STATEMENT OF
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Good afternoon, Chairwoman Brownley, Ranking Member Dunn, and distinguished Members of the Subcommittee. Thank you for the opportunity to discuss VA's Million Veteran Program and Precision Medicine research efforts. I am accompanied today by Dr. Rachel Ramoni, Chief Research and Development Officer, and Dr. Sumitra Muralidhar, Director of the Million Veteran Program.

Introduction

Precision medicine is the prevention, diagnosis, prognosis, and treatment of health conditions that considers individual variability in biology, environment, and lifestyle. Advances in biomedical research, informatics, computational science, and medical care are converging in the 21st century to reveal the complexity of human physiology and enable us to decode that information to improve health and well-being.

VA is the largest and most diverse health care system in the United States and has some of the richest data in the world. In combination, those two factors give VA the ability and the responsibility to lead the world in the practice of precision medicine. VA Research, in close partnership with clinical operations and education, is the discovery engine that drives the evolution towards ever more precise care of our Veterans.

As Deputy Under Secretary for Health for Discovery, Education, and Affiliate Networks, which includes the Office of Research and Development (ORD), I am pleased to be here to share our vision, investments, and deliverables in the field of precision medicine.

Strategic Priorities that Reflect VA Research Values

For more than 90 years, VA has conducted research within its health care system. In establishing VA Research, Congress recognized both the need to study Veterans' unique concerns and how essential research is to excellent clinical care. This was prescient: VA Research has resulted in three Nobel prizes, seven Lasker Awards, and numerous other national and international honors.

Today, ORD continues to honor its statutory commitment through the execution of three strategic priorities, which Dr. Rachel Ramoni, VA's Chief Research and Development Officer, articulated in early 2018 and includes the following:

1. To increase Veterans' access to high quality clinical trials;
2. To increase the substantial real-world impact of VA research; and
3. To put VA data to work for Veterans.

VA's Commitment to Real-World Innovation

Since its inception, VA Research's discoveries have contributed to real-world impact. The pacemaker and liver transplantation are well-known examples of early VA research advances that transformed health care. Fewer people know that the Gleason grading system, which is used worldwide predicting the prognosis of a man with prostate cancer, is named for its creator, Donald Gleason, who was a pathologist at the Minneapolis VA Health Care System. More recently, VA conducted the foundational trial that established active surveillance as a safe alternative to prostatectomy in low-risk prostate cancer. Importantly, this work not only led to several publications in the prestigious New England Journal of Medicine, but it also reshaped the care we provide. VA is ahead of the curve in adhering to this best practice, which improves the quality of life of men with prostate cancer.

The promise of ever more precise medicine is that we can go beyond general predictions like low-, medium-, and high-risk prostate cancer to specific predictions that will guide an individual Veteran's care. One of the ways that ORD is making this vision a reality for Veterans who are cared for by the Veterans Health Administration (VHA) is through our partnership with the VA National Clinical Oncology Program Office and the Prostate Cancer Foundation. The beachhead of this effort is six VA medical centers that will act as hubs of best-in-class care. The next phase will include adding hubs and extending from hubs to spokes. The first precision oncology milestone is to ensure that men with metastatic prostate cancer receive Deoxyribonucleic acid (DNA) sequencing. Already, this effort has identified men who, based on their genetic variations, will benefit from precision therapies that are known to be effective against the specific type of cancer they have.

The Million Veteran Program: A Partnership with Veterans

One of ORD's major investments in precision medicine is the Million Veteran Program (MVP). The program was launched in 2011 with a goal to enroll at least one million Veteran partners by 2021 to build the world's largest research database of genetic, health, lifestyle, and military exposure information.

Enrollment

MVP has achieved its goal of being the largest program of its kind in the world, with over 750,000 Veterans enrolled. MVP includes Veterans from all 50 states, Guam, and Puerto Rico. MVP makes it easy for Veterans to become a part of the program by having enrollment sites at 58 VA medical centers; 83 community-based outpatient clinics; and Veterans Service Organization conventions.

To ensure that all can benefit from precision medicine, we must understand the genetic basis of diseases in diverse racial and ethnic populations. Most genetic research to date has been conducted in Caucasian populations. Findings in this group

sometimes do not translate well to other groups. MVP demographics track well with that of Veterans enrolled in VA health care. Approximately 18 percent are African American, and 7 percent are Hispanic. To enhance our ability to serve all Veterans, MVP is repeating the genetic analysis of samples from African American participants using a genetic test (genotyping chip) enriched for genetic variants found in the African American population.

Science

To put these data to work for Veterans, we must make use of the best technologies and engage the best researchers. MVP is at an important transition point, moving from a program focused exclusively on enrolling a diverse set of Veteran partners to a program that is both enrolling participants and making discoveries that will benefit those Veterans. At present, MVP is undertaking three primary scientific lines of effort:

1. Thirty-one alpha, beta, and gamma research projects have been funded by ORD to both make discoveries and to establish the resources, processes, and infrastructure necessary to responsibly support large-scale science. The research topics span diseases of high relevance to Veterans such as suicidality, posttraumatic stress disorder (PTSD), multi-substance abuse, schizophrenia and bipolar disease, Gulf War Illness, traumatic brain injury (TBI), Alzheimer's Disease, tinnitus, and Parkinson's Disease. They also include chronic diseases highly prevalent in Veterans such as cardiovascular and cardiometabolic diseases, chronic kidney disease, cancer (prostate, breast, lung, and multiple myeloma), osteoarthritis, and age-related macular degeneration.

2. Three exemplar projects are being conducted in collaboration with the Department of Energy (DOE). These data science-intensive projects focus on suicide, prostate cancer progression, and cardiovascular disease risk prediction. Over 75 researchers from VA and DOE national laboratories are engaged in these projects. Each project includes a requirement to work collaboratively with VHA clinical operations to ensure real-world impact. For example, more accurate prostate cancer progression risk predictions will improve our ability to identify those Veterans with low-risk prostate cancer who should undergo surgery versus active surveillance. The suicide risk prediction project will use the power of artificial intelligence (AI) to improve the precision of VA's Recovery Engagement and Coordination for Health – Veterans Enhanced Treatment (REACH VET) algorithm, which is used to identify Veterans at highest risk of suicide.

3. ORD is funding two projects to determine the feasibility and value of offering to return important individual genetic results to MVP participants, following re-consenting of the MVP participant and validating the MVP finding in certified clinical laboratories. The first is the return of genetic variants for familial hypercholesteremia (FH), which is genetic high cholesterol. Veterans found to have FH will be offered treatment, which reduces the risk of serious health

problems like heart attacks and stroke. The second project will reach out to Veterans with a diagnosis of metastatic prostate cancer and harmful variants in three DNA repair genes. This information will guide treatment options and participation in clinical trials. These projects are in the regulatory review phase and are expected to launch by the end of Fiscal Year (FY) 2019.

Since the initiation of the MVP science effort in 2017, VA researchers have presented over 100 abstracts at national and international scientific and medical meetings, and over 15 peer-reviewed original scientific papers have been published. Six recent publications are in high-impact journals such as *Nature Medicine*, *Nature Genetics*, and *Nature Communications*. These communicate novel discoveries in the genetics of high blood pressure, high cholesterol, alcohol use disorder, and PTSD.

MVP Data Access

MVP exists because our Veteran partners are willing to continue to serve our Nation through participation in research. Respecting the concerns voiced by Veterans in focus groups and surveys, MVP committed to not distribute its datasets. Instead, researchers come to the data to conduct their work in a secure environment. Thus, an essential first step to realize our promise to MVP participants to advance precision medicine among Veterans is to establish a modern computational infrastructure that can scale to many studies occurring in parallel. To this end, ORD is establishing a pilot with the University of Chicago and the Open Commons Consortium to make de-identified MVP and electronic health record data broadly available to approved VA and non-VA researchers in a VA Data Commons. Continued investment in information and technology modernization will support projects in the VA Data Commons within the next two years.

To complement this effort, ORD is in the process of large-scale curation of the data contained within the electronic health record using natural language processing and other advanced computational techniques. What we mean by curation is transforming the wealth of disparate and identifiable information contained within electronic health records into valid descriptors of an individual's health conditions, such as metastatic prostate cancer, Gulf War Illness, and PTSD. Having these curated data means that research projects can begin more quickly and that we can share more meaningful de-identified data with non-VA collaborators while protecting Veterans' privacy. By the end of FY 2021, we pledge to create a library of at least 1,000 curated health conditions.

Beyond MVP: Big Data, Biomarkers, and the Invisible Wounds of War

While MVP is a substantial VA Research investment in precision medicine for Veterans, it is by no means the only such effort. The individual projects are too numerous to enumerate in this statement, so I highlight some exemplars focused on healing the invisible wounds of war.

In 2017, ORD funded the Precision Medicine for Mental Health (PRIME) Care clinical trial which is conducting genetic testing to guide the selection of antidepressant medication among 2,000 Veterans with major depressive disorder. The trial will

determine both how Veterans and clinicians use this information and whether it improves outcomes. As of May 2019, the study was past the halfway point in recruitment.

The Chronic Effects of Neurotrauma Consortium (CENC), pronounced "sen-see," is a nationwide effort to understand the mechanisms of combat-associated mild traumatic brain injury (mTBI), to evaluate how co-morbidities like mental health conditions may be affected by combat-associated mTBI, and to study treatment and rehabilitation strategies for the short- and long-term effects of combat-associated mTBI. It includes a longitudinal study with intensive biosampling and imaging for biomarker development. CENC is funded by VA and the Department of Defense (DoD). Data from CENC are available through the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System, which shares TBI research data, methodologies, and associated tools. As of March 1, 2019, the consortium has submitted approximately 171,000 records on over 2,000 subjects who are enrolled in CENC studies. In addition, CENC is in the process of uploading over 1,500 Magnetic Resonance Images to FITBIR. Notably, the epidemiologic components of CENC already are yielding important findings, such as that women Veterans with diagnoses of TBI, PTSD, or depression had a significantly increased risk of dementia compared to women Veterans without these diagnoses.

The Translational Research Center for TBI and Stress Disorders (TRACTS) study is another longitudinal study with biomarker collection to understand the complex changes in the brain, thinking, and psychological well-being that result from TBI and PTSD. TRACTS focuses on Veterans who served in Operation Enduring Freedom/Operation Iraqi Freedom.

Expanding Veterans' Access to Clinical Trials

Clinical trials are essential to both generating the evidence necessary to bring precision medicine research discoveries into the clinic and to provide hope when Veterans reach the limits of what standard medical care can provide. To achieve their goal to increase Veterans' access to high quality clinical trials, ORD launched the Access to Clinical Trials (ACT) for Veterans initiative in 2018 with the support of several non-profits including the National Association of Veterans' Research and Education Foundations (NAVREF), Us Against Alzheimers, Lungevity, and Cohen Veterans Bioscience. ACT's goal is to get VA clinical trial startup times to within 25 percent of industry standards by the end of FY 2021.

Policy, infrastructure, and education must also evolve to support the changing landscape of clinical trials, especially in light of the single Institutional Review Board (IRB) review mandate that will take effect on January 20, 2020. To lead this change, in late October 2018, ORD welcomed Dr. Molly Klote, a retired Army colonel, as Director of the Office of Research Protections, Policy, and Education. In December 2018, she and her team began a "moonshoot" initiative that identified 13 regulatory steps needed to be ready to meet the new national mandate. They have thus far completed 7 of those required elements and are on track to complete all by Jan 2020

Policy changes

The use of commercial IRBs was prohibited in VHA Directive 1200.05, *Requirements for the Protection of Human Subjects in Research*. This will be revised to allow their use in circumstances where a third party pays the IRB fees. This update will dramatically increase VA's ability to participate in multi-site clinical trials and to offer Veterans the benefit of these trials. Master service agreements with the country's two largest commercial IRB companies are being finalized. The item remaining to realize these groundbreaking agreements is the Federal Information Security Modernization Act (FISMA) data rating for data that will need to be transferred to the commercial IRB to complete their reviews.

Additionally, to facilitate our ability to partner with DoD to help Servicemembers and Veterans, ORD is hosting a meeting on August 23, 2019, to document differences in regulatory, legal, privacy, contracting, human resources and information security as it relates to data sharing and clinical trial operations. At that point, we will begin needed updates to the VA/DoD research handbook. DoD and VA already allow for reliance on each other's IRBs.

Infrastructure

ORD is in the process of contracting to purchase a commercial off-the-shelf, VHA-wide research management platform to support multisite trials, increase efficiency, standardize process, and allow more complete tracking and oversight of research and the research review process. We anticipate a contracting decision by mid-July 2019. In addition, ORD is standing up a process to review and approve applications from VHA facilities to rely on non-affiliated IRBs for research studies to support the single IRB review mandate. Finally, VA Central IRB is doubling its capacity by adding a second national expansion panel to decrease the wait time to receive IRB review. We anticipate stand up by the end of this fiscal year. Future panel will be added as the review demand is assessed.

Education

In addition to numerous regular education Webinars, ORD will be hosting a workshop on August 20-21, 2019, to prepare local VA medical center IRB personnel for research and regulatory requirements for the shift to single IRB review.

Conclusion

On behalf of ORD and the many VA researchers across the country, I thank you for your attention. As the Deputy Under Secretary for Health for Discovery, Innovation, and Affiliate Networks, I am fortunate to represent these superlative individuals in sharing the progress we have made towards fulfilling our commitment to discover and bring the advances of precision medicine to our Nation's Veterans. My colleagues and I look forward to responding to your questions.