

Medical Research & COVID-19: Updates from NIH's National Institute of Neurological Disorders and Stroke (NINDS)

Walter Koroshetz, MD, *Director, NINDS*

May 4, 2021

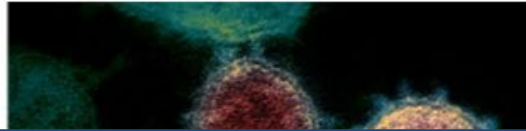


NIH Research on COVID-19

Therapeutics



Vaccines

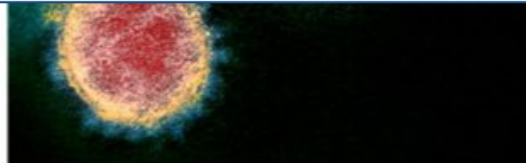


How to address an emerging problem:
recovery from SARS-CoV-2 infection?

Natural History



Basic Research



Accelerating COVID-19 Therapeutic Interventions and Vaccines(ACTIV)

<https://fnih.org/our-programs/activ/about>

ACTIV Partnership
Leadership Group

ACTIV Executive Committee

Co-Chairs

- Francis Collins, NIH
- Paul Stoffels, J&J

Members

- Gary Disbrow, BARDA
- Mikael Dolsten, Pfizer
- Anthony Fauci, NIH
- Gary Gibbons, NIH
- Peter Marks, FDA
- William Pao, Roche
- Andrew Plump, Takeda
- Janet Woodcock, FDA

Preclinical Working Group

- Animal Models
- In Vitro Assays

Therapeutics Clinical Working Group

- Agent Prioritization
- Master Protocol

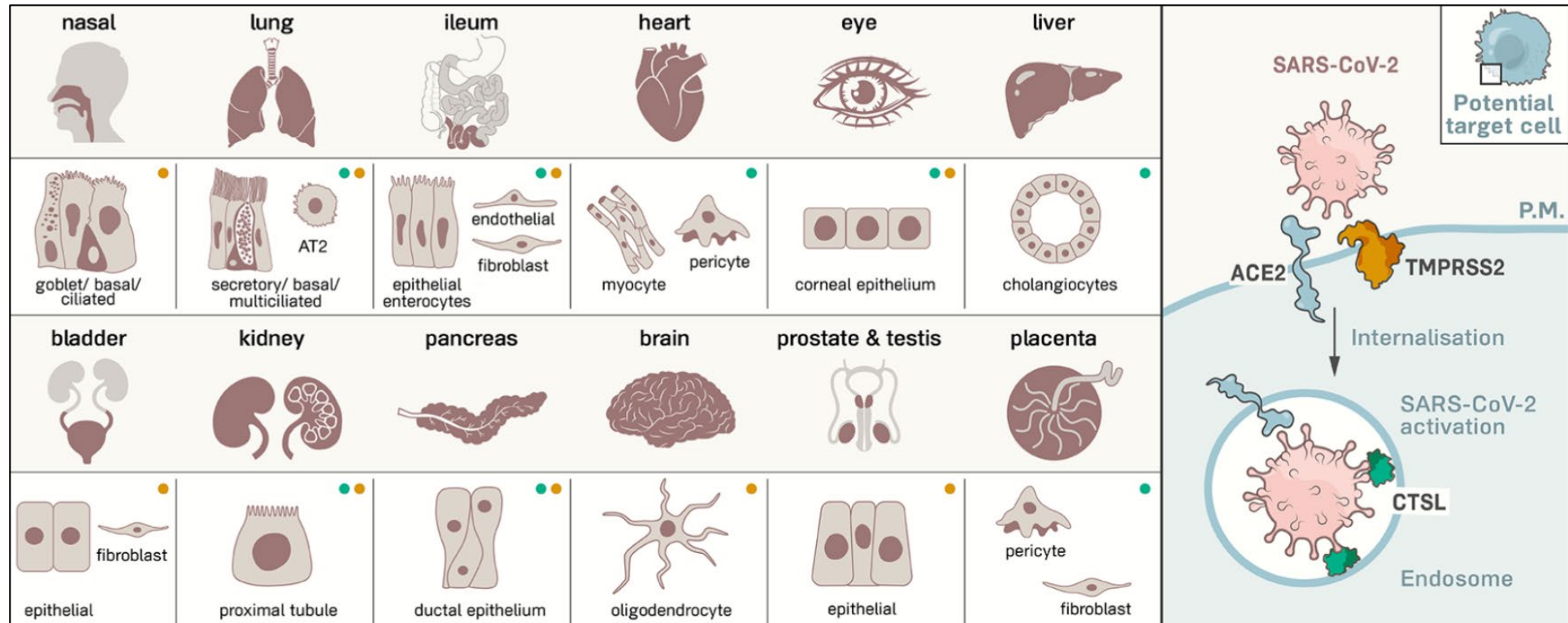
Clinical Trial Capacity Working Group

- Survey Development
- Clinical Trial Network
Inventory
- Design Innovations

Vaccines Working Group

- Vaccines Clinical Trials
- Protective Immune
Responses
- Vaccine-Associated Immune
Enhancement

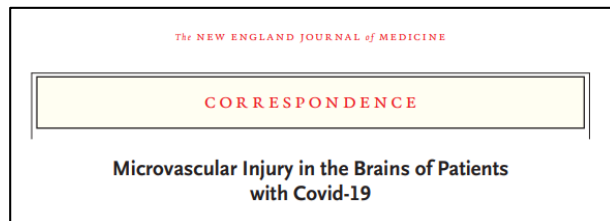
COVID-19 Affects Multiple Organs



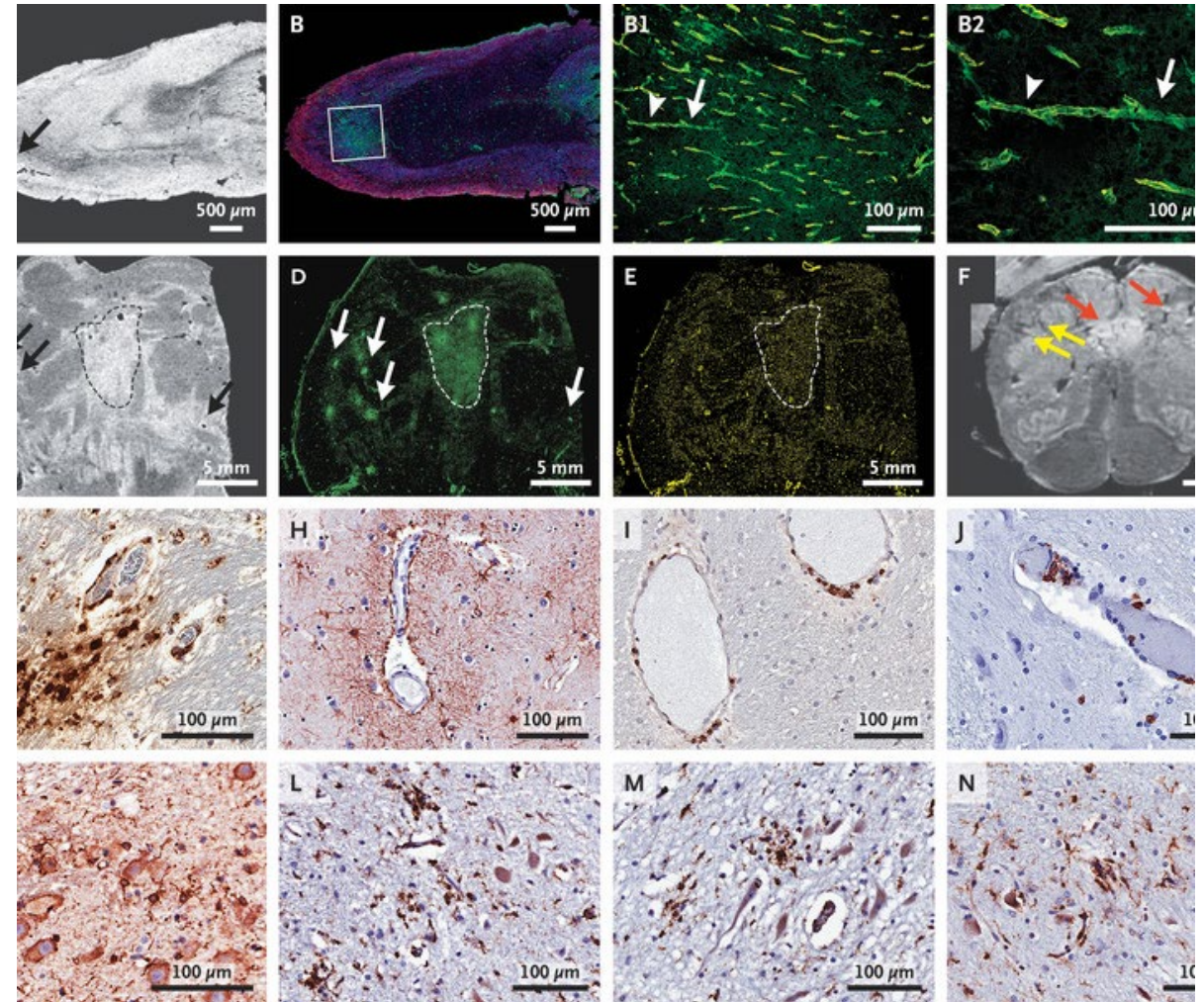
[The Scientist](#), April 2020

Is SARS-CoV-2 in the brain?

- Post-mortem study of brains of individuals who had COVID-19
- No evidence of viral infection in brain
- Widespread evidence of inflammation and damage, including:
 - Multifocal breakdown of the blood brain barrier, small infarcts, microhemorrhages, inflammatory infiltrates, and microglial nodules,
- Infection can lead to blood clots → stroke

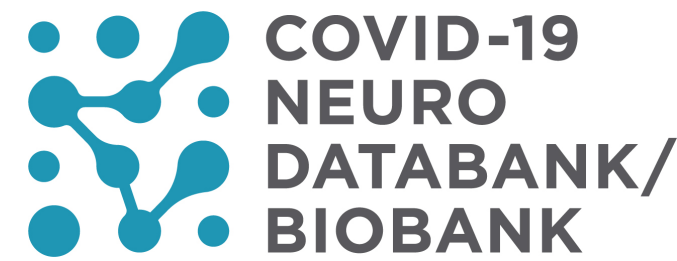


Nath et al, [NEJM](#), NINDS



Pathological Studies of Microvascular Injury in the Brains of Patients Who Died from COVID-19

COVID-19 NEURO DATABANK/BIOBANK



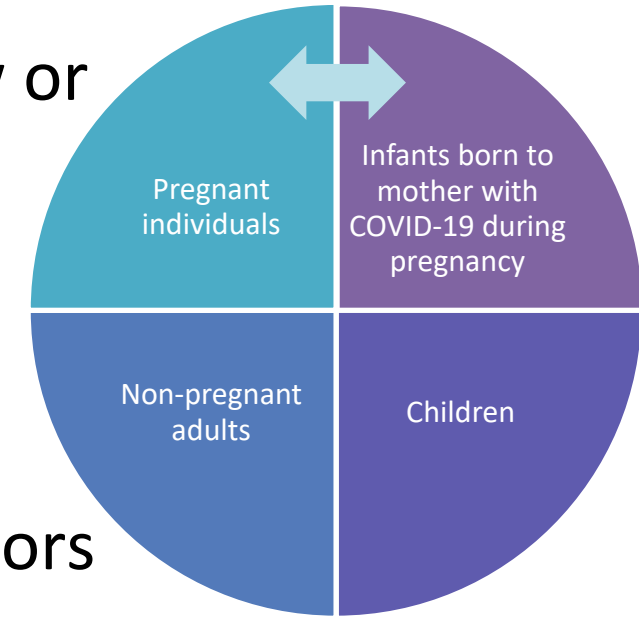
PIs Andrea Troxel, Sc.D.; Eva Petkova, Ph.D.

Data repository

Documented COVID-19 inpatients & outpatients with new or worsened neurological conditions
Infants born to mothers with COVID-19 during pregnancy

Objectives:

Rapidly collect high-quality data and linked biospecimens
Accelerate pace of research
Leverage talent, commitment, experience of all collaborators
Data and biospecimens available for sharing



Participation from Academic medical centers and individual medical practitioners

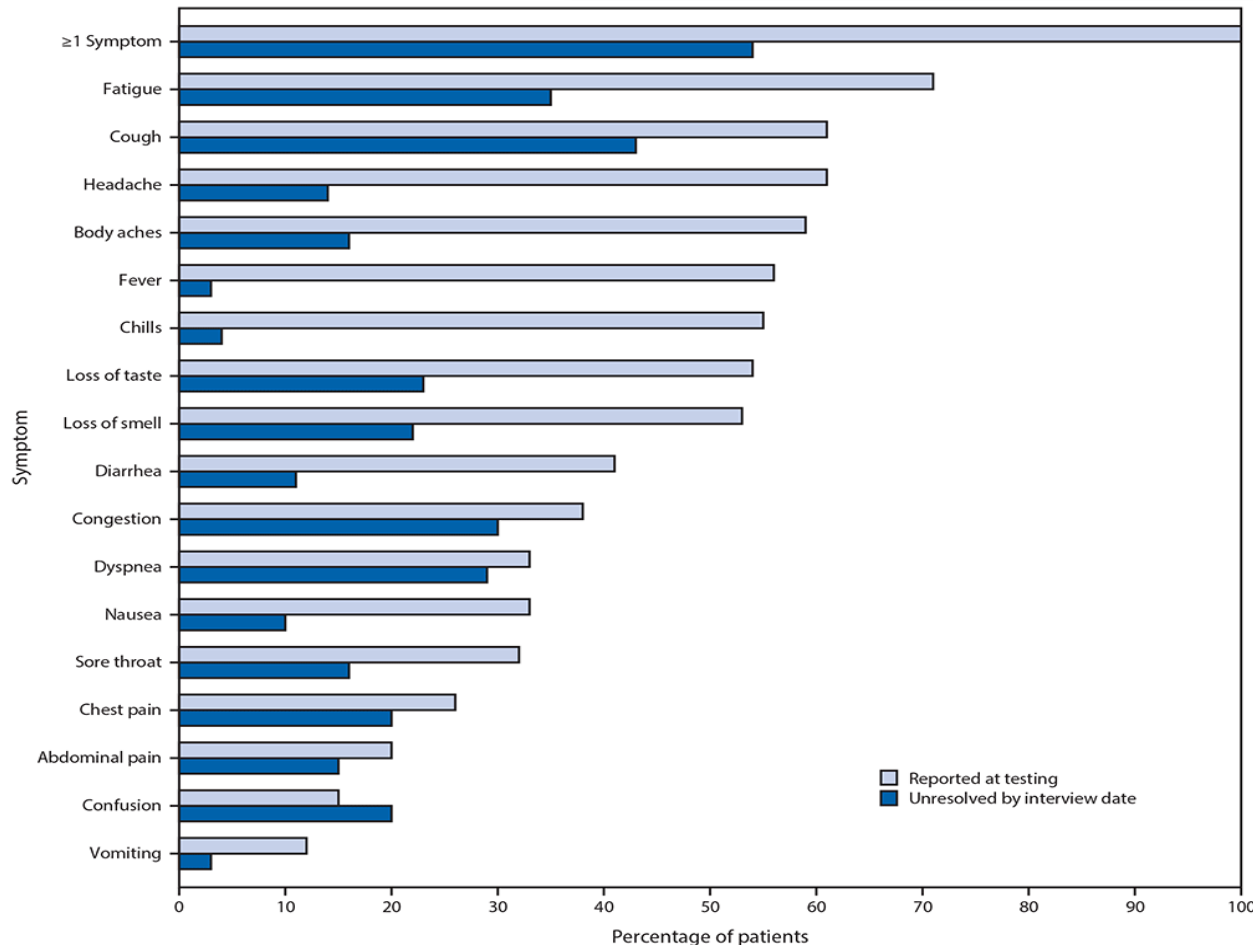




Morbidity and Mortality Weekly Report (MMWR)

Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020

MW Tenforde, LR Feldstein et al. for the IVY Network Investigators and CDC COVID-19 Response Team



Among symptomatic non hospitalized patients with positive test for SARS-CoV-2, 35% not returned to baseline health 2-3 weeks after testing

Older age and comorbidities associated with lack of return to baseline health
19% of young adults (18-34) with no comorbidities had not returned to baseline health

In contrast 90% of influenza outpatients recover within 2 weeks

The Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

High variability in symptoms and symptom severity

PASC can affect individuals who had severe, mild, or asymptomatic primary infection

Preliminary studies indicate 10-60% of COVID infections result in PASC

Neurologic

- Fatigue
- Memory/word finding difficulties
- Concentration difficulties, e.g., “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
- Confused state/psychosis

Cardio/Pulmonary

- Shortness of breath
- Dry cough
- Chest pain
- Exercise intolerance/ Post-exercise malaise
- 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

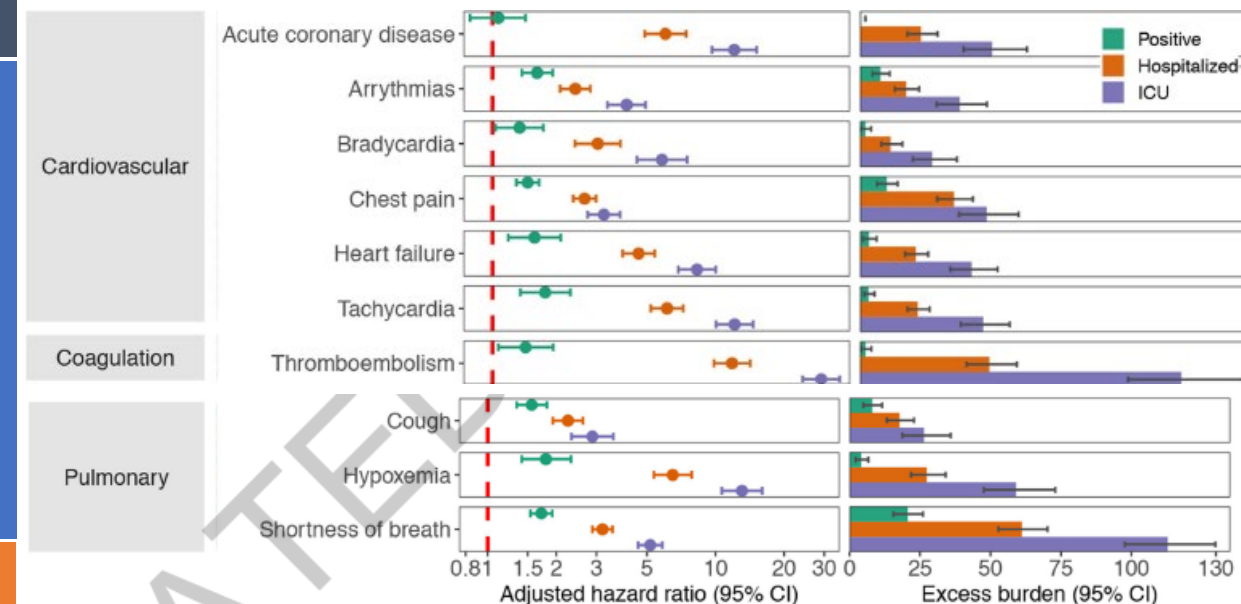
- Elevated temperature
- Chills, flushing sweats
- Sore throat
- Extreme thirst
- Skin changes
- Menstrual changes

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>

High-dimensional characterization of post-acute sequelae of COVID-19

Received: 18 January 2021

Ziyad Al-Aly, Yan Xie & Benjamin Bowe



Mental health

Musculoskeletal

Neurologic

Veterans Administration Study of incident diagnoses 1-6 months post COVID-19 infection

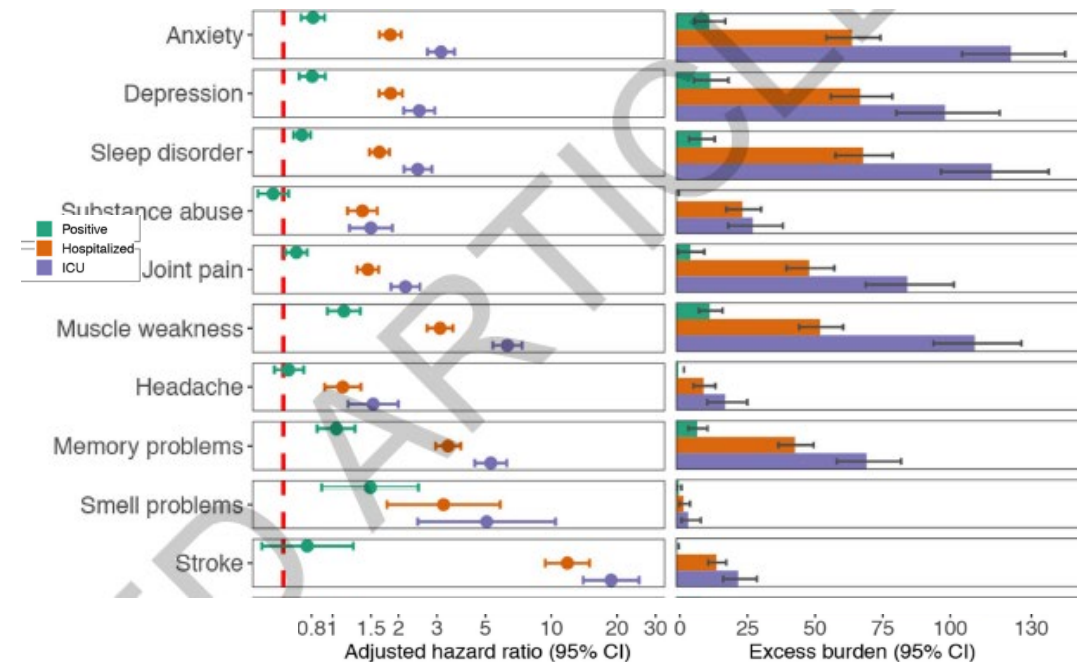
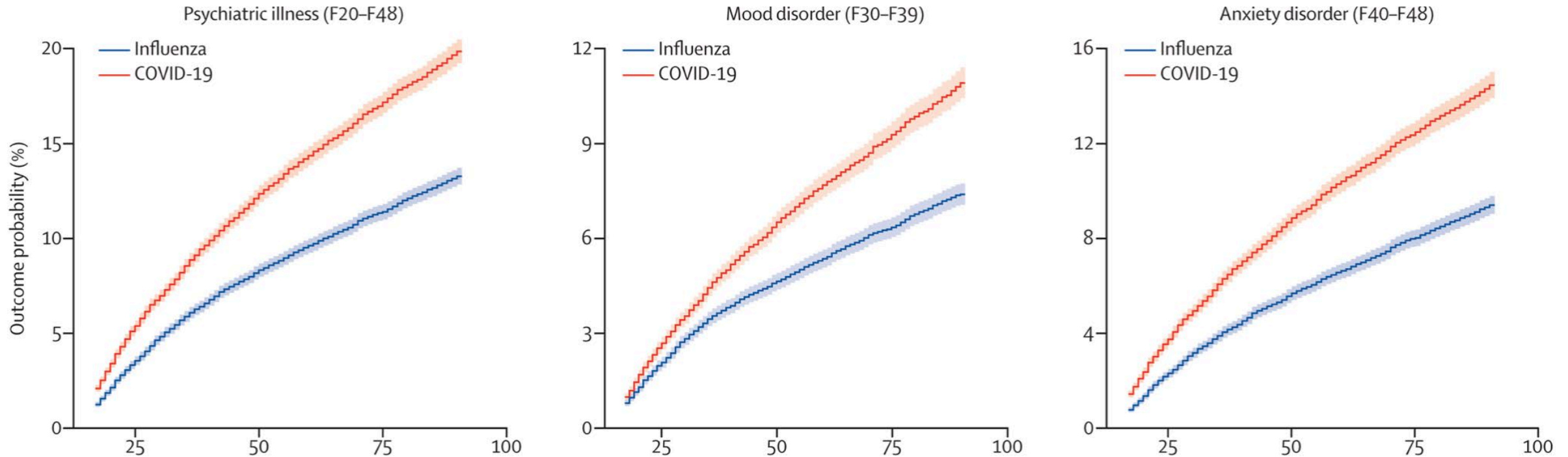


Fig. 3 | Risks and burdens of incident pre-specified high resolution post-acute COVID-19 outcomes at 6 months in mutually exclusive cohorts of people with non-hospitalized COVID-19 (green), people hospitalized for COVID-19 (orange), and people admitted to intensive care for COVID-19 (blue) during the acute phase (first 30 days) of the infection. ; all users of the

New diagnoses of anxiety, insomnia, dementia and mood disorders as well as psychiatric disorders in general, were increased after COVID-19 illness



What we need to understand about recovery

What is the spectrum of clinical “recovery” from COVID-19 infection?

Of those with symptoms 2-3 weeks post infection the rate of improvement is not yet known.

What interventions might enhance or hasten recovery?

In the immediate post infection phase as well as in the more chronic phase

What is the spectrum of tissue injury due to COVID-19 infection?

Are the various tissue injuries reversible, static, or contribute to progressive organ dysfunction?

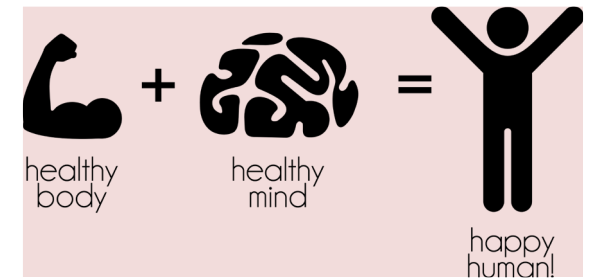
How to identify those with tissue injury in heart, lung, nervous system, kidney

Will unabated symptoms lead to chronic illness(s) in a subset of people?

If so, what is its pathophysiology (s)?

Is so, what are the drivers of special vulnerability or resilience across the lifespan and in special populations?

Will COVID-19 infection predispose people to other diseases in the future?



NIH PASC Research: Toward Recovery from SARS-CoV-2 Infection

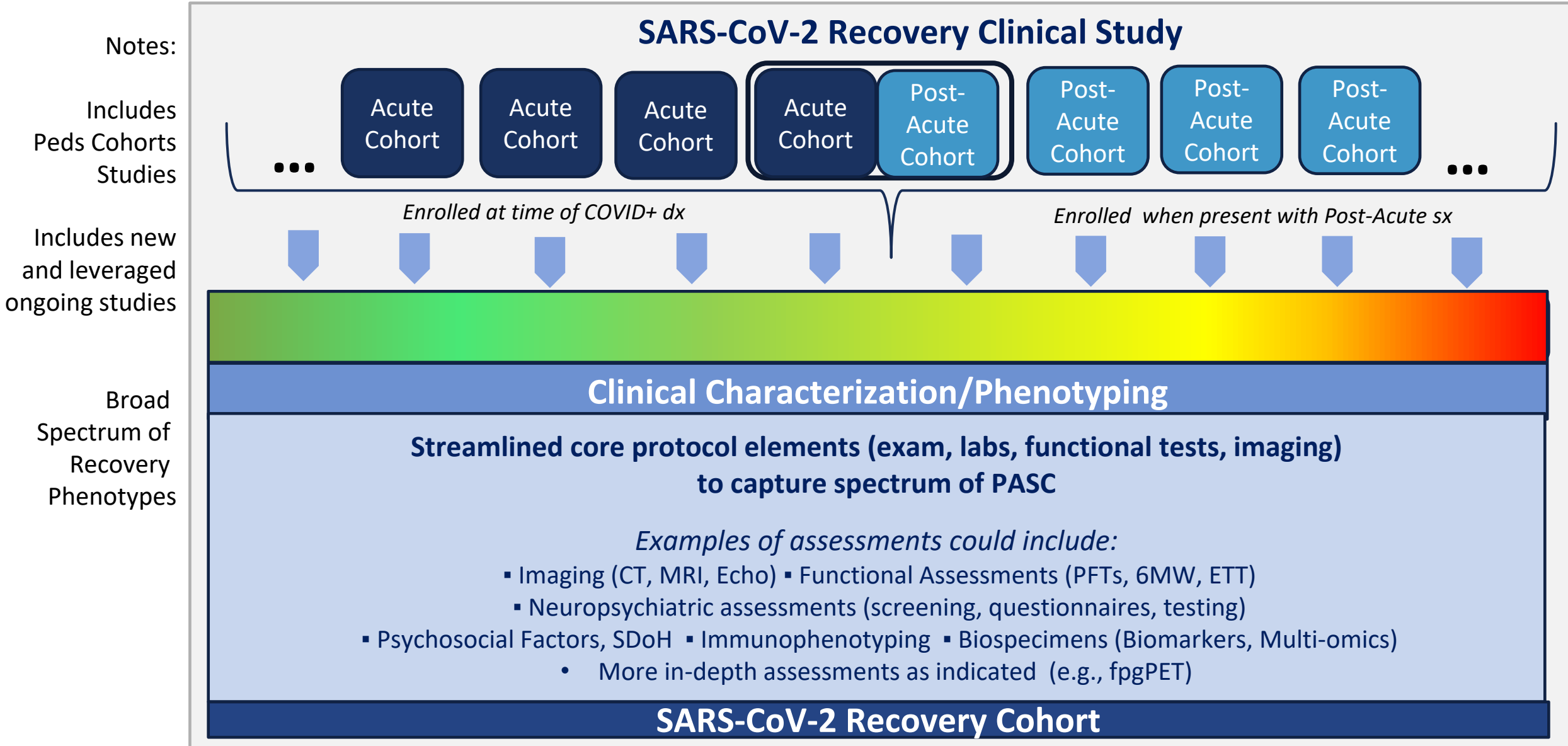
Goal

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

Key Scientific Questions

- 1 What are the clinical spectrum of and biology underlying recovery from infection over time?
- 2 What are the incidence/prevalence, natural history, clinical spectrum, underlying biology, and subtypes of PASC?
- 3 Does infection promote delayed organ dysfunction or increase the risk of developing other disorders?

PASC Characterization Strategy



PASC Recovery Cohorts— “Meta-cohort”

Leverage existing cohorts/Establish new cohorts/Engage long COVID community

**Acute
SARS-CoV-2
Infection Cohorts**



**Post-Acute
SARS-CoV-2
Infection Cohorts**



**NIH
SARS-CoV-2
Recovery Cohort**

*What are the clinical spectrum
of and biology underlying
recovery from infection over
time?*

*What is the clinical
spectrum and underlying
biology?*

*Does infection lead to later organ
dysfunction or increase the risk of
developing other disorders?*

EHR- and Other Real-World Data-Based Studies

*Autopsy studies of tissue
injury and persistent
viral effects.*

PASC Initiative Components

SARS-CoV-2 Recovery Meta-Cohort

- Clinical Recovery Cohort
- Autopsy Cohort (Acute and PASC)
- EHR-/ Other Real-World Data-Based Studies



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Investigator Consortium

- In this innovative approach, all study investigators will work together to achieve **speed and scale**:
 - Develop a streamlined set of common core protocol elements (specific hypotheses, design elements, screening evaluations, exams, lab tests, functional assessments, imaging, etc.)
 - Conduct rapid systematic screening and follow-up evaluations of infected individuals, to provide a resource for in-depth multi-disciplinary phenotyping, and to pool data and share biospecimens and data from across studies

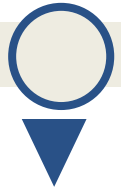
The goals of the Recovery Cohort and Investigator Consortium will be supported by **administrative coordination** and **oversight** as well as **three cores**:

Clinical Science Core

Data Resource Core

PASC Biorepository Core

Key Milestones and Timeline



February

OTA approved

NOITP issued

ACC Launched

Website and listserv Launched

Research Opportunity Announcements issued for Cores and Research Studies



March

Technical Assistance Workshop

273 PASC Applications Received

Screened >600 potential reviewers to secure 210 SEP and 170 SMEs for review of PASC Applications

Posted 112 FAQs in response to >700 questions received



April

273 PASC Applications Reviewed

NOITP issued for Mobile Health Platform and Data Repositories

Cores Award Recommendations

Draft Common Screening Assessment and Protocol

PASC listening sessions launch



May

PASC Awards made

PASC Cores launch

PASC Consortium convenes and studies launch

ROAs issue for Mobile Health Platform and Data Repositories

PASC Information Channels



The public may direct questions about the program to: PASCinfo@nih.gov.

Questions