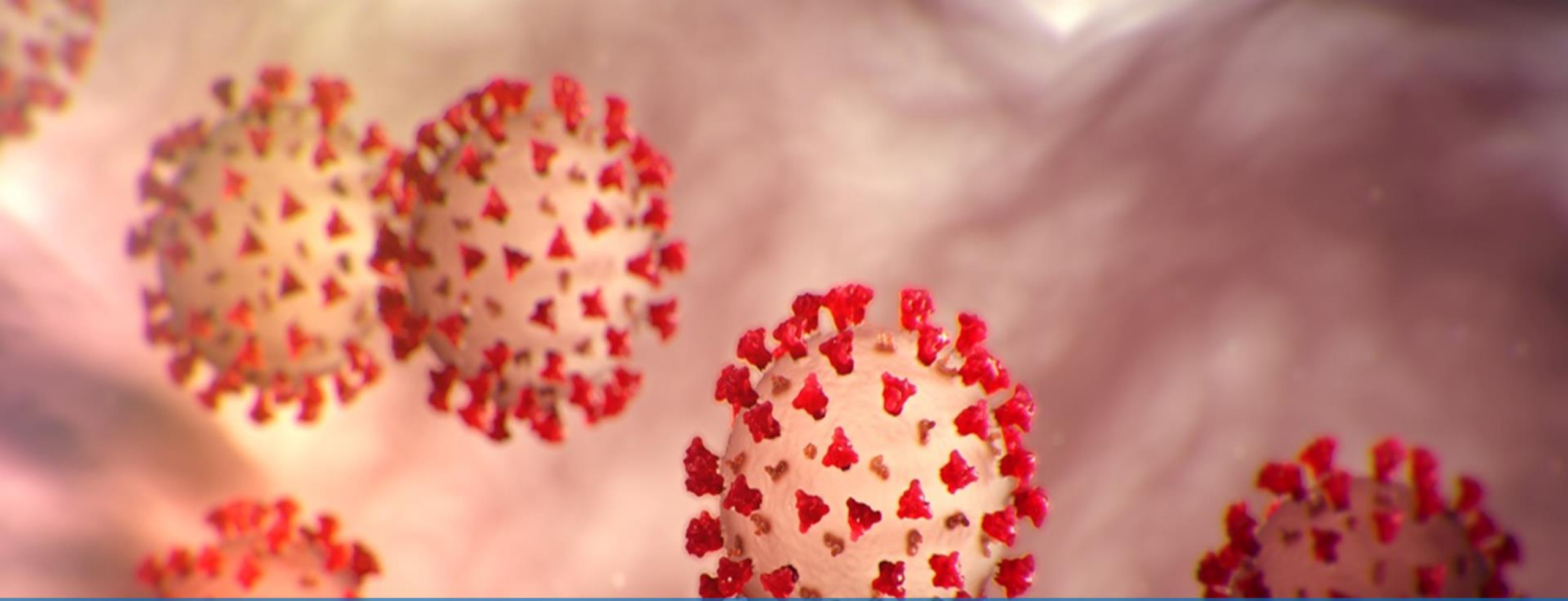

Long COVID in the Primary Immunodeficiency (PI) Community

Thursday, April 7, 2022

Immune Deficiency Foundation

WELCOME!

DISCLAIMER

Immune Deficiency Foundation (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.

Immune Deficiency Foundation

Immune Deficiency Foundation

MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education, and research.

VISION

IDF seeks to ensure that everyone in the U.S. affected by PI has a fully informed understanding of

1. the PI diagnosis that affects them,
2. all available treatment options,
3. the expected standard of care,
4. all their opportunities for connection and support within the PI community.

THANK YOU TO OUR SPONSORS

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X4 PHARMACEUTICALS

Chiesi

A WORD FROM OUR SPONSOR

Immune Deficiency Foundation

X4 Mission

X4's mission is to develop treatments that have a clear and profound impact for people with rare diseases, including primary immunodeficiencies and cancer.

We incorporate the **patient perspective** into our work in pursuit of our mission

The patient perspective is not the only data point, but it is a data point in **every decision we make**

WHIM Syndrome

Chronic Neutropenia

X4's Chosen Business Model to Achieve Our Mission

To Achieve our Mission:

X4 Aspires To Be a For-Profit, Stand-Alone, Research, Development and Commercialization Business

("FIPCO" **F**ully **I**ntegrated ~~**P**harma~~ **P**atient-focused **CO**mpany)

Because We Put Patients First

WHIM Syndrome

Chronic Neutropenia

HOW DOES IT WORK?

You can order the test through your doctor or through PATH4WARD.

Questions? Email patientinfo@x4pharma.com or visit www.Invitae.com/PATH4WARD.

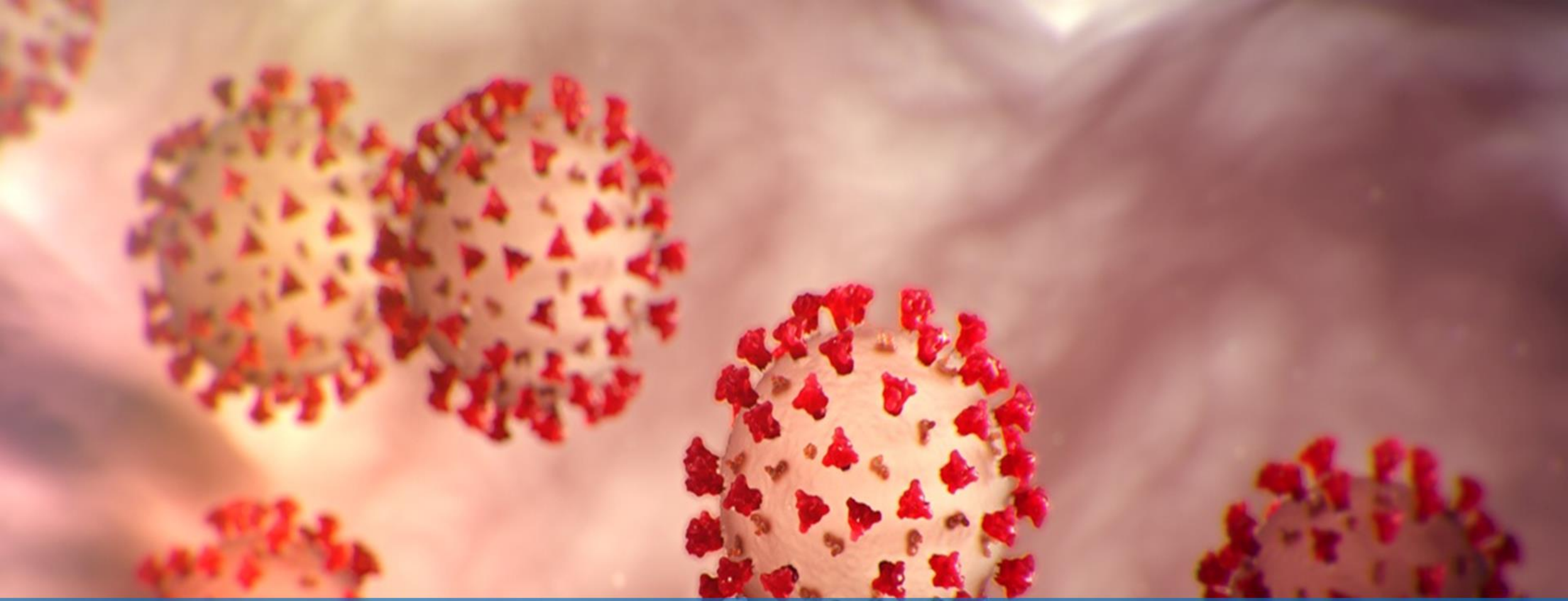
PHARMACEUTICALS

ORDER THROUGH PATH4WARD

1. **Visit www.Invitae.com/PATH4WARD**. Click "Patient" and schedule time to speak with a genetic counselor to see if you are eligible for the no-cost genetic test.
2. Once you receive the test kit, **complete the test kit** instructions and provide a saliva sample
3. **Mail the test kit** back
4. The PATH4WARD team will **share results** with you in about 20 days
5. **Schedule** a no-cost genetic counseling appointment to discuss your results. Call Genome Medical at 877-688-0992 or email clinical@genomemedical.com

ORDER THROUGH YOUR DOCTOR

1. **Ask your doctor** to request a saliva test kit from Invitae.com/PATH4WARD
2. **Provide a saliva sample** at your doctor's office or at home
3. **Your doctor** will mail the test kit back if you provided a sample at the office. If you do the test at home, mail the test kit back with the completed requisition form from your doctor.
4. **Results are emailed** to your doctor. Check with your doctor in about 20 days for results.
5. **Schedule** a genetic counseling appointment to discuss your results. Call GeneMatters at 1-866-741-5331 or schedule online at www.gene-matters.com code: PATH



Long COVID in the Primary Immunodeficiency (PI) Community

James R. Heath, PhD – Institute of Systems Biology

Immune Deficiency Foundation

Identifying Factors that put Patients at risk of Long-COVID

ISB

Jim Heath
Professor and President, ISB
plus a cast of many

Disclosures

Founder and board member of

- PACT Pharma
- Isoplexis
- Indi Molecular
- BioAnalytica

SAB of Nanostring, Virtualitics, AtlasXomics

Research $$ from Merck, Gilead (no consulting $$)

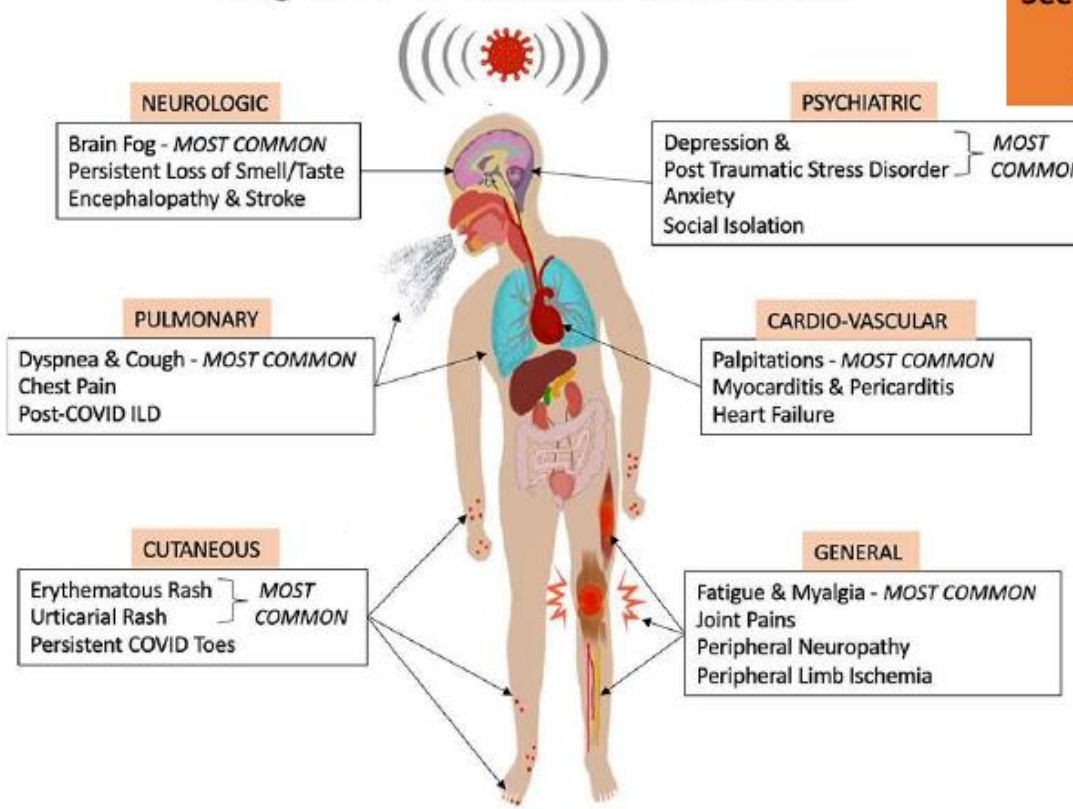
Consulting $$ from Regeneron

Long-Covid, or PASC

ISB and the Swedish Medical Center (w Jason Goldman)

ISB

Long-COVID-19 : Common Manifestations



See also Chemo Brain
'post-treatment Lyme'
etc.

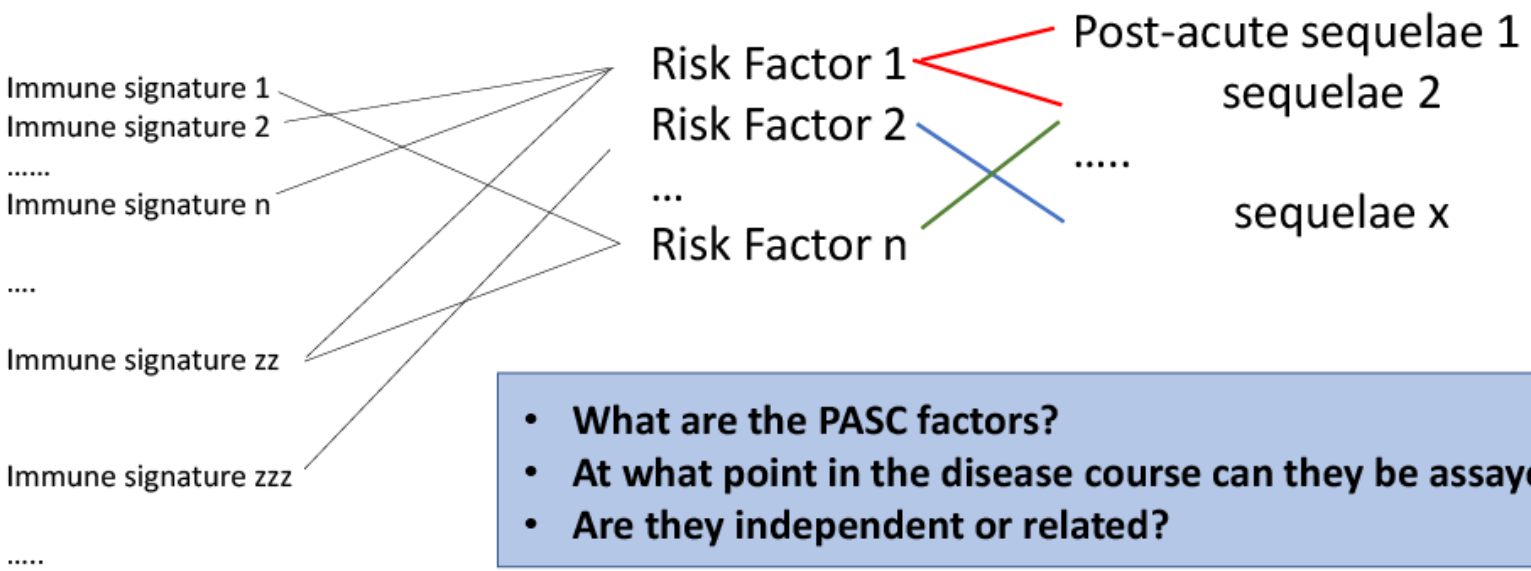
Su, et al., Cell (2022) DOI: https://doi.org/10.1016/j.cell.2022.01.014

For PASC we worked out these matrices to answer 3 questions

Very large matrix of measurements

~10 PASC risk factors (perhaps some are causal)

~20 separate symptoms

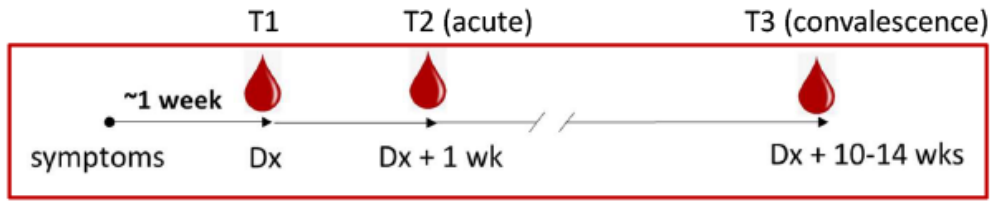


- **What are the PASC factors?**
- **At what point in the disease course can they be assayed?**
- **Are they independent or related?**

Su, et al., Cell (2022) DOI: https://doi.org/10.1016/j.cell.2022.01.014

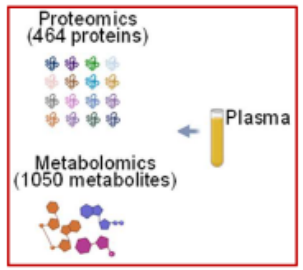
The Depth of our Studies

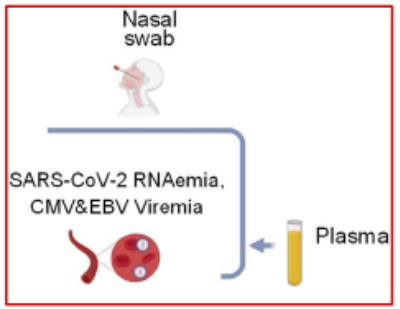
- **Comprehensive epidemiology (electronic health records and questionnaires)**
- **Comprehensive serology (proteomics, metabolomics, viral load, Ab and auto-ab titers)**
- **Comprehensive immuno-phenotyping**

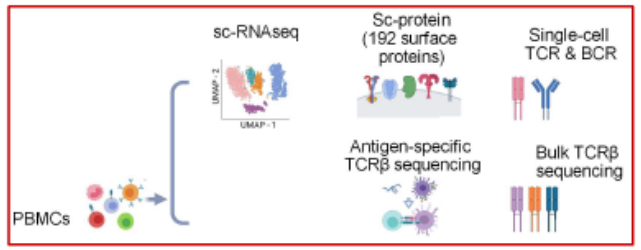


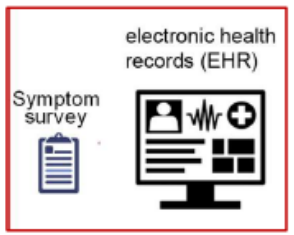
All bloods went from patient arm to processing to cryo-storage in < 4 hours

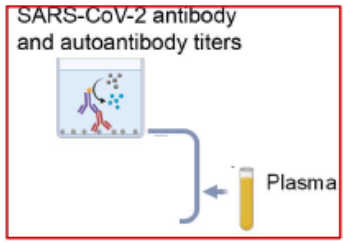
Interpreting our Findings









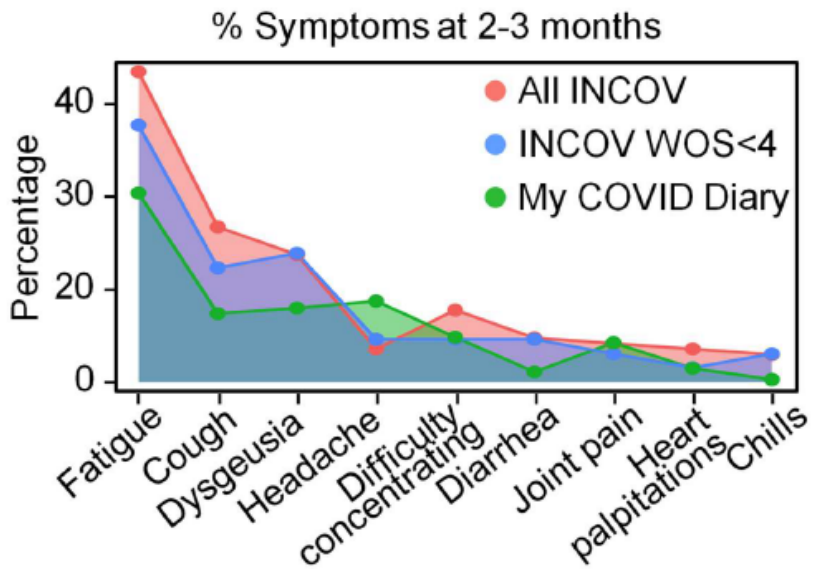


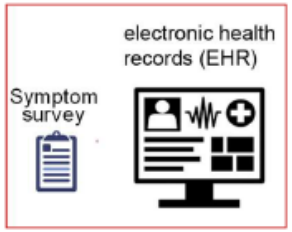
Comprehensive phenotyping can be confusing!

What data is used for what?

Throughout my talk, I will use symbols such as those shown at left to illustrate what data is used for what analyses.

Long-Covid, or PASC



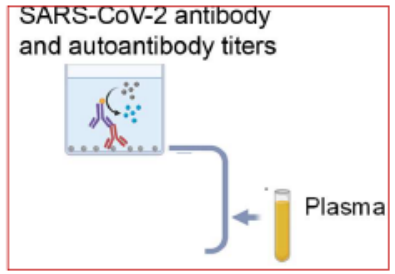


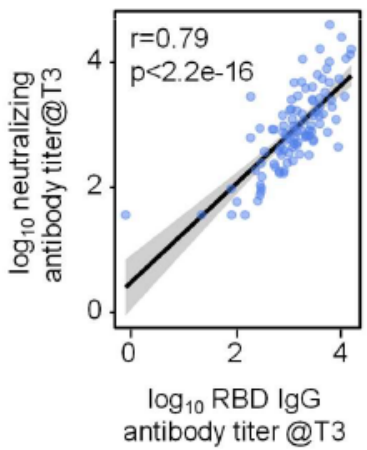
Our symptom data was collected through direct questionnaires, and validated through comparisons against electronic health records.

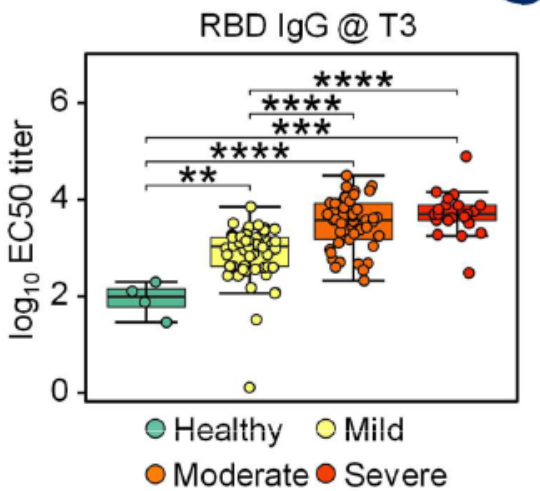
My Covid Diary study: Ari Robicsek and Bill Wright

And Heather Algren and Julie Wallick of Swedish Med Ctr

Anti-spike RBD Abs are seen in nearly all patients, scaling with severity



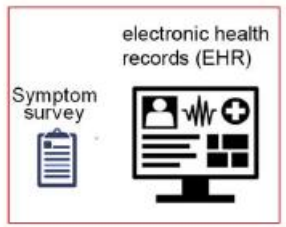


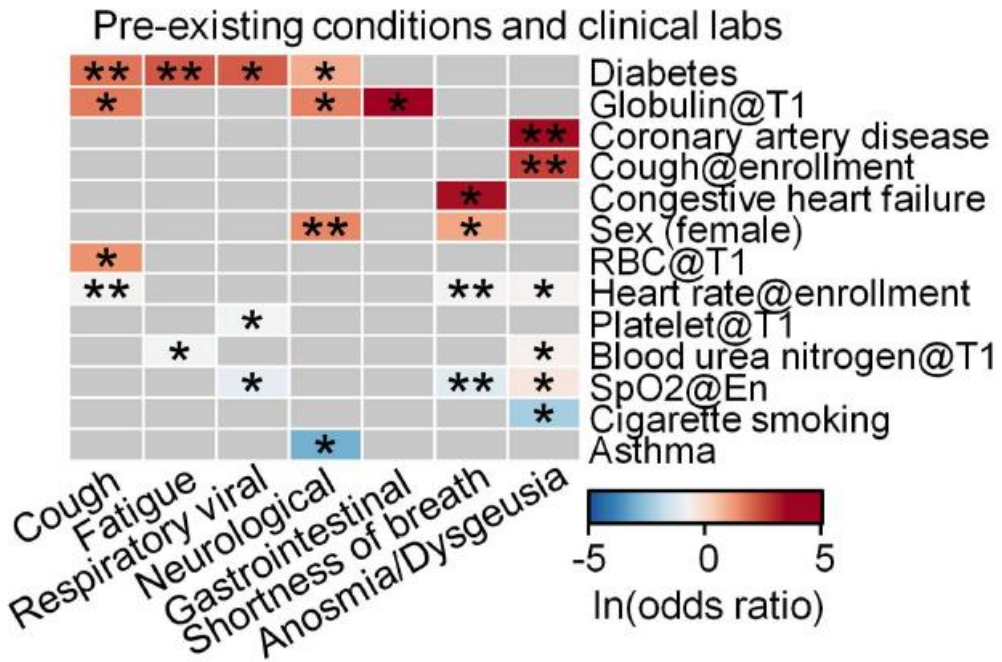


Consistent with known literature

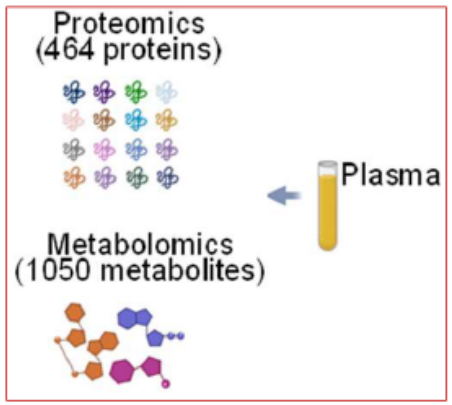
Gaebler, C., Wang, Z., Lorenzi, J.C.C. *et al.* Evolution of Ab immunity to SARS-CoV-2. ***Nature* 591,** 639–644 (2021). https://doi.org/10.1038/s41586-021-03207-w

Clinical Labs and PASC Symptoms reported by patients



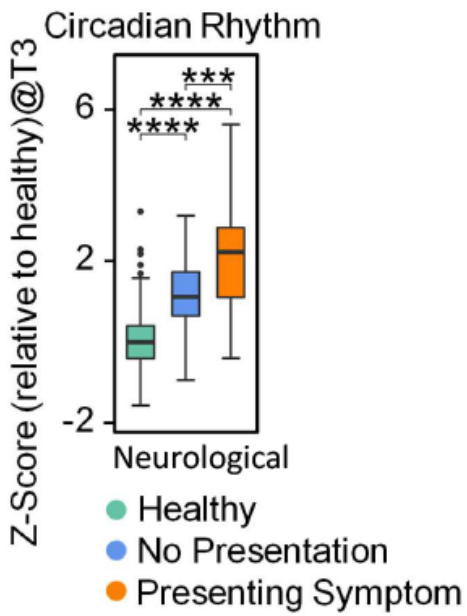


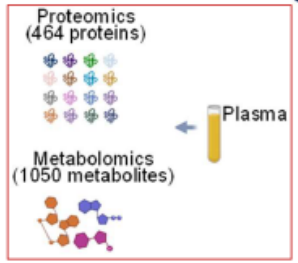
Plasma Based Biomarkers of specific PASC



- We mined patient plasma for protein or metabolomic markers that associate with specific PASC
- Measurements are from plasma samples at T3 (at convalescence) for symptoms reported at T3.
- The overall goal was to simply provide some initial disease definition

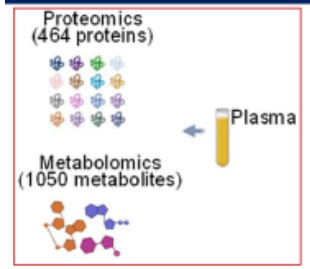
Plasma Based Biomarkers of specific PASC



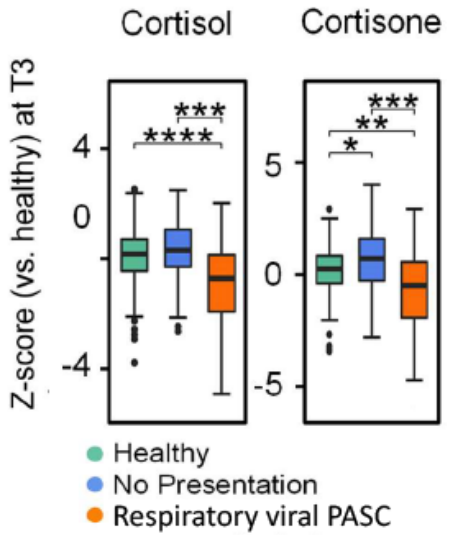


Evidence of an altered circadian rhythm (2 proteins) was the only proteomic or metabolic signature found that associates with neurological PASC, and the association was highly significant.

Low Cortisol/Cortisone and Respiratory Viral PASC



Symptom survey



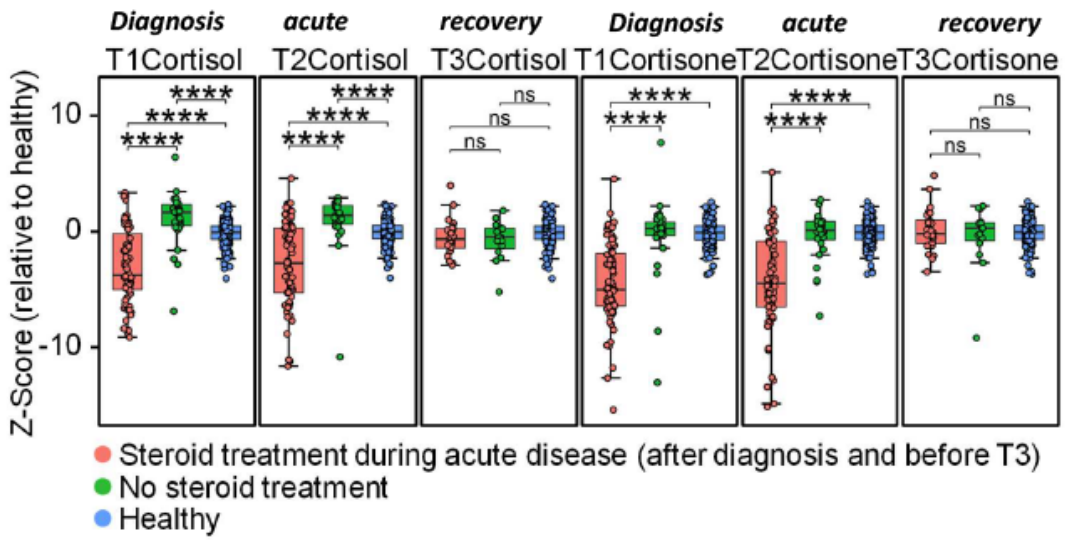
Adrenal Insufficiency (Addisonian Crisis) (low cortisol)

Symptoms may include:

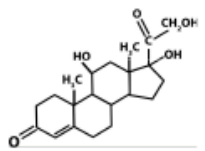
- Extreme fatigue
- Weight loss and decreased appetite
- Low blood pressure
- GI symptoms
- Muscle or joint pains
- Depression or other behavioral symptoms

…..

Low Cortisol at convalescence is not associated with steroid treatment



Cortisol

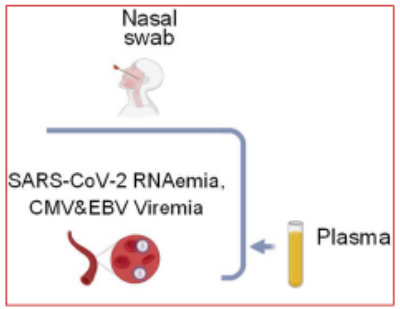


Some steroids are chemically similar to cortisol, and can alter cortisol regulation

Broersen, J Clin **Endocrin & Metob**. 2015. https://doi.org/10.1210/jc.2015-1218

Younes, A.K., and Younes, N.K. (2017). Recovery of steroid induced adrenal insufficiency. **Transl. Pediatr**. *6*, 269–273.

Viral Loads: SARS-CoV-2, EBV, and CMV



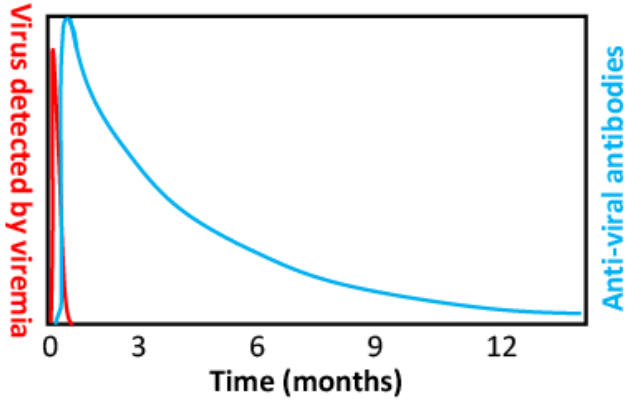
Around 90% Americans are + for EBV

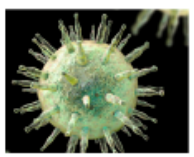
Around 50% are + for CMV

These viruses are latent, but can be reactivated

Infections and solid organ transplant rejection: a cause-and-effect relationship? (CMV reactivation)
The Lancet Infect. Dis. https://doi.org/10.1016/S1473-3099(02)00370-5

Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation ***Pathogens* 2021**, *10*(6), 763; https://doi.org/10.3390/pathogens10060763

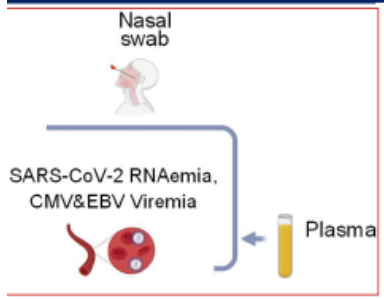


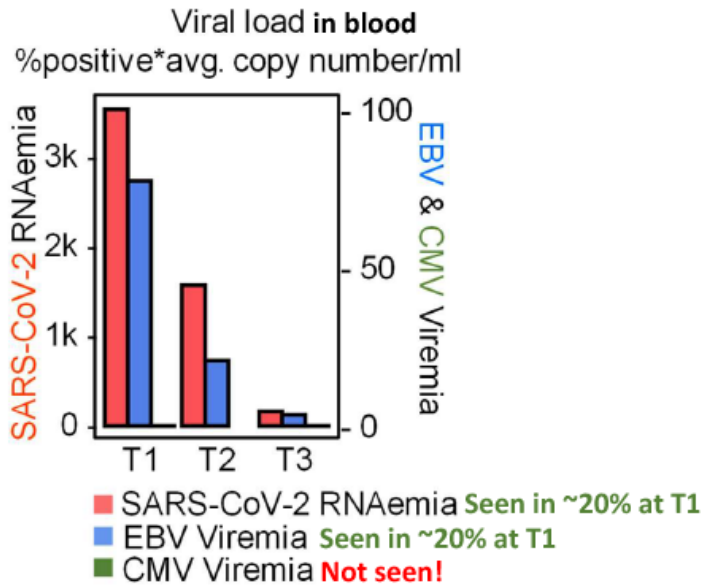


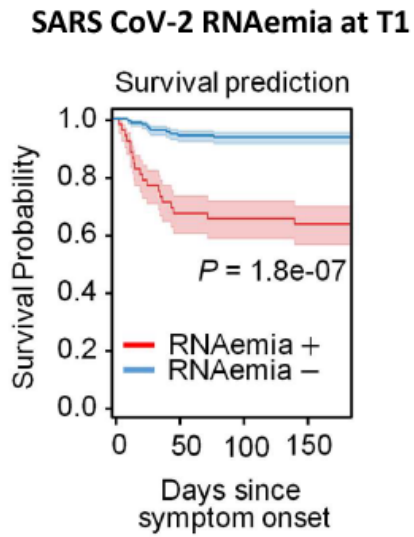
EBV

CMV

Viral Loads of SARS-CoV-2 and EBV peak early in COVID-19 infection

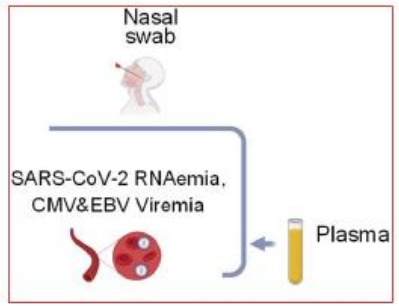




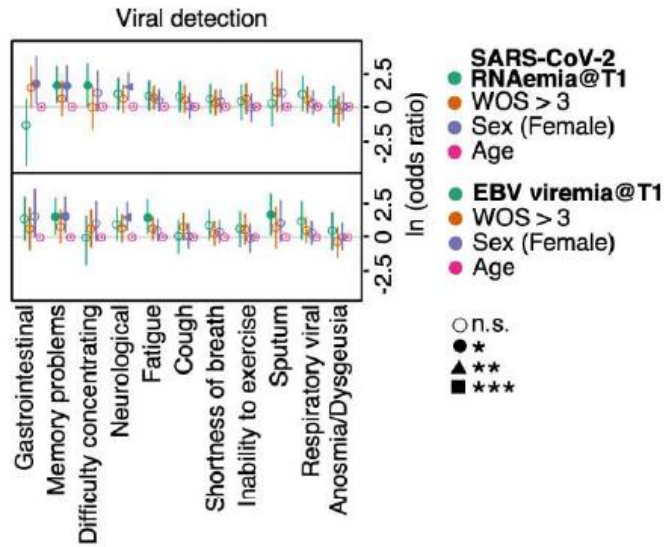


Gutmann, C., et al. (2021). SARS-CoV-2. *Nat. Commun*. ***12***, 3406.

SARS-CoV-2 RNAemia and EBV Viremia at diagnosis are PASC factors

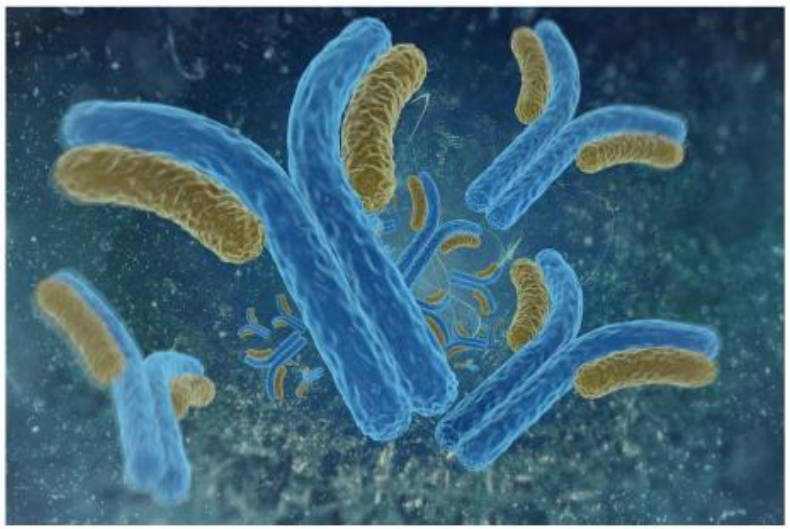


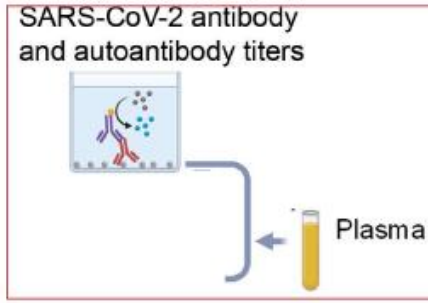
Viral Load PASC Factors (corrected for acute disease severity) ***in blood***



Nasal swab SARS-CoV-2 viral load at T2 (acute stage) is a PASC factor ***for taste/smell loss only (when corrected for infection severity)***

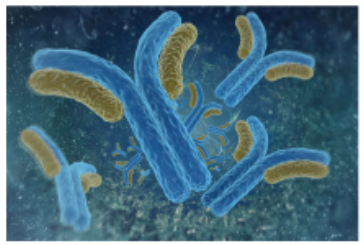
Autoantibodies





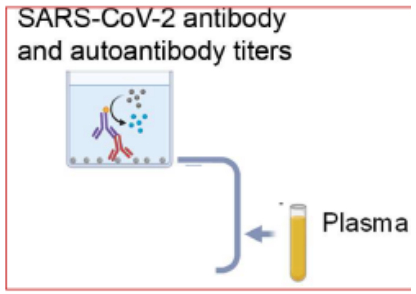
Autoantibodies

Autoantibodies

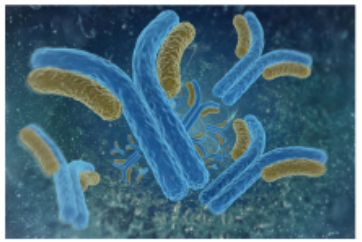


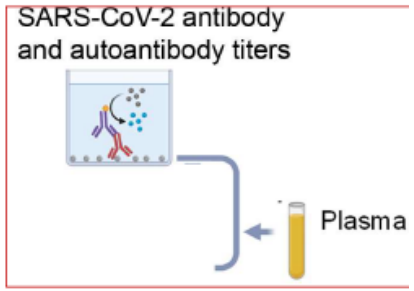
Bastard, et al., Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. *Science Immun.* 2021

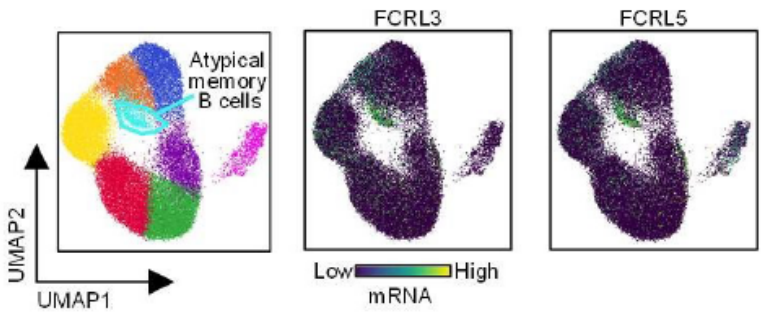
IFNα2



Autoantibodies







Fu, Q., Zhang, X. **From blood to tissue: take a deeper look at B cells in lupus**. *Cell Mol Immunol* **18,** 2073 (2021).

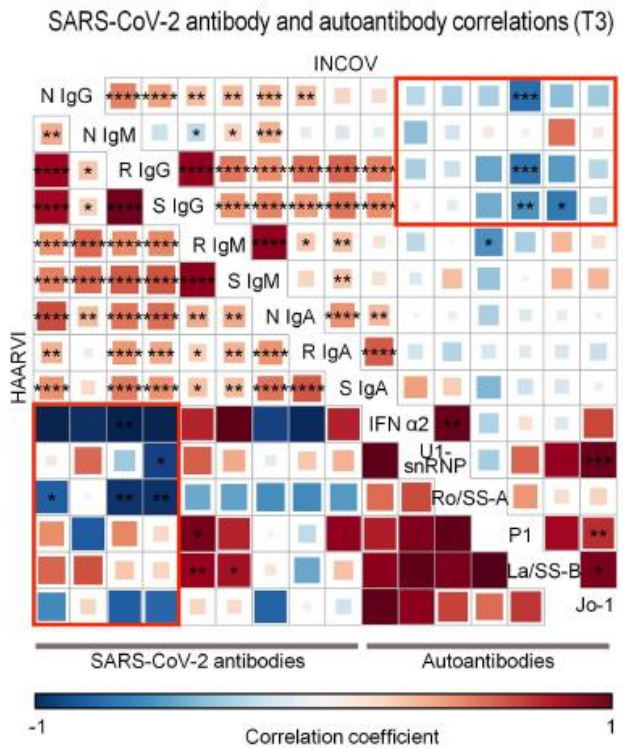
Atypical memory cells are B cells that mature to form IgG antibodies, but outside of the normal tissue process that occurs within B cell follicles. They are pretty unusual, but reports on how they associate with infections, comorbidities, etc are mixed.

We saw them in acute covid (as did others). Su, et al, **Cell** 2020

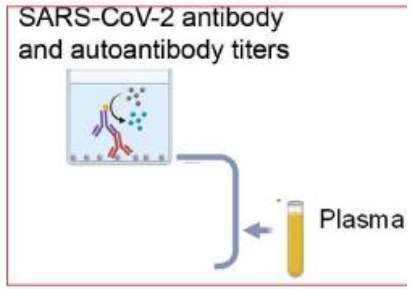
Autoantibodies associated with systemic lupus erythematosus (SLE)

La/SS-B **Ro/SS-A** **Jo-1** **P1** **U1-snRNP**

Autoantibodies and COVID-19



Protective abs against SARS-CoV-2

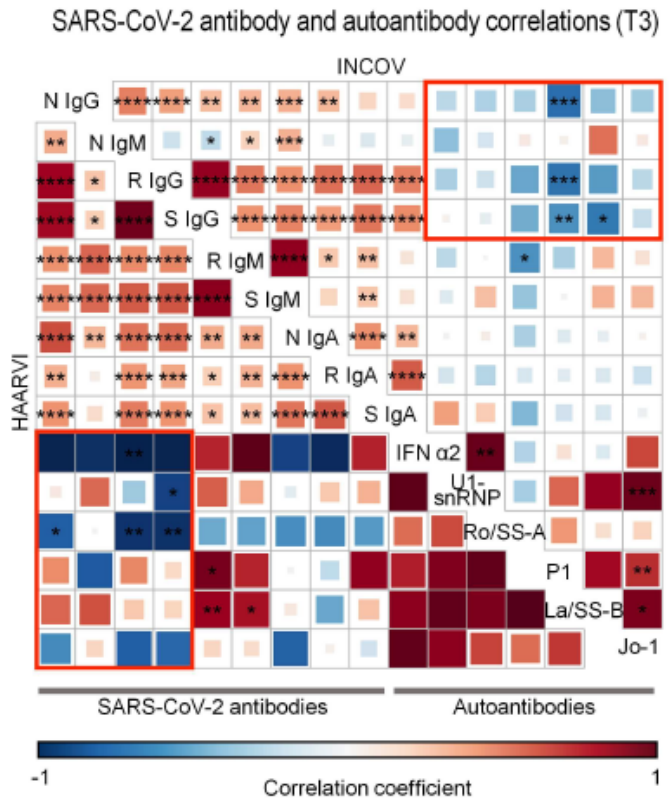


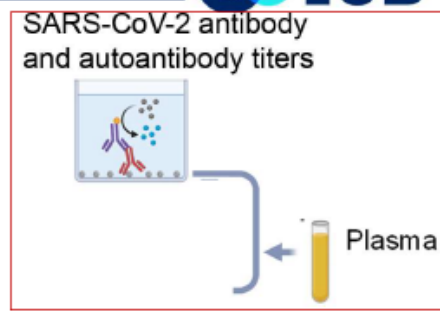
may explain serious breakthrough infections

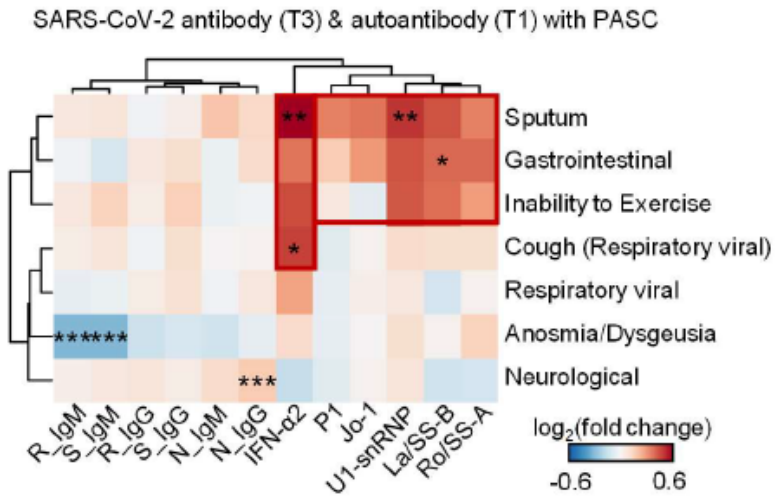
autoantibodies

Autoantibodies at COVID-19 diagnosis are PASC Factors

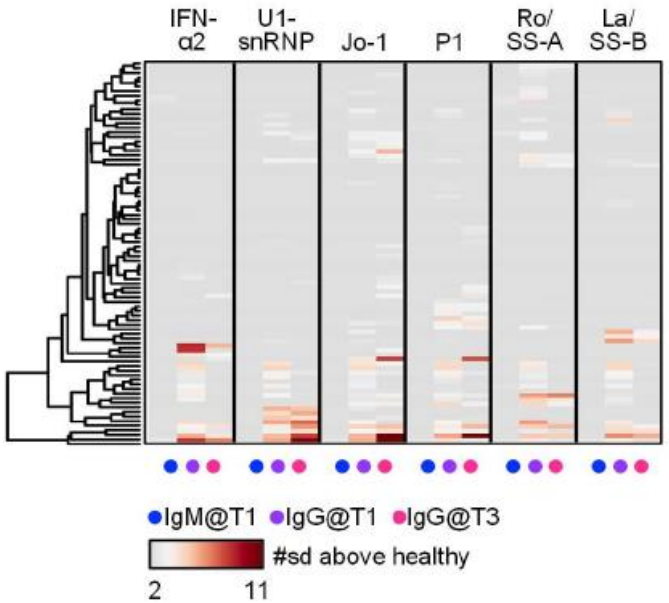
2 independent cohorts (300 patients)

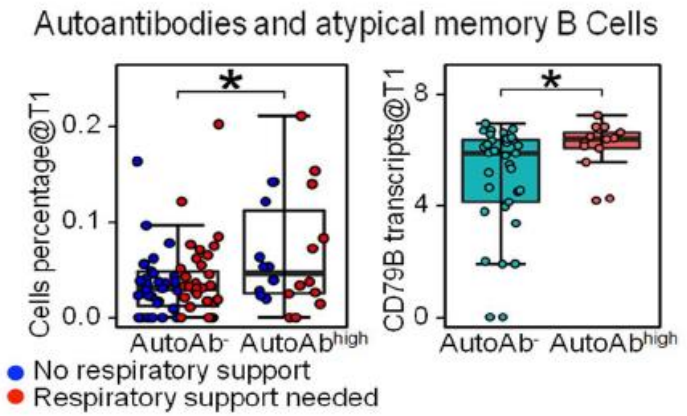


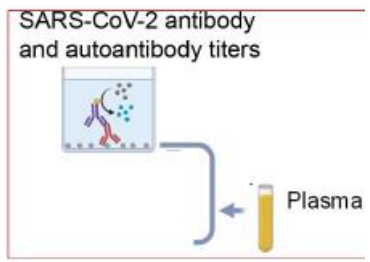




Autoantibodies are already mature during early disease and persist

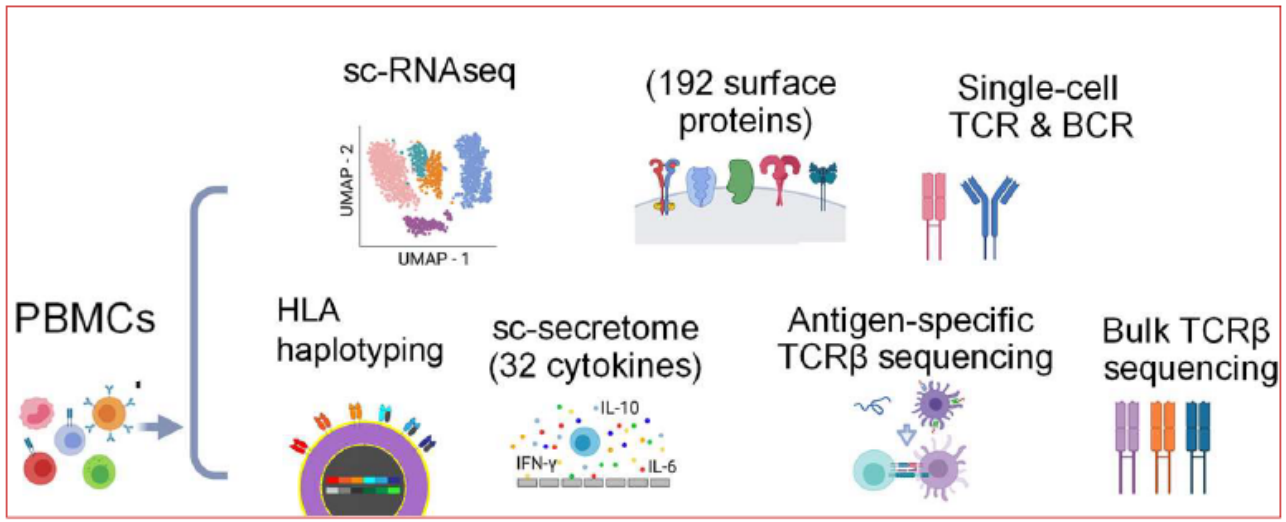






Wu, et al., Lupus associated AtM B cells. **Rheum. Dis**. (2019).
Sutton, et al., AtM B cells in response to vaccination and infection. **Cell Rep**. (2021)

What is learned from single cell analytics? (just a small piece covered here)

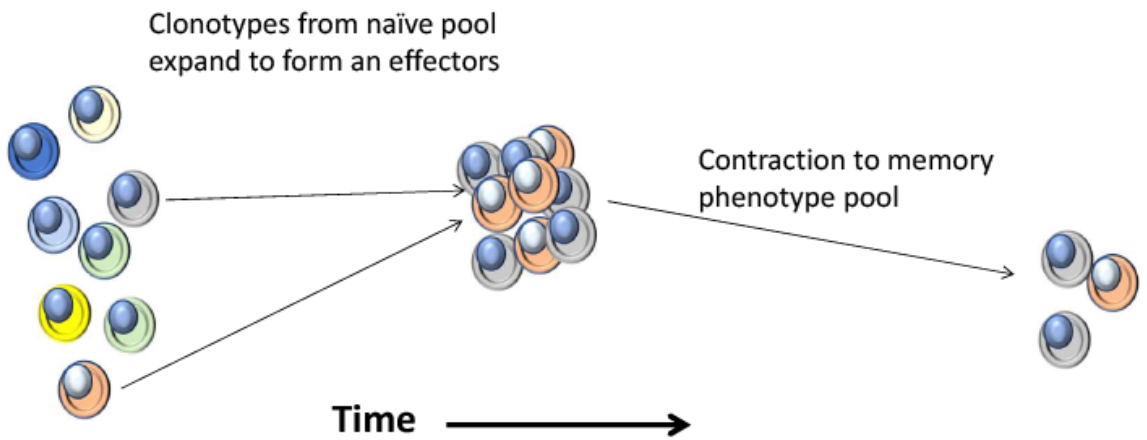


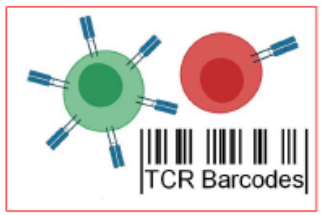
Individual data sets, taken in isolation, are not particularly useful for understanding PASC

Integrated analysis is much richer

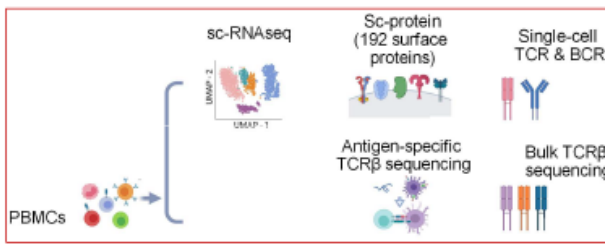
- integrated analysis of sc-RNAseq with clinical data (Cell 2020)
- Integrated sc-RNAseq data with analysis of viral antigen-specific T cells (in prep)
- Integrating sc-RNAseq with plasma metabalomics (Nat Biotech, 2021).

Following T cell populations from diagnosis to recovery in 200 patients



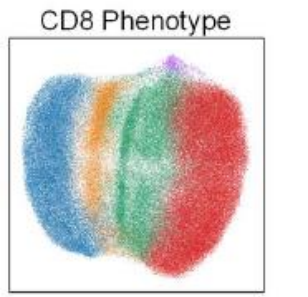


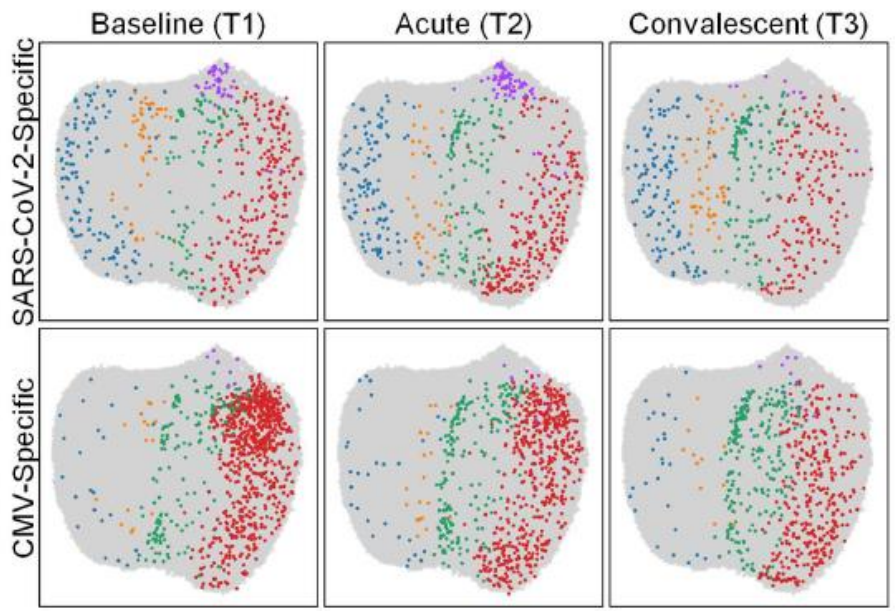
This is how we think a T cell response should evolve over the time course of an infection

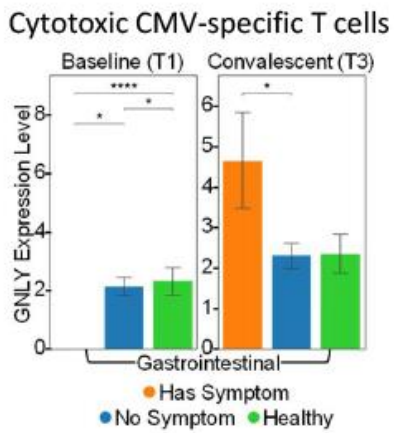


Su, et al., Cell (2022) https://doi.org/10.1016/j.cell.2022.01.014

What do these TCRs recognize?



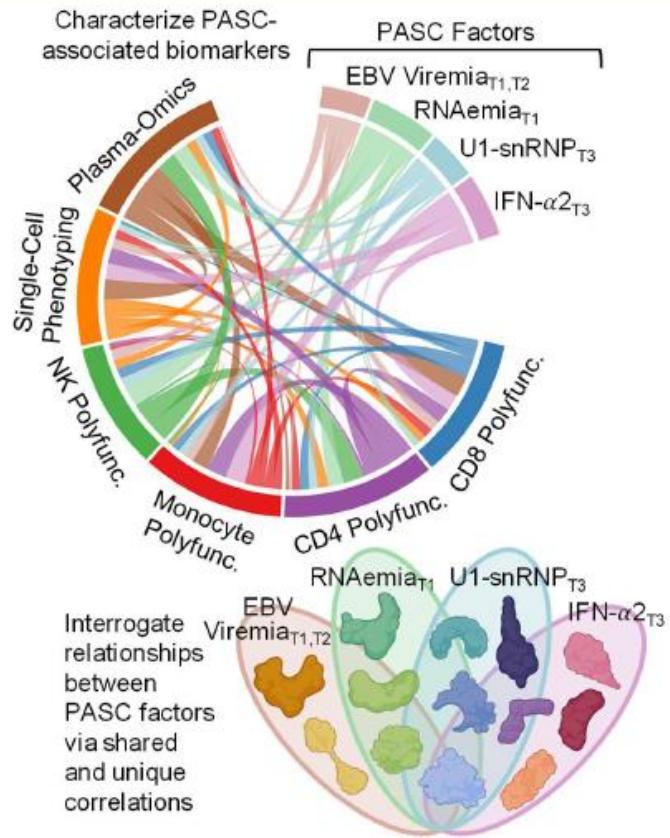




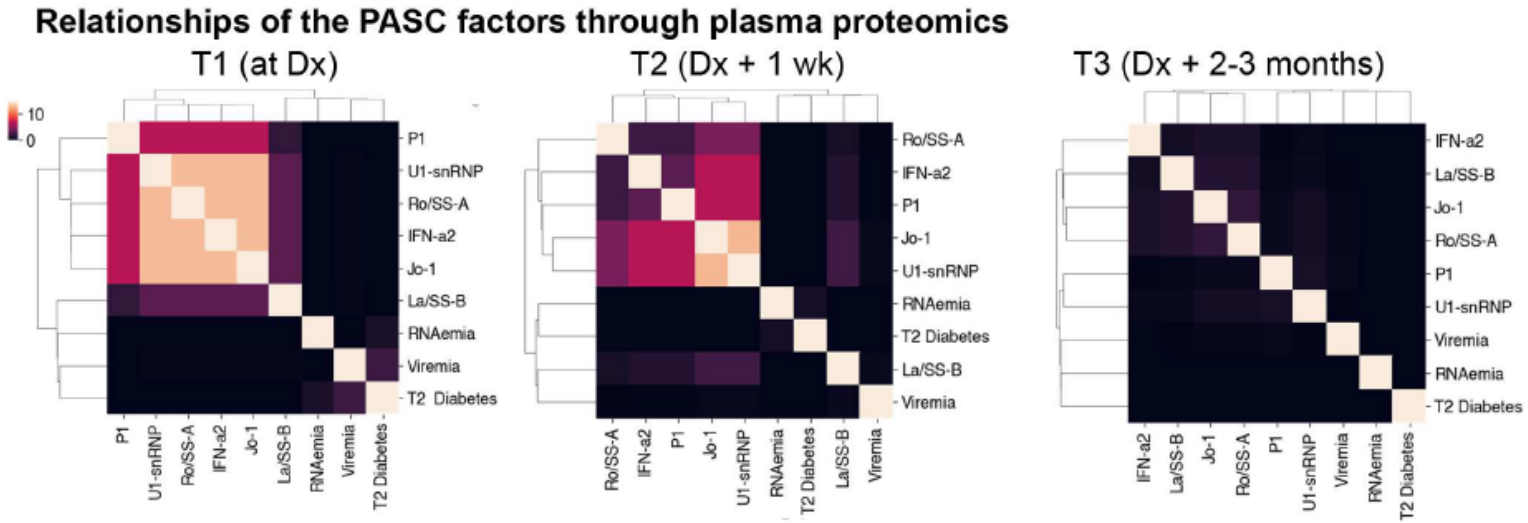
With Adaptive Biotech research team

Su, et al., Cell (2022)
https://doi.org/10.1016/j.cell.2022.01.014

Testing for Co-dependences between the PASC Factors



Relationships between PASC factors are lost over time



The implication is that at COVID-19 diagnosis

relationships between PASC factors are evident

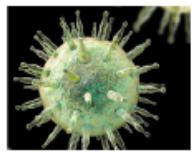
suggests a limited number of therapies

At convalescence

relationships between PASC factors are lost.

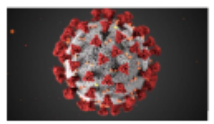
hypothesis: this falsely suggests that many therapies are needed?

PASC Factors: Each of these explained around 30% of PASC



EBV Viremia in the blood

In about 14% of patients at diagnosis → Neurological PASC



SARS-CoV-2 RNAemia (in blood)

In about 25% of patients a diagnosis →

- Neurological PASC
- Fatigue PASC
- Covid-19 mortality
- sputum

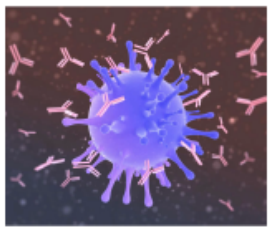
Type 2 Diabetes

In about 22% of patients a diagnosis →

- Respiratory viral (multiple symptoms)

Su, et al., Cell (2022) DOI: https://doi.org/10.1016/j.cell.2022.01.014

PASC Factors: Autoantibodies explain around 67% of PASC



Anti-IFNα2

AutoAb - PASC associations: sputum, GI, inability to exercise

Anti-nuclear antibody panel
(systems lupus erythematosus (SLE)) → Covid-19 patients positive for these autoAbs had additional immunological signatures also seen in lupus – perhaps suggesting that lupus treatments might be worth exploring?

Important Notes

- Most clinical autoAb labs will report back positive if patient titers are around 4 standard deviations above neg controls. (Perhaps 2-4% of patients).
- Patients that have autoAbs at 2 standard deviations (99% level) above negative controls are much more common (as high as 20% or so) – typically these autoAbs are subclinical, but they matter for PASC.
- High autoAb levels in both mild and severely infected patients correlated with reduced anti-SARS-CoV-2 Ab levels, perhaps suggesting susceptibility for re-infection.

Su, et al., Cell (2022) DOI: https://doi.org/10.1016/j.cell.2022.01.014

Caveats and limitations

- Our study only followed patients out to 2-3 months post diagnosis
- Study size was limited to around 300 COVID-19 patients
- We probably resolve type 2 diabetes as a PASC Factor because it is such a common co-morbidity. Other co-morbidities may be important, but we don't have the statistics to tell (except that congestive heart failure, unsurprisingly, is also a PASC factor).
- We only looked at a few autoAbs. We are now interrogating for autoAbs against the full human proteome with Mike Snyder (Stanford).
- We aren't sensitive to PASC from the Omicron variant
- The national RECOVER study will look at 17,000 patients over 4 year periods and should resolve much more than we did, including cardiac PASC, and perhaps other PASC.

PASC Factors and predictions

Thank you!

ISB

I am looking for talented postdocs! Please contact me at jheath@isbscience.org

Jeff and Liesl Wilke Foundation

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