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

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

June 8, 2023

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RECOVER
Researching COVID to Enhance Recovery

An Initiative Funded by the National Institutes of Health

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

RECOVER's Principles In Action: Meaningful Patient Engagement

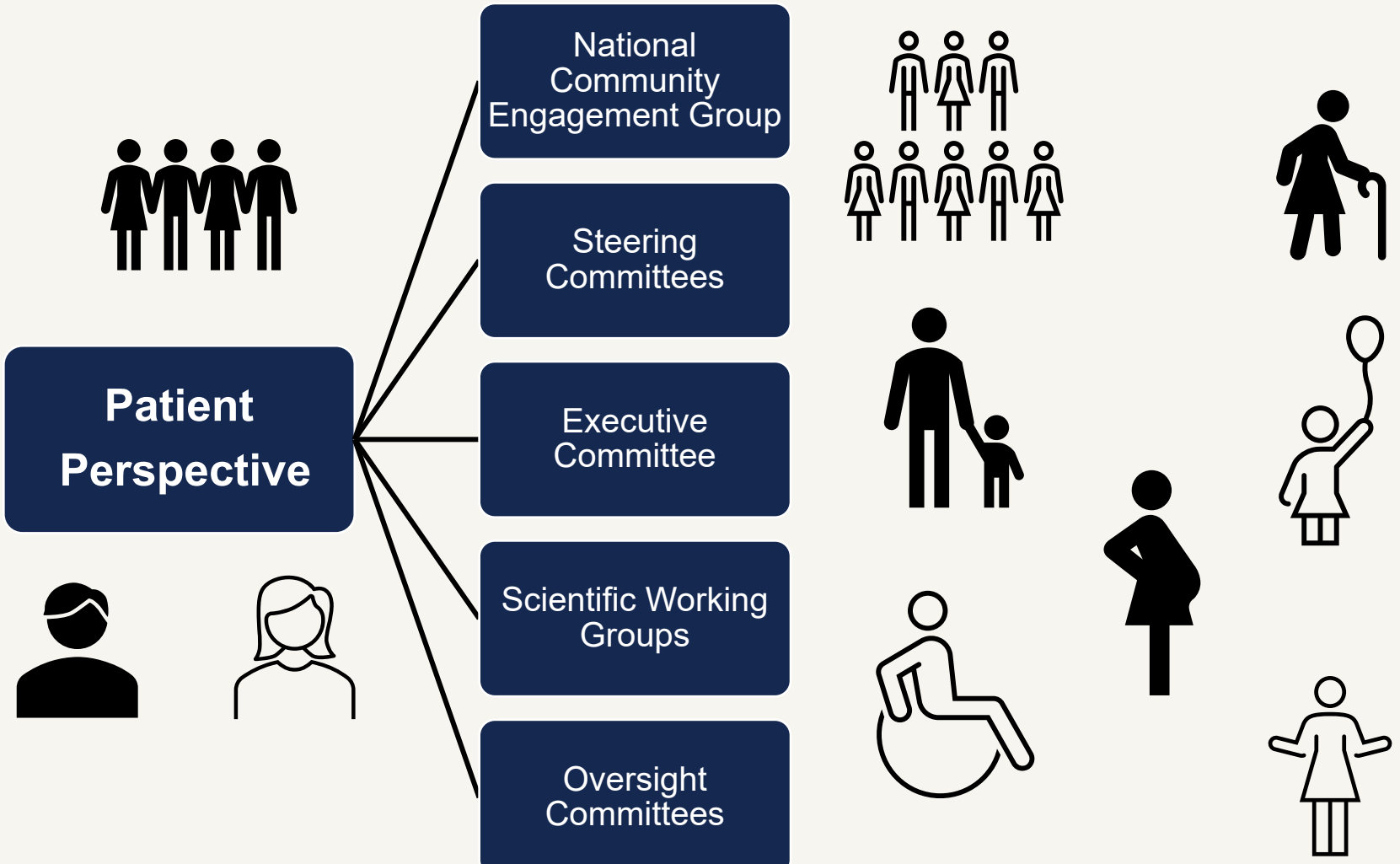
Guiding Principles

Patient-centered

National scale with inclusive, diverse participation & community engagement

Patient Perspective

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



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

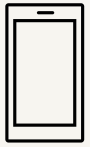
Clinical Trials

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

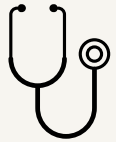
RECOVER Data Types

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

NIH RECOVER Initiative: Status Update

Observational

- Developed **largest, most diverse, and deeply characterized** longitudinal clinical cohort of PASC patients
- **Identified sub-phenotypes** and specific symptom criteria of PASC
- Data supports **vaccination safe** for children who have had MIS-C

Pathobiology

- **Funded 40+ studies**, including on symptom-specific pathology, epigenetics, and **multiomics**
- **Enrolled 140+ decedents**

Clinical Trials

- **Worked alongside patients** to design adaptable clinical trials
- Established **synergistic industry collaborations**
- Developed **5 platform protocols**
- Initial launch of patient enrollment in **Q3/Q4 2023**

RECOVER has established a robust foundation for continued knowledge generation on PASC

Observational: Capturing Real-World Facets of Long COVID at Large Scale

EHR/Health Systems Studies

Strategy

Analysis of **60 million records** with **>7 million COVID** cases across **diverse populations**

Objectives

- Understand **incidence, prevalence, risk factors** over time
- Capture **longitudinal data** with **minimal participant burden**
- Define **sub-phenotypes** to inform clinical approaches

Progress

- Computable phenotypes of PASC in adults and children
- Pre-COVID vaccination reduces risk of Long COVID
- **Prevalence:**
  - **Children:** 3.7% develop PASC.
- **Risk factors:**
  - **Adult:** severity of disease, comorbidities, female sex, racial/ethnic minority
  - **Pediatric:** < 5 yrs old, ICD admission for acute infection, complex chronic conditions
  - **Increased risk of new-onset conditions** in PASC pts: T2DM, anxiety, ataxia, myoneural disorders

Future Directions

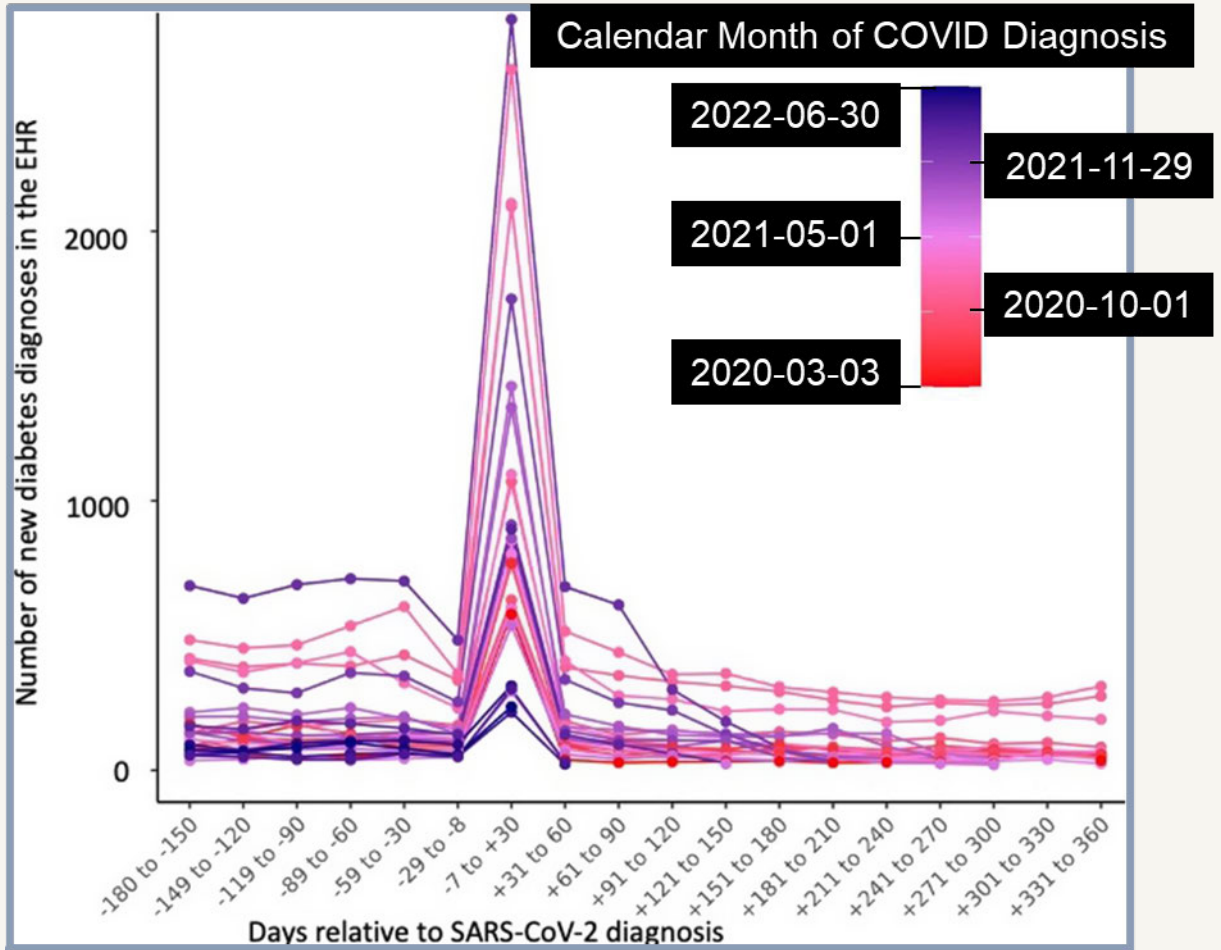
Cross-validate EHR findings and other **real-world data** with data from observational **clinical cohorts** at scale

EHR Cohorts: Diabetes mellitus and SARS-CoV-2 Infection

Does PASC increase the incidence of other conditions/disorders?

Sharp increase in new cases of type 2 DM during the acute phase of SARS-CoV-2 infection.

Infection with SARS-CoV-2 is showing **dysregulation in glucose homeostasis** that could accelerate T2DM diagnosis.



Number of new DM cases in the N3C enclave, by 30-day windows relative to SARS-CoV-2 infection.

Reddy, et al. 2023. *Clin Transl Sci.*

EHR Cohorts: Impact of Pre-existing Obstructive Sleep Apnea (OSA) on the Risk for PASC

Harmonized analysis across three EHR Cohorts
(N3C, PCORnet, PEDSnet)

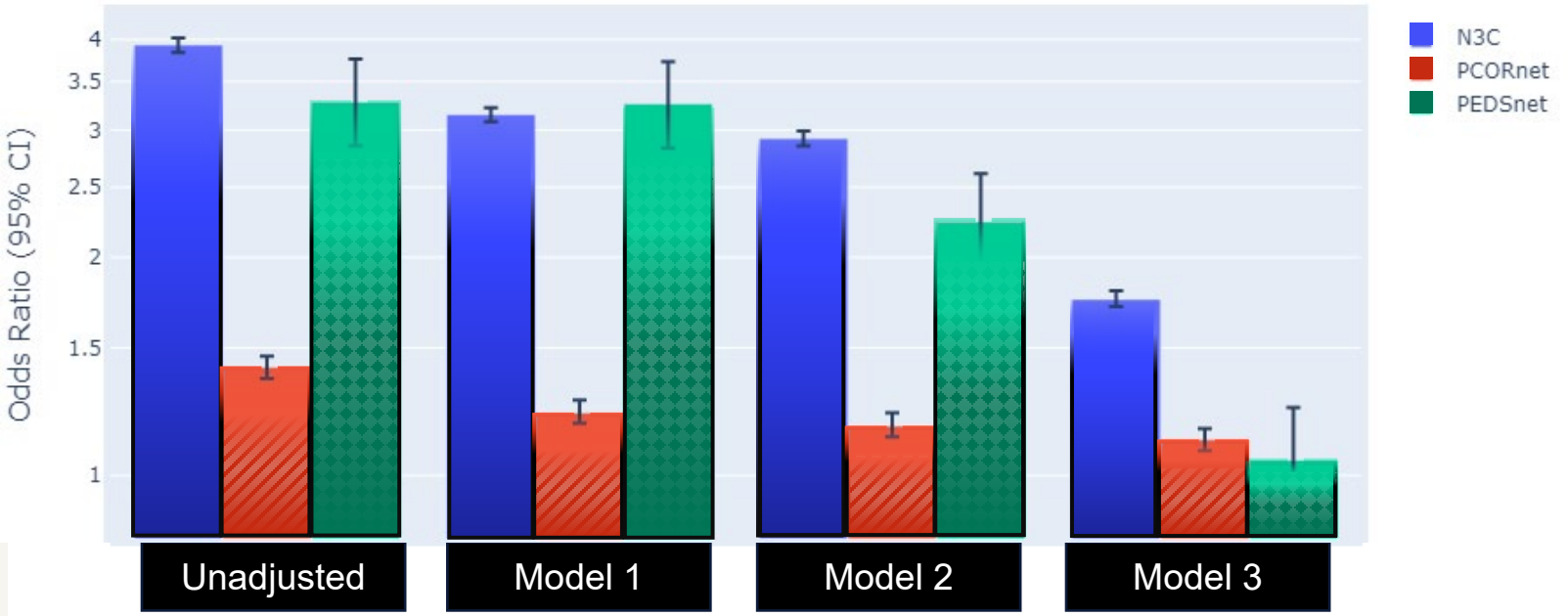
Unadjusted OR for probable PASC associated with preexisting OSA diagnosis in adults and children ranged from 1.41 to 3.93

Adults w/ preexisting OSA increased odds of developing PASC
→ may benefit from increased monitoring after SARS-CoV-2 infection

Mandel, et al. 2023. *Sleep.*

OSA as a risk factor of PASC?

Association between preexisting OSA and probable PASC across different EHR Networks



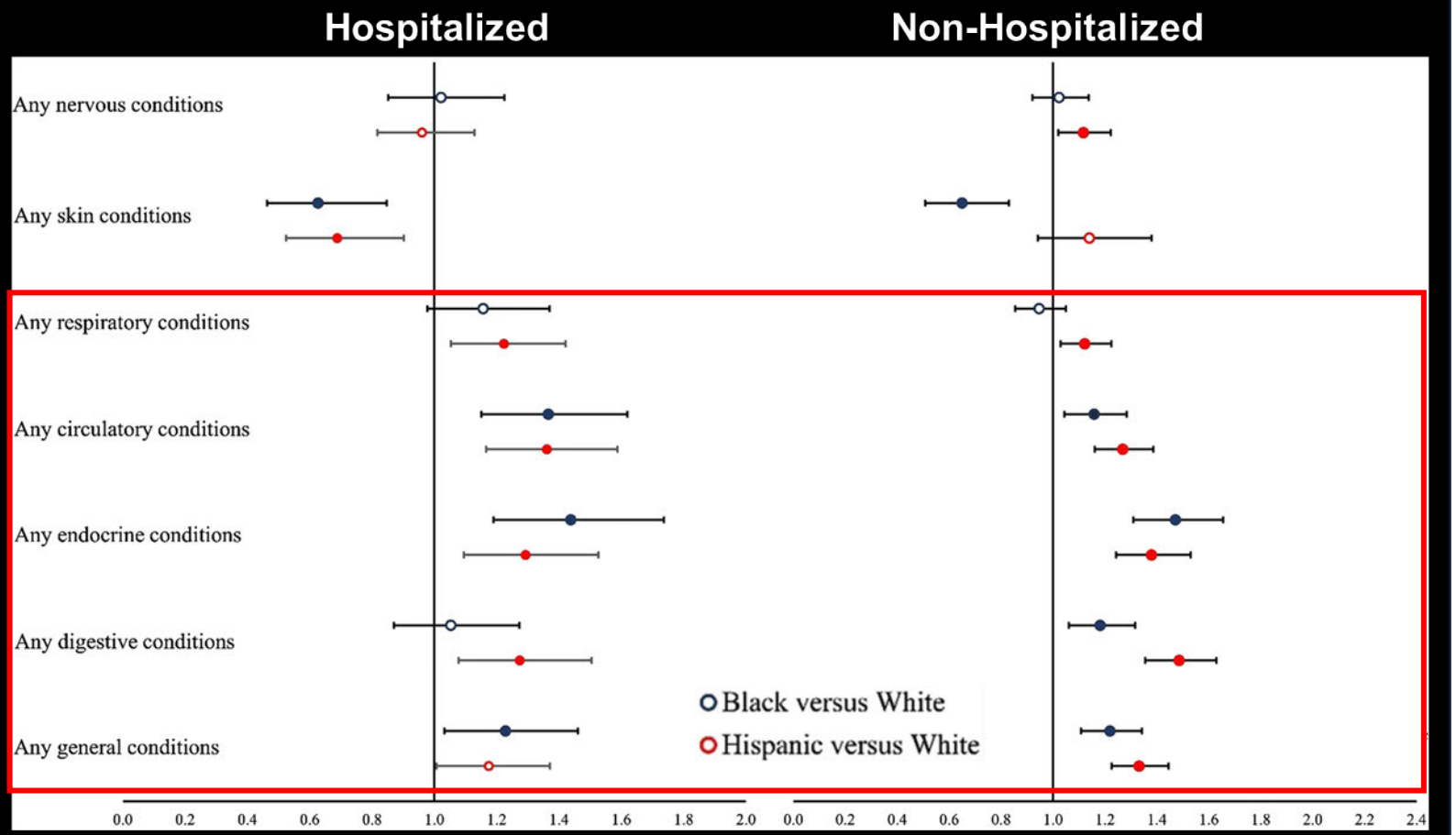
Unadjusted: Odds ratios and 95% CI for association of preexisting OSA and probable PASC.
Model 1: Adjusted for age group, sex, and race/ethnicity.
Model 2: Adjusted for age group, sex, race/ethnicity, and hospitalization status.
Model 3: Adjusted for age group, sex, race/ethnicity, hospitalization status, obesity, and comorbidities.

EHR Cohorts: Examining Racial/Ethnic Differences in PASC

31-180 days post positive SARS-CoV-2 test.

Black and Hispanic patients **higher odds** of new respiratory, circulatory system, endocrine, and digestive conditions

Adjusted racial/ethnic differences in incident symptoms and conditions grouped by organ system and hospitalization status.



Khullar, et al. 2023. *Journal of General Internal Medicine*

Opportunity for Cross-Validation

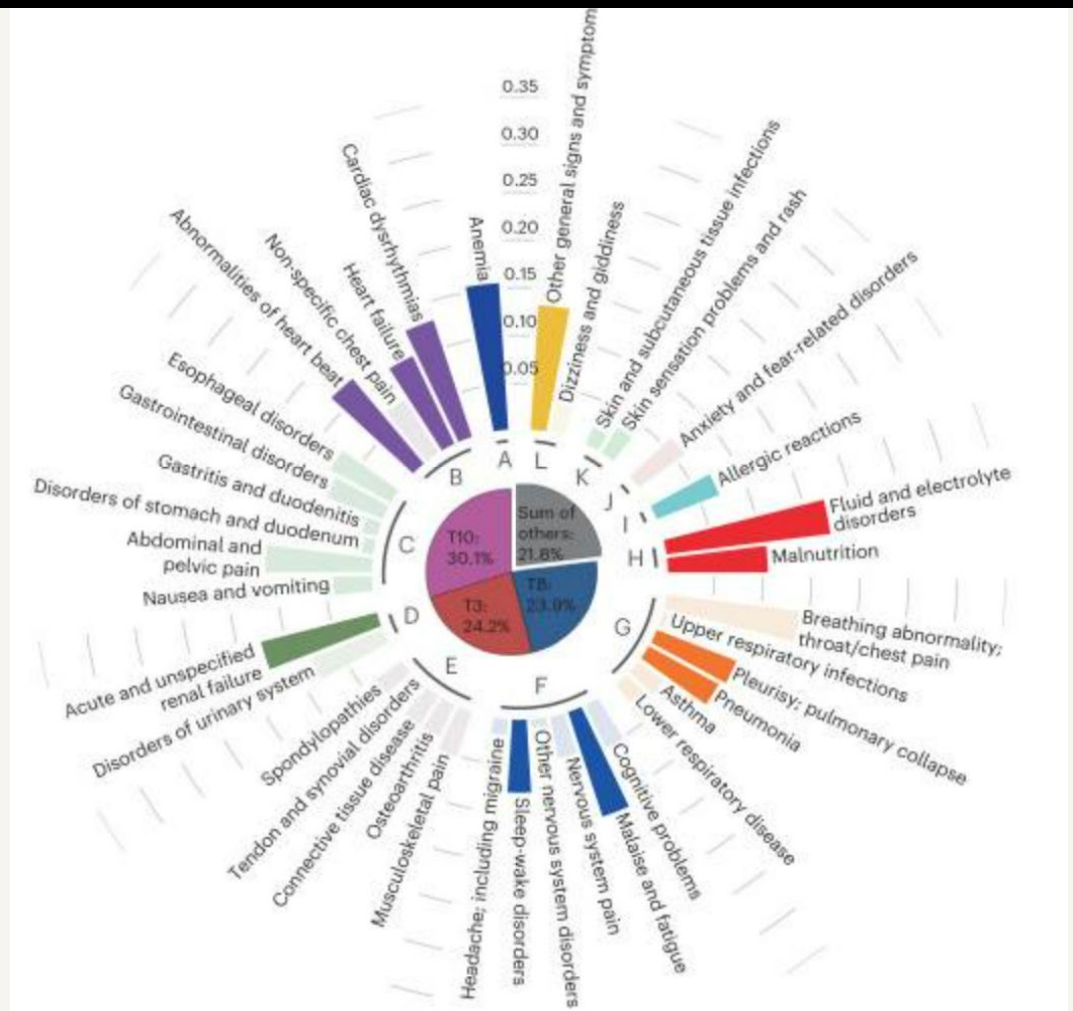
Refine PASC/Long COVID computable phenotypes **through cross-validation with RECOVER enrolling cohorts and EHR teams.**

Accelerate our understanding of sequalae of SARS-CoV-2 infection.

Improve and validate methods developed with EHR data analyses and **augment clinical cohort data.**

Reproducible and comparable phenotypes across healthcare systems.

Incidence rates of potential PASC conditions in Subphenotype1 (cardiac and renal)



Zhang, et al. 2022. *Nature Med.*

Observational: Characterizing the Clinical Spectrum of Long COVID, In-Depth at Large Scale

Enrolling Clinical Cohorts

Strategy

Deep phenotyping of diverse participants **across lifespan** and **clinical continuum**

Progress

- **Enrollment:** ~93% adult participants (Complete Q3); ~44% pediatric participants (Complete Q4)
  - **Tier 1 testing underway – Tiers 2 and 3 forthcoming, including deeper phenotyping**
- **20+ reports in process (pubs/preprints)**
- **MUSIC Study (MIS-C)**: vaccination safe for children who have had MIS-C
- Identified sub-phenotypes and specific symptom criteria of PASC
- Biomarker testing underway
- Characterized **impacts of different variants and vaccination**: symptoms consistent across infection waves
- **Defined PASC prevalence in adults**:
  - Of pts recruited during acute infection, **20-30% reported symptoms** 3 mos. post enrollment

Objectives

- Enroll **acute & post-acute infection patients** from **200+ sites**
- Define Long COVID **trajectory, incidence, clinical spectrum,** and **subphenotypes**
- Discover **Long COVID biomarkers**

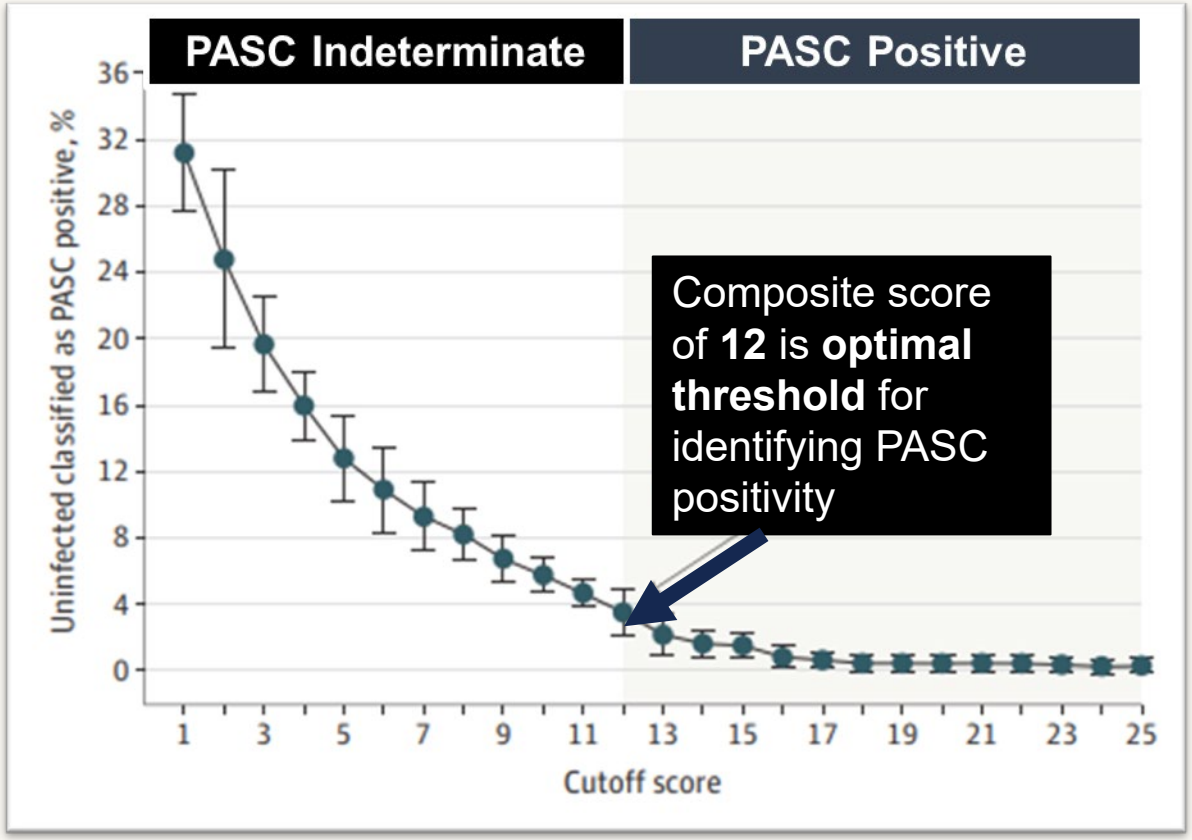
Future Directions

- Integrate **wearable sensor data**
- In depth clinical characterization
- **Biomarker** analyses
- Pathobiology studies underway

RECOVER Clinical Cohort Updates: Developing a Definition of PASC

What symptom-based criteria can be used to identify PASC cases in adults?

- **9,764 participants**
- **6-month** follow-up visit

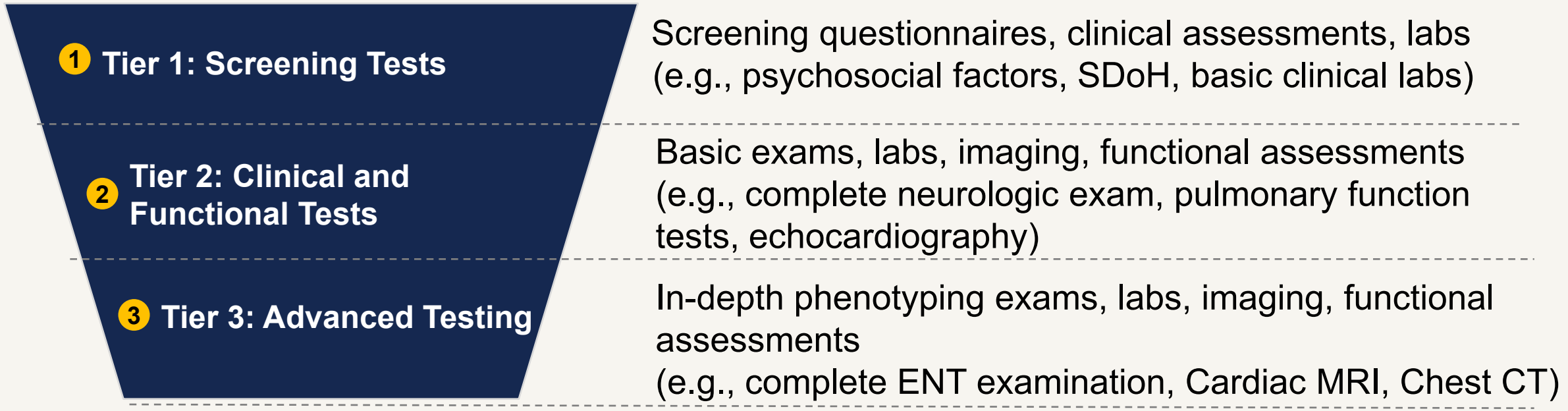


Symptom	PASC Score
Smell/taste	8
P-E Malaise	7
Chronic cough	4
Brain Fog	3
Thirst	3
Palpitations	2
Chest pain	2
Fatigue	1
Sexual desire/capacity	1
Dizziness	1
GI	1
Abnormal movements	1
Hair loss	0

Thaweethai, et al. 2023. *JAMA Network Open.*

Enrolling Clinical Cohort 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.



PASC Frequencies Overall and Stratified by Subcohort and Infection

Infected post acute pre-Omicron participants most likely to be PASC positive (35%) compared to infected acute (10%) or post acute Omicron (17%)

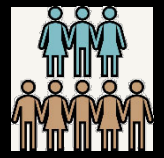
	Total No.	PASC Positive, No (%)
All Participants (full cohort)	9764	2031 (21)
Infected	8646	1990 (23)
Uninfected	1118	41 (3.7)
Acute Omicron		
Infected	2231	224 (10)
Uninfected	388	18 (4.6)
Post acute pre-Omicron		
Infected	3732	1320 (35)
Uninfected	290	11 (3.8)
Post acute Omicron		
Infected	2666	442 (17)
Uninfected	438	12 (2.7)

Note: Acute cohort participants with a pre-Omicron index date were included in the full cohort analysis.

Thaweethai, et al. 2023. *JAMA Network Open.*

Observational: Defining the Burden, Risk Factors, and Trajectory of Long COVID

Longitudinal, Community-Based Cohorts



Strategy

Leverage 14 existing longitudinal, community-based cohorts with 49K adult (e.g., C4R) and 12K (e.g., ABCD) pediatric Long COVID patients

Progress

- 16K+ sero-surveys performed
- 6,600+ COVID cases (1,500 COVID related events)
- Risk factor data analysis underway
  - Smoking and hospitalized COVID associated with slower recovery
- Identified incidence and prevalence across variants (Delta)
- Developed Wave 3 Questionnaire harmonized with RECOVER

Objectives

- Investigate **incidence** and **prevalence across variants**
- Study **risk factors** on **health trajectory**
- Understand **long-term impact of Long COVID**
- Provide **deep genotypic characterization**
- Validate findings from EHR studies

Future Directions

- Evaluate influence of SDoH
- Elucidate resilience factors
- Prevalence across omicron
- Biomarker discovery

Pathobiology Studies: Understanding Long Covid Across Mechanisms, Approaches, and Systems

Strategy

- **Test leading hypotheses to elucidate** natural history and etiology leading to Long COVID
- **Integrate** predictive and **analytic assays** with **clinical observation**

Objectives

- Perform mechanistic studies to identify biomarkers
- Discover **therapeutic targets** that inform clinical trials
- Enable improved diagnosis, monitoring, and patient stratification

Progress

- **40+ studies funded** focused on:
  - Consequences of Acute Infection
  - System-Specific Pathology (Neurological, Cardiac, Respiratory)
  - Immune Response, Inflammation, Autoimmunity
  - Epigenetics, **Multiomics**
  - Animal Models

Future Directions

- **Mechanistic studies**
- Risk stratification
- Biomarker identification

Investigating Pathobiology Across a Range of Mechanisms, Approaches, and Systems

Hypotheses

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

Mechanistic Assays

- B and T cell responses
- Mass cytometry
- Cytokine profiling
- Proteomics
- Genomics
- Transcriptomics
- Metabolomics

Assays Integrated With Clinical Observation

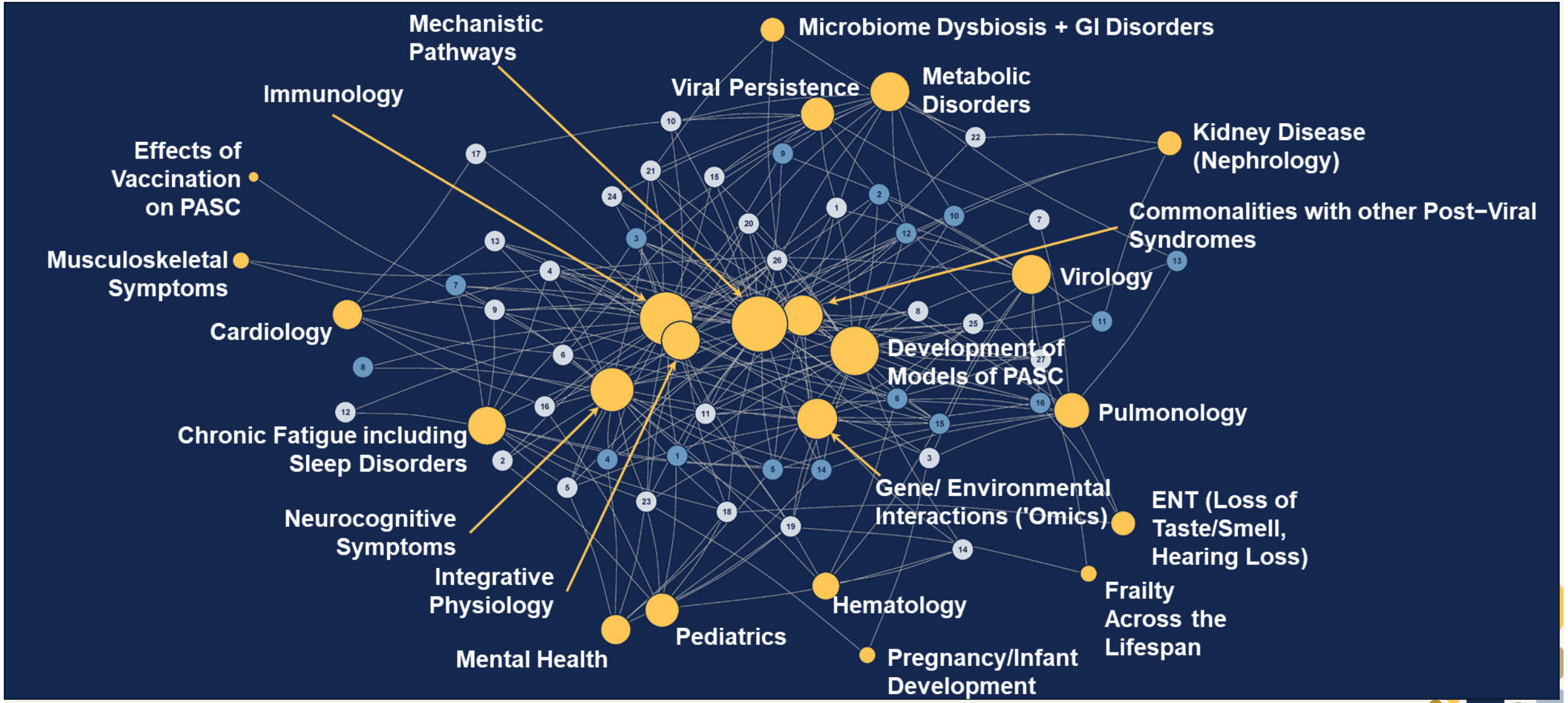
- Predictive & correlation analyses
- Mechanistic & perturbation analyses
- AI/ML analytics

Approaches Proposed

- CSF collection
- Cardiac MRI
- Epigenetics
- Autopsy
- Autoantibody characterization

Comprehensive RECOVER Pathobiology Portfolio

Graph-theoretic layout of Pathobiology NOSI-ROA awards and their study focus



Clinical Trials: Identifying Safe & Effective PASC Treatment Strategies

Clinical Trials

Strategy

- Rigorous, integrated, and adaptive platform protocols to investigate safe and effective treatments for PASC

Objectives

- Investigate priority symptom clusters and their causes
- Test known and novel interventions across domains (drugs, devices, rehabilitation, etc.)
- Evaluate treatments to improve Long COVID symptoms

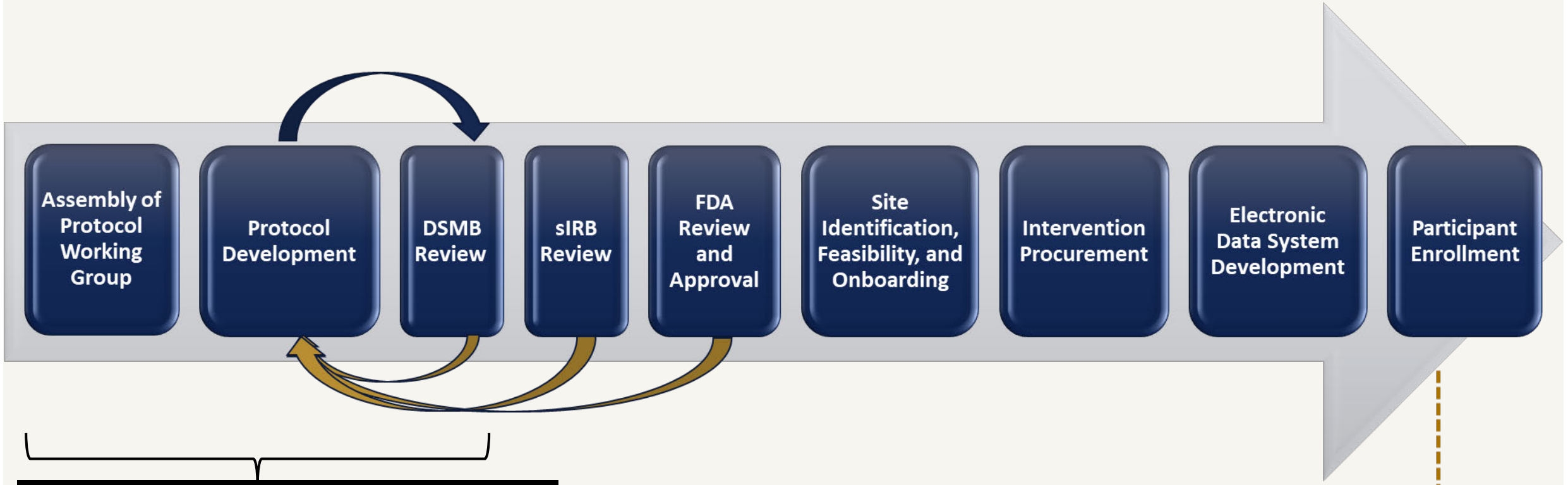
Progress

- **Engaged community and patient advocacy groups** throughout protocol development and intervention prioritization
- Cross-consortium data and published literature informed clinical trial development
- Established synergistic industry collaborations for materializing multiple interventions
- Developed **5 platform protocols poised to launch in Q3/Q4 2023**

Future Directions

- Adaptive clinical trials
- Cross-cutting Mechanistic Studies

Steps to Ensure Patient-Centeredness and Safety in Clinical Trials



Patient perspectives are involved in:

- Protocol Working Groups
- Protocol Development
- DSMB
- Other Trial Elements

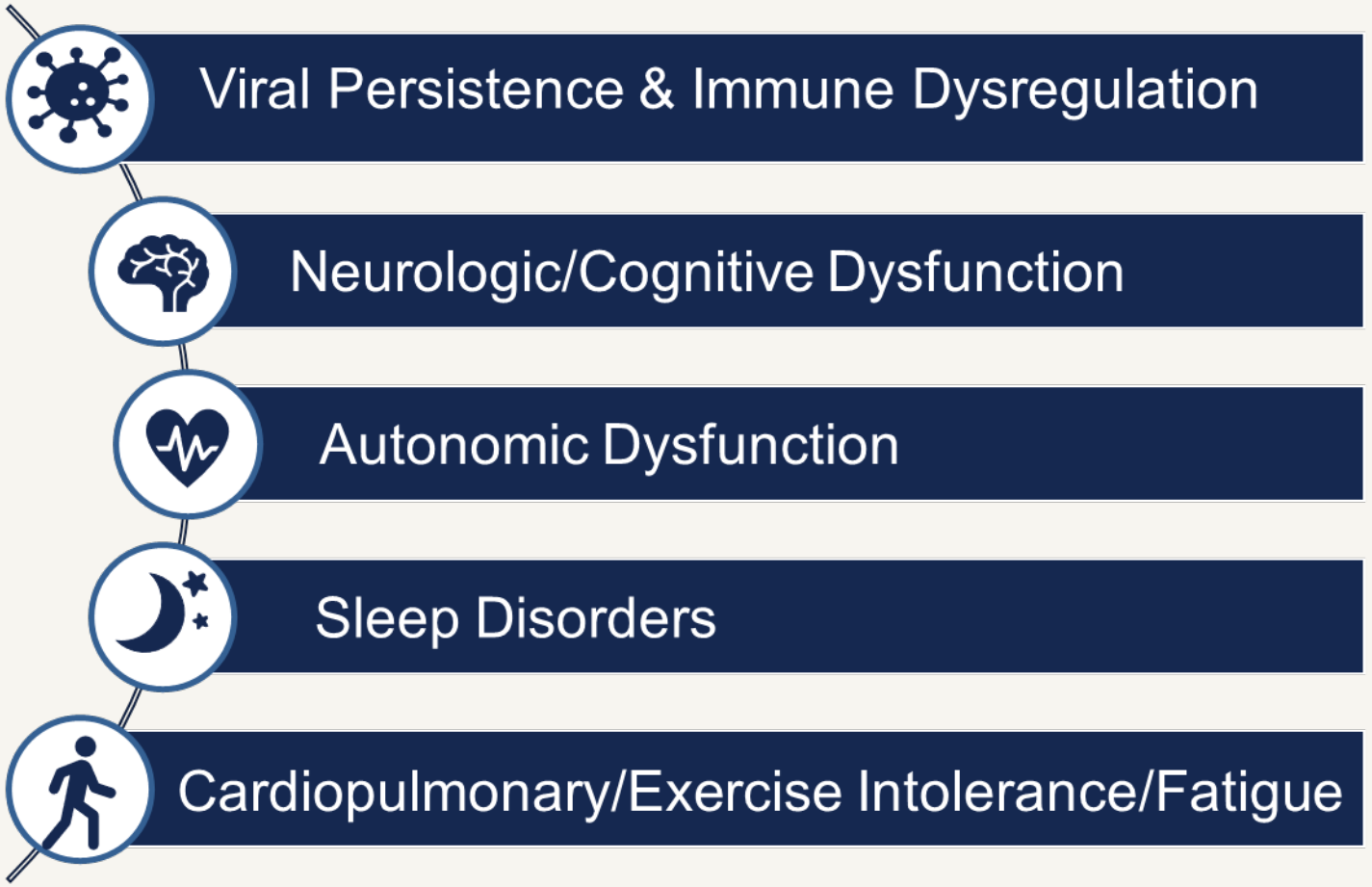
Estimated Q3/Q4 2023

Designing and Launching RECOVER Clinical Trials

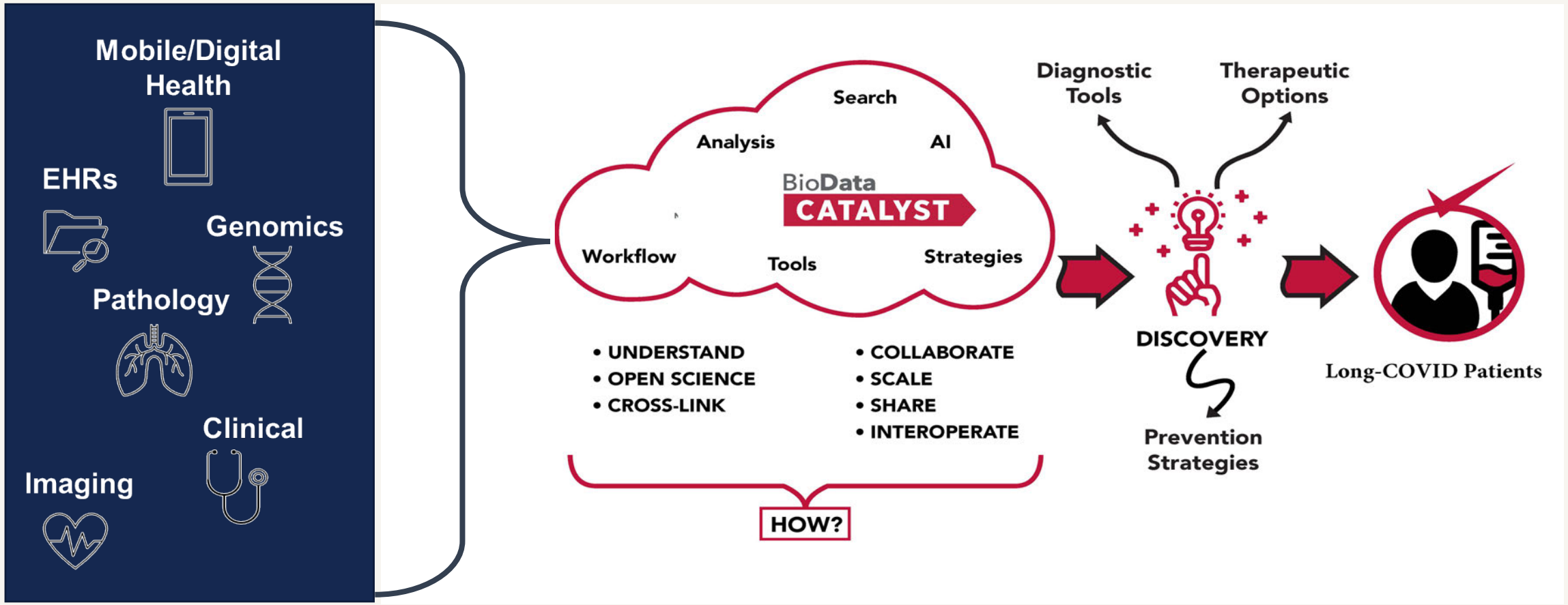
RECOVER CLINICAL TRIAL PLATFORMS PORTFOLIO

Platform Integrates Five Adaptive Master Protocols

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



RECOVER Data Sharing and Release



RECOVER Current Progress and Future Directions

Largest, diverse, deeply characterized clinical cohort of PASC patients (Adult completion Q3; Pediatrics Q4)

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

Cohorts that support deep and longitudinal characterization of PASC patients

40+ pathobiology studies that will characterize pathophysiology of PASC

5 master protocol-driven platform clinical trials poised to launch

Future Directions

- Ongoing in-depth clinical characterization and biomarker analyses
- Cross-validation and ‘real time’ follow-up from EHR findings
- Integrate wearable sensor data
- Mechanistic studies, risk stratification, biomarker identification
- Coordinated, high-throughput testing of therapies