Assessing the Public Health Threat of Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

NIH RECOVER Initiative: Briefing for the Advisory Council to the Director (ACD)

December 9, 2022

NIH Sr Oversight Committee Co-Chairs

Anthony S. Fauci, MD
Director, NIAID

Gary H. Gibbons, MD
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Walter J. Koroshetz, MD
Director, NINDS

Co-Chair Designees

Joseph Breen, PhD
Section Chief, NIAID

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RECOVER
Researching COVID to Enhance Recovery

An Initiative Funded by the National Institutes of Health

RECOVER: Characterizing a New Multisystem Disorder

Wide Clinical Spectrum of PASC Requires Multi-disciplinary Approach

Symptoms

- Fatigue
- Dizziness
- Brain Fog
- Paresthesia
- Joint Pain, Muscle Weakness
- Cough, Shortness of Breath
- Sleep Disturbance
- Chest or Stomach Pain
- Heart Palpitations
- Menstrual changes
- Depression
- Anxiety

200+ more symptoms and counting

Affected Systems

- Neurologic Impairment
- Autonomic Dysfunction
- Lung Dysfunction/Damage
- Heart Dysfunction/Damage
- Gastrointestinal Dysfunction
- Diabetes
- Kidney Damage
- Reproductive System Dysfunction
- Mental Health Disorder

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
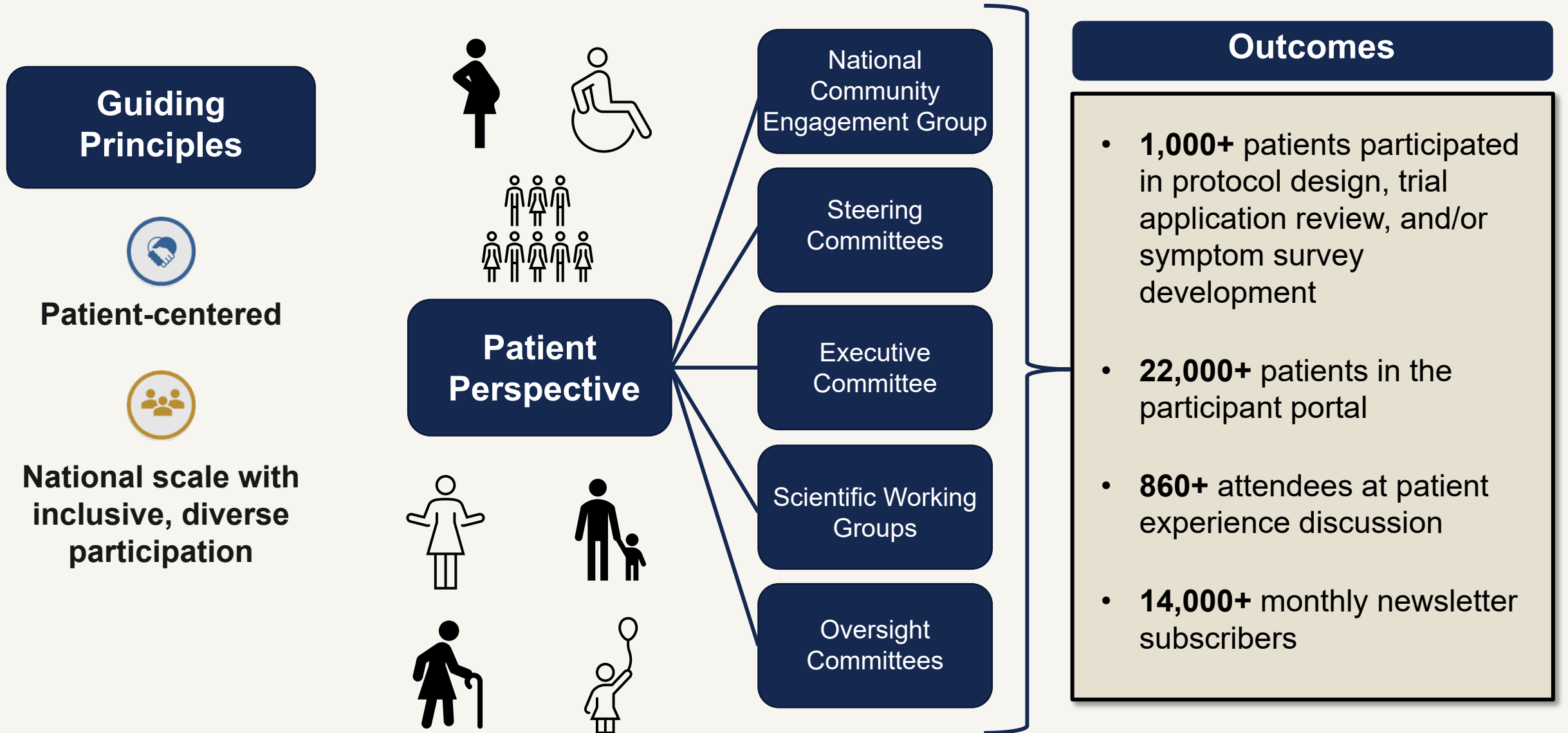
recoverCOVID.org

Research Response to PASC Across Federal Agencies

The National Action Plan outlines priorities in seven areas:

- Characterizing the full clinical spectrum of long COVID and diagnostic strategies

- Pathophysiology

- Surveillance and epidemiology

- Long COVID and overall wellbeing

- Therapeutics and other health interventions

- Human services, supports, and interventions

- Health services and health economics research

recoverCOVID.org
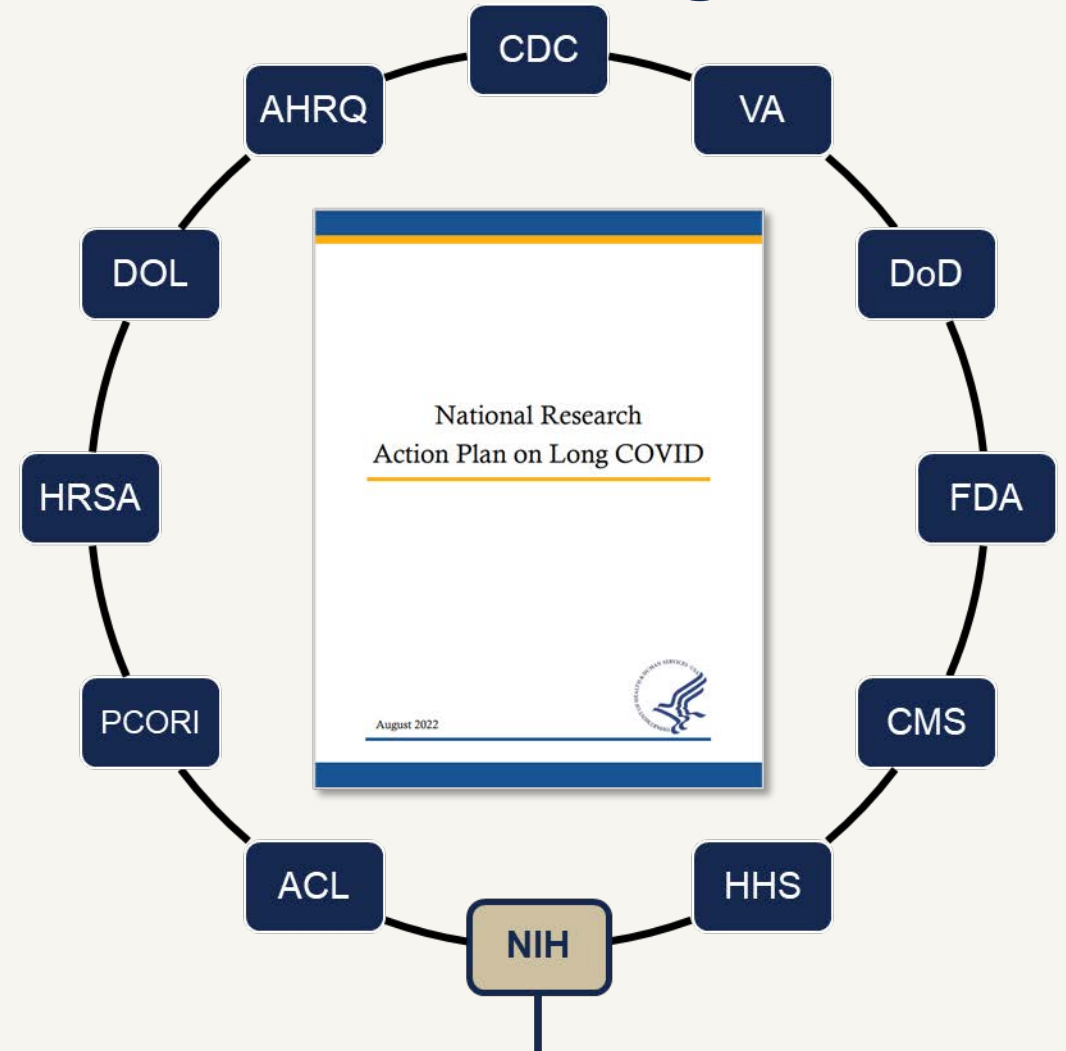
RECOVER's Principles In Action: Meaningful Patient Engagement

Guiding Principles

Patient-centered

National scale with inclusive, diverse participation

Patient Perspective

- National Community Engagement Group
- Steering Committees
- Executive Committee
- Scientific Working Groups
- Oversight Committees

Outcomes

- **1,000+** patients participated in protocol design, trial application review, and/or symptom survey development

- **22,000+** patients in the participant portal

- **860+** attendees at patient experience discussion

- **14,000+** monthly newsletter subscribers

RECOVER's Principles In Action: Building Diverse Cohorts

RECOVER has made progress toward **enriching enrollment of disproportionately affected communities from across the U.S.** by leveraging community engagement, multidisciplinary partnerships, and collaboration with patient groups.

Guiding Principles

Patient-centered

National scale with inclusive, diverse participation

Community-Campus Partnerships for Health
Promoting Health Equity and Social Justice

NIH CEAL

Institutional Development Award (IDeA) Program States

	% Entire U.S. Population[1]	% Entire U.S. COVID Cases[2]	% Adult Current Cohort (as of 11/30/22)
White	75.8	53.5	62.4
Hispanic/ Latinx	18.9	24.6	15.5
Black	12.6	12.4	16.1
Asian	5.9	4.3	7.3
Native Hawaiian/ Pacific Islander	0.2	0.3	0.4
American Indian/ Alaska Native	0.7	1.0	2.4

[1]United States Census Bureau (2021)

[2]CDC COVID Data Tracker

NIH RECOVER Initiative: Research Components

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub- Phenotypes	Pathogenesis	Interventions

Observational
- EHR Data
- Clinical Cohorts
- Community-based Cohorts

Pathobiology
- Biomarker Discovery
- Viral Persistence/Reactivation
- Immune Dysregulation
- Organ Damage/Dysfunction
- Tissue Pathology

Clinical Trials
- Drugs
- Biologics
- Devices
- Behavioral
- Complementary and Integrative Medicine

RECOVER Data Types

Imaging   Mobile/Digital Health   Clinical   EHR   Genomics   Pathology

RECOVER Cores

Patient Engagement Core	Clinical Trial Data Coordinating Center	Clinical Science Core	Data Resource Core	Biorepository Core

Progress Update: EHR/Health Systems Studies

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions
EHR/ Health Systems Studies	Clinical Cohort Studies	Longitudinal Cohort Studies	Pathobiology Studies		Clinical Trials

RECOVER EHR Cohorts: Multi-Platform Collaborative Adult and Pediatric Data Assets Facilitate Research at Large Scale

- Patient-Centered Research (PCORnet) – **38M+ records**

- National COVID Cohort Collaborative (N3C) – **16M+ records**

- *All of Us* – **9,000+ COVID cases**

- Issued **42 reports** (7 published/in press, 8 preprint, 7 submitted, 20 draft)

  - Validated machine learning 'computable phenotype' algorithms and usage of ICD-10 codes for identifying PASC

  - Incidence, prevalence, risk factors, impact of variant and vaccinations, health disparities, intervention usage

EHR Studies – Early Findings: Cross-Validating RECOVER Algorithm Identifying PASC in *All of Us*

RECOVER Key Scientific Aims

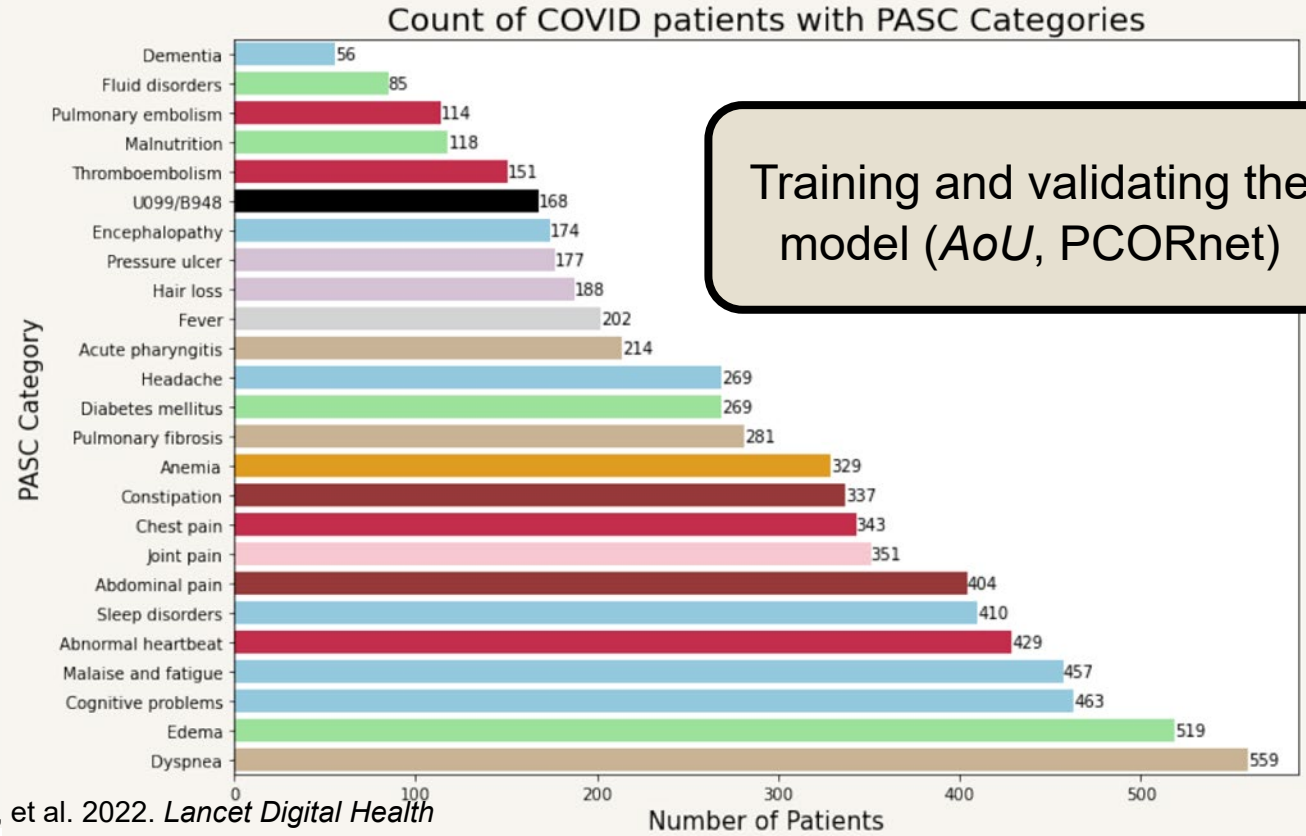| Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

Who is getting PASC?
What is the full clinical spectrum, including sub-phenotypes?

Identifying who has long COVID in the USA: a machine learning approach using N3C data

Emily R Pfaff*, Andrew T Girvin*, Tellen D Bennett, Abhishek Bhatia, Ian M Brooks, Rachel R Deer, Jonathan P Dekermanjian, Sarah Elizabeth Jolley, Michael G Kahn, Kristin Kostka, Julie A McMurry, Richard Moffitt, Anita Walden, Christopher G Chute, Melissa A Haendel, The N3C Consortium†

Created machine learning models to identify patients with potential long COVID using EHR records from N3C patients who attended long COVID specialty clinics

Training and validating the model (*AoU*, PCORnet)

Count of COVID patients with PASC Categories

PASC Category	Number of Patients
Dementia	56
Fluid disorders	85
Pulmonary embolism	114
Malnutrition	118
Thromboembolism	151
U099/B948	168
Encephalopathy	174
Pressure ulcer	177
Hair loss	188
Fever	202
Acute pharyngitis	214
Headache	269
Diabetes mellitus	269
Pulmonary fibrosis	281
Anemia	329
Constipation	337
Chest pain	343
Joint pain	351
Abdominal pain	404
Sleep disorders	410
Abnormal heartbeat	429
Malaise and fatigue	457
Cognitive problems	463
Edema	519
Dyspnea	559

Pfaff, et al. 2022. *Lancet Digital Health*

EHR Cohorts – Early Findings: Risk Factors and Sub-Phenotypes

RECOVER Key Scientific Aims

| Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

What are the risk factors and various forms of PASC?
What is the full clinical spectrum and sequelae of PASC?

PASC Risk Factors in Adults[1,2]:

- Severity of disease
- Comorbidities
  - Cancer
  - Chronic kidney disease
  - Chronic lung disease
  - Depression
  - Mental health disorders
  - Obesity
- Female sex
- Racial/Ethnic Minorities

[1]Hill et al. 2022. *medRxiv*.
[2]In review, *J. General Internal Medicine*.

137 PASC-related diagnoses

44 clinical features

21 Syndromic Clusters
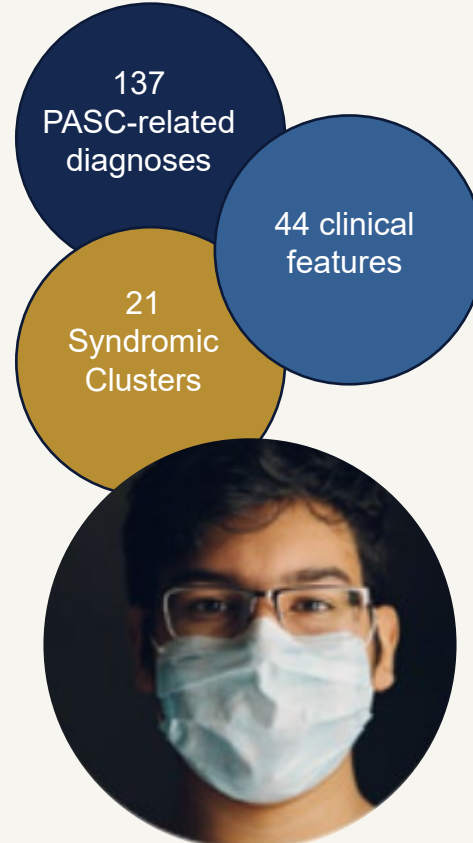
Dominant PASC Sub-Phenotypes in Adults[3,4]:

- Cardiovascular
- Respiratory
- Musculoskeletal
- Neurologic
- Digestive
- Constitutional

[3]Reese et al. 2022. *medRxiv*
[4]Zhang et al. 2022. *medRxiv*.

EHR Cohorts – Early Findings: Effect of Co-Morbidities and New Onset Conditions

RECOVER Key Scientific Aims

| Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

Does PASC increase the risk for other conditions/disorders?

Prevalence Ratios of New Conditions Among Adults with Medical Encounters 31 to 150 Days After a First SARS-CoV-2 Test Between March and December 2020
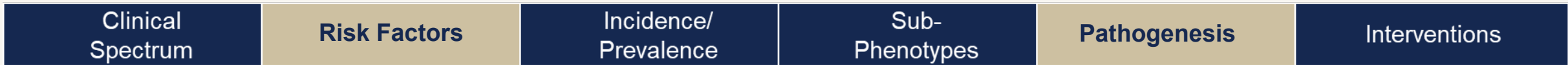
Increased risk of new onset conditions in PASC patients like

- Myoneural disorders
- Type 2 diabetes
- Anxiety and depression
- Ataxia or trouble walking

Hernandez-Romieu, et al. 2022. *JAMA Network Open.*
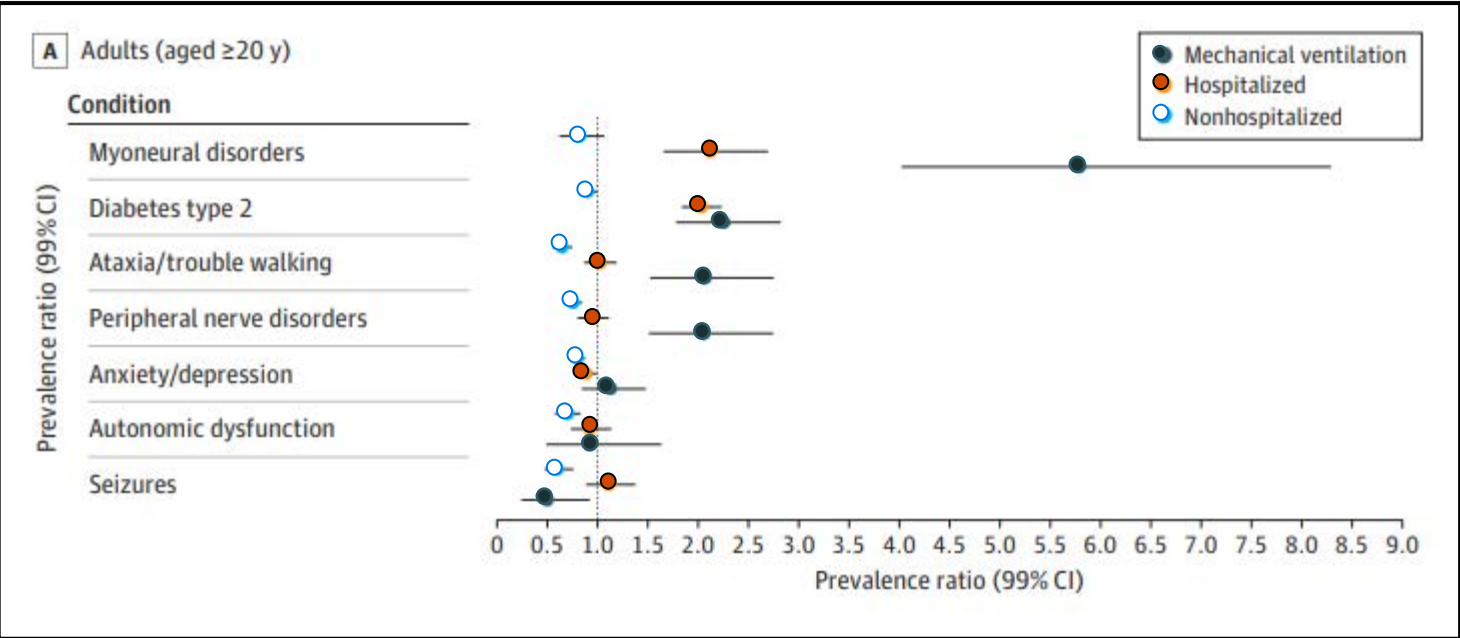
EHR Cohorts – Early Findings: Vaccination and the Risk of PASC

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

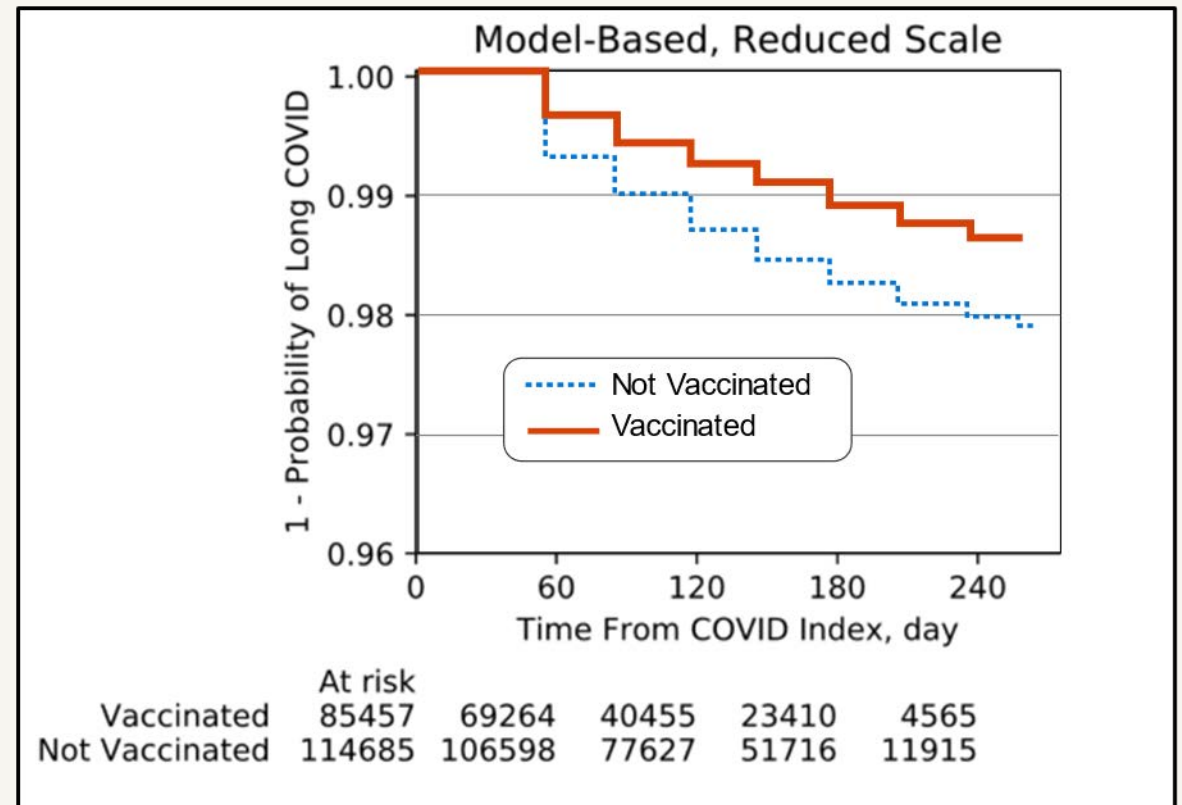> *Does vaccination protect against PASC?*

Pre-COVID vaccination associated with a **reduced risk of long COVID**

- Model-Based Cohort = ML model developed from N3C data

Model-Based, Reduced Scale

Not Vaccinated / Vaccinated

At risk
Vaccinated	85457	69264	40455	23410	4565
Not Vaccinated	114685	106598	77627	51716	11915

Brannock, et al. 2022. *medRxiv*

EHR Cohorts – Early Findings: Using EHR to Characterize PASC in Pediatric Populations

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

Who is getting PASC?
What are the various forms of and risk factors for PASC?
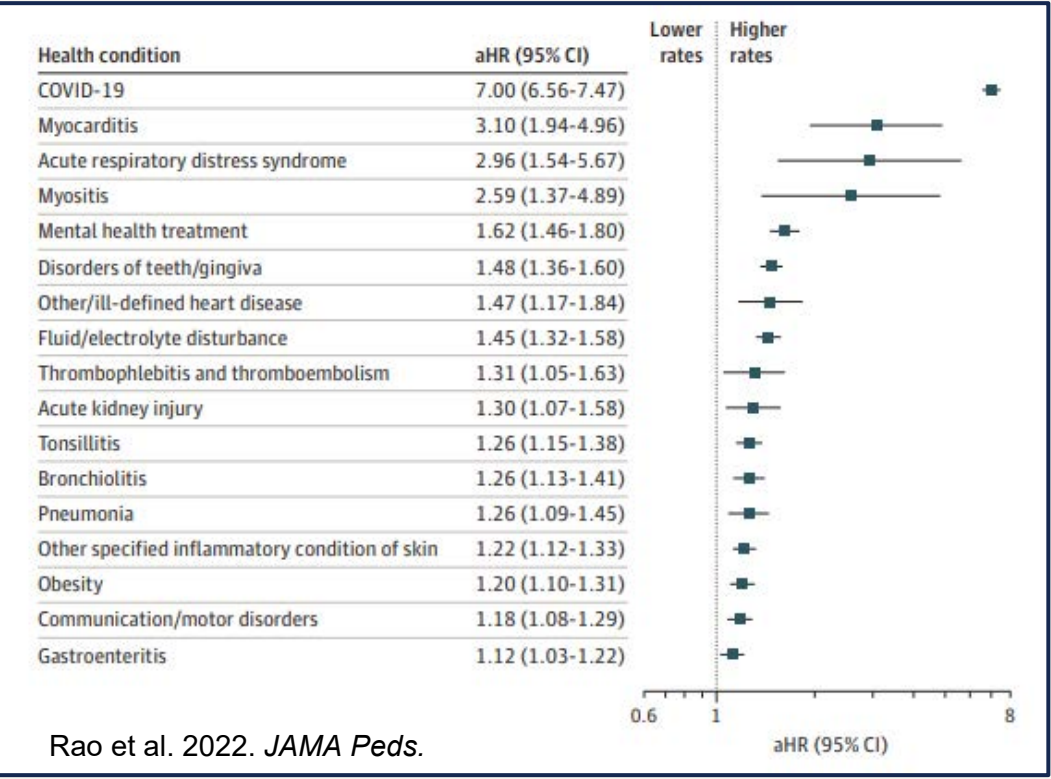*What is the full clinical spectrum, including sub-phenotypes?*

Incidence/Prevalence

3.7% of SARS-CoV-2 children go on to develop PASC.

Risk Factors

- Age < 5 years
- ICU admission for acute SARS-CoV-2 infection
- Complex chronic conditions

Rao et al. 2022. *JAMA Peds.*

121 Syndromic & Symptomatic Features

Health condition	aHR (95% CI)
COVID-19	7.00 (6.56-7.47)
Myocarditis	3.10 (1.94-4.96)
Acute respiratory distress syndrome	2.96 (1.54-5.67)
Myositis	2.59 (1.37-4.89)
Mental health treatment	1.62 (1.46-1.80)
Disorders of teeth/gingiva	1.48 (1.36-1.60)
Other/ill-defined heart disease	1.47 (1.17-1.84)
Fluid/electrolyte disturbance	1.45 (1.32-1.58)
Thrombophlebitis and thromboembolism	1.31 (1.05-1.63)
Acute kidney injury	1.30 (1.07-1.58)
Tonsillitis	1.26 (1.15-1.38)
Bronchiolitis	1.26 (1.13-1.41)
Pneumonia	1.26 (1.09-1.45)
Other specified inflammatory condition of skin	1.22 (1.12-1.33)
Obesity	1.20 (1.10-1.31)
Communication/motor disorders	1.18 (1.08-1.29)
Gastroenteritis	1.12 (1.03-1.22)

Rao et al. 2022. *JAMA Peds.*

Progress Update: Clinical Cohort Studies

RECOVER Key Scientific Aims

Progress: Enrolling Adult RECOVER Clinical Cohorts

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub- Phenotypes	Pathogenesis	Interventions

Adult Cohort

	ACUTE INFECTION COHORT	**POST-ACUTE INFECTION COHORT**
	• Patients with confirmed acute SARS-CoV-2 infections • Prospective, nested PASC cases vs. controls	• PASC patients 4+ weeks after confirmed acute SARS-CoV-2 infection • Matched PASC case-control design • Retrospective data capture
Goal	~8-9k adults	~8-9k adults
Start	Jan 2022	Jan 2022
Progress (as of 11/30/2022)	**50% enrolled**	**80% enrolled**
Anticipated End	**Q2 2023**	**Q1 2023**

Observational Study – Early Findings: Characterizing Clinical Spectrum, In-Depth At Large Scale

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

Who is getting PASC?

Among adult patients recruited during acute infection, **20-30% reported symptoms** 3 months after enrollment.

What are the impacts of different variants and vaccination?

- Predominant symptoms are consistent across infection waves.

- Lower overall rates of symptoms observed in participants infected in later years.

- Vaccinated individuals infected with Omicron variant continue to be at risk for PASC, though the chance of PASC is lower than individuals infected pre-Omicron.

Progress: Enrolling Pediatric RECOVER Clinical Cohorts

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

Pediatric Cohort

	ACUTE INFECTION COHORT	POST-ACUTE INFECTION COHORT
	• Patients with confirmed acute SARS-CoV-2 infections • Prospective, nested PASC cases vs. controls	• PASC patients 4+ weeks after confirmed acute SARS-CoV-2 infection • Matched PASC case-control design • Retrospective data capture
Goal	800 children	4,000 children in main cohort 800 children in RECOVER-MUSIC
Start	May 2022	May 2022
Progress (as of 11/30/2022)	**21% enrolled**	**22.2% enrolled in main cohort** **100% enrolled in RECOVER-MUSIC**
Anticipated End	**Q3 2023**	**Q3 2023**

Early Findings: Investigating Vaccine Safety in Children After MIS-C

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

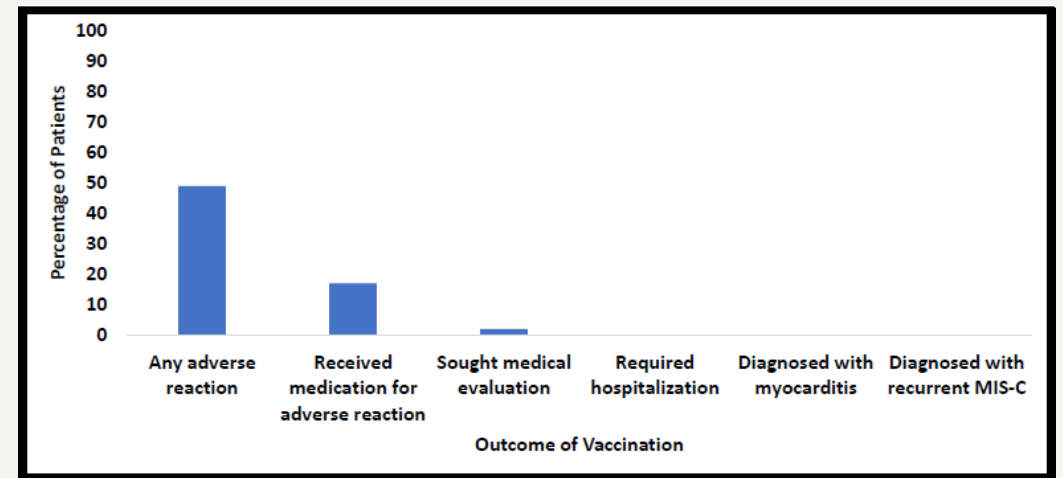**COVID MUSIC STUDY**
Understanding MIS-C

Long-Term Outcomes after the MUltisystem Inflammatory Syndrome In Children (MUSIC)

- Launched late 2020 and within 7 months, had enrolled **20% of MIS-C patients** in the U.S.
- Target enrollment complete

MUSIC results show **vaccination** for children who have had MIS-C **is safe**.

Most common reactions:
- Arm soreness (34%), fatigue (17%), fever (11%)

Adverse Reactions to COVID-19 Vaccination Among 185 Patients With a History of MIS-C

Elias, et al. *JAMA Network Open*. In press.

Progress Update: Longitudinal Cohort Studies

RECOVER Key Scientific Aims

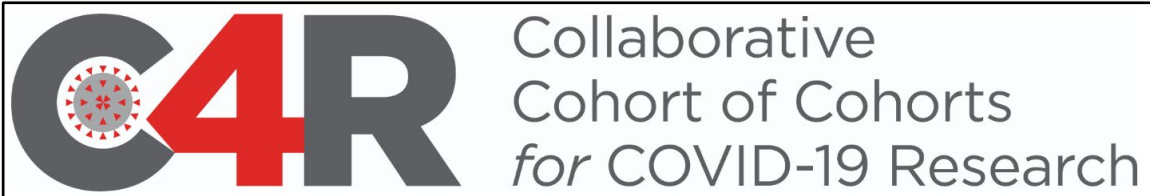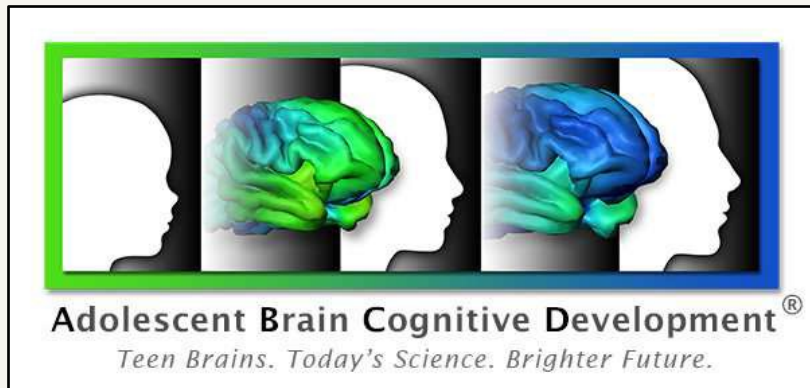| Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub- Phenotypes	Pathogenesis	Interventions
EHR/ Health Systems Studies	Clinical Cohort Studies	Longitudinal Cohort Studies	Pathobiology Studies		Clinical Trials

Progress: Leveraging Cohorts to Conduct Longitudinal, Community-Based Research

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub- Phenotypes	Pathogenesis	Interventions

- Enrolled **49,000 adults** from 14 existing community-based cohorts, including C4R

  - Adult cohort includes 7,680 COVID cases and 1,504 PASC cases

  - Biospecimens

  - Sero-surveillance

- Enrolled **12,000 adolescents & families** from Adolescent Brain Cognitive Development Study[SM] (ABCD)

Progress Update: Pathobiology Studies

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions
EHR/ Health Systems Studies	Clinical Cohort Studies	Longitudinal Cohort Studies	Pathobiology Studies		Clinical Trials

Progress: Investigating Disease Pathways Underlying PASC

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

RECOVER Pathobiology Studies: Areas of Focus

- Launched more than 42 studies

- Evaluating candidate biomarkers

Consequences of Acute Infection

System-Specific Pathology (Neurological, Cardiac, Respiratory)

Immune Response, Inflammation, Autoimmunity

**Influence on Metabolism**

Epigenetics, Multiomics

Animal Models

recoverCOVID.org

Building on Recent Studies Within RECOVER at Scale

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

Longitudinal, multi-omics reveal PASC risk factors:
type 2 diabetes, SARS-CoV-2 RNAemia, Epstein-Barr virus viremia, and specific auto-antibodies

Su *et al., Cell*, 2022
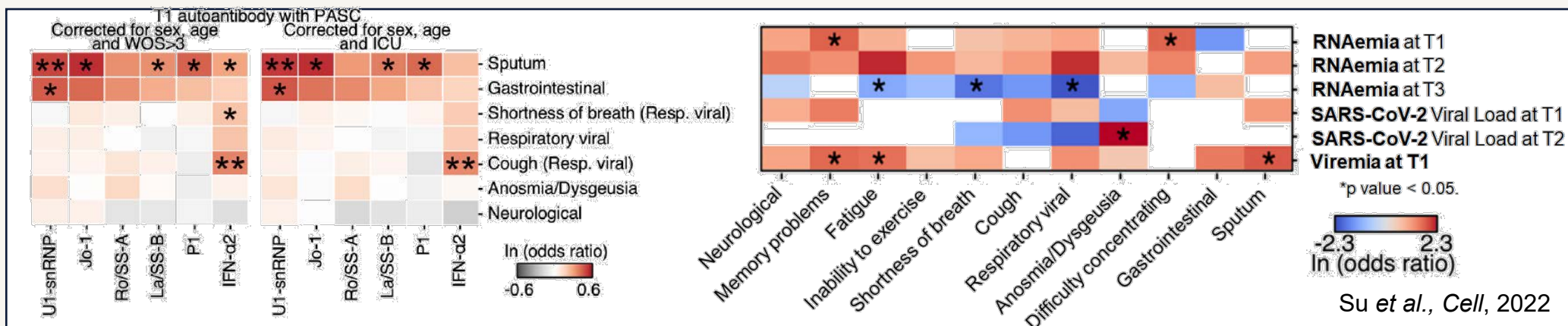
RECOVER is supporting follow-up studies to connect multi-omics results with clinical cohort data to develop an AI tool to identify targets of COVID-19 pathology.

Support from RECOVER allows researchers to:

- Test these results at scale (original study ~300 patients)
- Understand pathophysiological mechanisms of PASC

RECOVER
Researching COVID to Enhance Recovery

Pediatric Cohort Goals: Characterizing MIS-C in Children

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

> *What is our current understanding of the similarities and differences between Kawasaki and MIS-C?*

	Kawasaki Disease	MIS-C	BOTH
Demographics	• 6 months to 5 years • Male predominance	• 6-11 years • No gender predominance	
Immunological Characteristics	T-cell activation by conventional antigen	SARS-CoV-2 spike protein triggers cytokine storm	Enhancement of IL-1β$^+$ neutrophils and immature neutrophils
Clinical Features	Conjunctival infection & oral mucous membrane changes	GI symptoms, myocarditis & shock, and coagulopathy	Fever, rash, neurological symptoms
Management			IVIG, glucocorticoids, acetylsalicylic acid

Pediatric Cohort Goals: Characterizing MIS-C in Children

RECOVER Key Scientific Aims
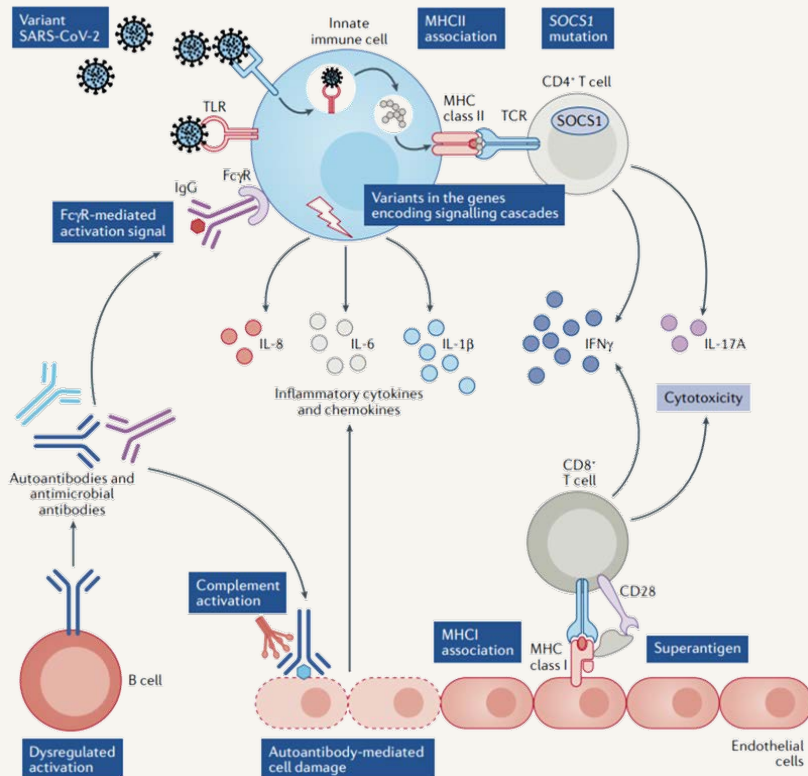
Clinical Spectrum	Risk Factors	Incidence/Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

What is our current understanding of MIS-C pathobiology?

Potential immunological underpinnings

SARS-CoV-2 viral S protein as a superantigen

- SARS-CoV-2 infection → cytokine storm → hyperinflammatory responses
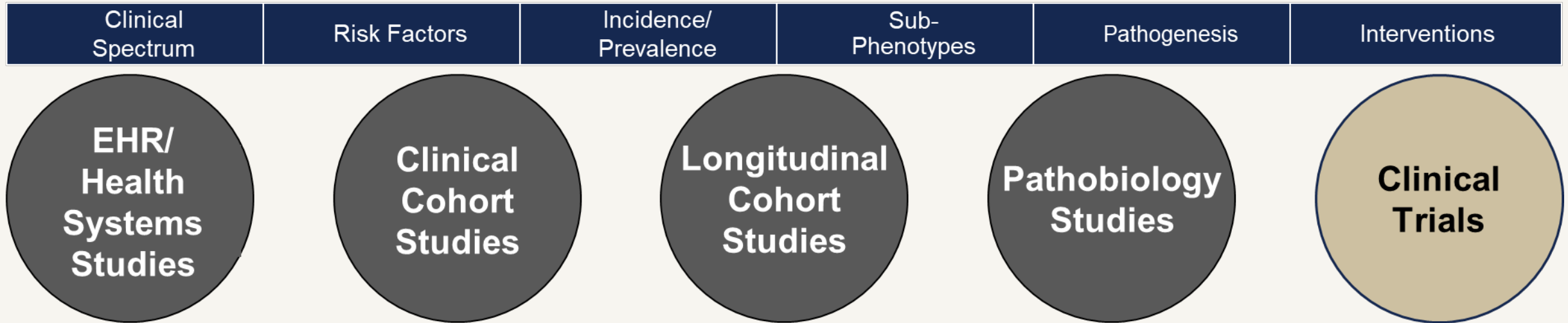
Immunological aberrations

- Dysregulated activation of lymphocytes

- Autoantibody-mediated cell damage

Genetic Susceptibility

- SARS-CoV-2 infection → dysregulation of immune responses in predisposed children of certain genetic backgrounds

Sharma, et al. 2021. *Nat Rev.*

Progress Update: Clinical Trials

RECOVER Key Scientific Aims

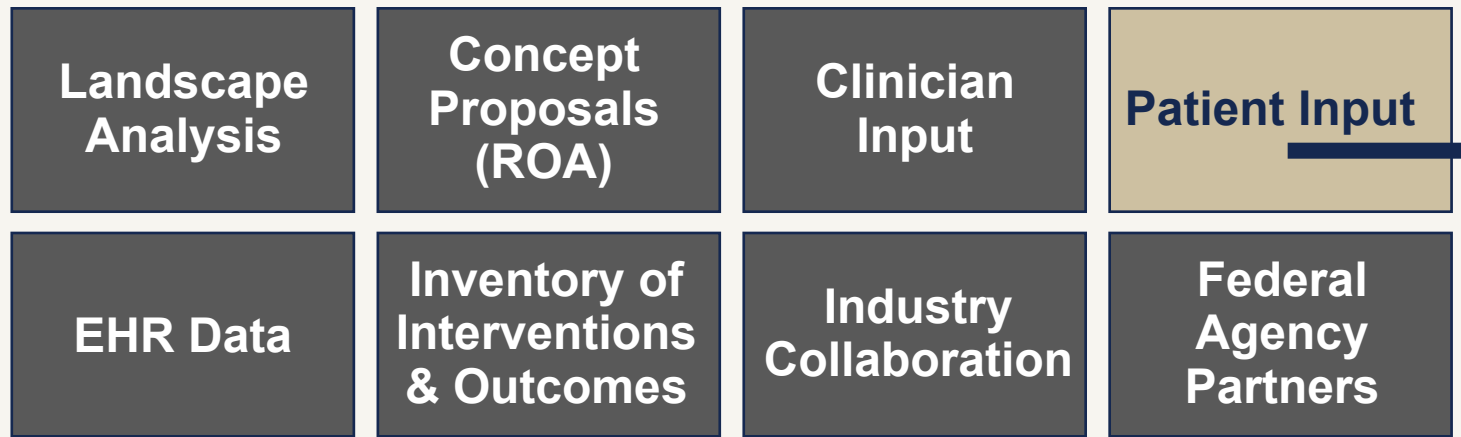| Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub- Phenotypes	Pathogenesis	Interventions
EHR/ Health Systems Studies	Clinical Cohort Studies	Longitudinal Cohort Studies	Pathobiology Studies		Clinical Trials

Building Patient-Centered RECOVER Clinical Trials Infrastructure

Critical inputs from patients, clinicians, and other perspectives shaped clinical trial priorities and design.

Patient Input

Sources & Inputs

Landscape Analysis	Concept Proposals (ROA)	Clinician Input	Patient Input
EHR Data	Inventory of Interventions & Outcomes	Industry Collaboration	Federal Agency Partners

Design Stages

- Identify symptom clusters
- Prioritize interventions
- Define outcome measures

 Input on master protocol development

 Focus groups and interviews to learn patient perspectives

 Survey data from RECOVER and non-RECOVER patients

 Insights from National Community Engagement Group

recoverCOVID.org

Designing and Launching RECOVER Clinical Trials

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

RECOVER Clinical Trial Platforms Portfolio

Platform Integrates Five Adaptive Master Protocols

- Shared endpoints, common data elements
- Shared approach to patient inclusion
- Ability to rapidly assess target therapeutics
- Enables cross-trial analysis

Launch Q1-Q2 2023

Viral Persistence/Reactivation & Immune Dysregulation

Neurologic/Cognitive Dysfunction

Autonomic Dysfunction

Sleep Disorders

Cardiopulmonary/Exercise Intolerance/Fatigue

RECOVER Current Progress and Upcoming

Largest, diverse, deeply characterized clinical cohort of PASC patients

EHR studies providing insights on PASC prevalence, risk factors, impact, disparities

Cohorts that support deep and longitudinal characterization of PASC patients

42+ pathobiology studies that will characterize pathophysiology of PASC

5 master protocol-driven platform clinical trials under development

Upcoming

Interim analyses in early 2023

Cross-validate EHR findings

Integrate wearable sensor data

Mechanistic studies, risk stratification, biomarker identification

Trials evaluating therapies launching in Q1 and Q2 2023