



RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs

Photo courtesy of Southern Nevada VA



VA pharmacist donates blood plasma

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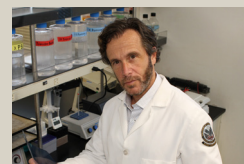
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Prolonged exposure therapy reduces trauma-related guilt

Prolonged exposure therapy for PTSD and substance use disorder reduces feelings of guilt, according to a VA study. PTSD is often accompanied by trauma-related guilt, which is usually related to negative views of one's actions or inactions during a traumatic event. Researchers assessed guilt in more than 100 Veterans with both PTSD and SUD. Half received prolonged exposure therapy designed to treat both conditions together. The rest received therapy focusing on coping skills. The prolonged exposure group reported significantly lower guilt over time, compared to the other group. The results show that exposure-based treatment for both PTSD and SUD is more effective at reducing guilt than non-exposure treatment, conclude the researchers. (*Journal of Traumatic Stress*, June 10, 2020)




Photo: ©iStock/kieferpix

Cover photo: Dr. Parisa Khan is a clinical pharmacist who specializes in infectious diseases at the VA Southern Nevada Healthcare System. As a recovered COVID-19 patient, she donated her convalescent plasma to help others struggling with the illness. *Read more on page 6.*

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U.S. Department
of Veterans Affairs

Psychotic symptoms linked to solitary confinement in incarcerated individuals

Incarcerated people with psychotic symptoms are more likely to be placed in solitary confinement, found a Maryland VA researcher and colleague. People with psychiatric disorders are disproportionately represented in the U.S. prison system. The researchers surveyed 176 previously incarcerated people. Those with a schizophrenia diagnosis or psychotic symptoms were more than twice as likely to have been placed in solitary confinement, compared to those without psychiatric conditions. More research is needed to determine whether prisoners are placed in solitary confinement based solely on behaviors related to psychiatric illness, according to the researchers. Such action could violate the Americans with Disabilities Act, they say. (*Psychiatry Research*, May 21, 2020)



Photo: ©iStock/Rattankun Thongbun

Secure messaging from clinicians improves diabetes patient self-management

Diabetes patients who received online messaging support from their clinicians better self-managed their care, in a study by researchers at the Edith Nourse Rogers Memorial Veterans Hospital in Massachusetts. Secure messaging over the internet allows doctors and patients to communicate in between visits. The study included more than 400 Veterans with diabetes who used VA's My HealtheVet online patient portal. Patients who received at least one proactive message

about their care were more likely to engage in better diabetes self-management, compared to patients who were not messaged. They also reported a higher sense of self-confidence. Proactive communication from clinical teams can foster a patient's sense of autonomy and encourage better self-care, conclude the researchers. (*Journal of General Internal Medicine*, May 21, 2020)

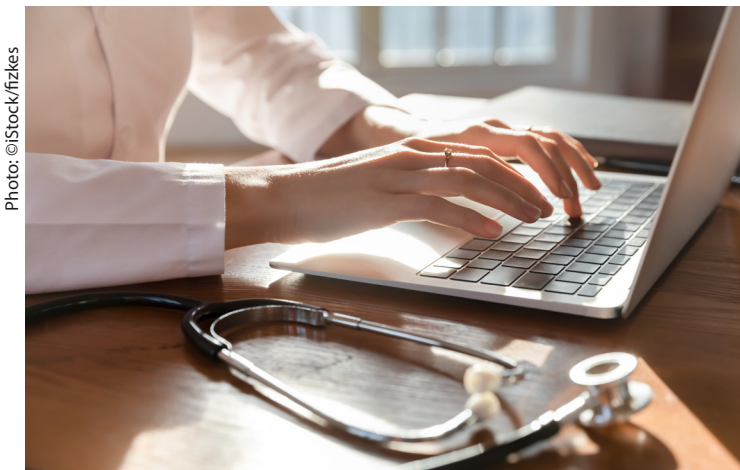


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Photo: ©Stock/Halishadow



Blood thinner linked to higher fracture risk

Atrial fibrillation patients taking the blood thinner warfarin had a higher risk of fractures than patients taking other blood-thinning drugs, in a study by Minneapolis VA researchers and colleagues. Atrial fibrillation is an irregular heart rate that causes poor blood flow. Patients with the condition are often prescribed blood thinners (anticoagulants) to prevent stroke and other problems. Some evidence has shown that the common anticoagulant warfarin may be linked to poor bone health. The researchers looked at data on nearly 170,000 patients with

atrial fibrillation. They found that patients taking warfarin were more likely to have bone fractures, compared to those taking newer oral anticoagulants. This difference was especially high in patients with osteoporosis. The drug apixaban had the lowest fracture risk. The findings suggest that caution should be used when prescribing warfarin to patients with a high risk of fracture, say the researchers. (*JAMA Internal Medicine*, February 2020)

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PTSD suppresses the brain's immune system

A study by VA Connecticut and Yale University researchers showed how PTSD is linked with neuroimmune suppression. The researchers compared brain scans of 23 patients with PTSD and 26 without. They found that patients with lower levels of a protein TSPO in the prefrontal-limbic part of the brain had worse PTSD symptom severity. This protein is a biomarker for activation of microglial cells, the brain's first form of immune defense. Those with PTSD had significantly lower TSPO levels than those without PTSD. Those with lower TSPO concentration also

had higher levels of C-reactive protein, a protein that is increased when inflammation is present in the body. The findings suggest that PTSD hinders the function of the immune system in the brain, according to the researchers. (*Nature Communications*, May 12, 2020)



Veterans from lower ranks less likely to use mental health care

Veterans from lower ranks were less likely to use VA mental health care, found a VA study. Researchers analyzed data on almost 10,000 post-9/11 Veterans. Of those, 34% had at least one mental health condition. Veterans from junior enlisted ranks were significantly less likely than those from higher ranks to use mental health programs and services. Use of these services was similar between male and female Veterans. The study also showed more similarities than differences in mental health care use between Veterans of different racial/ethnic

backgrounds. Veterans exposed to combat, with a medical discharge, or with ongoing medical conditions were much more likely to use VA health care services. The results highlight the need to encourage Veterans from lower ranks to seek mental health services, say the researchers. (*Psychiatric Services*, May 12, 2020)



PTSD and alcohol use disorder feed into each other

PTSD and alcohol use disorder can feed into one another and make both worse, according to a VA San Diego study. PTSD and alcohol use disorder often occur together. Researchers studied symptoms in 107 Veterans being treated for PTSD and alcohol use disorder. They found that greater PTSD symptom severity was linked with greater future alcohol use. Likewise, greater alcohol use was linked with greater future PTSD symptom severity. The effect of PTSD on drinking was higher than the other way around. The

findings support the idea of mutual maintenance between PTSD and alcohol use. Integrated treatments for both PTSD and alcohol use may be better than expecting patients to reduce alcohol use before beginning trauma-focused treatment, say the researchers. (*Psychology of Addictive Behavior*, Feb. 27, 2020)



Dr. Jason Dazely, an infectious disease specialist at the Southern Nevada VA, checks in on Dr. Parisa Khan as she prepares to donate her plasma.

VA pharmacist donates blood plasma as part of efforts to find treatment for COVID-19

Dr. Parisa Khan, a VA pharmacist and recovered COVID-19 patient, donated her convalescent plasma so it could be used as an investigational treatment for another patient struggling with the illness, as part of a nationwide program.

Dr. Parisa Khan is a clinical pharmacist who specializes in infectious diseases at the VA Southern Nevada Healthcare System. As a recovered COVID-19 patient, she's a candidate to help others who are experiencing symptoms from the disease.

Recently, Khan donated her convalescent plasma at the Southern Nevada VA. People who have recovered from the disease have immune-boosting antibodies in their plasma—convalescent plasma—that are being used as an experimental treatment for critically ill COVID-19 patients.

The U.S. Food and Drug Administration (FDA) has regulated COVID-19 convalescent plasma as an investigational COVID-19 treatment. It's a way to treat critically ill patients who have few options left.

Khan followed the news about convalescent plasma antibody treatments during her 41-day quarantine, when she was mostly asymptomatic. She was eager to be a donor.

'Message of hope and gratitude'

"I'm more than happy to do this," she said while donating her plasma at a blood bank in Las Vegas. "I consider myself so fortunate to be able to recover from the disease. The best news possible is that my experience can hopefully help other people.

"I want to be a message of hope and gratitude for our Veterans," she added. "If my plasma can help Veterans who are coming to our hospital, that would be great. I want more employees who have recovered and can come back to work to take something from this story and think about donating themselves."

Khan's donation was part of VA's most far-reaching effort thus far to study potential treatments for COVID-19. The agency is cooperating with the Mayo Clinic, a renowned U.S.-based medical center, on an expanded access study to evaluate convalescent plasma therapy for COVID-19. The FDA has approved an expanded access protocol for convalescent plasma transfusions. Expanded access is a way for a patient with a life-threatening or otherwise serious condition to gain access to an investigational medical product for treatment outside of a clinical trial when no comparable or satisfactory therapies are available.

"I want to be a message of hope and gratitude for our Veterans."

More than 80 VA facilities in Mayo Clinic program

As of May 20, more than 80 VA medical centers had signed up for the program so their patients could benefit from convalescent plasma transfusions. More than 180 units of convalescent plasma had been transfused to 158 Veterans fighting the disease. Typically, only one unit is given to a Veteran, but patients can receive a maximum of two.

Convalescent plasma is the liquid part of blood that contains antibodies. The body generates these blood proteins to fight against specific infections, such as COVID-19. The plasma must be typed as if someone were giving a transfusion of blood with red or white cells in it. Plasma by itself doesn't contain red or white cells.



(Photo courtesy of Southern Nevada VA)

Dr. Parisa Khan is a recovered COVID-19 patient who donated her convalescent plasma to help others struggling with the illness.

Antibodies can directly attack the virus that causes COVID-19, as well as cells that the virus has entered. Thus, it's believed that COVID-19 patients may improve faster if they receive plasma from those who have recovered from the disease.

Plasma transfusions are generally safe and well-tolerated by most patients. But side effects have been reported, including mild fever, allergic and transfusion reactions, acute lung injury, and bronchospasm, a sudden constriction of the muscles in the walls of the bronchioles. There is also a rare risk of infectious disease transmission from donated plasma.

Veterans who have recovered from COVID-19 encouraged to donate blood

VA's Office of Research and Development (ORD) played a key role in enabling VA medical centers to participate in the Mayo Clinic program. ORD developed an infrastructure to support any VA facility, including those without research programs, that wants to take part. VA clinicians at those facilities can request access to the investigational convalescent plasma treatment for their patients. The VA medical centers are working under the Mayo Clinic's protocol for convalescent plasma.



The plasma is being collected at American Association of Blood Bank (AABB) locations. VA is not collecting the plasma.

It is unknown how many Veterans will donate plasma or how many will require convalescent plasma, according to Dr. Molly Klote, a senior official in ORD.

VA involved in series of COVID-19 studies

In addition to the Mayo Clinic program, VA researchers are developing or joining clinical trials that will offer even more treatment opportunities for Veterans with COVID-19. Many trials are in the planning stage, and some have already enrolled volunteer participants.

- VA medical centers in Denver, New Orleans, Atlanta, and Palo Alto have joined a clinical trial led by the National Institute of Allergy and Infectious

Diseases that is assessing whether the antiviral remdesivir and additional drugs are effective against COVID-19.

- In Atlanta, VA is working with Regeneron Pharmaceuticals to assess whether sarilumab, a drug normally taken to treat rheumatoid arthritis, may be an effective treatment.
- VA has launched a study in parallel with the Department of Defense to better understand the epidemiology and clinical characteristics of COVID-19. That study is being coordinated by the VA Puget Sound Health Care System.
- In a randomized controlled trial, VA scientists will compare the effectiveness of the prostate cancer drug degarelix (trade name Firmagon) to placebo for improving the clinical outcomes of nearly 200 male Veterans who have been hospitalized with COVID-19.

The trials demonstrate the ability of VA—America’s largest integrated health care network, with a significant capacity for research—to work with government and industry partners on a wide range of solutions during the COVID-19 national health crisis.

“We’re in a position to do things that no one else in the world can do to improve the health of our Veterans, the nation, and the world,” VA Secretary Robert Wilkie said. “VA is bringing all of its expertise to bear during this crisis, and now we’re leading the way on research into pharmaceuticals and treatments that could improve the lives of thousands of patients.” ★

Can community engagement help Veterans at high risk of suicide?

Social isolation is often associated with suicidal behaviors, and feelings of loneliness can also increase suicidal thoughts in some people. The more people feel disconnected from their friends, peers, and colleagues, the more isolated they become.

One antidote for social isolation is social connectedness—people coming together and interacting. But there's been little research on suicide prevention programs that target social connectedness.

With that in mind, Dr. Jason Chen of the VA Portland Health Care System is leading a study that aims to establish a stronger sense of social connectedness for Veterans at high risk of suicide by increasing their participation in community activities.

Chen and his team have been identifying the community engagement needs and preferences of Veterans who were hospitalized and evaluated for psychiatric conditions. The participants were interviewed within a week of discharging from an inpatient psychiatric unit. Veterans analyzed for psychiatric conditions, such as PTSD, are at much greater risk than other cohorts of taking their own lives within three months after leaving the hospital.

The researchers are also gathering opinions from VA staff and community representatives on Veteran community engagement following psychiatric hospitalization.

Chen and his colleagues plan to eventually create clinical toolkits for VA and community figures that focus on increasing social connectedness for Veterans in this vulnerable population.

VA considers suicide prevention its top clinical priority. The most updated analysis of Veteran suicide rates, issued in 2016, notes that Veterans accounted for 18% of all deaths from suicide among U.S. adults, compared with 22% in 2010.

Chen, who is also an assistant professor at Oregon Health & Science University, spoke to VA Research Currents.



Photo: ©iStock/Vasyi Dolmatov

Playing music, taking part in tai chi classes, and going fishing with others are the types of activities that boost social connectedness, says Dr. Jason Chen.

VA Research Currents: What inspired you to pursue this study?

Chen: When working with Veterans, I noticed that many didn't have social connections. We know that feeling connected to others can be a form of protection against suicide. So I thought to myself if the Veterans I work with don't have many connections, perhaps we could help them create new connections through community activities. My hope is that by helping Veterans increase their engagement in community activities, they'll feel a stronger sense of social connection that will, in turn, decrease their level of suicidal thoughts.

One thing I've found in my research is that we don't really know why Veterans aren't connecting with others. So the first part of our study was to learn more from Veterans about what gets in the way of connecting. We interviewed 30 Veterans to learn about their past experiences connecting to the community and their thoughts about what would get in the way in the future. Our Veteran sample varied in age from their 20s through their 70s. The average age was 48. We wanted to understand a broad range of experiences across different eras of conflict and generations.

Read more at www.research.va.gov/currents ★



World War II Veteran and current MVP participant Rosalie Liotta poses with Kaitlyn Nelsen, MVP research coordinator at the New Mexico VA Health Care System.

Women Veterans Day

Women Veterans Day, celebrated recently in June, was an appropriate time to recognize the role of women in VA's Million Veteran Program. More than 830,000 Vets are now enrolled in MVP, of which 80,000 are women.

Rosalie Liotta and her caregiver, Cathy Adkins, are both Veterans. Liotta enlisted in WAVES, the women's branch of the U.S. Naval Reserve, during World War II. Adkins served in the U.S. Air Force from 1980 to 1995. In one of her assignments, she worked as an aerospace ground equipment maintenance technician during the Persian Gulf War.

That's not the only commonality between the two. They're both enrolled in VA's Million Veteran Program (MVP), which is aimed at learning how genes, lifestyle, and military exposures affect the health of former service members. The two are proud to participate in the program because, just like when they were in the military, they feel they're making a sincere effort to give back to their country.

"MVP is fabulous," Adkins says. "I'm very excited about it and glad that VA is allowing me to participate. I really appreciate what VA is doing for all of our Veterans."

Women underrepresented in medical, biological research

Women Veterans Day, June 12, is an appropriate time to recognize the contributions of female Veterans like Liotta and Adkins in the Million Veteran Program. More than 830,000 former service members are enrolled in MVP, of which 80,000 are women. Their genetic information and other health data are being used to study diseases, such as breast cancer, and to research gender differences in other common conditions, including depression and heart disease. The goal is to provide better, more personalized ways of identifying and treating diseases based upon a person's characteristics.

Historically, women have been underrepresented in medical and biological research, leading to knowledge gaps that can result in misdiagnoses and drugs that may affect men and women differently. Although these trends have been changing in recent years, the status of women as minorities in the Veteran population can make it harder for VA researchers to recruit enough women to get valid study results. Thus, by volunteering for MVP, female Vets can make a big difference for other Veterans of today and the future.

Number of female Veterans in program on the rise

Since MVP Online was launched nearly a year ago, the number of female Veterans joining the Million Veteran Program has increased because of the ease of enrolling online. This marks an important development to ensure their proper representation in the program. When doing genetic research, it's also key to have women from different demographic backgrounds. A person who is African-American, for example, may respond differently to a medication than a person who is white.

Dozens of studies have been published using MVP data, including a 2019 paper that looked at health characteristics among women Veterans. The researchers found that compared with men, women were more likely to experience migraines, arthritis, gastrointestinal issues, and mental health conditions. Women reported

less frequent exercise and greater use of VA for their health care needs, including the pharmacy. Depression was one of the most commonly reported conditions in women Veterans. These findings are important to inform VA screening and treatment policies, which may include easing the process for women to receive care for the conditions that matter most to them, including those involving mental health.

'Most wonderful time of my life'

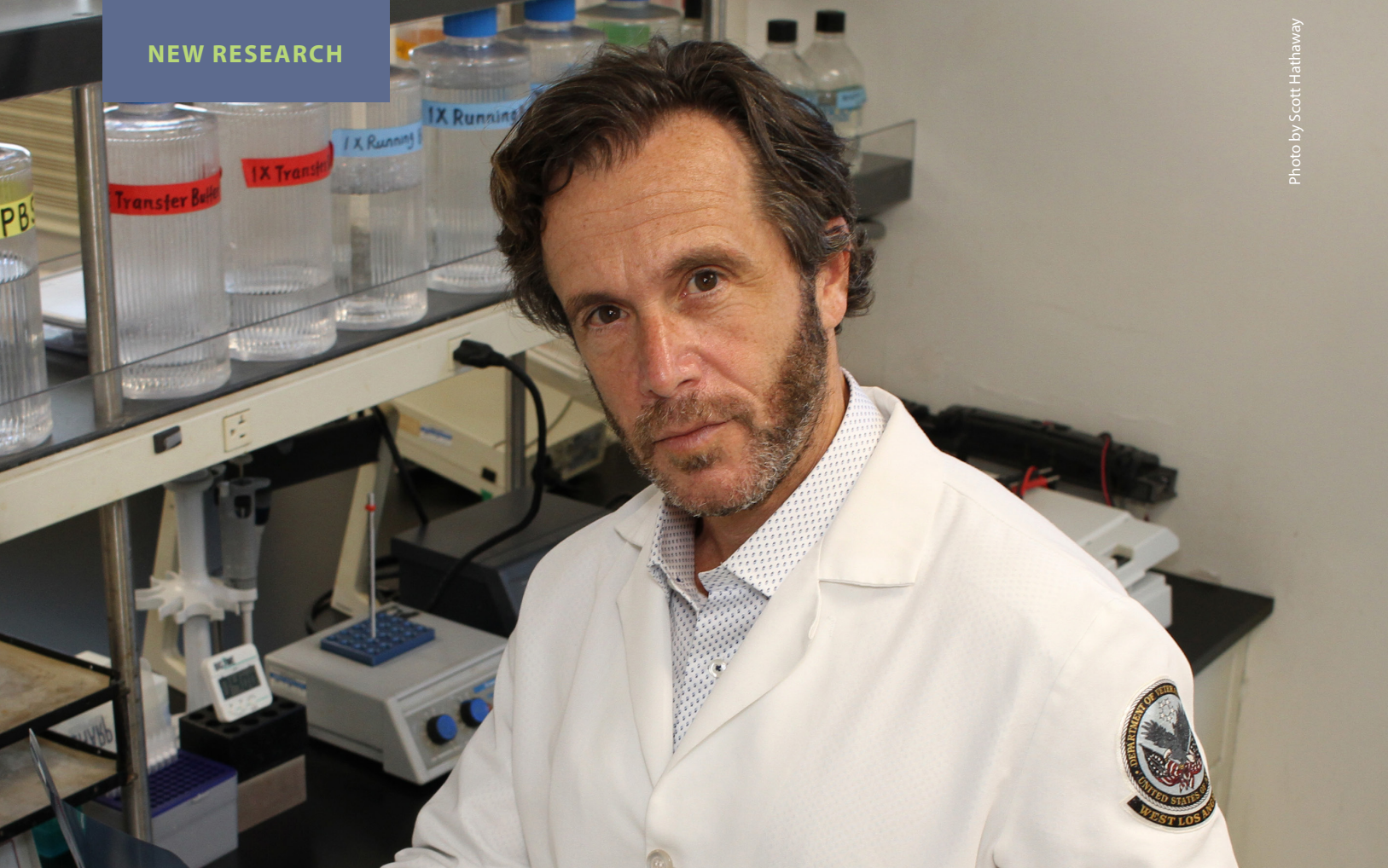
In terms of breast cancer, VA researchers are using MVP data to study genetic and clinical markers on the risk of this disease and to develop more personalized screening strategies for women, rather than relying on age alone. They are also looking at how military experience and race might affect breast cancer risk. MVP provides a way to look at a more diverse population of women who served. Most current screening plans are based on studies of civilian, white women.

Rosalie Liotta and Cathy Adkins both use the New Mexico VA Health Care System in Albuquerque. Liotta thanks VA for taking such good care of her, nearly 80 years after she volunteered for the WAVES program. Stationed in San Francisco, she was assigned to type up orders from admirals. She wanted to do more but knew her duty as a yeoman was just as significant as being on a battleship.

"MVP is fabulous. I really appreciate what VA is doing for all of our Veterans."

"That was the most productive and wonderful time of my life," Liotta says. "I felt I was worthwhile and that my life was worthwhile ... that I was accomplishing something for my country. My parents had to sign for me because I was 20 years old when I went into the service. I knew I was doing something important for my country."

To learn more about participating in MVP, visit [MVP Online](#). ★



Dr. Matthew Rettig, chief of hematology and oncology at the VA Greater Los Angeles Health Care System and one of VA's top prostate cancer researchers, is leading a clinical trial to investigate a prostate cancer drug as a potential treatment for male Veterans with COVID-19.

VA scientists race to determine effectiveness of prostate cancer drug in treating COVID-19 patients

Nearly 200 Veterans are expected to take part in a study on the drug degarelix for treating male Veterans with the disease.

Dr. Matthew Rettig is one of the leading VA researchers on prostate cancer.

The chief of hematology and oncology at the VA Greater Los Angeles Health Care System, he has played a major role in some 50 clinical trials, with a focus on studying potential drugs for aggressive prostate cancer.

Until now, though, Rettig has never faced such urgency to generate evidence of how well a treatment works. He's leading a clinical trial to investigate a prostate cancer drug as a potential treatment for male Veterans with COVID-19. In a double-blind randomized controlled study, he and his colleagues are comparing the drug degarelix (trade name Firmagon) to placebo for improving the clinical outcomes of nearly 200 Veterans who have been hospitalized with COVID-19.

Degarelix is often used to treat cases of prostate cancer that metastasize. The male hormone testosterone can fuel the spread of prostate cancer. Degarelix rapidly but temporarily suppresses the body's production of testosterone, which

regulates the protein TMPRSS2. The virus that causes COVID-19, a respiratory disease, relies on TMPRSS2 to penetrate lung cells. By using degarelix, Rettig and his team believe they can reduce the production of TMPRSS2 in lung tissue and prevent the virus from entering lung cells. “Anytime we’re doing a clinical trial for advanced prostate cancer, there’s not that much of a time pressure where we’re looking at days,” he says. “This is something where the pressure to deliver in a timely fashion is very high because of the lethality of this disease and the potential for it to expand, as well as the fact that we don’t have a really good viable therapy for sick patients with COVID-19.”

"This is something where the pressure to deliver in a timely fashion is very high because of the lethality of this disease and the potential for it to expand. "

'Something that has global impact'

To Rettig, the trial could have implications far beyond VA.

“This is not about just helping people in VA,” he says. “This is something that has global impact because of the lack of treatment for COVID-19 and all of the fear and anxiety that accompanies this pandemic. So most importantly, I would like to be able to make an impact for the millions of people who are affected and are concerned about getting infected with this virus. So many people are dependent on something that may reduce the severity of COVID-19. This drug has great potential.”

Rettig designed the trial, known as HITCH, in just a few weeks. Patient enrollment began in mid-May. About two-thirds of the 200 participants are taking degarelix, with the rest assigned to placebo. He hopes to complete patient data analysis in no more than five months.

The Prostate Cancer Foundation (PCF) is not directly supporting the trial. But the VA medical centers that were chosen for the testing—West Los Angeles, Puget Sound in Washington State, and New York City (Manhattan and Brooklyn)—are in COVID-19 hot spots where there are VA-PCF Centers of Excellence. That

means an infrastructure already exists with investigators, rooms, and equipment for research that normally focuses on prostate cancer but is now targeted at a COVID-19 treatment.

Coordinators of the trial are in the process of also recruiting the VA hospitals in Chicago, Philadelphia, and the Bronx, New York.

“This is an amazing story of dedication and nimbleness in VA, which is jumping into the COVID-19 research fight during a time of national emergency, and it will be remembered as an act of patriotism for years to come,” says Dr. Jonathan Simons, president and CEO of the Prostate Cancer Foundation. “The clinical research nurses, data managers, pharmacists and everyone else on the VA-PCF teams are voluntarily ‘redeploying’ their expertise to COVID-19 TMPRSS2 anti-viral clinical trials, including the use of degarelix.”

The University of California, Los Angeles, where Rettig directs the prostate cancer program in the Institute of Urologic Oncology, is involved in the analysis of research specimens but not the clinical side of the VA trial.

Veterans in trial do not have prostate cancer

To be clear, the Veterans in the trial are not undergoing treatment for prostate cancer. They have been hospitalized only because they have contracted COVID-19. Symptoms from the disease include signs of a cold or the flu, trouble breathing, persistent chest pain or pressure, or bluish lips or face. The sickest patients who are on ventilation due to COVID-19 are not being enrolled. “We think that population is really suffering from an overactive immune response to the virus,” Rettig says. “Therefore, the therapy we’re using in the trial, which aims to reduce the virus and its entry into the human lung tissue, probably will not be relevant in patients who are the most severely ill. We’re trying to narrow this down to men who are sick enough to require treatment but not sick enough to be in the ICU.”

Continued on next page

The study is not suitable for female Veterans. Evidence exists that degarelix may have the opposite effect in the female body by increasing TMRSS2 production and thus worsening the severity of COVID-19 symptoms.

Plus, research has shown that men in the United States and other countries are much more likely to suffer severe effects from coronavirus than women.

“Male hormones and female hormones seem to have different or opposing effects for COVID-19,” Rettig explains. “We think male hormones may be driving the susceptibility and severity of COVID-19, whereas female hormones [estrogen] seem to suppress the severity of the disease.

So if we were to give the same therapy to a woman and lower female hormone levels, we might actually exacerbate COVID-19. That’s why we didn’t want to use this therapy with women.”

Italian-based study supports researcher’s hypothesis

The HITCH trial comes on the heels of an Italian-based observational study that showed men with prostate cancer who were being treated with drugs that suppress male hormones had much better COVID-19 outcomes. The study suggested that men with prostate cancer who were taking ADT were four times less likely to be infected with the coronavirus than men who were not on ADT and five times less likely to die.

The researchers looked at more than 9,000 patients with confirmed COVID-19 in the Veneto region of Italy. They used data on all cancer patients in the region for comparison.

Among all prostate cancer patients, only four out of more than 5,200 men on ADT developed COVID-19 infection. None of them died. Among more than 37,000 men with prostate cancer who were not receiving ADT, 114 developed COVID-19 and 18 died.

Degarelix was one of the hormone suppression drugs the patients used, along with lupron (trade name Leuprolide). Those medications all have the same effect when used on chronically ill people, Rettig notes.

Rettig says the findings from the study support his belief that degarelix may be effective in treating COVID-19. Degarelix was chosen over other drugs for the HITCH trial because it’s the only one that rapidly drops male hormone levels, he notes.

“On average, hormone levels drop about 90% in 24 hours with degarelix,” Rettig says, “whereas, with all of the other ADT drugs, it can take a few weeks to reduce testosterone levels. We don’t have

the luxury of time when we’re talking about sick COVID patients who are hospitalized. So we chose degarelix. It works rapidly, and it’s temporary, and the effects on testosterone levels, as well as the side effects, resolve in just a few weeks. Most if not all of the side effects of degarelix are attributable to its long-term use for prostate cancer.”

Independent of the clinical trial, Rettig is also leading an observational study that involves nearly 40,000 VA prostate cancer patients who are on ADT drugs, such as degarelix. He and his colleagues are looking at data to determine if these patients have a lower severity rate of COVID-19, compared with patients who are not on ADT therapy. The Italian-based study concluded that hormone therapy protects prostate cancer patients from contracting COVID-19 and experiencing symptoms from the disease.

A ‘serendipitous’ occurrence

Rettig first had the idea for the clinical trial when reading a research paper that appeared in April in the journal Cell. The paper described how the TMRSS2 protein lives on the surface of lung tissue, and how the

"Male hormones and female hormones seem to have different or opposing effects for COVID-19. We think male hormones may be driving the susceptibility and severity of COVID-19, whereas female hormones [estrogen] seem to suppress the severity of the disease."

coronavirus uses it to infect cells. “If you do prostate cancer research, you know that TMPRSS2 is regulated by male hormones,” he says. “It was natural to me to hypothesize that shutting down androgens to prevent TMPRSS entry into the lung cells could reduce the severity of COVID-19.”

It was “serendipitous,” Rettig says, how his idea took on a new life. He co-chairs a national VA program on precision oncology with Dr. Bruce Montgomery of the VA Puget Sound Health Care System in Washington state. During one of the group’s meetings, he presented his idea when someone in the meeting, Dr. Rachel Ramoni, VA’s chief research and development officer, told Rettig she had been contacted by two university researchers who came up with the same hypothesis.

The researchers, one at Columbia University and the other at the University of Alabama at Birmingham, had applied artificial intelligence and computational genomics techniques to emerging COVID-19 data. That approach produced lab evidence suggesting that male hormones trigger the growth of TMPRSS2 on lung tissue. Ramoni immediately put Rettig in touch with the two university researchers.

“Rachel mobilized a lot of VA resources to bring the trial to fruition,” Rettig says. “It has been a very intense period. We’ve condensed a process that typically takes a minimum of 10 to 12 months into a matter of just weeks to get this trial approved and up and running.”

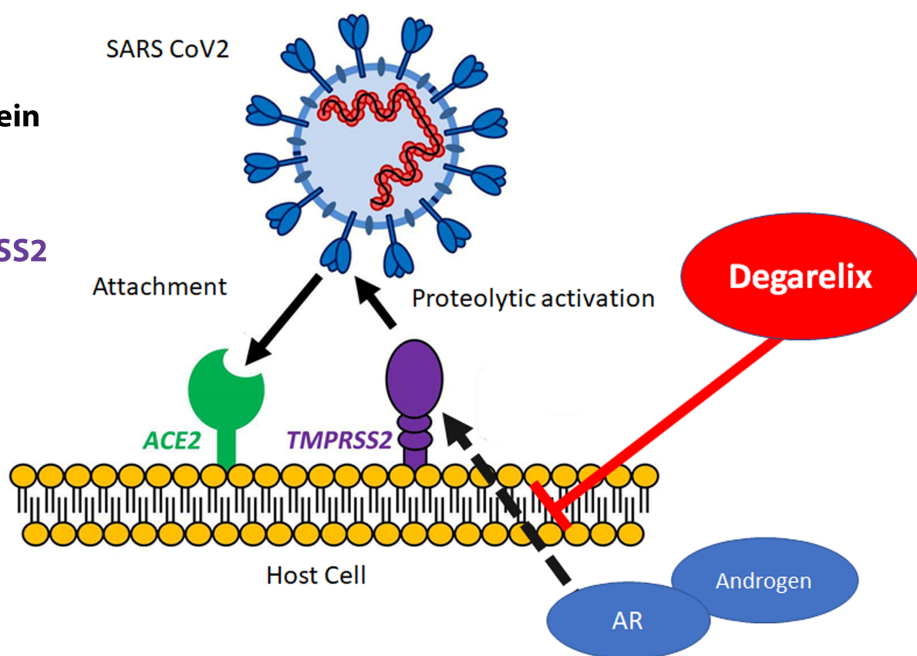
Read more at www.research.va.gov/currents ★

VA Trial on Potential COVID-19 Treatment

VA is testing the prostate cancer drug degarelix as a potential COVID-19 treatment.

SARS CoV2: Viral Entry

- **Degarelix** suppresses testosterone production
- Testosterone regulates the protein **TMPRSS2** in the body
- **Coronavirus** relies on **TMPRSS2** to penetrate **lung cells**
- **Degarelix** may stop the **virus** from entering lung cells



The VA trial will test the drug versus a placebo in nearly 200 male Veterans with COVID-19.

Mike Richman. “VA scientists race to determine effectiveness of prostate cancer drug in treating COVID-19 patients.” VA Research Currents. May 22, 2020. Infographic by VA Research Communications.



VA is sponsoring or partnering with industry or other federal agencies on a number of clinical trials on COVID-19.

VA Research works with industry, other partners to launch COVID-19 clinical trials

VA medical centers are involved in a number of clinical trials and other studies focused on COVID-19. VA's research office is also seeking to expand its role in COVID-19 trials.

As the COVID-19 pandemic unfolded across the country, VA was invited to take part in a clinical trial of remdesivir, a promising but not yet FDA-approved treatment for COVID-19. Within a record-setting four days, on March 18, the first VA site in the trial, Palo Alto, was approved to start enrolling Veterans hospitalized with the illness.

“This was a huge milestone for VA research—we cut start-up time for collaborative research from months to days,” says Dr. Molly Klote, a retired Army Medical Corps colonel who now runs the Office of Research Policy, Protections, and Education, part of VA’s Office of Research and Development (ORD).

The multisite trial is sponsored by the National Institute of Allergy and Infectious Diseases. That agency is led by Dr. Anthony Fauci, now a household name for his role in the White House response to the pandemic.

NIAID had contracted with a commercial institutional review board (IRB) to oversee the study. VA had to jump through extra regulatory hoops to join in the arrangement, but Klote's dedicated team made it happen quickly—and made history in the process.

"This was the first time a VA research program was able to rely on a commercial IRB for the required ethical review," notes Klote. No small feat, considering VA started doing multisite clinical trials in the 1940s.

Importantly, adds Klote, VA's ability to now use commercial IRBs when needed "positions us to be a much more viable research partner for industry."

Two additional VA sites, Denver and New Orleans, have since joined the NIAID remdesivir trial.

Remdesivir trial among several COVID-19 studies in VA

The trial is one of several focused on COVID-19 that VA medical centers are now involved in, and more trials are in the works.

"VA research is embedded in the largest integrated health care system in the country," says Dr. Rachel Ramoni, VA's chief research and development officer. "We're in a position to do things that no one else in the world can do to improve the health of our Veterans, the country, and the world."

Since assuming her role in 2017, Ramoni has made it a top priority to increase Veterans' access to clinical trials.

With the advent of the COVID-19 pandemic, her office convened a response team that huddles daily to identify and advance research opportunities for VA investigators nationwide. They work closely with a steering committee of VA experts in virology, infectious disease, and epidemiology. That group has been doing expedited reviews of incoming ideas and proposals from VA investigators to identify the most viable and promising studies to fund.

"Together, VA and industry can rapidly generate desperately needed knowledge for the prevention and treatment of COVID-19."

The ORD response team is particularly focused on linking with the pharmaceutical industry. That happens through legal arrangements known as "cooperative research and development agreements." The agreements have been used for years to allow VA to partner with companies to test promising drugs or medical devices with Veteran study volunteers.

Now these public-private contracts are especially crucial. Drug companies with promising vaccines or treatments for COVID-19 need to urgently get their products into clinical trials. "Together, VA and industry can rapidly generate desperately needed knowledge for the prevention and treatment of COVID-19," says Ramoni.

New landscape for clinical trials between VA, industry

In past years, regulatory hurdles were more cumbersome—in some cases, prohibitive. Many companies were deterred from partnering with VA to test new treatments.

Under Ramoni's leadership, that landscape has shifted. There's been a concerted effort since 2018, in the framework of an initiative that ORD calls Access to Clinical Trials (ACT) for Veterans, to educate potential partners—from industry as well as the federal sector—and break down barriers to collaboration.

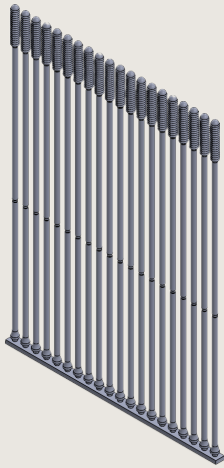
VA is now a far more attractive partner for industry. The organization has a nationwide cadre of experienced investigators, a clinical trial infrastructure that is tested and ready to move quickly, and a large pool of potentially eligible Veterans study participants.

"We want to become the partner of choice for industry," says Ramoni.

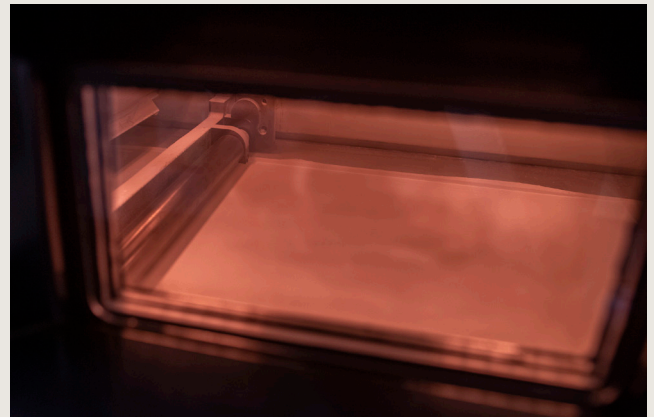
Read more at www.research.va.gov/currents ★

HERL helping meet the demand for COVID-19 medical supplies

The Human Engineering Research Laboratories (HERL), a large VA facility that does research, development, and testing on an assortment of technologies, has been helping meet the demand for medical supplies triggered by the COVID-19 health crisis. HERL, a collaborative effort between VA Pittsburgh and the University of Pittsburgh, has been making such items as face shields, desk shields, and nasal testing swabs. These photos show various stages of the fabrication process to create the testing swabs, which are printed on HERL's laser-powered 3D printing machine. The technology center may ramp up its production to develop as many as 100,000 swabs per week. *(Photos courtesy of VA Pittsburgh and the Human Engineering Research Laboratories)*



A computer-aided design model that the 3D printer uses to fabricate the swabs.



A view from the observation window of the part cake in the selective laser sintering machine, with the laser fusing the nylon powder together to create the swabs. The part cake is a mixture of compressed nylon powder that is not bonded.



VA Acting Deputy Secretary Pamela Powers peers through the view port to watch the fabrication of COVID-19 swabs, along with VISN-4 (Veterans Integrated Service Network) director Timothy Liezert. The computer screen shows the laser going through the scan process for the layer in progress.



The part cake (left) after being removed from the plastic container on the right. The swabs are inside the part cake. They are made by bonding the nylon powder together one layer at a time using a precisely controlled laser machine.



HERL technicians Beth Carmona and Nicholas Gatto remove the swabs from the part cake and conduct an initial cleaning.



Swabs removed from part cake (front) but not yet cleaned. In the rear is the part cake removed from its container, but with swabs still within the unbound powder. The process is a bit like that of archeologists separating dinosaur bones from the soil where they are buried. The swabs need to be carefully removed from the part cake powder, just like the bones are carefully removed from the soil.



HERL technician Ian Eckstein (R) and Dr. Garrett Grindle, the associate director of engineering at HERL, at the station where 3D-printed swabs are broken-out of the part cake after cooling in an oxygen-free chamber.



The swabs once they have been separated from the powder and cleaned. They are bagged in lots. Samples are removed to undergo engineering tests and for traceability in case of an unforeseen problem. The bags are then sent for further cleaning and sterilization, after which the swabs are put in a sealed sterile bag and labeled for VA inventory.



Cleaned, sterilized, and bagged swabs ready for use in the VA health care system.

HERL's director, Dr. Rory Cooper, on the possible large-scale production of snare swabs: "VA could potentially build the capability for many people who enter a VA medical facility to do a screening test, including patients, doctors, nurses, and therapists, if there were a need or plans to do so. People could potentially take a quick test, which includes answering a few questions, get a temperature measurement, and provide a rapid sample with a snare swab if warranted."



A VA study of women Veterans has linked PTSD and moral injury with subsequent pregnancy complications.

PTSD, moral injury tied to pregnancy complications

Elevated symptoms of PTSD and moral injury can lead to pregnancy complications, found a VA study of women Veterans.

Both PTSD and moral injury were predictors of adverse pregnancy outcomes such as preterm birth and gestational diabetes, while PTSD symptoms also predicted postpartum depression, anxiety, and a self-described difficult pregnancy.

The results led study author Dr. Yael I. Nillni, a researcher with the National Center for PTSD at the VA Boston Healthcare System and Boston University School of Medicine, to suggest that “screening for PTSD and moral injury during the perinatal period is important to identify women who may need treatment for these problems.”

The findings appear April 14, 2020, in the *Journal of Traumatic Stress*.

Moral injury involves shame, guilt

Posttraumatic stress disorder results from experiencing traumatic events, such as military combat. Symptoms include re-experiencing the trauma through flashbacks or nightmares, numbness, sudden anger, and hyperarousal. PTSD is more common in women Veterans than civilian women. In addition to combat, experiences such as childhood

abuse, military sexual trauma, and sexual harassment can cause PTSD in women Veterans.

Moral injury refers to distress related to transgression of deeply held moral beliefs. It can lead to feelings of shame, guilt, and demoralization. Moral injury can result from a number of experiences, such as combat and military sexual trauma. Experiencing leadership failures or perceived betrayal by peers, the military, or the government have also been linked with moral injury in Veterans. Past research has shown that a person does not need to be directly involved in a transgressive act to face moral injury. Being exposed to transgressions can also lead to moral injury.

While PTSD and moral injury frequently occur together in Veterans, they are distinct conditions.

Previous VA research has shown PTSD may increase the risk of gestational diabetes, preeclampsia, and preterm birth. Some evidence suggests that moral injury can negatively impact physical health, but its effects on pregnancy have not been studied.

Study tracked more than 300 women Veterans

To better understand how these two conditions affect pregnancy, the researchers followed 318 women Veterans who became pregnant within three years of separating from military service.

They found that women with elevated PTSD symptoms were at greater risk of adverse pregnancy outcomes than women with lower symptoms PTSD.

Elevated symptoms of moral injury also increased the risk of adverse outcomes. Both conditions raised the risk of gestational diabetes, preeclampsia, and preterm birth. Only PTSD increased the risk of postpartum depression, anxiety, and the perception of a difficult pregnancy.

For both PTSD and moral injury, the more severe the symptoms, the higher the likelihood of pregnancy complications.

Results consistent with past research

The results were consistent with other studies on PTSD and pregnancy. In 2018, VA and the Department of Defense published clinical practice guidelines that emphasize the importance of screening for mental health conditions during pregnancy. The new findings

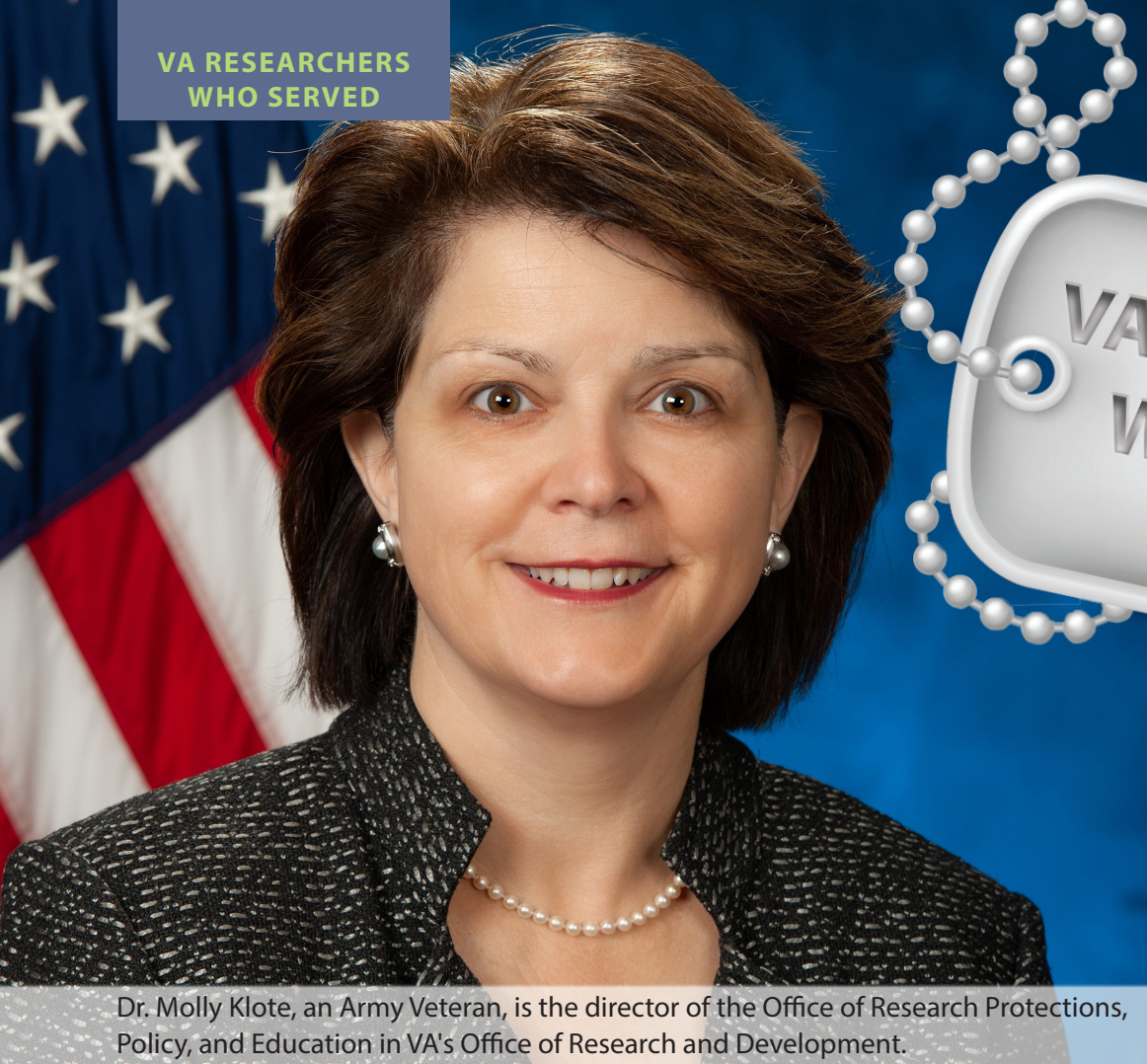
add evidence to the idea that both PTSD and moral injury should be screened for and treated during pregnancy.

Nillni stressed the importance of screening for pregnant women both within and outside VA health

care settings. “Given that many women receive obstetric care outside of the VA,” she explained, “increased awareness of the impact of PTSD and moral injury on perinatal outcomes is imperative to improve screening during this sensitive time and connect at-risk women Veterans to services.”

For more on VA research into PTSD, visit the Posttraumatic Stress Disorder topic page on the VA research website. ★

"Increased awareness of the impact of PTSD and moral injury on perinatal outcomes is imperative to improve screening during this sensitive time and connect at-risk women Veterans to services."



Dr. Molly Klote, an Army Veteran, is the director of the Office of Research Protections, Policy, and Education in VA's Office of Research and Development.

VA Researchers Who Served: Dr. Molly Klote

Dr. Mary (Molly) Klote, an Army Veteran, is the director of the Office of Research Protections, Policy, and Education in VA's Office of Research and Development. Previously, as an active-duty Army colonel with 30 years of service, she oversaw all human research policy, education, and compliance for the Army through the office of the Army surgeon general. She has published 15 peer-reviewed research papers that involve her expertise as an internist and allergist-immunologist. Her military honors include the Legion of Merit, the Defense Meritorious Service Medal, the Korea Defense Service Medal, the Iraq Campaign Medal, the Expert Field Medical Badge, and the Army Staff Identification Badge.

What motivated you to join the military?

I am the third generation in my family to join the Army. I grew up as an Army brat and could not have imagined another life. My dad was so happy in his career. His enormous love for the Army inspired me to join

What inspired your research career?

If I hadn't been a doctor, I likely would have been a detective. I like solving problems and getting to the answer. Beyond caring for patients, research is an opportunity in medicine to uncover and discover.

Did you have mentors who inspired you in life, the military, or your research career?

There are too many medical professionals and Army officers who inspired me, including my father, to name them all. My parents come from large Irish Catholic families, and my aunts, uncles, and cousins, many of whom served, had

a major impact on my upbringing. I am one of seven girls in my family, and each of my sisters has impacted my life. My Catholic faith plays a significant role in my life. I am a member of the Order of Malta, a Catholic service organization that is dedicated to caring for the sick and the poor. My husband and children also help to ground me in the things that are most important.

At the Walter Reed Army Medical Center, Dr. Renata Engler, the allergy-immunology fellowship program director, and Dr. Michael Nelson, the clinical laboratory immunology program director, had the most profound impact on my research career. Dr. Bryan Martin, the deputy allergy department chief, allowed me to join the research department at Walter Reed. That move set me on a course in research regulatory positions where I could influence issues and policy. Dr. Laura Brosch, now at the Uniformed Services University of the Health Sciences, has been my research regulatory mentor for many years. She has challenged me to question why we do what we do and to always make sure there is added value to any policy decision I make.

Describe your military experience.

I began my Army service through an ROTC scholarship at James Madison University in Virginia. I majored in computer information systems and earned a regular Army commission in the Military Intelligence Corps upon graduation. I served as an Army intelligence officer for five years. It was a wonderful time to mature, develop leadership skills, and be given responsibility at a young age. I served for 16 months in South Korea, nine months in Honduras, one year at Fort Meade in Maryland, and one year as a detachment commander at the Rosman Research Station in North Carolina.

Before my military intelligence time ended, I decided to take night classes to complete the necessary requirements to apply to medical school. I was accepted to the Uniformed Services University and graduated with a medical degree and the Esprit de Corps award, which is recognition for a spirit of teamwork that is voted on by the class. I then trained in internal medicine, allergy immunology, and clinical laboratory immunology at Water Reed Army Medical Center.



Photo courtesy of James Madison University

Dr. Molly Klote as a physician in the allergy department at Walter Reed Army Medical Center in 2011.

What kinds of research have you been involved in? How has it impacted Veterans?

My research was mainly focused on vaccines and immunodeficiency. I conducted studies on the small-pox and influenza vaccines and on the incidence of infections after kidney transplantation, among other research projects. Today, I no longer have my own research projects. The focus of the last eight years of my Army career had been to help streamline the research regulatory process to make research easier for others. That is my goal for VA research, as well.

As an allergist-immunologist, I saw the benefit of medical research but was frustrated with the policy issues that seemed to slow the research review process down. I convinced my boss to let me join the department of clinical investigation at Walter Reed. After 18 months, I became the department chief. After making major changes and improvements in the process, I was chosen to provide regulatory oversight to eight Army medical center departments of clinical investigation. I was later selected to stand up the Department of Research Programs at the new Walter Reed National Military Medical Center.

Read more at www.research.va.gov/researchers_whoserved ★



RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs

Many Veterans prefer virtual health care visits

Many patients using VA-issued tablets preferred video health care to in-person care, found a VA Palo Alto study. In 2016, VA began issuing tablets to Veterans to allow them to receive care virtually. The program aimed to improve care access for Veterans who face barriers such as transportation issues. Researchers surveyed about 600 tablet recipients about their experiences with telehealth. Satisfaction with the tablet program was high. Almost a third of patients said they preferred virtual care to in-person visits, while 36% said care was “about the same.” Patients were more likely to prefer video visits if they felt uncomfortable in a VA setting, had communicated well with their doctor, had substance use disorder, or lived in a place with better broadband coverage. Patients with more chronic conditions were less likely to prefer video visits. The results will help identify which patients would benefit from virtual care, say the researchers. The study was conducted prior to the COVID-19 pandemic. Since the pandemic, telehealth has come to play an even greater role in VA care. (*Journal of Medical Internet Research*, April 15, 2020)



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