NIH RECOVER

Presentation to the Council of Councils

May 11, 2022

NIH Senior Oversight Committee Co-Chairs

Hugh Auchincloss, MD
Acting Director, NIAID

Gary H. Gibbons, MD
Director, NHLBI

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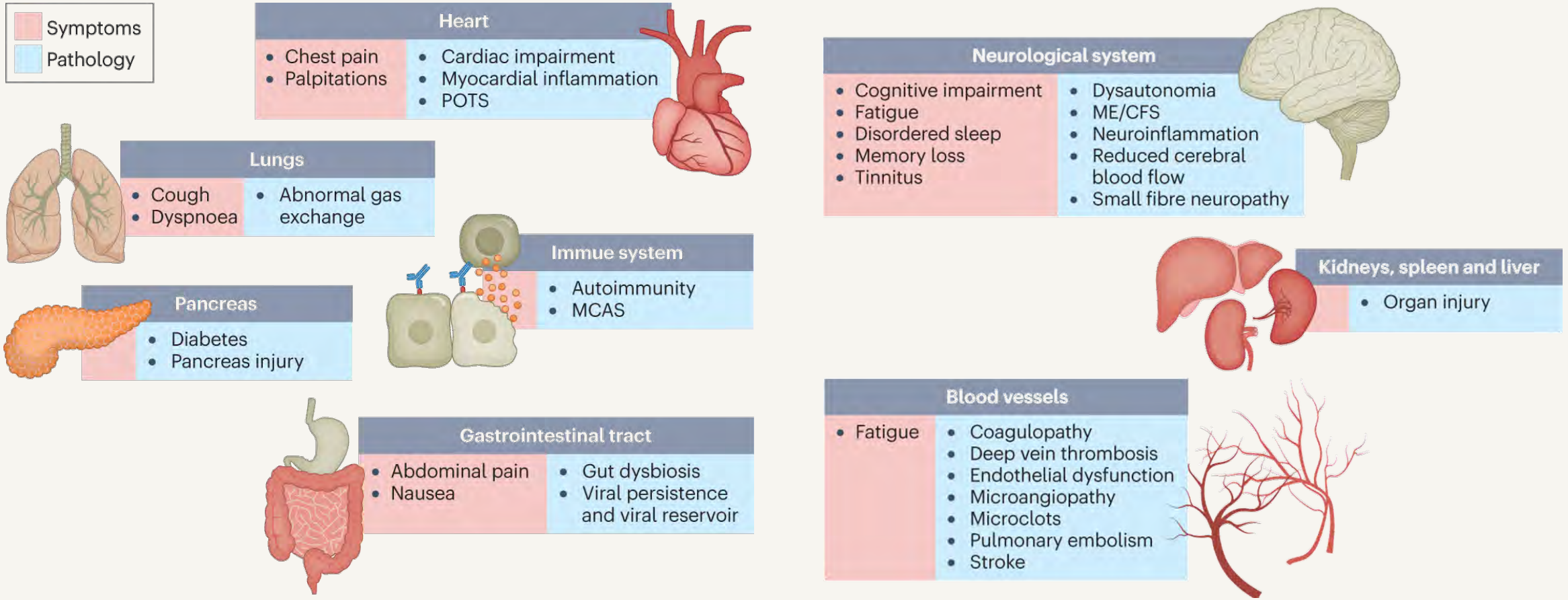
RECOVER
Researching COVID to Enhance Recovery

NIH National Institutes of Health
Researching COVID to Enhance Recovery

Researching COVID to Enhance Recovery (RECOVER): Characterizing a New Post-Viral Disorder

Wide Multi-Symptom Clinical Spectrum of Post-Acute Sequelae of COVID-19 (PASC) Requires Multi-Disciplinary Approach



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Davis et al. (2023) Nature Reviews Microbiology

The Post-Acute Sequelae of COVID-19: Symptom clusters overlap with ME/CFS

Fatigue in almost 90% of those with PASC. Prevalence of post-exertional malaise maybe as high as well.

Neurologic

- Memory/Word finding difficulties
- Concentration difficulties/"brain fog"
- Executive function difficulties
- Sleep disorders
- Pain syndromes- muscle, joint
- Abnormal sensations- tingling
- Headache
- Postural Orthostatic Tachycardia
- Abnormal smell/taste
- Visual abnormalities
- Dizziness/balance problems

CardioPulmonary

- Shortness of breath
- Dry cough
- Chest pain
- Exercise intolerance
- Postural Orthostatic Tachycardia
- Palpitations/ Fast heart rate
- Myocarditis
- Pulmonary fibrosis

Mental Health

- Post traumatic stress disorder
- Anxiety
- Depression

Gastrointestinal

- Diarrhea
- Decreased appetite
- Nausea
- Abdominal pain

Other

- Abnormal temperature regulation
- Chills, flushing sweats
- Sore throat
- Extreme thirst
- Skin changes
- Menstrual changes

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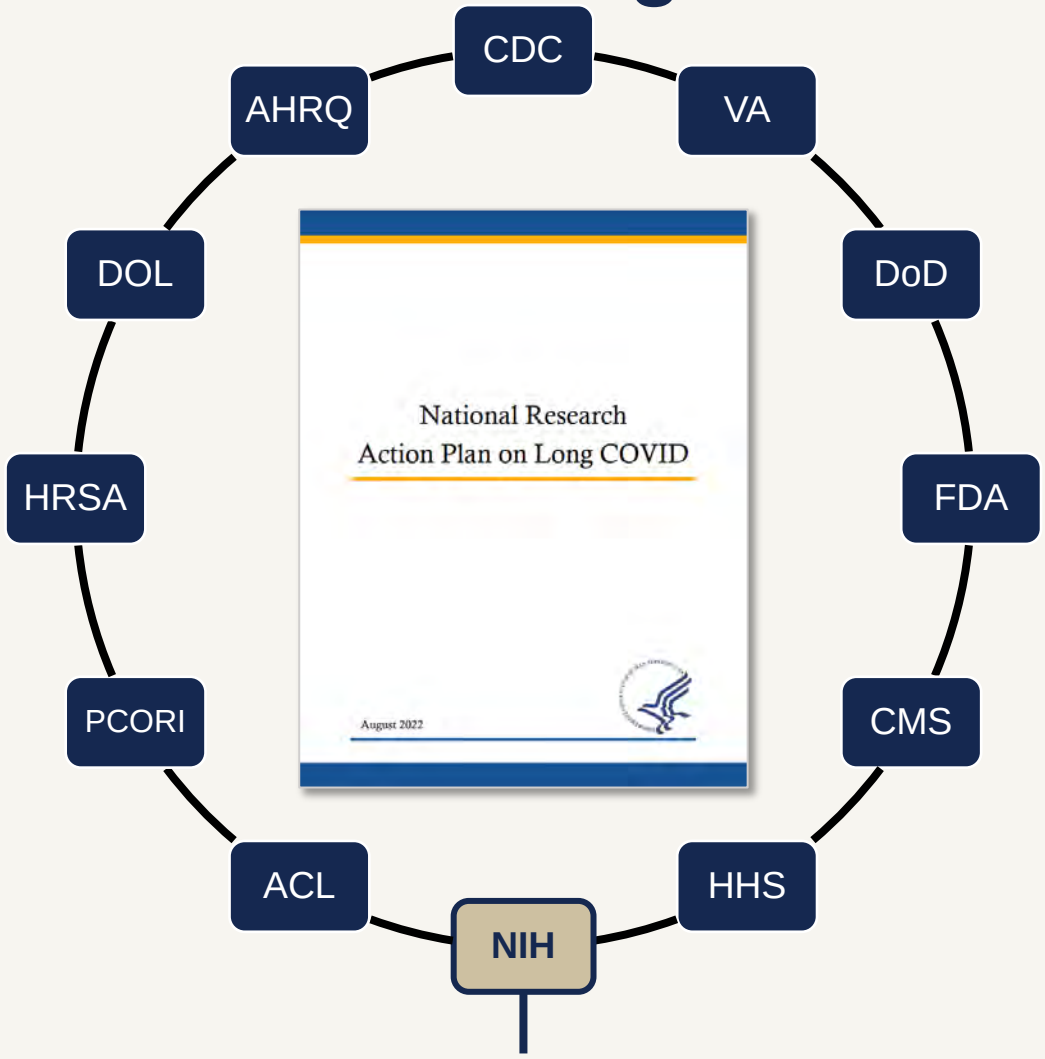
See Davis HE et. al. (2021) Characterizing Long Covid in an International Cohort: **7 months** of symptoms and their impact. medRxiv preprint https://www.medrxiv.org/content/10.1101/2020.12.24.20248802v2

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



RECOVER
Researching COVID to Enhance Recovery

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'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
- **900+** attendees at patient experience discussion
- **15,400+** monthly newsletter subscribers
- **30+** patients involved in manuscript development and presentations

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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

	% U.S. Population	% U.S. COVID Cases	% Current Cohort (as of 5/5/23)
	Entire[1]	Entire[2]	Adult
White	75.8	53.5	61.2
Hispanic/ Latinx	18.9	24.6	16.4
Black	12.6	12.4	16.2
Asian	5.9	4.3	7.5
Native Hawaiian/ Pacific Islander	0.2	0.3	0.4
American Indian/ Alaska Native	0.7	1.0	2.3

[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
- Autopsy Path Study

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

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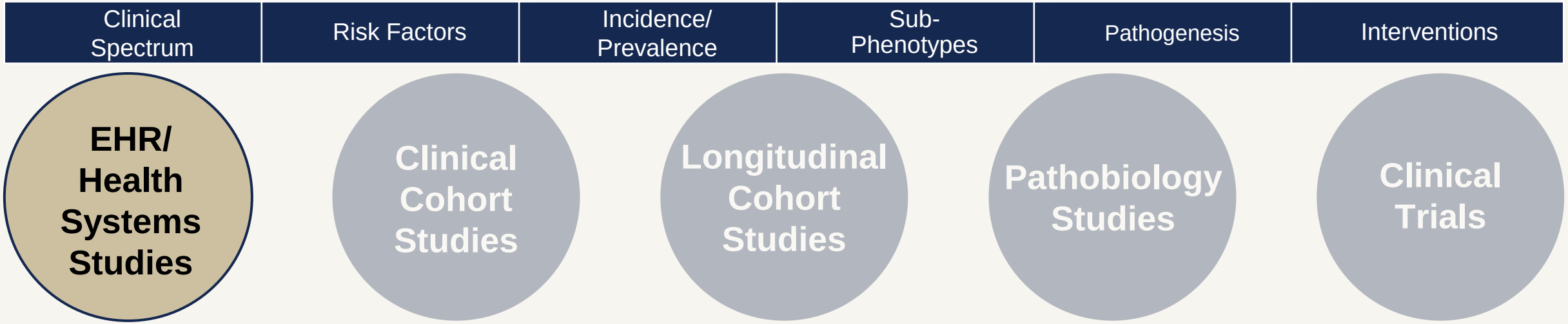
Progress Update: EHR/Health Systems Studies

RECOVER Key Scientific Aims



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) – **19M+ records**
- *All of Us* (*AoU*) – **20,000+ COVID cases**
- Issued **37 reports** (15 published/in press, 9 preprint/submitted, 13 draft)
  - Initial validation of 'computable phenotype' models (N3C + *AoU*) for identifying PASC and future model cross-validation with RECOVER teams
  - Incidence, prevalence, risk factors, impact of variant and vaccinations, health disparities, intervention usage

pcornet®
The National Patient-Centered Clinical Research Network

National COVID Cohort Collaborative

All of Us RESEARCH PROGRAM

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

RECOVER Key Scientific Aims

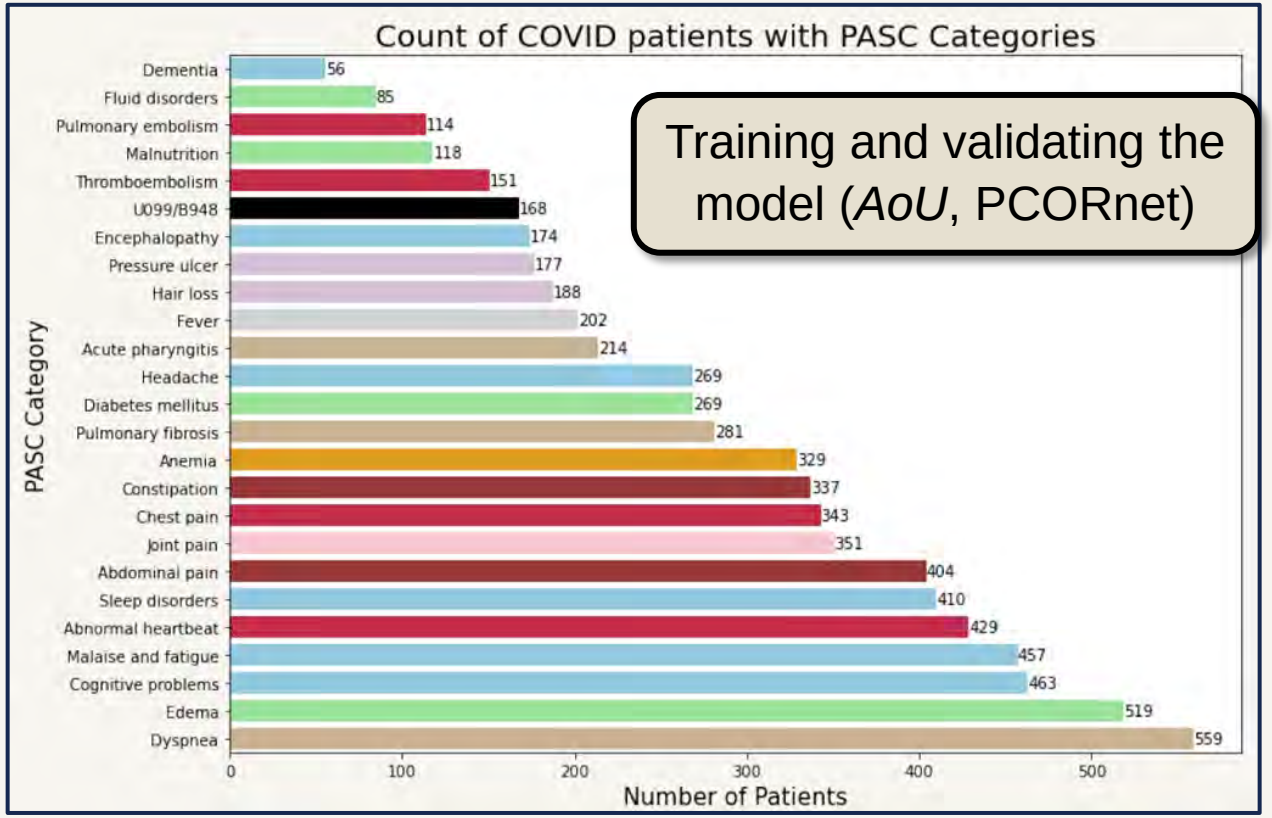
Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-Phenotypes	Pathogenesis	Interventions

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)

Pffaf, et al. 2022. *Lancet Digit Health*

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

RECOVER Key Scientific Aims

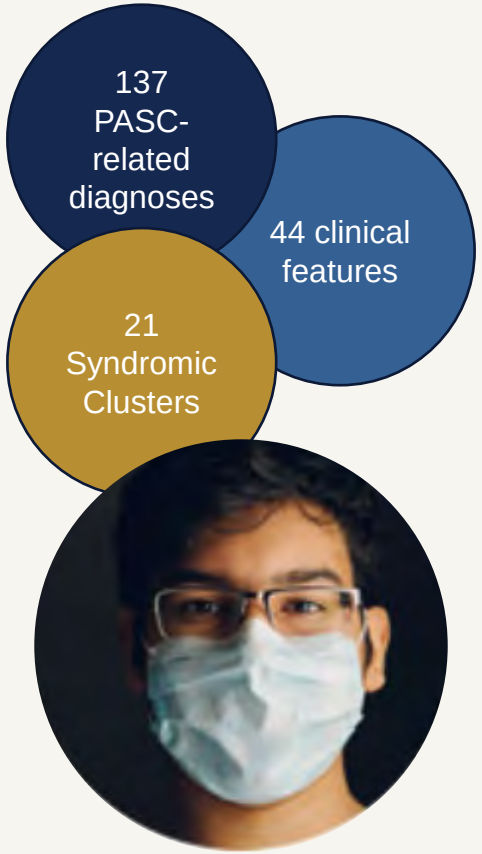
Clinical Spectrum	**Risk Factors**	Incidence/ Prevalence	**Sub-Phenotypes**	Pathogenesis	Interventions

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*.



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

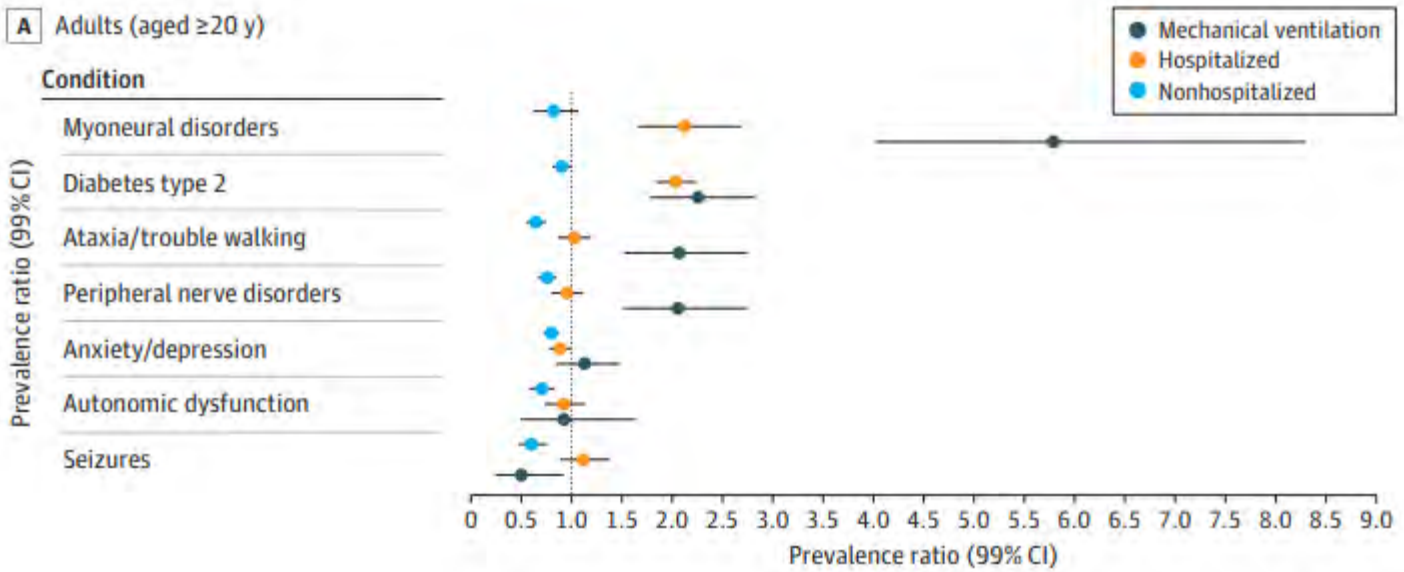
RECOVER Key Scientific Aims

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

Does PASC increase the risk for other conditions/disorders?

- **Increased risk of new onset conditions** in PASC patients like
  - Myoneural disorders
  - Type 2 diabetes
  - Anxiety and depression
  - Ataxia or trouble walking

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



Hernandez-Romieu, et al. 2022. *JAMA Network Open.*

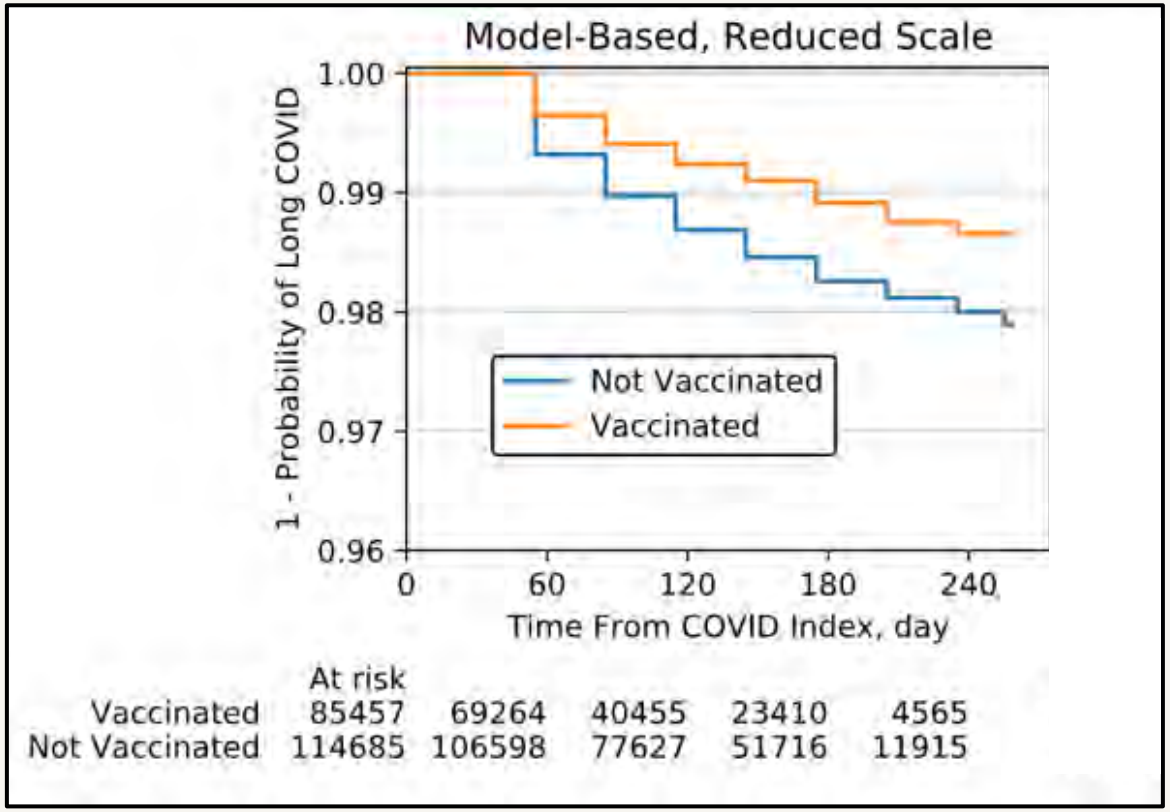
EHR Cohorts – Early Findings: Vaccination and the Risk of PASC

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



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.

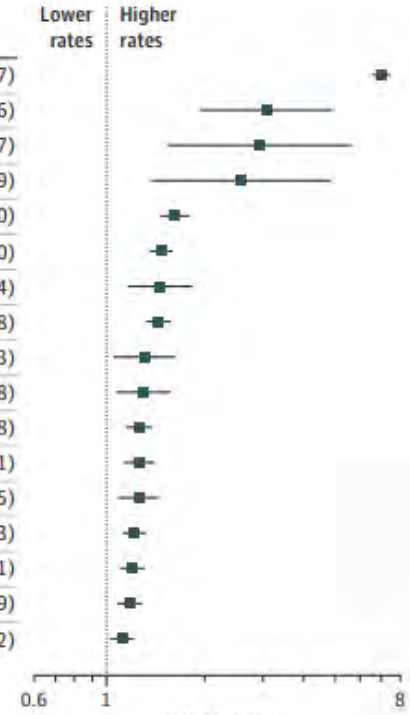
Risk Factors

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

Rao et al. 2022. *JAMA Peds.*

121 Syndromic & Symptomatic Features

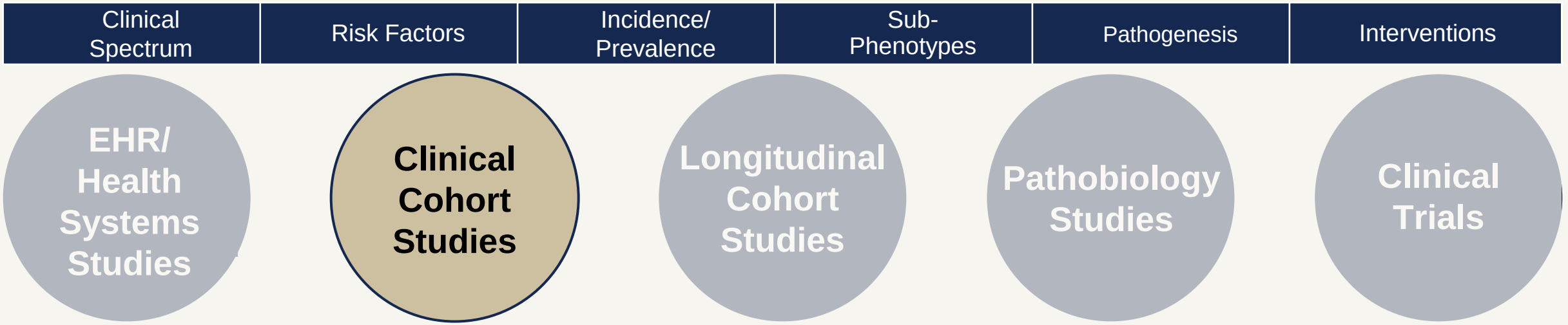
Health condition	aHR (95% CI)
COVID-19	7.00 (6.56-7.47)
Myocarditis	3.10 (1.94-4.96)
Acute respiratory distress syndrome	2.96 (1.54-5.67)
Myositis	2.59 (1.37-4.89)
Mental health treatment	1.62 (1.46-1.80)
Disorders of teeth/gingiva	1.48 (1.36-1.60)
Other/ill-defined heart disease	1.47 (1.17-1.84)
Fluid/electrolyte 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)

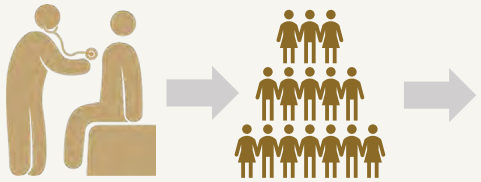


Rao et al. 2022. *JAMA Peds.*

Progress Update: Clinical Cohort Studies

RECOVER Key Scientific Aims





RECOVER Enrolling Clinical Cohorts: Status Update

Status: >18,100 new ppts *(as of May 9, 2023)*

- **Adult enrolling clinical cohort:** ~ 96% enrolled
  - Data-driven readjustment of adult targets;
  - Major accomplishment ~14K diverse population and characterized at Tier 1 in ~17 months
  - Ongoing RECOVER data releases to consortium
  - Primary Analyses of Adult Cohort Interim results to published soon
- **Pediatric enrolling meta-cohort: ~**47% enrolled *(since June 2022*);
  - Anticipate completion in Q4 2023 with focus on:
    - Community-engaged recruitment and diversity
    - Life course perspective from birth through young adulthood

RECOVER Enrolling Clinical Cohorts: Participant Diversity

	% U.S. Population	% U.S. COVID Cases	% Current Cohort (as of 5/5/23)	% Current Cohort (as of 5/5/23)
	Entire[1]	Entire[2]	Adult	Pediatric
White	75.8	53.5	61.2	60.5
Hispanic/ Latinx	18.9	24.6	16.4	23.7
Black	12.6	12.4	16.2	13
Asian	5.9	4.3	7.5	8
Native Hawaiian/ Pacific Islander	0.2	0.3	0.4	0.7
American Indian/ Alaska Native	0.7	1.0	2.3	2

RECOVER Cohorts: A National Scale Platform

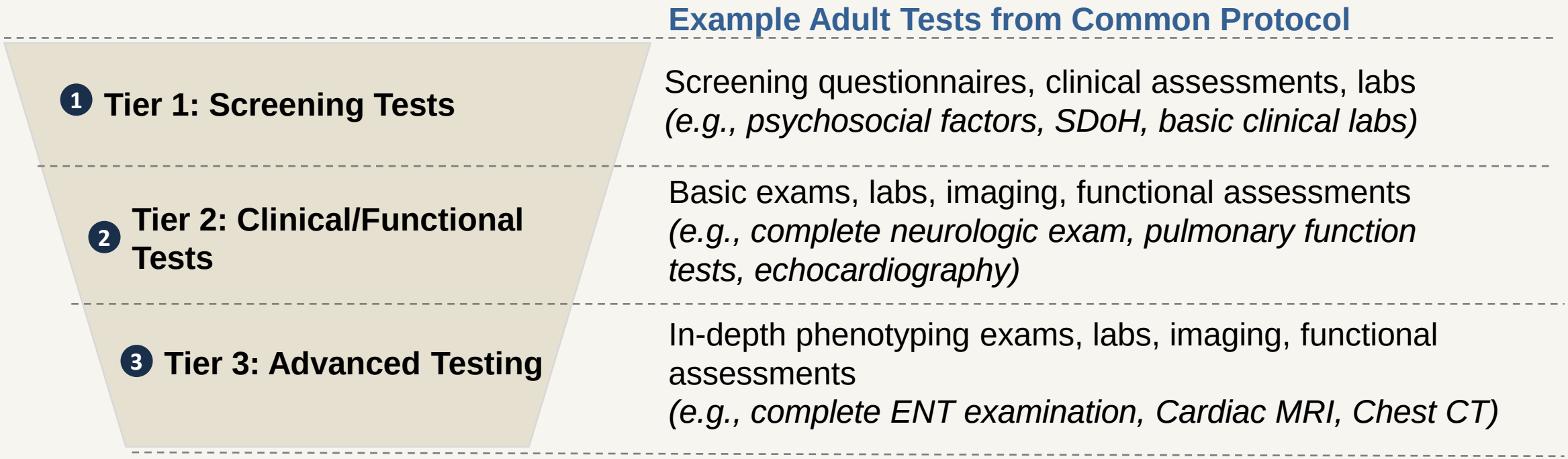
- **Clinical Cohort Studies, Adult and Pediatric**
  - **30 Hubs:**
    - 15 Adult Cohorts
    - 2 Pregnancy Cohorts
    - 8 Pediatric Cohorts
    - 5 Autopsy Centers
- **EHR Studies, Adult and Pediatric**
  - 60,000,000+ patient records

Enrolling participants from 200+ sites across the Nation

(Will also include clinical trials and patient registry)

Meta-Cohort Clinical Characterization: Tiered Assessment Strategy

Assessments tailored to stage of life will capture a **broad spectrum of PASC recovery phenotypes** with in-depth characterization using Common Protocols and Common Data Elements.



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?

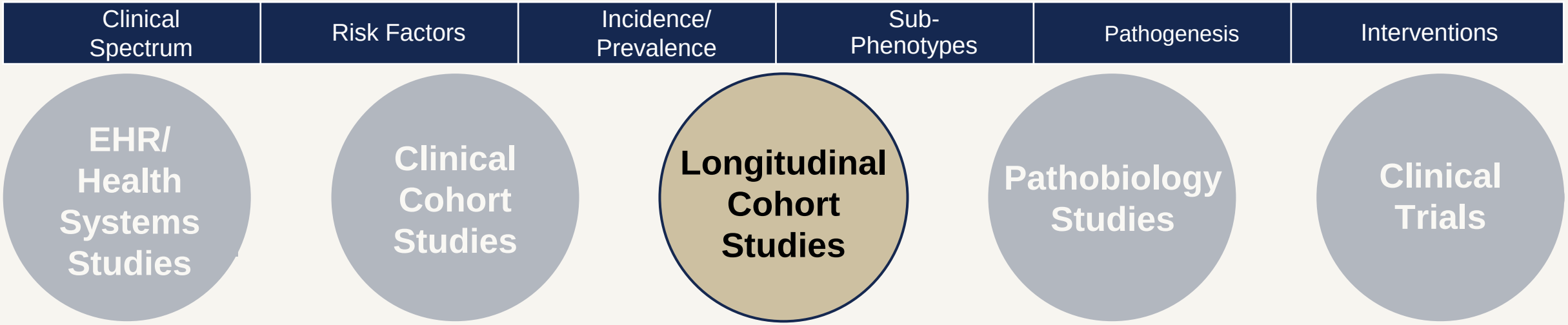
Among adult patients recruited during acute infection, **20-30% reported symptoms** 3 months after enrollment.

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 Update: Longitudinal Cohort Studies

RECOVER Key Scientific Aims



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

RECOVER Key Scientific Aims

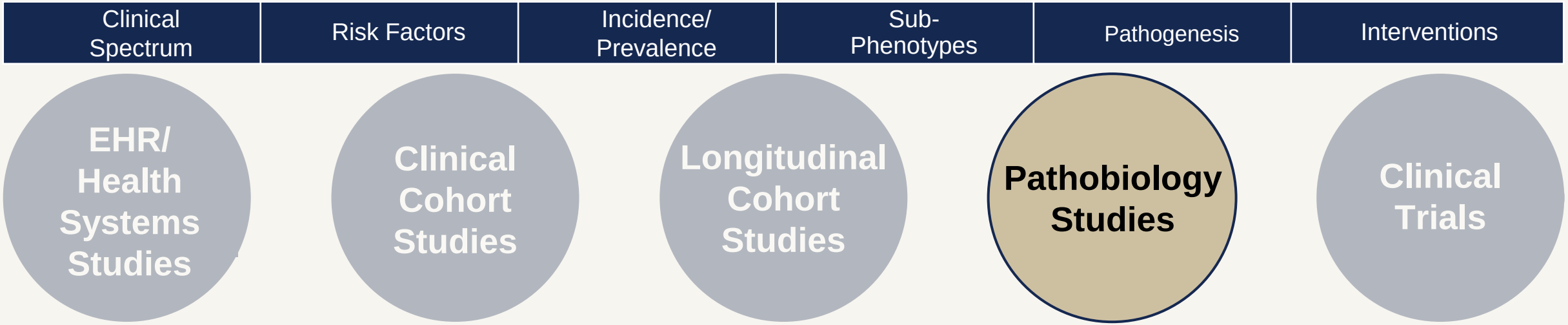
Clinical Spectrum	**Risk Factors**	Incidence/ Prevalence	Sub-Phenotypes	**Pathogenesis**	**Interventions**

C4R Collaborative Cohort of Cohorts *for* COVID-19 Research

- Includes **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℠ (ABCD)

Progress Update: Pathobiology Studies

RECOVER Key Scientific Aims



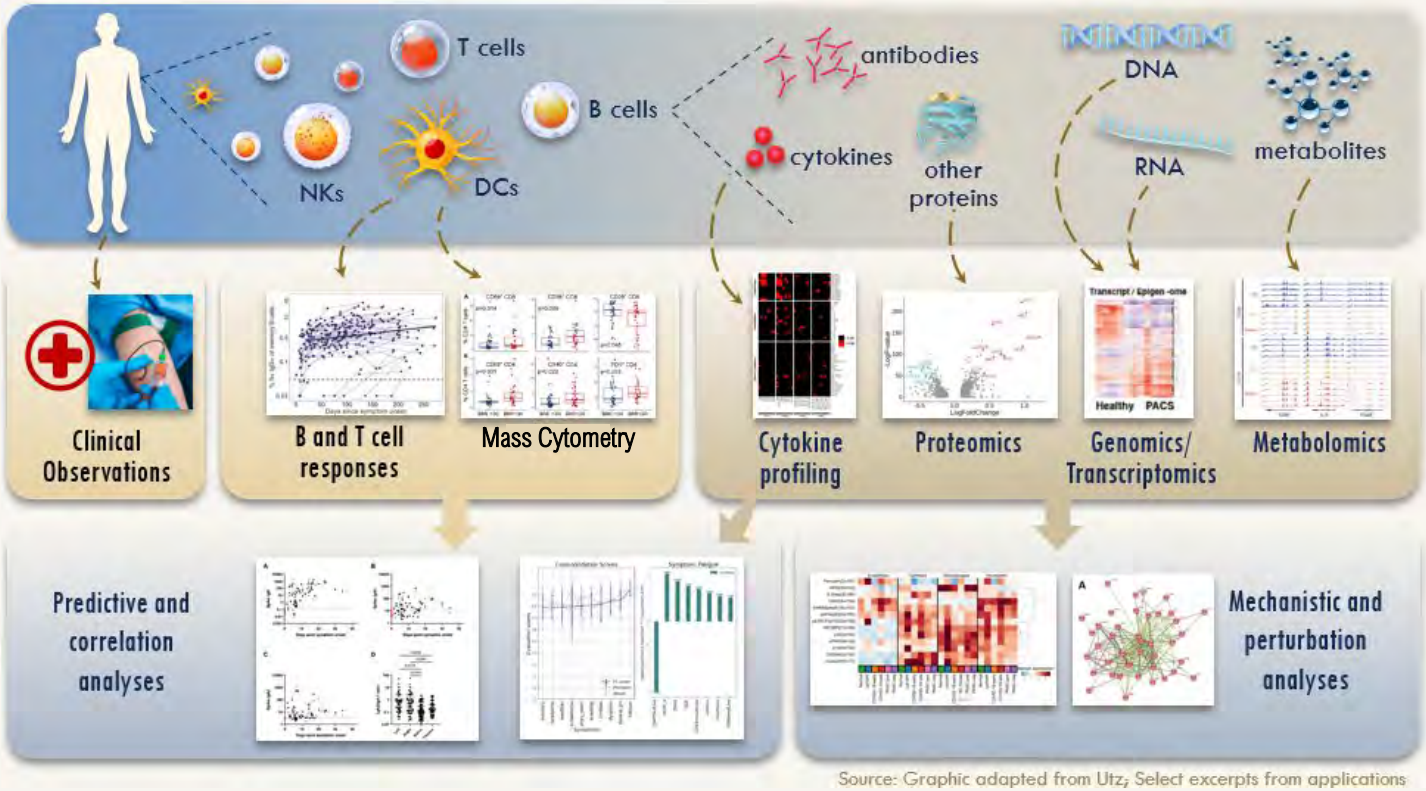
What are the underlying biologic mechanisms responsible for PASC?

Suite of 42+ Multi-disciplinary Studies Underway

COVID-19 patients with and without PASC will be studied using multiple large cohorts

Mechanistic assays

Data from mechanistic assays will be integrated with clinical data



Source: Graphic adapted from Utz; Select excerpts from applications

- Consequences of Acute Infection
- Viral Persistence Viral Reservoirs
- Secondary Damage Reprogramming of Host Tissue/Organ
- Immune Response, Inflammation, Autoimmunity
- Residual Tissue Organ Damage Injury
- Risk, Epigenetics

Article

SARS-CoV-2 infection and persistence in the human body and brain at autopsy

https://doi.org/10.1038/s41586-022-05542-y

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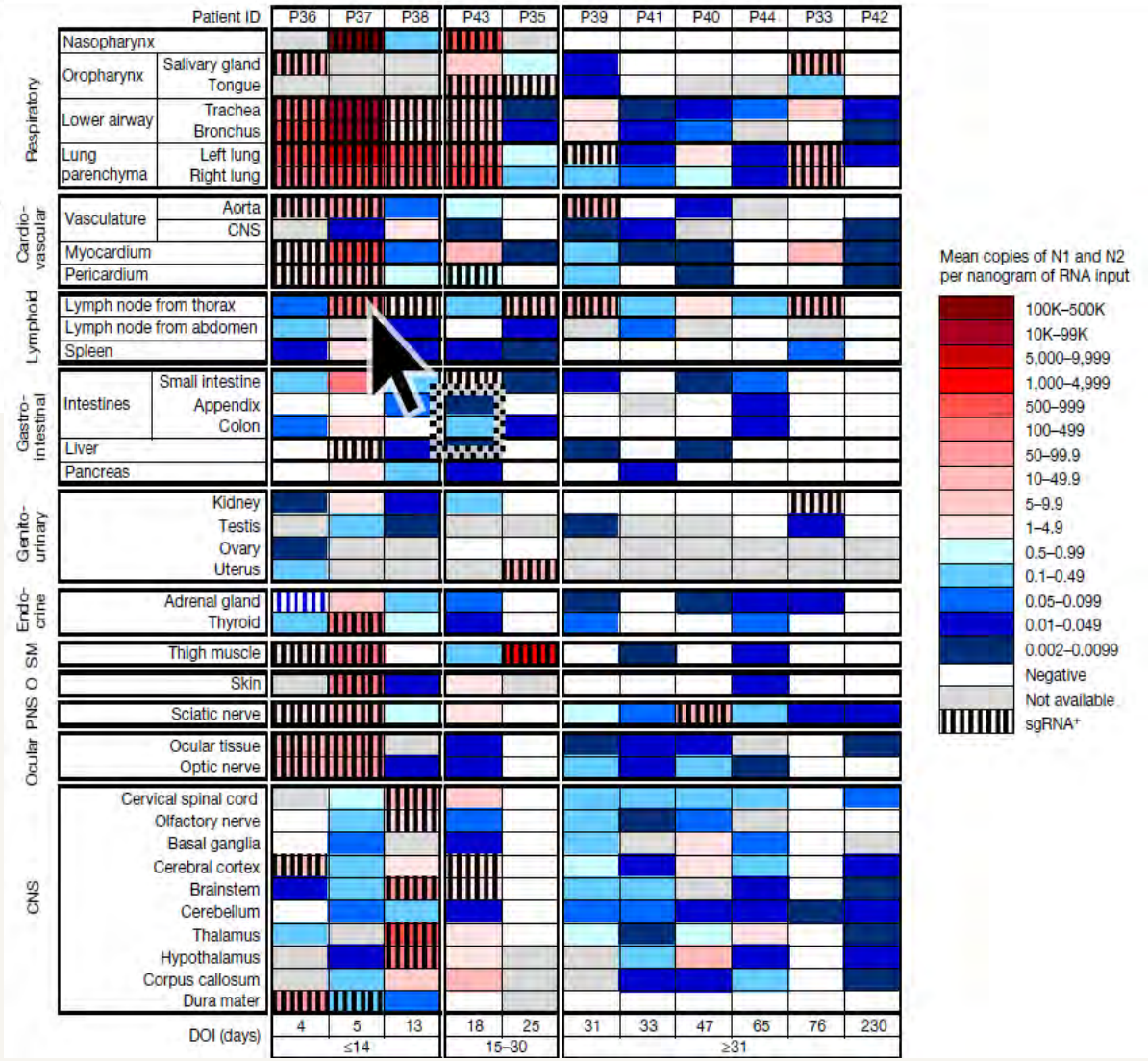
Published online: 14 December 2022

Check for updates

[illegible]ney R. Stein[1,2], Sabrina C. Ramelli[3], Alison Grazioli[4], Joon-Yong Chung[5], Manmeet Singh[6], [illegible]laude Kwe Yinda[6], Clayton W. Winkler[7], Junfeng Sun[3], James M. Dickey[1,2], Kris Ylaya[5], [illegible]ung Hee Ko[8], Andrew P. Platt[1,2], Peter D. Burbelo[9], Martha Quezado[5], Stefania Pittaluga[5], [illegible]adeleine Purcell[10], Vincent J. Munster[6], Frida Belinky[8], Marcos J. Ramos-Benitez[1,2,11], [illegible]. Boritz[8], Izabella A. Lach[1,2], Daniel L. Herr[12], Joseph Rabin[13], Kapil K. Saharia[14,15], Ronson J. Madathil[16], Ali Tabatabai[17], Shahabuddin Soherwardi[18], Michael T. McCurdy[17,19], NIH COVID-19 Autopsy Consortium*, Karin E. Peterson[7], Jeffrey I. Cohen[20], Emmie de Wit[6], Kevin M. Vannella[1,2], Stephen M. Hewitt[5], David E. Kleiner[5] & Daniel S. Chertow[1,2]✉



Autopsies on 44 COVID-19 patients from acute infection through over 7 months following symptom onset.

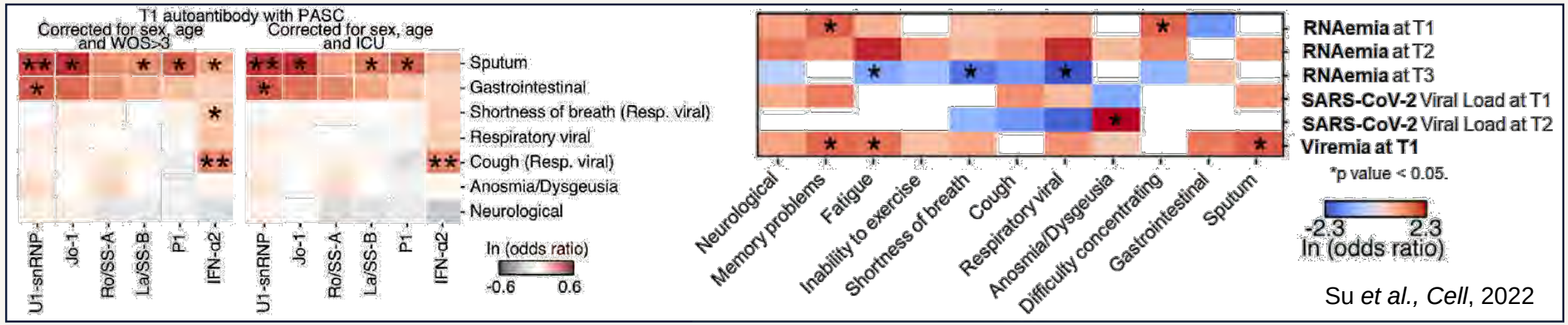
- SARS-CoV-2 is widely distributed even in patients who died with asymptomatic or mild infection
- Virus replication is present in multiple pulmonary and extrapulmonary tissues early in infection
- RNA in multiple anatomic sites, including brain, for up to 230 days after symptom onset.
- Paucity of inflammation or viral cytopathology outside the lung

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.

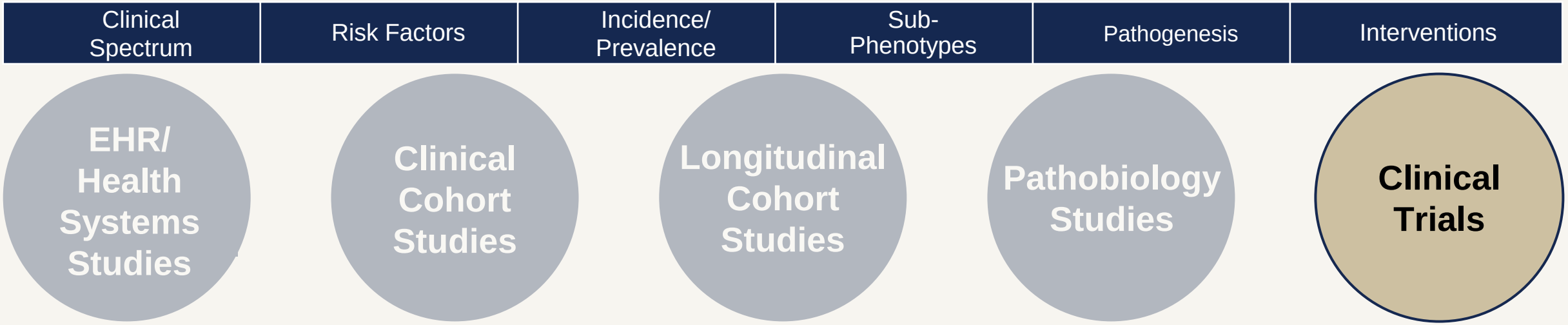
Support from RECOVER allows researchers to:

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

RECOVER
Researching COVID to Enhance Recovery

Progress Update: Clinical Trials

RECOVER Key Scientific Aims



Building Patient-Centered RECOVER Clinical Trials Infrastructure

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

Sources & Inputs

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

Design Stages

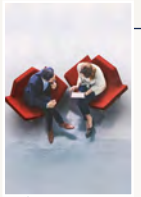
- Identify symptom clusters
- Prioritize interventions
- Define outcome measures

Patient Input

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

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 Q3-Q4 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

Future Directions

- Interim analyses in early 2023
- Cross-validate EHR findings
- Integrate wearable sensor data
- Mechanistic studies, risk stratification, biomarker identification
- Trials evaluating therapies launching in Q3-Q4 2023

RECOVER

Researching COVID to Enhance Recovery

An Initiative Funded by the National Institutes of Health

recoverCOVID.org