Long-COVID Studies Within the RECOVER Platform

DCRI NIH Collaboratory Grand Rounds

May 20, 2022

Upinder Singh, MD

Chief, Division of Infectious Diseases and Geographic Medicine

Stanford University School of Medicine

Outline

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- Long-Haul Covid
  - Definition and epidemiology
  - Patient Perspective
- RECOVER Trial
  - Summary
  - Current state
  - Opportunities

Disclosures

- Advisory committees
  - Regeneron Pharmaceuticals
  - Gilead Sciences
  - Medscape

- NIH

Long COVID Definitions

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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- ✓"Post-COVID Conditions" (**≥4 weeks** since first symptoms)

NIH National Institutes of Health
Turning Discovery Into Health

- ✓"Post-Acute Sequelae of SARS-CoV-2 infection (PASC)" (**>4 weeks**)

NICE National Institute for Health and Care Excellence

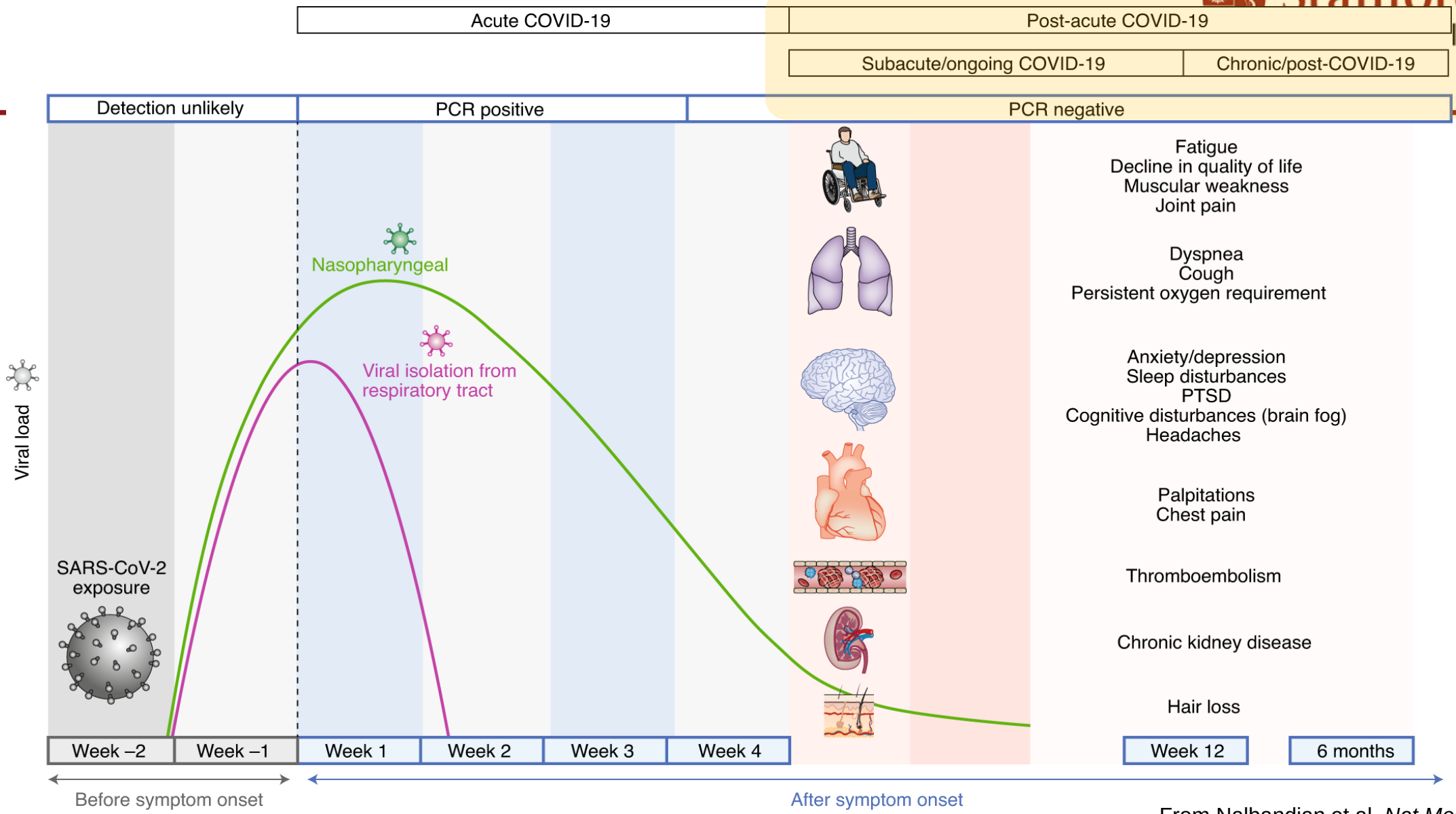
- ✓"Ongoing symptomatic COVID-19" (from 4 to 12 weeks)
- ✓"Post-COVID-19 syndrome" (**>12 weeks**)

World Health Organization

Clinical Case Definition by Delphi consensus, 6 October 2021

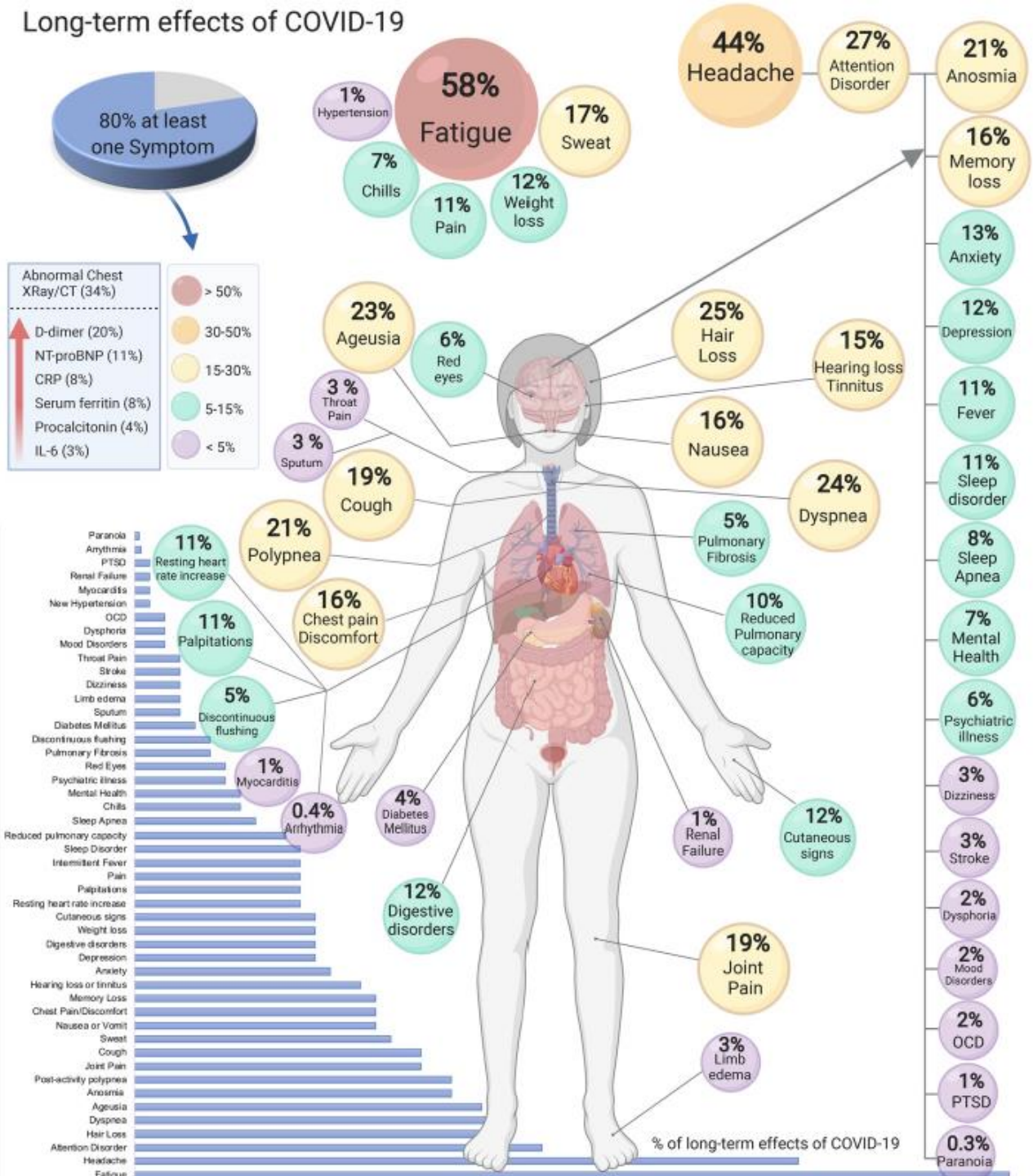
- ✓**3 months** from onset of COVID-19 symptoms and that last > 2 months and cannot be explained by an alternative diagnosis

Long-Covid



From Nalbandian et al. *Nat Med.* (2021)

Clinical symptoms



Lopez-Leon et al. *Sci. Rep.* 2021

LETTERS
https://doi.org/10.1038/s41591-021-01292-y
nature medicine
Check for updates

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Attributes and predictors of long COVID

Carole H. Sudre[1,2,3], Benjamin Murray[1], Thomas Varsavsky[1], Mark S. Graham[1], Rose S. Penfold[4], Ruth C. Bowyer[5], Joan Capdevila Pujol[5], Kerstin Klaser[1], Michela Antonelli[1], Liane S. Canas[1], Erika Molteni[1], Marc Modat[1], M. Jorge Cardoso[1], Anna May[5], Sajaysurya Ganesh[5], Richard Davies[5], Long H. Nguyen[6], David A. Drew[6], Christina M. Astley[7], Amit D. Joshi[6], Jordi Merino[8,9,10], Neli Tsereteli[11], Tove Fall[12], Maria F. Gomez[11], Emma L. Duncan[4], Cristina Menni[4], Frances M. K. Williams[4], Paul W. Franks[4,11], Andrew T. Chan[6], Jonathan Wolf[5], Sebastien Ourselin[1,13,14], Tim Spector[4,14] and Claire J. Steves[4,14] ✉

COVID-19 (+) 4,182 (self-report)

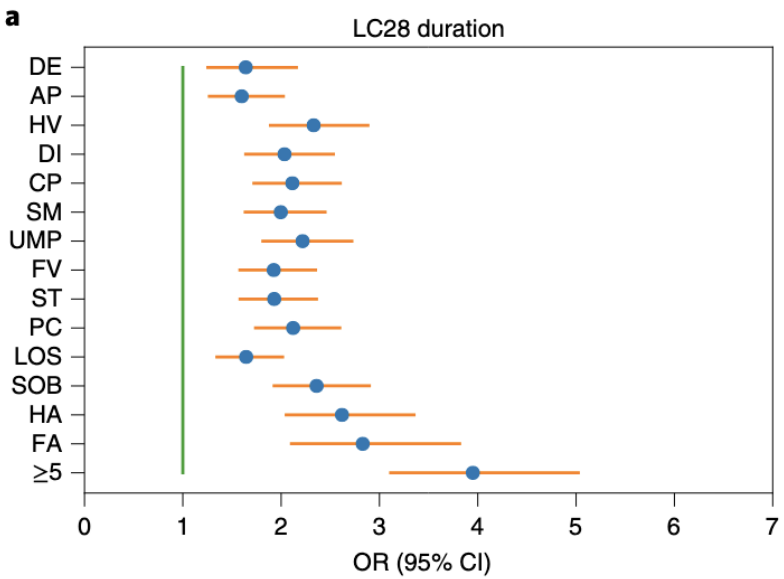
Symptomatic:

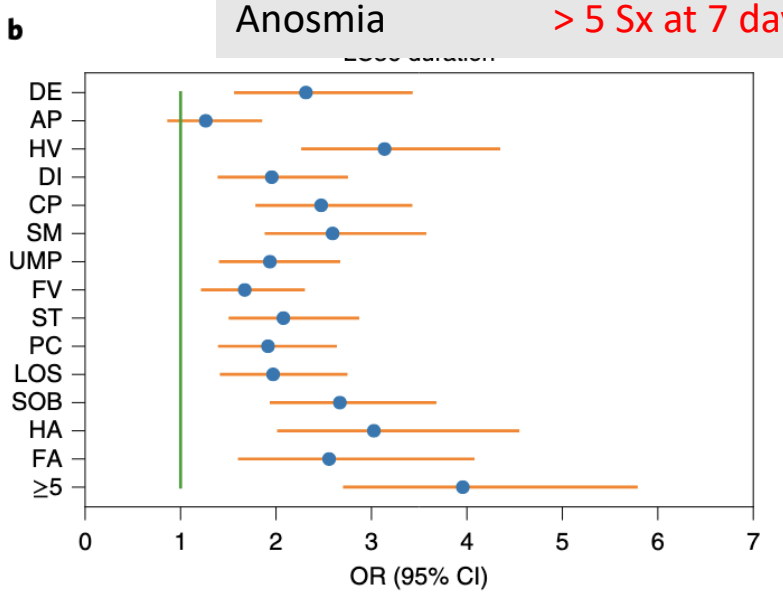
558 (13.3%) >28 days

189 (4.5%) 8 weeks

95 (2.3%) >12 weeks

Symptoms:	Risk groups:
Fatigue	↑age
Headache	↑ BMI
Dyspnea	Female
Anosmia	> 5 Sx at 7 days





Sudre CH. Nat Med 2021

Review

Post COVID-19 Syndrome in Patients with Asymptomatic/Mild Form

Pathogens (Nov 2021)

Anna Malkova [1,*], Igor Kudryavtsev [2], Anna Starshinova [3], Dmitry Kudlay [4,5], Yulia Zinchenko [6], Anzhela Glushkova [7], Piotr Yablonskiy [1,6] and Yehuda Shoenfeld [1,8,9]

reviewed literature on asymptomatic or mild cases of COVID-19 December 2019 to September 2021

- Post-COVID syndrome developed among **30–60%** of patients with asymptomatic or mild forms of COVID-19 on average.
- Occurs more commonly among **women** (on average 60%)

Post-vaccination Long Covid

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- UK-based, adult (≥18 years) users of the COVID Symptom Study mobile phone app. Dec 8, 2020 - July 4, 2021
- 1,240,009 reported 1st dose, (0.5%) COVID (+)
- 971,504 reported 2nd dose, (0.2%) COVID (+)
  - ✓Fewer symptoms
  - ✓More likely asymptomatic
  - ✓Odds of symptoms > 28 days were halved with two vaccine doses

Antonelli et al. *Lancet Infect Dis* (Jan 2022)

Confronting Our Next National Health Disaster — Long-Haul Covid

Steven Phillips, M.D., M.P.H., and Michelle A. Williams, Sc.D.

Aug, 2021

The NEW ENGLAND JOURNAL of MEDICINE

"…we can conservatively expect more than 15 million cases of long Covid resulting from this pandemic. And though data are still emerging, the average age of patients with long Covid is about 40, which means that the majority are in their prime working years. Given these demographics, **long Covid is likely to cast a long shadow on our health care system and economic recovery.**"

~ **1.3 million people in the UK** (2.0% of the population) with self-reported long COVID as of 6 December 2021.

Office for National Statistics

Updated estimates: American Academy of Physical Medicine and Rehabilitation

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Post-Acute Sequelae of SARS-CoV-2 Infections (PASC) Estimates and Insights

American Academy of Physical Medicine and Rehabilitation

Data as of 5/4/2022

View Dashboard Assumptions, Methodology, and Sources

SUMMARY | BY STATE

FILTERS
(reset to default)
Select Est. PASC %
30%
Select a State
All
Select a County
All

MODEL ASSUMPTIONS AND SOURCES
(see all)

1. Model assumes 30% of COVID-19 surviving cases in the U.S. result in PASC.

2. COVID-19 surviving cases are confirmed cases less deaths.

3. U.S. case data is pulled nightly from JHU CSSE COVID-19 Data. U.S. Census data uses 2019 1-year estimates.

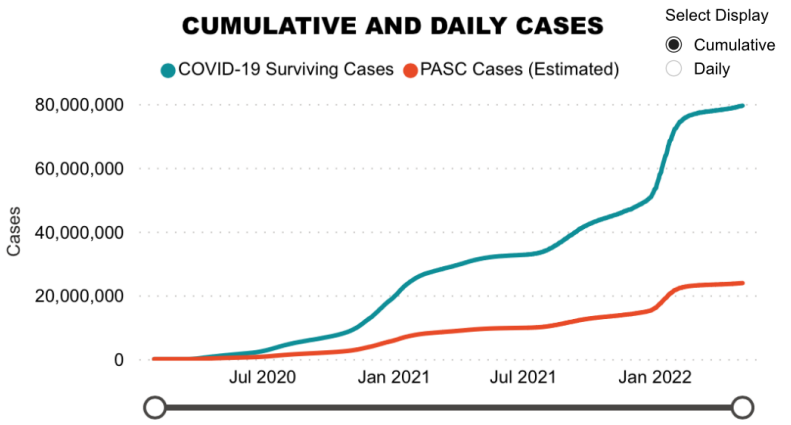
Powered by

COVID-19 SURVIVING CASES (TOTAL)	PASC CASES (ESTIMATED)
80,449,750	24,134,925

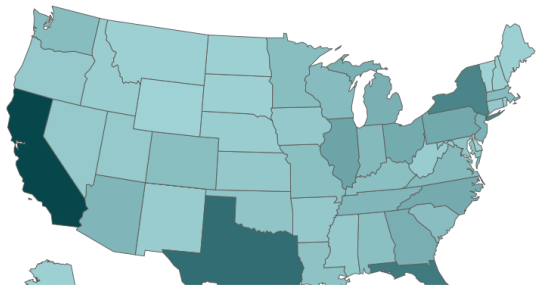
ESTIMATED PASC CASES PER STATE

State	PASC Cases (Estimated)
California	2,744,772
Texas	1,999,902
Florida	1,759,779
New York	1,534,067
Illinois	934,190
Pennsylvania	833,536
Ohio	797,591
North Carolina	790,755
Georgia	716,423
Michigan	703,696
New Jersey	669,093
Arizona	597,472
Tennessee	575,096
Indiana	504,002
Virginia	503,912

CUMULATIVE AND DAILY CASES



PASC CASES (ESTIMATED)

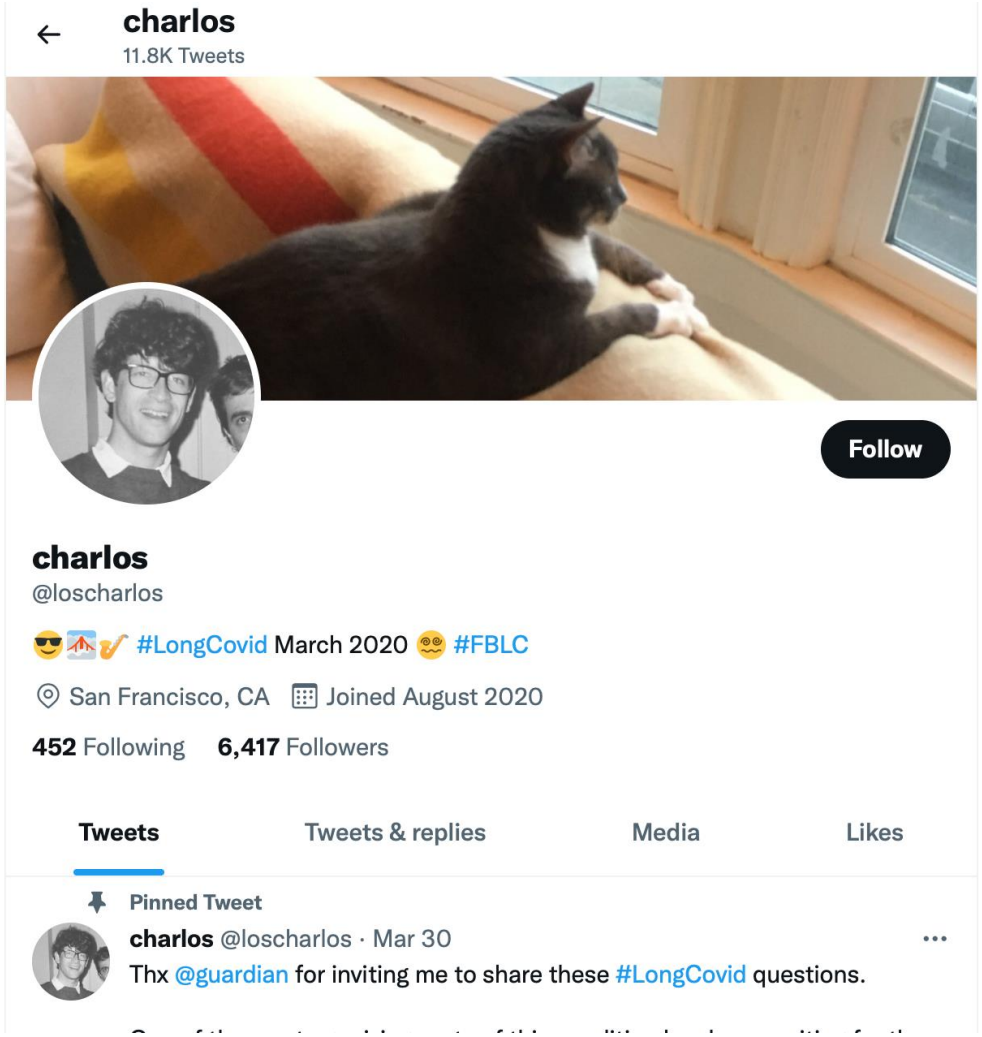


Other estimates of >39 million with PASC in the US

American Academy of Physical Medicine and Rehabilitation (AAPM&R): https://pascdashboard.aapmr.org

Patient Perspective

- Charlie McCone
  - https://www.sfchronicle.com/bayarea/heatherknight/article/S-F-Millennial-was-fit-and-healthy-before-15857253.php
  - We need answers to these four long Covid questions - The Guardian
  - A cause of America's labor shortage: Millions with long COVID https://www.cbsnews.com/news/long-covid-labor-market-missing-workers/



Patient Perspective

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- Charlie McCone
  - https://www.sfchronicle.com/bayarea/heatherknight/article/S-F-Millennial-was-fit-and-healthy-before-15857253.php
  - We need answers to these four long Covid questions - The Guardian
  - A cause of America's labor shortage: Millions with long COVID https://www.cbsnews.com/news/long-covid-labor-market-missing-workers/

- What priorities should healthcare community consider
  - Diagnostics, Healthcare access, Therapeutics
  - ** Healthcare providers to acknowledge our current limitations re PASC
  - ** As pandemic enters a different phase – with associated societal pandemic fatigue - acknowledge that many still suffering with no resolution or solutions in sight
  - ** Educate patients about syndrome so they can self advocate

Broader issues: unexplained post-acute infection syndromes

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nature medicine

REVIEW ARTICLE

https://doi.org/10.1038/s41591-022-01810-6

Check for updates

Unexplained post-acute infection syndromes

Jan Choutka[1], Viraj Jansari[2], Mady Hornig[3] and Akiko Iwasaki[2,4,5,6]

SARS-CoV-2 is not unique in its ability to cause post-acute sequelae; certain acute infections have long been associated with an unexplained chronic disability in a minority of patients. These post-acute infection syndromes (PAISs) represent a substantial healthcare burden, but there is a lack of understanding of the underlying mechanisms, representing a significant blind spot in the field of medicine. The relatively similar symptom profiles of individual PAISs, irrespective of the infectious agent, as well as the overlap of clinical features with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), suggest the potential involvement of a common etiopathogenesis. In this Review, we summarize what is known about unexplained PAISs, provide context for post-acute sequelae of SARS-CoV-2 infection (PASC), and delineate the need for basic biomedical research into the underlying mechanisms behind this group of enigmatic chronic illnesses.

Table 1 | Overview of unexplained PAISs associated with documented infections

Pathogen	Name of PAIS
Viral pathogens	
SARS-CoV-2	Post-acute sequelae of SARS-CoV-2 infection (PASC) Post-acute COVID-19 syndrome (PACS) Long COVID
Ebola	Post-Ebola syndrome (PES) Post-Ebola virus disease syndrome (PEVDS)
Dengue	Post-dengue fatigue syndrome (PDFS)
Polio	Post-polio syndrome (PPS)
SARS	Post-SARS syndrome (PSS)
Chikungunya	Post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR) Post-chikungunya disease
EBV	No name
West Nile virus	No name
Ross River virus[a]	No name
Coxsackie B[a]	No name
H1N1/09 influenza[a,b]	No name
VZV[a,b]	No name
Non-viral pathogens	
Coxiella burnetii	Q fever fatigue syndrome (QFS)
Borrelia[c]	Post-treatment Lyme disease syndrome (PTLDS)
Giardia lamblia[a,d]	No name

[a]Limited or very limited evidence base. [b]Association with increased use of ME/CFS diagnosis in health registry. [c]Contradicting or unclear evidence base. [d]Supporting evidence derives from a single outbreak in Norway.

Syndromic overlaps

- ME/CFS
- Fibromyalgia

Pathophysiology

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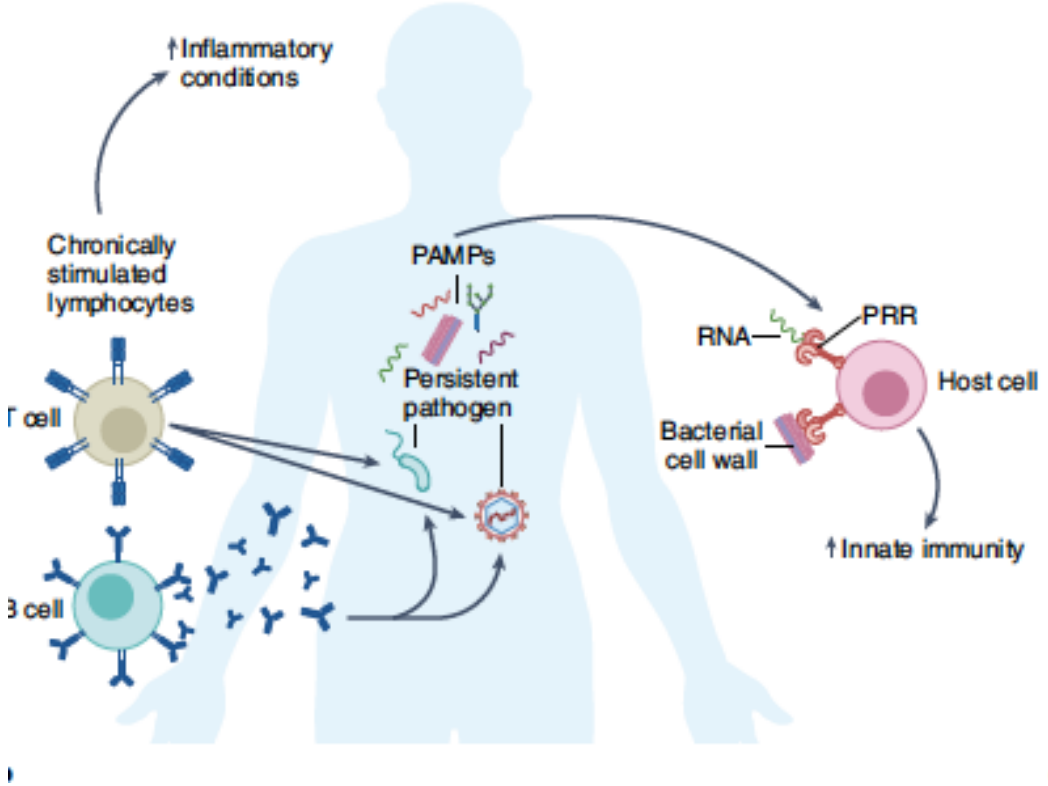
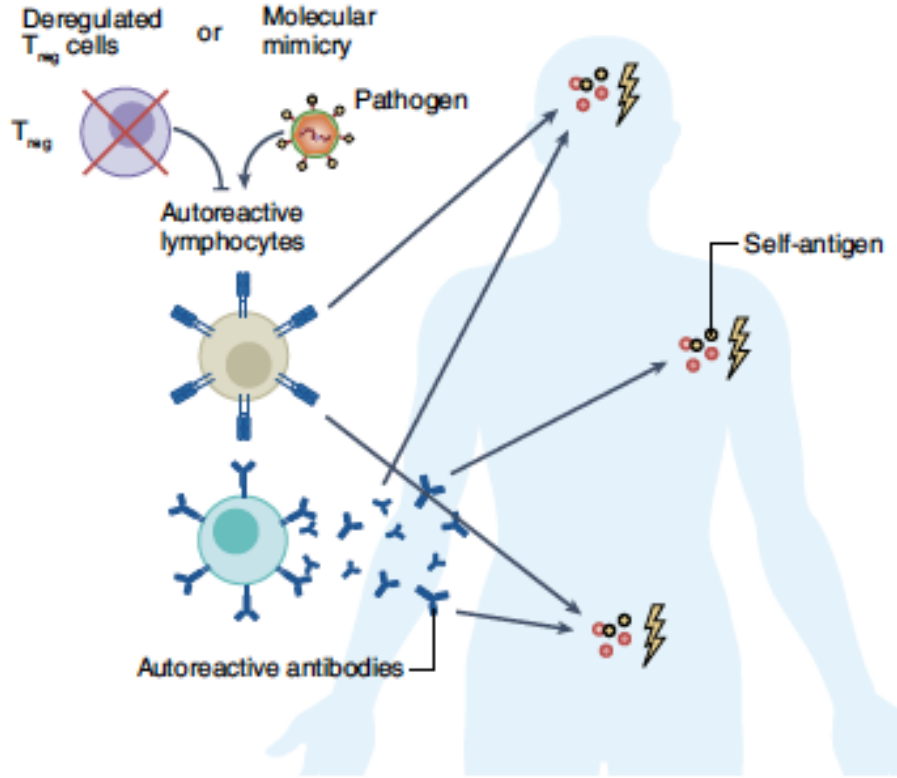
Pathogen reservoir or remnants



Autoimmunity



Nature Medicine | VOL 912 28 | May 2022 | 911–923 | www.nature.com/naturemedicine

Pathophysiology

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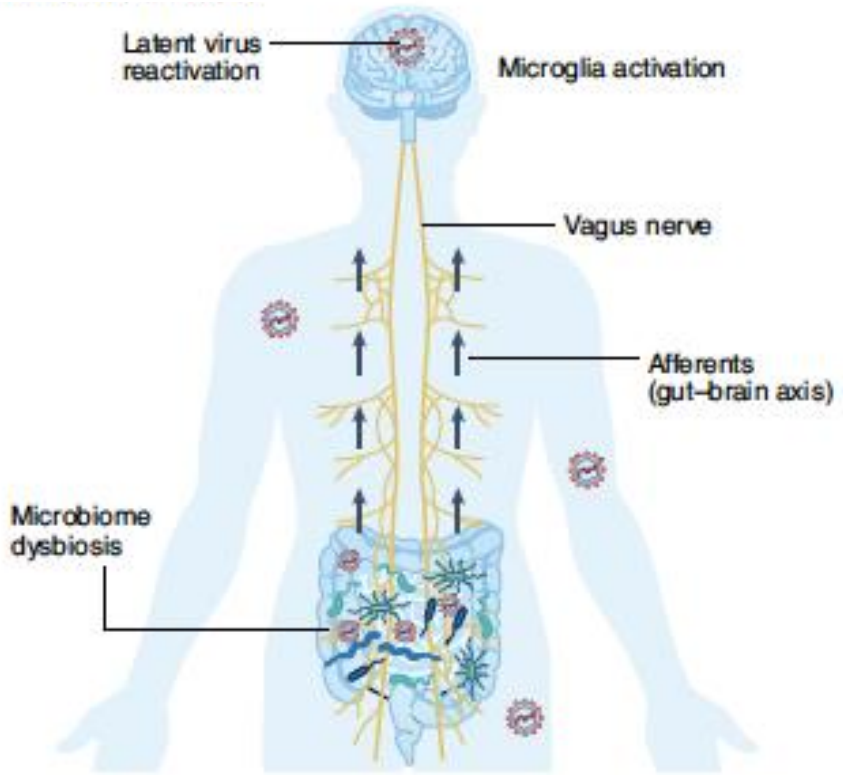
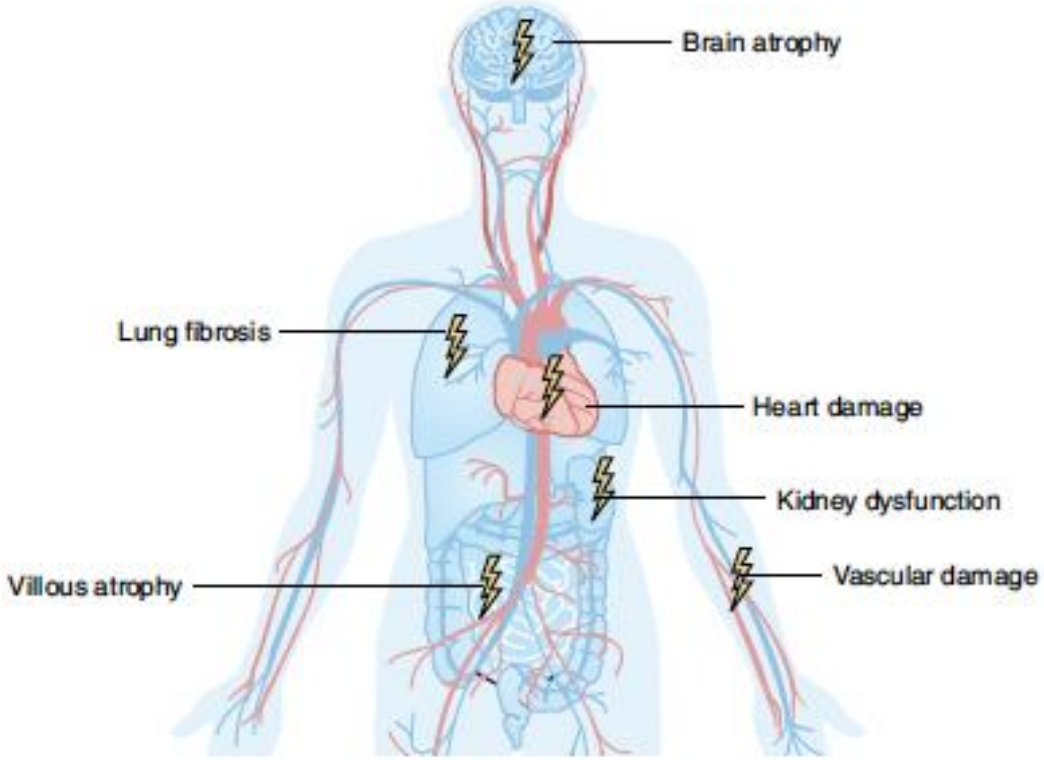
Dysbiosis/reactivation



Tissue damage



Nature Medicine | VOL 912 28 | May 2022 | 911–923 | www.nature.com/naturemedicine

Congress approves 1.15 Billion dollars to study long-covid

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February 23, 2021

NIH launches new initiative to study “Long COVID”

I write to announce a major new NIH initiative to identify the causes and ultimately the means of prevention and treatment of individuals who have been sickened by COVID-19, but don’t recover fully over a period of a few weeks. Large numbers of patients who have been infected with SARS-CoV-2 continue to experience a constellation of symptoms long past the time that they’ve recovered from the initial stages of COVID-19 illness. Often referred to as “Long COVID”, these symptoms, which can include fatigue, shortness of breath, “brain fog”, sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression, can persist for months and can range from mild to incapacitating. In some cases, new symptoms arise well after the time of infection or evolve over time. In December, NIH held a workshop to summarize what is known about these patients who do not fully recover and identify key gaps in our knowledge about the effects of COVID-19 after the initial stages of infection. In January, I shared the results from the largest global study of these emerging symptoms. While still being defined, these effects can be collectively referred to as Post-Acute Sequelae of SARS-CoV-2 infection (PASC). We do not know yet the magnitude of the problem, but given the number of individuals of all ages who have been or will be infected with SARS-CoV-2, the coronavirus that causes COVID-19, the public health impact could be profound.

RECOVER: Researching COVID to Enhance Recovery

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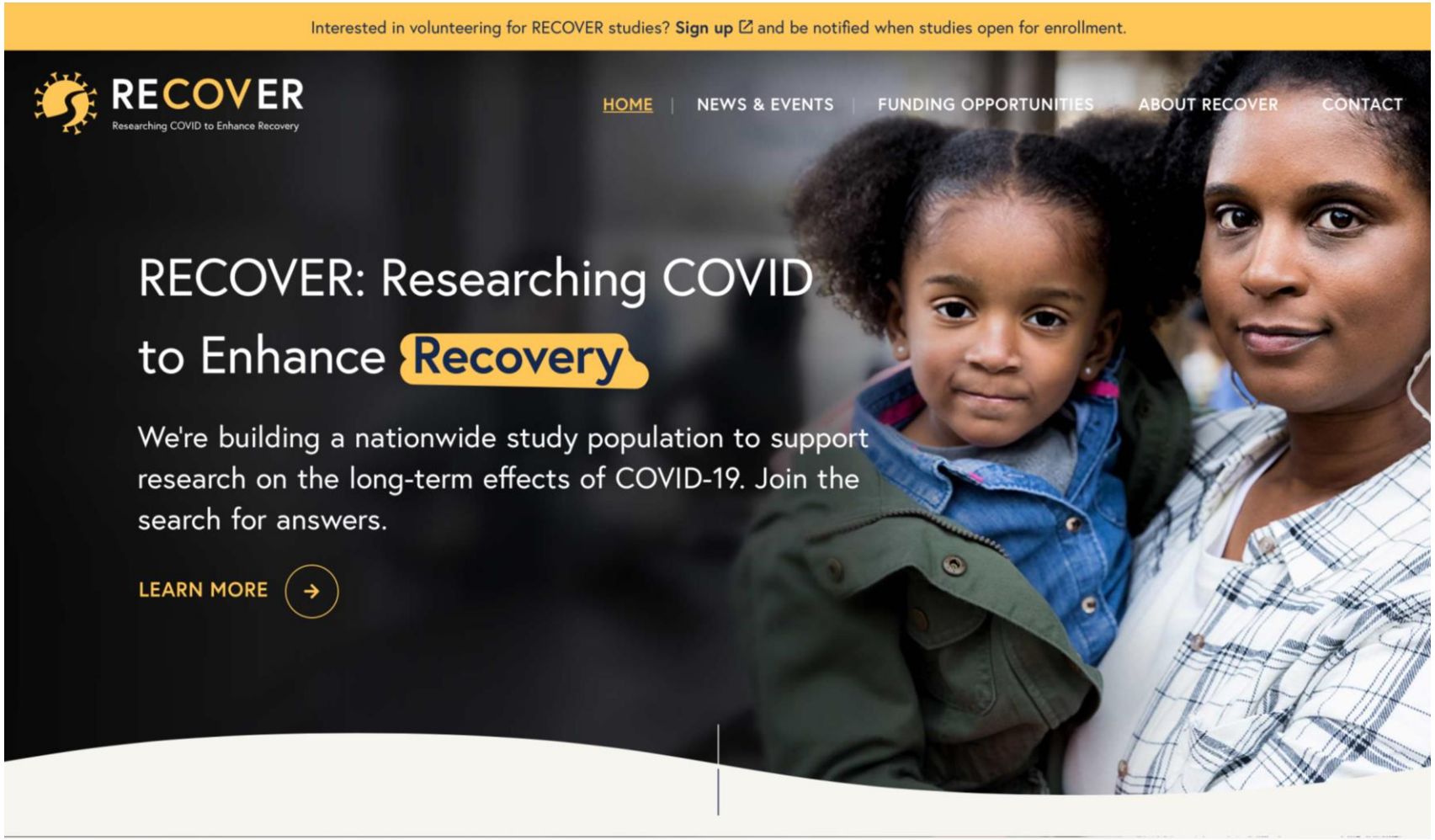

https://recovercovid.org

Focus on Post Acute Sequelae of SARS-CoV2 (Long Haul COVID)

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GOAL	**To improve understanding of and develop strategies to treat and prevent post-acute manifestations of SARS-CoV-2 infection through a multi-pronged research framework**
Understand	**COVID-19 clinical sequelae, risk factors for illness, severity, outcomes**
Recognize	**SARS-CoV-2 infected individuals at risk for post-acute manifestations**
Identify	**Pathogenic mechanisms and therapeutic targets**
Develop	**Therapeutic strategies for people with post-acute sequelae**

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- include adult, pregnant and pediatric populations
- enroll patients during the acute as well as post-acute phases of SARS-CoV-2 infection
- evaluate tissue pathology and autopsy studies
- analyze data from millions of electronic health records
- use mobile health technologies, such as smartphone apps and wearable devices, which will gather real-world data in real time
- Hope to gain information about overlap with other post-viral illnesses (such as ME/CFS)
- Clinical trials to begin in late 2022

RECOVER Study

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Pediatric Phase I Participants

Contact PI	Institution
Rachel Greenberg	Duke Univ.
Terry Jernigan	Univ. Of California, San Diego
Julie Miller	New England Research Institutes, Inc.
Leonardo Trasande	NYU Grossman School Of Med.
Sean Deoni	Rhode Island Hosp.
Melissa Stockwell	Columbia Univ. Health Sciences
Steven Webber	Vanderbilt Univ. Medical Center
Lawrence Kleinman	Robert Wood Johnson Med. School
David Warburton	Children's Hosp. Los Angeles
Kelan Tantisira	Univ. Of California, San Diego

Adult Phase I Participants

~17,680 participants

Contact PI	Institution
Sally Hodder	West Virginia Research Corp.
Bruce Levy	Brigham And Women's Hospital
Grace McComsey	Case Western Reserve Univ.
Jeanne Marrazzo	Univ. Of Alabama At Birmingham
Steven Deeks	Univ. Of California, San Francisco
Hassan Brim	Howard Univ.
Graham Barr	The Trustees Of Columbia Univ In The City Of NY
Rachel Hess	University Of Utah
Thomas Patterson	Univ. Of Texas Hlth, Sci. Ctr. San Antonio
Janko Nikolich-Zugich	Arizona Board Of Regents, Univ. Of Arizona
Alexander Charney	Icahn School Of Medicine At Mt. Sinai
Igho Ofotokun	Emory Univ.
James Heath	Institute For Systems Biology
Jerry Krishnan	Univ. Of Illinois At Chicago
Upinder Singh	Stanford Univ.

Autopsy Phase I Participants

Contact PI	Institution
Lauren Decker	Univ. of New Mexico
Aloke Finn	CV Path Institute, Inc.
Ross Reichard	Mayo Clinic
Chris Woods	Duke Univ.
Kelly Gebo	Johns Hopkins Univ.
Carlos Cordon-Cardo	Icahn School Of Med At Mt.Sinai
Bruce Levy	Brigham And Women's Hosp.

Pregnancy Phase I Participants

>2,000 participants

Contact PI	Institution
Torri Metz	Univ. of Utah
Vanessa Jacoby	Univ. of California, San Francisco

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Researching COVID to Enhance Recovery

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Key Features for RECOVER PASC Consortium Main Protocol Development

- Harmonized scientific aims
- Harmonized entry criteria based on WHO criteria for all cohorts
- Harmonized data structure across all cohorts based on use of Common Data Elements
- Targeted enrollment for study sample diversity
- Tiered phenotyping approach for adult and pediatric cohorts
- Harmonized data management and data analysis plans
- Fit-for-purpose modular design to leverage existing data from extant cohorts

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Researching COVID to Enhance Recovery

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RECOVER Cohort Study Protocols: Main Elements

- Overall Design:
  - Ambi-directional longitudinal meta-cohort study (combined retro- and perspective) with nested case control studies
  - All participants followed prospectively under single main protocol
  - Flexible study design
- Observational Model: Hybrid model includes acute, harmonized post-acute, and de novo cohorts
- Time Perspective: Hybrid retrospective and prospective

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RECOVER PASC Cohorts Study Overview

Recruitment in all 50 States
Hospitals/Clinics/Communities/Electronic Health Records
Diverse population with and without COVID-19
Infants/Children/Adults/Pregnant women

↓

Tier 1 Screening Tests (60,000 participants)
What are the symptoms of PASC?
What is the risk of PASC after COVID-19?
How does pandemic-related stress impact PASC?

↓

Tier 2 Clinical Testing over 2-4 years (10,000 participants)
What are the risk factors for PASC?
What is the time course of PASC?
How does PASC affect child development?

↓

Tier 3 Advanced Testing (4,500 participants)
What are the causes of PASC?
How does PASC affect organ function over time?
Is PASC associated with new onset chronic diseases?

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Researching COVID to Enhance Recovery

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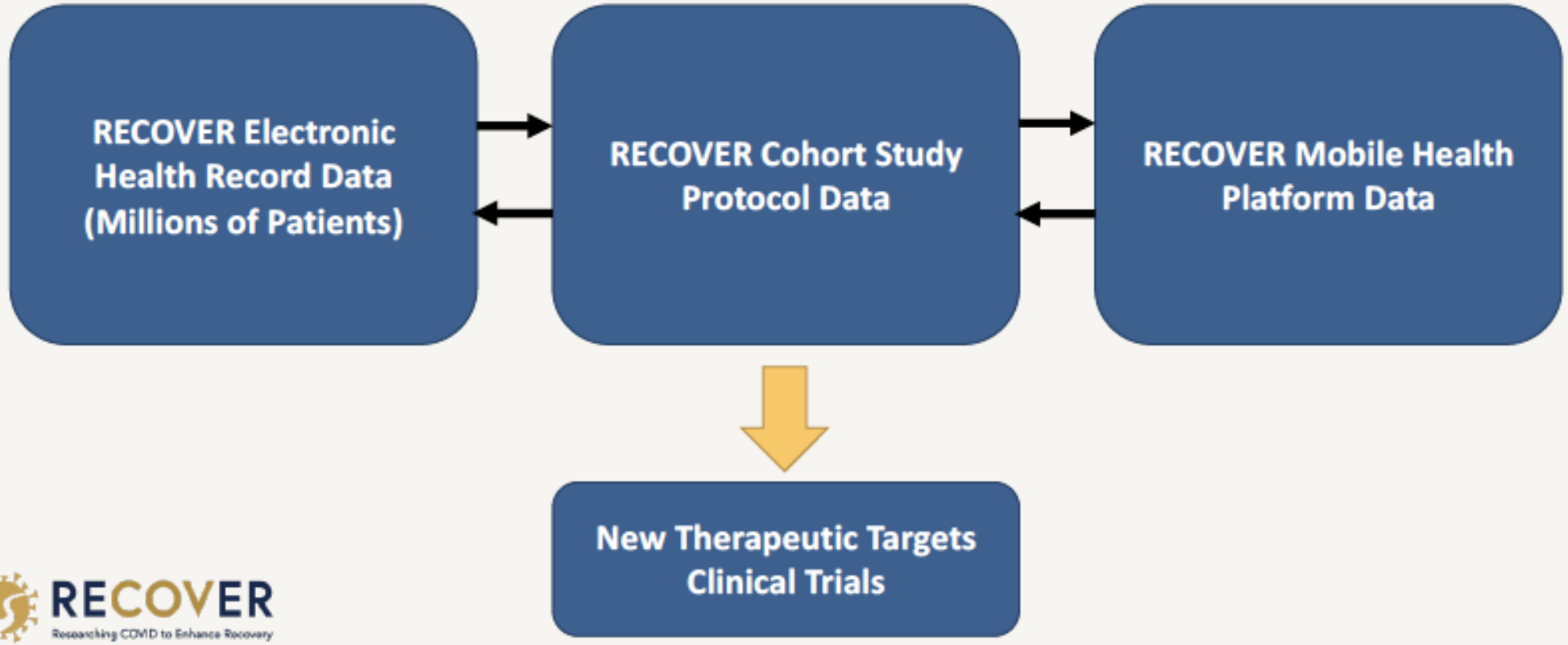
RECOVER Cohort Studies: Integration of Real World Data



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Researching COVID to Enhance Recovery

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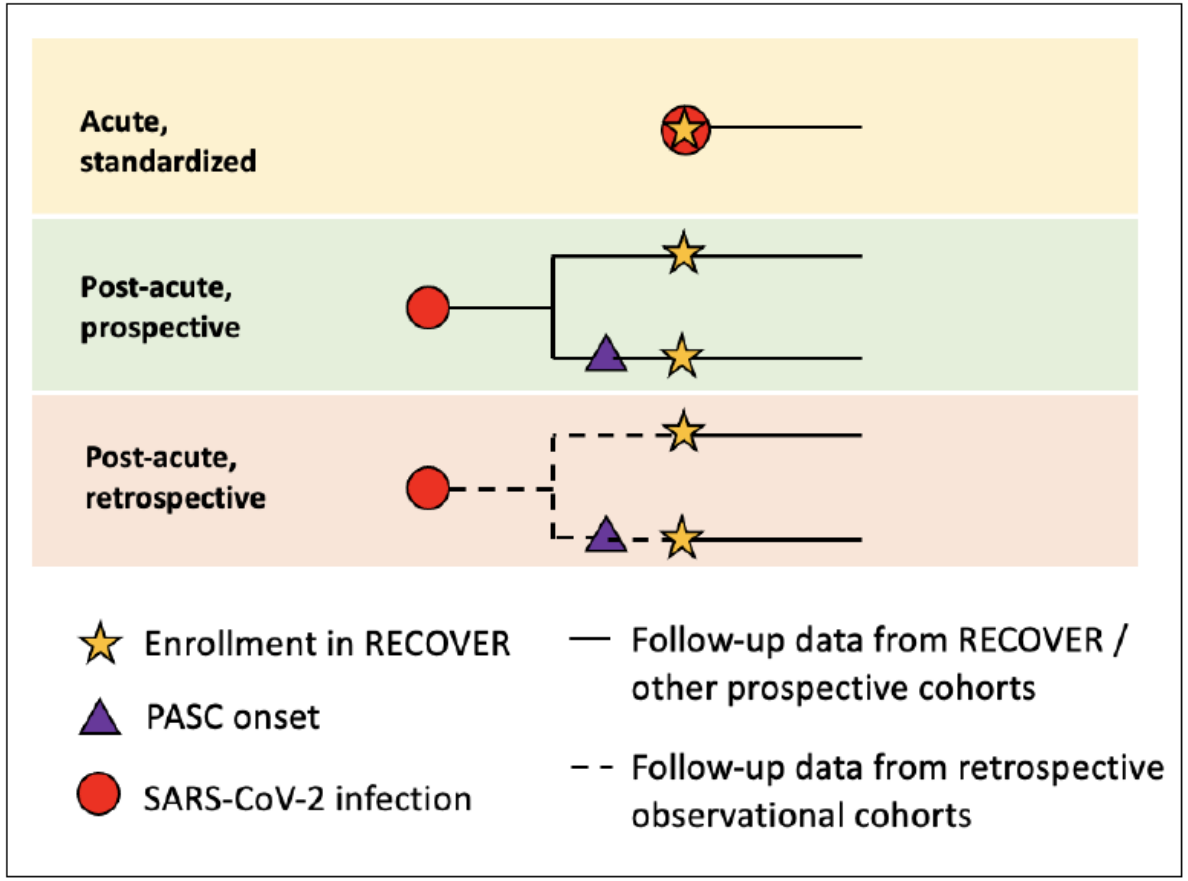
Study overview



60% acutely infected
40% previously infected

25% hospitalized for index covid infection
75% not-hospitalized

Extensive questionnaire at enrollment

Inclusive protocol
Broad patient engagement and stakeholders

Schedule of events

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		Time Point after index date															
eCRF	Baseline	3m	6m	9m	12m	15m	18m	21m	24m	27m	30m	33m	36m	39m	42m	45m	48m
Enrollment	●																
Tier 1-2 Consent	●																
Identity	●																
Visit	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Comorbidities	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
COVID Treatment*	●																
Medications	●																
Change in Medications		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Demographics	●																
PASC Symptoms	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Vaccine	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
SDoH	●																
SDoH Follow-up		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Alcohol/Tobacco	●																
Alcohol/Tobacco Follow-up		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Disability	●																
Pregnancy	●																
Pregnancy Follow-up		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tier 1 office visit	●		●		●				●				●				●
Biospecimens	●	●	●		●				●				●				●
Lab Results	●	●	●		●				●				●				●
Tier 2/Tier 3 Tests																	

Legend

- ● Completed by Research Coordinator
- ● Completed by participant
- ● Completed by Research Coordinator with review/validation by participant

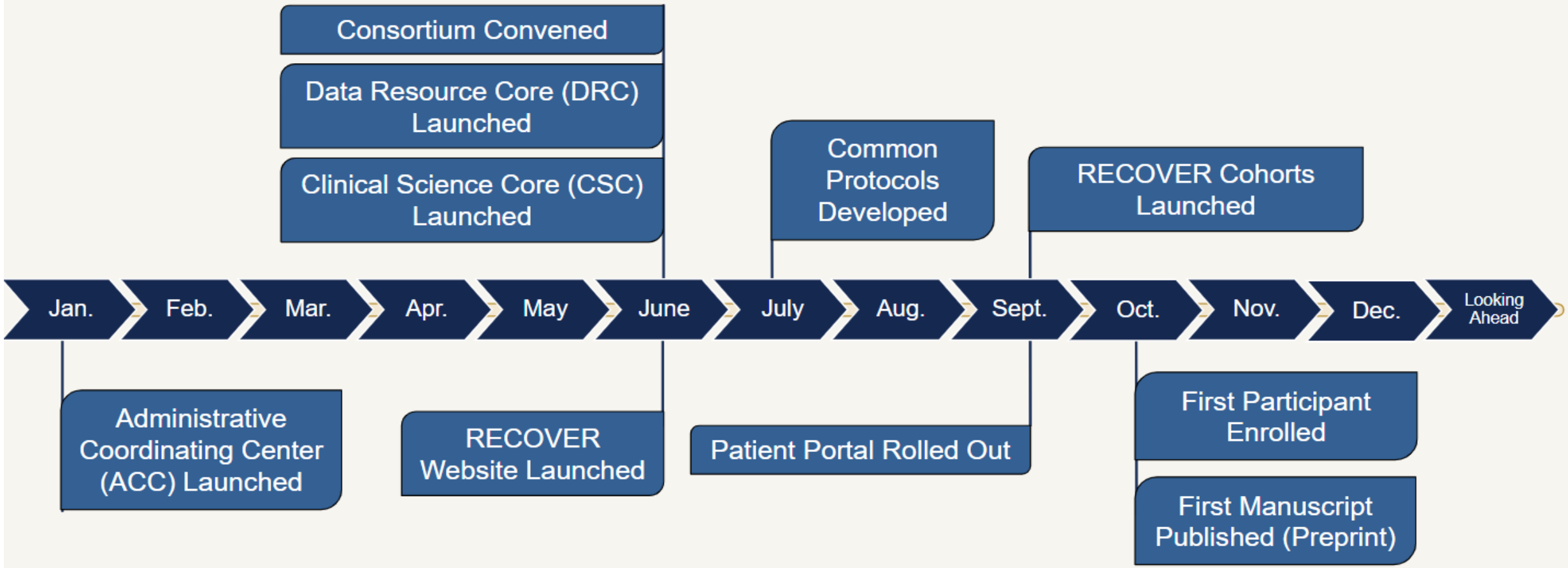
Tier 1 Testing (general labs)

Tier 2 Testing

Tier 3 Testing (most invasive)

RECOVER: Rapid Progress in 2021

- To date, the NIH has obligated over **$500M** to support the RECOVER Initiative.



recoverCOVID.org

Progress to date: Stanford

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Id	Hub Name	Cohort	Enrollment Progress	Target Enrollment	Current Enrollment
RA116	Stanford University	Adult (Non-Pregnancy)	38%	909	344

Id	Hub Name	Acute Infected	Acute Uninfected	Post-Acute Infected	Post-Acute Uninfected	Total Acute	Total Post-Acute	Total Infected	Total Uninfected
RA116	Stanford University	189	3	150	2	192	152	339	5

Progress to date: Stanford

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Id	Hub Name	Sex (Female)	Sex (Male)	Sex (Intersex)	Sex (Unknown)
RA116	Stanford University	207	114	0	23

Id	Hub Name	Jnderrepresented in Biomedical Research	Race/Ethnicity (AIAN)	Race/Ethnicity (Asian)	Race/Ethnicity (Black)	Race/Ethnicity (Hispanic)	Race/Ethnicity (NHPI)	Race/Ethnicity (White)	Race/Ethnicity (Multiple)
RA116	Stanford University	51%	0	50	17	35	6	167	35

Progress to date: Stanford

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- Accomplishments
  - On target to meet enrollment goals by end 2022
  - Able to enroll >50% acutely infected individuals (baseline labs/biosamples)
    - Engaged MAB treatment sites
    - Co-enrolled with clinical trials
    - Aggressive outreach to HCW and university colleagues
  - >50% enrolled are underrepresented in biomedical research
    - Representative of the San Francisco Bay Area
    - Greater efforts to enroll non-English speaking participants
  - Engaged in the science and clinical care of Long-Covid
    - Scientific projects launched by stakeholders and provided new clinical research opportunities
    - Long-Covid clinic established May 2021

Progress to date: Stanford

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- Challenges
  - Evolving pandemic; waves of infection; how identify negative controls
  - Healthcare systems stretched
  - Healthcare provider fatigue (and Covid impact on healthcare providers)
  - Complex study with evolving protocol

- Advantages
  - General high interest in study – ability to participate (infected, never infected)
  - Linked with clinical efforts and long-covid clinic
  - Engages broad stakeholders within health system to consider disease and research opportunities
  - Impact understanding of other post-viral syndromes with syndromic overlap
  - Clinical Trials (end 2022)

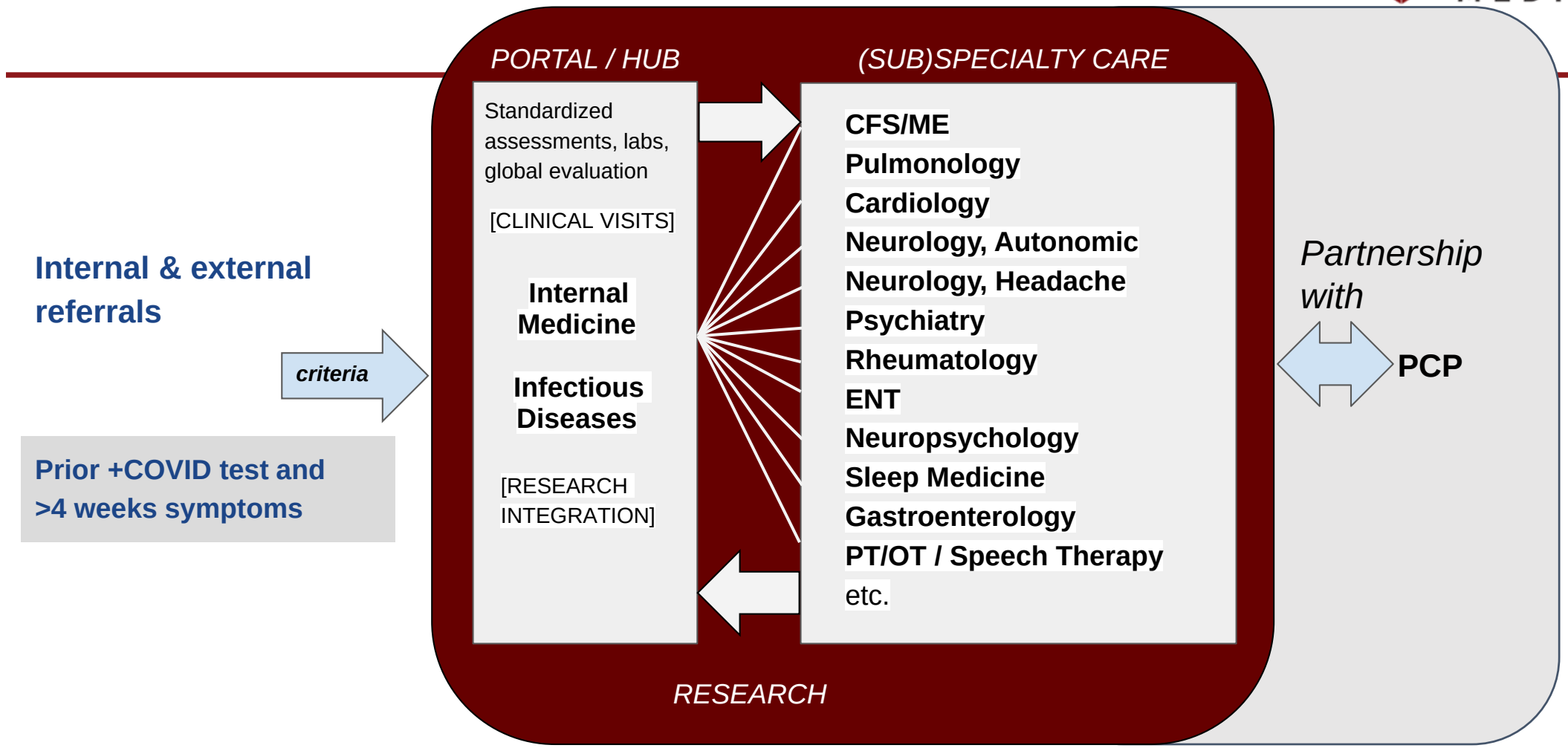
RECOVER Study – Stanford team

Emergency Department
Infectious Diseases
Immunology
Hospital Medicine
Primary Care
SCCR team

SCCR Team

PJ Utz
Catherine Blish
Bonnie Maldonado
Andra Blomkalns
Hannah Valantine

Stanford Post-Acute COVID-19 Syndrome (PACS) Care Model



Stanford PACS Clinical Team for Post-COVID Care

Dept of Medicine

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Dr. Lauren Eggert **(Pulmonary, Allergy & Critical Care)**
Dr. Linda Geng* **(Internal Medicine)**
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**hub/portal clinic*

Dept of Neurology

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Dept. of Otolaryngology

Dr. Zara Patel **(ENT: Skull Base, Rhinology)**

RECOVER Study – Stanford team

Emergency Department
Infectious Diseases
Immunology
Hospital Medicine
Primary Care
SCCR team

SCCR Team

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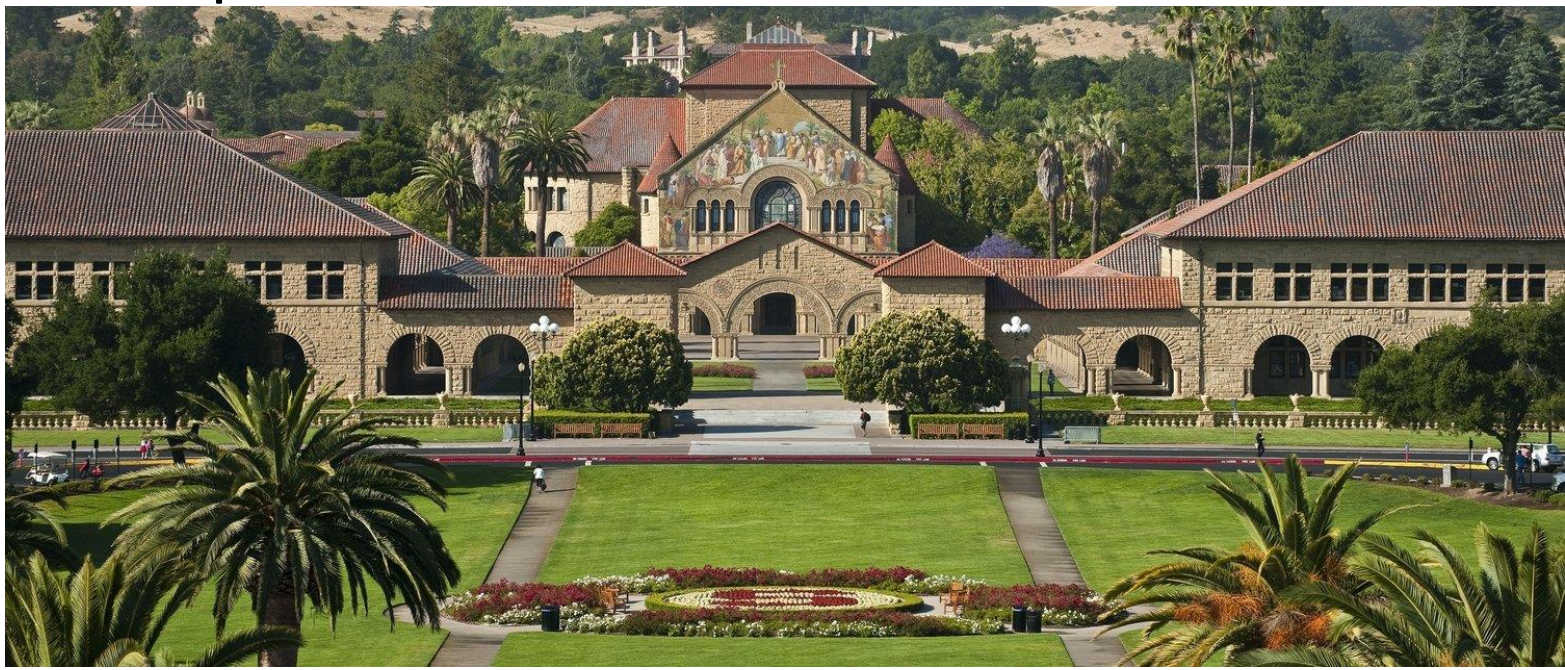
Acknowledgements

- Stanford RECOVER Team
- Stanford DoM and SoM leadership
- Stanford Clinicians and Participants
- RECOVER Adult Cohort Leadership
- NYU - CSC

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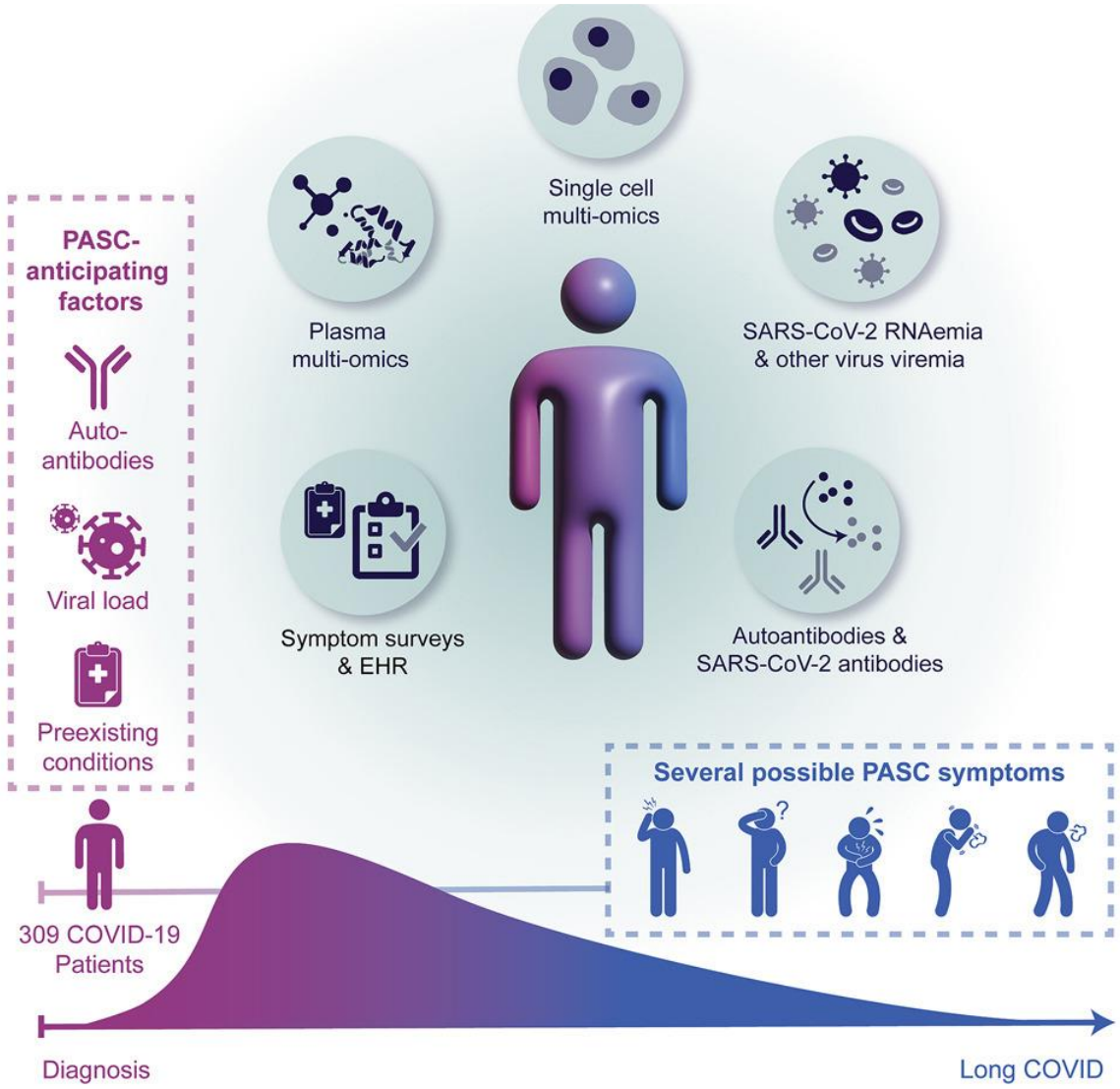
Multiple early factors anticipate post-acute COVID-19 sequelae

- Deep multi-omic, longitudinal investigation of 309 COVID-19 patients from initial diagnosis to convalescence (2–3 months later)
- Integrated with clinical data and patient-reported symptoms
- Resolved four PASC-anticipating risk factors at the time of initial COVID-19 diagnosis:
  - type 2 diabetes
  - SARS-CoV-2 RNAemia
  - Epstein-Barr virus viremia
  - specific auto-antibodies.

- Longitudinal multi-omics associate PASC with auto-antibodies, viremia, and comorbidities
- Reactivation of latent viruses during initial infection may contribute to PASC
- Subclinical auto-antibodies negatively correlate with anti-SARS-CoV-2 antibodies
- Gastrointestinal PASC uniquely present with post-acute expansion of cytotoxic T cells



https://www.sciencedirect.com/science/article/pii/S0092867422000721

Current Clinical Guidelines

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Evaluating and Caring for Patients with Post-COVID Conditions: Interim Guidance

Updated June 14, 2021

- "**Goal**…is to optimize function and quality of life"
- "**Transparency** is important…advise patients that post-COVID conditions are not yet well understood, and assure them that support will continue to be provided as new information emerges."
- "Symptoms not explained by, or out of proportion to, objective findings are not uncommon after COVID-19 and should **not be dismissed** even if there is not yet a full understanding of their etiology or their expected duration."

GUIDELINES

Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline

Waqaar Shah, [1] Toby Hillman, [2] E Diane Playford, [3] Lyth Hishmeh

What you need to know

- The likelihood of developing long term effects of covid-19 is not thought to be related to the severity of the acute infection
- The most common symptoms of long term covid-19 are fatigue and breathlessness. Symptoms may be singular, multiple, constant, transient, or fluctuating, and can change in nature over time
- Offer a chest radiograph by 12 weeks after acute covid-19 if the person has not had one already and has continuing respiratory symptoms

BMJ (Jan 2021)

aapm&r consensus statements

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CLINICAL GUIDANCE

(Aug 2021) PM&R

Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients

In press:
- Breathing discomfort
- Cognitive symptoms

In progress:
- Autonomic dysfunction
- Cardiovascular complications
- Mental Health
- Pediatrics

TABLE 4 PASC fatigue treatment recommendations

#	Statement
1	Begin an individualized and structured, titrated return to activity program.
2	Discuss energy conservation strategies.
3	Encourage a healthy dietary pattern and hydration.
4	Treat, in collaboration with appropriate specialists, underlying medical conditions, such as pain, insomnia/sleep disorders (including poor sleep hygiene), and mood issues that may be contributing to fatigue.

RECOVER Pediatric Cohort Enrollment (Modular)

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Pregnancy Cohort Module

Tier 1 (2500 Participants)
COVID Positive (80%)
COVID Negative (20%)

Tier 1 (2500 Participants)
COVID Positive (80%)
COVID Negative (20%)

Main PASC Cohort Module

Tier 1 (6000 participants)
COVID Positive (80%)
COVID Negative (20%)
15% Acute COVID-19

Tier 2 (6000 participants)
COVID Positive (90%)
COVID Negative (10%)

Tier 3 (600 participants)
400 PASC Positive/200 PASC Negative

ABCD Cohort Module

Tier 1 (10K participants)
COVID Positive (15%)
COVID Negative (85%)

MIS-C Cohort Module

Tier 2 (1000 participants)
MIS-C/Post-Vax MC

MIS-C Cohort Module

Tier 3 (1000 participants
MIS-C/Post-Vax MC

Child enrollment numbers shown. Caregiver/child dyads will participate in Tier 1.

RECOVER Adult Cohort Enrollment (Modular)

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Pregnancy Cohort Module	Main PASC Cohort Module	C4R Cohort Module
Tier 1 (2450 Participants) COVID Positive (76%) COVID Negative (24%)	Tier 1 (n=12,730) COVID Positive (83.5%) COVID Negative (16.5%)	Tier 1 (n=2500) COVID Positive (83.5%) COVID Negative (16.5%)
Tier 2 (735 Participants) COVID Positive (90%) COVID Negative (10%)	Tier 2 (n=3,819) COVID Positive (90%) COVID Negative (10%)	Tier 2 (n=750) COVID Positive (90%) COVID Negative (10%)
Tier 2 (490 Participants) COVID Positive (90%) COVID Negative (10%)	Tier 3 (2,546) COVID Positive (90%) COVID Negative (10%)	Tier 1 (n=500) COVID Positive (90%) COVID Negative (10%)

RECOVER Autopsy Cohort Enrollment

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