Research Advisory Committee on Gulf War Veterans' Illnesses

Committee Meeting Minutes
January 27, 2022

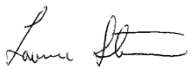
U.S. Department of Veterans Affairs
Washington, DC

Virtual meeting was held due to COVID-19 restrictions

Research Advisory Committee on Gulf War Veterans' Illnesses

Committee Meeting Minutes

I hereby certify the following minutes as being an accurate record of what transpired at the January 27, 2022, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.



Lawrence Steinman, M.D.
Chair, Research Advisory Committee on Gulf War Veterans' Illnesses

Attendance Record	
Members of the Committee:	**RACGWVI Subcommittee Members:**
Dr. Lawrence Steinman, Chair	Dr. Lawrence Steinman
Dr. James Baraniuk	Dr. Karen Block
Mr. Brent Casey	Retired Col. Richard Gaard
Retired Col. Richard Gaard	Dr. Drew Helmer
Dr. Drew Helmer	Ms. Jane Wasvick
Dr. Carey Pope	Ms. Barbara Ward
Ms. Jane Wasvick	Mr. William Watts
Ms. Barbara Ward	
Mr. William Watts	**Invited Speakers:**
Dr. James Woody	Dr. LaTonya Small
	Dr. Cheryl Walker
Designated Federal Officer:	Dr. Elizabeth Hauser
Dr. Karen Block	Ms. Jacqueline Vahey
	Dr. Lea Steele
Alternate DFO:	Dr. Byron Jones
Marsha Turner	Dr. James O'Callaghan
	Dr. Kimberly Sullivan
Committee Staff:	Dr. Sumitra Muralidhar
Mr. Stanley Corpus	
Ms. Marsha Turner	
Mr. Daniel Sloper	**Fireside Chat Participants:**
	Dr. Cheryl Walker
Employee Education System (EES):	Dr. Elizabeth Hauser
Brian Peplinski	Ms. Jacqueline Vahey
	Dr. Lea Steele
Public Attendance:	Dr. Byron Jones
Online via Webex: 990	Dr. James O'Callaghan
Telephone: 343	Dr. Kimberly Sullivan
Total: 1333	Dr. Sumitra Muralidhar

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI)
Department of Veterans Affairs
LOCATION: Virtual via Webex:

Agenda
Thursday, January 27, 2022
11:00 a.m. – 4:00 p.m. Eastern Time Zone

Meeting Purpose	**The purpose of the Research Advisory Committee on Gulf War Veterans' Illnesses is to advise the Secretary on research, plans and strategies related to understanding and treating the health consequences of military service in the Southwest Asia theater of operations during the 1990 - 1991 Gulf War.**	
Meeting Focus	**The effects of environmental and military exposures on genetics, epigenetics and Gulf War Veteran health.**	
11:00 – 11:10 a.m.	**Welcome/Opening Remarks**	**Dr. Karen Block, DFO** **Dr. Lawrence Steinman, Committee Chair**
11:10 – 11:30 a.m.	**Federal Advisory Committee Training (FACA 101)**	**Dr. LaTonya Small** **VA Advisory Committee Management Office**
11:30 – 11:40 a.m.	**VA Gulf War Updates and the Military Exposures Research Program**	**Dr. Karen Block** **Gulf War Research Program VA Office of Research & Development**
11:40 a.m. – 12:15 p.m.	**Environmental Epigenomics**	**Dr. Cheryl Walker** **Director, Center for Precision Environmental Health, Baylor College of Medicine**
12:15 – 12:45 p.m.	**Gene–Toxicant Interactions in Gulf War Illness: Differential Effects of the PON1 Genotype**	**Ms. Jacqueline Vahey (PhD Candidate)** **Computational Biology & Bioinformatics** **Duke University Graduate School** **Dr. Elizabeth Hauser** **Director of Computational Biology** **Dept of Biostatistics and Bioinformatics** **Duke Molecular Physiology Institute** **Durham VA Cooperative Studies Program & Epidemiology Center**

12:45 – 1:05 p.m.	**Butyrylcholinesterase genotype and enzyme activity in relation to Gulf War Illness: preliminary evidence and ongoing studies of gene-exposure interaction**	**Dr. Lea Steele Veterans' Health Research Program Professor, Yudofsky Division of Neuropsychiatry Baylor College of Medicine**
1:05 – 1:35 p.m.	**Modeling the Genetic Basis of Individual Differences in Susceptibility to Gulf War Illness**	**Dr. Byron Jones Professor, Genetics, Genomics and Informatics Univ of Tennessee College of Medicine Dept of Genetics, Genomics, and Informatics Dept of Pharmacology Dr. James O'Callaghan Head, Molecular Neurotoxicology Laboratory and CDC Distinguished Consultant, NIOSH Laboratory of Molecular Neurotoxicology Centers for Disease Control & Prevention**
1:35 – 1:55 p.m.	**Associations of Immune Genetic Variability with Gulf War Illness in 1990-1991 Gulf War Veterans from the Gulf War Illness Consortium (GWIC) Multisite Case-Control Study**	**Dr. Kimberly Sullivan Research Associate Professor Boston University School of Public Health Dept of Environmental Health**
1:55pm – 2:15pm	**Million Veteran Program**	**Dr. Sumitra Muralidhar Director, VA Million Veteran Program**
2:15pm – 2:30pm	**Break**	
2:30pm – 3:30pm	**Fireside Chat**	**Invited Speakers and Committee**
3:30pm – 4:00pm	**Public Comment**	**Visitors and Invited Guests**
4:00pm	**Adjourn**	**DFO/Committee Chair**

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI)

U.S. Department of Veterans Affairs (VA)

Wednesday, January 27, 2022

Committee Meeting Minutes

Welcome and Opening Remarks

— Karen Block, Ph.D., VA Office of Research & Development and Designated Federal Officer, RACGWVI

Dr. Block, Designated Federal Officer and Director of the Office of Research and Development Gulf War Research Program in Washington, D.C., opened the meeting and confirmed a quorum was present. This was a virtual, public meeting due to the COVID-19 pandemic, social distancing, Centers for Disease Control and Prevention (CDC) guidelines and VA Travel restrictions. An overview of the meeting agenda and purpose was provided. Those in attendance were asked to mute all phones; to introduce themselves when speaking; to be respectful of all people attending and gave instructions on how to submit written questions to the committee. A special thank you was given to RACGWVI administrative staff for their hard work putting the meeting together and to all invited guests for taking the time to be part of the meeting. A welcome was extended to the Committee members and Alternative Designated Federal Officer (Alt-DFO). Dr. Block then introduced Dr. Lawrence Steinman, RACGWVI Chairman.

Welcome, Overview and Introductions

— Lawrence Steinman, M.D., Chair, Research Advisory Committee on Gulf War Veterans' Illnesses.

Dr. Steinman called the meeting to order, welcomed all participants and introduced committee members and guest speakers. He gave a special thank you to the Southern Arizona VA Healthcare System, Associate Chief of Staff (ACOS) for Research Dr. Dawn Schwenke, and Public Affairs Officer Luke Johnson, who continued to assist with planning even after in-person travel was cancelled. Further comments were made to thank Karen Block and the RAC staff for their hard work. Dr. Steinman yielded the floor to Dr. Block, who introduced the first speaker on the agenda, Dr. LaTonya Small.

Session 1: Federal Advisory Committee Training (FACA 101)

— LaTonya Small, Ph.D., VA Advisory Committee Management Office

Dr. Small, Program Specialist for the Advisory Committee Management Office (ACMO) provided the annual mandatory Federal Advisory Committee Act (FACA) training to the RACGWVI committee. Dr. Small reminded the committee that FACA is a federal statute that governs the establishment, termination and management of Federal Advisory Committees enacted to promote openness, transparency and accountability, and regulate the number and duration of committees. FACA applies to all groups with at least one non-Federal employee established or utilized by an agency to obtain advice or recommendations. FACA requirements include a charter stating the purpose and function of the committee, a committee chair for management and oversight and a Designated Federal Officer (DFO) to ensure compliance. All committee meetings are public, announced in the Federal Register and open to inspection of records. A committee should have a balanced membership reflecting its constituents. Dr. Small reminded members of the difference between open and closed meetings, and what is permissible as a committee member vs a private

citizen. For example, as private citizens, committee members can testify in court, post on social media in a normal manner; however, they are not allowed to speak for the committee in any official capacity. In discussion of committee best practices, Dr. Small referenced cross-committee collaboration between the 26 advisory committees to learn ways to improve meetings and combine recommendations. She suggested using SMART (specific, measurable, action-oriented, realistic/relevant and time-based) goals for the development of recommendations and promoted VA Library Services as a strong resource option. With the completion of this presentation RACGWVI members had met their annual FACA training requirement for 2022.

Q: Male Audience Member: Why don't we [the RACGWVI] do these [required training/education] during a closed meeting?
A. Dr. Steinman responded that FACA training is mandated to be held publicly for transparency.

Further questions should be sent by email to Dr. Block or if FACA-specific, to Dr. Small.

Session 2: Gulf War Research Program Update

— Karen Block, Ph.D., Director of Gulf War, VA Office of Research and Development (ORD)

Dr. Block presented information on current VA Gulf War Research projects funded by ORD. For fiscal year 2021, ORD received 15 GWI research proposals, funded three GWI research projects (20%) with 4.5 million dollars approved funding. The 2021 Gulf War Portfolio Balance breakdown: 24% Clinical Trials, 28% Model Systems, 48% Biomarkers/Mechanisms. Several of those studies have published their findings. There are 12 ongoing GWI preclinical mechanism and/or biomarker studies.

Dr. Block, noting questions previously raised about the Department of Defense (DoD) Congressionally Directed Medical Research Program (CDMRP), described its inception in 2006 to study adverse health effects caused by overseas deployment in the 1990-91 Persian Gulf War. However, she reported that program is currently transitioning to a wider toxic exposure research program. She suggested RACGWVI recommend VA and DoD team up and share information between biorepositories and research information.

Session 3: Committee Update

— Ms. Marsha Turner

Ms. Turner confirmed all committee members had met all required training upon receipt of the committee member handbook, RACGWVI charter and completion of today's FACA training. She reminded members that RACGWVI prepares quarterly research alerts on GWI which can be found on the RACGWVI website and are available for any and all interested persons. Providing updates, she reported that RACGWVI recommendations to the VA Secretary had been submitted and were still under review. An update will be provided as new information is received. RACGWVI posted solicitations for member nominations in the Federal Register and several referrals had been received. The plan is to submit the package for concurrence in early February 2022. Ms. Turner added a thank you to the VA Employee Education System (EES) for helping to promote the meeting.

Dr. Steinman: Addressing the live comments posted in the Webex chat, Dr. Steinman reminded everyone that the research advisory committee is exactly that, an advisory committee and does not actually conduct any form of GWI research. The task of the RACGWVI is to advise the VA Secretary on research and/or topics that can benefit Gulf War Veterans (GWV) and improve not just their lives, but possibly help and support all Veterans and their families.

An overview of the meeting agenda was given, and the first speaker was introduced.

Session 4: Environmental Epigenomics

— Dr. Cheryl Walker

Director, Center for Precision Environmental Health, Baylor College of Medicine.

Dr. Walker defined Environmental Epigenomics as the process of studying how various environmental exposures may affect a person's health. In the context of this meeting and GWI, how multiple environmental exposures experienced by GWV, such as burn pit smoke, jet fuel, depleted uranium, may have contributed to GWI and its varying degrees of severity.

The emphasis of environmental epigenomics is to help identify what exposures experienced by Veterans were harmful; develop biomarkers for exposure and/or adverse health effects; and stratify individuals in the Veteran population to determine who is at greatest risk. The ultimate goal of the research being the development of interventions to prevent or treat disease associated with military environmental exposures.

The epigenome is the heritable patterns of DNA and histone modifications in chromatin that change gene expression in the absence of changes in DNA sequence. The epigenome is vulnerable to the environment and perturbation of the epigenome persists long after an environmental exposure. Also, this process studies how different cells respond to those exposures; just because a brain cell and a liver cell share the same DNA, they are both very different in structure and function and therefore each is susceptible to different diseases. Those environmental-exposure induced alterations can be used as both a biomarker of exposure and predictor of disease risk. The research presented animal models (mouse) as well as human cell studies, both models demonstrated how specific toxins affect specific genes and how those studies provide a basis for moving beyond correlation to causality and testing strategies. Using blood as the test tissue of choice, research is looking at DNA methylation factors (specific biomarkers) such as chemical mixtures, smoking, lead, climate, social environment and how those and others may possibly lead to a future risk of disease.

Epigenetic research is using DNA methylation as a type of biological clock to measure biological aging. Epigenetic clocks reveal differences in biological age between individuals of the same chronological age. The ultimate goal of epigenome research is to target and develop biomarkers for environmental exposures. To look at how environmental perturbation of the epigenome and epigenetic clocks have tremendous potential to detect environmental exposures and understand their adverse health effects. Then use that information to develop biomarkers to aid in the diagnosis of, and treatment of disease.

Session 5: Gene–Toxicant Interactions in Gulf War Illness: Differential Effects of the PON1 Genotype

— 1. Dr. Elizabeth Hauser
Director of Computational Biology, Dept of Biostatistics and Bioinformatics, Duke Molecular Physiology Institute
Durham VA Cooperative Studies Program & Epidemiology Center

— 2. Ms. Jacqueline Vahey (PhD Candidate)
Computational Biology & Bioinformatics Duke University Graduate School

Dr. Hauser and Ms. Vahey presented a two-part seminar.
"Genetic Studies of Gulf War Illness Cooperative Studies Program (CSP) 585/Gulf War Era Cohort and Biorepository (GWECB)"

The aim of the GWECB/CSP 585 project was to develop a cohort of Veterans who served in the 1990-91 Gulf War and create a data and specimen repository for future research. The project has two goals; first, to determine if genetic variants associated with GWI could be identified, which if yes, then try to understand how those variants might impact biomedical pathways associated with GWI. The discovery process looked at identifying genes and pathways associated with differential response.

The second part is to foster interest in GWI research in the next generation of researchers by providing research opportunities within the VA. There was a comprehensive screening and enrollment process to ensure integrity of the samples collected (i.e., actual "in country" GWV, geographic inclusion). A total of 1,275 Veterans were fully enrolled, completing the consent process, a paper survey with questions about their military service and geographic location, lifestyle behaviors, physical/mental health, and family health, and provided a blood sample. There was also a partial sample of Veterans who completed all consent documents and the survey but did not provide a blood sample.

Data from CSP 585 resulted in confirmation of the RAC-recommended research case definitions, and lead to several genetic phenotypes analyses, as well as multiple training projects and research studies specific to GWI, including the second part of this presentation.
For further information about the CSP 585 Repository, go to:
https://www.vacsp.research.va.gov/CSPEC/Studies/INVESTD-R/Gulf-War-Biorepository-CSP-585.asp

"Gene-toxicant interactions in Gulf War Illness; differential effects of the PON1 genotype."
The results of this study were able to show that both exposure and risk-genes together are associated with greater risk of developing GWI, and increased severity level of GWI. This research replicates and supports a previous study that identified gene and environment interaction that is significantly associated with GWI.

A high prevalence of GWI required common genetic variants and widespread exposures. CDC reported severe GWI among 26.9% of deployed Veterans. Of those 59% reported taking PB pills, and 55% reported chronic pesticide exposure. Those two factors are unique to GWV who were deployed in the Middle East. Those interactions could help identify a biological basis for GWI.

From previous research and documents there is evidence to support PB pills as a causative factor for GWI.

Thanks to the Million Veteran Program (MVP) and the CSP 585 participation, there are sample datasets large enough to statistically perform these GWI toxicity studies. Targeted genetic research demonstrated with statistical significance, how PB pills affected a specific gene function, specifically rs662, a functional variant of PON1. The purpose of the PON1 gene is to make proteins that process and break down toxic chemicals. This gene was also identified in early GWI and occupational hazards studies involving organophosphate exposures. This research was able to show that exposure alone or genetic factors alone increases risk; however, exposure and genetic factor together increase the risk significantly. Further research studies to replicate these findings and to further explain the function of identified SNPs and genes are needed to verify these findings.

Session 6: Butyrylcholinesterase genotype and enzyme activity in relation to Gulf War Illness: Preliminary evidence and ongoing studies of gene-exposure interaction
— Dr. Lea Steele
Veterans Health Research Program, Professor, Yudofsky Division of Neuropsychiatry
Baylor College of Medicine

The focus of Dr. Steele's presentation was her 2015 study with Midwest Research Institute to evaluate the association of butyrylcholinesterase (BChE) enzyme activity and genotype with the risk of developing GWI. She provided a brief synthesis of evidence from the large body of studies of GWVs that have identified neurotoxicant exposures, prominently acetylcholinesterase inhibitors (AChEi), as the most consistent risk factors for GWI. She then summarized the role of BChE in protecting the body from adverse effects of AChEi and preliminary studies suggesting that some BChE genetic variants potentially convey greater vulnerability to AChEi. Her 2015 study objective was to determine if GWI case status and/or GWI risk associated with "cholinergic exposures" differ in relation to Veterans' BChE enzyme activity and/or genotype. There were 304 participants in the study: 144 (Kansas definition) GWI cases, 160 GWV controls. When GW exposures were not considered, no differences were identified between GWI cases and controls in relation to BChE enzyme activity or genotype. In contrast, veterans with less common genetic variants (LCV) of BChE, associated with reduced BChE enzyme activity, were found to have markedly greater odds for having GWI (OR = 40.0, $p < 0.001$) if they used pyridostigmine bromide (PB) in theater, compared to LCV veterans who did not use PB. This represented a substantially greater PB-associated risk had occurred among veterans with more common/more active BChE genotypes (OR = 2.68, $p < 0.001$). Study results provided preliminary evidence suggesting that GWV carriers of slow-acting BChE genetic variants were more vulnerable to long-term effects of the carbamate PB, taken prophylactically during the Gulf War as a protective measure against adverse effects of nerve agents. Findings also underscore the importance of a key methodological issue for GWI genetic studies. That is, effects of genetic variants potentially linked to vulnerability to particular GW exposures must be evaluated in conjunction with those exposures. Dr. Steele then presented results from a small exploratory GWI–PON1 evaluation study that demonstrated this principle. Findings from both the BChE and PON1 studies are currently being followed up in larger, multi-cohort studies led by Dr. Linda Chao (PON1) and Dr. Tricia Janulewicz Lloyd (BChE).

Session 7: Modeling the Genetic Basis of Individual Differences in Susceptibility to Gulf War Illness

— 1. Dr. James O'Callaghan
Head, Molecular Neurotoxicology Laboratory and CDC Distinguished Consultant, NIOSH
Laboratory of Molecular Neurotoxicology, Centers for Disease Control & Prevention

— 2. Dr. Byron Jones
Professor, Genetics, Genomics and Informatics
Univ of Tennessee College of Medicine, Dept of Genetics, Genomics, and Informatics
Dept of Pharmacology

This was a two-part presentation by Drs James O'Callaghan and Byron Jones. The first part was presented by Dr. O'Callaghan. Dr. O'Callaghan's Laboratory developed a mouse model of GWI to mirror exposures and neuroimmune effects exhibited by ill veterans. Exposures included a nerve agent surrogate diisopropyl fluorophosphate (DFP), sarin, chloropyrifos, dichlorvos (DDVP), pyridostigmine bromide, N, N-Diethyl-meta-toluamide (DEET) and corticosterone (CORT) used to mimic physiological stress of the war theater. As GWI symptoms are similar to sickness behavior, neuroimmune effects in the brain were examined that are known to underlie sickness behavior. A two-pronged approach was developed: an acute "In Theatre" and a chronic "Long-Term" GWI phenotype. Under each of those model systems specific environmental and genetic factors, both direct and indirect, were looked at to determine possible causes for GWI. The C57BL6 male mouse was selected as both the "in theater" and "long-term" model; however, the experimental system was also extended to a rat model. To conduct the study the models were exposed to chemicals and conditions reported in the Gulf War such as the organophosphates (DFT, CPF DDVP, Sarin), PB pills and stressor surrogates CORT and test potential therapies for those substances. The animals were tested at established time-points to determine the GWI-relevant compounds and treatments. The results indicated that all the organophosphates induced neuroinflammation in the acute model and this effect was markedly enhanced by prior administration of CORT. Episodic stressor CORT exposures followed by immune challenge with LPS, in the long-term model, revealed an enhanced neuroinflammatory response caused by the initial exposures to organophosphates and CORT. Treatment of the long-term GWI mouse phenotype with propranolol ameliorated the enhanced neuroinflammatory response to innate immune challenge with LPS. Studies indicated that exposure to CORT and DFT not only instigates acute neuroinflammation, but also affects the long-term response to future immune challenge. The treatment used was a beta-blocker propranolol (blood pressure, chest pain medication). Model results showed a reduction in induced GWI.

Dr. Jones presented the second part of this study. Dr. Jones' research was based on Dr. O'Callaghan's C57BL/6 mouse model; however, he focused on genetics and genomics. The research question Dr. Jones asked was, if 25 to 30% of GWV developed GWI, what about the other GWV? To do this research he developed another model using 30 BXD mouse strains, derived from C57BL/6 and DBA/2 hybrids. The research model was able to identify two candidate genes, namely *Spon1* and *Ccr6.*that underlie individual differences in susceptibility. The Ccr6 gene is part of the Ccr6-CCL20 pathway which is involved in inflammatory diseases and immune system function *Spon1* has similar roles in neuroimmunity. *Ccr6* may also have a role in autoimmune diseases like ALS.

Conclusion from the study determined: a) there were specific gene-environment interactions in the mouse model of GWI; b) a sex-based difference in GWI; c) identification of phenotypic and expression-based candidate genes; d) possible new therapy targets.

Session 8: Associations of Immune Genetic Variability with Gulf War Illness in 1990-1991 Gulf War Veterans from the Gulf War Illness Consortium (GWIC) Multisite Case-Control Study

— Dr. Kimberly Sullivan
Research Associate Professor, Boston University School of Public Health, Dept of Environmental Health

The GWIC was designed to bring preclinical (cell and animal) and clinical (human) research together to speed development of understanding the pathobiology of GWI, identify diagnostic markers and to develop treatments for the disorder. The consortium consisted of 16 collaborators from nine study sites including the United States and Australia. The primary focus of the consortium was to research the brain-immune pathways and chronic release of chemical messengers and excitatory neurotransmitters (cytokines and chemokines) from the immune cells of the brain that lead to chronic inflammation.

One focus of this study program was to look for biological differences in development of GWI and to answer the question why some Gulf War veterans developed GWI while others did not. Another important question was why there are variations in illness severity in those who did develop GWI. A study hypothesis was formed to address these questions and determine whether GWI biomarkers reside in genes that control or enhance inflammation (e.g., transforming growth factor (TGF), TGF beta (TGF-β)) and could account for these differences in GWI susceptibility and severity of illness.

The specific study aim of this study was to investigate the associations between a number and location of genes that are associated with immunity and pain and GWI in Veterans with and without the illness. To perform this study, a GWI genetic risk model was used to implicate immune genetic variability. This study compared biomarkers from Veterans recruited from the (GWIC) Study which included 223 GWV with GWI and 46 asymptomatic GWV. Veterans participating in the study met the Kansas GWI case definition for inclusion and exclusion. The researchers analyzed genomic DNA isolated from collected saliva samples. Due to a lack of statistically acceptable sample population, the final study analysis consisted of Caucasian only including 170 GWI cases and 34 controls.

From a large group of suspected immune, inflammatory, and pain factors/markers commonly associated with GWI, the study identified the TGF-β, Interleukin 6 receptor (IL6R) and Toll-like Receptor 4 (TLR4) genes as being markers of risk that are both specific and sensitive. When those factors were statistically modeled to accurately predict GWI, TFG was 60%, IL6R was 65%, TLR4 was 58%, and all three combined had a 71% accuracy for predicting GWI. Working with these results further studies can be initiated to identify specific therapies to improve the daily life of GWV living with GWI by personalizing treatments based on the person's genetics. This was the first study to model the impact of genetic variability in pro-, and anti-inflammatory cytokines and receptors, immune pathways and pain signaling pathways to determine the risk of GWI.

The increased levels of TGF-β and IL6 can cause a heightened and prolonged inflammatory response commonly associated with GWI. While the TLR4 variant protected against the inflammatory response associated with GWI. This GWIC study was the first of its type to implicate an immune genetic variability of several specific genes associated with GWI. From these initial results, a further study is now funded to increase the sample size to increase accuracy of results; to refine the model to increase the accuracy of prediction percentage of GWV with GWI and/or to identify additional GWI-associated gene subgroups for risk and resiliency of GWI.

Session 9: Million Veteran Program
— Dr. Sumitra Muralidhar
Director, VA Million Veteran Program

The Million Veteran Program (MVP) is a national VA research program launched in 2011. It was designed to advance precision health care by learning how genes, lifestyle, and military experiences and exposures affect health and illness. It is one of the world's largest research programs of its kind with over 864,000 Veterans enrolled as of December 2021. Despite its size, MVP still has several limitations. A breakdown of participants shows that 91% of participants are male and 70% are Caucasion. African Americans make up 17.3%, Hispanic 8.2%. The average participant's age is 67 and date of service is 1964 through 1975 (Vietnam Era). To increase participation and diversity, a focused women's marketing campaign, which included podcasts, social media, blogs and engagement sessions, was initiated. Between March and September 2021, MVP successfully enrolled over 4,000 women Veterans.

As a research program, MVP has helped launch several research databases and initiatives. MVP-MIND (Measures Investigating Neuropsychiatric Disorders) is a mental health precision medicine initiative to identify and validate brain and mental health biomarkers. CIPHER (Centralized Interactive PHEnomics Resource) is a catalog and knowledge-sharing platform of electronic health records (EHR)-based phenomics metadata and annotations whose aim is to optimize Veterans' health data, drive research and improve clinical operations. CIPHER serves as a central location for collaborating, sharing and browsing content curated by researchers and clinical stakeholders across the VA community. In addition, MVP has contributed to over 30 research projects, 75 publications, was a resource for over 500 researchers and affiliates, and helped in the filing of four patents. As of 2020, MVP has helped in COVID-19 research. These MVP contributions and resources have helped determine genetic basis of infections, severity, complications, response to treatment, disease mechanisms and post-COVID symptoms.

In the future MVP plans to increase diversity of participants, expand data access and continue to analyze and publish findings; expand analyses to address other important questions related to GWI using the CSP 2006 cohort, and to look at GWV experiencing neurologic conditions, to name but a few initiatives. But most importantly, according to Dr. Muralidhar, MVP looks to establish health care pipelines to move the scientific discoveries into the clinic to improve Veterans' health and well-being.

Session 10: Fireside Chat
— Invited Speakers and Committee

DR. STEINMAN: Okay. Well, I'll tee up the question. One of the most extreme interpretations of what I've heard about genomics and risk factors, there is contemplation of using VA data to inform the DoD of who is at risk for certain exposures and to try to minimize those risks where possible? That's just a starting question. And people can get more central, but any reaction to that radical type of question? In other words, don't send people near burn pits if they have genes that make them at great risk factors for burn pits.

DR. HAUSER: Thank you, Dr. Steinman. I've been working in human genetics for 30 years and it's been a constant disappointment at how poorly these genetic variants by themselves predict disease. And so I don't think we're nearly ready for that. One of the things we see is that in, you know, extreme heterogeneity across all of the different exposures and the way they manifest themselves in these Veterans. And so we have a lot more work to do. I don't think it's ready for prime time in that way at all.

DR. STEINMAN: Probably an intervention like, if at all possible, don't make tobacco usage so easy, even with all the stresses on the combat theater of operation, that smoking's not going to be helpful to you downstream and the risk factor for smoking outweighs many of the other subtle risk factors.

DR. HAUSER: That's a good analogy.

DR. STEINMAN: All right. Somebody else key up a question please, or comment.

DR. WALKER: Dr. Steinman, could I address a question that came up in the chat after my talk? This is Cheryl Walker.

DR. STEINMAN: Yes, please.

DR. WALKER: You know, one of the really interesting things that I saw several people pose was what kind of intervention or would these epigenetic alterations be reversible? And I have to say there's a lot of promise that they can be. And so this is actually one of the great differences about a disease that's driven through an epigenetic alteration versus a disease that might be driven through a genetic mutation. The mutations, of course, are essentially irreversible. But it does seem like we can reset the epigenome. So there's some promising research there, not ready for prime time yet, but the answer to the question is we really think we can.

DR. STEINMAN: I think your point is well-taken, even for genetic mutations, the ones that I'm familiar with as a neurologist, many of the mutations don't bite you until you're 50 or 60 years old. And that comes from everything from Huntington's Disease with a small number of polyglutamine repeats to the SOD (superoxide dismutase) mutation and motor neuron disease. You have it in every cell of your body, and you've had it all your life. Why does it only hit you when you're 40, 50, 60 years old? You were fine playing first base like Lou Gehrig until you were 39 years old and, all of the sudden, something got you. So anything one could do, if you could put the clock way to

the future, then you could live throughout your life with those mutations and not even know about it, just an idea.

DR. WALKER: A great aspirational goal. I love it.

DR. STEINMAN: But it's staring us in the face. We've got those mutations all our life for the genetic diseases. Some diseases will bite you very early, there's no doubt about it, the spinal muscular atrophies, as an example, from something I know about. But anyway, fire out some other questions, reactions, comments.

DR. MURALIDHAR: This is Sumitra. I just want to also add that who knows where the new quest for technology will take us. Maybe we will be able to fix changes in genes as well in the future.

DR. STEINMAN: Very good.

DR. SULLIVAN: This is Kim Sullivan and I'd just like to go back to your first question, Dr. Steinman and, you know, I agree with Dr. Hauser. I'm not sure we're ready to say that, you know, certain people can't be in particular jobs and things like that, but I do think we have enough evidence to show that the PON1 -- I'm sorry, that the PB pills, the pyridostigmine bromide pills should not be used in deployments any longer because we certainly seem to have enough people that were very, very affected by it and have chronic health effects, you know, whether some genetically related and some not, but I think that should be something that should not be used in future deployments.

DR. STEINMAN: Yeah. I mean your point is well-taken. Speaking far outside my expertise, but my guess is you can't fly an F-15 if your vision is not real good. And, you know, so we already have -- you know, you can't fly an F-15 if you're too tall, but you can do other things in the military. So, we do have a certain set of screening procedures for different roles. So, I don't think it takes anything off the board to be intelligent about who does what.

DR. HELMER: Can I follow-up on that? So, one of the questions that came to my mind is, you know, even if we're not ready to institute some sort of policy that says you have this mutation, therefore, you shouldn't be doing this or you shouldn't be taking this medicine or something, even if we're not quite there yet, would it be helpful to be more systematic and include some of the genetic characterization in our clinical workup of Veterans? I saw that show up in the chat as well. I think maybe that's where we are in terms of taking it out of the research environment and, perhaps, and I want everybody's reaction to this, moving it into, perhaps, a protocolized clinical evaluation of Veterans with Gulf War Illness.

DR. STEINMAN: Well, I think that point is very well taken.

Dr. Jim Woody, you were very much involved with medical research command. Any reflections from your perspective?

DR. WOODY. Well, we know that, you know, some people are more susceptible to things and unfortunately, with the Gulf War, the wide range of toxins that they were exposed to make it very, very difficult to sort this out, but I think that your epigenetic stuff is very interesting and there's a

whole host of epigenetic modifiers out there for cancer therapy. So, it'd be nice to be able to reverse some of these and your comment was very well-received.

DR. STEINMAN: Jim, there's about 500 listeners on the call. Could you just describe, if you care to, what your role in the medical research command was in the Gulf War?

DR. WOODY: Yes. I served in Cairo, Egypt for four years, running Navy Medical Research Institute No. 3. We did infectious disease surveillance over entire Eastern Africa, Saudi Arabia, a whole range of things for anything ranging from Ebola, Congo-Crimean Hemorrhagic fever, AIDs, tuberculosis, hepatitis. And so, we had a huge database of information for the entire area. And when the Gulf War started, you know, we didn't know what would be there. When we went, they asked us to set up a very sophisticated lab on the front lines of the first Gulf War, and so we did. We had about 30 people over there who were monitoring for all infectious disease and biological warfare agents. And the chain-of-command reported directly pretty much to Schwarzkopf's staff. So, we actually didn't find a lot of infectious disease. There was some, sandfly fever, but that was one of the reasons people wore these vests with pesticides in them, because they were afraid of sandfly fever; which caused its own set of problems, as we just heard. We didn't find any. There were no biological warfare agents used. Although, they were in the area and my team found them later, but they had been buried or burned, so that was the role that we played until the war was over.

DR. STEINMAN: Thanks, just for some colorful background from one of the members of the Committee.

What do people think about having participants better informed about what the study is? I know there was informed consent, but along the way, after they start participating to give them interim peeks at what's going on, how much awareness is that among people running these studies? If you're doing a study on genomic variants, do you invite the participants for a biannual fireside chat like this to have them ask you and you tell them what's going on in the field and what's going on in the study? Is there any move to do something like that?

DR. HAUSER: So, I can say in CSP 585, we just sent out our fourth newsletter to all the participants and invited comments and, you know, from them as well, so they have an opportunity to comment if they want. And it's lovely to sit down and write for that newsletter to, you know, bring forward the results we have. And I look forward to doing that more.

DR. STEINMAN: Great. Any other questions, comments from others on our committee on what you heard, what you think can be improved and anything you think we should not be doing?

DR. BLOCK: Larry, this is Karen. I was wondering if I could ask some of the scientists some questions.

DR. STEINMAN: Please.

DR. BLOCK: I have a few, and Dr. Walker, maybe I could start with you. Here, let me turn my camera on. I really enjoyed your talk. And I think that it was really interesting to hear you talk about the road map and how these methylation patterns can be mapped like that, and then you

talked about the epigenomic clock as well. One question I have is do you think that these kind of signatures or strategies could be used to help diagnose exposure assessment or to do exposure assessments?

DR. WALKER: Theoretically, yes. You know, our knowledge of how any specific agent affects the epigenome is very limited right now. And as you might imagine, it could be very different from one cell type or one tissue or even one individual, based on their genetic background to another. For exposure assessment, I think we're still a little bit further away. I think, though, that possibly, for understanding whether epigenomic reprogramming, for example, is a contributor to the Gulf War Illness, you know, I think a survey of the epigenome, of Veterans that are suffering from that, would be one strategy and then compare with those that are not for comparison. I really loved the talk on the Million Veterans Program. I think that's a wonderful program and was delighted to hear that epigenetics is being looked at. I just might want to make one small comment. There's really two flavors of epigenetics and epigenome out there. One is the epigenetic marks that are directly on the DNA itself and the other, the epigenetic marks that are on the proteins that complex with the DNA make up chromatin. The marks that go directly on the DNA tend to be more like light switches. They'll tend to turn things on and off, whereas the ones on the proteins are more like rheostats and for the most part, when we see disease associations, not always, obviously, cancer is an exception and a few others, but very often, the disease association is the rheostat, something is too high or too low, not that it's completely on or off. So, I would love to hear some more about whether or not the Million Veterans Program is looking at both DNA methylation as well as some of these histone marks. But I don't want to cut off your time to ask questions, so I'll be happy to follow up myself afterwards.

DR. MURALIDHAR: Well, I'll just say that we're looking at DNA methylation at this point because we're just starting our initial mix work, just piloting. We haven't really advanced that far yet.

DR. WALKER: Thank you.

DR. BLOCK: And another question I had was for Dr. Sullivan. I was wondering, like, in your study where you look at and found TGF-beta, you know, that's a very high marker with people with type 2 diabetes and it can lead to, like, type 2 diabetic neuropathy, for example. When you have these proteins or other kind of genes that are functioning, I guess, in so many common backgrounds, like diabetes, did you control for that or do you know how that might play a role in Gulf War Illness?

DR. SULLIVAN: Yes, Karen. Good question. So that's why I was really making sure I mentioned that, you know, we use the Kansas Gulf War Illness criteria in this study and that we did not have people who have had other disorders. So if someone, for example, had, you know, uncontrolled diabetes, they were not included in our study. That wasn't what we were particularly looking at. I hope that answers your question.

DR. BLOCK: Yeah. It does. Of course, a lot of people have some kind of maybe diabetes, or they're predisposed or they're on that line and they don't realize it, of course.

DR. SULLIVAN: Sure. Yeah. And do we have some of those folks within our group that don't have it now, yeah, absolutely. And that's a very good point and something we'll make sure we're

watching because in our new BBRAIN study, we're bringing some of the same people in from the GWIC, so we will do longitudinal follow-up of some of the same folks.

DR. BLOCK: And then the other question I had was on the BChE and the PON1. Are those redundant pathways? I mean it seems like there was a talk earlier, I think it was the second talk, but I'm not really sure. But anyway, the activity of the BChE didn't change, and so they were looking at the genetic variants and they were trying to apply that towards Gulf War Illness. And I'm just wondering if the activity isn't changing or if there is a redundancy between PON1 and the BHC pathway, how relevant do you think that these players really are for Gulf War Illness?

DR. STEELE: Karen, are you asking me? It's Lea. I can respond.

DR. BLOCK: Okay.

DR. STEELE: Okay, yeah. So those are really, really important questions. The findings for butyrylcholinesterase enzyme activity is that it does not differ between cases and controls, but also butyrylcholinesterase does not have a stable level of enzyme activity over time, so it could've been way low during the Gulf War and it would just be normal now or it could be different from day-to-day, depending on different things. So, so far, it doesn't look like butyrylcholinesterase enzyme activity is informative in relation to Gulf War Illness. The opposite is true for PON1. The enzyme activity is more stable over time. And it is associated with the PON1 genotype. The PON1 experts of the world say that we really need to consider both in evaluating risk factors related to PON1. Now, the other question about whether the genotypes and enzyme activities are independent of each other between PON1 and butyrylcholinesterase, the common wisdom is that they are independent of each other. These are two separate pathways, and they are not the same genes. People don't believe they're linked. I will tell you we had a little pilot information from our earlier studies that say they might be, so that will be one of the questions we look at in the current studies with Dr. Chao and Dr. Janulewicz.

DR. BLOCK: Yeah, and I was also, Doctor, still looking at your data regarding the PB pills and the logs for, you know, the scores that you were talking about, about it being relevant or not relevant to Gulf War Illness, but I thought was interesting is when it's -- like the PB pills were associated but then it was like you heard the alarms go off and that wasn't giving you the same kind of high signal that it was with the other, but many times when people heard the alarms, they were taking the PB pills. So how do you know they weren't? I mean you're shaking your head no, but how do you know in your cohort how many times they were taking that?

DR. STEELE: No, I'm so agreeing with you, actually, the ascertainment of exposure during the Gulf War has been a challenge from the get-go. And we just used the chemical alarms question as a proxy for possible exposure to nerve agents. We don't know whether or not people took pyridostigmine bromide at the same time and if they heard chemical alarms, if all did or some did, you know, what the proximity was. So, you know, we just asked, and we can tease out in our analyses whether the combined exposure is more important than either one of them individually. That's been a real challenge in Gulf War research, using population studies, being sure to control for the effects of one exposure when we're looking at another exposure. And it's completely doable and in our butyrylcholinesterase studies, there was no connection between butyrylcholinesterase and being in proximity to chemical alarms and possible exposure to nerve agents. But that is

possibly as expected because PB is a carbamate and the preliminary indicators we have are that butyrylcholinesterase, some genotypes are poor in binding carbamates, but the chemical alarms would've been going off if there were nerve agents that were organophosphates and that would've been a different chemical connection and not necessarily associated with butyrylcholinesterase at all. We expected to be potentially associated with PON1, though. And so there, we're so interested in seeing if the different Q and R alleles predict whether you're at high-risk for exposure from possible chemical agent exposure or possible pesticide exposure. I think what's coming home study after study is that this is complex and it's not probably just one exposure. And it may not be the same exposures for different people. So, you know, teasing out this puzzle, I think is definitely worth doing to, one, prevent anything like this happening again, but also inform us about the path of virology of what's causing the symptoms.

DR. BLOCK: Yeah, I agree. Thank you so much. Back to you, Larry.

DR. STEINMAN: Fine. Let's go around and sort of do this as a volleying in a game with a net. Let's have Dr. Jones and O'Callaghan reflect on Dr. Steele's talk. And Dr. Steele, if you could reflect on the talk from your colleges, Dr. Hauser and Dr. Vahey and I just wanted to see if we can elicit some kind of controversy. I don't think we are going to. I think we're going to have agreement and a nuanced discussion but let me try that as a technique to challenge, too. Or pick on any one you want.

DR. O'CALLAGHAN: All right. Lea and I picked on each other in a collegial way over way too many years, but I think the point Lea just brought up, its complexity keeps on emerging, so, you know, PON1, butyrylcholinesterase, variants, these are all contributors to the overall phenotype that we see that is diverse across all ill Veterans. And it's not surprising that animal models cannot exactly address all of these potential differences. And after all, what we have are models, in rodents predominantly, to try and reflect what's going on in man. All we can do is correlate, associate what we see with what emerges in the variety of studies of ill Veterans. And I think that we've made a lot of progress under the consortiums that Dr. Sullivan mentioned and showed data from. For example, we know that we're really pretty firm on this being a neuroimmune disorder because we can see in ill Veterans, through PET imaging, evidence of neuro-inflammation that is consistent with animal models and the other — all the other data we've seen related to cholinesterase inhibition and variants of the enzymes. It's not supposed to be clear. It's complex. And we just need to move on.

DR. STEINMAN: Very good.

DR. STEELE: You didn't pick on me very much there, Jim.

DR. O'CALLAGHAN: I'm sorry.

DR. STEELE: I just want to concur with what you said, yeah. And I would just say that, to me, it's been rather remarkable. We have some pretty darn consistent results across all the human studies, both clinical and the larger population studies. And then in the animal studies, Jim's model and even some other models that actually look at somewhat different combinations of exposures, they produce a biological profile that is associated with the kinds of symptoms we see in Gulf War Veterans. And not only that, but the pathobiology would be expected to precipitate those

symptoms. So I feel like this isn't as much of a big mystery as we've always thought. The etiology is complex, definitely, and we're not going to understand this without embracing that issue.
But just in terms of understanding the pathobiology, I think between the animal models and what we're seeing in humans and then the preliminary studies, like from Kim's GWIC study and the genetics, and I feel like it's really converging to give us a picture that's consistent.

DR. BARANIUK: This is Jim Baraniuk. I have to really reinforce that, especially for the Veterans that are on the line, think back 10 years ago. Think back to when Dr. Steele helped edit the first Gulf War Review. How much has been learned, how the far the technology has taken us and now there's actually drug studies being run at several institutes around the country. I think this is a fabulous example of federal dollars through the DoD Congressional Directed Medical Research Program (CDMRP) really being put to good use. And the emphasis that they put upon moving towards treatment, all of these studies, such as the Million Veteran Group are going to have fantastic data. If you're a Gulf War Veteran and you haven't volunteered or aren't part of that, then shame on you. You're not part of the solution to this issue. One of the things that sort of bothers me from the Million Veteran Program, though, is I'm not sure what is going to happen with the Gulf War Illness group. From the presentation, it sounds like you've got 14,000 deployed; 26,000 not deployed, but we can't move forward because there's no definition. And I've been hearing this, oh, we're going to talk about a definition, going to work on the definition. It seems like it's years, they're still talking. And you're saying without a definition, you won't proceed to analysis. Fair enough, I suppose. Once you get a decision, who is the group that's actually going to be reviewing the Gulf War Illness data? And has that been designated or are we going to have to compete with grants to access that data? What's the timeline for understanding the Gulf War Illness group out of the Million Veteran database? What's the timeline? And another point is that you've got Gulf War Illness and I've seen a lot of PTSD, over a lot, and some traumatic brain injury. It's going to be important, at some point in the analysis to include those overlapping phenotypes because some of the symptoms are very similar. Can I get a better idea as to who is going to be working on this analysis?

DR. HAUSER: I'd like to respond to that. I think that's a great question. We know that the case definition has been extremely difficult. We've had a hard time as researchers applying -- you know, relatively new researchers to go forward on this, applying it. But one of the great things about having such a large data set in the MVP program is that instead of using a defined Gulf War case illness definition, we can use all the symptoms that go into the definition itself and look to see what clusters on a genetic basis. So, we're using structural equation modeling. My colleague at Yale, Renato Polimanti, is leading this very highly, really exciting analysis, using structural equation modeling on the symptoms themselves. So, we'll be able to compare how those line up with the classic Kansas definition, the classic CDC definition that we've already implied. But the same analysis is true for the exposures. We can put all of the exposures in there at the same time and look to see what clusters on a genetic basis. So the large size of that data set allows us to do things that we haven't been able to do before. And if we can get an even bigger data set, it will be even better, so I'm extremely excited and Renato and his team are pushing forward.

DR. BARANIUK: So, the big data set is essential because of the effect size?

DR. HAUSER: And the complexity.

DR. BARANIUK: Well, we've seen lots of studies come out. I liked the epigenetics in particular that showed the survival curve and that, to me, is the type of intuitive informative statistics that we need. But from that, we need to get an effect size for how large the difference is between the two sets of epigenomic outcomes so we can predict the sample size for future studies, but none of the investigators have mentioned anything like that. And it's often not even in scientific publications. So, if you can think about what your effect sizes are like, I'd like to hear it. With the epigenetics, I'm also wondering, the saliva DNA was used by Dr. Sullivan and their group with the Oragene tubes. Has the saliva cell type been included in the NIH's epigenome database?

DR. WALKER: This is Cheryl Walker.

DR. BARANIUK: Hi.

DR. WALKER: Hi, great questions. I would actually want to go and double-check. You know, those could be buccal cells. They could be long epithelial cells. I would be surprised if they were not, particularly considering it's such an easily accessible biofluid. But maybe while this conversation is going on, I'll quickly go to the website and see, thanks.

DR. MURALIDHAR: This is Sumitra and I just wanted to address the question about data access and future research in the Million Veteran Program. You know, up until now, we were largely constrained by the computing that's available and how many people and also being within the VA competing environment. We are expanding, as I mentioned, and once the data comments goes live as to which we're expecting to start that in fiscal year 2023 (FY23), there, you know, the de-identified data sets will be available to all researchers to apply for. Also, starting this spring and summer, all VA investigators can apply for MVP data access through the existing mechanisms we have within the VA Office of Research and Development and we are starting to see that. And we have a great group that's working on a lot of things now. And a lot of the work products will be, you know, like all of the case definitions that they define will become part of the centralized library I mentioned, so first year researchers don't have to start from scratch and do it all over again. They will be able to take advantage of the current work that's being done and make progress more quickly. That's the plan.

DR. HELMER: This is Drew Helmer. Let me chime in here. So Dr. Baraniuk, I think a couple of things, so the goal of the CSP 2006 is not to create a new case definition. As we described in the design manuscript how we're proposing to start with these analyses and we basically adopted, you know, the CDC and the Kansas definitions and a couple of, you know minor variants. But, you know, it's been a challenge to operationalize that with the data we have available, but we're there. We actually have a what we call the phenotype paper where we're going to describe the cohort, deployed versus not deployed and get this information out to the public so that they can see how we did this and see how this looks in this cohort of 41,000 Gulf War Era Veterans. And so, you know, stay tuned. That's hopefully going to come out very soon. And as Dr. Muralidhar has shown you, we've done some internal presentations of these results at these MVP science meetings, so this is a work in progress and something that's been the highest priority, actually, for this working group in CSP 2006. There is a lot of opportunity to refine or explore alternative phenotypes that might be consistent with Gulf War Illness or variations on a Gulf War Illness theme, as opposed to the unbiased approach that Dr. Hauser was talking about, which I think is an opportunity that hasn't been available to anybody because we haven't had the sample size to

really explore some of these things. There's been a lot of vetting of these data, you know? We got access to our cohort data basically about a year ago, maybe a year-and-a-half ago. And it's been a lot of effort to wrangle the raw responses into usable variables. And so we're just now getting to the point where we're able to disseminate the important findings you're asking about and that we're looking for.

DR. BARANIUK: Good, thank you. I'll look forward to it. Yeah, it -- now, will a new parallel, excuse me, definition or set of criteria, will that have long-term effects on VA disability decisions? That, of course, is a VA decision that they will make behind closed doors. I'd just throw that out there. Again, they tried to use the SEID, Systemic Exercise Intolerance Disease criteria as an additional criteria for Gulf War Illness without ever testing whether that criteria applied to Gulf War Veterans, so this will be very good, I think, because it -- the information is being derived for a large population of Gulf War Illness and deployed Veterans.

DR. SULLIVAN: This is Kim Sullivan. I just want to respond to Jim Baraniuk's good and poignant comments and just want to make the pitch again for some kind of a code for Gulf War Illness. So I think VA has needed an ICD-10 code for a very, very long time. And if there's any way to make that happen, I think this would greatly speed up, you know, these studies to be able to identify, you know, who has Gulf War Illness and who doesn't and also not only on the research side, but as you mentioned, Dr. Baraniuk, on the political side as well.

DR. BARANIUK: Just to go a step further, applying this research, translating it into a Gulf War Illness dashboard for doctors in the Veterans Affairs, VA Hospitals to be able to make the diagnosis is going to be important. And I think talks like this, it's amazing. Why don't we have anyone from the -- doctors from the VA that are interested in listening to us? How many presentations have we made of the VA -- of the research at VA hospitals? I was involved in one at Tampa, but I think we had mostly Veterans with Gulf War that were there and really think that is there a way that this Committee can be charged to show what the research is, present what the research is to clinicians?

DR. STEELE: Hi, it's Lea Steele. I am just going to answer that because I have been watching the chat throughout this meeting and a repeated comment is that for all of the research that's been done and all we've learned about Gulf War Illness, you know, the Veterans go to the doctor at the VA and/or their own primary care provider and they've never heard of Gulf War Illness or they tell them it doesn't exist. And so they're just really stuck. They can't find a doctor to take care of them that knows much about this. And that's not a good thing at all 30 years after the war. I don't know if that would be a charge to the committee to actually help educate the clinicians or perhaps the risk? I know they hold different seminars and things for VA doctors, but it's really a much-needed education effort, for sure.

DR. STEINMAN: Yeah. Let me just remind everyone that I am a huge supporter of communicating science at all levels. I think it's the responsibility of us scientists, but this is, and we have to remember the context of this committee. And I say this again and again, I don't particularly like the context of this committee, but the context is the context is something that we have to take --

DR. STEINMAN: I'm just hesitating because it's hard for me to think and talk and listen at the same time, so if people can mute.

MR. PEPINSKI: Sir, I just muted everybody for you, if you could go ahead and continue.

DR. BLOCK: Larry, you're muted.

DR. STEINMAN: Oh, okay. I'll make this short. We're the Research Advisory Committee and I'm a physician. I'm a strong believer in communicating science to the public and communicating science to individuals who I take care of as a physician, but this is a government committee. We're the Research Advisory Committee. Our mission is to advise the VA on research into Gulf War Illness. So I think it's a tragedy that a person goes to a doctor and the doctor has no idea and never heard of the illness. Maybe research grants should be given to help communication and we could deal with that issue, but I don't think research grants are the way to deal with that issue. I'll just give you one anecdote and then I'll be quiet. One of our earliest face-to-face meetings was at the Houston VA. And they have a trophy case of major combat operations. And there was no mention of Gulf War in this, no mention of the Gulf War at all. And there's been a tragic amount of miscommunication about the duration of that war, the impact of that war, the risks that people took in fighting that war. And it was stark and members of our committee served in the Gulf War and there they were having a meeting and out in the room that's supposed to acknowledge this service, there was nothing. Anyway, we're the Research Advisory Committee. And I just don't think we can help doctors. It's a VA problem. Maybe in my next gig, I'll try to do something on that front, but I really think it's outside our mission of the Research Advisory Committee to solve everything and to solve this specific horrendous problem when doctors in the VA have no idea what the Gulf War Veterans were even talking about or what the Gulf War was. That's the end of my talking points.

DR. BARANIUK: Thank you.

MR. WATTS: This is Bill Watts, one of the RAC members and a Gulf War Veteran. I have a question for all of the researchers that presented today. And that question is, of your Veterans that went through and did your research, how many of them were recycled Veterans from previous research? And do you feel that that previous research could have affected your results of your current research?

DR. BARANIUK: Hi, this is Dr. Baraniuk. Let's say that maybe 20 percent have been in other studies. I don't feel that their participation in the other studies altered the results that I found or had an influence on the studies that I did.

DR. STEINMAN: It's a good question you do raise, Bill. There are certain circumstances I could imagine if blood specimens or spinal fluid specimens are taken, it may have a minimal impact or it may not. If it were more in the area of psychological testing or psychological scales, previous encounters with testing could have a compound on the study. So that's a really good question you're posing.

Male Gulf War Veteran: Hello, doctors.

DR. SULLIVAN: This is Dr. Sullivan. I just want to answer that, also. And I would say, you know, we end up with probably less than 20 percent in some of our studies, but it depends on the study.

So some studies are designed to be longitudinal studies, so we want the same people to come back so we can follow your symptoms over time. So it depends on the study design, but I would also mentioned that, you know, as a neuropsychologist, we are very mindful of people who have already done cognitive parts of our testing. And we've done cognitive assessments for 20 plus years. And so we're very careful about making sure if someone has done some of these pieces before that we span it out a certain amount of time so that it's not -- you know, you're not testing now and then you test in another study a week later and then you know all the tests. So that's a very, very important thing, Dr. Steinman, to mention. And that's something we are very mindful of in all of our studies. Now, that said, we also want to be careful, if we're doing multi-site genetic studies, that we don't get the same people and then we're counting them twice. So that's another issue. And so we've had conversations about things like universal IDs, where you de-identify, but you have a universal ID for someone so that you're not counting them multiple times. So that's something we're dealing with in some of our studies and I would think some of these bigger studies like the Million Veteran are doing as well. But these are very, very important things to be thinking about from a methodological standpoint when you design your study.

DR. STEINMAN: I recall there being a memory test in a certain study at some time in my career and the individual who was the subject of the test said, "Doctor, at this point, aren't you supposed to ask me if I remember those five things you said five minutes ago?" And I had to say, "Oh, I forgot. Thank you for reminding me." So that individual was definitely influenced by previous testing and made me look like the rookie that I was.

Male GWV: I'm not sure the format here and I apologize if this has been answered already. I've been bouncing between this and a litany of other things I have ongoing here, but as a Gulf War vet, a combat vet that's been diagnosed with a litany of different maladies and ailments, I've come across peripheral data that suggests some of our maladies are passed on to our children. Is there any substantive research that discusses how our kids are affected? And I ask that because I have a child that's been hit with a litany of autoimmune concerns because they can't be diagnosed. And, of course, Western medicine strives to bridge that gap by saying that it's, you know, somatic symptom disorder because they can't diagnose it any other way. And so I'd like to know if there's research available that I can dig into deeper that, you know, can help bridge that gap and get better care for my daughter because I think that, you know, while I did volunteer, she didn't, but she's paying the price for my decision some 30 years ago.

DR. STEINMAN: Karen, maybe you can talk about the portfolio of work going on regarding that subject. Thank you.

Male GWV: Thank you.

DR. BLOCK: Yeah. Thanks for that question. We were going to have a talk today a little bit about the National Academy of Medicine report that came out in 2018 on the generational effects of military exposures, but we couldn't get the person in to give that talk. Actually, I would like to have maybe Dr. Walker explain a little bit about this subject. She has a lot of research on it. But just for, I guess, bottom line up front, the literature does not support, you know, health problems in Gulf War Veterans' children, like from exposures. So we don't have any evidence yet. And there has been a number of studies to suggest it's even happening. But maybe Dr. Walker can talk about some of the general biology. And one question I was going to ask Dr. Walker to talk about

was if it's a genetic inheritance, doesn't it have to skip a generation? So is it fair to say that some exposure would have to happen either during pregnancy or if it was some modification to some germ line cell type that it wouldn't have an effect on the generation, the first generation, it would skip a generation. It would be more seen in grandchildren, rather than the children themselves?

DR. WALKER: So thank you so much, Karen, for the invitation to make a comment. This could take up an entire meeting. And it is an incredibly important as the science is moving very fast around this area. I actually was a member of that committee. And like a lot of these academy reports, it was heavily, heavily weighted onto the epidemiology side, which is completely appropriate. And in this particular realm of science, most of the data for proof of concept that transgenerational inheritance occurs is not from human populations. We take too long to get to multiple generations. Most of the data are in model systems, but if Mother Nature has taught us anything, it's that we are not that unique in our biology. You know, when you think of the Nobel Prize and what we learned about cell division, most of those studies were done in yeast. And so we know from model organisms much more about the biology and how transgenerational inheritance happens than we do in people. And so actually, the report essentially said, at the end of the day, was we don't know. And what we understand is absence of evidence is not the same as evidence of absence. So but Karen what you are right, no matter what we are exposed to, if we don't transmit information through the germ cells, through the egg or through the sperm, it doesn't become generational. It doesn't become part of the next and subsequent generations. And so some of the most exciting work that's going to on out there is we are starting to understand what it is in the sperm and the egg that can be transmitted to the next generation. And at least in terms of the epigenome, reprogram that epigenome of the next generation and the following generation. So you can tell I'm kind of going on and an on because I think this is an incredibly important area. But if the Committee is looking for opportunities, and my guess, your dance card is already pretty full, but this whole concept of transgenerational inheritance of the military exposure, the adverse health effects, I think, would be a great one to consider.

DR. STEINMAN: Has it been put to rest that some of the exposures in the combat theater of the Gulf War were actually mutagenic? We know that, you know, if you were in Hiroshima or Nagasaki, radiation is mutagenic. What about some of the environmental materials? Are they mutagenic? Because then it reverts the question back to straightforward, it damaged the genome.

DR. WALKER: I'm going to leave that to my genetics colleagues to answer.

DR. STEINMAN: I'm saying this to Spencer and many that we've had in previous meetings and discussing this in our Veteran Engagement Sessions about generational effects. But one statement you made is that absence of evidence is not evidence of absence. So maybe the people at NIOSH or other places can just say whether they believe or not that it's slowly been put to rest, that there was nothing mutagenic that our soldiers encountered.

Male GWV: By the way, I love that term. Thank you so much and to add a little color to this, we've spent the better part of a decade trying to figure out what our daughter is going through and we've gone so far as to have conversations with geneticists here at the Medical College of Wisconsin. And in a conversation with one of those subject matter experts in the space, roughly, he had said that even with the human genome project, mapping out the genome some 20 years ago and then studying it subsequently over the last couple of decades, while we have identified them, we

haven't accurately mapped them to the point of, at this time, a couple years ago, I think he said it was something to the extent of 80/20 percent of what the connection of that and what that network looks like. And of those, maybe have a thorough understanding of what's happening at the genetic level down to two percent, suggesting then that we have a 98 percent gap of a thorough understanding of the root cause or the base reflection of health as we know it. And I think that touches back on, you know, the absence of evidence is not evidence of absence. And I think that taking that humble approach on what we know now reflects the opinion we can share. However, we're nowhere near knowing what we need to understand thoroughly, and more research needs to go forward, rather than an absolute opinion with diagnosis after diagnosis after diagnosis, arguing that the evidence says as much. I appreciate your time and thank you for hearing me out.

DR. STEELE: Spencer, I might have some information that might be helpful to you, Spencer.

DR. STEINMAN: I'm sorry, go ahead.

DR. STEELE: And that is that exactly what Cheryl just said, the absence of evidence and evidence of absence has been an ongoing issue and definitely there's nothing definitive. But there were a number of early studies looking at birth defects and very limited studies looking at other health problems in children. Again, they're not definitive, but there are -- there was a private registry established for people to report problems their children were having.
And so they assembled a report and they had some information about what other parents have said their children have experienced. And also, there are a few online groups of parents who served in the Gulf War who have children with health problems. So, you know, sorry we don't have better strong evidence, but there are some resources.

Male GWV: Given the robust feedback that Dr. Google and Mr. Bing provide, do you have something specific I can search and look for those groups and that evidence?

DR. STEELE: I would have to look up those Facebook group members, but I bet some of the Veterans of the chat could give it to you right away. I don't have it off the top of my head. We could contact later if you want.

Male GWV: I've seen chat on the subject already. Thank you.

DR. RUMM: Dr. Steinman, can I jump in? This is Dr. Rumm.

DR. STEINMAN: Sure.

DR. RUMM: Okay. I work in the VA Office that's now called Health Outcomes & Military Exposures (HOME). And I can just tell you there's a lot going on in looking at all kinds of disease conditions throughout all deployments and conflicts and also with garrisons. Dr. Dursa, one of my colleagues in the office actually published with some other people on the Gulf War and in one with brain cancer did have in the Khamisiyah plume an increase in the first ten years and then it went away. So we're looking at, in particular, cancers and rare cancers and doing a lot of work. I also just want to mention very briefly, I know it's not the focus of this, but there is training that's now been mandated for providers in the VA on military exposures and the VA Secretary signed it off about a month-and-a-half ago. And we're working with the American College of Preventative Medicine

to have a two-level certification process in environmental exposures. So there's a lot going on in that spirit. And finally, we, like Karen, get written a lot of these things about intergenerational health effects and I shared with Karen on a work group that gave recommendations back to the Secretary. And it's a topic that comes up, not only in this conflict, it also comes up in the Vietnam conflict quite frequently. And so I can just tell you it has the interest of our leadership.

DR. STEINMAN: Thank you very much on all of those fronts. And I want to thank everybody who gave a lecture today and participated in this chat for all of the effort. I learned a tremendous amount and I hope everyone else did.

Session 11: Public Comments
— Visitors and Invited Guests
— Moderator: Mr. William Watts, Committee Member and 1990 – 91 Gulf War Veteran

MR. WATTS: Thank you very much, Dr. Steinman. First of all, I'd like to thank all of the Veterans that showed up today. Since I've been doing this, today has been the highest number ever that has joined one of our RAC meetings. First, please, everyone be cordial with your questions. You don't have to get outrageous with them, use curse words. Be very respectful. If someone is speaking, please don't unmute yourself and interrupt them. Let them complete it and let the doctors answer their questions. When you ask your question, please use your first name, your location and maybe the unit you were assigned to during Desert Storm. Each person will be given three minutes of time to speak and since there was such a great number of people that have showed up today, if you've previously spoken at an RAC meeting, please allow those that have never been able to speak to have a chance to go in the beginning. And going from there, there is one gentleman that we've already scheduled to speak first. That would be a Mr. Paul Sullivan. Are you available, sir?

MR. SULLIVAN: Good morning, Mr. Watts. Yes, this is Paul Sullivan. I'm available.

MR. WATTS: Can you go ahead and please let us know what it is you'd like to know about?

MR. SULLIVAN: Yes, Mr. Watts. Good afternoon, Chairman Steinman and members of the RAC. And my special thanks to Dr. Block for facilitating my participation in today's meeting. My comments are as an individual Desert Storm Veteran. I was with the 1st Armored Division as a calvary scout during the ground invasion. Hard to believe that was 31 years ago. I guess we're getting old.

As one of the authors of the legislation to create the RAC and as the author or one of them of the RAC's original charter, what I'd like to do today is share with the RAC and the audience how the RAC fits into the larger and interconnected picture of the research, treatment and benefits for the hundreds of thousands of Gulf War Veterans. I start off by mentioning that Secretary McDonough told the Senate during his confirmation hearing that he would place improving access to VA healthcare and benefits at the top of his list of priorities for the Biden Administration. Therefore, consistent with the RAC's mission, I'm an ill Gulf War Veteran stakeholder providing input as a consumer so the RAC continues to be a key player informing the Secretary so he can continue to improve access to VA care and benefits. Because in 1991, there were about 700,000 of us and now there are about 4 million of us who have gone to the War in the last 31 years.

The law I mentioned, the Persian Gulf Veterans Act of 1998 established the RAC to provide Veteran stakeholders with direct input to the Secretary. I would really hope that he would attend the meetings and see and hear for himself what's going on. The law also provided for two years of free care for Gulf War Veterans who went to Southwest Asia and the 1998 laws setup a process for VA to review scientific research so that VA could grant disability benefit claims. Such a process, called presumptive service connection is needed because generally, a Veteran can only receive free VA care after a Veteran has filed and won a VA disability claim for service connection. The main exception to that rule is now the five years of free care that I helped to work to enact in 2008 where a Veteran gets five years of free care at VA if they deployed to a war zone since 1998.

I submitted a long statement, but in the interest of time, what I want to do is boil this down please to five quick requests. The first is the most important and I ask that the RAC should be alerted and should alert the Secretary to the urgent need to preserve the standalone Gulf War Illness CDMRP. It's currently facing redlining in congress and it's now pending before Congress. This would have a very serious and adverse impact on the research for Gulf War Veterans, especially for treatments that we fought for outside the VA.

Again, the main mission of the RAC revolves around research. It's clearly within the RAC's mission to reach out to the Secretary so the administration relays to congress full support to restore the status quo of the standalone Gulf War Illness CDMRP. I want to note that CDMRP has funded the majority of the Gulf War Illness treatment for the entire federal government for 16 years. I and others that I know have worked tirelessly to make sure that that research continues.

Moving on quickly to my second ask of the RAC, please, I know you do a good job in this meeting, please use the correct name, Gulf War Illness, because it's a physiological condition. I just want to point out that yes, words matter. In the notice that went out to this meeting, it mentions a collection of symptoms. Yes, there are symptoms, but this is a physiological condition associated to toxic exposures. It's very clear. Let's make sure we get that right. The third, and this is very important, it connects to the fifth request. I asked the Research Advisory Committee to ask the VA Secretary to produce the texts for all of the VA contracts to the National Academy of Sciences. It's important for the Research Advisory Committee, and the role you have on research, to know what it is that VA has asked the Institute of Medicine (IOM) and now the National Academies of Sciences, Engineering, and Medicine (NASEM) to do. Why is that? The 1998 law mandated that NASEM consider animal studies for benefits. However, in the NASEM reports, the NASEM doesn't make any recommendations based on animal studies. We believe that happened because someone took out a portion of the 1998 law that should've been in the contract that would allow the NASEM to make a recommendation on service connection for conditions found to be associated with exposure when the studies were done on lab animals.

So again, this was very important, and I'll connect the dots in a couple of minutes. My next request, and I was really glad to hear someone mention that there are new clinical guidelines coming up. Thank you for mentioning that. I just want to ask if someone could answer when I'm done, was the set of new guidelines passed through the Research Advisory Committee, was it vetted? And if so, what was the input that the RAC gave? Were the Veteran services organizations involved in vetting it? Were Gulf War Stakeholders, like me, and others who are seriously ill involved? I

would kindly ask that if those vetting opportunities were not done, that VA consider doing those before releasing the materials. And I say this as a Gulf War Veteran who has gone into VA for more than 30 years, not once ever has a VA medical professional ever known that we were exposed to sarin, mustard gas, military strength pesticides, pyridostigmine bromide, oil-well fire pollution, particulate matter, burn pits, radioactive uranium, et cetera, et cetera, unless, the one exception is the Gulf War Registry Exam, where those people were specially trained. So the clinical practices I would really like to see that and all Veterans should see it before it goes VA-wide. Let's make sure it's ready for prime time.

And then the last request for the RAC would be to make sure that the RAC knows that research and treatment and claims are connected. When a Veteran wants to get care from VA, the Veteran has to file and win their disability claim, unless they're within that five-year window. However, VA is denying 80 percent of the claims. What that does is VA's denial prevents the Veteran from accessing the care that the RAC and others are trying to provide to Veterans. We have to fix that. If all the great treatment in the world is provided and we have all of this understanding of Gulf War illness, but VBA still denies the claims, the Veterans are still locked out of the system.

And I remember the first time I mentioned this to a RAC and then to the Institute of Medicine, there were top scientists and VA employees who were unaware of the linkage between the work of the RAC, the work of the NASEM and the Veterans Benefits Administration and treatment. So I really want to wrap up by saying please, when the RAC and others who are involved in this issue are looking at Gulf War Illness, remember it's a big picture involving research, treatment and claims about real people, Veterans who are sick like me, who have faced enormous problems trying to get into the VA system. I really hope the RAC will listen to the other Veterans who are speaking today and collaborate with us so that we get the best research, so that we get the best treatments and the claims process can be fixed so that Veterans can get into the research and the treatment.

And I thank you very much, Mr. Chairman. That concludes my comments. And if anybody has any questions, please let me know.

MR. WATTS: Dr. Block or Dr. Steinman, would either one of you like to address any of that?

DR. STEINMAN: I prefer, that was very articulate. We hear your message. We're in communication. I'd like to leave the last 20 minutes so that other people can also speak.

MR. WATTS: Okay. I was asked to allow Marsha to say something real quick. Marsha, are you there?

MS. TURNER: Yes, thank you, Bill. I just wanted to let you know that there are two GWV that have asked to speak next?

Female GWV: Good afternoon. First of all, thank you for all of the great information you've provided here today. I am a retired first sergeant in the Gulf War and theater of the 689th Quarter Master Company. My concern here today is a lack of diversity on your study samples. Hopefully, we can be included in all sectors where there are females or people of color in your next study. My company was completely devised, and I have asked them before have they had any one reach

out to them concerning any studies and they have stated no. So, if that could be included in some of the studies, I would appreciate it. And again, thank you very much.

MS. TURNER: Thank you. A male GWV had mentioned he wanted to be sure that joint pain and the anthrax vaccine, are you on the line? He's unable to speak but sent in a message. He just wanted to make sure that this goes on the record, that joint pain, knees and elbows, et cetera, as the result of anthrax vaccination inoculation programs isn't on the record for today's meeting.

MR. WATTS: Okay. Thank you very much, Marsha. You have anything else?

MS. TURNER: No, thanks.

MR. WATTS: Okay. Next person, are you where you can speak?

Male GWV: Yes, yes, I am.

MR. WATTS: All right, sir. Please go ahead.

Male GWV: Certainly. And hey, I wanted to thank everybody for doing the research. I think it's interesting, but I'll get straight to the question. I was a Marine. I served in Afghanistan with Regimental Combat Team 7. So, I know I'm not an older Gulf War Vet, but the question is, is this a one-way street, you know? Is the damage to our bodies reversible in any way if we were to exercise or to, you know, have a proper diet to mitigate some of these things? And I guess that's a question to the genetic researchers. Thank you.

MR. WATTS: Thank you very much. One of the researchers want to answer that, please?

FEMALE VOICE: I'm just a statistician, so I don't, I can't answer that directly, but I really liked what Dr. Walker presented in terms of the biological aging measurements. I think that if we can understand what treatments would allow us to back those up a little bit, it would be really impactful.

MR. WATTS: Thank you very much. Any of the other researchers?

DR. STEELE: This is Lea Steele. Actually, there are some studies looking at dietary interventions that suggest that some dietary changes could be helpful in Gulf War Illness. There are also reports, a subgroup of Gulf War Veterans have appear to have exacerbation of their symptoms. If they exercise so it's actually the answer is we don't really know, but there's not a cookie-cutter answer that we know or something that could help reverse your symptoms.

MS. VAHEY: This is Jackie Vahey who gave the presentation with Dr. Hauser. I think, also, this is why this research is so important because we can't fix what we don't know about. And so as we learn more on the biology side, we can start asking better questions about how to fix the problem and we can't do that until we really understand what's going on.

Female GWV: My question is we should go ahead and publish from the VA or from the states that we have these conditions, like if we don't know that Alzheimer's is out there, then we don't know how to fix it or what we can do to help people with that. I think that's important. I'm also a Veteran

who has stress dementia and with PTSD and depression. I think it's very important for people to know that there are these types of disabilities that you are trying to do research on. I'm also an African-American and I also agree that we should do more studies on people of color. Thank you.

MR. WATTS: Thank you very much, ma'am. Next on the list, okay.

MR. WATTS: Next speaker, are you there? Speaker, if you're there, you may need to unmute yourself.

Male GWV: How do I get on the list?

MR. WATTS: What's your name? I will add it.

MR. WATTS: Okay. Hold on one second. Next speaker.

MR. WATTS: I got you on my list. Next speaker, are you there?

MR. WATTS: All right.

Male GWV: I am.

MR. WATTS: Oh, thank you, sir.

Male GWV: Yes, I was in the Gulf War '90, '91 with the First Cav 43rd Support Group. I have been kind of just present through life here and recently, in the last few years, have, through counseling, been kind of finding out that I've had some issues related to the Gulf War and so this is kind of new to me. I did have a question, though. I had cancer a few years ago, but it was human papilloma virus (HPV) and had a lot of surgery and chemo and all of that kind of stuff and my question is there's been a lot of research that shows how the immune system is affected and lowered basically by some of this toxic exposure. And I'm wondering is this a -- no one in my family has ever had HPV or anything like that and for me to get that and have all of the issues I did, especially at my age, it was kind of a shock to even the doctors. And I'm curious, is that a common thing among Gulf War Veterans? And thank you for everyone that's participated today.

MR. WATTS: Dr. Drew, Dr. Helmer, Karen? Would any of you like to answer?

DR. HELMER: This is Drew Helmer. I'm not aware of any specific research on HPV, which I'm assuming you mean human papillomavirus, which is a virus that has been associated with cancers, causes cancers. And the epi studies, the epidemiologic studies of cancer in Gulf War Veterans is ongoing because, you know, as this cohort -- as our Gulf War veterans age, cancer isn't a condition of aging, it does increase with age and we are still trying to make sure that we are not missing a signal with regard to cancer among Gulf War Veterans.

Male GWV: Okay, thank you.

DR. BLOCK: Bill, can I just read a couple emails that came through from my end?

MR. WATTS: Sure. Go ahead, Karen.

DR. BLOCK: One is a GWV whom wasn't able to speak, but he wants to know if anybody has any issues. He has joint problems or he's looking to see if anyone else is experiencing joint problems as a result of the anthrax vaccine. So if you can put that in the chat, that would be great. Another one just came in and a Veteran asked, "Should I be part of the Million Veteran Program to assist in research or should Veterans continue to try to explain their disabilities to VA doctors who continue not to understand or connect medical problems to their military service?"
I would say yes to both, not one or the other. I think the Million Veteran Program, definitely getting as many Gulf War Veterans as we can to sign up through there so that we can do those genetic studies, they are so powerful and they're telling us a lot. And regarding your doctor, as Dr. Rumm mentioned, there is a lot of education going on to physicians and there's a lot of outreach to do that, but it doesn't -- it's always good to have those discussions with your doctor. So let's all work together to keep the physicians knowing what Gulf War Illness is and we'll also rely on our VA partners at home to help outcomes in military exposures to do their training. Thank you, Bill.

MR. WATTS: All right. Thanks, Karen. Next up.

Female GWV: Hey, no, I'm sorry. I'm a Veteran, but I'm actually on this because of my husband who fought in the Gulf War. He was the first unit to go, 24th Infantry. He was a medic. So my question is, at the time, VA had denied all sinusitis, rhinitis, anything related once it had been diagnosed as asthma. I do know because there was a letter that came out, I got it August the 2nd, and I have gone out there and redone his thing to put the claim for his asthma, but my question is he has since had COVID twice, the first time with pneumonia, asthma attack; the second time, he got a pulmonary embolism and asthma attack. Is any of these researchers including COVID, especially when it comes to asthma and breathing issues?

MR. WATTS: Karen, Dr. Drew, I think that may be one of yours.

DR. HELMER: Well, so I was going to see if Dr. Muralidhar was still on, since she talked about this in her MVP presentation. We are proposing to use the CSP 2006 cohort of Gulf War Veterans from the Million Veteran Program, so that's the cohort of 41,000 Gulf War Veterans and to look at some COVID-specific questions, such as are Gulf War Veterans more vulnerable? Are Gulf War Veterans with Gulf War Illness more vulnerable to COVID? Are they more likely to have a certain type of complication? We are proposing that project right now. And maybe Dr. Block, if you want to say a little bit more, but that's where we are right now. Yeah, the VA has taken a big role in understanding, you know, COVID and clinical trials and long repercussions of COVID, long-haulers and hospitalizations and everything.

DR. BLOCK: The VA is very involved. Regarding Gulf War and Gulf War Illness and COVID, I think Dr. Helmer's, you know, research studies are the best opportunity we have to answer some of those hard questions, so we are currently working on that.

MR. WATTS: I'm trying to get people that haven't been here before. You may have to take yourself off of mute.

Male GWV: How would I get on the list, sir?

MR. WATTS: You ask to be on there. Are you ready to ask your question or do you want me to come back to you?

Male GWV: I am, sir.

MR. WATTS: Okay. Please go ahead and ask your question, sir.

Male GWV: I'm a Persian Gulf Veteran, 1st Cav Division. Is there any way -- I've listened to this entire thing. I'm amazed at the amount of research that has went on, very unaware of it. I don't know if I signed up for the Million Vet Program, but I will after this call. Is there any way to access VA's records for people that have claimed Gulf War Illness and solicit them for the information you're looking for?

MR. WATTS: Karen, that may be yours.

DR. BLOCK: Drew, can you explain the process for that? It's a little bit more involved, so Drew, I was wondering if you could just explain the process of how studies go about finding their cohort.

MR. HELMER: Yeah. So I think, you know, there were various studies presented and they probably all had slightly different ways of doing this. For example, Dr. Hauser talked about the CSP585 cohort where they went to the DoD and actually got a list of Veterans who had served in the Gulf War during a certain time period and asked for what we call a representative sample, so kind of a random sample. Other studies, like the Million Veteran Program, actually take volunteers. And so they advertise, you know, the opportunity to participate in the research and then the eligibility criteria.
So that's where that cohort comes from. And so it's more representative of Gulf War Veterans who use the VA. And then there are other studies that take kind of a -- you know, just a volunteer approach, send it out as wide as possible. I really want to echo the earlier comments about, you know, the need and desire to enhance diversity in research participation and I did notice in the chat that there are some challenges around the economics of this and also just the geography of this. So a lot of the research happens in the larger urban centers. And so we are very aware of that and generally, as a research community, try to find ways to counteract some of those barriers.

MR. WATTS: All right. Thank you very much, Drew. Okay. Next up are you available?

Male GWV: Yeah, Bill, I was unaware that I asked for a question, I guess.

MR. WATTS: I saw that up in the chat and I called on you.

Male GWV: No, I don't have any questions. I appreciate it.

MR. WATTS: Okay. Thank you, sir.

MR. WATTS: Okay.

Female GWV: I was with the 7th of the 101st Aviation Unit in the Gulf War during Desert Storm and Shield. I have been trying to get help on this matter and I guess for a long time. And I know you have studies and stuff that I guess a lot of us Veterans weren't even aware that was being conducted. I am not currently a member of the Million Dollar Veterans thing because I thought that was not going to affect my Gulf War — you know, the results way down the line because it's — I guess they don't know who you are, that's basically a random blind study. But a lot of the stuff that I've seen is only for certain people, so as a minority person, I haven't even seen any of these test things -- you know, the studies that you guys are having. But I would love to find out and get some research because I've had some issues since 2006, even the VA where I was going to school at, the VOC rehab (Vocational Rehabilitation) signed off and sent me down to have a specialist test my blood and everything before that. And exactly what the scientists are saying is what they figured out in me and that was over 10 years ago. But nothing ever went through to the registry about it or through up to Phoenix where they have the ratings and stuff as going on. So how — I know you said this RAC was different but how do we get everybody involved with it, I mean if everybody says it's not my job? For Veterans, we're the ones that get held with that, you know, what do we do next?

MR. WATTS: Okay, Karen. Do you want to give her some places to look so she can get into research?

DR. BLOCK: Yeah. That's a great question, and I appreciate that question. And I know that there's a lot of you on the call that have kind of asked this question. And usually, when a clinical study or a project is funded, then it's up to the research to identify the people that will be in their project participating. And that's how things are usually done, so there's — it's no surprise that a lot of people are -- that want to participate may not be called upon, but what we are working on at Office of Research and Development is more of a national list where hopefully we can get people like yourself and others that are interested in research, you know, come online and join a registry, if you will. So I'm going to get more information on that and get the information out. I'm trying to figure out how we're going to get it to all of the great people who have joined us today. We will talk about it at our next parent committee meeting, but that's not until September. We'll also be talking about it during our Veteran engagement sessions. If you can go on to the website, the RAC website, the Research Advisory Committee for Gulf War Veterans' illnesses, we'll put some information out there so that might be the easiest way. Otherwise, you can email us at our RAC website and give us your name and your email and we can send, you know, information out to you like when our meetings are coming up, et cetera. And then as I get that information about recruitment, I can let you know. So I really appreciate that and everyone on the call today has just been phenomenal and I really appreciate everybody joining us. It's been a really wonderful day.

Female GWV: Thank you.

DR. STEINMAN: Thank you, Karen.

MR. WATTS: Thank you very much, Karen.

DR. STEINMAN: So this is Dr. Larry Steinman. I want to close the meeting, thanking all of the participants. This was our biggest turnout. We still, according to what I see on my screen, still have about 375 people on the line.

Male GWV: No more questions.

DR. STEINMAN: This tells me that in the past, we have done two half-day meetings and that may be more appropriate. I hate to end any meeting when there are so many people that have pressing questions to ask and hopefully receive some answers, but we have been going at it for five hours and this is the formal time when we're stopping the meeting, but we've learned a lot and we hope we've answered questions. And I want to thank everyone for their service and for participating today, so I am going to sign off for the RAC Gulf War Illness Committee.

Male GWV: So there's no more questions?

DR. STEINMAN: No more. Well, I see that middle finger. And all I can do is smile. I sometimes feel the same way, but I'm going to be signing off and thank you everyone.

Male GWV: Can I ask a question real quick? Is there any way that people who didn't get their questions asked, maybe that some of the doctors would leave their emails in the chat that we could send something to? That would be great.

Male GWV: Why not leave the room open and let us talk? Why not leave the room open and let us talk? We're here.

Male GWV: Well, are the doctors going to stay on?

DR. BLOCK: We have to close the meeting, but feel free to send me your questions and I'll make sure they get to the doctors. This is Karen Block.

Male GWV: Hey, guys. Hey, guys. Listen, I am a diagnosed PTSD Desert Storm Veteran. I have Gulf War Syndrome and I have 100 percent. It took me 17 years and 7 retries. Do not give up. It can be done. It feels like it can't be, but it can be. This is a section that you guys need to examine is how hard the VA makes it for us to get our benefits. It's a huge factor of stress. It's probably the number one for me in the whole pursuit of this and it definitely needs to be included in your studies of us is how much that hurt us.

Male GWV: Thanks, Karen. I'm going to email you right now. Thank you.

DR. STEINMAN: Well, with immense respect to everyone on the phone who has questions, if we had a month, we wouldn't be able to answer them all, so we really have to sign off now and I thank everyone.

Meeting adjourned.

Acronym List

This list contains all acronyms from the January 27, 2022, RACGWVI Committee Meeting.

Acronym	Name
ACMO	Advisory Committee Management Office
ACOS	Associate Chief of Staff
AChEi	Acetylcholinesterase inhibitor
Alt-DFO	Alternate Designated Federal Officer
BChE	Butyrylcholinesterase
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Program
CIPHER	Centralized Interactive Phenomics Resource
CORT	Corticosterone
COVID-19	Coronavirus disease of 2019
CSP	Cooperative Studies Program
CSPEC	Cooperative Studies Program & Epidemiology Center
DDVP	Dichlorvos
DEET	N, N-Diethyl-meta-toluamide
DFO	Designated Federal Officer
DFP	Diisopropyl fluorophosphate
DNA	Deoxyribose Nucleic Acid
DoD	Department of Defense
EES	Employee Education System
EHR	Electronic Health Records
FAC	Federal Advisory Committee

FACA	Federal Advisory Committee Act
GWECB	Gulf War Era Cohort and Biorepository
GWI	Gulf War Illness
GWV	Gulf War Veteran(s)
HOME	Health Outcomes & Military Exposures
HPV	Human Papilloma Virus
IOM	Institute of Medicine
MIND	Measures Investigating Neuropsychiatric Disorders
MVP	Million Veteran Program
NASEM	National Academies of Sciences, Engineering, and Medicine
NIOSH	National Institute for Occupational Safety and Health
ORD	Office of Research and Development
PB	Pyridostigmine Bromide
PTSD	Post-Traumatic Stress Disorder
RAC	Research Advisory Committee
RACGWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
SMART (ACMO)	Specific (and strategic), Measurable, Action-oriented, Realistic (relevant/results oriented) and Time-based
SMART (VA)	Specific, Measurable, Attainable, Relevant, Time Bound.

U.S.	United States
VA	Veterans Affairs
VES	Veterans Engagement Session
VHA	Veterans Health Administration
VOC rehab	Vocational Rehabilitation
WRIISC	War Related Illness and Injury Study Center