Research considerations for Long COVID: What we need to figure it out

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LIINC

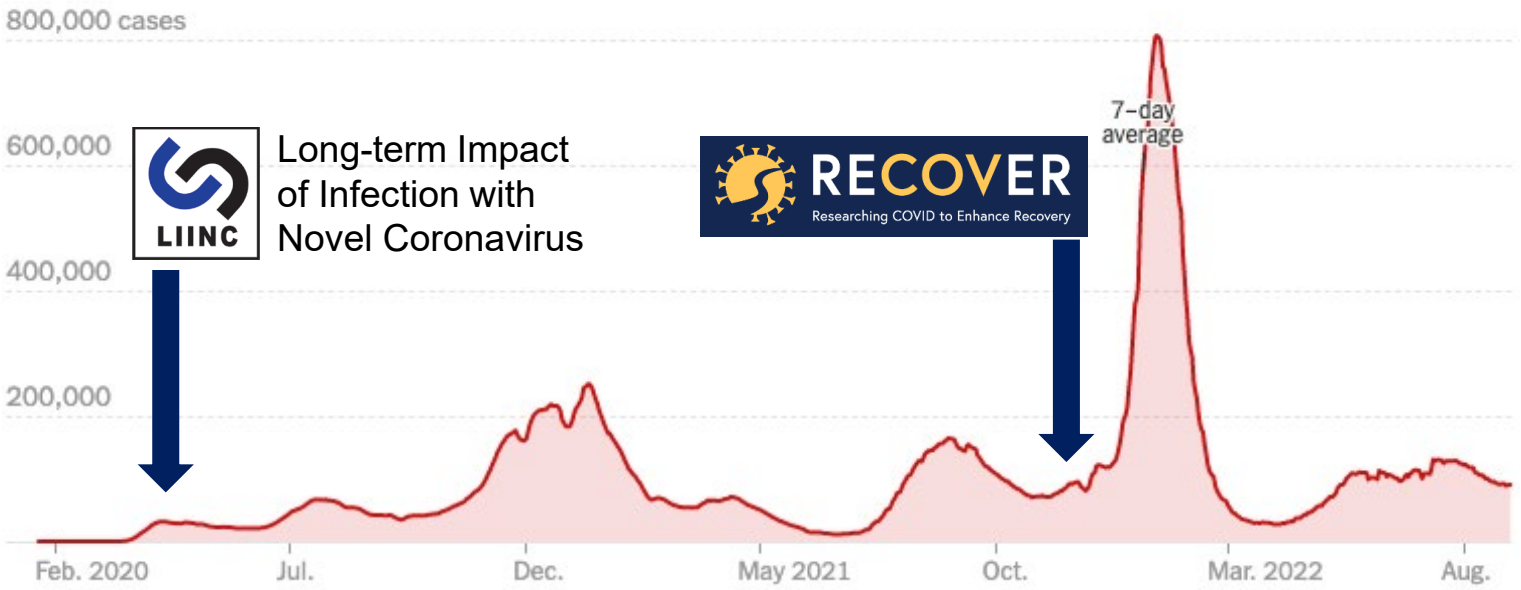
RECOVER
Researching COVID to Enhance Recovery

UCSF
University of California
San Francisco

ZUCKERBERG
SAN FRANCISCO GENERAL
Hospital and Trauma Center

LIINC: Long-term Impact of Infection With Novel Coronavirus

Built on UCSF HIV/ID research infrastructure, now supporting RECOVER



- **> 700 participants**
- **Detailed longitudinal phenotyping**
- **> 50K specimens banked**
- **> 50 collaborations**
- **>25 publications**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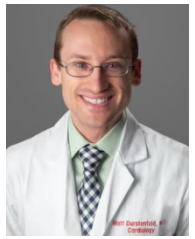
Priscilla Hsue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LIINC Approach to Measurement

- Ask everyone the same questions in the same way, regardless of whether they believe they have Long COVID
- Account for pre-existing symptoms
- Make comparisons among those who had COVID (LC vs non-LC) rather than to those who never had COVID
- Use similar time since infection/vaccination, number of infections, (and symptom stability?)

1. We need coordinated case definitions

- Syndromic PASC vs. Objectively Measured PASC
  - Probably exist on a spectrum (shared biology) but grouping comes with risks
  - Long COVID is a condition of how people feel
  - Physiologic correlates would be helpful but difficult to require at this point
- Timescale has evolved
  - Sub-phases of the post-acute phase (early vs late post-acute)
  - I still believe 3 months is right, but biology might change over time
- We may need different definitions for clinical (more inclusive) and research (more restrictive)

Long COVID can wax and wane, resolve slowly, or even worsen

Open Forum Infectious Diseases

Persistence, Magnitude, and Patterns of Postacute Symptoms and Quality of Life Following Onset of SARS-CoV-2 Infection: Cohort Description and Approaches for Measurement

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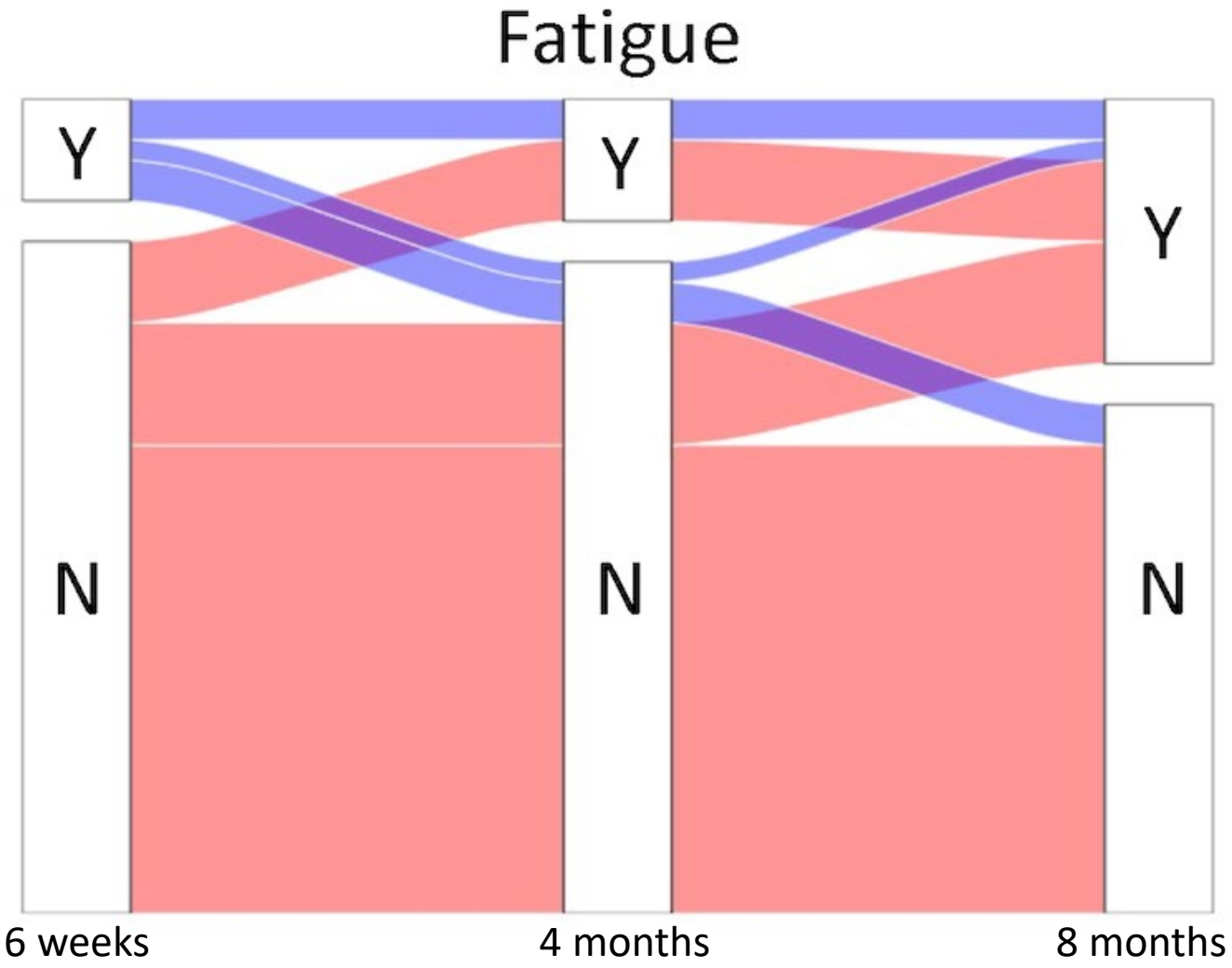
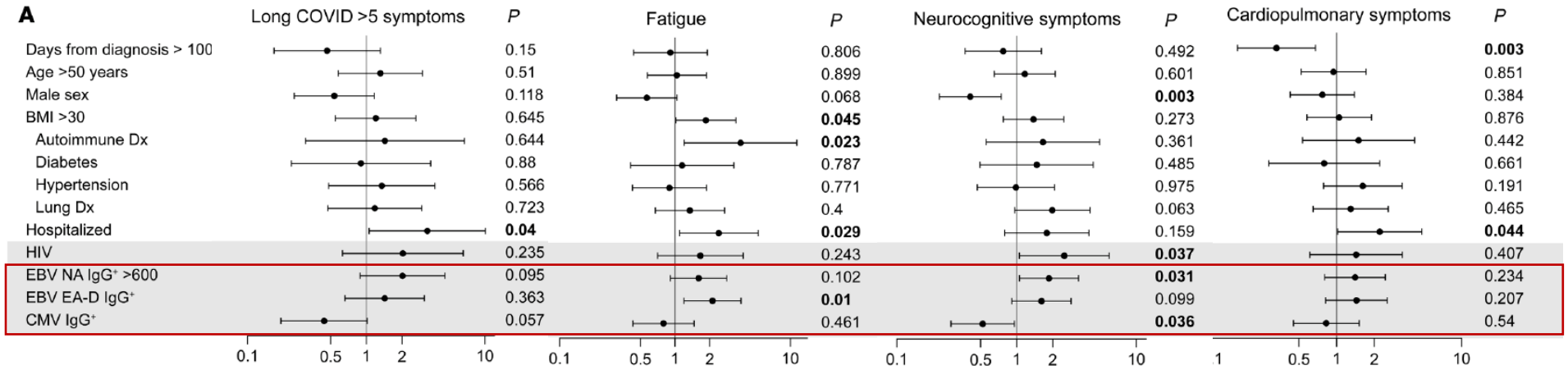


- Cross-sectional measurements don't pain the full picture of **within-person variability**
  - Some symptoms will **resolve**
  - Some symptoms have **late onset**
  - Some symptoms will **recur**
- Binary present/absent misses the **severity** and **impact** of symptoms

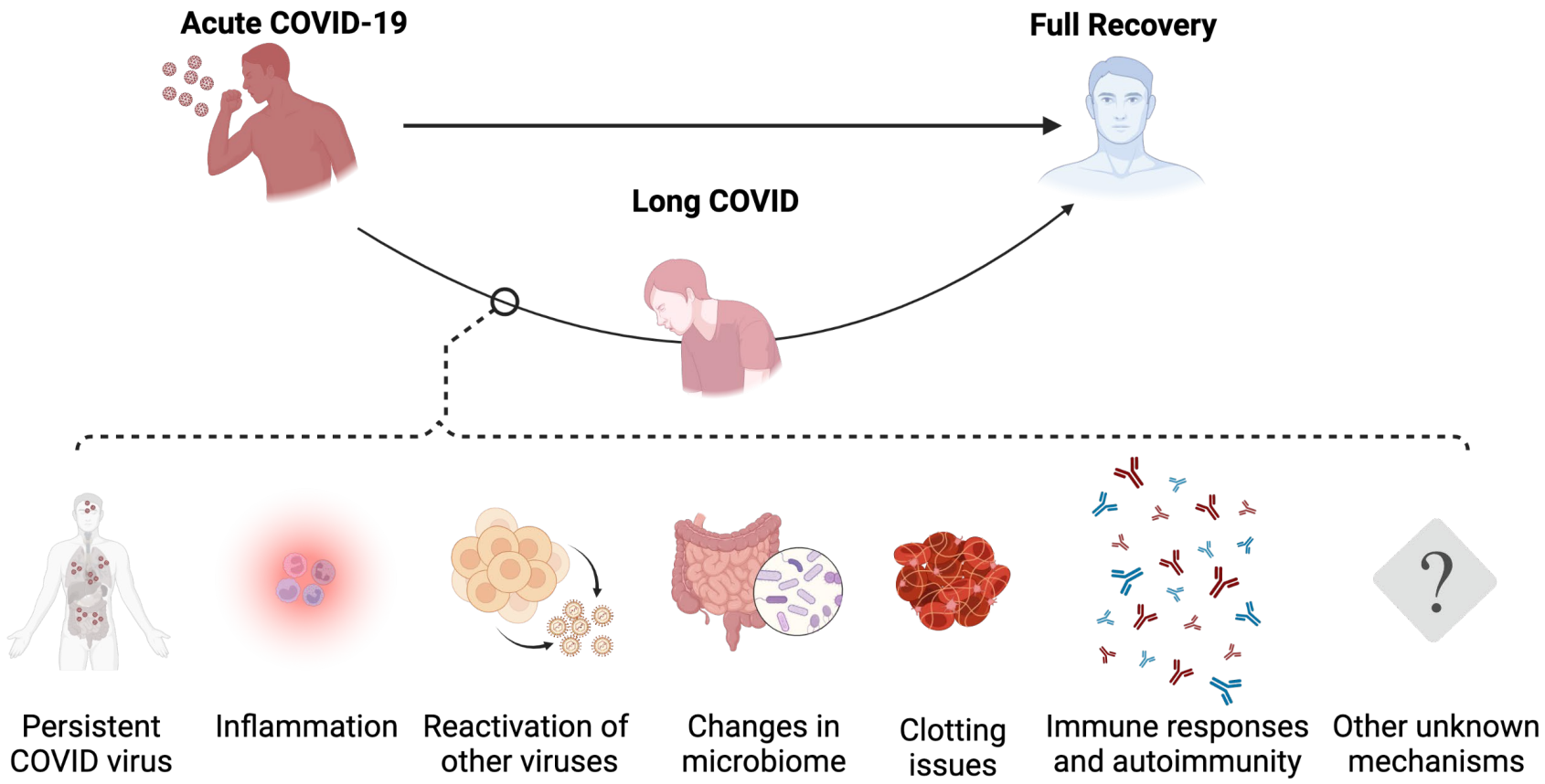
Focusing on specific endotypes may yield helpful insight into biology that could otherwise be missed



Endotypes could include: # of Long COVID symptoms, specific symptoms, or symptom groups

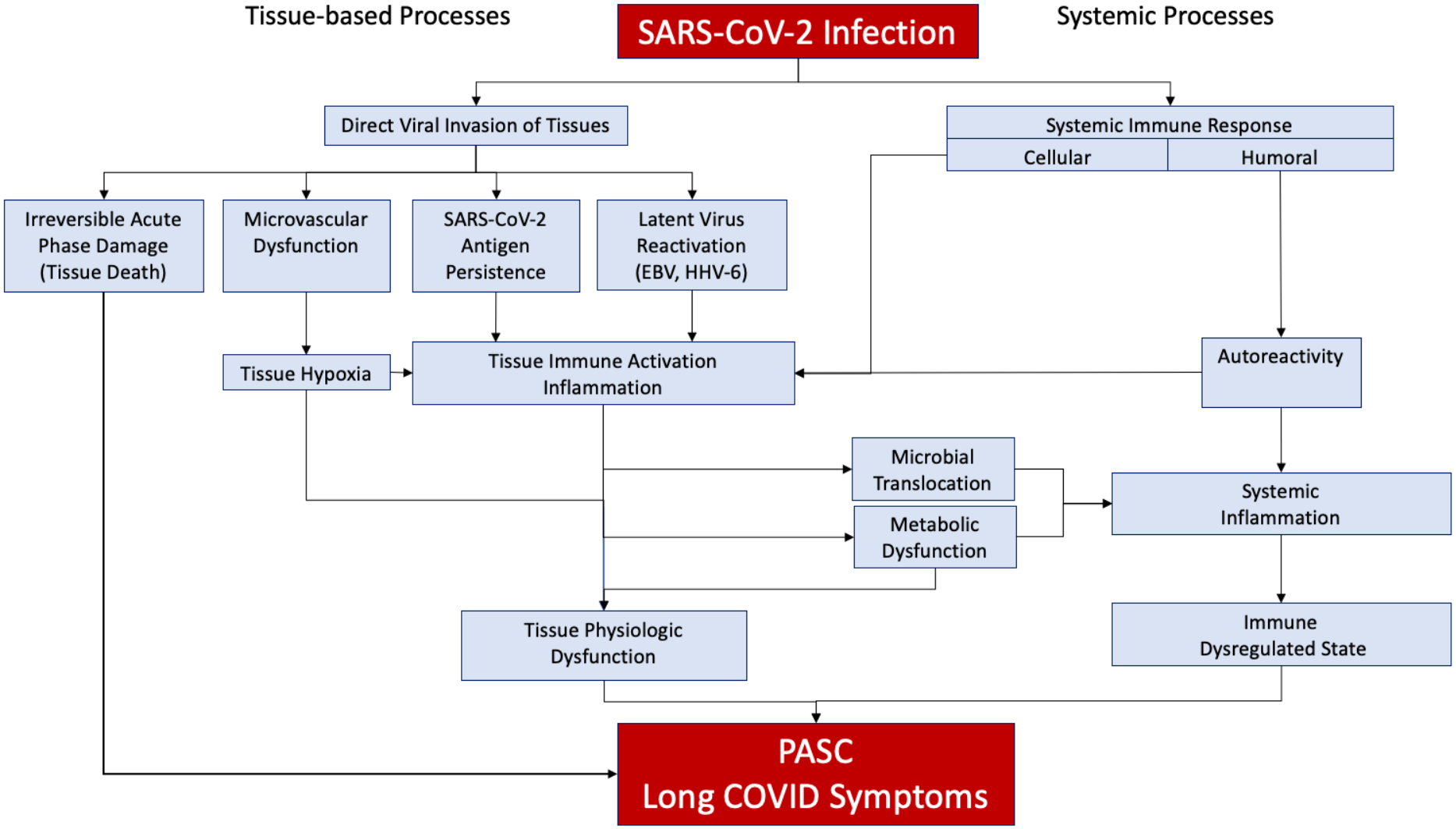
Peluso, Henrich J Clin Invest 2023

Pathogenic Mechanisms of Long COVID



Peluso & Deeks Trends in Immunology 2022; Images: Biorender

2. We need to construct a unified model



3. We need a biomarker

Mechanistic: “This biological pathway contributes to Long COVID”

Diagnostic: “Your shortness of breath is caused by Long COVID and not something else”

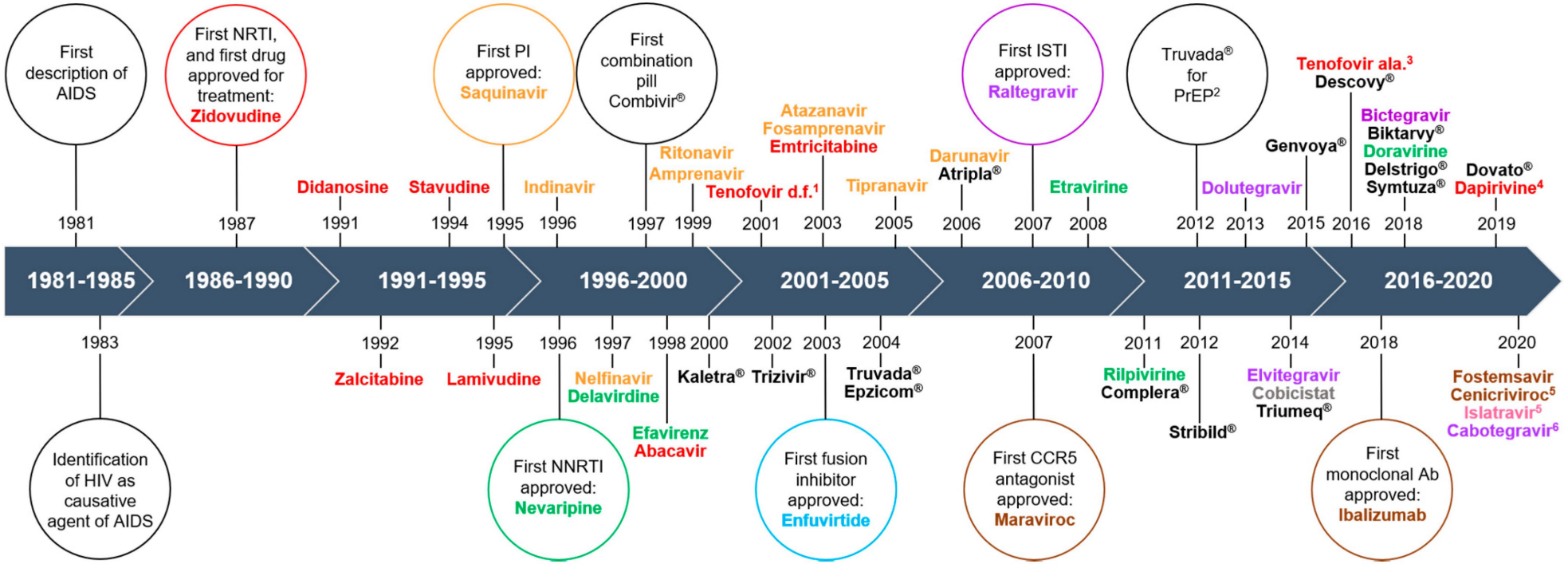
Predictive: “Based on your test during this COVID infection, you are likely to develop Long COVID and we should do a, b, or c differently”

Surrogate: “We know that decreasing the level of this blood test value from x to y will result in improvement in your Long COVID symptoms over the next (month, year)

3. We need a biomarker

Identification of plasma HIV RNA as biomarker for HIV resulted in:

- HIV clinical endpoints (CD4 reduction, AIDS & death) vanishing
- Accelerated development and approval of ART

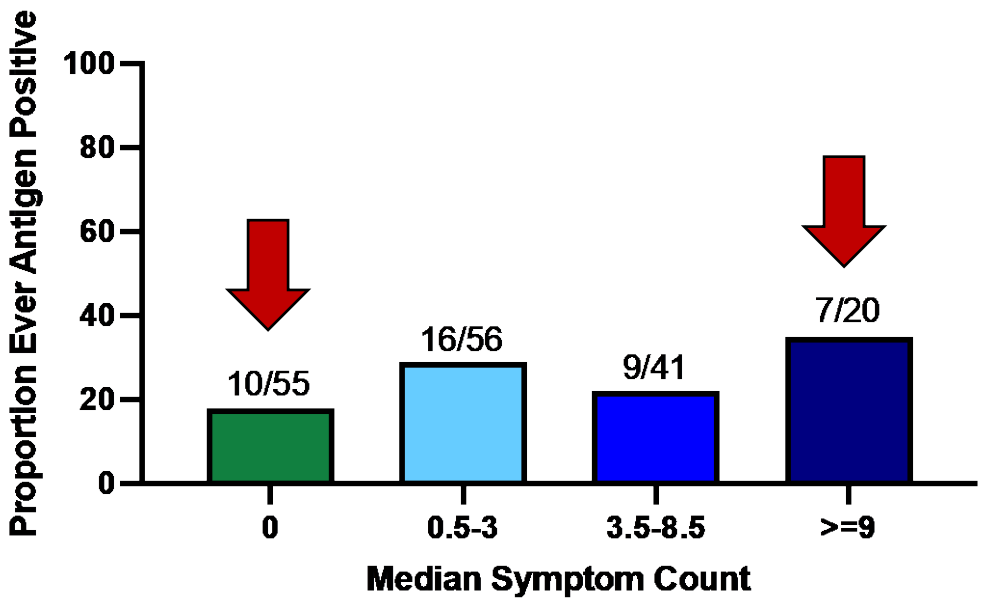


Cheny et al. Cells. 2021.

Slide credit: John Mellors

LIINC Post-Acute Antigen Project

- 25% of 170 individuals positive at >=1 post-acute timepoint 1 month to 1 year post-COVID
- Associated with more severe initial illness (hospitalization)
- Most common in severe Long COVID
- Present in those without Long COVID



Key Questions:
What is the significance of post-acute antigen persistence? Can it serve as a biomarker?

Peluso, Walt, Martin CROI 2023 and in preparation

4. We need experimental medicine trials

- RCTs of low-barrier therapies → try to improve symptoms, large n
- Proof-of-concept experimental studies → therapeutic as probe, small n
  - Exploratory
  - Lower cost
  - Faster
  - Will push the field forward but may not lead to regulatory approval
- Balance between open and restrictive inclusion criteria
  - Risks of “lumping” different endotypes together → caution from ME/CFS
  - Feasibility (e.g., requiring antigen persistence for anti-viral trial)
  - Must have community/patient buy-in for design
- All of this requires regulatory engagement that is open and flexible

Acknowledgements

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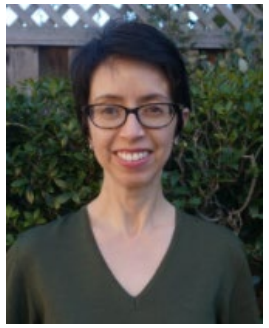
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amfAR MAKING AIDS HISTORY

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