Academy of Sciences. She is a past president of the American Association of Immunologists. In the past, Dr. Diamond served as a consultant for Pfizer and Moderna.

**Abigail Dumes, PH.D.,** is an assistant professor in the Department of Women's and Gender Studies at the University of Michigan. She is a medical and cultural anthropologist with research interests in gender, infectious disease, contested illness, and environmental health. She received her Ph.D. in sociocultural anthropology from Yale University and is the author of *Divided Bodies: Lyme Disease, Contested Illness, and Evidence-Based Medicine* (Duke University Press, 2020). Dr. Dumes's current research is on Long COVID. In 2021, she received the University of Michigan's Public Engagement Faculty Fellowship and, in 2023 she launched a fellowship-supported project titled "Working Toward Health Equity through Free and Accessible COVID-19 Testing," which distributed at-home test kits to under-resourced families in Ann Arbor, Michigan. Between December 2021 and August 2022, she conducted interviews with Long COVID patient advocates that are archived on the University of Michigan's Global Feminisms Project website for research and educational purposes. And since 2022, Dr. Dumes has been conducting a collaborative qualitative pilot study on Long COVID through the University of Michigan's Michigan COVID-19 Recovery Surveillance Study (MI CReSS).

**E. Wesley Ely, M.D., M.P.H.,** is a physician–scientist and tenured professor of medicine and critical care at Vanderbilt University and the associate director of aging research for the TN Valley VA Geriatric Research Education Clinical Center. He has been continuously funded by the National Institutes of Health and the Department of Veterans Affairs (VA) funded for over 20 years and was the principal architect of multiple landmark trials (published in the *New England Journal of Medicine*, *JAMA*, and *The Lancet*) that have transformed intensive care unit (ICU) medicine and improved the survival of critically ill patients with and without COVID-19.

In the ICU, Dr. Ely's evidence-based ABCDEF safety bundle is translated into over 35 languages and is part of daily care for critically ill patients globally. His work defined ICU-acquired delirium and dementia as major public health problems that ruin lives and cost society billions annually. During the COVID pandemic, Dr. Ely conducted the largest international cohort study of acute brain dysfunction which investigated risk factors for COVID-induced delirium. Dr. Ely is an academic member of the National Academy of Medicine's Forum on Traumatic Brain Injury. He is a leader in studies focused on reducing the risk of post-intensive care syndrome (PICS), which is particularly relevant to Long COVID since both syndromes lead to rapidly acquired forms of disabling cognitive impairment. Dr. Ely hopes to draw on these experiences to improve survivorship for millions of people suffering from the cognitive, physical, and mental health disabilities of Long COVID. Dr. Ely was an unfunded investigator for Eli Lilly who designed the COV-Barrier study of baricitinib. Likewise, he is conducting a combined pilot and phase III investigation of baricitinib for Long COVID, and Eli Lilly is providing study drug for this investigation, which will be called the REVERSE-Long COVID clinical trial. He provided educational lectures (approved continuing medical education activities) within the past 5 years to medical audiences about topics related to clinical outcomes of ICU care and severe COVID-19 infection that were sponsored by Pfizer.

**Dennis Larry Kolson, M.D., PH.D.,** is a professor of neurology and vice chair for faculty affairs in the Department of Neurology at the University of Pennsylvania. He is the past chair of the neurological complications of HIV sub-committee of the program committee for the International Conference on Retroviruses and Opportunistic Infections, and he continues to serve as a reviewer of the HIV and COVID-19 neurological complications program. His laboratory research (funded by the National Institutes of Health) is focused on the neuropathogenesis of HIV infection and simian immunodeficiency virus infection in the rhesus macaque model. He is the co-founder and co-director of the Penn NeuroCOVID clinic. His clinical areas of expertise include HIV-associated neurocognitive disorders, the use of immunomodulating therapies for the treatment of multiple sclerosis, and the diagnosis and management of neurological complications of COVID-19. He is a member of the American Academy of Neurology and the American Neurological Association, and he serves as associate editor for *Neurology: Neuroimmunology & Neuroinflammation*. He completed his M.D. and Ph.D. degrees at the University of Pittsburgh, his neurology residency at Duke University Medical Center, and his postdoctoral fellowship in neurovirology at the University of Pennsylvania. He joined the University of Pennsylvania faculty in 1992.

**Jerry A. Krishnan, M.D., Ph.D.,** is a physician–scientist with clinical experience caring for people with asthma, chronic obstructive pulmonary disease, and Long COVID. He is a professor and associate vice chancellor for population health sciences at the University of Illinois–Chicago with research expertise in the methods and implementation of pragmatic clinical trials to generate real-world evidence, development of clinical practice guidelines, and the application of human-centered design in research. He is an investigator in the National Institutes of Health (NIH)– and Patient-Centered Outcomes Research Institute–funded research networks, including the NIH RECOVER adult cohort study and clinical trials. Dr. Krishnan previously served as a member of the Pulmonary-Allergy Drugs Advisory Committee for the U.S. Food and Drug Administration from 2007 to 2012 (chair, 2011–2012), the National Committee for Quality Assurance's Respiratory Measurement Advisory Panel (2010–2015), and the National Heart, Lung, and Blood Institute's Clinical Trials Review Committee (2012–2017; chair 2016–2017). He has authored more than 300 peer-reviewed publications in major medical journals, including *JAMA*, the *New England Journal of Medicine*, and the *American Journal of Respiratory and Critical Care Medicine*. Dr. Krishnan received his medical degree from the Baylor College of Medicine, completed his clinical training in internal medicine and pulmonary/critical care medicine at Johns Hopkins, and received a Ph.D. in clinical investigation from the Hopkins Bloomberg School of Public Health. In the previous 24 months, Dr. Krishnan received personal consulting fees for the following organizations: AstraZeneca, CereVu Medical, BData, Inc, Goodwin Proctor LLC/TEVA pharmaceuticals.

**Peter Palese, Ph.D.,** received his Ph.D. from the University of Vienna in 1969. After completing a postdoctoral fellowship at The Roche Institute of Molecular Biology in Nutley, New Jersey, he was recruited to the Mount Sinai School of Medicine as an assistant professor. Dr. Palese was the chair of the Department of Microbiology at the Icahn School of Medicine at Mount Sinai from 1987 to 2023, and he continues his research as a professor of microbiology and of medicine. His interest is in the area of RNA-containing viruses with a special emphasis on influenza viruses. Specifically, he established the first genetic maps for influenza A, B, and C viruses, identified the function of several viral genes, and defined the mechanism of neuraminidase inhibitors (which are now U.S. Food and Drug Administration–approved antivirals). He was also a pioneer in the field of reverse genetics for negative strand RNA viruses, which allows the introduction of site-specific mutations into the genomes of these viruses. This technique is crucial for the study of the structure–function relationships of viral genes, for the investigation of viral pathogenicity, and for the development and manufacture of novel vaccines. An improvement of this technique has

been effectively used by him and his colleagues to reconstruct and study the pathogenicity of the highly virulent, but extinct, 1918 pandemic influenza virus. Work in collaboration with Adolfo García-Sastre has revealed that most negative strand RNA viruses possess proteins with interferon antagonist activity, enabling them to counteract the antiviral response of the infected host. In recent years most of the efforts by Dr. Palese and by his collaborators at Mount Sinai, Adolfo García-Sastre and Florian Krammer, have been directed at developing a universal influenza virus vaccine. Since the beginning of the pandemic, there has been a shift in direction as work on COVID-19 has become central to his efforts. At present, a major focus is the development of COVID-19 vaccines. In collaboration with Adolfo García-Sastre and Florian Krammer, Dr. Palese has developed a vaccine to combat COVID-19. These vaccines are based on Newcastle disease virus (an avian virus) as a vector expressing the spike protein (S) of SARS-CoV-2. Clinical trials using these SARS-CoV-2 vaccines are going on in five different countries. Dr. Palese is a member of the National Academy of Sciences, a member of the National Academy of Medicine, a fellow of the American Academy of Arts and Sciences, and a fellow of the National Academy of Inventors. Dr. Palese is also a corresponding member of the Austrian Academy of Sciences and a member of the German Academy of Sciences (Leopoldina).

**Caitlin Pedati, M.D., M.P.H., FAAP,** is the public health district director of the Virginia Beach Department of Public Health. She is a board-certified pediatrician and started her career working in public health at the Centers for Disease Control and Prevention in the Epidemic Intelligence Service and then in state public health as a medical epidemiologist for the Nebraska Department of Health and Human Services and as the medical director and state epidemiologist for the Iowa Department of Public Health. Dr. Pedati has been a member of the Council of State and Territorial Epidemiologists (CSTE) since 2015 and has served as co-chair of the Healthcare Associated Infections subcommittee and a state epidemiologist, contributing to a variety of workgroups, case definitions, and position statements, including the CSTE COVID-19 case definition and CSTE's current long COVID workgroup. During her career in applied governmental public health at the federal, state, and local levels across the United States, she has served as a leader through infectious disease responses, natural disasters, behavioral health crises, and more. Dr. Pedati has several peer-reviewed publications in basic science HIV research, clinical pediatrics, and public health. She is a fellow of the American Academy of Pediatrics and a member of the Gold Humanism Honor Society and the Delta Omega Honorary Society in Public Health. Dr. Pedati earned her M.D./M.P.H. from George Washington University and completed a pediatric residency with a Certificate in Global Child Health at Children's National Hospital in Washington D.C.

Dr. Pedati conducts consulting work for the Council of State and Territorial Epidemiologists Healthcare Associated Infections Committee (editing and compiling resources).

**Linda Sprague Martinez, Ph.D.,** is a professor in the departments of Medicine and Public Health Sciences at UConn Health, where she directs the Health Disparities Institute. In addition, she is a faculty affiliate with the UConn School of Social Work. Dr. Sprague Martinez's scholarly impact has been in the area of community engagement and participatory research approaches. She has been recognized locally and nationally for her work to advance health equity and community engagement. In 2017 she was named a Resident Empowerment Honoree by the Boston Housing Authority, Center for Community Engagement and Civil Rights, and Resident Empowerment Coalition. In 2023 she received the National Institutes of Health's HEAL Director's Award for community partnerships. Dr. Sprague Martinez was also named a Society for Social Work Research fellow in 2023.

**Mark Smolinski, M.D., M.P.H.,** currently serves as president of Ending Pandemics. Dr. Smolinski brings 25 years of experience in applying innovative solutions to improve disease prediction, prevention, and response across the globe. He is leading a well-knit team—bringing together technologists; human, animal, and environmental health experts; and key community stakeholders to co-create tools for early detection, advanced warning, and prevention of pandemic threats. Since 2009, Dr. Smolinski has served as the chief medical officer and director of global health at the Skoll Global Threats Fund (SGTF), where he developed the Ending Pandemics in Our Lifetime Initiative in 2012. His work at SGTF created a solid foundation for the work of Ending Pandemics, which branched out as an independent entity on January 1, 2018. Prior to SGTF, Dr. Smolinski developed the Predict and Prevent Initiative at Google.org, as part of the start-up team at Google's philanthropic arm. Working with a team of engineers, Google Flu Trends (a project that had a tremendous impact on the use of big data for disease surveillance) was created in partnership with the U.S. Centers for Disease Control and Prevention (CDC). Dr. Smolinski has served as vice president for biological programs at the Nuclear Threat Initiative (NTI), a public charity directed by CNN founder Ted Turner and former U.S. Senator Sam Nunn. Before NTI, he led an 18-member expert committee of the National Academy of Medicine on the 2003 landmark report *Microbial Threats to Health: Emergence, Detection, and Response*. Dr. Smolinski served as the sixth Luther Terry Fellow in Washington, D.C., in the Office of the U.S. Surgeon General and as an epidemic intelligence officer with the CDC. Dr. Smolinski received his B.S. in biology and M.D. from the

University of Michigan in Ann Arbor. He is board-certified in preventive medicine and public health and holds an M.P.H. from the University of Arizona.

**Andrea B. Troxel, Sc.D.**, is a professor of population health and the director of the Division of Biostatistics at New York University's Grossman School of Medicine, leading a growing group of over 60 faculty, staff, and trainees conducting methodological and collaborative research in medicine and population health. Dr. Troxel has extensive experience in the design, conduct, and analysis of all phases of clinical studies and has published on missing data, sensitivity analyses, and statistical methodology for the analysis of clinical trials. She is the author of over 300 peer-reviewed publications in the literature of statistical methodology, behavioral research, and other areas of medicine, and is an expert on randomized trials of behavioral interventions and on adaptive trial designs, with a special focus on pragmatic trials and hybrid effectiveness/implementation studies. She currently serves as multiple principal investigator (MPI) for three data coordinating centers—the National Eye Institute–funded multi-center international randomized Zoster Eye Disease Study; the National Heart, Lung, and Blood Institutes–funded multi-center Pulmonary Embolism–Thrombus Removal with Catheter-Directed Therapy Trial; and the National Institutes of Health (NIH) HEAL Initiative's Data Coordinating Center for the Early Phase Pain Investigation Clinical Trials Network. She is also MPI of the Clinical Science Core for the NIH's RECOVER Initiative to study Long COVID. She is an elected fellow of the American Statistical Association and has served on data safety monitoring boards (DSMBs) for randomized trials in cancer, cardiac devices, smoking cessation, and behavioral therapies. She earned her undergraduate degree in applied mathematics at Yale University and her doctorate in biostatistics at Harvard University. Dr. Troxel is the statistical editor for the *New England Journal of Medicine*. She is also on DSMBs for the NIH's Roybal Centers, for an National Institute on Aging trial being run by investigators at the University of Pennsylvania, for a trial of CAR-T cell therapy sponsored by Cellectis, Inc, and for a National Institute of Arthritis and Musculoskeletal and Skin Diseases knee osteoarthritis trial being run by investigators at Johns Hopkins.

**Monica Verduzco-Gutierrez, M.D.,** is an academic physiatrist and professor and chair of the Department of Rehabilitation Medicine at the Joe R. and Teresa Lozano Long School of Medicine at UT Health in San Antonio, Texas. She also is currently the clinical chief of physical medicine and rehabilitation at the University Hospital System and the medical director of critical illness recovery and neurorehabilitation at Warm Springs Rehabilitation Hospitals in San Antonio. She previously served as the medical

director of the Brain Injury and Stroke Program at TIRR Memorial Hermann in Houston. Her areas of clinical expertise are traumatic brain injury, stroke rehabilitation, interventional spasticity management, and now the post-acute sequelae of SARS-CoV-2 (PASC). She is currently directing a COVID-19 recovery clinic, the first in southern Texas, which aligns with her mission to increase access to interdisciplinary care, optimize function, and improve quality of life for survivors with long COVID. She is a co-principal investigator at one of National Institutes of Health's RECOVER Initiative sites. As a member of the American Academy of Physical Medicine and Rehabilitation's Multi-Disciplinary Post-Acute Sequelae of SARS-CoV-2 infection (PASC) Collaborative, Dr. Verduzco-Gutierrez is a coauthor on all six of the collaborative's current published guidance statements. She is an associate editor of the *American Journal of Physical Medicine & Rehabilitation*. Dr. Verduzco-Gutierrez has current consultancies with AbbVie, Merz, Ipsen, Medtronic, and Piramal, related to her work in interventional spasticity management, and a past consultancy with ReNeuron. She also is an uncompensated consultant to AstraZeneca, addressing outcomes data for patients with cancer and immunodeficiencies. Dr. Verduzco-Gutierrez has testified twice in front of Congress on issues pertaining to Long COVID. She has received the Top 25 Women in Healthcare Award from the National Diversity Council and Healthcare Diversity Council and the Distinguished Member Award from the American Academy of Physical Medicine and Rehabilitation. Dr. Verduzco-Gutierrez serves as a consultant for AbbVie, Ipsen, Merz, Piramal, Medtronic.

## NATIONAL ACADEMY OF MEDICINE FELLOWS

**Paule Joseph, Ph.D., M.B.A., CRNP, FAAN,** is a National Institutes of Health (NIH) Lasker Scholar and Distinguished Scholar. She is the chief of the Section of Sensory Science and Metabolism in the Division of Intramural Clinical and Biological Research at the National Institute on Alcohol Abuse and Alcoholism, with a dual appointment at the National Institute of Nursing Research. She is an international expert in chemosensation (taste and smell) and metabolic diseases, and she bridges the intersections of nursing, science, nutrition, public health, policy, and health disparities. She is also co-director of the NIH National Taste and Smell Center. Dr. Joseph leads a multidimensional translational research program combining basic and clinical research focused on chemosensation, obesity, and substance abuse. Her interdisciplinary laboratory team conducts research focused on understanding neurological and molecular mechanisms underlying chemosensation and motivational pathways of eating behaviors and how they might differ among individuals with obesity, alcohol, and substance use disorders. When

individuals reported taste and smell loss during the COVID-19 pandemic, Dr. Joseph and her team began investigating the effects of the SARS-CoV-2 virus on the chemical senses, and she currently also studies Long COVID effects on these senses. She co-founded the Global Consortium for Chemosensory Research. Her work has been showcased in top-tier academic journals and captured the attention of the media, such as *Time*, National Public Radio, and *The New York Times*. Dr. Joseph has been honored with multiple awards from several global organizations such as the Friends of the National Institutes of Nursing Research, the National Minority Quality Forum 40 under 40 award, the National Association of Hispanic Nurses, the Johnson & Johnson–American Association of Colleges of Nursing, and The Rockefeller University Heilbrunn Nurse Scholar. She has been recognized with the Ajinomoto Award for Young Investigators in Gustation from the Association of Chemoreception Sciences. She is a fellow of the American Academy of Nursing, a fellow of the New York Academy of Medicine, a fellow of the Transcultural Nursing Society, and a member of the Royal Society of Medicine, United Kingdom. She is the 2022–2024 Inaugural American Academy of Nursing Fellow at the National Academy of Medicine. Dr. Joseph is a certified nurse practitioner with clinical privileges at the NIH Clinical Center and outside NIH. Dr. Joseph is a leader of national and global nonprofit organizations dedicated to decreasing health disparities and increasing minority health promotion and access. She received an A.A.S. in nursing at Hostos Community College, a B.S.N. from the College of New Rochelle, a master of science with a specialty as a family nurse practitioner from Pace University, a Ph.D. in nursing and genomics from the University of Pennsylvania, and an executive M.B.A. from Quantic School of Business and Technology.

**Ben Weston, M.D., M.P.H.,** is an associate professor in the Department of Emergency Medicine at the Medical College of Wisconsin. He serves as the chief health policy advisor for Milwaukee County and was the medical director for the regional COVID-19 Unified Emergency Operations Center. In addition, Dr. Weston is the chief medical director for the Milwaukee County Office of Emergency Management, directing medical services for 15 fire departments with 120,000 annual patient encounters. He was recently among seven selected fellows to the National Academy of Medicine as the Fellow to Advance State Health Policy. He has been featured on MSNBC, CNN, BBC, and in *The New York Times* and provided medical oversight for the NFL, NBA, MLB, Indycar, and USA Triathlon. He practices clinically in the emergency department at Froedtert Hospital, a level 1 trauma center and is a National Institutes of Health–funded researcher with a focus on prehospital care, resuscitation, health equity, and public health surveillance.

## STAFF AND CONSULTANT

**Lisa Brown, M.P.H.** (*Study Director*), is a senior program officer on the Board on Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine (the National Academies) and develops and manages projects at the National Academies related to solving the nation's most pressing health security issues. She currently serves as a director for the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats and the Forum on Medical and Public Health Preparedness for Disasters and Emergencies. She has directed several projects, including the Committee on Equitable Allocation of Vaccine for the Novel Coronavirus, the Committee on Data Needs to Monitor Evolution of SARS-CoV-2, the Committee on Evidence-Based Practices for Public Health Emergency Preparedness and Response, and the Committee on Strengthening the Disaster Resilience of Academic Research Communities. Prior to the National Academies, Ms. Brown served as senior program analyst for public health preparedness and environment health at the National Association of County and City Health Officials (NACCHO). In this capacity, Ms. Brown served as project lead for medical countermeasures and the Strategic National Stockpile; researched radiation preparedness issues; and was involved in high-level Centers for Disease Control and Prevention initiatives for the development of clinical guidance for smallpox, anthrax, and botulism countermeasures in a mass casualty event. In 2015 she was selected as a fellow in the Emerging Leaders in Biosecurity Initiative at the Center for Health Security, a highly competitive program to prepare the next generation of leaders in the field of biosecurity. Prior to her work at NACCHO, Ms. Brown worked as an environmental public health scientist at Public Health England (PHE) in London, England. While at PHE, she focused on climate change, the recovery process following disasters, and the impact of droughts and floods on emerging infectious diseases. She received her master of public health from King's College London in 2012 and her bachelor of science in biology from The University of Findlay in 2010.

**Tequam Worku, M.P.H.,** is a program officer for the Board on Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine. Her previous work with the National Academies includes directing a study on Improving the CDC Quarantine Station Network's Response to Emerging Threats with the Board on Global Health. Prior to that, she worked at the Association of State and Territorial Health Officials as a senior analyst for Clinical to Community Connections, managing federally funded projects on community health workers and ending the HIV epidemic. Her past experience also includes working on projects related to chronic diseases and the development of healthy communities, including

the promotion of healthy aging and hypertension prevention and control (the Million Hearts Initiative). Ms. Tequam has worked on various research projects on topics including breast cancer disparities and cultural competency in health care. Additionally, she has worked internationally supporting knowledge management and data analysis efforts at the national level. She is committed to efforts aimed at bridging disparities in health and has been actively involved in health-equity initiatives. She earned her B.A. in biology from University of Maryland Baltimore County and an M.P.H. from The George Washington University; she is currently a Dr.P.H. candidate at Morgan State University.

**Shalini Singaravelu, M.Sc.,** is a program officer at the National Academies of Sciences, Engineering, and Medicine with the Board on Health Sciences Policy, where she supports the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats and the Forum on Medical and Public Health Preparedness for Disasters and Emergencies. Before joining the National Academies, Ms. Singaravelu managed a portfolio of digital health tools as a program manager at IBM. From 2015 to 2019, she was a consultant for the World Health Organization Health Emergencies Programme in Geneva. In this role, she supported preparedness and response to emerging infectious disease epidemics with a focus on operational data systems, risk communication, and community engagement. Prior to this, she worked on psychosocial support programming for HIV-affected orphans and vulnerable children in South Africa. Ms. Singaravelu was a 2022 Emerging Leaders in Biosecurity Initiative (ELBI) fellow with the Johns Hopkins Center for Health Security. She has a graduate certificate in risk sciences and public policy from Johns Hopkins Bloomberg School of Public Health (2021), where she is currently a Dr.P.H. candidate in environmental health and health security. She received her M.Sc. in global mental health from the London School of Hygiene and Tropical Medicine (2014) and a B.A. in anthropology from Union College (2012).

**Matthew Masiello, M.P.H.,** is an associate program officer on the Board on Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine where he supports projects that focus on health security and public health emergency preparedness and response. He completed his M.P.H. in May 2021 at Emory University Rollins School of Public Health, where he focused on disaster epidemiology and COVID-19 vaccine uptake. His thesis measured COVID-19 vaccine intent among the Emory student body and captured predictors for vaccine uptake and hesitancy. While completing his M.P.H., Mr. Masiello interned at the Council for State and Territorial Epidemiologists where he supported the Tribal Epidemiology Subcommittee and the Epidemiological Capacity Assessment. Prior to his

M.P.H. program, Mr. Masiello spent 3 years at the National Academies supporting four consensus studies across the Health and Medicine Division. He earned his B.A. at American University in May 2016.

**Margaret McCarthy, M.Sc.,** is a research associate with the International Networks and Cooperation Theme within the Policy and Global Affairs Division. For the last 2.5 years, she worked with the Board on Health Sciences Policy within the Health and Medicine Division on projects related to health security and pandemic preparedness. Before joining the National Academies, Ms. McCarthy worked at Brigham and Women's Hospital in the Division of Infectious Diseases. She graduated from American University with a B.A. in international studies and a master's degree in global health and development from University College London. She is currently pursuing an online, part-time master's degree in global security from King's College London.

**Burgess Manobah, M.D., M.P.H.,** is a research associate at the Health and Medicine Division (HMD) Executive Office. He is from Liberia, West Africa, and a physician by training. He obtained his undergraduate degree in biology (B.Sc.) from Cuttington University in Suakoko, Liberia, in 2010 and subsequently enrolled at the A.M. Dogliotti College of Medicine, University of Liberia, where he obtained his doctor of medicine (M.D.) degree in 2016. He worked at multiple hospitals in different regions within his native country (Liberia) and completed a general surgery residency at the J.F.K. Memorial Hospital in Sinkor, Liberia, in June 2021. In August 2022, he obtained a master of public health (M.P.H.) degree from Johns Hopkins University Bloomberg School of Public Health in Baltimore, Maryland. He has had several international trainings and certifications and holds a professional membership with the Liberia College of Physicians and Surgeons. He has worked with multiple nongovernmental organizations and international organizations, with the World Health Organization (WHO) being top of the list. His areas of interest include trauma/injury prevention, food and nutrition research, and the use of Health in All Policies (HiAP) approach in bettering the lives of the population.

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**Ilana Goldowitz, Ph.D.,** supported the study as the science writer and is a scientific writer and consultant and the owner of Striga Scientific, LLC. She obtained her Ph.D. from Harvard University's chemical biology program in 2015 and her B.S. from Cornell University's plant sciences program in 2008. Her Ph.D. dissertation research at the Harvard School of Public Health focused on malaria transmission biology. Ilana writes about a variety of topics but is especially interested in infectious diseases, immunology, drug development, host–pathogen and host–microbe biology, and agricultural plant pathology.

**Jacqueline Brenner, B.S.,** supported the study as an intern and is an M.D./M.P.H. candidate at the University of Miami Miller School of Medicine, class of 2026. As part of her M.P.H. Capstone project, she supported the activity on examining the working definition for Long COVID with Lisa Brown and Dr. Harvey Feinberg as her advisors. She was an elected National Institutes of Health IRTA Summer Fellow in 2023, and worked under Dr. Bradford Wood, melding technology, AI, and immunology in interventional radiology. She is a cofounder of SIA Precision Education, which harnesses Al to revolutionize medical education; founder and CEO of Scope, an AI-based medical social media platform; and founder of STEM Potential, a science-based mentorship network. She continues to conduct research on the importance and future applications of AI in medical education under Dr. Gauri Agarwal at the University of Miami Miller School of Medicine. Additional research in neurosurgery at the University of Miami Neurosurgery Lab delves into advanced applications of focused ultrasound for treating neurological diseases in the scope of global health and investigates the use of connectomics to understand the effects of brain tumors.