The 22\textsuperscript{nd} meeting of the Veterans Affairs (VA) Genomic Medicine Program Advisory Committee (GMPAC) took place on November 2, 2017 in Washington, DC. The following members were in attendance: Cynthia Morton, PhD (chair, ex officio); Kevin Coombes, PhD; Thomas Berger, PhD; Lt Col David G. Watson, USAF, BSC; Andrea Ferreira-Gonzalez, PhD; Dan Roden, MD; Julia Bridge, M.D.; along with invited guests and speakers. Sumitra Muralidhar, PhD, Designated Federal Officer (DFO) opened the meeting and introduced Chief Research & Development Officer, Dr. Rachel Ramoni, DMC, ScD. The Chair, Dr. Cynthia Morton welcomed the committee members, guests, and members of the public.

The meeting began with, and most of the morning was dedicated to, a discussion on the return of research results. The speakers were Robert Green, MD, MPH of Brigham and Women’s Hospital and Harvard Medical School, and Adam Berger, PhD of the FDA. It was noted that in most large clinical research studies, at least some results are returned. For example, imaging tests are sent to clinical radiology for review and incidental findings are reported to participants. However, the scientific community hasn’t reached a consensus on what should be returned (if anything) in the clinical genomics domain. The committee heard about the current clinical uses of genetic testing, which are for diagnosis of rare conditions, some preconceptual screening, prenatal and newborn screenings, and targeted cancer therapies. In the near future, clinical genetics is anticipated to facilitate with expanded drug selection, carrier screening, population screening and prenatal sequencing.

One of the overarching concerns of returning results is what patients and providers do with genetic information, and whether it could be misunderstood, potentially leading to distressing sequelae for provider and participant, as well as increased costs and resource use in healthcare. Several specific fears were outlined: inappropriate diagnoses, inappropriate prescriptions, false reassurances, reproductive actions, provider confusion and expense.

The American College of Medical Genetics and Genomics recommends returning secondary results from 59 specific genes, but not all of these are evidence based, and these are not the ONLY actionable genes. It is merely a minimum set with sufficient penetrance and effect. There are several drivers of the push toward returning results, including capital investments, respect for patients/participants rights, ethical concerns, fear of litigation, and the precision medicine narrative that information is empowering that will lead to disease prevention.

Discussion during and after the presentations included questions about how genetic information is communicated to the Veteran community, and whether some of the negative perception of genetic testing could be eliminated through improved outreach and communication. Another question was raised about how this impacts family members of participating Veterans. In the VA, only Veterans can be treated in the VHA, so any return of results will not involve the testing of family members (by the VA). Many committee members agree that the current stance of MVP
not returning research results being a very reasonable approach, but, they also acknowledged the reality that the field is moving towards returning more and more results. They recommended that the program be prepared with answers and consider further dialogue around this topic.

Dr. Green mentioned that those favoring the return of results tend to argue that its benefits outweigh negatives. They say that it increases transparency, respects autonomy, is an ethical obligation, is necessary when there is a significant disease risk/when there is a medically actionable result and is non-paternalistic. However, the converse side opines that health care resources could be used inappropriately, and that there could be significant negative impact for research. There is also a fear that return of results blurs line between research and clinical practice, by potentially pushing researchers towards providing health care. Additionally, there is a lack of knowledge currently to interpret every single potential piece of information that could be derived from a genetic test.

Considerations for the return of research results include: 1) Are the materials used in research tests adequately validated? 2) Should results be returned if there is no confirmatory testing? 3) Are there systems in place to ensure samples aren’t mixed up? 4) What’s the potential for harm? 5) Who will be responsible for tracking these things?

Dr. Ramoni, CRADO, discussed the potential for a pilot project to return genetic results to participants. One of the goals would be to understand how Veterans will benefit from genetic test results. She stated that it could be done in a CLIA setting with proper re-contact, re-consent and clinical infrastructure in place. A pilot like this could also help inform how to proceed with implementation on a large scale. Dr. Larry Meyer of the National Clinical Genetics service mentioned the additional resources needed to support and increase VA’s genetic counseling services. He also brought up issues with increased liability, risk, IT (especially in the form of computerized decision support), Primary Care Provider education and data availability.

The committee discussed this potential pilot study at length and offered suggestions about next steps. There were concerns about not getting data from a representative population, because the study will get self-selected participants who want to know the results of their genetic tests. A randomized trial was suggested as a possibility, although admittedly, it takes longer to conduct. The committee suggested identifying discrete VA specific burdens for determining what types of genetic information to return. Another suggestion was partnering with civilian genetic testing and counseling service to facilitate the pilot. The chair, Dr. Morton, proposed a working group to discuss potential topic areas and study design.

Dr. Dave Oslin, of the Philadelphia VAMC updated the committee about Prime Care study, a VA ORD funded pilot project on mental health with the goals of 1) understanding the pharmacogenomics of depression in Veterans, 2) developing individualized approaches to treat depression in Veterans, and 3) developing and implementing a responsible process of returning genetic data to providers and patients. This study is being funded with help from the MVP, and proposes to enroll 2,000 participants. Many companies are already approaching VA to study pharmacogenomics. In addition, VA/DoD and an evidence synthesis review from the VA QUERI program determined more evidence is needed to incorporate pharmacogenomic test results into routine clinical practice.
Deputy Secretary Tom Bowman met with and spoke to the committee on priorities within the VA. He introduced himself as a Marine Corps Veteran, former JAG, who has a personal connection with MVP and genetics. He discussed the importance of Big Data Precision Medicine, PTSD research, collaboration, and continued outreach to the Veterans. He then outlined Secretary Shulkin’s priorities to the committee as follows:

1. CHOICE--Same day service for primary care and mental health
2. Modernizing systems and technology
3. Maximizing resources
4. Improving timeliness in services and benefits
5. Preventing veteran suicide

The committee then heard an update on the Million Veteran Program (MVP) by several MVP leaders, including Mike Gaziano, MD, MPH and John Concate MD, MPH, Co-PIs of MVP; Saiju Pyarajan, PhD, of the Boston VA, Phil Tsao, PhD, of the Palo Alto VA, and Chris O’Donnell, MD of the Boston VA. Over 600,000 Veterans have enrolled in MVP, around 380,000 baseline surveys have been returned from enrollees, and there are 60 VA sites nationwide actively recruiting. The three alpha projects include studies on schizophrenia/bipolar disorder, Gulf War syndrome, and Post Traumatic Stress Disorder in Veterans. The beta test projects cover myriad topics like cardiovascular risk factors and cardio-metabolic conditions, multi-substance abuse disorders, age-related macular degeneration, and chronic kidney disease. A few gamma test projects were recently selected for funding from peer review, and these include topic areas like suicidal behavior, tinnitus, TBI, diabetes, and breast cancer. There have been over 40 abstracts selected for presentation at national scientific conferences, including the American Society for Human Genetics, which was held in October 2017.

Dr. O’Donnell discussed the working group model of the MVP studies. Working groups allow researchers from different studies and within studies to cross-collaborate. He stated that they have multiplied the investigative abilities of the researchers and help make good use of the MVP data source. The MVP group discussed the status of ‘-omics ‘ within MVP, and the desire to expand the universe of data collected on the biospecimens, which currently includes contracts for 45,000 whole genome sequences, along with genotyping every sample. They asked the committee what kinds of other samples should be collected and recommendations for study design. Recommendations from the committee include fasted blood samples and increased plasma collection. Dr. Gaziano mentioned that a pilot for metabolomics was being completed in the coming year, with a couple thousand samples being analyzed for several thousand different metabolites.

In the discussion portion of the meeting, the DFO, Dr. Muralidhar, solicited the GMPAC members for their interest in participating in the Working Group on return of research results. The charge of the Working Group would be to assess and make recommendations on 1) which genetic variants could be returned to MVP participants in a pilot project, and 2) what minimum infrastructure and resources should be in place within the VA, on both the research and clinical sides to conduct the pilot.

There were no public comments, and the meeting adjourned at 4:17.
The next meeting will be held in June 2018.

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