Insights into Long COVID through IDCRP studies

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IDCRP
Infectious Disease Clinical Research Program

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Infectious Disease Clinical Research Program (IDCRP)

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Vision: To substantially reduce the impact of infectious disease in the military population through collaborative clinical research.

Mission: To conduct multicenter infectious diseases clinical research, focusing on high-impact cohort and interventional trials, to inform and improve care of the Warfighter.

- The IDCRP is a Tri-Service DoD research center at the Uniformed Services University (USU) chartered by Assistant Secretary of Defense for Health Affairs

- Collaborative research network including USU, MTFs, DoD Biomedical R&D commands, NIAID, other partners

- **Research areas focused on military-relevant infectious diseases among MHS beneficiaries:** Acute Respiratory Infections (including COVID-19), Wound, Deployment & Travel Medicine, HIV & Sexually Transmitted Infections

EPICC: pandemic insights through an adaptive protocol in a multi-site clinical network

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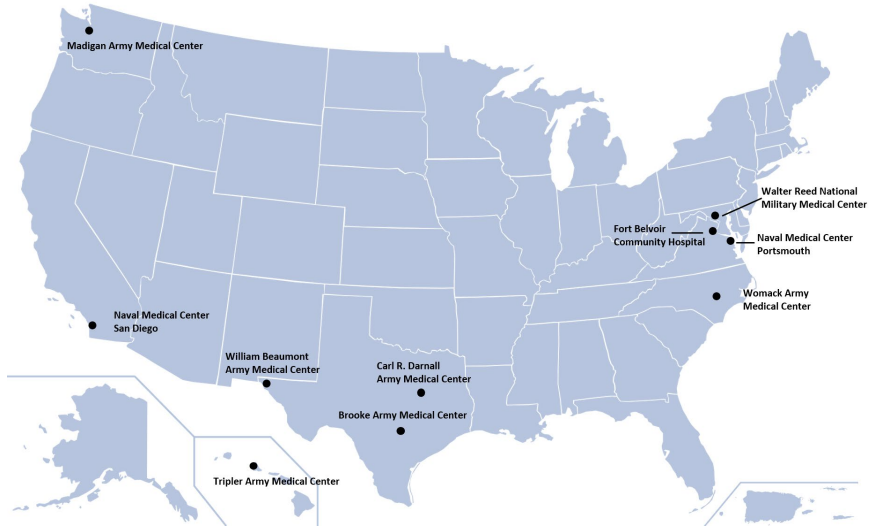
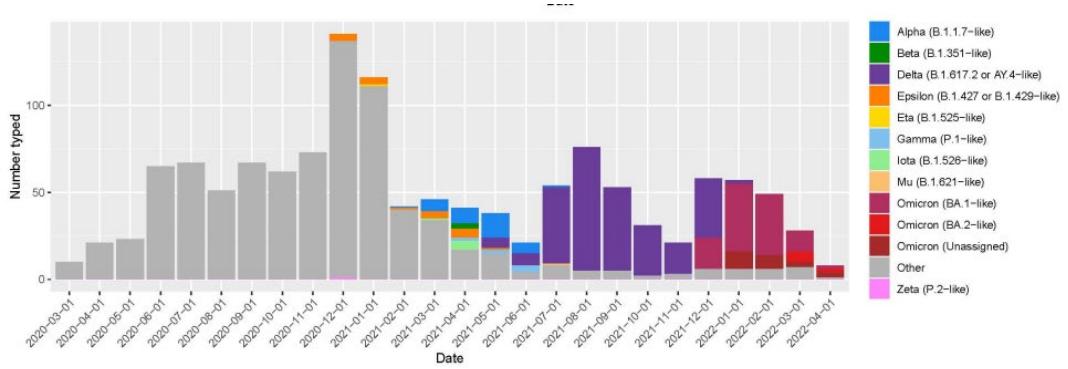
- **EPICC (Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential**) was established in 2017, activated for COVID-19
- **Broad objectives:** Describe the epidemiology, immunology and clinical characteristics, course and outcomes of SARS-CoV-2 infection in MHS beneficiaries
- **Eligibility criteria includes** MHS beneficiary study populations (includes adults and children), outpatient or inpatient confirmed COVID-19 cases; vaccine recipients
- **Enrollment March 2020 - April 2022:**
  - 10 EPICC Study Sites, online recruitment pathway (incl. OCONUS locations)
  - 2530 MTF enrolled, 5405 online, follow-up through 2023





CONUS-wide enrollment enabled rapid variant characterization and large total sample size

EPICC highlights the value of longitudinal data in pandemic research

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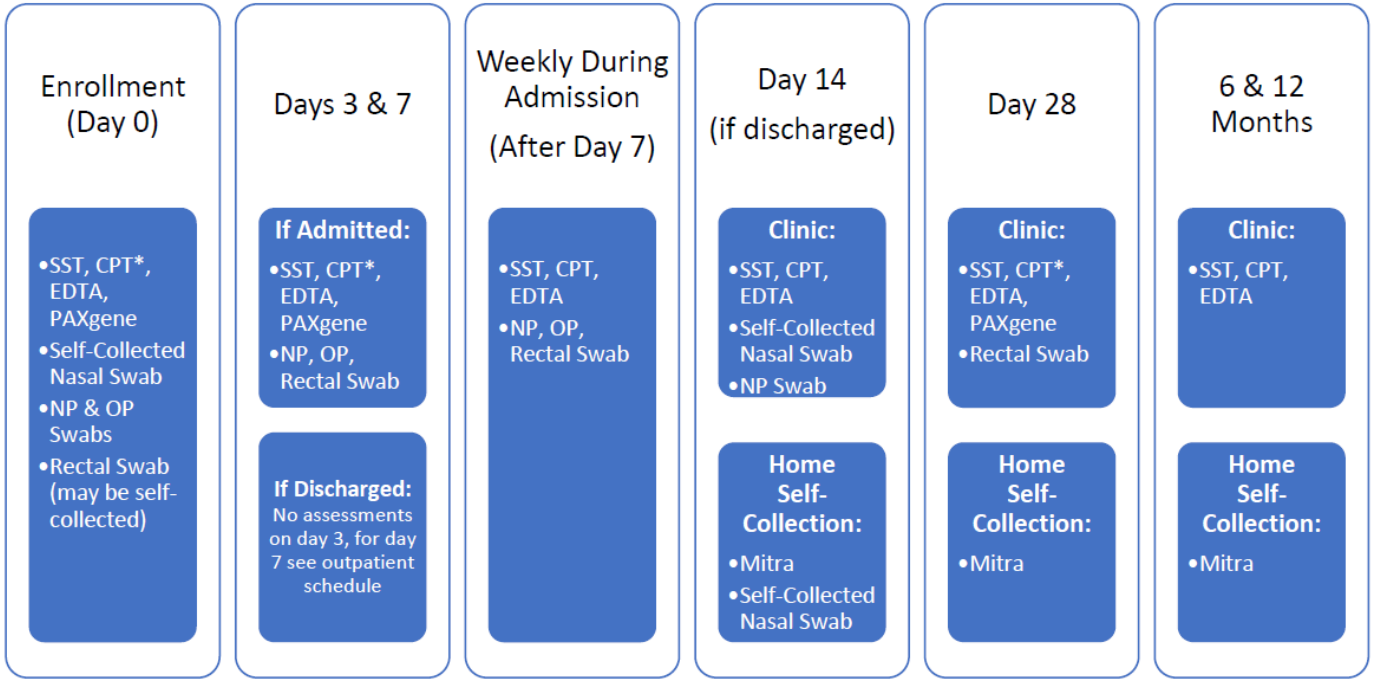
- Demographic, comorbidity, clinical information from surveys and case report forms, and Military Health System Data Repository (MDR):
  - Acute and long-term outcomes (12 months)
  - MDR data has 5-year follow-up and pre-COVID-19 eMR records
- Specimen collection over one year:
  - Immunology, biomarkers, virology
- DoD Serum Repository (DoDSR) access
  - Pre-COVID-19 sera

Figure 1: Inpatient MTF-based enrolled subject with specimen collection occurring at the clinic versus at-home self-collection:



EPICC uses multiple Military Health System research assets

IDCRP cohorts link a diverse lab network to prospective biospecimens and outcomes

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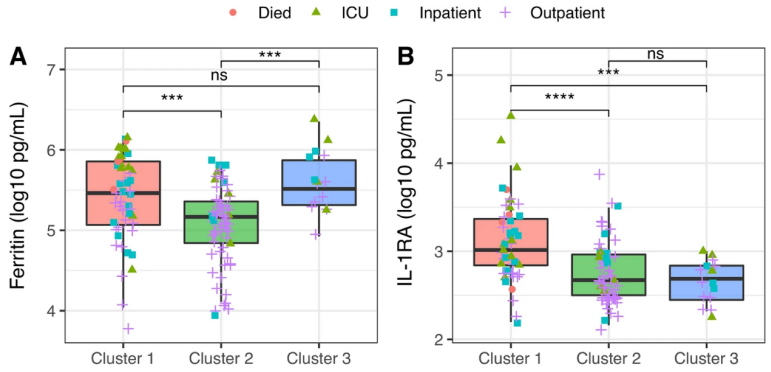
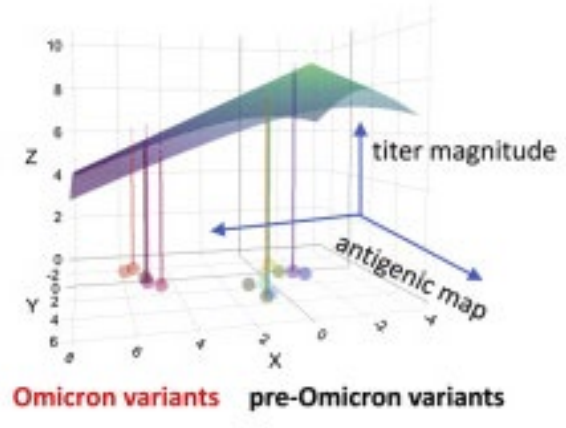
- Host response (USU, ACESO, FDA, NMRC, NIAID, Broad Inst., UCSF)
  - Binding Ab (high throughput)
  - Neutralizing + non-neutralizing Ab (multiplex)
  - Transcriptomics
  - T cell immunity, single cell sequencing
  - Host genomics
  - Proteomics
  - Autoimmunity



Blair, Sci Rep, 2022

- Virology (WRAIR, USAMRIID, NIAID, USAFSAM, MHRP, NMRC-BDRD)
  - Live culture, subgenomic PCR, qPCR
  - Sequencing & genomic analysis, inc. minor variants
  - Immunoinformatics and cartography



Wang, Cell Host Microbe, 2022

Interdisciplinary working groups and science road maps are key

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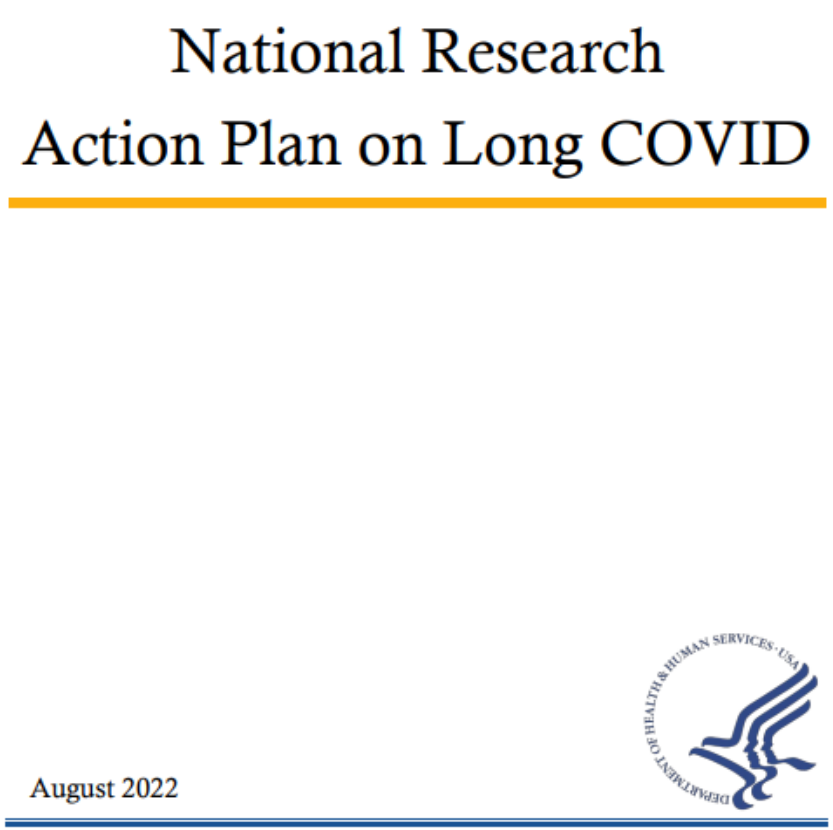
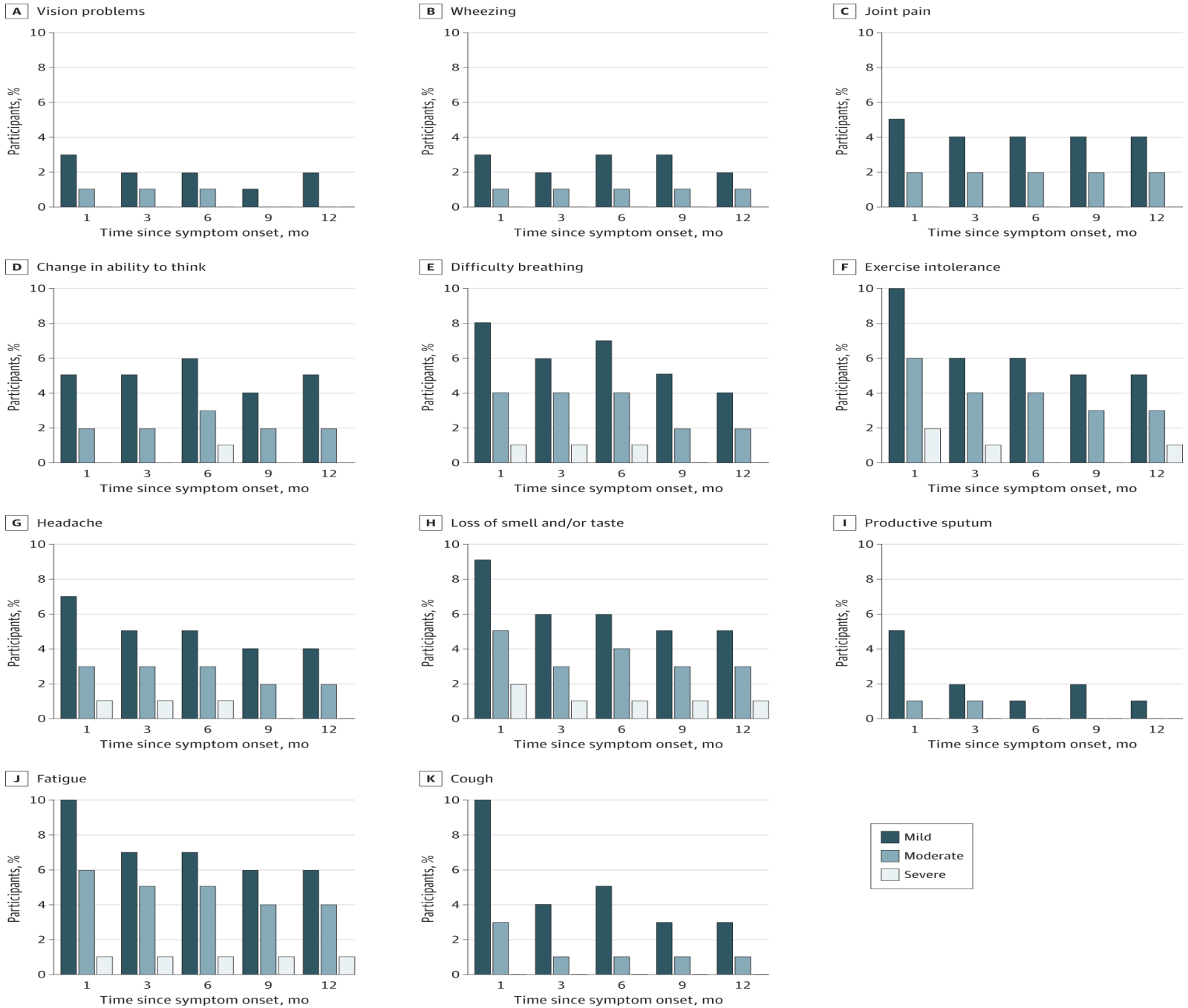
EPICC: research insights into Long COVID



*"**EPICC also includes machine learning approaches to identify Long COVID early symptom clusters, predict return to pre-illness health, and identify subtypes of Long COVID.** In conjunction with EPICC, the VA launched the Epidemiology, Immunology, and Clinical Characteristics of COVID-19 (EPIC^3), which is following a cohort of Veterans after a positive or negative test result for the presence of SARS-CoV-2. The study will describe the clinical trajectory from acute to Long COVID over time, as well as examine the role of biomarkers influencing the risk for Long COVID. **At completion of the respective studies (EPICC and EPIC^3), researchers plan to compare findings from the two participant groups"***

https://www.covid.gov/assets/files/National-Research-Action-Plan-on-Long-COVID-08012022.pdf



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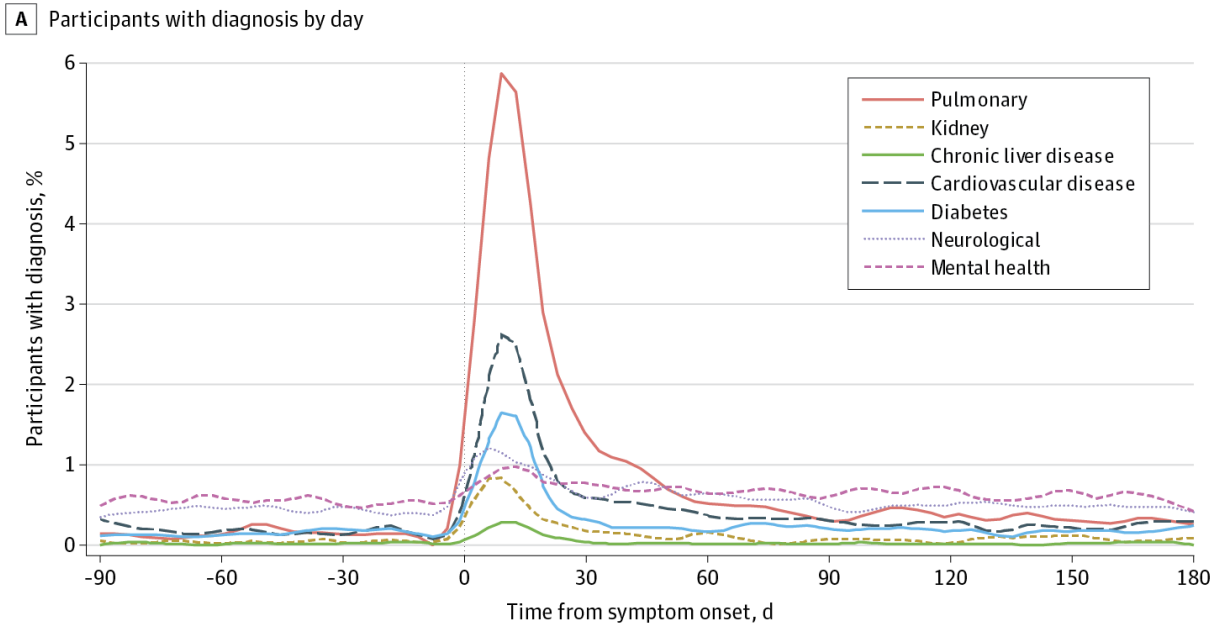
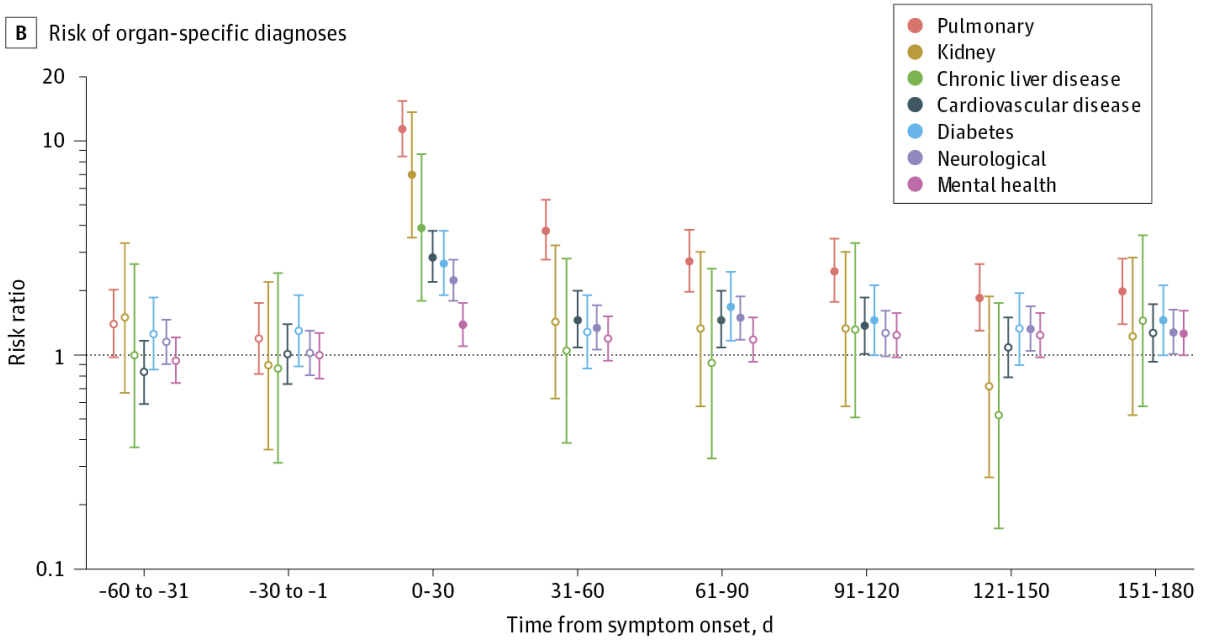
Percentage of Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases With Pandemic Potential (EPICC) Study Participants Who Endorsed Specific Symptoms on Surveys Conducted at 1, 3, 6, 9, and 12 Months

Richard et al, JAMA Netw Open. 2023





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Participants who were unvaccinated prior to infection more likely to report 28 or more days of symptoms (risk ratio [RR], 1.39; 95% CI, 1.04-1.85)

Among unvaccinated participants, postinfection vaccination was associated with a 41% lower risk of reporting symptoms at 6 months

Those who were unvaccinated prior to infection were more likely to have encounters for some illness categories (pulmonary: RR, 1.72; 95% CI, 1.32-2.27; neurological: RR, 1.27; 95% CI, 1.00-1.59) at 6 months (adjusting for pre-COVID healthcare use)

More recent analysis has examined risk and risk factors at 12 months, with time-matched SARS-CoV-2 negative controls

Richard et al, JAMA Netw Open. 2023

Responses to fitness survey questions

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Survey question responses among those active-duty participants who responded to at least one EPICC survey[a,b]

	SARS-CoV-2- (N=1983)	SARS-CoV-2+ (N=2109)	p value[c]
Do you have new/increased difficulty exercising?			
Yes	339 (17.1%)	798 (37.8%)	<0.01
No	1639 (82.7%)	1298 (61.5%)	
N/A ("I don't exercise")	5 (0.2%)	13 (0.6%)	
If yes, is this new/increased difficulty due to any of the following? (Check all that apply)			
Fatigue or tiredness	247 (72.9%)	608 (76.2%)	0.23
Shortness of breath or difficulty breathing	230 (67.8%)	639 (80.1%)	<0.01
Joint pain	154 (45.4%)	330 (41.4%)	0.20
Difficulty moving or poor coordination	43 (12.7%)	112 (14.0%)	0.54
Other	35 (10.3%)	52 (6.5%)	0.03

[a]Questions about difficulty exercising, daily activities, and physical fitness are summarized across all surveys if a participant responded to multiple surveys; answers represent whether they ever reported difficulties in any survey during the study
[b]Questions in this section are from the survey – wording represents the actual questions asked in the survey
[C] Pearson's Chi-squared test

- More SARS-CoV-2+ active duty participants reported new/increased difficulty exercising
- Shortness of breath was more commonly reported as the cause of difficulty exercising in SARS-CoV-2+ participants
- Reported difficulty with exercising and daily activities peaks at one month, reaches pre-COVID levels by 6-9 months
- Frequency of report of impaired physical fitness tests score remains elevated at 12 months

Richard et al IDWeek 2022

Association between pre-infection vaccination status and reported impaired fitness after COVID-19

Self reported fitness impairment outcome	Adjusted risk ratio for vaccination[a]	95% CI	p value
Difficulty exercising	0.82	0.69-0.96	0.015
Difficulty with daily activities	0.76	0.63-0.93	0.007
Physical fitness test score affected	0.89	0.77-1.04	0.136

[a]Generalized linear model fit using each category as the outcome (difficulty exercising, difficulty with daily activities, and reports physical fitness was affected). In addition to vaccination status, models included time since first SARS-CoV-2 positive, sex, age, BMI category, DOD affiliation, and random effect for the participant.

Richard et al IDWeek 2022

- Further (unpublished) analysis has examined effect of vaccine and boosting in larger numbers, adjusting for variant era

https://www.army.mil/article/254875/secretary_approves_implementation_of_revised_army_combat_fitness_test

Precision phenotyping of Long COVID through machine learning (EPICC)

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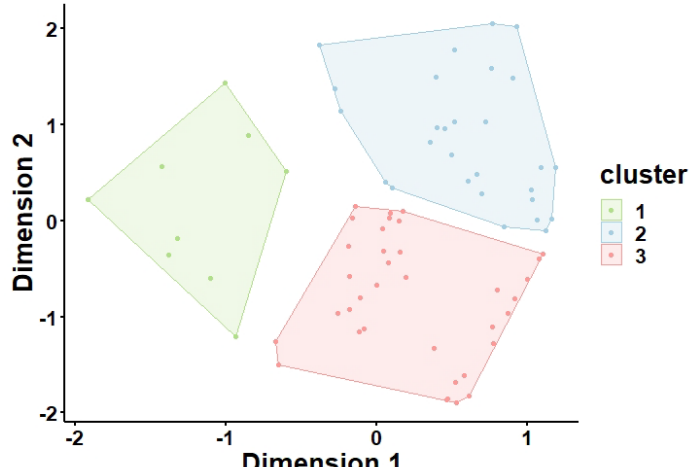
- Existing Long COVID definition frameworks are limited by heterogeneity of possible symptoms and pathologies (e.g., WHO definition)[1]

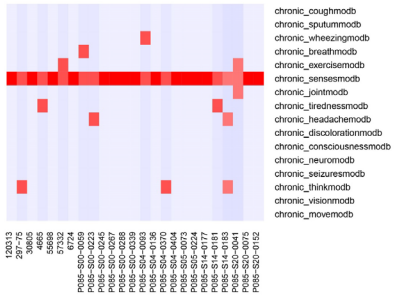
- In EPICC we are seeking to identify more precise phenotypes of chronic symptoms including analysis of
  - Predictors/correlates (e.g. variant, prior health)
  - Functional outcomes & recovery beyond 6 months
  - Biomarker analysis (miRNA, RNAseq, proteomics)

Principal component analysis and Kmeans clustering analysis of moderate-severe symptoms reported 6 months after COVID-19 in EPICC subjects

Epsi et al. IDWeek 2022

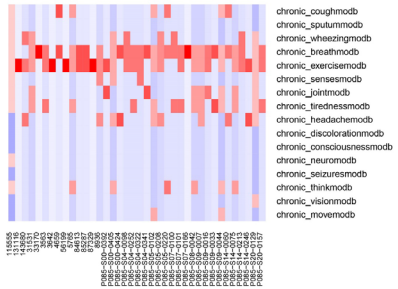


Cluster 1



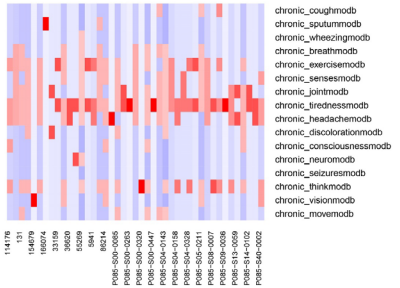
Sensory symptoms

Cluster 2



Breathing difficulty & exercise intolerance symptoms

Cluster 3



Fatigue & difficulty thinking symptoms

[1]https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

Organ-focused post-COVID assessments, examples (EPICC)

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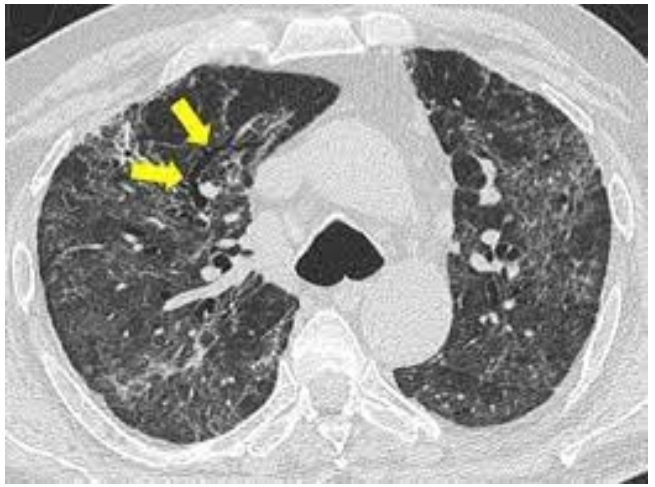
- Clinical, Radiographic, and Physiological Correlates of post-COVID-19 Dyspnea (**Dr Morris, BAMC**):
  - HRCT/6MWT/PFTs/echo/EKG in cases and controls
  - Toward "imaging biomarkers"
- Long term follow-up of SARS-CoV-2 myocarditis and post-SARS-CoV-2 echo abnormalities in ages < 21 years (**LTC Flanagan, TAMC**)
- Understanding COVID-19 impacts on longer term brain health, mental health and sleep (**Dr Brian Agan, IDCRP**):
  - Subjective and app-based objective measurements
- Laboratory based biomarkers mapped to these phenotypes (e.g. viral genotype, host RNAseq, miRNA, autoimmunity, proteomics, brain injury biomarkers)



George et al, Thorax, 2020

SARS-CoV-2 post-acute neuropsychological symptoms and performance among EPICC subjects

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EPICC Neurocognitive Sub-study Design:

Neurocognitive symptom questionnaires (N=2383)

- eQuestionnaires via REDCap – cross-sectional & 6 monthfollow-up

BRACE neurocognitive performance measures (N=465)

- Brain Baseline Assessment of Cognition and Everyday Functioning
- BRACE administered via iOS App [iPhone or iPad]

Neurocognitive Symptom Measures:

Depression (PHQ-9, Patient Health Questionnaire-9)

Anxiety (GAD-7, General Anxiety Disorder-7)

Fatigue (PROMIS® Fatigue 7a)

Cognitive function (PROMIS® Cognitive Function 8a and PROMIS® Cognitive Function abilities 8a)

Sleep (PSQI, Pittsburgh Sleep Quality Index) ***OR***

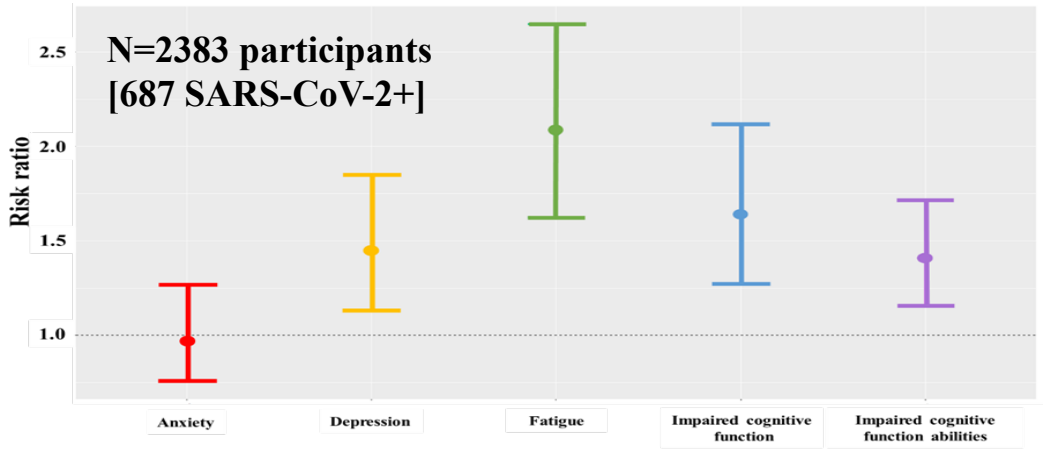
HRQOL (SF-36, Standard Form 36) – *50% each*

Neurocognitive Performance Measures (BRACE®)

Test	Measure of…
Trail Making Test Part A	Psychomotor speed
Trail Making Test Part B	Set-shifting and mental flexibility (Exec. function)
Stroop Color, Word, Interference	Processing speed
Visual-Spatial Learning Test (VSTM)	Visuospatial learning and memory

- Self-administered
- Clinic (iPad) version validated in HIV: Rubin et al. *JMIR Ment Health*. 2021 Sep 9;8(9):e25660.

Neurocog. symptoms are more prevalent in SARS2+ vs -



Adjusted for time since symptom onset/enrollment, sex, race/ethnicity, age, BMI, and active military status

Understanding the impact of COVID-19 using a scalable, app-based, self-administered cognitive assessment tool in the Military Health System

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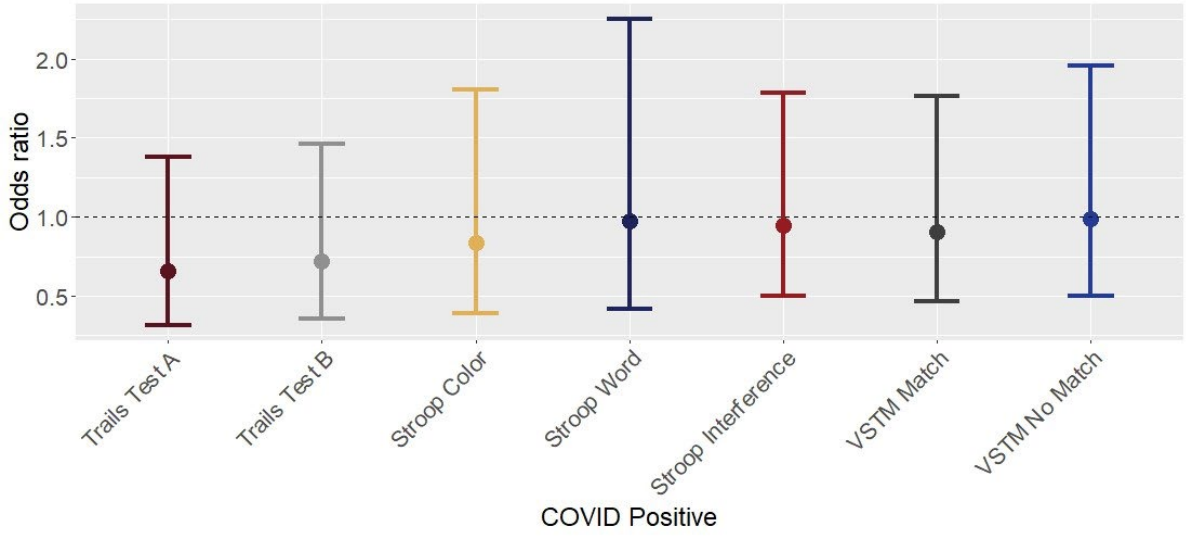
Table 1. Participant Characteristics

	SARS-CoV-2 Negative (n=142)	SARS-CoV-2 Positive (n=340)	Total (N=482)	P-value
Male	105 (73.9%)	211 (62.1%)	316 (65.6%)	0.012
Ethnicity				0.777
White	97 (68.3%)	242 (71.2%)	339 (70.3%)	
Black	7 (4.9%)	15 (4.4%)	22 (4.6%)	
Hispanic or Latino	18 (12.7%)	46 (13.5%)	64 (13.3%)	
Other	20 (14.1%)	37 (10.9%)	57 (11.8%)	
Age				0.969
Mean (SD)	39.3 (9.2)	39.8 (10.5)	39.7 (10.1)	
Median (Q1, Q3)	39.0 (33.2, 45.0)	39.0 (33.0, 45.0)	39.0 (33.0, 45.0)	
Min - Max	20.0 - 65.0	20.0 - 78.0	20.0 - 78.0	
Active duty	127 (89.4%)	260 (76.5%)	387 (80.3%)	0.001
Education				0.786
High School-Some College	21 (14.8%)	59 (17.4%)	80 (16.6%)	
Associate-Bachelor	56 (39.4%)	129 (37.9%)	185 (38.4%)	
Graduate	65 (45.8%)	152 (44.7%)	217 (45.0%)	
Hospitalized		14 (4.1%)		
Months post enrollment or symptom onset, mean (SD)	9.6 (2.2)	8.6 (5.3)	8.9 (4.6)	<0.001

Figure 1. Adjusted odds of impairment among cases



Adjusted for age, sex, ethnicity, and education
Impairment: >1 SD above mean completion time of SARS-CoV-2 negative

Other IDCRP Long COVID research activities

- EPICC extension 2023: cross sectional survey to evaluate patient perceptions of Long COVID healthcare in the MHS

- COVID-19 Military Registry Analysis Project (**PI = Dr David Tribble**)
  - Virtual cohort > 1 million ADSM and 9 million MHS beneficiaries
  - Includes eMR based Long COVID endpoints

- USU Military Infectious Disease Hub Long COVID Working Group – includes efforts for common endpoint definitions within MHS Long COVID research (**Dr Brian Agan**, co-chair)

- Currently working on Long COVID Research Road Map / Review for Military Health System research:
  - Includes considerations of research endpoints and research definitions

Considerations on Long COVID research definitions: an IDCRP perspective

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- "One size fits all" definitions are challenging and lack specificity; a suite of standardized definitions should be considered.
- Definitions will vary with the research question (e.g., mechanistic studies, prognostic studies, clinical trial endpoints).
- Consider statistical efficiency when harmonizing endpoints (e.g., continuous variables versus categorical/binary outcomes).

- Clinically evaluated and patient reported outcomes are both important in Long COVID definitions to ensure this disease is holistically studied and treated.
- Military Health System (MHS) research may offer some relatively unique, functionally important endpoints of relevance to Long COVID research in general (e.g., service mandated fitness tests).

- Definitions which generalize between MHS studies, between MHS and non-MHS studies, and between research and clinical practice/policy are ideal.
- Standardization of independent variable definitions (predictors of Long COVID) is also key.

Acknowledgements – EPICC Team

- IDCRP Leadership
- DHA & NIAID support
- MTF PIs and AIs
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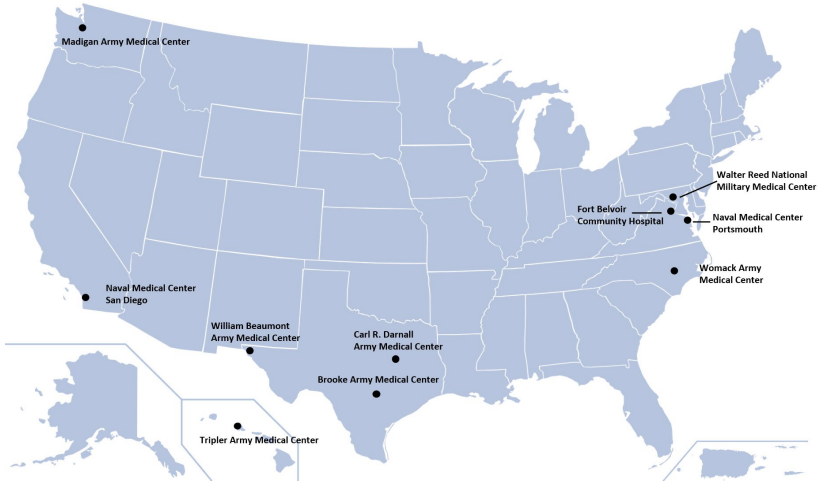
  - USUHS
  - DoD (USAFSAM, WRAIR, USAMRIID, NMRC/BDRD, HJF ACESO)
  - FDA CBER
  - NIAID
- Other stakeholders:
  - AFHSD/GEIS
- IDCRP:
  - Study PIs, AIs
  - CRMs and site teams
  - HQ PM & Data Management Teams
- USU:
  - IRB and HPA
  - Site HPAs and IRBs



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