MILLION VETERAN PROGRAM

A Partnership with Veterans

IHCC COVID-19 Panel: MVP

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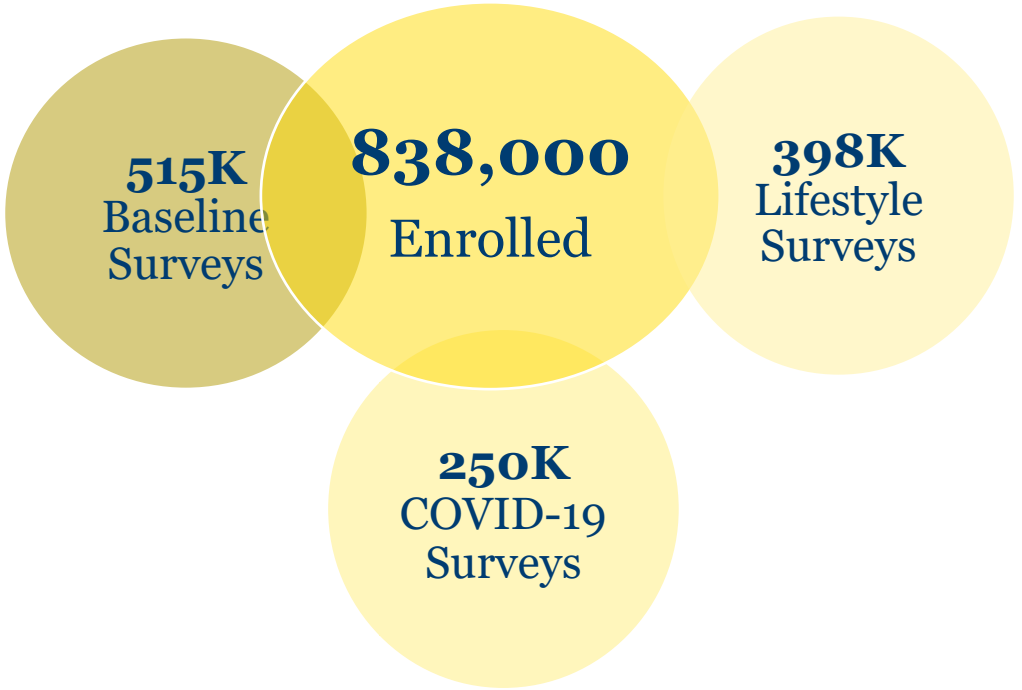
May 27, 2021

VA | U.S. Department of Veterans Affairs

DISCOVERY ★ INNOVATION ★ ADVANCEMENT

MVP at a Glance



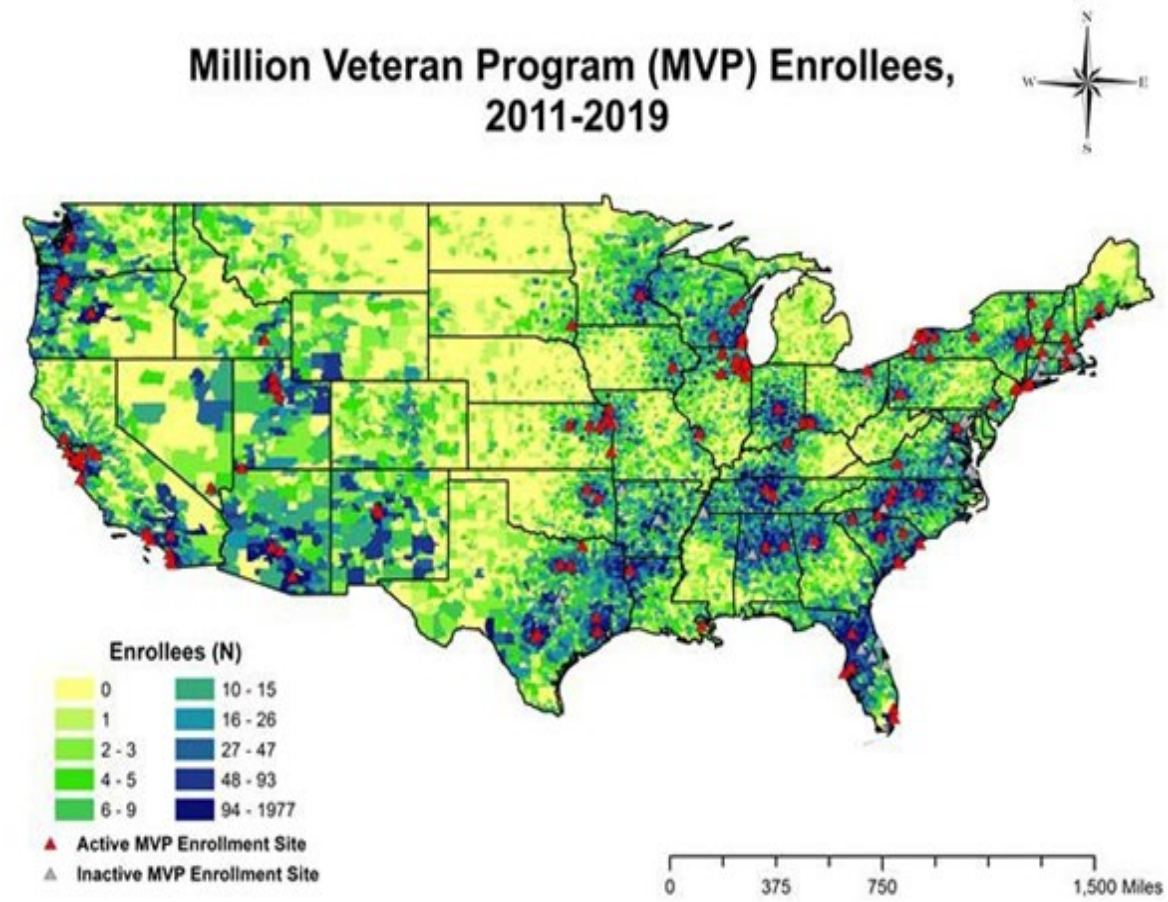
66 Current Sites

78 Sites Ever

18,439,866 Total Mailings

5,951,740 Individuals Contacted

MVP Enrollment Map



MVP COVID-19 rapid response: Chronology

Dec 31st China reported a cluster of cases of pneumonia in Wuhan, Hubei province

Jan 20th first COVID-19 case reported in US by CDC

March 2nd VA Palo Alto received the 1st Veteran tested positive for COVID-19

March 11th WHO declared COVID-19 a pandemic

March 16th MVP suspended active recruitment (but continue on-line recruitment)

March 31st 56 research concepts submitted in response to RFI on COVID-19

May 5th Release of COVID-19 survey printed and online (**May 8th**)

May 7th submission of MVP COVID-19 Science protocol - rapid response

June 5th Six COVID-19 science working groups were established

June 16th MVP COVID-19 protocol fully approved - cIRB and 5 local R&Ds

June 22nd First meetings COVID-19 WGs

Nov 23rd: MVP identify drug-repurposing opportunities for early COVID-19

Nov 24th: MVP contribute GWAS data to release 4 HGI COVID-19

Dec 20th: MVP launch the pilot for at home (capillary blood devices) COVID-19 biospecimens

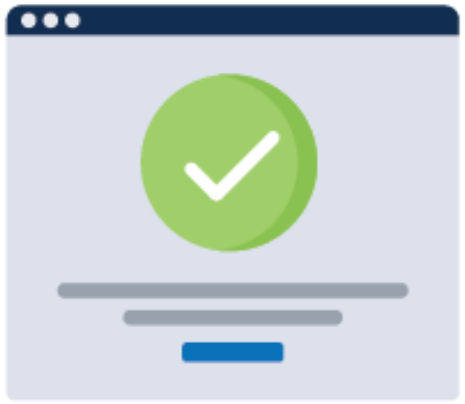
MVP COVID-19 Activities

- Recruitment shifted to Online in April
- MVP COVID-19 Survey finalized and distributed in May
- Exploration of at-home specimen collection for COVID-19 serological test
- Scientific collaboration with MVP Core and 6 working groups established in June.

MVP Online For Expanded Enrollment

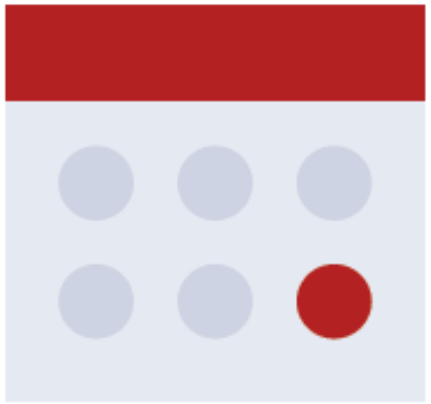
SIGN IN

using the same credentials as other VA partners (such as My HealtheVet or eBenefits).



COMPLETE

the consent process and allow access to health records.



SCHEDULE

an MVP visit to provide a blood sample.

FILL OUT

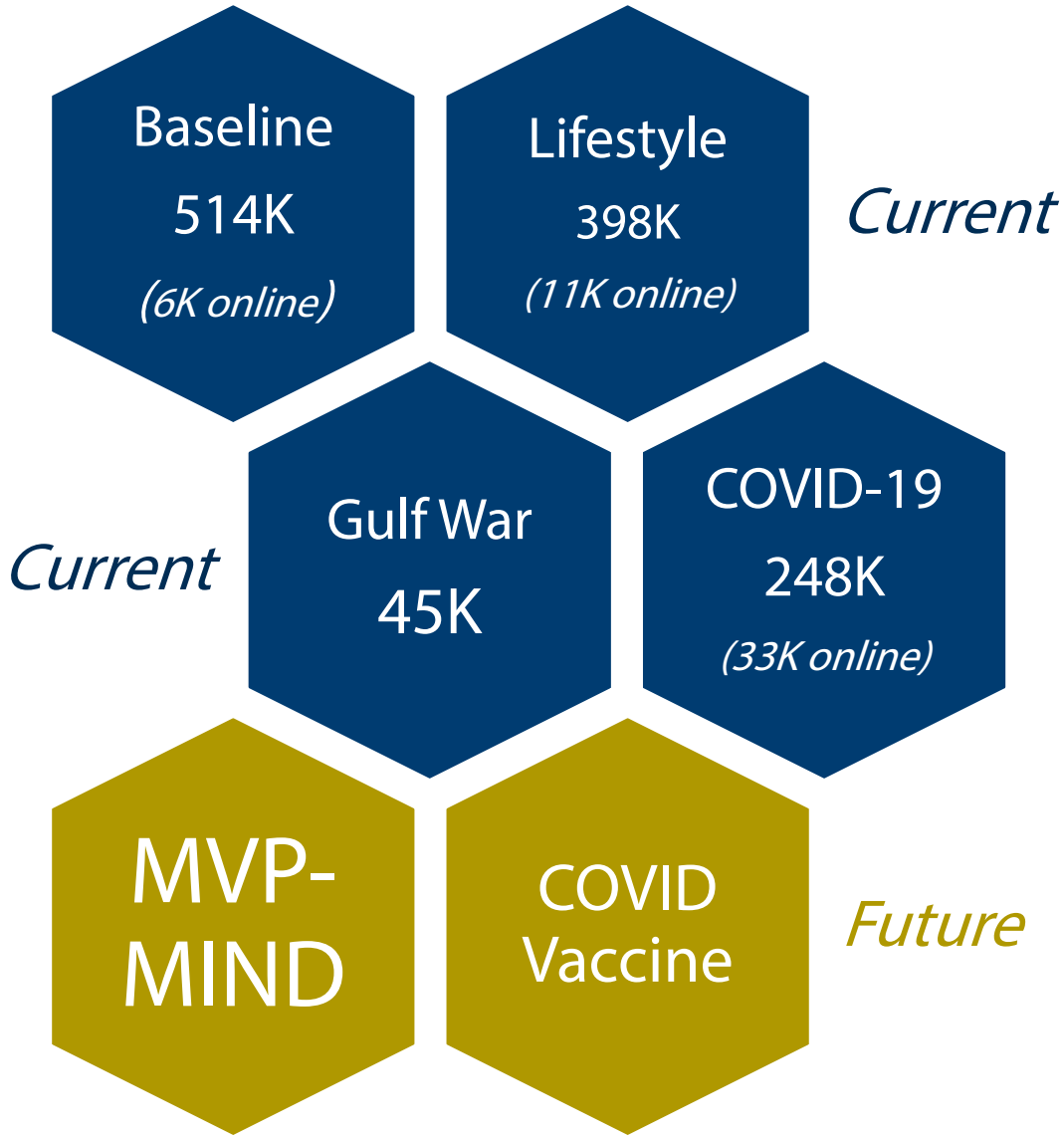
surveys about health and lifestyle.

mvp.va.gov

Launched 09/19

6,500 Enrolled Online

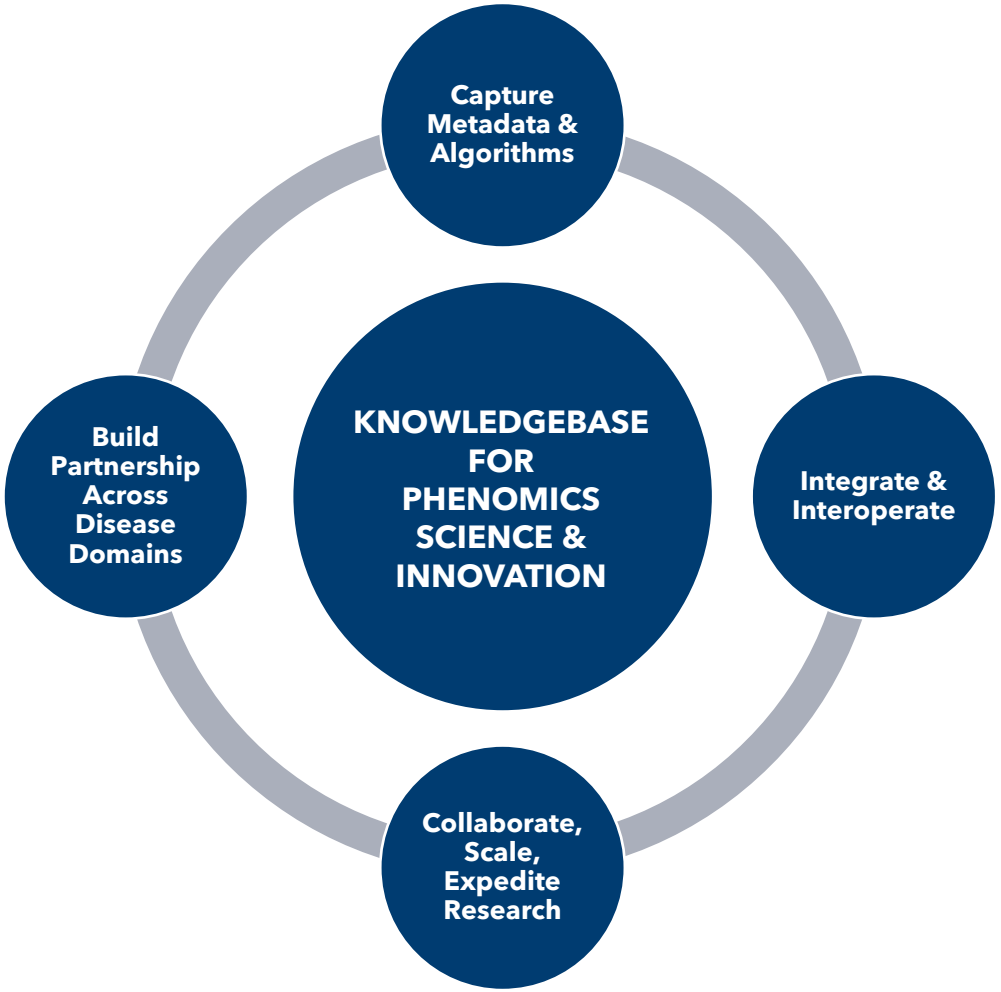
Self-Report Data Collection



Additional Upcoming Activities

- Updated Baseline/Lifestyle (inclusion of Space Force/Gender Identity)
- MVP-MIND to existing enrollees
- Rollout of Follow-Up
- Gulf War online

Phenomics Library
CIPHER



MVP-COVID19 Case Summary

MVP-COVID 19 Data Report (GRRS#2787)

Report generated on: 04/23/2021
Data as of: 04/22/2021
Source of Data: MVP Roster 20.1, CDW COVID-19 Shared Data Source

	COVID-19		
Cohort	**Positive**	**Negative**	**Total Tested**
VA-wide (COVID case list)	*224,433*	*984,243*	*1,208,676*
MVP Roster V20.1 (N=819,417)	*33,064*	*179,904*	*212,968*
MVP Genotyped V4.0 (N=658,311)	*26,292*	*143,453*	*169,745*
MVP WGS Sample (N=100,112)	*3,575*	*20,801*	*24,376*
MVP Methylation Sample (N=38,192)	*1,306*	*7,600*	*8,906*
MVP Metabolomics Sample (N=1,985)	*91*	*431*	*522*

COVID Severity Scale - WHO

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Figure: **WHO clinical progression scale**
ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. NIV=non-invasive ventilation. pO_2=partial pressure of oxygen. SpO_2=oxygen saturation. *If hospitalised for isolation only, record status as for ambulatory patient.

- Version 1: Severity Scale based on WHO scale
  - Captured all data elements available in EHR structured data
  - Checking data quality and completeness

1. MILD – Lab positive + Not Hospitalized
2. MODERATE – Lab positive + hospitalized/w or wo oxygen therapy (low flow)
3. SEVERE – Lab positive + hospitalized + oxygen therapy (high flow) /intubation/mechanical ventilation/vasopressors/dialysis/ECMO)
4. DEATH

Biospecimen Expansion:
What are we doing in terms of biospecimens expansion?

Strategies tested

- Saliva: DNA

- Tasso SST

- Mitra

- Mobile phlebotomy

- Tasso+

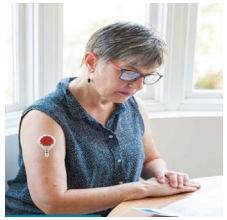
Pre-COVID

COVID

Tasso experience in 5 steps : Tasso SST

Mail 2 veterans (Tasso)

Veterans follows Instructions



Biospecimen collected 5 minutes After pressing the red button

Returned the tube by mail

Received VA Palo Alto - Holodniy Lab

Tasso SST

- Type of biospecimen: **serum**
- >150 MVP participants have tested with high levels of acceptability
- Average **blood** >**230 microlit** / Average **serum** >**112 microlit**
- 53% consent rate & 94% devices received
- 4 different COVID related assays (infection & vaccination) being tested

MVP COVID-19 Science Program: Nature of Differences from Other MVP Science Projects

- Necessity: Scientific privilege borne of a unique emergency/pandemic
- Need for Speed: Rapid Scientific Output
- Core Leadership: Heavy Reliance on Core Teams to Accomplish Goals
- Collaboration: Collaboration Among Working Groups
- Short-Term: Project Completion within 6-12 Months
- Data sharing with non-MVP science community and dbGaP strongly encouraged (eg HGI)
- Pre-print publication strongly encouraged
- Opportunity to highlight VA teamwork and collaboration

COVID – 19 Working Groups
Specific Aims

Disease Mechanisms

- Study disease mechanisms in Covid-19 infection (coagulation, thrombosis and pulmonary mechanism)
  - Outline approved
- Role of Androgen Mechanisms in Covid-19 severity and outcome
  - Proposal Approved

Druggable Genome

- Identify drug repurposing opportunity to minimize risk of hospitalization
  - Paper published in Nature Medicine
- To prevent complications in patients hospitalized with COVID-19
  - Proposal Approved

Genomics & PRS

- Study outcomes and resilience against COVID
  - Paper completed and shopping journal?????

Pharmacogenomics

- Identify drug repurposing
  - Proposal Approved
- Pharmacogenomics of Thrombocytopenia induced by heparin in CVOID 19
  - Heparin-focused manuscript approved by P&P
- Safety Ascertainment PheWAS
  - Proposal approved

PheWAS

- Somatic Mosaicism and Infectious disease in MVP dataset
  - Proposal approved
- Phenome-Wide association of SARS-CoV-2 infection and related respiratory infection host genetics
  - Manuscript completed shopping Journal???????????

GWAS

- Identification of genomic variation related to COVID-19 “caseness” defined as susceptibility, severity, and mortality
  - Manuscript under review @ Nature Genetics
- Targeted genomic regions associated with COVID-19 severity: ACE2, Interferon and IL6 system variation--main effects and GXE
  - Proposal approved

Epidemiology

- Understanding Baseline characteristics of VA and MVP COVID-19 patients (Final Submission title TBD)
  - Manuscript accepted at PLOS One

Cohort Management

- Department of Veterans Affairs Million Veteran Program’s Rapid Response to COVID-19: Survey Development and Findings
  - Manuscript submitted to PLOS One

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01310-z

Check for updates

Actionable druggable genome-wide Mendelian randomization identifies repurposing opportunities for COVID-19

Liam Gaziano[1,2], Claudia Giambartolomei[3,4], Alexandre C. Pereira[5,6], Anna Gaulton[7], Daniel C. Posner[1], Sonja A. Swanson[8], Yuk-Lam Ho[1], Sudha K. Iyengar[9,10], Nicole M. Kosik[1], Marijana Vujkovic[11,12], David R. Gagnon[1,13], A. Patrícia Bento[7], Inigo Barrio-Hernandez[14], Lars Rönnblom[15], Niklas Hagberg[15], Christian Lundtoft[15], Claudia Langenberg[16,17], Maik Pietzner[17], Dennis Valentine[18,19], Stefano Gustincich[3], Gian Gaetano Tartaglia[3], Elias Allara[2], Praveen Surendran[2,20,21,22], Stephen Burgess[2,23], Jing Hua Zhao[2], James E. Peters[21,24], Bram P. Prins[2,21], Emanuele Di Angelantonio[2,20,21,25,26], Poornima Devineni[1], Yunling Shi[1], Kristine E. Lynch[27,28], Scott L. DuVall[27,28], Helene Garcon[1], Lauren O. Thomann[1], Jin J. Zhou[29,30], Bryan R. Gorman[1], Jennifer E. Huffman[31], Christopher J. O'Donnell[32,33], Philip S. Tsao[34,35], Jean C. Beckham[36,37], Saiju Pyarajan[1], Sumitra Muralidhar[38], Grant D. Huang[38], Rachel Ramoni[38], Pedro Beltrao[14], John Danesh[2,20,21,25,26], Adriana M. Hung[39,40], Kyong-Mi Chang[12,41], Yan V. Sun[42,43], Jacob Joseph[1,44], Andrew R. Leach[7], Todd L. Edwards[45,46], Kelly Cho[1,47], J. Michael Gaziano[1,47], Adam S. Butterworth[2,20,21,25,26] ✉, Juan P. Casas[1,47] ✉ and VA Million Veteran Program COVID-19 Science Initiative*

Drug repurposing provides a rapid approach to meet the urgent need for therapeutics to address COVID-19. To identify therapeutic targets relevant to COVID-19, we conducted Mendelian randomization analyses, deriving genetic instruments based on transcriptomic and proteomic data for 1,263 actionable proteins that are targeted by approved drugs or in clinical phase of drug development. Using summary statistics from the Host Genetics Initiative and the Million Veteran Program, we studied 7,554 patients hospitalized with COVID-19 and >1 million controls. We found significant Mendelian randomization results for three proteins (ACE2, $P = 1.6 \times 10^{-6}$; IFNAR2, $P = 9.8 \times 10^{-11}$ and IL-10RB, $P = 2.3 \times 10^{-14}$) using *cis*-expression quantitative trait loci genetic instruments that also had strong evidence for colocalization with COVID-19 hospitalization. To disentangle the shared expression quantitative trait loci signal for *IL10RB* and *IFNAR2*, we conducted phenome-wide association scans and pathway enrichment analysis, which suggested that *IFNAR2* is more likely to play a role in COVID-19 hospitalization. Our findings prioritize trials of drugs targeting IFNAR2 and ACE2 for early management of COVID-19.

MVP COVID-19 Science Program:

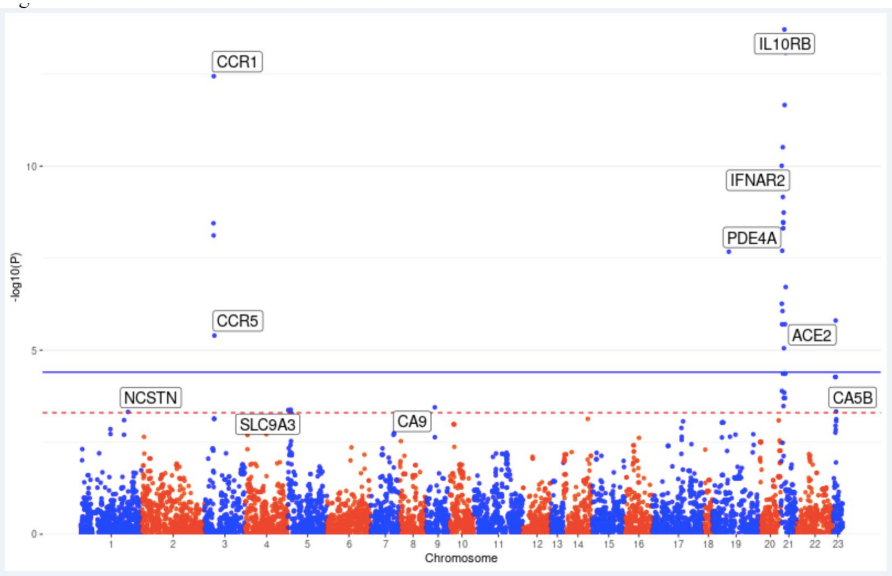
Actionable Druggable Genome Mendelian Randomization identify repurposing opportunities for outpatient management in COVID-19

https://www.medrxiv.org/content/10.1101/2020.11.19.20234120v1

7,554 patients hospitalized with COVID-19 and >1 million controls (MVP + HGI)

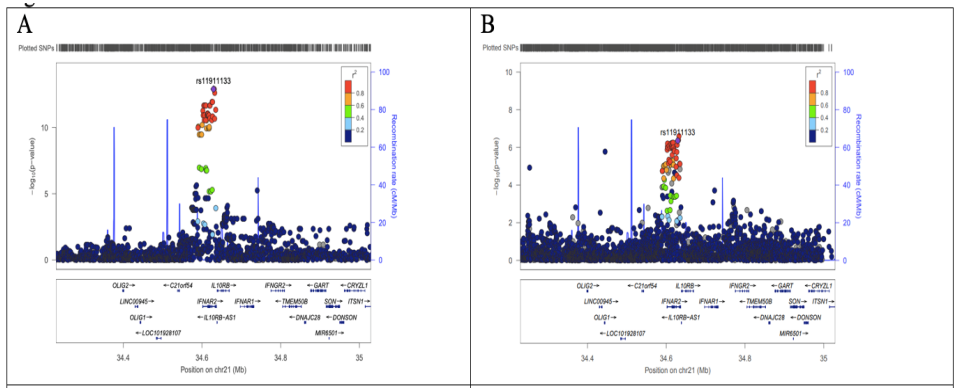
MR-WAS of 1263 druggable genes against hospitalization in COVID-19 identified IFNAR2: ***P*=9.8×10^{-11}**

IFNAR2 is one the 2 co-receptor for Type-I Interferons



IFNAR2 and COVID-19 hospitalization: Colocalization analysis

Strong evidence of colocalization for lead SNP (rs11911133) between the mRNA and hospitalization COVID19 (**PP4=0.99**)



A) IFNAR2 mRNA esophagus mucosa tissue

B) IFNAR2 and Hospitalization in COVID+

Thanks to our Veterans in MVP

"I have always known someone in the family with Diabetes or Hypertension. I eagerly volunteered to participate in MVP so I can help medical researchers better understand how genes influence diseases. One blood draw is all it took… yet the potential to contribute to scientific discoveries is enormous!"

"I'm participating in the Million Veteran Program so that I can do my part to help future generations of not just Veterans, but everyone who can benefit from this research."

"When I was young, the service gave me a reason. Today, my reason is to help answer those questions yet to be asked……"

"I believe that the data collected from me and other Veterans in the Million Veterans Program will someday provide better ways to diagnose and treat patients. I volunteered to participate in the MVP because I want to do my part to make this a reality one day."