Advancing Toward Recovery from Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

NIH RECOVER Initiative

NIH Advisory Committee to the Director Meeting

June 9, 2022

Walter J. Koroshetz, MD
Director, NINDS

RECOVER
Researching COVID to Enhance Recovery

NIH National Institutes of Health
Researching COVID to Enhance Recovery

Short- and Long-term Rates of Post-acute Sequelae of SARS-CoV-2 Infection: A Systematic Review

(57 studies, Total n=250,351 COVID-19 survivors , 79% hospitalized)
At six month time point 55% were judged to have at least one sequelae of COVID-19 infection.

- **Frequency of PASC varies widely depending on time from infection and severity of illness (e.g., 5-80%).**
- **Heterogeneous symptom set.**

JAMA Network Open

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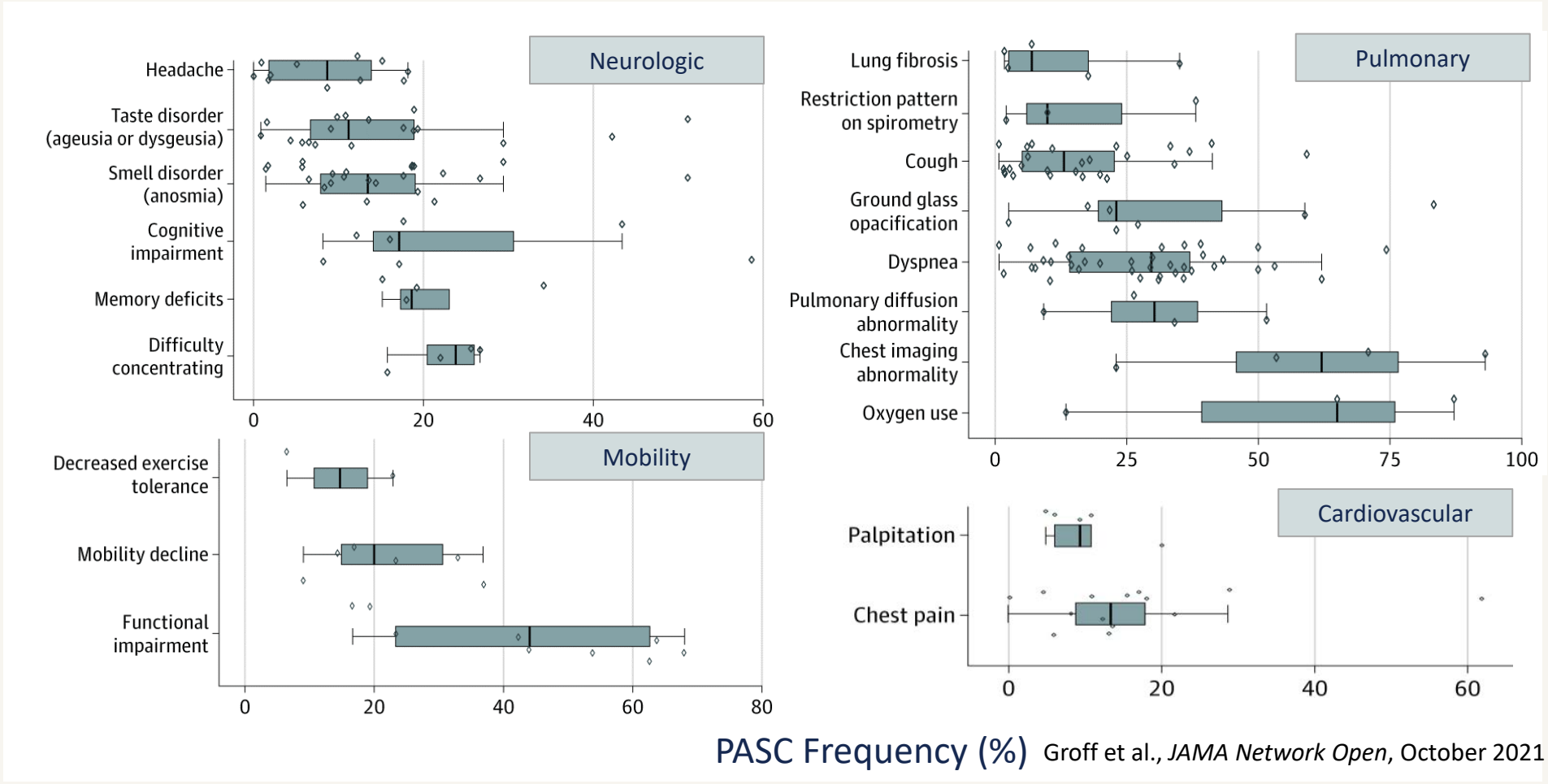

PASC Frequency (%) Groff et al., *JAMA Network Open*, October 2021

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JAMA Network Open

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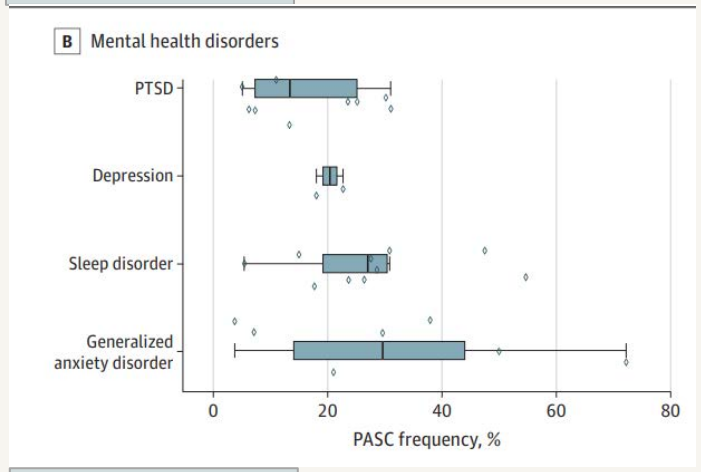
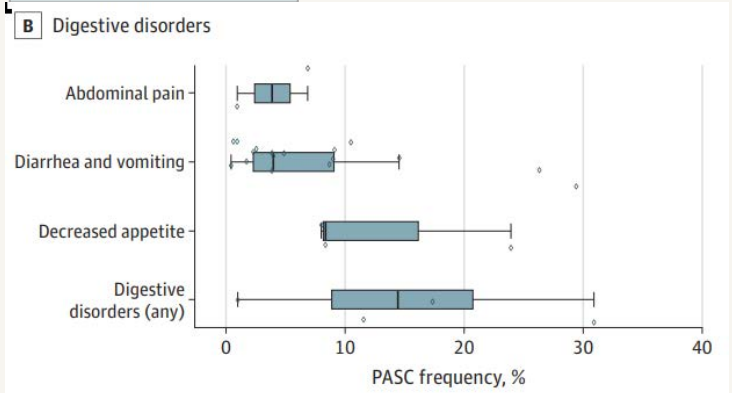
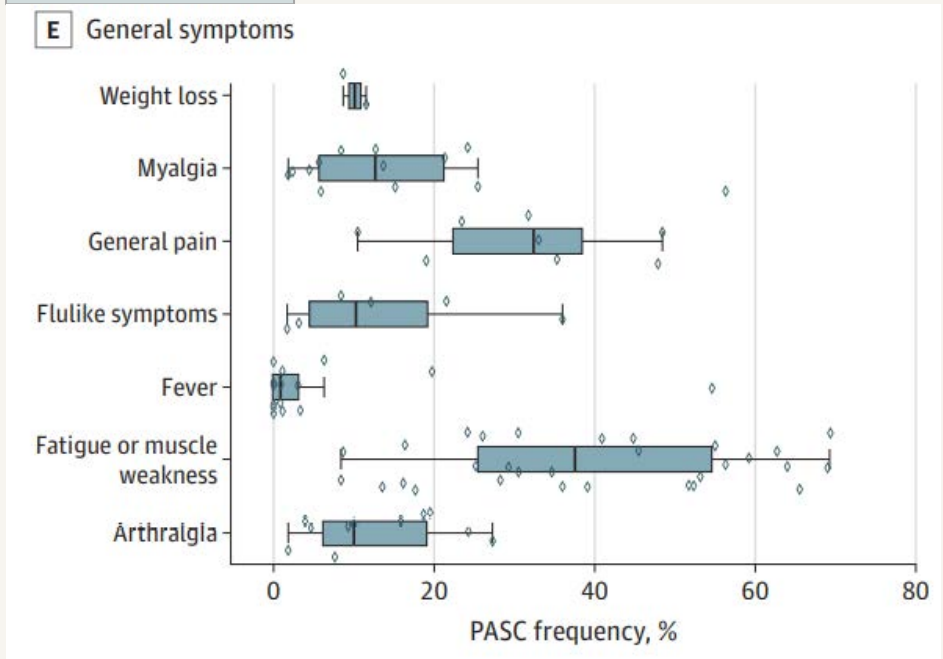
Mental Health



Digestive



General Symptoms



PASC Frequency (%)

Groff et al., *JAMA Network Open*, October 2021

Post-COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020 –November 2021

Lara Bull-Otterson, PhD1; Sarah Baca1,2; Sharon Saydah, PhD1; Tegan K. Boehmer, PhD1; Stacey Adjei, MPH1; Simone Gray, PhD1; Aaron M. Harris, MD1

MMWR / May 27, 2022 / Vol. 71 / No. 21

Followed patients in Cerner Electronic Health Records for incident conditions occurring after 30 days of infection vs. control group without infection. Hospitalization status not defined.

- 38% of previously infected individuals developed an incident condition compared with 16% of controls.
- One in five COVID-19 survivors ≥ 18 years old experienced an incident condition that might be attributable to previous COVID-19.
- One in four survivors aged > 65 did so.

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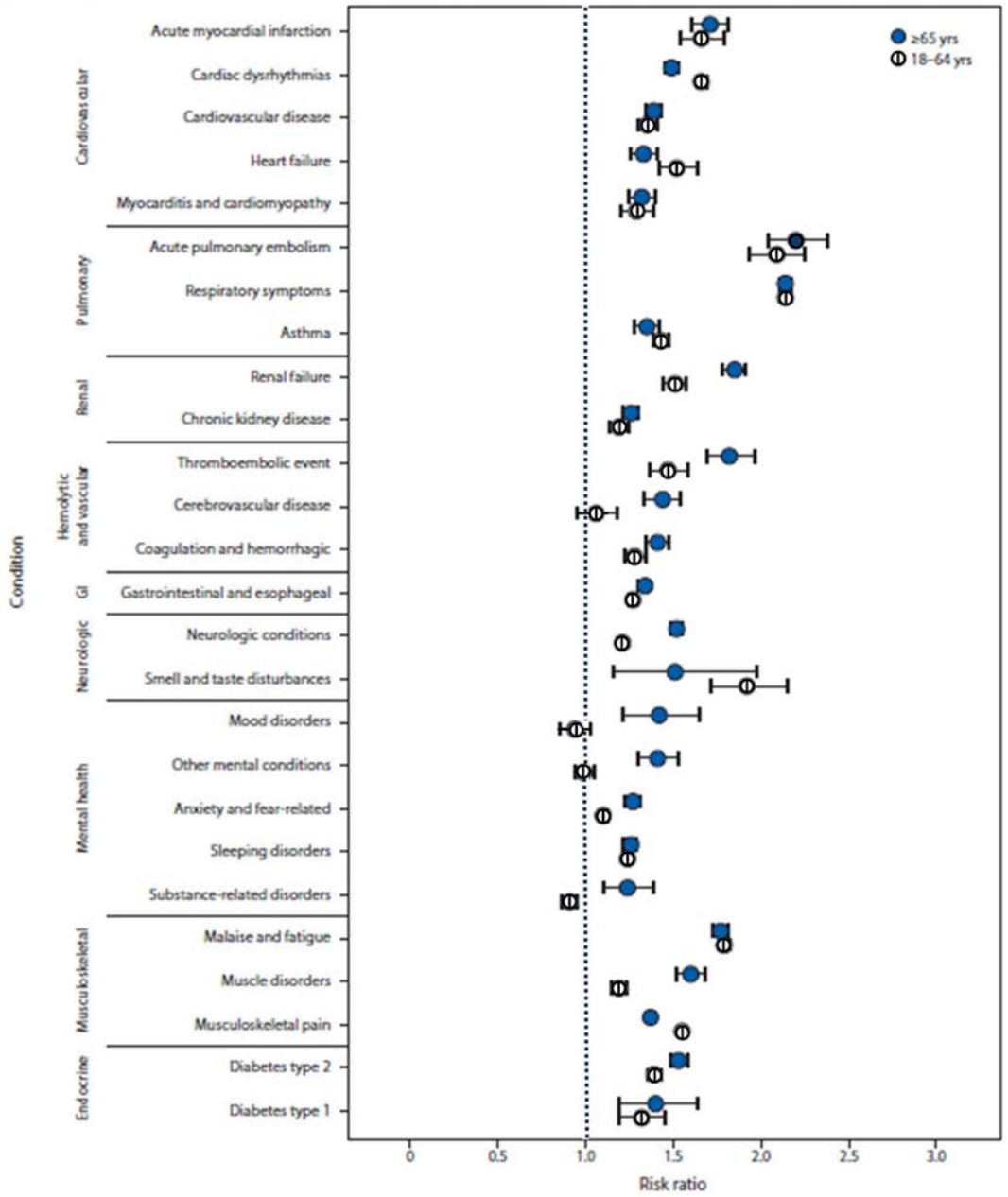
FIGURE. Risk ratios* for developing post-COVID conditions among adults aged 18–64 years and ≥65 years — United States, March 2020–November 2021



Abbreviation: GI = gastrointestinal.
* With CIs indicated by error bars; some error bars are not visible because of small CIs.

UK Office for National Statistics:

Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021

- Persistent symptoms after 12 weeks of acute infection are **3.0% based on tracking specific symptoms, to 11.7% based on self-classification** of long COVID, using data to 1 August 2021.
- Among study participants **with COVID-19, 5.0% reported any of 12 common symptoms** 12 to 16 weeks after infection; however, **prevalence was 3.4% in a control** group of participants without a positive test for COVID-19, demonstrating the relative commonness of these symptoms in the population at any given time.
- Among study participants with COVID-19**, 3.0%** experienced any of 12 common symptoms for a **continuous period of at least 12 weeks** from infection, compared with **0.5% in the control** group.
- Prevalence of **self-reported long COVID is 11.7%** of study subjects experiencing long COVID (based on self-classification rather than reporting one of the 12 common symptoms) 12 weeks after infection, falling to 7.5% when considering long COVID that resulted in limitation to day-to-day activities; these percentages increased to 17.7% and 11.8% respectively when considering only participants who were symptomatic at the acute phase of infection.
- Prevalence was highest in **females, adults aged 50 to 69 years, people with a pre-existing** health condition, and those with **signs of high viral load at the time of infection.**

ICD-10 code for “post COVID-19” condition (U09.9) available October 1, 2021

- Large, mostly private, insurance database with 1,959,982 COVID-19 patients.
- 4% with diagnosis of Post COVID condition (U09.9)10/1/21-1/31/22
  - 24% of those with Post COVID dx. were hospitalized vs. 8.4% of total infected
    - 75.8 % of those with Post COVID dx. were not hospitalized
    - 81.6% of females with Post COVID dx. were not hospitalized
  - Most common co-occurring conditions
    - Breathing abnormality 23.2%
    - Cough 18.9%
    - Malaise and fatigue 16.7%
    - Increased risk of: “unspecified myopathy” (11x’s), Pulmonary embolism (2x’s), other disorders of the brain (2x’s)

BRIEFING ROOM

Memorandum on Addressing the Long-Term Effects of COVID-19

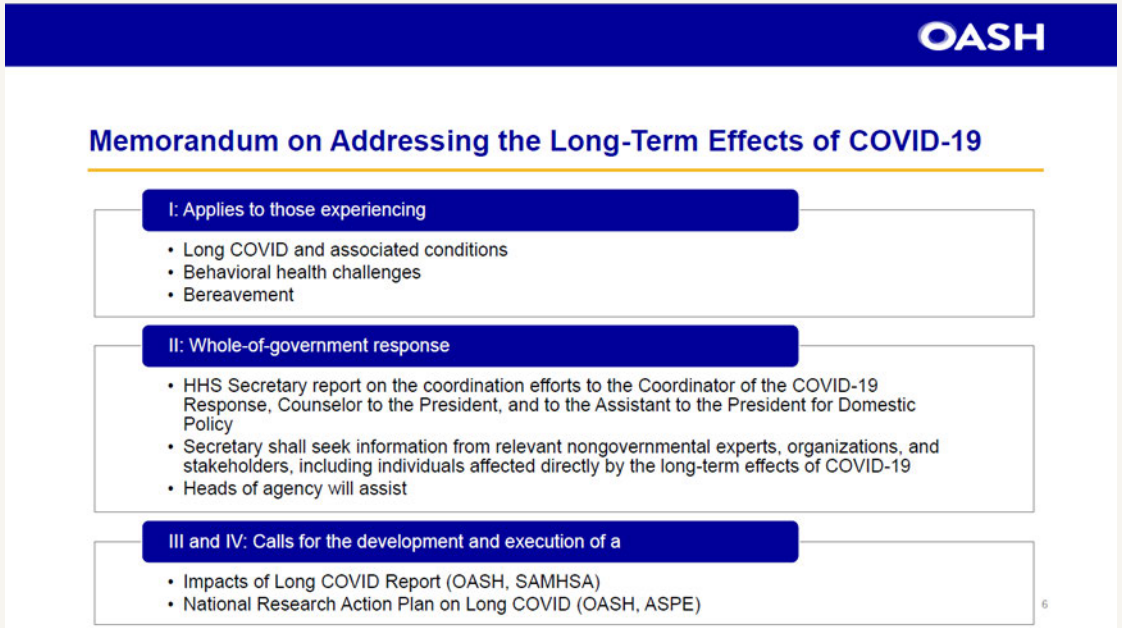
APRIL 05, 2022 • PRESIDENTIAL ACTIONS

MEMORANDUM FOR THE HEADS OF EXECUTIVE DEPARTMENTS AND AGENCIES

SUBJECT: Addressing the Long-Term Effects of COVID-19

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. Policy. My Administration has made combating the coronavirus disease 2019 (COVID-19) pandemic, and guiding the Nation through the worst



- **Study of 175 COVID-19 patients.**
- **In contrast to the elevated IgG3 levels in both mild and severe COVID-19 cases, IgG3 showed a trend to being lower in patients developing PACS.**
- **Patients with both high IgM and high IgG3 were less likely to develop PACS.**

nature COMMUNICATIONS

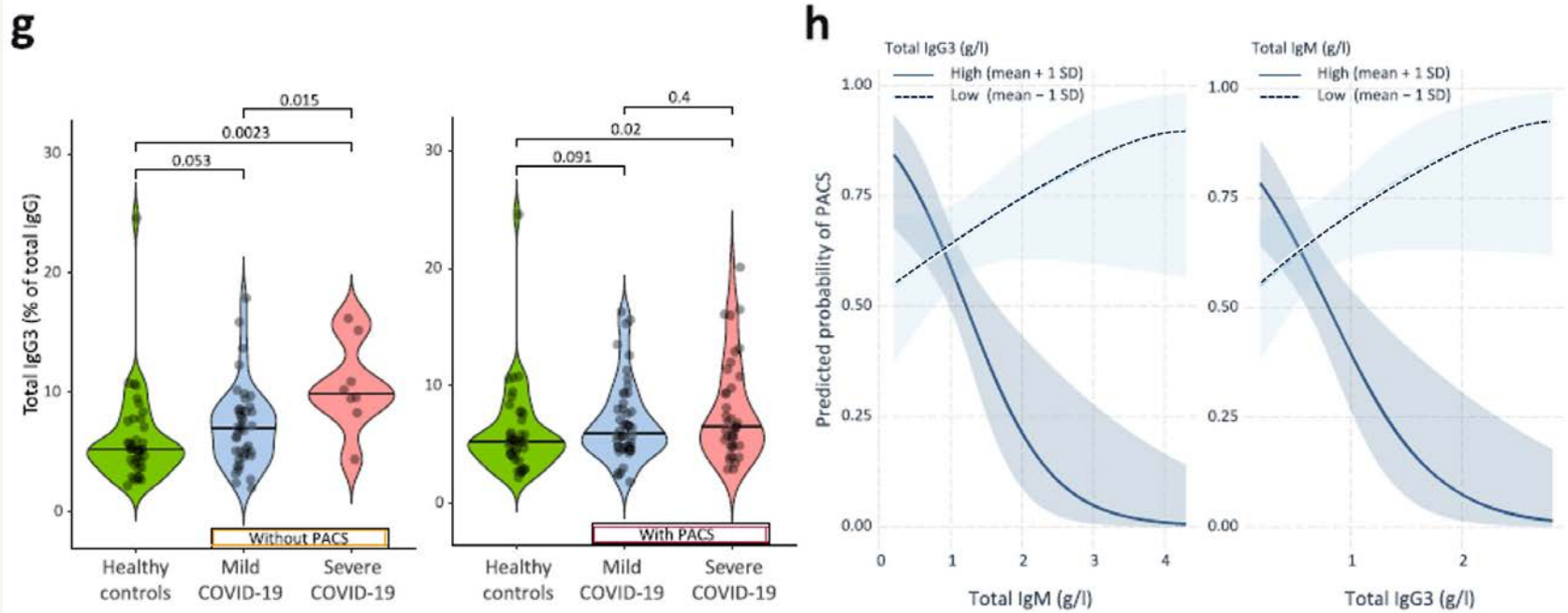
ARTICLE

https://doi.org/10.1038/s41467-021-27797-1 OPEN

Check for updates

Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome

Carlo Cervia[1], Yves Zurbuchen[1], Patrick Taeschler[1], Tala Ballouz[2], Dominik Menges[2], Sara Hasler[1], Sarah Adamo[1], Miro E. Raeber[1], Esther Bächli[3], Alain Rudiger[4], Melina Stüssi-Helbling[5], Lars C. Huber[5],

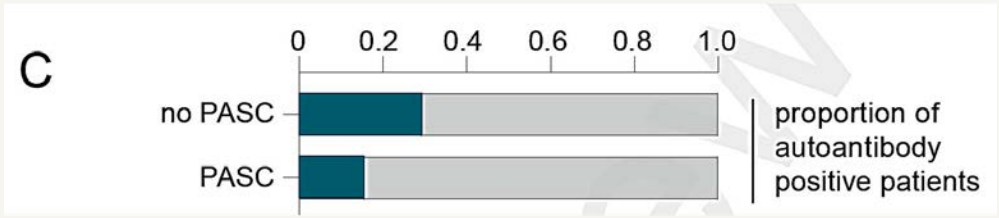


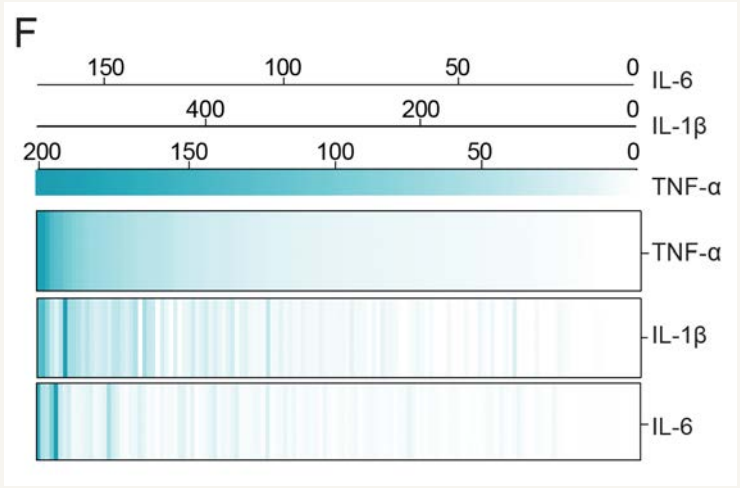
From online data collection to identification of disease mechanisms: The IL-1ß, IL-6 and TNF-α cytokine triad is associated with post-acute sequelae of COVID-19 in a digital research cohort.

Christoph Schultheiss, Edith Willscher, Lisa Paschold, Lidia Bosurgi, Jochen Dutzmann, Daniel Sedding, Thomas Frese, Matthias Girndt, Jessica Höll, Michael Gekle, Rafael Mikolajczyk, Mascha Binder

medRχiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

- The analysis is based on 258 persons eight months after mostly mild infection from Halle Germany. PASC were reported in 40% of cases at 6 months and consisted predominantly in fatigue, dyspnea and concentration deficit.

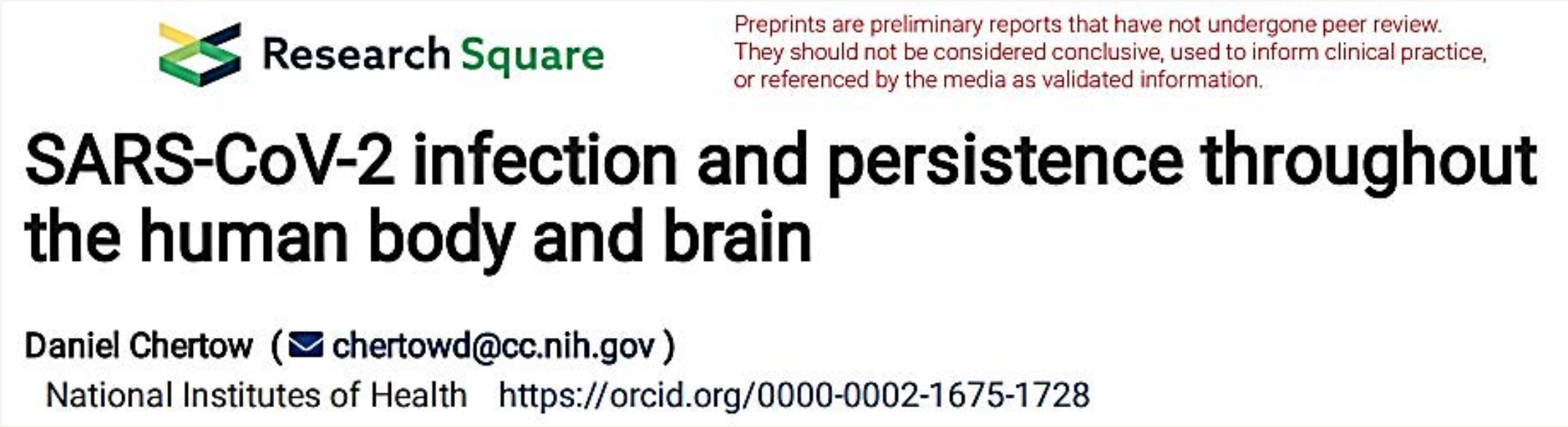




Correlation of TNF-α, IL-1β and IL-6 plasma levels in patients with ongoing PASC. Concentrations shown as pg/ml.

- The recovery from PASC was not associated with post-infection vaccination suggesting that it may not be driven by a cryptic SARS-CoV-2 reservoir.
- We confirmed the high percentage of individuals with autoantibodies after COVID-19, but found no association with PASC.
- Data show that a broad range of cytokines remain deregulated long after infection, IL-1ß, IL-6 and TNF-α represented a triad that was associated with PASC.
- Blood profiling and single-cell data from early infection indicated that these cytokines are induced in COVID-19 lung pro-inflammatory macrophages creating a feedback loop that may trigger their long-term activation.

Is there persistence of viral material?



- **Autopsies on 44 COVID-19 patients from acute infection through over 7 months following symptom onset.**
  - SARS-CoV-2 is widely distributed even in patients who died with asymptomatic or mild infection.
  - Virus replication is present in multiple pulmonary and extrapulmonary tissues early in infection.
  - RNA in multiple anatomic sites, including brain, for up to 230 days after symptom onset.
  - Paucity of inflammation or viral cytopathology outside the lung.

https://videocast.nih.gov/watch=45296

Advancing Toward Recovery from Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

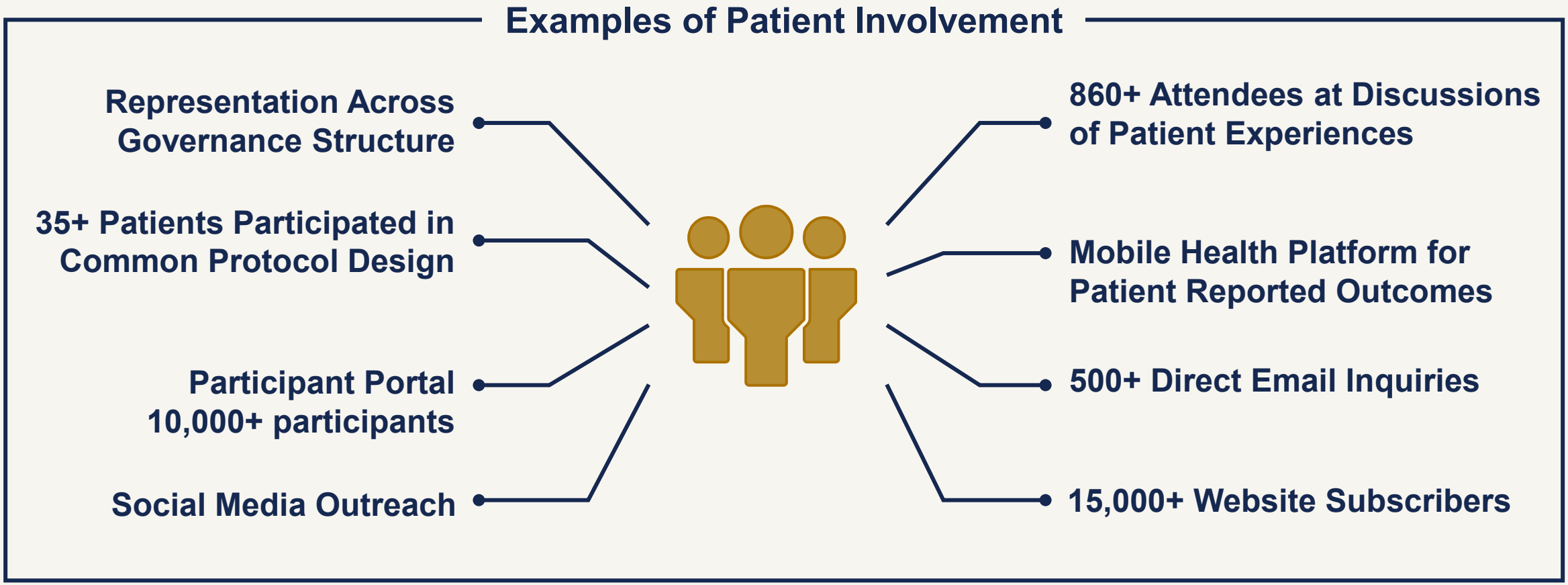
NIH RECOVER Initiative

RECOVER Listening Sessions

Videos available: https://recovercovid.org/news-events

RECOVER Patient-Centered Approach

Patient perspectives are a critical element of the RECOVER Initiative and **patient engagement is integral** to every element of the program.



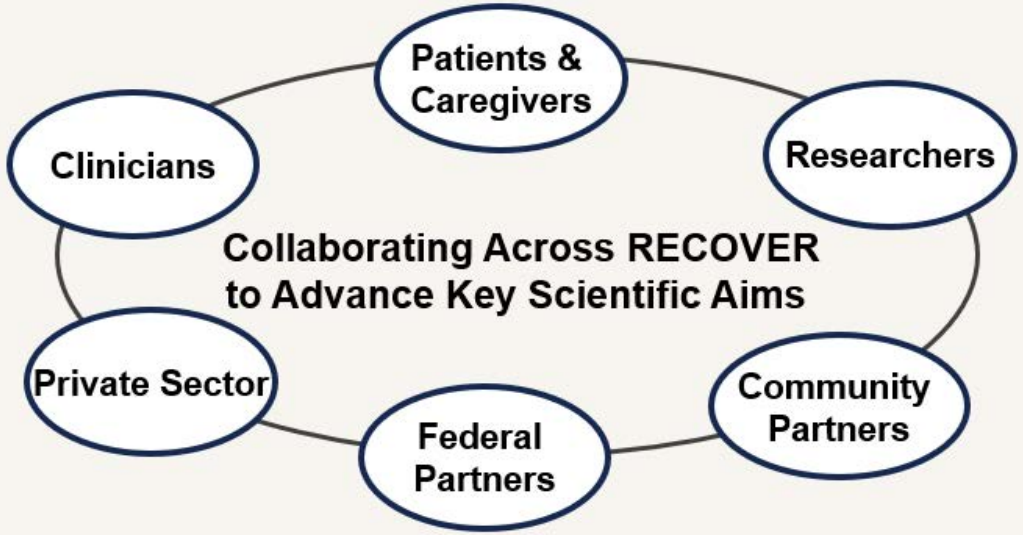
NIH RECOVER Initiative

Goal

Rapidly improve our **understanding** of and ability to **predict, treat, and prevent** PASC

Key Scientific Aims

1. Understand clinical spectrum/biology underlying recovery over time
2. Define risk factors, incidence/prevalence, and distinct PASC sub-phenotypes
3. Study pathogenesis over time and possible relation to other organ dysfunction/disorders
4. Identify interventions to treat and prevent PASC



Guiding Principles

Patient-centered, participants as partners

National Scale with Inclusive, **diverse** participation & community engagement

Platform protocols, standardized methodologies, and common data elements

Adaptive approaches based on emerging science

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RECOVER Study Components

RECOVER Cores

Clinical Trial Data Cord. Center	Clinical Science Core	Data Resource Core	Biorepository Core

Elements





RECOVER Clinical Trials	RECOVER Enrolling Cohorts	EHR/ Health Systems Studies	Pathobiology Studies	Autopsy Pathology Studies
Clinical Platform with Multi-therapeutic domains	**~40,000** participants	**60 million+** records; **~4 million+** COVID cases	Mechanistic studies of pathogenesis	**50+** tissue types

Data Resources

Clinical	Imaging	Mobile and Digital Health	EHR / Other Real-World Data	Pathology

RECOVER Cohorts: A National Scale Platform

- **Clinical Cohort Studies, Adult and Pediatric**
  - **30 Hubs:**
    - 15 Adult Cohorts
    - 2 Pregnancy Cohorts
    - 8 Pediatric Cohorts
    - 5 Autopsy Centers
- **EHR Studies, Adult and Pediatric**
  - 60,000,000+ patient records

Enrolling participants from 200+ sites across the Nation

(Will also include clinical trials and patient registry)

RECOVER Cohorts: A National Scale Platform
Current Enrollment (as of May 31, 2022)

Clinical Cohort Studies, Adult and Pediatric

- Adult Population
  - **3,712** participants across 58 sites
- Pediatric cohort
  - **91** participants across 8 sites
- Autopsy cohort
  - **15** participants across 3 sites

Achieving Depth and Breadth in RECOVER Cohorts

Acute and post-acute cohort studies will use platform-protocol driven tiered approach to **characterize the trajectory of recovery over time and compare those who make a good recovery with those that develop PASC.**

Blank	ACUTE INFECTION COHORT	POST-ACUTE INFECTION COHORT
Overview	• Patients with confirmed acute SARS-CoV-2 infections • Prospectively followed for PASC, nested PASC cases vs. controls	• PASC patients 4+ weeks after acute SARS-CoV-2 infection • Matched PASC case-control design • Prospective and Retrospective data capture
Adults	**9k**, including 200+ pregnant persons	**9k**, including 2k pregnant persons
Children	**1k**	**18k**, including 800 with **MIS-C**

Adult Study Overview

Recruitment in 33 states + Washington, DC and Puerto Rico
Hospitals/Clinics/Communities/Electronic Health Records
Diverse population with and without COVID-19
Adults/Pregnant women

↓

Tier 1 Surveys, Labs, Biospecimens, Minimal Exam (17,680 participants)

↓

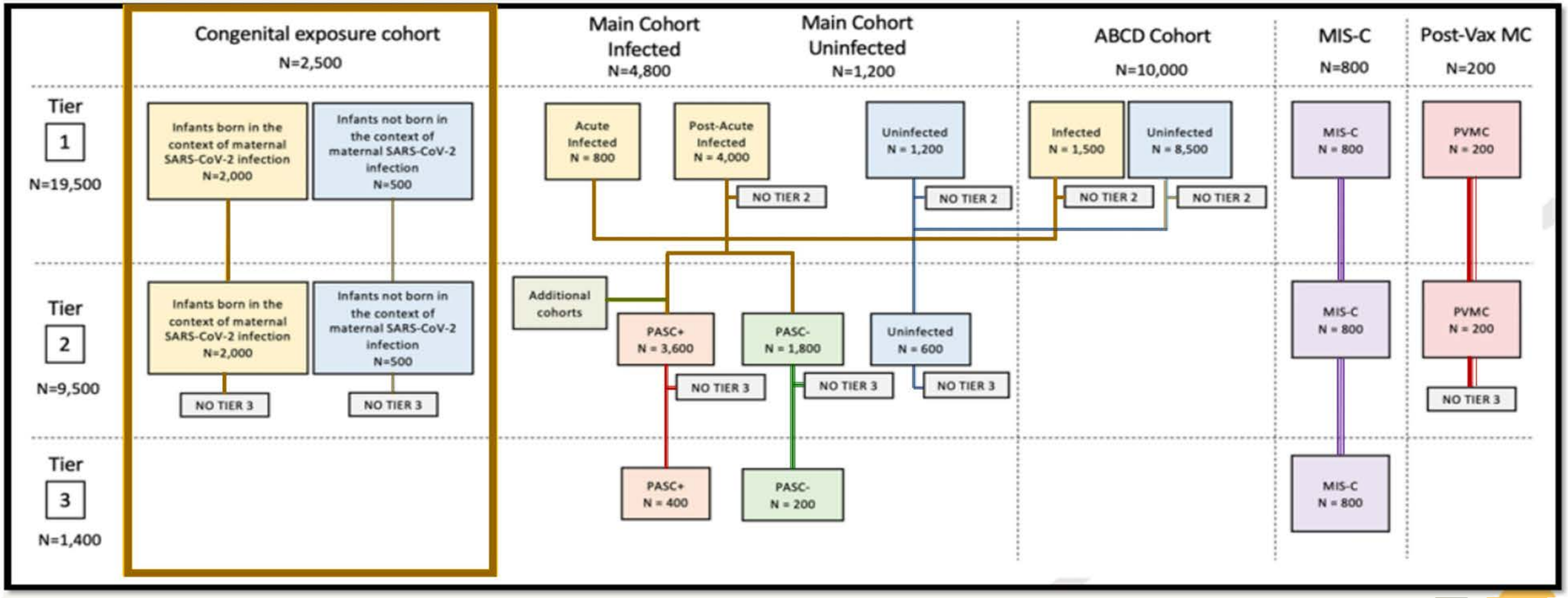
Tier 2 Low Risk Clinical Tests (5,300 participants)

↓

Tier 3 Advanced Testing (3.500 participants)

RECOVER PEDIATRIC COHORT STUDY

Overview of Enrollment for RECOVER Meta-Cohort



RECOVER
Researching COVID to Enhance Recovery

Goal of RECOVER | Who can join? | How it works | Learn more

Welcome to RECOVER Studies

Funded by the NIH, **RECOVER** is a research project that aims to learn about the long-term health effects of COVID, including what is sometimes called Long COVID. We need adults and kids who have and have not had COVID to join **RECOVER** and help us find answers to Long COVID.

Together, we can make progress towards recovery.

Find Studies near you at:
studies.recovercovid.org

Find a RECOVER study site and join today

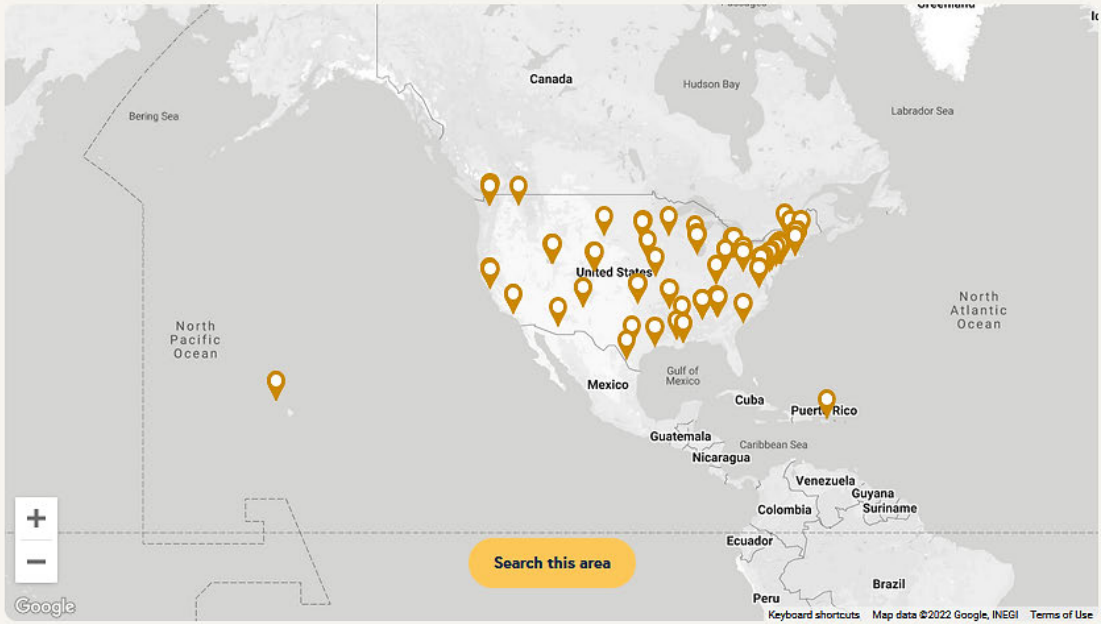
There are more than 80 sites in over 30 states, with more sites opening up all the time.

I want a study site enrolling | Enter a zip code | Find study site

How to use this map

You can join any study site.

1. Select a study site that is enrolling the study group you want to join
2. Enter a zip code
3. Click "Find study site"
4. Click the "Ask to join" button to contact a study site



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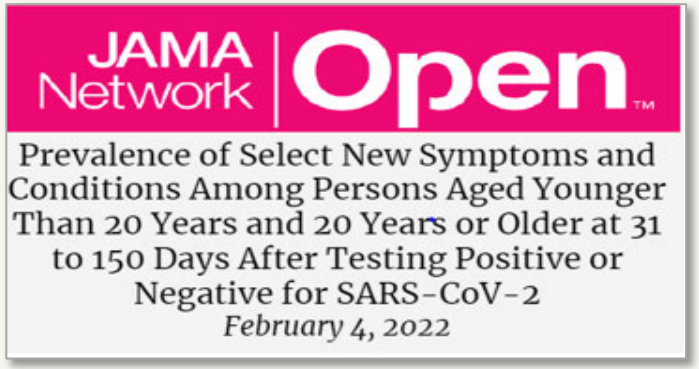
Challenges

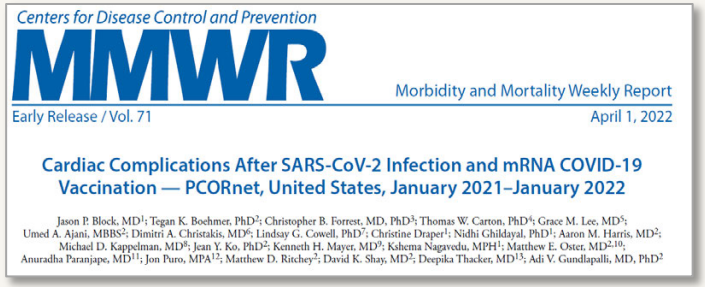
- Dynamic nature of pandemic
- Hurdles in enrollment
- Need for urgency
- Breadth and depth of protocol questionnaires and testing; frequency of multiple symptoms
- Wide heterogeneity of symptoms and clinical course within and across age group → will need
  - Adequate breadth and depth in clinical trial portfolio
  - Additional ancillary studies and assays to diagnose and monitor

RECOVER
Researching COVID to Enhance Recovery

RECOVER Electronic Health Record Studies: Addressing Key Public Health Questions at National Scale

- **NC3 and PCORnet- major electronic health record systems encompassing 60 million+ adult and pediatric patient records**
- Addressed key issues such as:
  - **PASC and PASC sub-phenotypes**
  - **PASC Cardiac complications**
  - **Development of new onset diabetes as part of PASC**
  - **Syndromic, systemic, and medication features of PASC**
  - **Impact of COVID-19 Vaccination and Viral Variants on PASC**
  - **PASC in children and adolescents**
  - **Racial, ethnic, and socioeconomic disparities in PASC**
- **Advanced and accelerated public health research by developing for broad use:**
  - **Validated machine learning methods and usage of ICD-10 codes for identifying PASC**
  - **Post-acute SARS-CoV-2 computable phenotype definitions**
  - **Best practices in use of AI, ML, NLP in analysis of COVID EHR and RWD**





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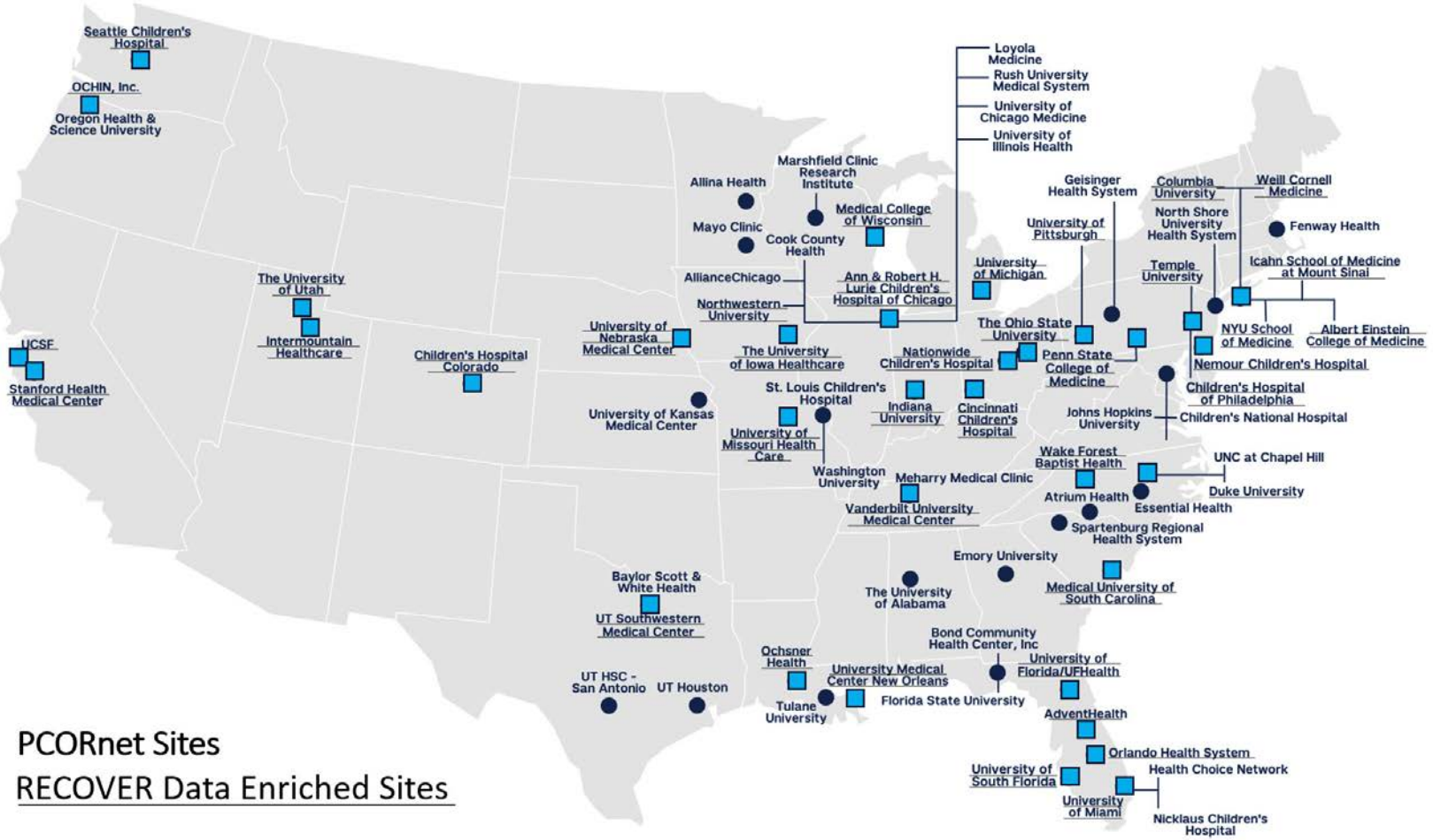
PCORnet & RECOVER (n=41) Sites

Funded by PCORI in 2014



158+ rows of data

- Electronic health records
  - >10m patients
  - structured
  - unstructured (Q3)
- Public payor data
- Exposome data
  - race/ethnicity
  - socio-economic
  - environmental
- Vaccine data

pcornet

RECOVER **Clinical Pathobiology** ROA

Overview

ROA released to Consortium Investigators on 12/7/2021

Focuses on examining the clinical pathobiology of PASC by leveraging the RECOVER cohort samples and data, limited to sites participating in the RECOVER PASC Consortium

Objectives:

1) To make rapid progress in understanding the clinical manifestations of PASC and the mechanisms leading to the various symptoms, dysfunction of multiple organs and biologic systems, and phenotypes seen in PASC patients
2) To inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the pathobiological mechanisms and pathways underpinning PASC, the molecular mediators of its protean symptomology, and possible multiple clinical clusters/sub-phenotypes

Application deadline was 1/31/2022

Requirements

- Be part of a RECOVER Cohort Site with a fully executed contract with the NYU CSC OR RECOVER Enrolling Sites operating under a RECOVER hub
- Have the potential to lead to rapid delineation of the pathogenesis of PASC clinical symptomatology, multi-organ dysfunction, and patients' sub-phenotypes to foster progress in diagnostic, therapeutic, and preventative avenues for PASC
- Rapidly share data and biospecimens with the NIH RECOVER data and biospecimen repositories and broader research community
- Pledge to rapidly submit results for publication
- Have a budget that does not exceed maximum direct cost of $500K per year and maximum total costs of $800K per year

RECOVER **Pathobiology** NOSI

Overview

NOSI released to Consortium Investigators on 12/7/2021

Focuses on advancing understanding of the pathobiological underpinnings of PASC; limited to series of activity codes for parent award

Objectives:

1) To make rapid progress in understanding the biological mechanisms underlying the pathogenesis of PASC (including the viral-host interactions that result in PASC)
2) To inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the pathogenesis of PASC and the identification of associated mechanistic pathways

Application deadline was 1/24/2022

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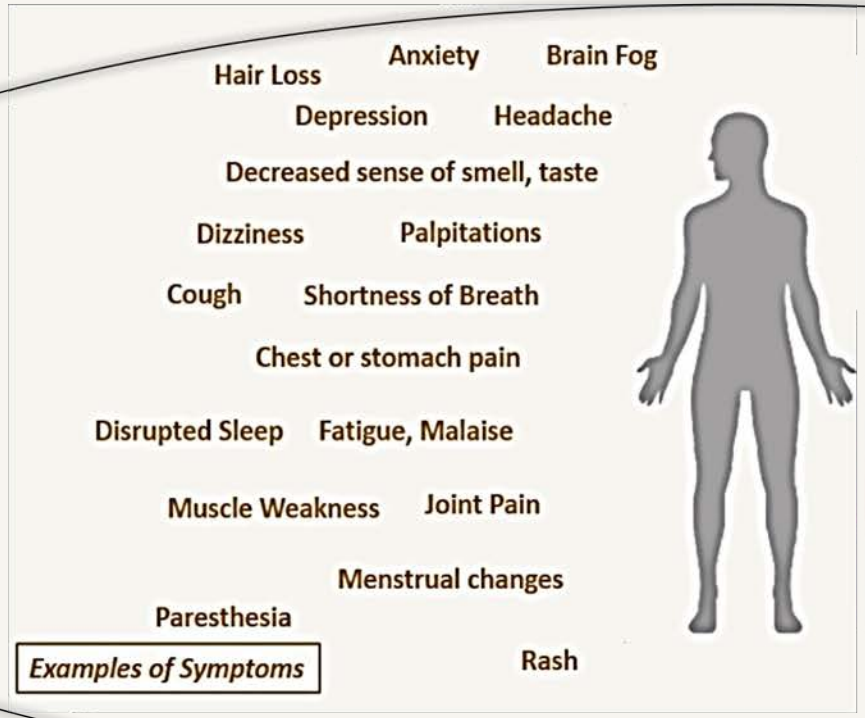
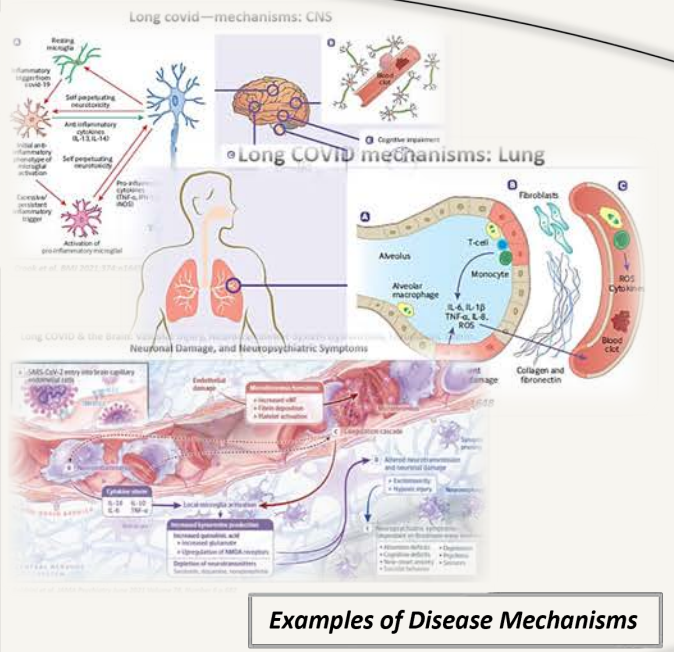
Requirements

- Have an active NIH parent award
- Describe how the project will inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the pathogenesis of PASC and identification of associated mechanistic pathways
- Provide rationale to justify the use and appropriateness of NHP or animal models (if utilizing)
- Describe plans to address relevant biological variables, such as sex
- Describe plan for rapidly sharing data and biospecimens with NIH RECOVER data and biospecimen repositories and broader research community
- Describe plan to rapidly submit results for publication
- Have a budget that does not exceed a maximum direct cost of $750K

RECOVER Clinical Trials for Identifying Treatment and Preventive Strategies for PASC: Key Features





- **Informed by patient and practitioner views on symptoms/symptom clusters and meaningful outcomes.**
- **Interventions addressing symptoms/symptom clusters and targeting specific disease/biologic pathways leading to PASC.**

Preparing for PASC Clinical Trials: Prioritization PASC Interventions

Landscape Analysis

Patient and Practitioner Perspectives on Health Impact of Symptoms/ Symptom Clusters

Intervention & Outcomes Inventory Across RECOVER clinicians

EHR Analysis of Interventions in Use

Set of candidate interventions evaluated according to evidence of safety, efficacy for PASC-relevant sx, MOA, availability, feasibility

RECOVER Clinical Trial –
Data Coordinating Center

RECOVER Clinical Trials Research Opportunity Announcement – clinical trials in those over 18 years old in the prevention and/or treatment of Post-Acute Sequelae of SARS-CoV-2 infection (PASC)

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An Initiative Funded by the National Institutes of Health

Opportunity

Critical, time sensitive, and unique opportunity to:

- Fully characterize clinical course, phenotypes, and underlying pathobiology across all populations and age groups
  - ➢ Enabling treatment of symptoms and modifying the course of PASC to cure or prevent it

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Researching COVID to Enhance Recovery

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