MILLION VETERAN PROGRAM

MVP INSIDER

A newsletter for our Veteran participants

Issue 10 | Fall 2022

What's next for MVP? More participants, more discoveries, and more impact

By Dr. Sumitra Muralidhar, Ph.D., MVP Program Director

MVP data is advancing our understanding of health concerns that impact Veterans—and millions of Americans. Just 8 months into the year, over 28 scientific and medical journals have published findings based on MVP data—shedding light on health conditions from heart disease to posttraumatic stress disorder (PTSD).

Each one of these studies was made possible by the men and women who have chosen to enroll in MVP. Because of you, MVP is speeding closer to a time when personalized medicine will be part of Veteran care at VA medical centers nationwide. We are excited to let you know what is coming next for MVP—and for you.

A commitment to representing all Veterans

The vast majority of genetic research performed around the world uses data from people of European ancestry. But because a racially and ethnically diverse group of Veterans has enrolled in MVP, scientists have been able to make discoveries that are specific to minority populations, including people of African ancestry and Hispanics.

For example, a recent study looked at MVP participants of African ancestry who were hospitalized with COVID-19. The study found that people with two copies of a particular gene variant are at a much higher risk for kidney disease—and at higher risk of dying from COVID-19. Findings like this will eventually help doctors identify people with greater risk and provide better care and treatment.

MVP is committed to building a strong cohort of women Veterans so that researchers can learn about diseases specific to women, like cervical cancers. Last March we launched a campaign to grow the number of women in MVP—and more than 10,000 of you joined by July 1, 2022. We are so grateful to the women who are part of MVP—and we extend a warm welcome to our 10,000 new members!

More access means more discovery

We know that qualified researchers can make more important discoveries when they have access to MVP data. This year we built processes to allow all Department of Veterans Affairs (VA) researchers to apply for secure access to MVP data in order to conduct studies. We also launched a pilot program to allow approved researchers outside VA to perform their own studies via the VA Data Commons.

Researchers do not see any information that directly links to MVP participants—like name, date of birth or social security number. Everything we are doing at MVP is designed to create an enhanced, diverse cohort of Veterans, broaden access and drive more science while protecting the privacy of MVP participants. All of this means more discoveries that can ultimately impact Veterans' health.

Looking ahead

Today, we have over 900,000 Veteran participants. We want to get to the million Veteran milestone next year!

At MVP, we are committed to using our research findings to improve health and wellness for Veterans. To achieve this, we are focused on using our research findings in the clinic to help Veterans—this year we launched a Clinical Translation Task Force to accelerate our efforts. We are also exploring ways to partner with industry, using MVP research to inform the development of new drugs or re-purposing existing drugs for other conditions.

There is so much exciting work happening at MVP, and we owe all of what we are achieving to Veteran participants. Each person who is a part of the MVP research community is grateful to every Veteran who participates in MVP—and we are committed to conducting research that will improve Veteran health and wellness.

New MVP research findings

- An MVP study identified genetic variants that put people at risk for PTSD and depression. Another study used those findings to grow medical understanding of PTSD even more, opening avenues to explore treatments that can help. Read more about this study on page 4.
- Researchers hope a study of the genes of people who attempt suicide can inform the way we approach suicide prevention. Read more about this study on page 6.
- A study found correlations between your height and your probability of developing several common conditions, including heart disease and circulatory disorders. Read more about this study on page 4.
- Is yogurt good for your heart? MVP research revealed new relationships between foods and health. Read more about this study on page 5.

Generations of Veterans find a new way to serve

Dear MVP Participants,

I hear it over and over—"I joined MVP because it's another way to serve."

Your service has allowed MVP to amass one of the largest, richest, most inclusive collections of information about genetics and lifestyle in the world.

That information has enabled scientists—just this year—to better understand who might be at risk of committing suicide, which genes could make someone more susceptible to posttraumatic stress disorder (PTSD), and what kinds of drugs might help people with COVID-19.

Those are just a few of the most recent discoveries made by MVP researchers. We are on track for even more cutting-edge research that has the promise to speed the delivery of precision health care to you—America's Veterans.

Over the next year, I look forward to welcoming more Veterans into our MVP family.

My hope is that by enrolling more Veterans into MVP, and by ensuring our cohort includes Veterans from all backgrounds and experiences, we can learn even more. For instance, we want to learn more about the serious mental health conditions that impact Veterans. So, this year, we launched MVP Measures Investigating Neuropsychiatric Disorders (MIND). We hope to enroll 50,000 Veterans to join the initiative, to better understand mental and behavioral health conditions such as schizophrenia, bipolar disorder, and opioid use disorder.

When we make significant discoveries at MVP, I believe that we've done more than just accomplish a scientific goal—we've strengthened the trust we have with the Veterans enrolled in MVP—people I think of as our MVP family.

Some of you may know that my father is a Vietnam-era Veteran. You may not know that he is also an MVP participant. Many of my aunts, uncles and cousins served in the military—and many of them are now part of the MVP family. When my son retired from the Army last year, he joined MVP.

I'm honored and proud that my two families—my biological family and my MVP family—are so connected and intertwined.

It is a dream and an honor for me to work with Veterans. Thank you for your service to our country, and your continued service to future generations through MVP.

Dr. Mike Gaziano, M.D., M.P.H., MVP Principal Investigator

In the photo above, Mike is pictured with his son Dante and his father Dominic—both of whom are MVP participants.

MVP is almost a million Veterans strong

- Over **900,000 Veterans** enrolled to date—representative of every service branch and era

Thanks to your participation, MVP has conducted some of the largest studies in the world.

PTSD: A study of more than **165,000 MVP** participants identified several genes related to re-experiencing traumatic memories, one of the symptoms of PTSD

Anxiety: A study of **200,000 MVP** participants uncovered genetic markers that could indicate increased risk of anxiety

Depression: A study that included **300,000 MVP** participants identified new gene variants that increase depression risk in people of European and African ancestry. This finding was made possible because of the diversity of MVP's Veteran participants

Nonalcoholic fatty liver disease (NAFLD): The **largest genetic** study to date on NAFLD identified several genetic markers that pave the way for improved risk prediction and therapy

MVP's research is stronger when it includes all types of people.

- **1 in 10 MVP** participants are **women**
- Almost **1 in 5 MVP** participants are **Black**
- MVP aims to be **representative of all Veterans, across race, ethnicity, gender and age**

At MVP, each participant is one in a million—every Veteran brings their unique genetics, experiences, and health backgrounds to the program. Below, two of our participants share their one-in-a-million story. What's yours?

One in a million: Molly Klote

"I believe we are on track to unlock the mysteries of our genes and how they relate to our lives and our health."

By Molly Klote, M.D., Col. (Ret.), Director of the Office of Research Protections, Policy, and Education in VA's Office of Research and Development (ORD)

I retired from the U.S. Army in 2018 after serving the better part of two decades as an allergist/immunologist and research regulator at Walter Reed National Military Medical Center as well as with the Medical Research and Materiel Command and the U.S. Army's Office of the Surgeon General.

When I joined VA, one of the first things I did was visit a recruitment event for MVP.

Today, I'm proud to be one of hundreds of thousands of Veterans who, by signing up to join MVP, are helping advance health care breakthroughs for our Veteran community.

I joined MVP because I am passionate about helping other Veterans—and because I believe that precision health care is the future of health care. But in health research, we need very large numbers of people to make new discoveries, and our discoveries are based on the people in our research cohort.

Thanks to women like me and others in MVP, researchers were able to verify that a genetic test developed in the private sector was accurate in predicting breast cancer among Veteran women as well. But the genetic test was developed based mostly on women of European descent. Researchers are not able to confirm its accuracy in women of other ancestry.

MVP wants to change this, for this study and for all other health research. And they can—but they need our help.

Join me in telling your Veteran family and friends about MVP. Share the message that we need more women and people of all backgrounds in MVP research, to make sure breakthroughs and discoveries apply to Veterans like us.

I believe we are on track to unlock the mysteries of our genes and how they relate to our lives and our health, and I am proud to be a part of unlocking that mystery for future generations of Veterans.

One in a million: Adib Sabree

The Army drafted Adib Sabree in 1969. He served as a Combat Infantryman in Vietnam in 1970 and received the Purple Heart and two Bronze Stars for Valor. While at the VA Medical Center in Washington, D.C. for an appointment, Adib saw a Million Veteran Program poster. He immediately decided to learn more and get involved.

"From the beginning, I was impressed that MVP wanted Veterans to help shape what VA health care might one day look like—whether it's for us or the men and women who come after us. I believe that participation in MVP is a way for me and other Veterans to have meaningful input into future health practices that directly—and uniquely—impact us as Veterans.

"While each of us is different, what connects Veterans to each other is what we experienced while serving in the military, and the impact it has on us after that service."

I appreciate MVP's commitment to include a varied group of Veterans. I spent a great deal of my career facilitating workshops on topics such as diversity in the workplace—most recently at NASA Headquarters where I led an effort by the Office of Personnel Management (OPM) to establish a position for diversity and inclusion within the Civil Service. Knowing that Veterans are a diverse group of people, I am pleased to know that MVP is making a strong effort to ensure participants in the program reflect who Veterans really are.

MVP invites all Veterans to participate in the program, regardless of age, education level, race/ethnicity, gender, health status, or where they live. It's this kind of participation that gives credibility to the program and adds validity to the data and information outputs.

While each of us is different, what connects Veterans to each other is what we experienced while serving in the military, and the impact it has on us after that service. I'm especially interested in what MVP can discover about PTSD, as I receive PTSD treatment at my local VA.

We need to know and understand a lot more about how PTSD affects Veterans and other trauma survivors. I hope MVP research can one day answer questions like: Is PTSD genetic? Is it related to your lifestyle, or military service, or where and how you were raised? I hope that my participation in MVP will contribute to doctors learning more about PTSD, so they can better treat other Veterans.

I'm honored to be a part of MVP, and to help improve the future of health care for the Veterans who will come after me.

A year of discoveries, a lifetime of impact

Since MVP's inception, researchers have used its large, varied collection of information about genes and health to make discoveries around numerous conditions that impact Veterans like you. MVP data is currently being studied by more than 540 researchers in more than 40 research projects that aim to uncover genetic links to health conditions. More than 150 scientific journals have published findings based on MVP data—more than 40 of those just this year. The number of new discoveries is accelerating, moving us closer to a future when we use what we've learned to improve the health and lives of Veterans. Below are some highlights from our recent work.

Does height impact your health?

Are you taller than average? If so, you may have a lower risk of developing high blood pressure and high cholesterol than your shorter friends. But the news isn't all good—tall people may be at higher risk for nerve damage and some types of skin and bone infections.

MVP researchers Dr. Themistocles (Tim) Assimes and Dr. Sridharan Raghavan analyzed the health and genetic data of more than 280,000 Veterans enrolled in MVP, exploring the association between height and more than 1,000 health conditions represented in the electronic health records of MVP participants.

They found more than 100 conditions for which height might be a risk factor or a protective factor.

Does being tall protect me from some diseases?

Height seems to protect against cardiovascular-related health conditions. For example, researchers found a link between height and lower risk of coronary heart disease. Taller people are also at lower risk of developing high blood pressure and high cholesterol.

If I'm tall, what conditions am I more at risk for?

People who are taller are more likely than shorter people to develop atrial fibrillation and varicose veins. They are also more likely to develop peripheral neuropathy—damage to the nerves outside the brain and spinal cord, particularly in the limbs. And tall people are more prone to developing skin and bone infections, such as leg and foot ulcers.

What does this mean for Veterans?

Looking forward, researchers hope to use these findings to identify individuals at risk for specific conditions—and then translate these findings to the clinic, where medical providers can offer screenings and preventive measures for those conditions. Dr. Assimes said,

"What we hope to do in the future is take findings like ours and use them to deliver precision medical care to Veterans, who are the men and women making this research possible."

Dr. Themistocles (Tim) Assimes is an MVP scientist at the VA Palo Alto Healthcare System.

Dr. Sridharan Raghavan is an MVP scientist at the VA Eastern Colorado Healthcare System.

MVP data sheds new light on PTSD

As a Veteran, you've probably heard of posttraumatic stress disorder (PTSD). It is a mental health problem that some people develop after experiencing or witnessing a traumatic event. Although there are still many questions surrounding PTSD, researchers have made great strides in studying it over the past ten years.

"Today, researchers know a lot more about PTSD. And thanks to Veterans enrolled in MVP, health care providers may soon know who is at higher risk and how to treat it."

When MVP researchers Dr. Murray Stein and Dr. Joel Gelernter began their careers in psychiatry in the 1980s, many doctors didn't believe that posttraumatic stress disorder (PTSD)—experienced by thousands of Veterans—really existed.

Today, researchers know a lot more about PTSD. And thanks to Veterans enrolled in MVP, health care providers may soon know who is at higher risk and how to treat it.

New knowledge about how and why PTSD develops

Anyone exposed to severe trauma can develop PTSD, but it is more likely that someone will develop it after experiencing specific types of trauma—such as sexual assault or combat. Over the past decade, MVP researchers have discovered some of the gene variants that can influence risk for PTSD. They've also learned that the likelihood of developing PTSD is partly heritable, meaning your parents may have passed on some of the risk to you through gene variants, or you may pass increased—or decreased—genetic risk along to your own children.

Knowing more about the genes that influence risk for a disease allows researchers to better understand the relationship of genetics and environment (or nature and nurture) on complex conditions like PTSD. It also helps researchers begin to understand how and why conditions like PTSD develop.

The main symptoms of PTSD—re-experiencing the traumatic event, hyper-arousal, having more negative thoughts and feelings than before the event, and avoidance—can seem to be very different. But when researchers study them genetically, they can see that they are closely related. Researchers have also found that these symptoms relate to specific regions of the brain that are involved with PTSD.

They hope to soon be able to help drug researchers identify new treatments to address symptoms—or even prevent symptoms from happening. Further studies of the genetics of PTSD will help determine if there are different types of PTSD that require different treatments. Researchers may also be able to tell if different medications are useful at various stages of someone's treatment journey.

How do I know if I have genes for PTSD?

There are many genes involved in risk for PTSD—hundreds if not thousands. And each gene variant has only a very small effect in increasing or decreasing risk. But it may be possible in the future to screen for a panel of gene variants that cumulatively predict the likelihood of someone developing PTSD (e.g., after combat, or after a traumatic accident) in a way that is helpful to medical providers.

"Without MVP, the medical community would know much less about PTSD than we do today. The Veterans who have chosen to enroll in MVP are helping not only Veterans, but people with PTSD worldwide."

– Dr. Joel Gelernter is Director of the Laboratory of Psychiatric Genetics at VA Connecticut Healthcare System. Dr. Murray Stein is Staff Psychiatrist at VA San Diego Healthcare System.

How your food choices could impact your health

When you fill out MVP's Lifestyle Survey, you answer questions about several different aspects of your life, including what foods you eat. This information, along with your blood sample and secure access to health records, offers MVP researchers a full picture of your health in a way never seen before by other researchers.

- Eating any kind of **yogurt** is good for your heart health. Eating yogurt is associated with higher levels of good (HDL) cholesterol
- Eating **nuts**—but not peanut butter—is associated with a lower risk of stroke, heart disease, and death from cardiovascular disease
- Those who eat five or more cups of **potatoes** each week are at higher risk for coronary artery disease
- People who consume high levels of **sodium** and low levels of **potassium** are at higher risk of coronary heart disease
- Adhering to a **healthy plant-based** diet is associated with a lower risk of death from any cause, including foods like: whole grains fruits, vegetables, nuts, legumes, vegetable oils, tea/coffee
- Adhering to an **unhealthy plant-based** diet is associated with a higher risk of dying from any cause, including foods like: fruit juice, sugar-sweetened beverages, refined grains, potatoes, sweets/desserts

"By highlighting the benefits of certain diets and foods—and the risks associated with others—we are giving both Veterans and their health care providers tools to help prevent or manage chronic illness."

– Dr. Luc Djousse, an MVP scientist at the VA Boston Healthcare System.

MVP's hope is that the research findings made possible by you, MVP Veterans, will one day help doctors develop individualized dietary recommendations that will be effective in preventing chronic diseases.

Gene variants reveal risks for kidney injury with COVID-19

As the global coronavirus pandemic surged, researchers worked to understand why more people of African ancestry than other ancestries developed acute kidney injury from COVID-19—and died at higher rates. To find answers, a team led by MVP scientist Dr. Adriana Hung studied the genetic data of 990 Veterans of African ancestry who were hospitalized with COVID-19.

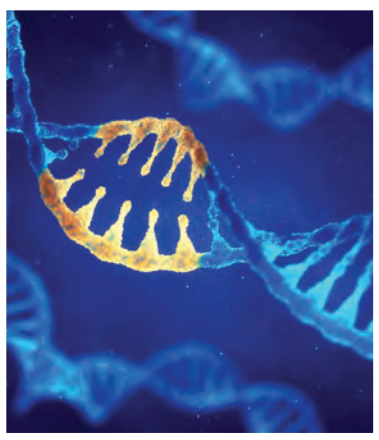
What they found was surprising.

Patients who had two copies of the APOL1 gene variants G1 and G2—which developed in the body by positive selection to fight African Trypanosomiasis—had a higher risk of acute kidney injury and death from COVID-19.

African Trypanosomiasis, also known as "sleeping sickness," is a lethal disease caused by microscopic parasites transmitted by the tsetse fly, which is found only in sub-Saharan Africa. People with one or two of the G1 and G2 variants are resistant to developing sleeping sickness. But people who have two variants are also at risk of developing chronic kidney disease. Dr. Hung's study showed that having two variants also increased the risk of acute kidney disease and/or death when patients experience illnesses or conditions that have an extensive inflammatory response like COVID-19.

In fact, when Veterans hospitalized with COVID had these two variants, their odds of acute kidney disease and death doubled over those who had no variants.

How would I know if I carry two copies of these gene variants?



These variants are rare. Most studies have shown that only 12–14% of the U.S. population with African ancestry have two copies of the gene and are considered a high-risk group.

If you have African ancestry—even if you're from the Caribbean or South America—you have a higher likelihood of having these gene variants.

People with a family history of kidney disease—including family members who developed kidney disease in their 30s or 40s, or who have been on dialysis—may have these gene variants.

If these risk factors apply to you, you should consider seeing a nephrologist and asking for genetic testing. You should also have genetic screening done if you are considering donating a kidney to a family member.

How can I find genetic testing?

If you feel you may be at risk, ask your doctor for genetic testing to screen for these variants. Most kidney donor centers will ask you if you want to be tested before agreeing to donate a kidney.

What should I do if I test positive for these variants, or if I suspect I carry these variants?

It is important to know that, even if you have two copies of the genetic variant, you may not develop kidney disease. But the way your body handles some illnesses may put you at higher risk.

The best way to keep your kidneys healthy is to keep your blood pressure under control. Work with your doctor to monitor your kidney function for early signs of kidney disease, like protein in urine.

Are there personalized treatments for Veterans with these variants who develop COVID?

While current recommendations include blood pressure control and close monitoring of early kidney disease, doctors hope that targeted treatments will be available sometime in the near future.

Dr. Hung said, "We were able to make these important discoveries about risk factors for severe COVID because of the large number of people with African ancestry enrolled in MVP and the ability of MVP to generate a fast response during an acute epidemic. We hope that our findings will soon lead to personalized treatments for Veterans with these gene variants who develop COVID-19 or other illnesses and infections."

Dr. Adriana Hung is a local principal investigator for MVP.

Research supports VA's most critical mission: reducing Veteran suicides

Preventing Veteran suicide is the highest clinical priority of the Department of Veterans Affairs. For over a decade, researchers have worked to better understand how to predict suicide attempts and stop attempts before they happen.

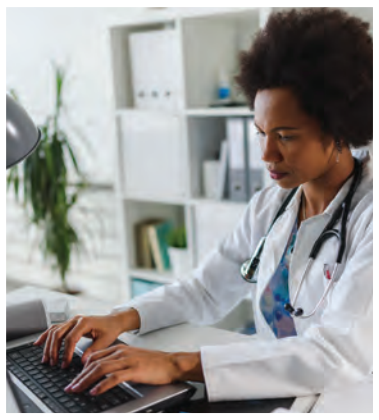
In the past, genetic studies of suicide risk neglected to look at race and ethnicity. But MVP has changed that.

Because researchers can study Veterans' electronic health records and the responses they provide to MVP's lifestyle survey as well as genetic information, they are better able to understand suicide risk and how it is tied to genetics.

In a recent study, researchers identified genetic influences for suicide attempts that exist across all ancestries—as well as influences that are specific to African Americans, Asian Americans and Hispanic Americans. The researchers also learned:

- Veterans who attempted suicide reported clinically higher sleep problems than Veterans who did not attempt suicide. The more severe the sleep disturbances, the higher the rate of suicide attempts.
- Those with lower concentrations of the hormone oxytocin—sometimes called 'the love hormone' for its associations with bonding and trust—had higher suicidal intent and attempts.
- Certain negative life events may increase risk of a suicide attempt, like a change in marital status, housing, job or food instability, and a lack of social connection, as can access to a lethal weapon.

Using new knowledge to improve REACH VET



VA's REACH VET, introduced in 2017, analyzes data from Veterans' health records to identify those at the highest risk for suicide in the subsequent month. It then alerts VA providers to deliver pre-emptive care and support to Veterans at risk. REACH VET has resulted in fewer mental health admissions, emergency department visits, and suicide attempts.

Now, MVP is leveraging the supercomputing capacity of the Department of Energy (DOE) in a partnership to enhance REACH VET by improving the predictions of suicide attempts in Veterans' medical records. They also hope to develop specific treatment interventions to address high-risk patients.

Dr. Jean Beckham said, "VA's goal is to be able to identify Veterans who are at the highest risk for suicide and put forward intensive and effective interventions to help them and prevent them from committing suicide."

"The findings from this study will truly expedite scientific discovery, allowing the medical community to move more quickly towards using our findings to treat patients."

– Dr. Jean Beckham is a Senior Research Career Scientist at VA Clinical Science Research and Development (CSR&D)

An impactful GWAS by PheWAS

When you enrolled in MVP, you gave a vial of blood that granted researchers secure access to your DNA. That DNA, along with secure access to electronic health records, is advancing understanding of the relationship between genes and health. Soon, MVP will release non-identifiable results from a groundbreaking, recently completed Genome-Wide Association Study by Phenome-Wide Association Study (GWAS by PheWAS).

But what does this actually mean, and why is it so important? First, some basics about genomics.

DNA: A blueprint for our bodies

Cells in your body contain all of the instructions for how your body will look and behave. Those instructions are known as deoxyribonucleic acid – DNA for short. They are encoded in your genetic material.

You can think of DNA as a blueprint used to create a new house. Blueprints contain all the information about what a house will look like and how it will function.

In the same way, your DNA contains all the instructions needed to create your body. Small sections of your DNA, called genes, indicate what color hair, skin and eyes you have, and your predispositions to things like athletic ability and certain illnesses and conditions.

Your genome is the total of all of the DNA in your body.

Types of genomic studies

The genetic differences among humans are very small. You are 99.999 percent identical in your genetic makeup to every other human being. The differences in the remaining .001 percent are what researchers study to find associations between genes and health conditions.

In a Genome-Wide Association Study, or GWAS, scientists examine the .001 percent of the genome that differs among people. They examine a single disease or trait (known as a phenotype) and look for variants in DNA to see if those variants are associated with the disease or trait.

A Phenome-Wide Association Study, or PHeWAS, does the reverse. Those studies begin with a single genetic variant and analyze many phenotypes (diseases or traits) to see if they associate with that genetic difference.

In a GWAS by PheWAS, scientists analyze the association of a large number of genetic variants with a large number of diseases or traits. This type of analysis requires supercomputers.

MVP's groundbreaking GWAS by PheWAS

In late fall, MVP will release findings from one of the world's largest GWAS by PheWAS studies, the result of analyzing the association of millions of genetic variants with nearly 2,000 known disease codes. Disease codes are a combination of letters and numbers representing certain health conditions in the medical record.

The result? Billions of associations between genetic variants and diseases that will be enormously valuable to scientists who study the relationship between genes and common diseases and conditions.

MVP Program Director Dr. Sumitra Muralidhar said, "The findings from this study will truly expedite scientific discovery, allowing the medical community to move more quickly towards using our findings to treat patients."

MVP Principal Investigator Mike Gaziano added, "The Veterans enrolled in MVP have given researchers access to the richest health data that exists. With this GWAS by PheWAS, we are making available an enormous bank of information—with no identifiable or individual data—that only exists because of Veterans, who are giving a gift of information to the world."

MVP launches MIND

MVP launched a new initiative this year called Measures Investigating Neuropsychiatric Disorders (MIND) to examine how genes, lifestyle, and military exposures affect mental health and substance use.

Mental health disorders are common in the United States, according to the National Institute of Mental Health (NIMH), with nearly one in five adults experiencing mental illness. In 2021, more than 1.7 million Veterans using VA health care had a confirmed mental illness, reflecting nearly 30% of all Veterans who use VHA services.

MVP aims to enroll at least 50,000 Veterans with mental health and substance use conditions in MIND in order to help researchers and clinicians better understand and potentially improve diagnosis, prevention, and treatment of these conditions.

In April 2022, MIND began enrollment at VA Medical Centers in San Diego and Philadelphia. In the coming year, more MIND enrollment sites will open across the country. Want to learn more? More information about MIND can be found on the MIND fact sheet at: www.research.va.gov/pubs/docs/va_factsheets/MVP-MIND.pdf

Veterans accelerate access to personalized health care

- Because of the Veterans enrolled in MVP, the medical community is moving closer to being able to deliver personalized health care. When health care is personalized, people are treated for their specific symptoms—ensuring that the right treatment gets to the right person at the right time.
- Thank you for helping improve the future of health care for Veterans and all people.