*Long COVID's Impact on Patients, Workers & Society*

*Webinar Nov. 1st, 2023*

*https://healthconference.org*

USA Health Watch

National Institute of Neurological Disorders and Stroke

# Exploring the Post-Acute Sequelae of COVID-19 at the National Institutes of Health

Brian Walitt MD MPH

Graphic Credit: Post-Acute Sequelae of COVID-19 (PASC) / Long COVID – What do we know? (isabelhealthcare.com)

National Institute of Neurological Disorders and Stroke

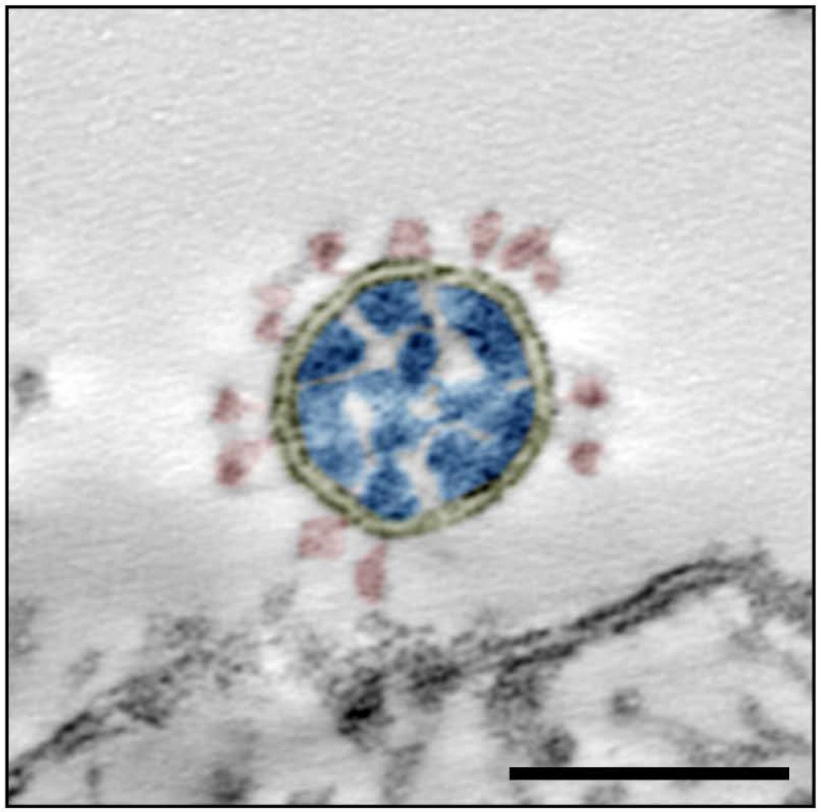
I have no conflicts of interest

**Morphometry of SARS-CoV and SARS-CoV-2 particles in ultrathin sections of infected Vero cell cultures**

Michael Laue, Anne Kauter, Tobias Hoffmann, Janine Michel, Andreas Nitsche

**doi:** https://doi.org/10.1101/2020.08.20.259531

Now published in *Scientific Reports* doi: 10.1038/s41598-021-82852-7



SARS-CoV-2

# Post-Acute Sequelae of COVID-19 (PASC) and long COVID

Post-acute sequelae of SARS-CoV-2 infection (PASC), also known as *long COVID*, is defined as ongoing, relapsing, or new symptoms or conditions present 30 or more days after infection

Thaweethai T, Jolley SE, Karlson EW, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA.* 2023;329(22):1934–1946. doi:10.1001/jama.2023.882

# Post-Acute Sequelae of COVID-19 (PASC) and long COVID

Post-acute sequelae of SARS-CoV-2 infection (PASC), also known as *long COVID*, is defined as ongoing, relapsing, or new symptoms or conditions present 30 or more days after infection

**What are the main physiological mechanisms of COVID-19 that are likely to lead to PASC?**

Thaweethai T, Jolley SE, Karlson EW, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA.* 2023;329(22):1934–1946. doi:10.1001/jama.2023.882

Pain Rep. 2021; 6(1): e887.
Published online 2021 Feb 16. doi: 10.1097/PR9.0000000000000887
PMCID: PMC7889402
PMID: 33615088

# A clinical primer for the expected and potential post-COVID-19 syndromes

Brian Walitt[a,*] and Elizabeth Bartrum[b]

# Inflammation

Review Article | Published: 28 April 2020
The trinity of COVID-19: immunity, inflammation and intervention
Matthew Zirui Tay, Chek Meng Poh, Laurent Rénia, Paul A. MacAry & Lisa F. P. Ng
Nature Reviews Immunology 20, 363–374 (2020) | Cite this article

Acute SARS-CoV-2 infection can directly trigger inflammation:

- Severe enough to cause tissue injury
- Can persist after the acute infection resolves

Innate Immune Response

- Excessive monocyte/macrophage activation
- Excessive inflammasome activation

Systemic Immune Response

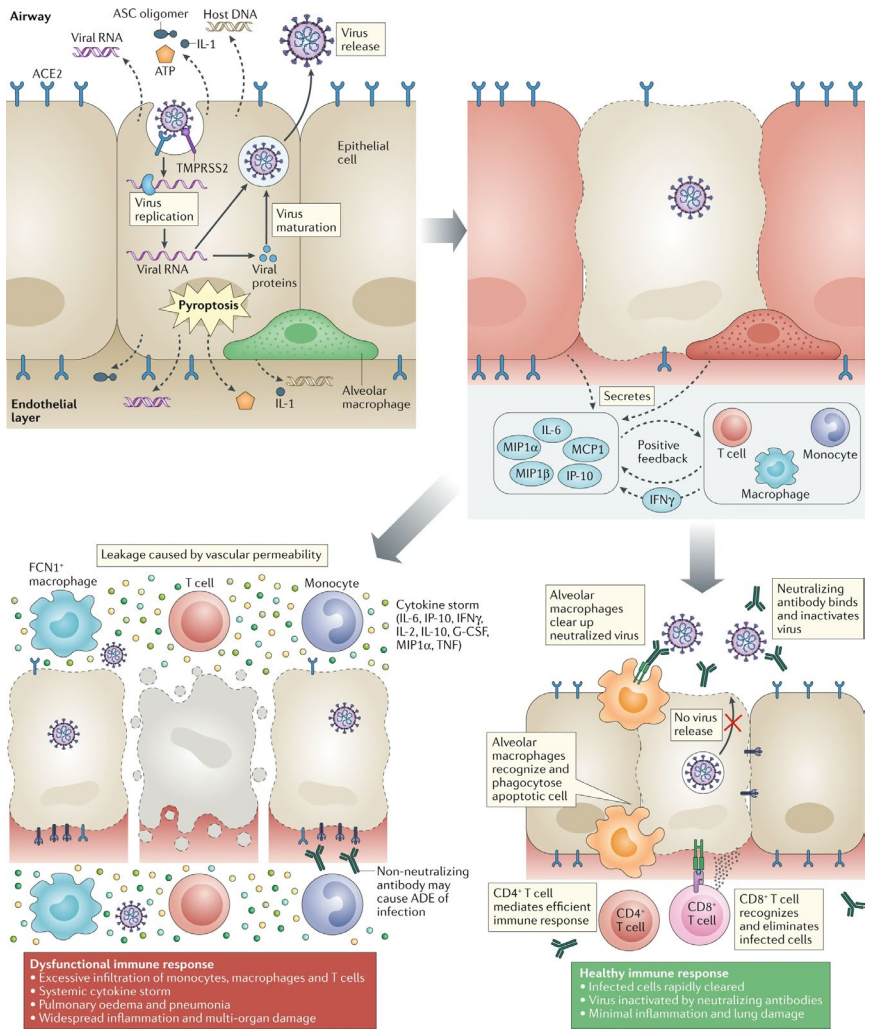
- Systemic cytokine imbalances
- Adaptive immunity failures

Immune Regulation and Restoration

- Persistent COVID-19 independent inflammation
- Development of autoimmunity

Persistent viral reservoirs; persistent viral antigens (?)

- Incomplete viral assembly




Initiation of inflammation from SARS-Cov-2

# Thrombosis

Acute SARS-CoV-2 infection can directly trigger thrombosis:

- Lasting complications of ischemic injury are well-known

Direct endothelial injury

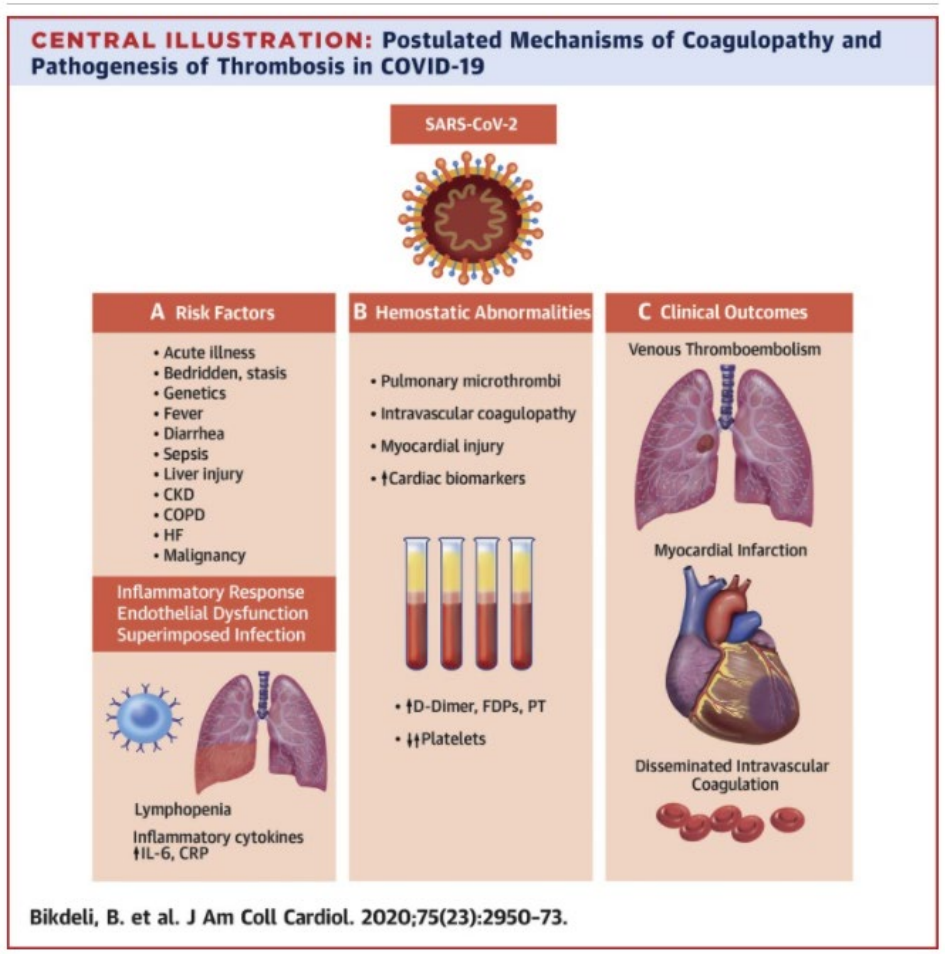
- Via ACE-2 receptors

Inflammatory activation of clotting cascades

- Via Tissue factor

Complement Activation

Antiphospholipid antibody development



# Fear, Stress, and Change

The SARS-CoV-2 pandemic has been a source of fear, stress, and change for all human beings:

- We have all been physiologically impacted
- Make us all more vulnerable to chronic illness

- Endocrine Effects
  - Hypothalamic-Pituitary-Adrenal Axis
- Neurological Effects
  - Autonomic Nervous System
- Immunological Effects
  - $T_{H1}/T_{H2}$ homeostasis
- Stress-Related Illnesses
  - Critical illness and Post-ICU stress disorders
  - Cardiovascular Disease
  - Asthma
  - Dysautonomia
  - Neuropsychological Illnesses

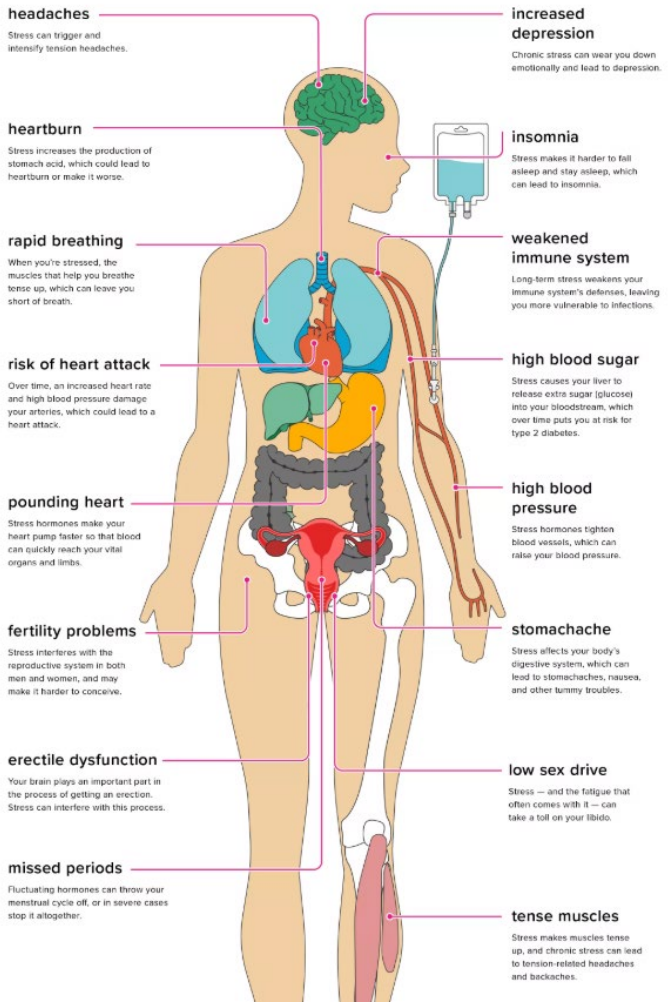



Image credit: https://www.stress.org/daily-life

# PASC Subtypes

- **Cardiac:**
  - Myocarditis, pericarditis, consequences of infarction, arrhythmias
- **Pulmonary:**
  - Pneumonitis, pleuritis, consequences of infarction, reactive bronchoconstriction
- **Neurologic:**
  - Direct neuronal inflammation, consequences of infarction and injury
  - Dysautonomia, movement disorders, headache disorders, neurocognitive disorders
  - Post-Viral Fatigue Syndrome, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Fibromyalgia

- All can be associated with similar phenotypes of pain, fatigue, exercise intolerance, weakness, altered sensation, altered cognition, and altered personality
- These subtypes are not mutually exclusive

# Post-Viral Fatiguing Syndromes

Initial description (1985): *"Principle symptom is severe muscle fatiguability, but there may be a range of secondary symptoms, such as the aching of muscles, disequilibrium, and psychiatric manifestations."*[1]

UK Viral Meningitis Study (1996):[2]

- 159 confirmed infections followed 6-24 months
- Chronic fatigue syndrome (CFS) prevalence: 12.6%

Dubbo Infection Outcomes Study (2006):[3]

- 253 confirmed infections followed 1 year
  - Six weeks CFS: 35%
  - Three months CFS: 27%
  - Six months CFS: 12%
  - One-year CFS: 9%

Severe Acute Respiratory Syndrome (SARS):[4]

- 181 survivors followed over 41.3 months:
  - 40.3% reported persistent fatigue
  - 27.1% met modified 1994 CDC criteria for CFS

History strongly suggested that post-viral fatigue was going to be a substantial problem


References:
1: Behan PO, Behan WM, Bell EJ. The postviral fatigue syndrome--an analysis of the findings in 50 cases. J Infect 1985;10:211–22.
2:Hotopf M, Noah N, Wessely S. Chronic fatigue and minor psychiatric morbidity after viral meningitis: a controlled study. J Neurol Neurosurg Psychiatry 1996;60:504–9
3: Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, Reeves WC, Lloyd A, Dubbo Infection Outcomes Study G. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. Bmj 2006;333:575
4:Ahmed H, Patel K, Greenwood DC, Halpin S, Lewthwaite P, Salawu A, Eyre L, Breen A, O'Connor R, Jones A, Sivan M. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. J Rehabil Med 2020;52:jrm00063.

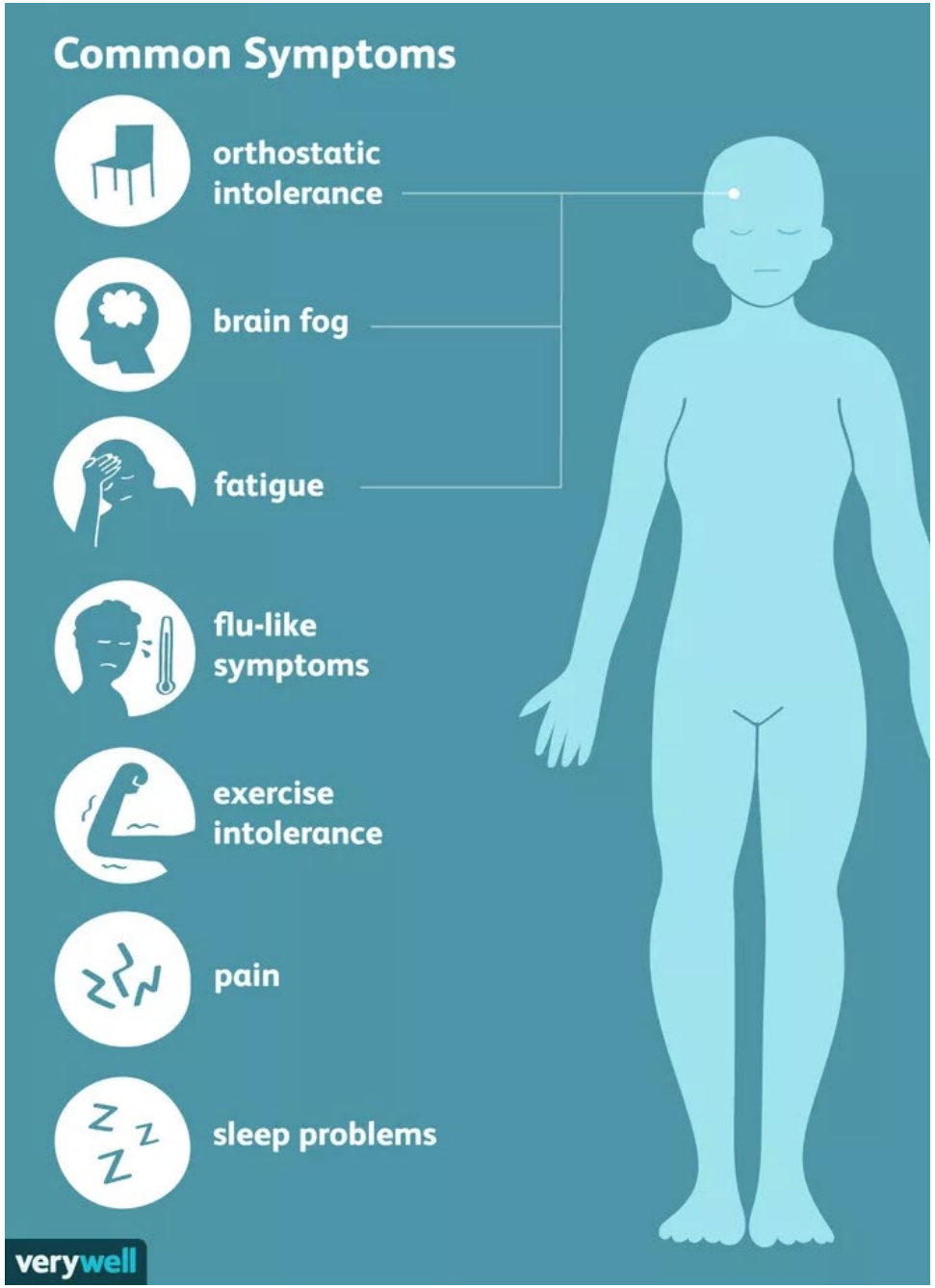




Image credit: https://www.verywellhealth.com/chronic-fatigue-syndrome-symptoms-716110

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The New York Times Magazine

FEATURE

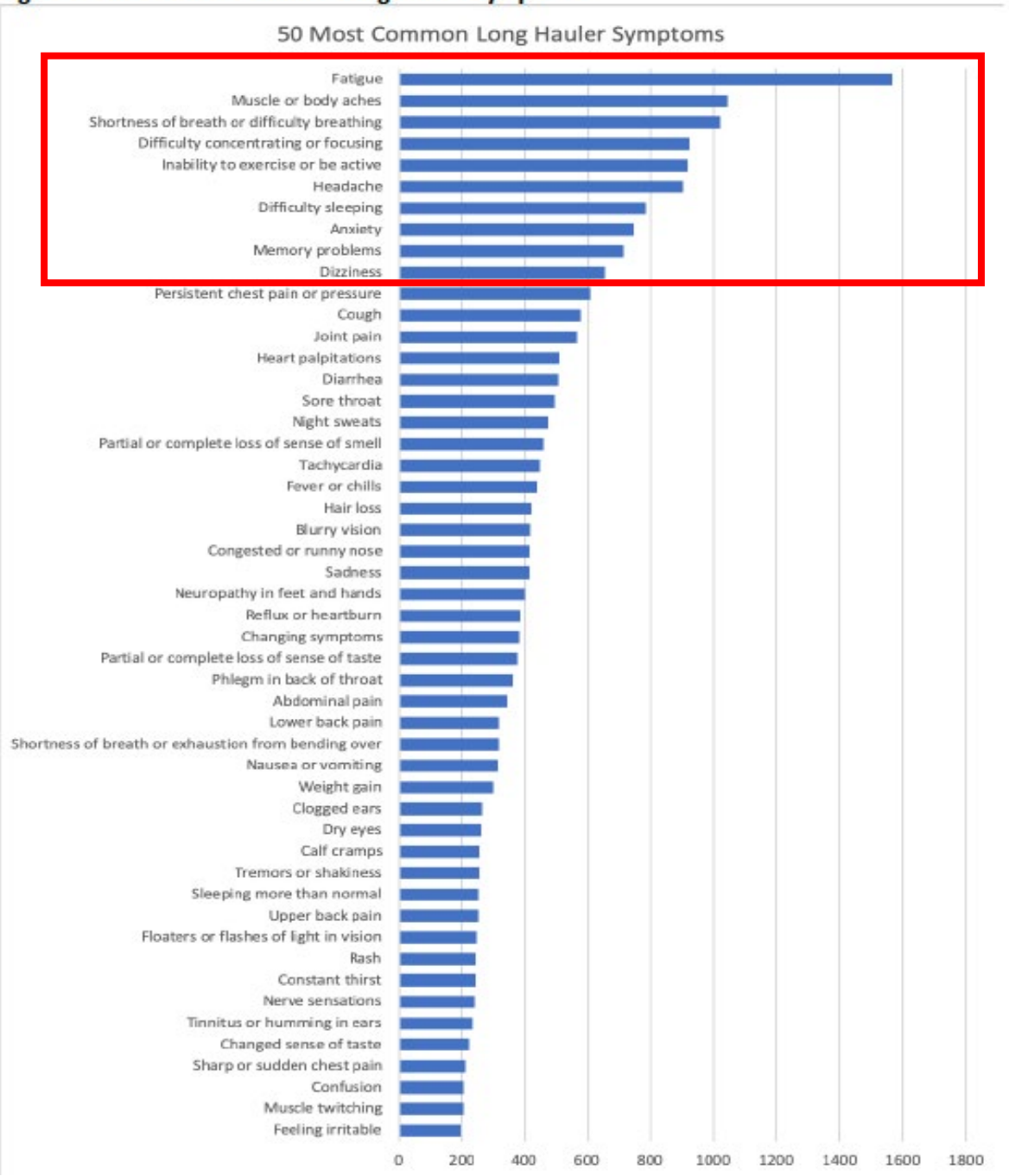
# What If You Never Get Better From Covid-19?

Some patients could be living with the aftereffects for years to come. Recent research into another persistent, mysterious disease might help us understand how to treat them.

**By Moises Velasquez-Manoff**

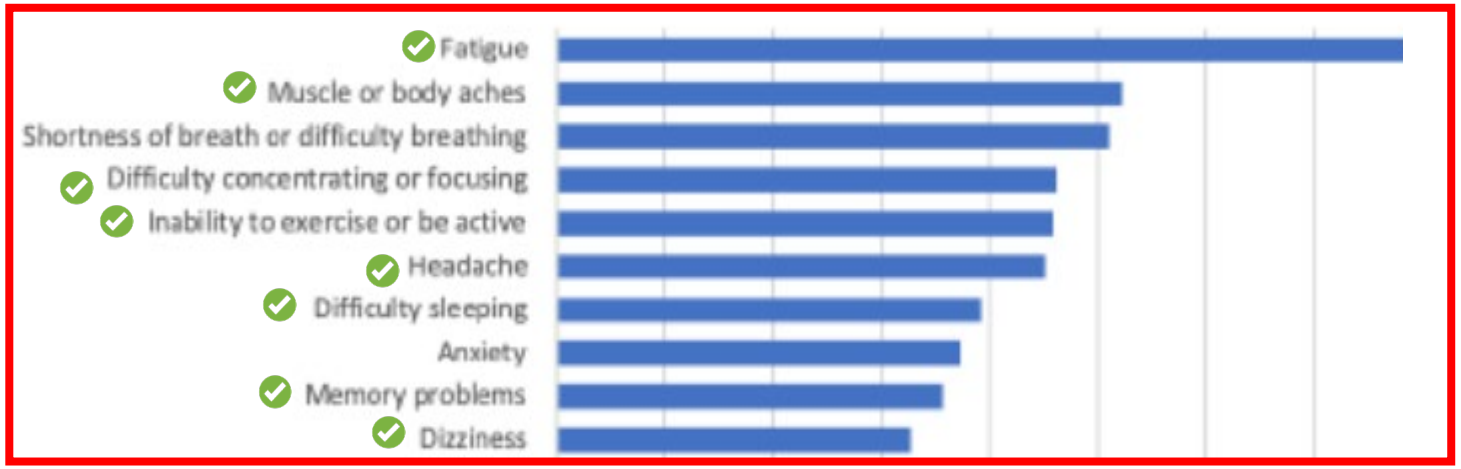
•Published New York Times Jan. 21, 2021

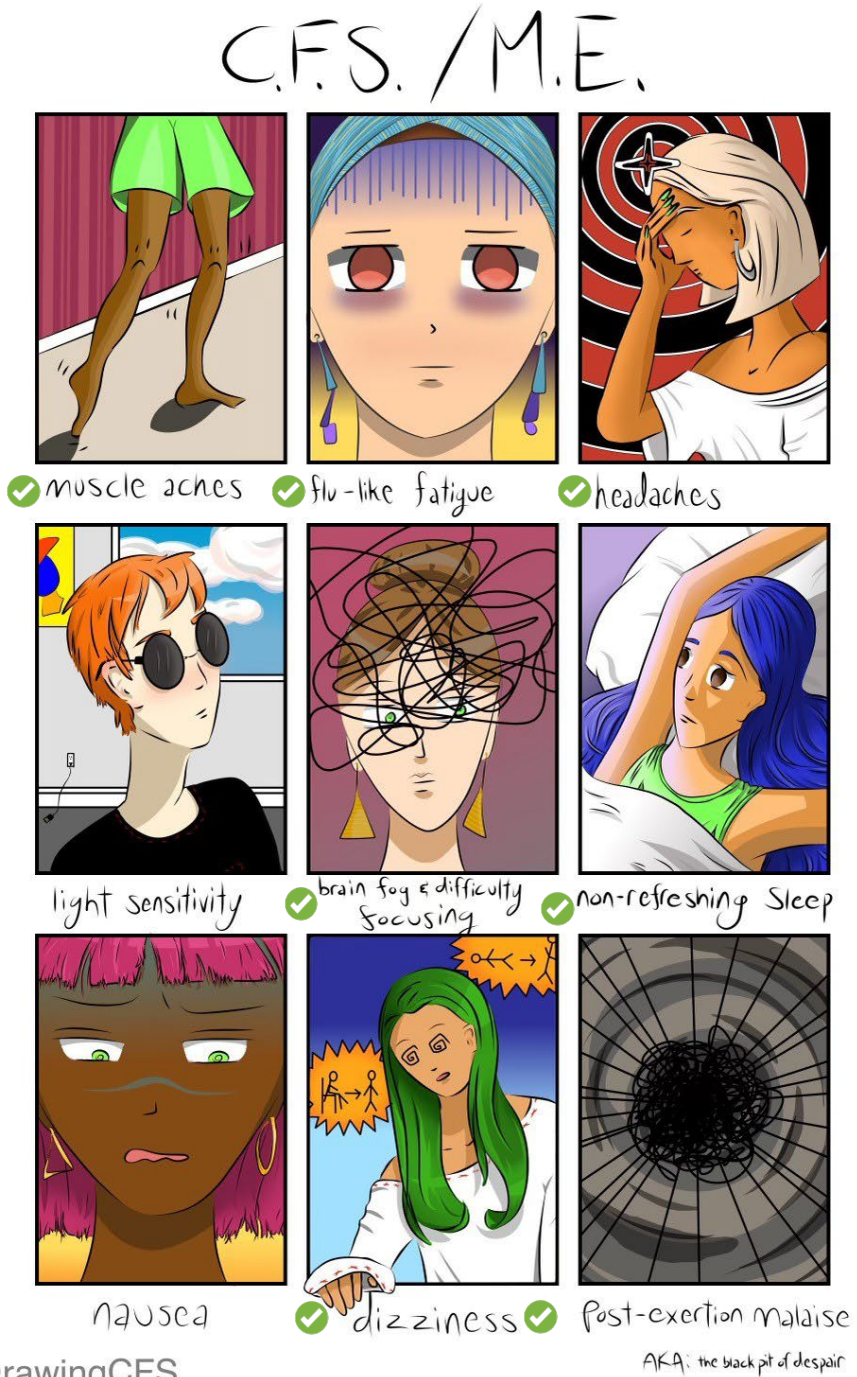
**Figure 2. The 50 Most Common Long Hauler Symptoms**



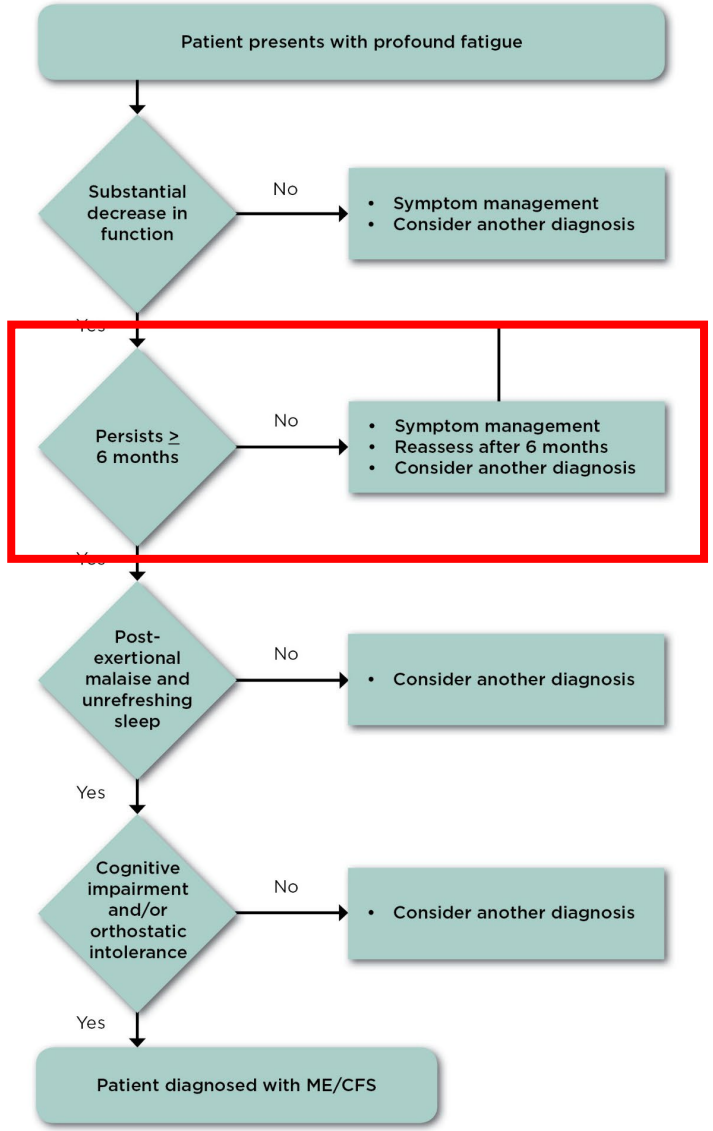

Lambert, N. J. & Survivor Corps.
COVID-19 “Long Hauler” Symptoms Survey Report. Indiana University School of Medicine; 2020.

## 50 Most Common Long Hauler Symptoms



# Diagnostic Algorithm for ME/CFS




For more information, visit **www.iom.edu/MECFS**

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
Advising the nation • Improving health

# Protocol 000089: Natural History of COVID-19 Convalescence at the National Institutes of Health

## Phase A-Survey: Phone Interviews and Online Questionnaires

- **PRIMARY OBJECTIVE:**
  - To observe and describe the range of medical syndromes that occur in the wake of acute SARS-CoV-2.

## Phase B- Evaluation: 5-day Inpatient visit

- **PRIMARY OBJECTIVE:**
- Phase B: to describe and medically characterize patients with PASC and those who fully recovered from SARS-Co-2.

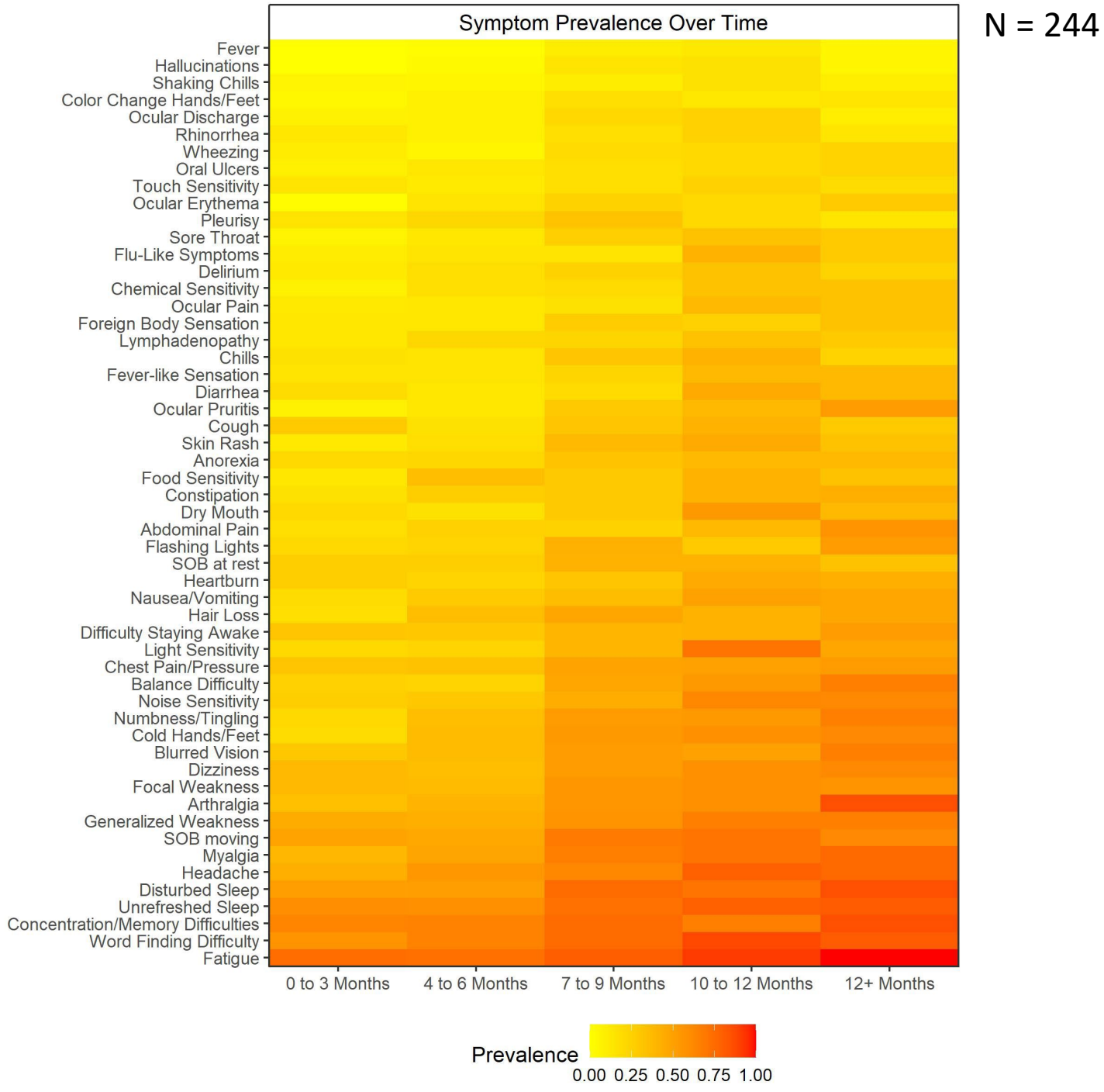
# Phase A: Survey

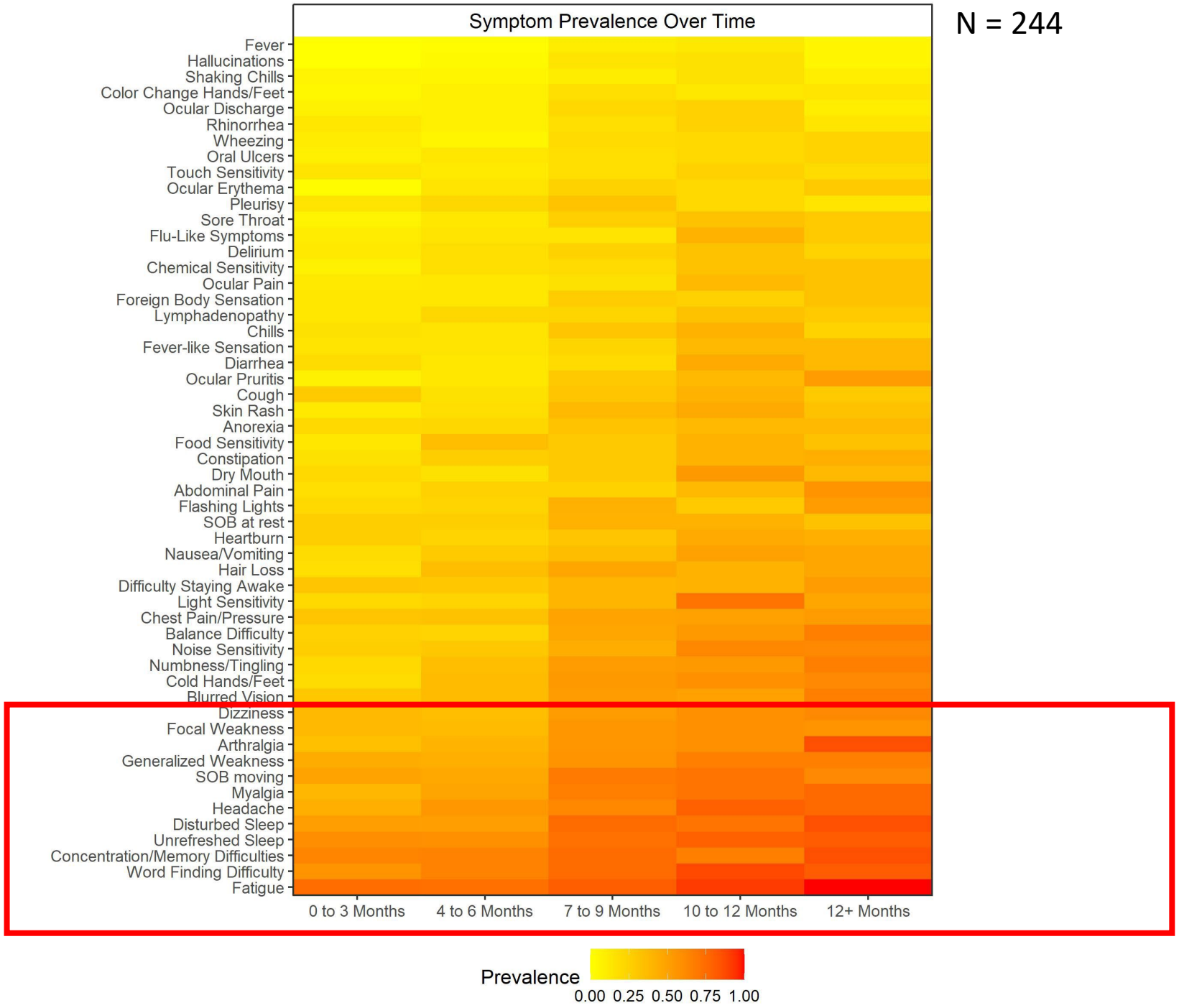
## Phase A-Surveying with Phone Interviews and Online Questionnaires

- **PRIMARY OBJECTIVE:**
  - To observe and describe the range of medical syndromes that occur in the wake of acute SARS/CoV2.
- Open since October 2020
- Screen and refer to other COVID -19 studies at NIH

## Phase A Procedures

- Eligibility Interview
- Medical Record Confirmation
- Survey Interview
- Online Questionnaires


Symptom Prevalence Over Time
N = 244
Fever
Hallucinations
Shaking Chills
Color Change Hands/Feet
Ocular Discharge
Rhinorrhea
Wheezing
Oral Ulcers
Touch Sensitivity
Ocular Erythema
Pleurisy
Sore Throat
Flu-Like Symptoms
Delirium
Chemical Sensitivity
Ocular Pain
Foreign Body Sensation
Lymphadenopathy
Chills
Fever-like Sensation
Diarrhea
Ocular Pruritis
Cough
Skin Rash
Anorexia
Food Sensitivity
Constipation
Dry Mouth
Abdominal Pain
Flashing Lights
SOB at rest
Heartburn
Nausea/Vomiting
Hair Loss
Difficulty Staying Awake
Light Sensitivity
Chest Pain/Pressure
Balance Difficulty
Noise Sensitivity
Numbness/Tingling
Cold Hands/Feet
Blurred Vision
Dizziness
Focal Weakness
Arthralgia
Generalized Weakness
SOB moving
Myalgia
Headache
Disturbed Sleep
Unrefreshed Sleep
Concentration/Memory Difficulties
Word Finding Difficulty
Fatigue
0 to 3 Months
4 to 6 Months
7 to 9 Months
10 to 12 Months
12+ Months
Prevalence
0.00 0.25 0.50 0.75 1.00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Ocular Pruritis
Cough
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Anorexia
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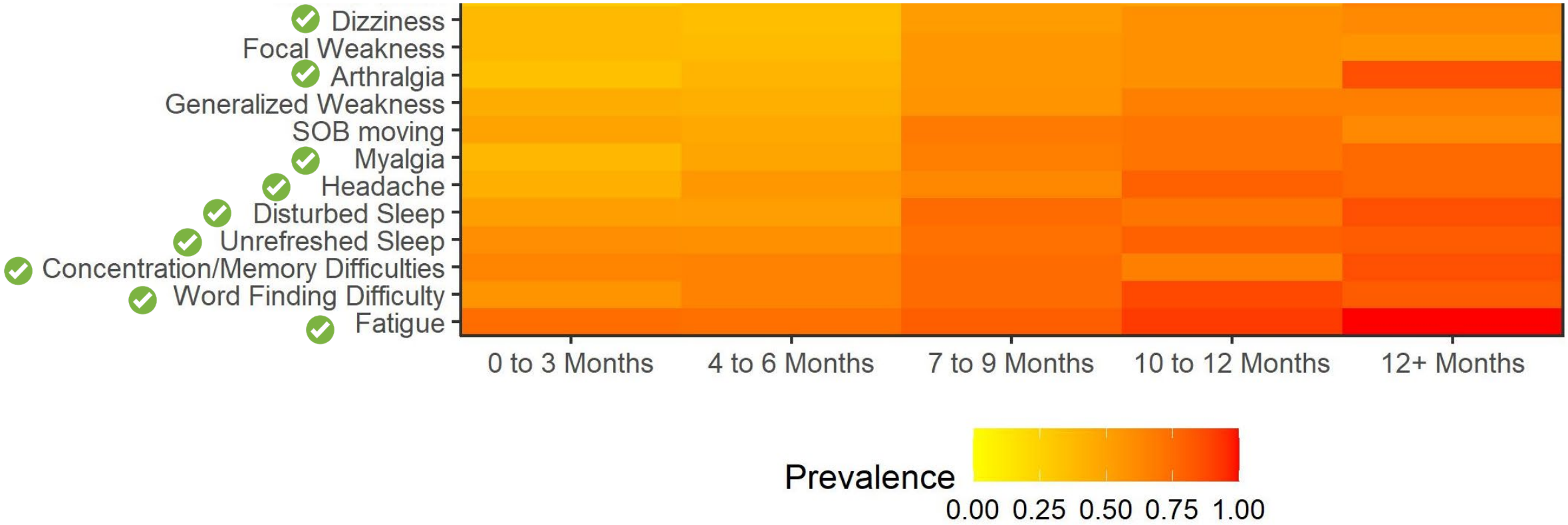
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12+ Months
Prevalence
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# Phase B: Evaluation

## Phase B: Evaluation

- **PRIMARY OBJECTIVE:** To describe and medically characterize patients with PASC and those who fully recovered from SARS/CoV2.

## CARDIAC

- Echocardiogram, EKG, 48-hour Holter, Stress Test

## PULMONARY

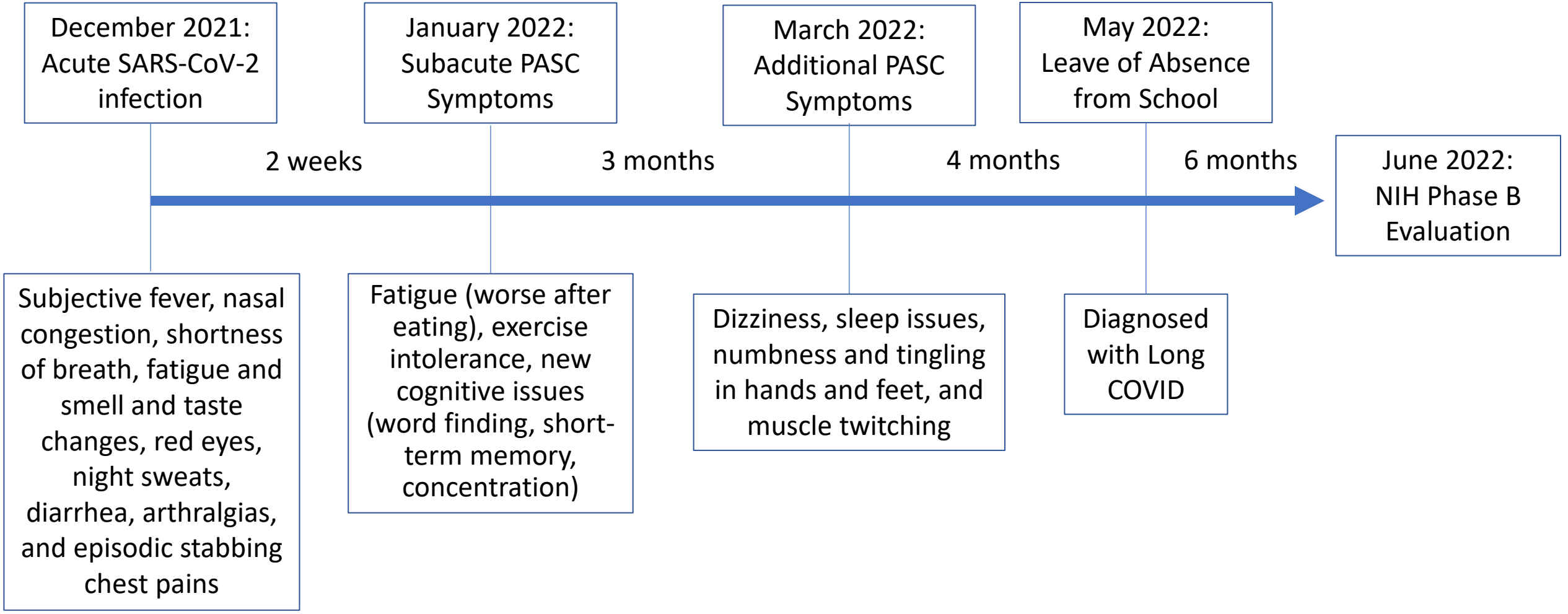
- Chest CT with contrast, PFTs, 6-minute walk

## NEUROLOGICAL

- Neurological exam, MRI Brain, Smell/Taste Evaluation, Neuropsychological Testing
- Optional Lumbar Puncture

# Case 1: The Medical Student

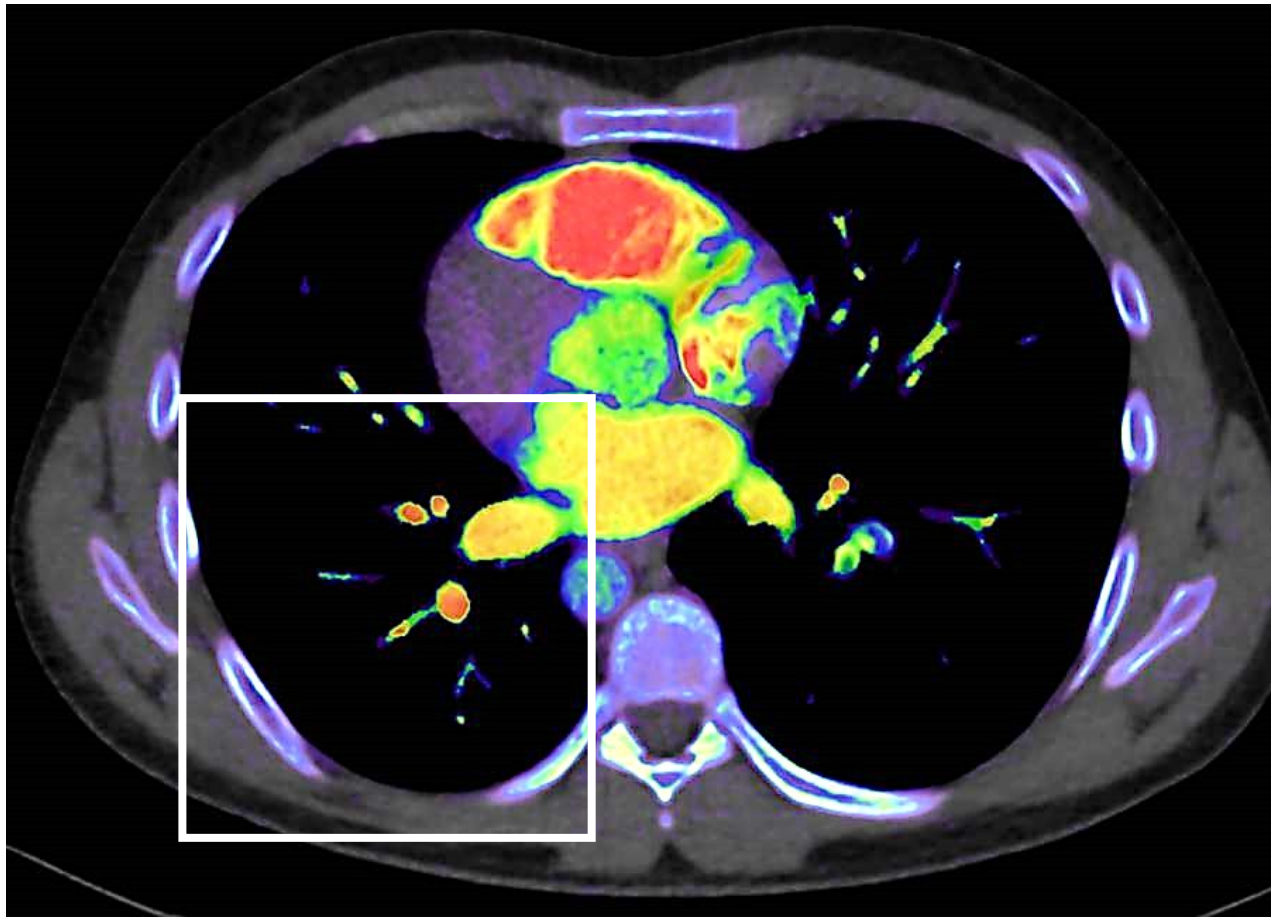
- 36-year-old Indian-Asian male second-year medical student
- Fully vaccinated and boosted with Moderna prior to infection

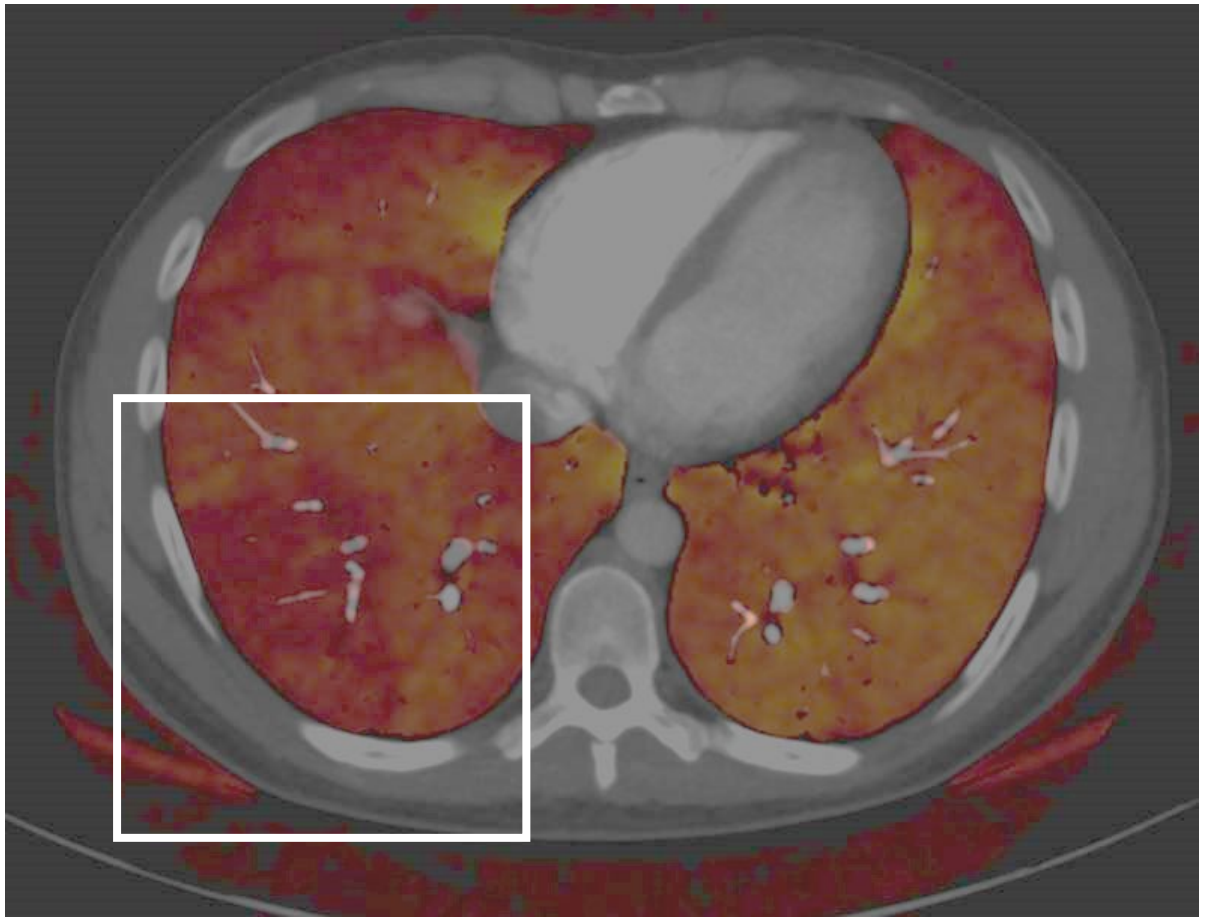


# Case 1: The Medical Student

Physical Exam:

- T: 36.3, BP: 97/77, HR: 54, RR: 18, 99% on Room Air
- Unremarkable detailed research physical examination
- Normal Labs:
  - CBC, CMP, TSH. ESR: 5, CRP: 0.2, D-Dimer: <0.27
- Normal EKG:
  - Heart rate 51, sinus bradycardia. Atrial premature complex-SV complex with short R-R interval early repolarization.
- Normal Transthoracic echocardiogram:
  - The left ventricle is normal in size and systolic function. There are no regional wall motion abnormalities. The LV diastolic function is normal by Doppler exam. The right ventricle is normal in size and function. No significant valvular abnormalities.
- Normal Exercise Stress Test:
  - Stopped due to dyspnea after reaching 16.1 METs at a peak HR of 192 bpm (104% APMHR. Normal resting blood pressure with normal response to stress. No arrythmias.
- Mildly abnormal Pulmonary Function Test:
  - Normal flows and total lung capacity. Mild restrictive ventilatory defect. Mild diffusion defect following adjustment of DLCO for hemoglobin. The flow volume loop reflects a normal pattern.





Chest CT with contrast:
There are multiple filling defects within the lobar, segmental and subsegmental pulmonary arteries to the right lower lobe compatible with pulmonary thromboembolism.

# Case 1: The Medical Student

Treatment:

- Apixaban for 3 months

After treatment:

- He noted 90% improvement in his cognitive symptoms within a few weeks.
- Fatigue improved substantially but some continues to linger on
- 15 months after infection, he returned to medical school as a third-year student

# Case 1: The Medical Student

- A substantial number of PASC cases will have alternative medical explanation than just “Long COVID”
  - Sometimes the clinical presentations will defy expectations
  - Some will be new diagnoses can be unrelated or accelerated by SARS-CoV-2 infection
  - Some will be legacy effects of injury related to SARS-CoV-2 infection
- After review of 16 cases, these clinically relevant medical issues were discovered:
  - Pulmonary emboli (1)
  - Newly diagnosed sleep apnea (4+)
  - Undiagnosed asthma (1)
  - Frontotemporal atrophy (1)
  - Increased intracranial hypertension on lumbar puncture (2)
  - Probable disruption of the blood/brain barrier on lumbar puncture (2)
  - Substantial deconditioning with new onset non-alcoholic steatohepatitis (1)
  - Ehlers Danlos Syndrome (1)
  - Functional movement disorder (1)

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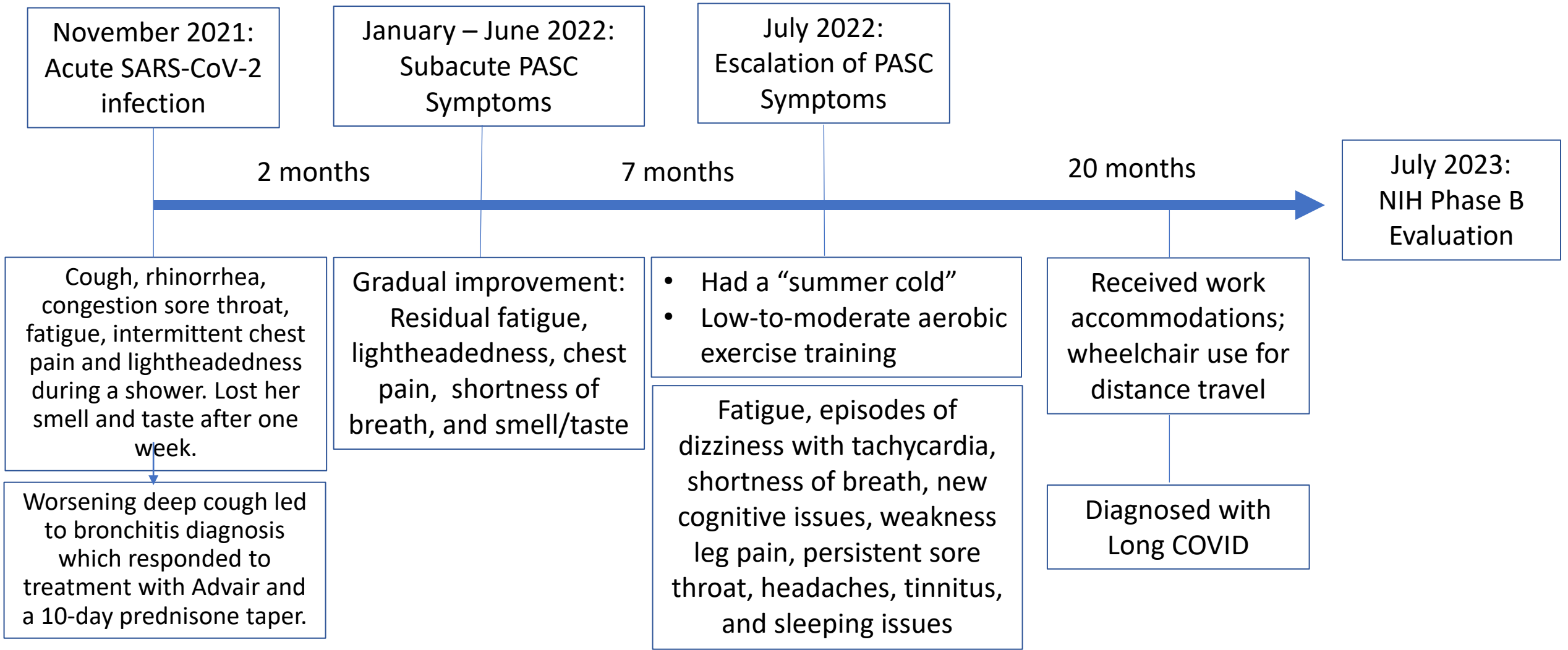
  - Ehlers Danlos Syndrome (1)
  - Functional movement disorder (1)

Diligence and follow-up over time will be important in understanding causality of ~30% of PASC cases

# Case 2: The Young Scientist

- 23-year-old non-Hispanic white woman working as a scientific researcher
- Fully vaccinated and boosted with J&J prior to infection; Pfizer series completed after in 2022



# Case 2: The Young Scientist

Physical Exam:

- T: 36.3, BP: 97/77, HR: 54, RR: 18, 99% on Room Air
- Essentially unremarkable detailed research physical examination
- Normal Labs:
  - CBC, CMP, TSH. ESR: 22, CRP: 5.4 (cutoff is 5) , D-Dimer: 0.36. Negative ANA, Lyme, Syphilis, antiphospholipid antibodies.
- Normal Lumbar Puncture:
  - 1 WBC, 4 RBC, glucose 56, protein 22, IgG 1.7, no oligoclonal bands
- Normal Brain MRI:
  - Unremarkable enhanced MRI of the brain
- Normal EKG:
  - Heart rate 60, normal sinus rhythm
- Normal Transthoracic echocardiogram:
  - The left ventricle is normal in size and systolic function. There are no regional wall motion abnormalities. The LV diastolic function is normal by Doppler exam. The right ventricle is normal in size and function. No significant valvular abnormalities.
- Mildly abnormal Pulmonary Function Test:
  - Normal flows. Elevated total lung capacity and reserve volume suggest air trapping. No diffusion defect. The flow volume loop reflects a normal pattern.
- Normal Chest CT with contrast:
  - The perfusion images of the lungs are unremarkable

# Case 2: The Young Scientist

- Submaximal but normal Exercise Stress Test:
  - Stopped due to leg fatigue after reaching 9.1METs (81% APMHR). Normal resting blood pressure with normal response to stress. No arrythmias.
  - **Developed post-exertional malaise about 24 hours after the exercise stress test that peaked at 48 hours post-exercise**

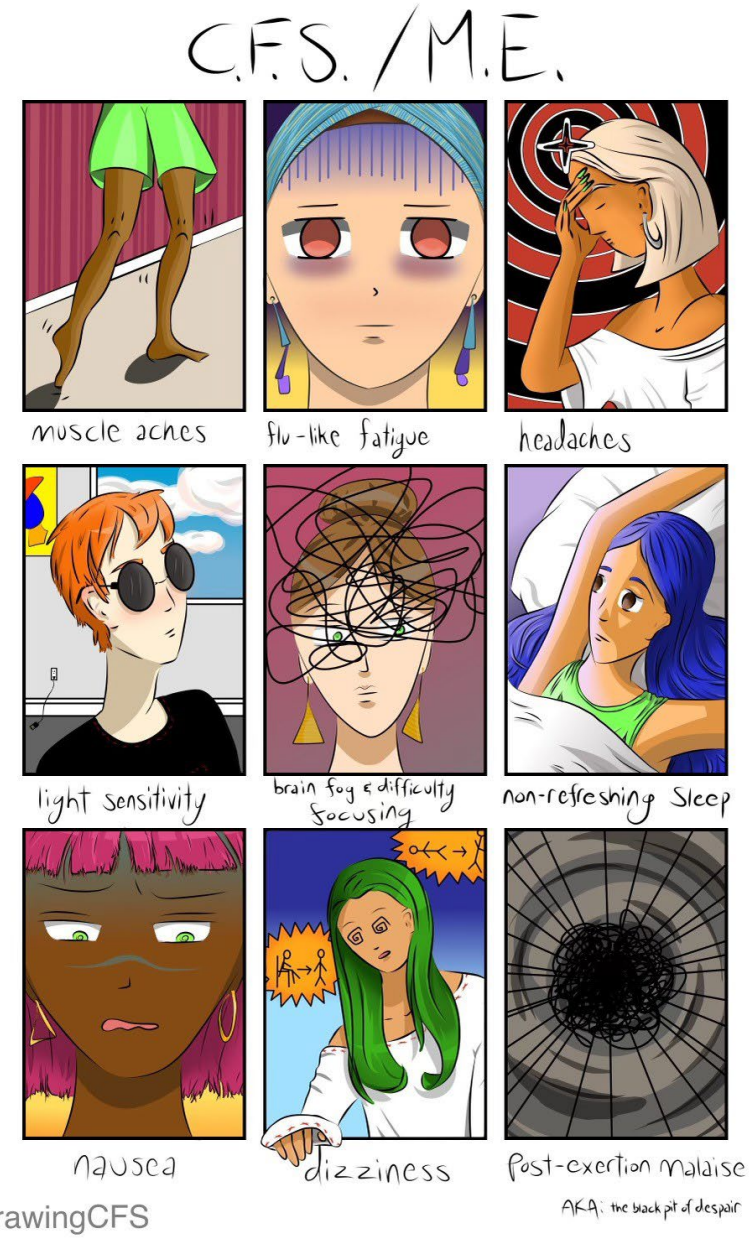
Abnormal Autonomic Testing:

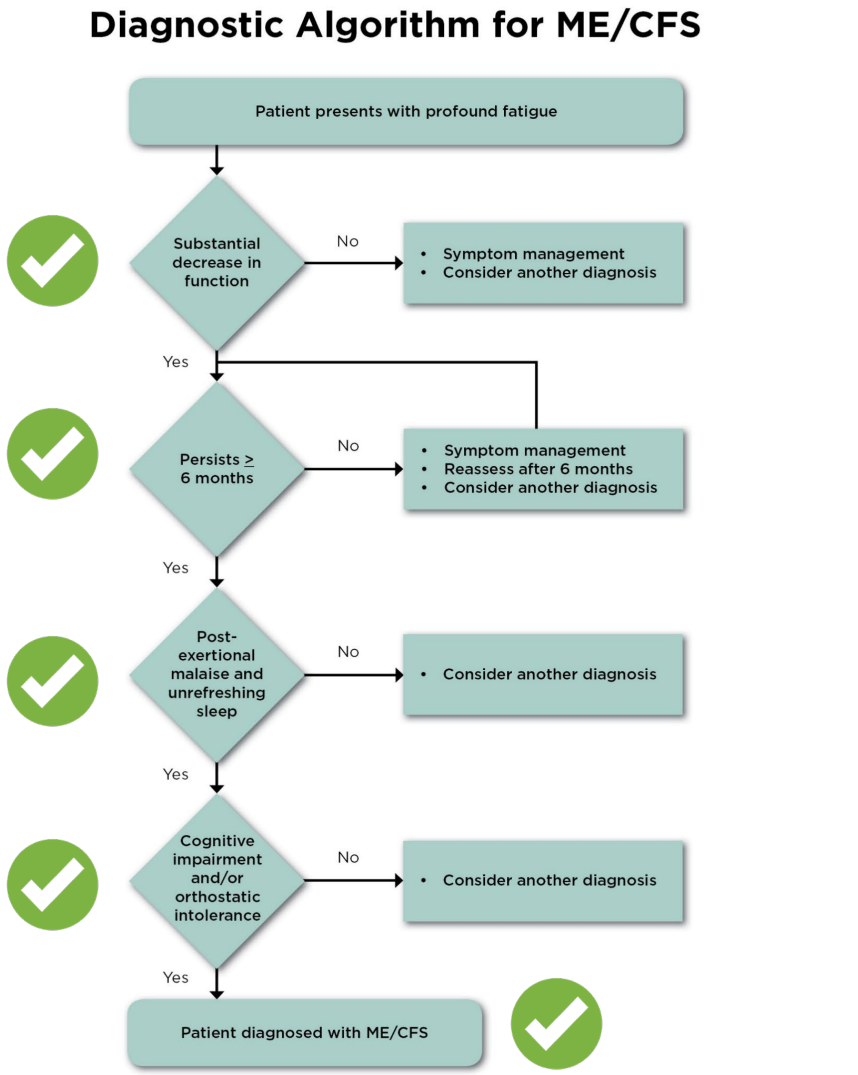
- Tilt-table test showed an orthostatic tachycardia with the delta HR max. 66 compared to baseline. SBP using finger cuff remained stable.

- There is orthostatic tachycardia of > 30 beats/min, compatible with diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS).

What is the diagnosis here?

# Post-Infectious Myalgia Encephalomyelitis/Chronic Fatigue Syndrome



# Post-Infectious Postural Orthostatic Tachycardia Syndrome

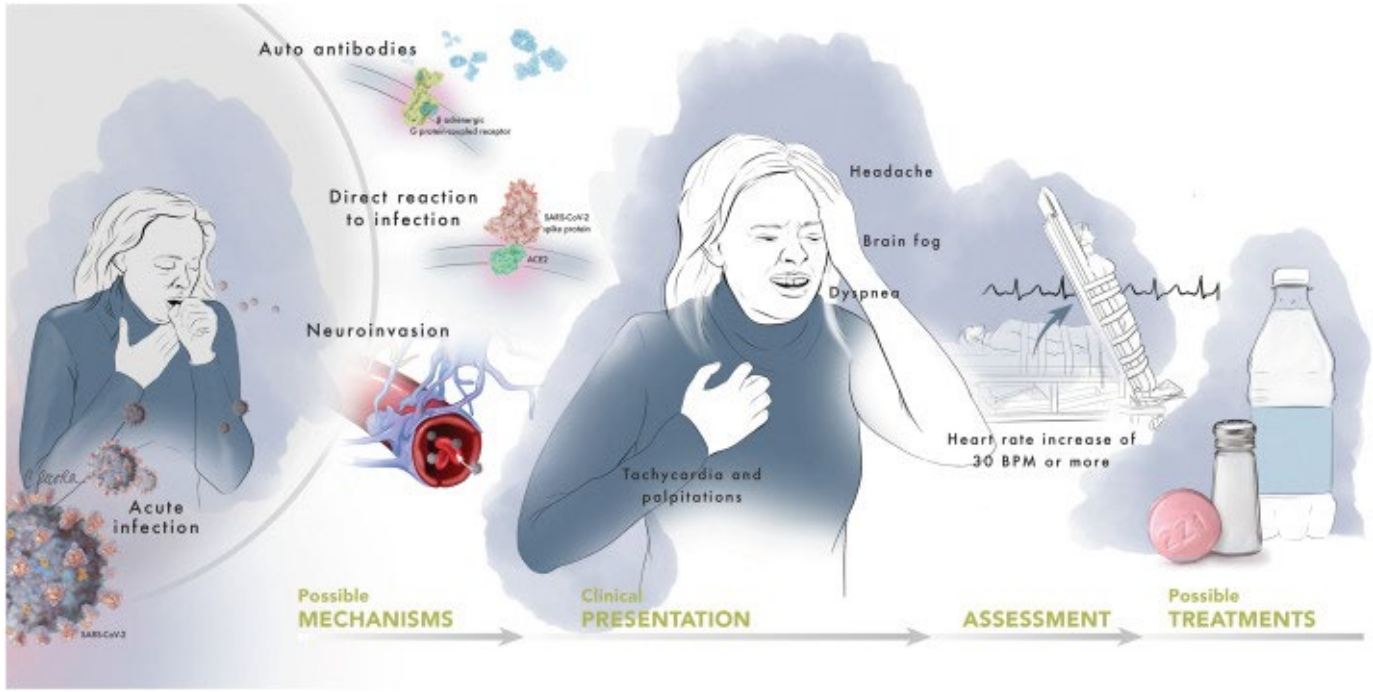



Illustration:Christina Pecora, MSMI, CMI.
Heart Rhythm 2022 191880-1889DOI: (10.1016/j.hrthm.2022.07.014)

Antecedent history of suspected viral infection reported in 20-50% of POTS patients

RESEARCH ARTICLE | VOLUME 235, 102828, NOVEMBER 2021 Download Full Issue

## Postural orthostatic tachycardia syndrome (POTS): State of the science and clinical care from a 2019 National Institutes of Health Expert Consensus Meeting - Part 1

Steven Vernino • Kate M. Bourne • Lauren E. Stiles • ... Hasan I. Abdallah • Anil Darbari • Satish R. Raj • Show all authors

Open Access • Published: June 04, 2021 • DOI: https://doi.org/10.1016/j.autneu.2021.102828 •

**Adult Definition:**

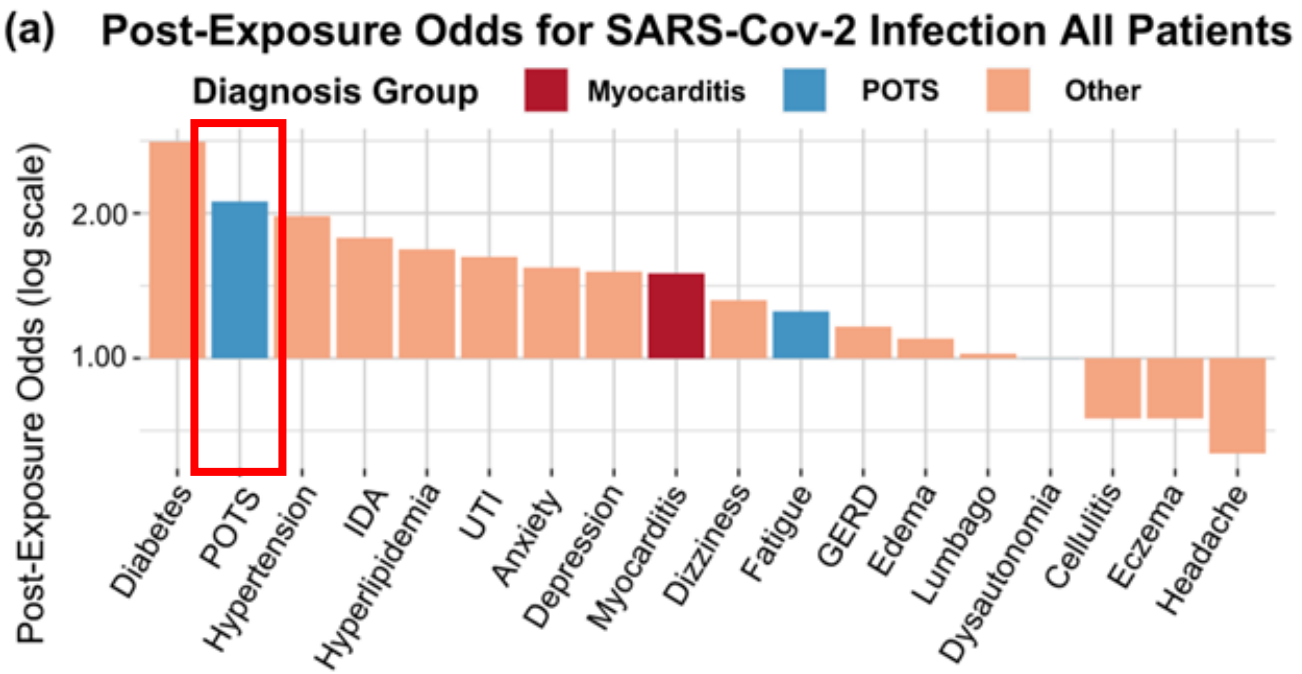
- **•1.** A sustained HR increment of not less than 30 beats/minute within 10 min of standing or head-up tilt; and
- **•2.**An absence of orthostatic hypotension (i.e. no sustained systolic blood pressure [BP] drop of 20 mmHg or more); and
- **•3.**Frequent symptoms of orthostatic intolerance during standing, with rapid improvement upon return to a supine position. Symptoms may include lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, and fatigue; and
- **•4.**Duration of symptoms for at least 3 months; and
- **•5.**Absence of other conditions explaining sinus tachycardia.

Nat Cardiovasc Res. 2022 Dec;1(12):1187-1194. doi: 10.1038/s44161-022-00177-8.
Epub 2022 Dec 12.

# Apparent Risks of Postural Orthostatic Tachycardia Syndrome Diagnoses After COVID-19 Vaccination and SARS-Cov-2 Infection

Alan C Kwan [1], Joseph E Ebinger [1], Janet Wei [1], Catherine N Le [2], Jillian R Oft [2], Rachel Zabner [2], Debbie Teodorescu [1], Patrick G Botting [1], Jesse Navarrette [1], David Ouyang [1], Matthew Driver [1], Brian Claggett [3], Brittany N Weber [3], Peng-Sheng Chen [1], Susan Cheng [1]

- 12,460 patients (age 47±23 years) with documented new SARS-Cov-2 infection
- Post-infection odds of new POTS-associated diagnoses (n=1,004, odds: 1.52 [1.33–1.72], p<0.001)
- Common Primary Care diagnoses (n=3,325, odds: 1.4 [1.31–1.50], p<0.001)
- OR was not significantly higher (1.08 [0.93–1.25], p=0.29).




Acute SARS-CoV-2 infection increases the odds of developing the PASC phenotype, but not more than what is typically seen in the community

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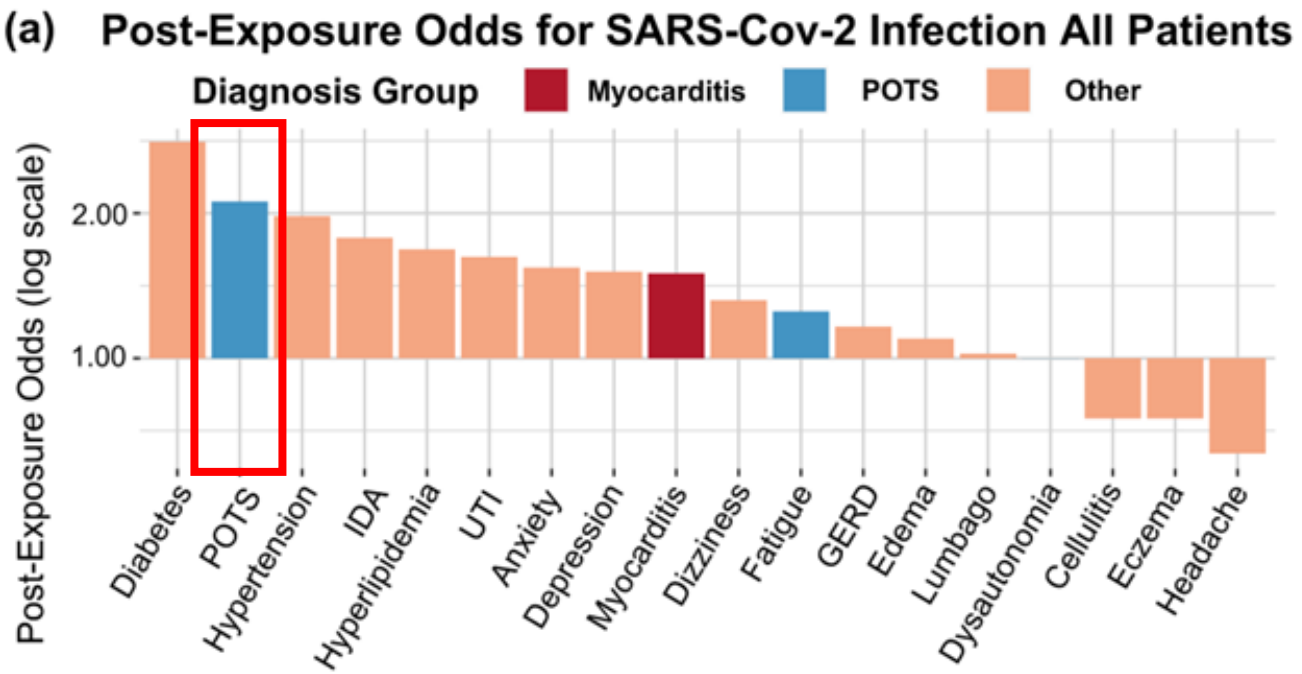
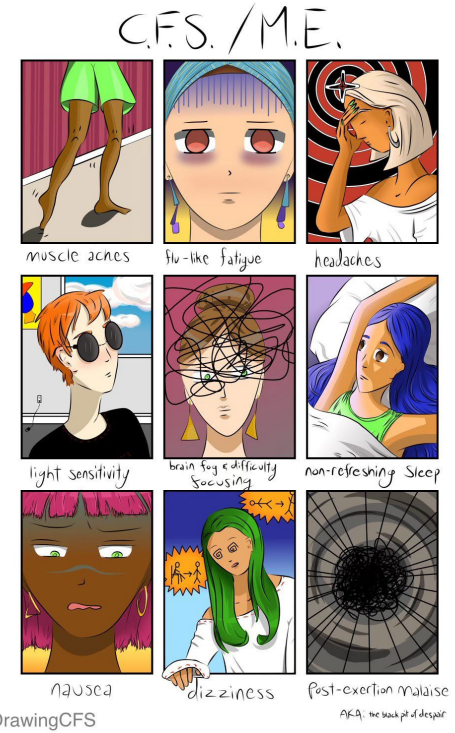



Acute SARS-CoV-2 infection increases the odds of developing the PASC phenotype, but not more than what is typically seen in the community

After review of 16 NIH PASC participants, 4 had positive tilt testing for POTS and 1 met criteria for neurogenic hypotension

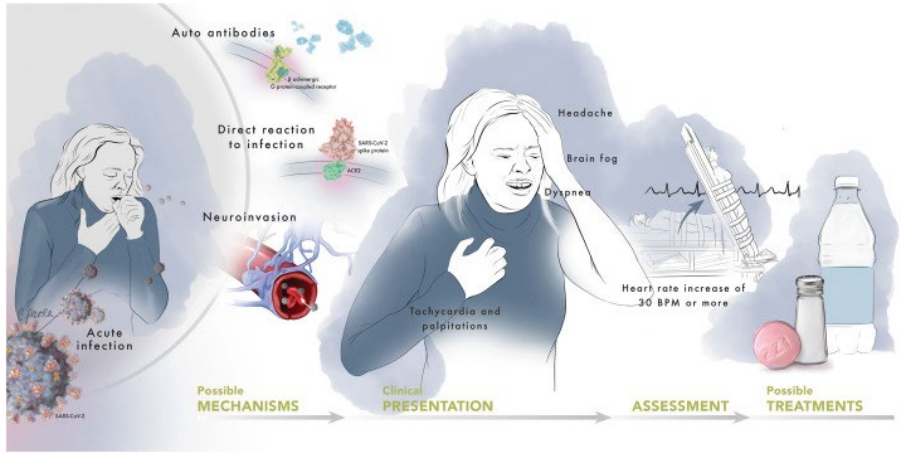
# Post-Epstein-Barr Viral Fatigue Syndrome




Front Immunol. 2021; 12: 656797.
Published online 2021 Nov 15. doi: 10.3389/fimmu.2021.656797
PMCID: PMC8634673
PMID: 34867935

## Epstein-Barr Virus and the Origin of Myalgic Encephalomyelitis or Chronic Fatigue Syndrome

Manuel Ruiz-Pablos,[1,*] Bruno Paiva,[2] Rosario Montero-Mateo,[3] Nicolas Garcia,[2] and Aintzane Zabaleta[2,*]




SAGE Open Med Case Rep. 2020; 8: 2050313X20915413.
Published online 2020 Apr 2. doi: 10.1177/2050313X20915413
PMCID: PMC7139175
PMID: 32284866

## Infectious mononucleosis complicated by peritonsillar abscess and postural orthostatic tachycardia syndrome: A case report

Kaspar L Yaxley

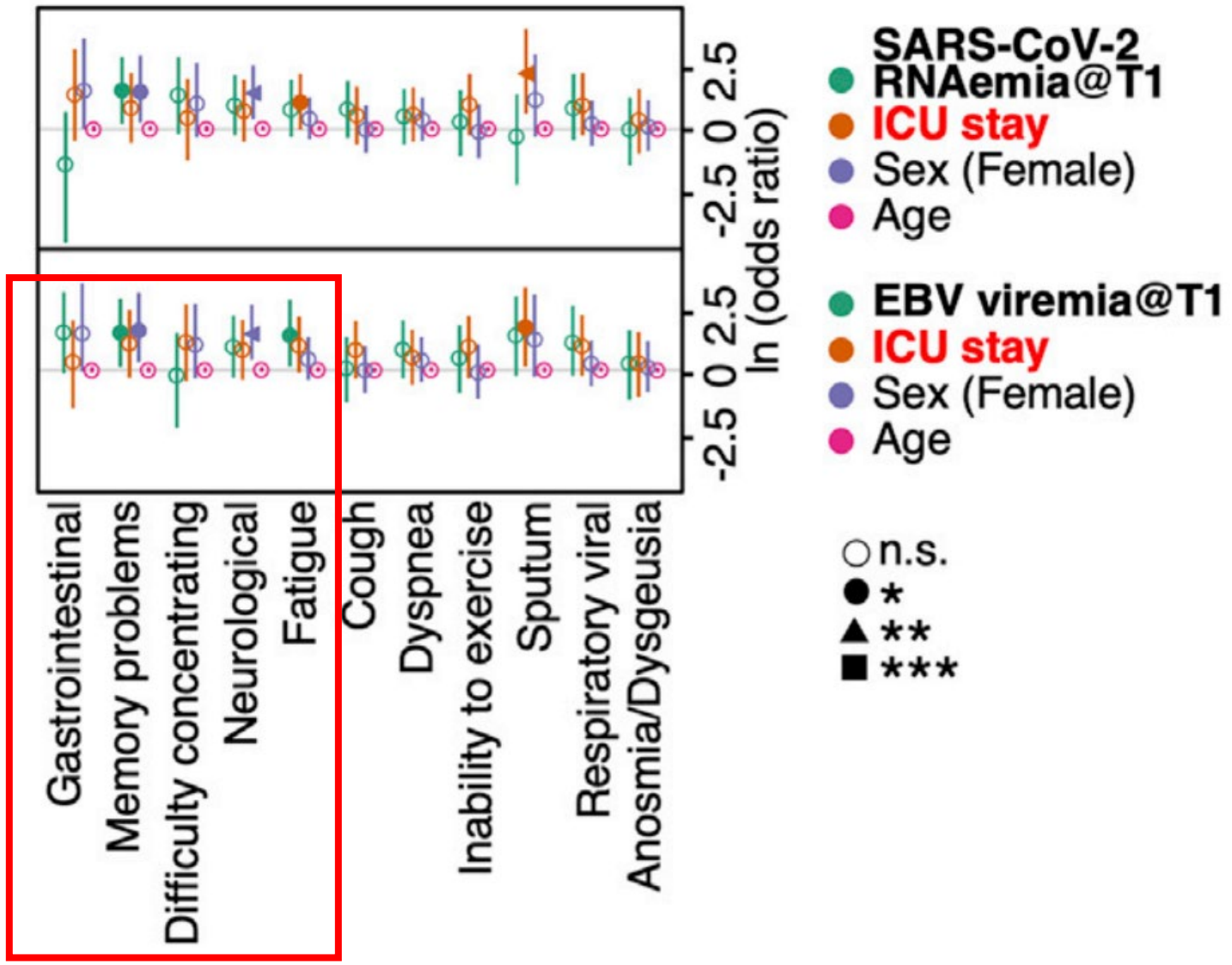
Cell. 2022 Mar 3; 185(5): 881–895.e20.
doi: 10.1016/j.cell.2022.01.014
PMCID: PMC8786632
PMID: 35216672

# Multiple early factors anticipate post-acute COVID-19 sequelae

Yapeng Su,[1,2,3,28,*] Dan Yuan,[1,4,28] Daniel G. Chen,[1,5,28] Rachel H. Ng,[1,4] Kai Wang,[1] Jongchan Choi,[1] Sarah Li,[1] Sunga Hong,[1] Rongyu Zhang,[1,4] Jingyi Xie,[1,6] Sergey A. Kornilov,[1] Kelsey Scherler,[1] Ana Jimena Pavlovitch-Bedzyk,[7] Shen Dong,[8] Christopher Lausted,[1] Inyoul Lee,[1] Shannon Fallen,[1] Chengzhen L. Dai,[1] Priyanka Baloni,[1] Brett Smith,[1] Venkata R. Duvvuri,[1] Kristin G. Anderson,[3,9] Jing Li,[7] Fan Yang,[10] Caroline J. Duncombe,[11] Denise J. McCulloch,[12] Clifford Rostomily,[1] Pamela Troisch,[1] Jing Zhou,[13] Sean Mackay,[13] Quinn DeGottardi,[14] Damon H. May,[14] Ruth Taniguchi,[14] Rachel M. Gittelman,[14] Mark Klinger,[14] Thomas M. Snyder,[14] Ryan Roper,[1] Gladys Wojciechowska,[1,15] Kim Murray,[1] Rick Edmark,[1] Simon Evans,[1] Lesley Jones,[1] Yong Zhou,[1] Lee Rowen,[1] Rachel Liu,[1] William Chour,[1] Heather A. Algren,[16,17] William R. Berrington,[16,17] Julie A. Wallick,[16,17] Rebecca A. Cochran,[16,17] Mary E. Micikas,[16,17] the ISB-Swedish COVID-19 Biobanking Unit,[1] Terri Wrin,[18] Christos J. Petropoulos,[18] Hunter R. Cole,[19] Trevan D. Fischer,[19] Wei Wei,[1] Dave S.B. Hoon,[19] Nathan D. Price,[1] Naeha Subramanian,[1,20] Joshua A. Hill,[2,12] Jennifer Hadlock,[1] Andrew T. Magis,[1] Antoni Ribas,[21] Lewis L. Lanier,[22] Scott D. Boyd,[10] Jeffrey A. Bluestone,[8] Helen Chu,[11,12] Leroy Hood,[1,17] Raphael Gottardo,[2,23,24,25] Philip D. Greenberg,[3,9] Mark M. Davis,[7,26,27] Jason D. Goldman,[2,12,16,17,**] and James R. Heath[1,4,29,***]

- EBV viremia at the time of initial clinical SARS-CoV-2 diagnosis (T1) increased the odds of developing PASC symptoms 2-3 months later.
- EBV viremia was not demonstrated later during the acute infection (T2) or 2-3 months later (T3).

**Epstein-Barr Virus reactivation early during SARS-CoV-2 infection is risk factor to developing the PASC phenotype**



# Case 2: The Young Scientist

- This PASC case does not have a good alternative medical explanation
  - No noted medical conditions appear to account for the entire clinical picture
- ME/CFS: Meets descriptive criteria; does not suggest a particular treatment
- POTS: Meets objective criteria; suggests POTS treatments
  - Prescribed Ivabradine 2.5 mg by mouth twice daily, Salt tablets as needed, LMNT electrolyte solution 1 packet by mouth daily, Vitassium electrolyte 2 capsules by mouth twice daily
  - Still quite disabled
- EBV reactivation:
  - EBV DNA PCR: undetected
  - Positive EBVCA-IgG, Negative EBVCA-IgM, Positive EBNA-IgG
  - EBV Throat swab: Negative

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Cases such as this emphasize the difficulties of PASC categorization, with the potential to confound PASC research

# Conclusions

- PASC represents a wide range of medical complications
  - Cardiovascular, pulmonary, neurological injuries
    - Legacy effects of injuries from acute SARS-CoV-2 infection
  - Coincidental and/or accelerated medical events
  - Post-viral fatiguing syndromes
- Post-viral fatiguing syndromes are common
  - Seems as common after SARS-CoV-2 as with other infections
  - Time seems to be important in distinguishing from other PASC subtypes
- The biology underlying Post-Viral Fatiguing Syndromes is not known
  - Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
  - Postural Orthostatic Tachycardia Syndrome
  - Epstein-Barr Virus Reactivation
  - Case heterogeneity will complicate PASC research

# Acknowledgements

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