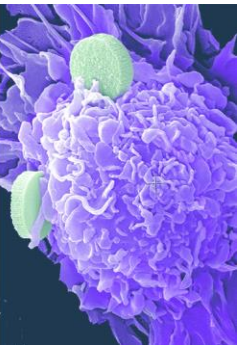
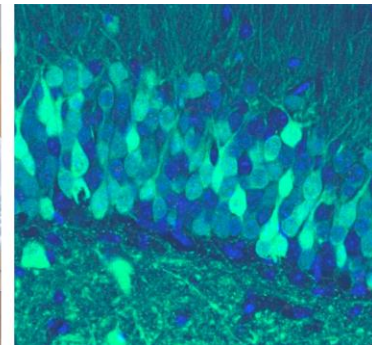
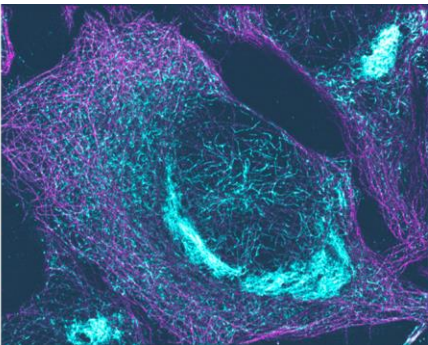
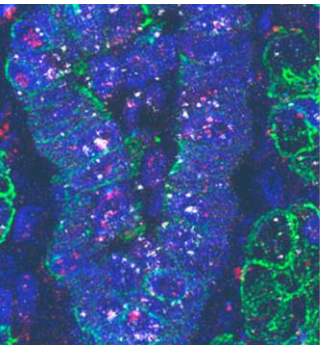


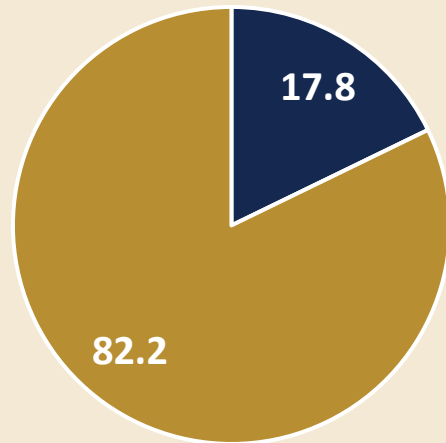
Dr. Joseph Breen

Immunoregulation Section Chief, Division of Allergy, Immunology, and Transplantation (DAIT)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health



Introduction

US Adults Aged 18 and Over



- Ever Experienced Long COVID
- Never Experienced Long COVID

- Approximately **17%** of adults aged 18 and over have **EVER** experienced post-COVID conditions (Long COVID). These adults had COVID and had some symptoms that lasted three months or longer.* **6.9%** are currently experiencing Long Covid.
- The Researching COVID to Enhance Recovery (RECOVER) Initiative – launched in 2021 – is an initial investment in research towards understanding Long COVID and other long-term, chronic illnesses that may appear post infection.

Source: U.S. Census Bureau, Household Pulse Survey, 2022-2024. Phase 4.1, April 2 – 29, 2024. <https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm>





NIH's RECOVER Initiative Objectives

Rapidly improve our **understanding** of and ability to **predict, treat, and prevent** post acute sequelae of COVID-19 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

RECOVER's National Scope

With observational research sites across the country, the RECOVER Cohort is enrolling adults, children and their caregivers, and pregnant participants and their newborn infants.



Adult and Pediatric enrollment takes place at over **30+ Hubs**



Enrollment sites are active at **155+ locations** across the Nation



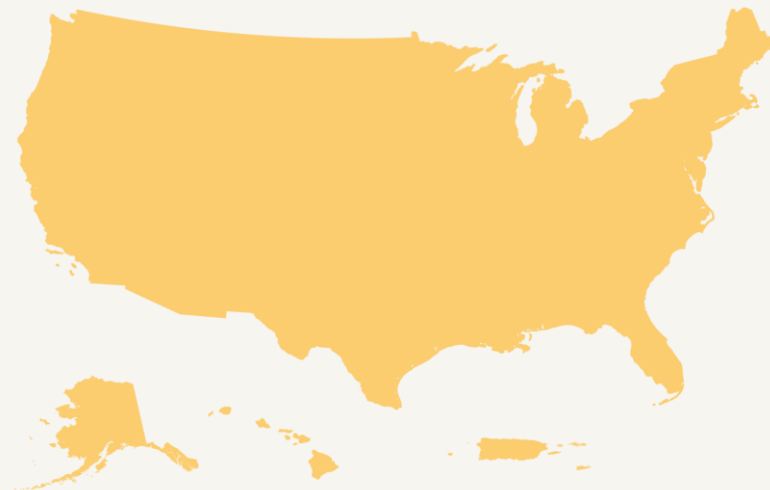
EHR, Adult, and Pediatric Studies include **60,000,000+ patient records**



Overall, there are:

- **15 Adult Cohorts**
- **2 Pregnancy Cohorts**
- **8 Pediatric Cohorts**
- **5 Autopsy Cohorts**
- **3 EHR Cohorts**

Enrollment Sites National Scope



RECOVER's Representative Engagement Approach & Frameworks

Representative Engagement Approach

- Patient and community members are **involved in every phase of RECOVER research** and **coalesce in National Community Engagement Group (NCEG)** at the center of RECOVER (e.g., planning, conducting, disseminating).
- Major RECOVER Initiative **decisions are made in partnership with patient and community Representatives**, and with broader input from patients and communities.
- Patient and community **members who are not Representatives are able to share ideas, concerns, hopes, and needs.**

Frameworks Leveraged

- **PCORI Engagement Rubric:**
Emphasizes patients as partners in planning, conducting, and disseminating research.
- **Meaningful Involvement of Patient Advocates (Spieldenner, et al, 2022):**
Emphasizes the voice of community members in decision-making and leadership.
- **Trauma-Informed Community Engagement:**
Engages people with histories of trauma, recognizes the presence of trauma symptoms, and acknowledges the role that this plays in their lives.

RECOVER by the Numbers

Observational

60 Million
Electronic Health Records

30,000
Enrolled in Clinical Cohorts

60,000
Participants in
Community-based Cohorts

Pathobiology

>40 active
Studies of Pathogenesis

12,000
Participants in Systems Biology

197
Autopsies Performed

Clinical Trials

>200
Candidate Interventions
Evaluated for Inclusion

8 trials
13 Interventions

5
Adaptive Platform
Master Protocols Across
Multi-therapeutic Domains

Patient and Community Engagement

>1,000
Patients included in Protocol
Design, Trial Application Review,
and/or Symptom Survey
Development

31
Public Seminars on Long
COVID/RECOVER

>500
Diverse and Multi-disciplinary
Investigators and Patients in
RECOVER Consortium

Findings

- **66** Scientific Reports Published/Accepted
- **16** Scientific Reports Under Journal Review
- **77** Scientific Reports In Preparation

Clinical characterization findings from the RECOVER observational cohorts



RECOVER: Helping Long COVID Patients by Informing Diagnosis, Care, and Treatment

Achieving RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/Prevalence	Sub-phenotypes	Pathogenesis	Interventions
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RECOVER Findings (Examples from 50+ publications)

- Symptom-based definition of Long COVID in adults and children (proposed)
 - Major step toward working case definition for diagnosis and patient monitoring
 [Adult: Thaweethai, et al. 2023. *JAMA Network Open*]
 [Pediatric: Gross, et al 2024 *PLOS One*]
- Symptoms and conditions specifically associated with Long COVID in children (e.g. circulatory and respiratory)
 [Lorman, et al., *JAMIA Open*, April 2023]
- Insights from an N3C RECOVER EHR-based cohort study characterizing SARS-CoV-2 reinfections and Long COVID
 [Hadley, et al., 2024. *Communications Medicine*]
- Higher risk of new cardiovascular, neurologic, endocrine, GI symptoms in Black and Hispanic patients
 [Khullar, et al. *JGIM*. 2023]
- Distinguishing immune features of Long COVID identified
 [Klein, et al. *Nature*. 2023]

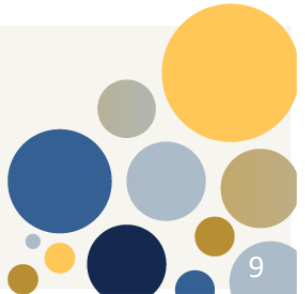
Patient Impact

Improved Diagnosis, Monitoring, and Care

Better Preventative Care

Better Diagnosis, Monitoring, Care, and Targeted Treatments

Findings from Long COVID Pathobiology Studies



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 may be 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

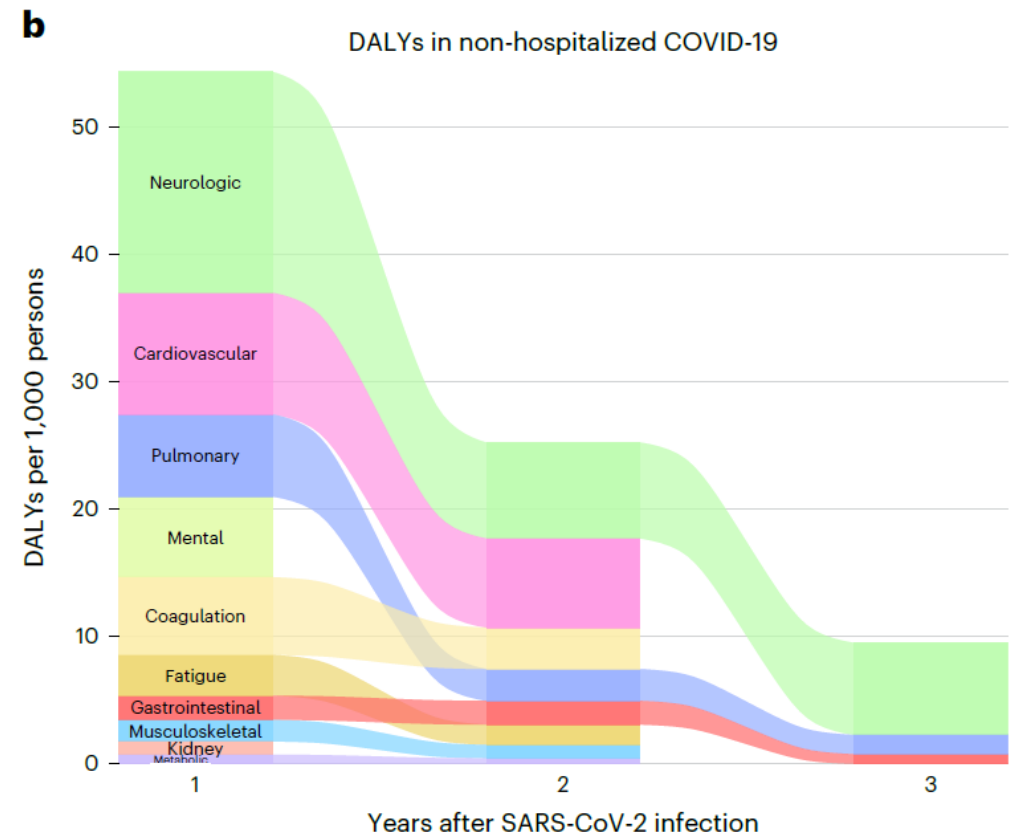
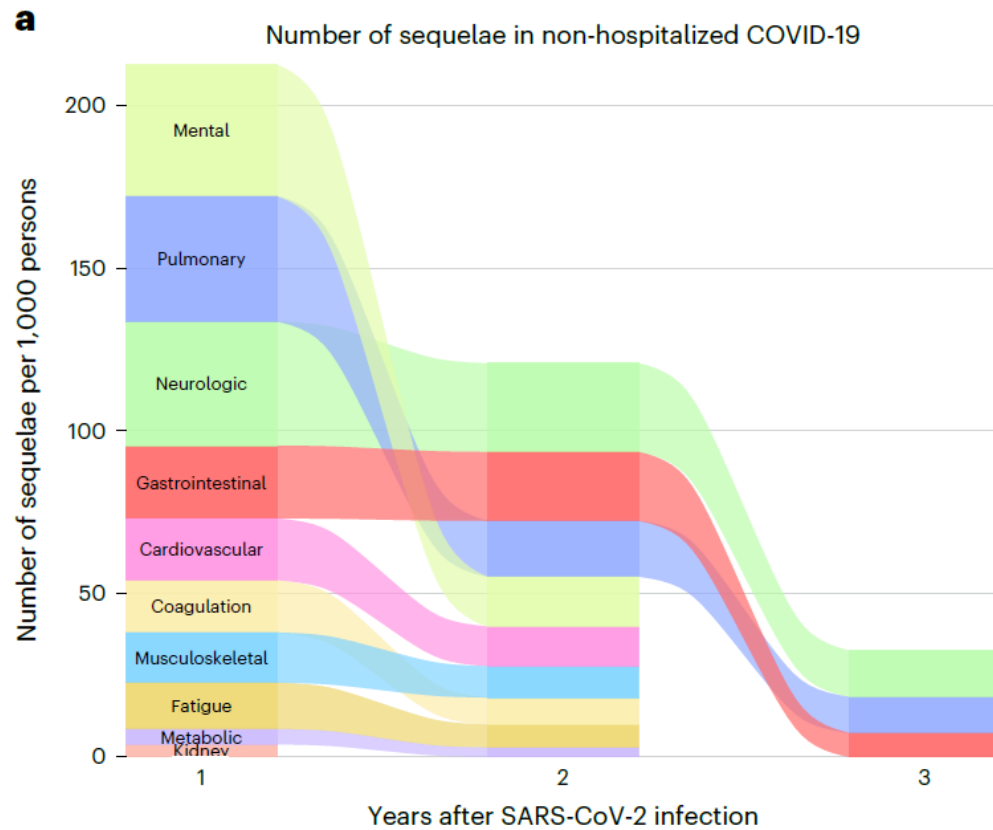
Other

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

Three-year outcomes of post-acute sequelae of COVID-19

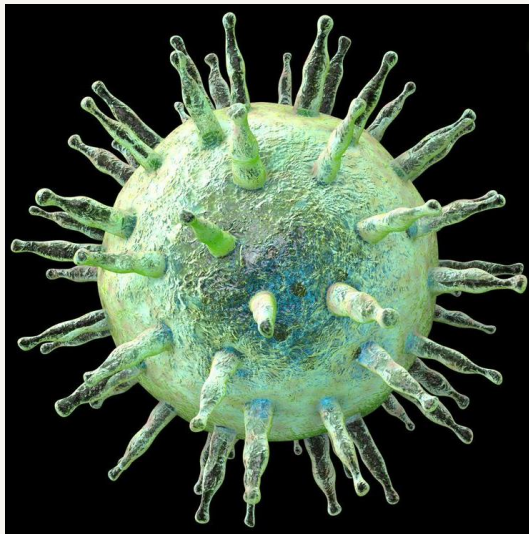
Received: 9 January 2024

Miao Cai^{1,2}, Yan Xie^{1,2,3}, Eric J. Topol⁴ & Ziyad Al-Aly^{1,2,5,6,7} ✉



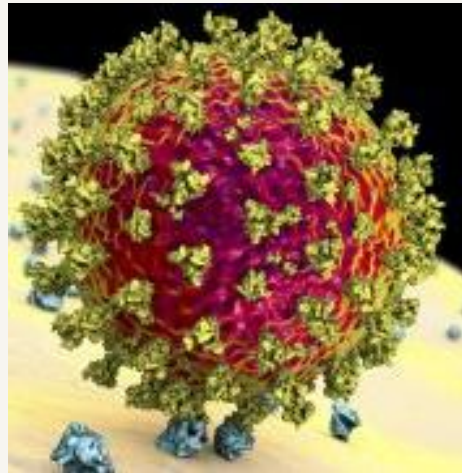
Pathogenesis of Long-COVID

Viral reactivation



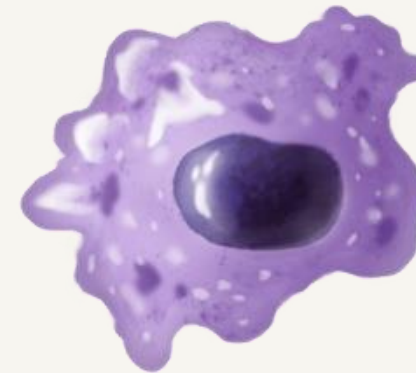
EBV

Persistent viral infection

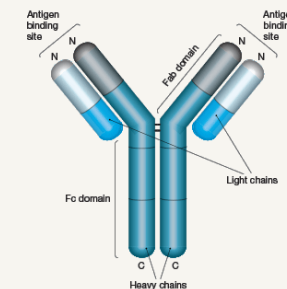


SARS-CoV-2 antigen

Immune dysregulation



Macrophages



Antibodies

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

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

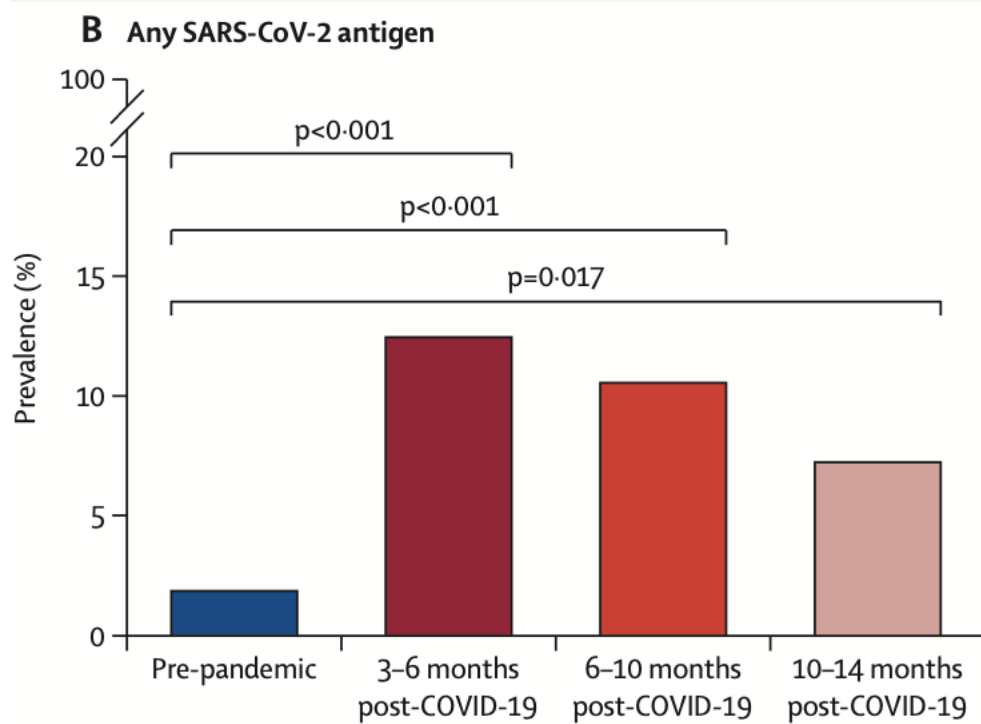


- SARS-CoV-2 infects many cell types and correlates with diverse pathologies
- Is persistence of virus protein(s) or viral RNA correlated with Long COVID or clinical course of disease?
 - Major question under intense investigation with NIH/RECOVER and NIAID support



Does Persistent Infection with SARS-CoV-2 Play a Role in PASC/Long COVID?

Plasma-based antigen persistence in the post-acute phase of COVID-19

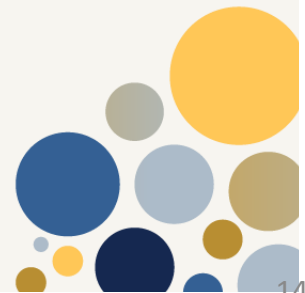


- Utilized a well characterized group of 171 adults at several timepoints in 14 months following RNA-confirmed SARS-CoV-2 infection
- Compared to 250 adults whose plasma was collected before 2020 (pre-pandemic)
- Simoa (Quanterix) single molecule array detection platform showed 10.6% prevalence at 3-6 months to 5.4% at 10-14 months for any SARS-CoV-2 antigen in plasma
- Pre-pandemic era participants had 2% assay positivity

Still needed: Clinical manifestations of SARS-CoV-2 antigen persistence?

Peluso et al (2024) *Lancet Infect Dis*

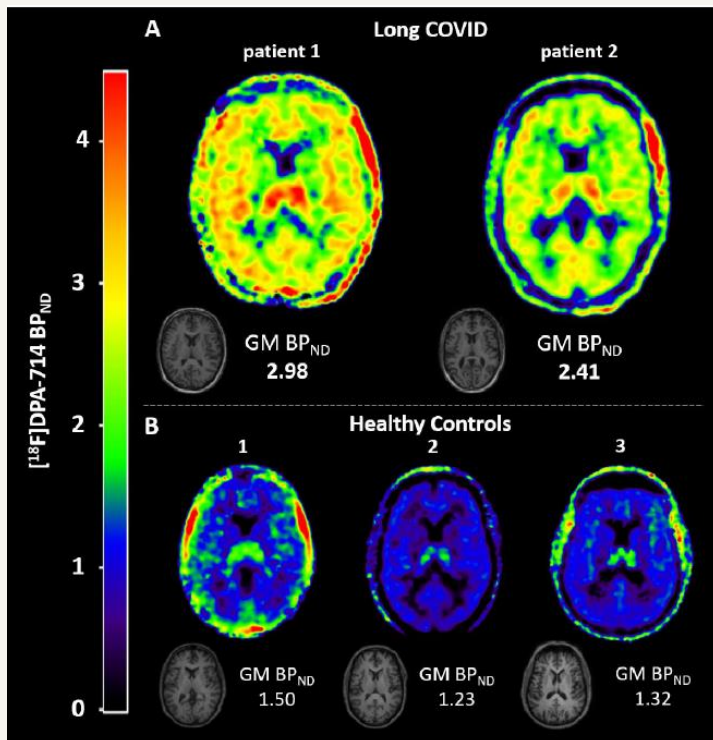
recoverCOVID.org



PET imaging suggestive of brain inflammation

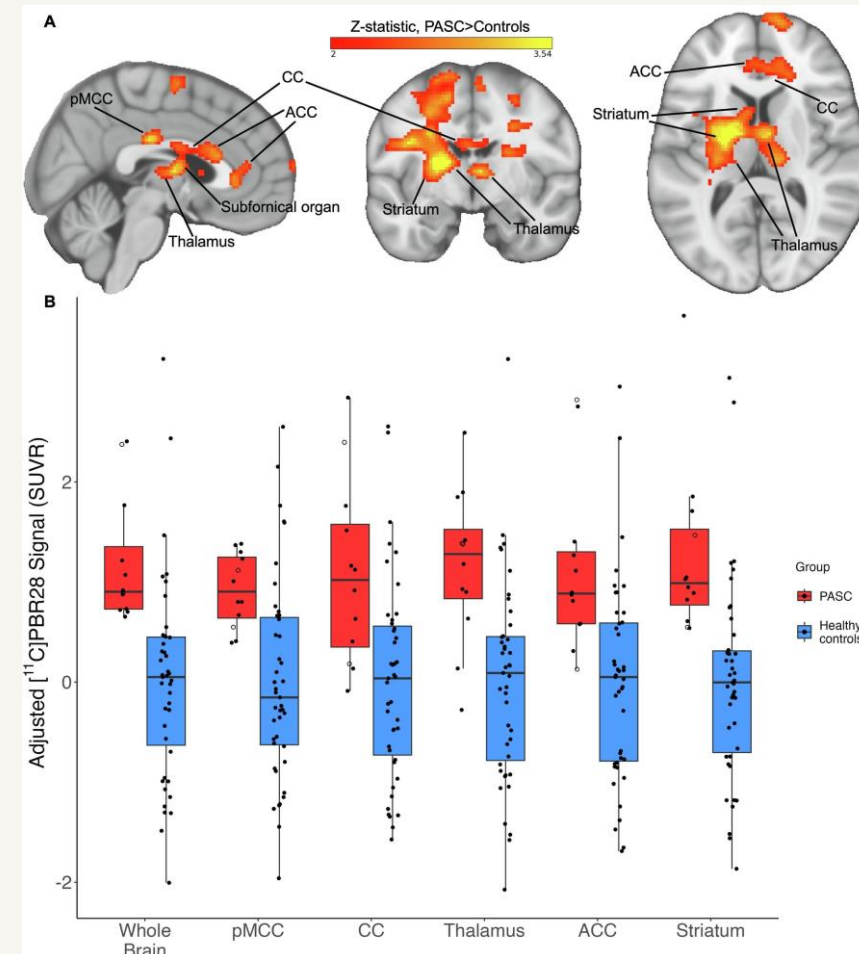
Long COVID is associated with extensive *in-vivo* neuroinflammation on [¹⁸F]DPA-714 PET

Denise Visser¹, Sandeep S.V. Golla¹, Sander C.J. Verfaillie², Emma M. Coomans¹, Roos M. Rikken¹, Elsmarieke M. van de Giessen¹, Marijke E. den Hollander¹, Anouk Verveen², Maqsood Yaqub¹, Frederik Barkhof^{1,3}, Janneke Horn⁴, Bart Koopman⁵, Patrick Schobert⁶, Dook W. Koch², Robert C. Schuit¹, Albert D. Windhorst¹, Michael Kassiou⁷, Ronald Boellaard¹, Michele van Vugt⁸, Hans Knoop², Nelleke Tolboom⁹, Bart N.M. van Berckel¹



Neuroinflammation in post-acute sequelae of COVID-19 (PASC) as assessed by [¹¹C]PBR28 PET correlates with vascular disease measures

Michael B. VanElzakker^{a,e,*}, Hannah F. Bues^a, Ludovica Brusaferrri^{b,c}, Minhae Kim^b, Deena Saadi^a, Eva-Maria Ratai^b, Darin D. Dougherty^a, Marco L. Loggia^{b,d}



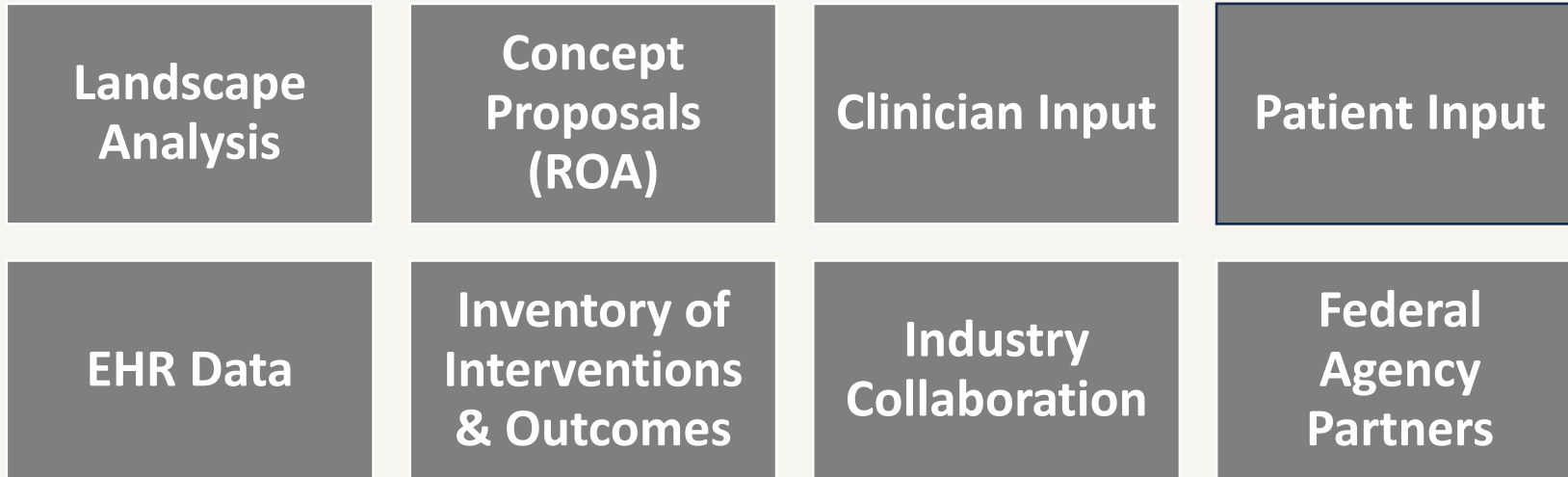
Clinical Trials Progress to Date

Development of RECOVER Clinical Trials Portfolio



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

Sources & Inputs



Design Stages



Input on master protocol development



Focus groups and interviews to learn patient perspectives

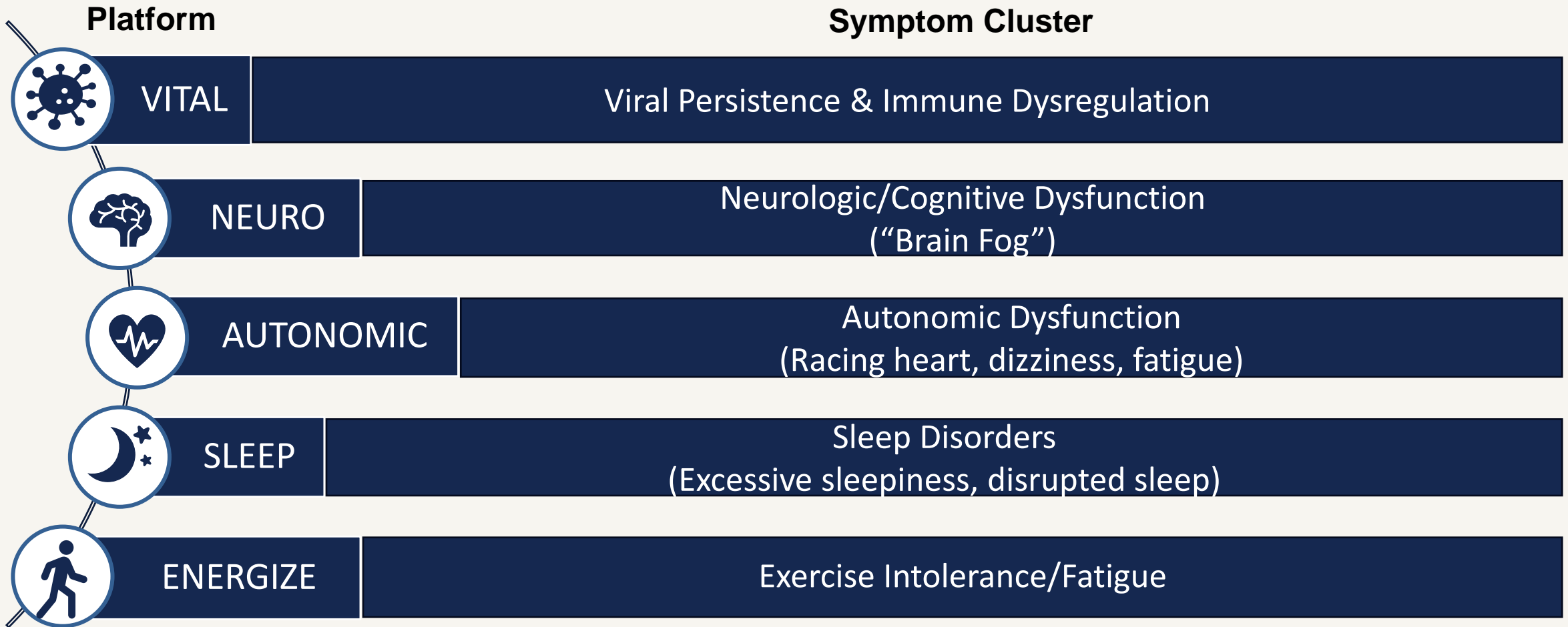


Survey data from RECOVER and non-RECOVER patients



Insights from National Community Engagement Group

RECOVER Clinical Trials Portfolio



5 adaptive platforms with 8 clinical trials collectively testing 13 active interventions
Shared clinical endpoints, approach to patient screening, and regulatory framework:
➡ **improved diagnosis/monitoring/care and paves the way for future treatments**

Long COVID Research Path Forward in 2024 and beyond

Deidentified data now available to researchers

BioData

CATALYST

- In April 2024, **secure data** from more than **14,000 adults** who participated in the RECOVER observational research on Long COVID became **available to authorized researchers** through the cloud-based ecosystem BioData Catalyst® (BDC).
- By giving researchers access to secure data, analysis tools, and resources, the BDC ecosystem aims to spur scientific innovation, collaboration, and discovery while providing a platform for sharing data and validating results.
- The addition of RECOVER data to BDC can help investigators identify and explore Long COVID connections that may benefit from or inform future studies.

This is just the beginning: Additional adult data – as well as pediatric and autopsy cohort data from RECOVER - will be released on an ongoing basis.



RECOVER

Researching COVID to Enhance Recovery

An Initiative Funded by the National Institutes of Health

recoverCOVID.org