MILLION VETERAN PROGRAM
A Partnership with Veterans

IHCC COVID-19 Panel: MVP
J. Michael Gaziano, MD, MPH
May 27, 2021
MVP at a Glance

- **515K Baseline Surveys**
- **838,000 Enrolled**
- **398K Lifestyle Surveys**
- **250K COVID-19 Surveys**

- **66 Current Sites**
- **78 Sites Ever**
- **18,439,866 Total Mailings**
- **5,951,740 Individuals Contacted**
MVP Enrollment Map

Million Veteran Program (MVP) Enrollees, 2011-2019

Enrollees (N)
- 0
- 1
- 2-3
- 4-5
- 6-9

Active MVP Enrollment Site
Inactive MVP Enrollment Site

0 375 750 1,500 Miles
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

Baseline
514K (6K online)

Lifestyle
398K (11K online)

Gulf War
45K

COVID-19
248K (33K online)

MVP-MIND

COVID Vaccine

Current

Additional Upcoming Activities

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

Future
Phenomics Library

CIPHER

Capture Metadata & Algorithms

Integrate & Interoperate

Build Partnership Across Disease Domains

KNOWLEDGEBASE FOR PHENOMICS SCIENCE & INNOVATION

Collaborate, Scale, Expedite Research

Centralized Interactive Phenomics Resource (CIPHER)

Announcements

The VA PheLib has a new name! As of December 2020, the VA PheLib is VA-CIPHER (Centralized Interactive Phenomics Resource). This transformative framework aims to optimize Veterans' health and accelerate research through the aggregation, integration, and sharing of data. By leveraging state-of-the-art technologies and methodologies, CIPHER facilitates a robust ecosystem for scientific innovation and discovery.

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Overview

CIPHER is a catalog and knowledge sharing platform that consolidates metadata that aims to optimize Veterans' health outcomes. As a collaborative effort within the VA to build on existing resources, the CIPHER Annotation Library includes an online interface for metadata. The web-based platform is also a tool for enhancing collaboration and communication among researchers and clinicians. Supported by the Million Veteran Program (MVP) and the Veterans Informatics Computing Infrastructure (VICI), this initiative will be used in ORD supported research and for investigating COVID-19.

Mission

To provide an encyclopedia of VHA EHR based phenotyping through integration of phenomics work from across the VA research community, to optimize VA data use for research and clinical operations VA research and to serve the VA research community.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Positive</th>
<th>Negative</th>
<th>Total Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA-wide (COVID case list)</td>
<td>224,433</td>
<td>984,243</td>
<td>1,208,676</td>
</tr>
<tr>
<td>MVP Roster V20.1 (N=819,417)</td>
<td>33,064</td>
<td>179,904</td>
<td>212,968</td>
</tr>
<tr>
<td>MVP Genotyped V4.0 (N=658,311)</td>
<td>26,292</td>
<td>143,453</td>
<td>169,745</td>
</tr>
<tr>
<td>MVP WGS Sample (N=100,112)</td>
<td>3,575</td>
<td>20,801</td>
<td>24,376</td>
</tr>
<tr>
<td>MVP Methylation Sample (N=38,192)</td>
<td>1,306</td>
<td>7,600</td>
<td>8,906</td>
</tr>
<tr>
<td>MVP Metabolomics Sample (N=1,985)</td>
<td>91</td>
<td>431</td>
<td>522</td>
</tr>
</tbody>
</table>
## COVID Severity Scale - WHO

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

*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

- 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
Disease Mechanisms
- Study disease mechanisms in Covid-19 infection (coagulation, thrombosis and pulmonary mechanism)
  - 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 CVID 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

COVID – 19 Working Groups
Specific Aims
Actionable druggable genome-wide Mendelian randomization identifies repurposing opportunities for COVID-19


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, $P = 1.6 \times 10^{-4}$; IFNAR2, $P = 9.8 \times 10^{-11}$ and IL-10RB, $P = 2.3 \times 10^{-8}$) 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 IL-10RB and IFNAR2, we conducted phenotype-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.
MR-WAS of 1263 druggable genes against hospitalization in COVID-19 identified IFNAR2: $P=9.8 \times 10^{-11}$

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

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

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

"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.”

“Thanks to our Veterans in MVP”