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Challenges for Implementing a PTSD Preventive Genomic Sequencing Program in the U.S. Military

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CHALLENGES FOR IMPLEMENTING A PTSD PREVENTIVE GENOMIC SEQUENCING PROGRAM IN THE U.S. MILITARY

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There is growing interest in using the quickly developing field of genomics to contribute to military readiness and effectiveness. Specifically, influential military advisory panels have recommended that the U.S. military apply genomics to help treat, prevent, or minimize the risk for post-traumatic stress disorder (PTSD) among service members. This article highlights some important scientific, legal, and ethical challenges regarding the development and deployment of a preventive genomic sequencing (PGS) program to predict the risk of PTSD among military service members.

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I. INTRODUCTION

Technological superiority is an essential aspect of military readiness and effectiveness. To achieve this, the United States Department of Defense (DoD) invests approximately $70 billion each year in research, development, test, and evaluation programs.[4] These investments advance technologies that range from precision strike weapons and unmanned vehicles to environmental quality and medical technologies.[5] There is growing interest in using the quickly developing field of genomics to contribute to military readiness and effectiveness.[6] Specifically, influential military advisory panels have

4. U.S. DEF. DEP'T, DEPARTMENT OF DEFENSE BUDGET FISCAL 2014: RESEARCH, DEVELOPMENT, TEST & EVALUATION (RDT&E) PROGRAMS (R-1) 3 (Apr. 2013), http://comptroller.defense.gov/Portals/45/Documents/defbudget/fy2014/fy2014_r1.pdf [hereinafter DoD RDT&E].

5. *Id.* at N-5, A-6, N-12, A-3, D-48.

6. JASON, THE $100 GENOME: IMPLICATIONS FOR THE DOD 1 (2010) [hereinafter, JASON Report]; PATRICK LIN, MAXWELL J. MEHLMAN & KEITH ABNEY, ENHANCED WARFIGHTERS: RISK, ETHICS, AND POLICY 2 (2014).

recommended that the U.S. military apply genomics to help treat, prevent, or minimize the risk for post-traumatic stress disorder (PTSD) among service members.[7] This article highlights some important scientific, legal, and ethical challenges regarding the development and deployment of a preventive genomic sequencing (PGS) program to predict the risk of PTSD among military service members.

The field of genomics examines the informational content and functional dynamics of the genes that make up the human genome. An important endeavor in genomics is the identification of genetic variants indicating that an individual is at an increased risk of developing a poor health outcome, such as different types of cancer, heart disease, diabetes, and mental health disorders. Recently, the development of massively parallel DNA-sequencing technologies (MPS) has fueled progress in genomics by allowing the sequencing of numerous genes at a time and decreasing the cost of sequencing an individual's genome.[8] MPS has made whole genome- and whole exome-sequencing (WGS/WES) more accessible to researchers and clinicians, which is quickly expanding the medical community's understanding of the genetics of certain diseases and the potential applications of genomic technologies to both the civilian and military contexts.

DoD has long demonstrated an interest in implementing genetic technologies in the military. To date, DoD has implemented a successful DNA registry for identifying human remains, and routinely screens service men and women for genetic conditions such as sickle cell anemia and Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency.[9] The recent surge in WGS/WES research has further increased DoD's interest in applying genomic technologies to the

7. *See* JASON Report, *supra* note 3, at 43; *Million Veteran Program (MVP)*, U.S. DEP'T VET. AFF. (Mar. 25, 2015), http://www.research.va.gov/MVP/.

8. *DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP)*, NAT'L HUM. GENOME RES. INST. (Oct. 31, 2014), http://www.genome.gov/sequencingcosts/; E.D. Green & M.S. Guyer. *Charting a Course for Genomic Medicine from Base Pairs to Bedside*, 470 NATURE 204, 205 (2011); *see* Tom Walsh et al., *Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing*, 107 PROC. NAT'L ACAD. SCIS. 12629, 12629–30 (2010).

9. Hemoglobin S and Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency Testing Program, DoD Instruction 6465.1 (Jul. 29, 1981); Susannah Baruch & Kathy Hudson, *Civilian and Military Genetics: Nondiscrimination Policy in a Post-GINA World*, 83 AM. J. HUM. GENETICS 435, 439 (2008); Mark Nunes, *GenePOPS—Genes in Uniform: Don't Test, Don't Tell*, GENETICS & PUB. POL'Y CTR. (Jan. 10, 2006) http://www.dnapolicy.org/video/genepops/011006/index.htm.

military context. In 2010, the JASON Defense Advisory Panel released a report on the opportunities and challenges of WGS/WES technologies for the military.[10] The JASON report's major recommendation was a call to action:

> The DoD should establish policies that result in the collection of genotype and phenotype data, the application of bioinformatics tools to support the health and effectiveness of military personnel, and the resolution of ethical and social issues that arise from these activities. The DoD and the VA should affiliate with or stand up a genotype/phenotype analysis program that addresses their respective needs. Waiting even two years to initiate this process may place them unrecoverably behind in the race for personal genomics information and applications. [11]

PTSD was one of the few phenotypes specifically identified by the JASON report, which could be of benefit to DoD because it "might reasonably be expected to have a genetic component [and] have special relevance to military performance and medical cost containment."[12] Nevertheless, the use of PTSD genomics in the military raises a number of questions that must be addressed to avoid extemporaneous applications of genomic technologies that do not sufficiently maximize the benefits and minimize the harms of using these technologies.[13]

An examination of the challenges of implementing a PTSD-PGS program in the military was beyond the scope of the JASON report. This article aims to examine some of the important issues to consider when evaluating the potential use of genomics to identify risk for PTSD in the military and making decisions based on this information. Part II of this article provides a clinical overview of PTSD and examines PTSD as a problem for service members and the military, Part III examines some of the scientific challenges of establishing a PTSD-PGS program and presents the current state of psychiatric and PTSD genomics. Part IV considers some of the legal challenges regarding the potential implementation of a PTSD-PGS in the military, and Part V considers some of the important ethical questions involved.

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10. JASON Report, *supra* note 3, at 1.

11. *Id.* at 50.

12. *Id.* at 43.

13. *See generally* B.S. Wilfond & K. Nolan, *National Policy Development for the Clinical Application of Genetic Diagnostic Technologies: Lessons from Cystic Fibrosis*, 270 JAMA 2948 (1993) (describing issues linked with the use of an extemporaneous model for health policy development and arguing in favor of an evidentiary model).

II. PTSD AS PROBLEM FOR SERVICE MEMBERS AND THE MILITARY

PTSD can be triggered by exposure to actual or threatened death, serious injury, or sexual violation.[14] However, PTSD is not just any stress or aversive memory related to an actual or threatened traumatic event. PTSD is a trauma- or stress-related disorder with specific symptoms that must be present for at least one month.[15] A PTSD diagnosis requires the presence of one or two symptoms from each of the following symptom groups: Re-experiencing (e.g. flashbacks, spontaneous memories or recurrent dreams of the traumatic event); Avoidance (e.g. when an individual tries to avoid trauma-related thoughts, feelings or external reminders of the event); Negative cognitions and mood (e.g. persistent and distorted sense of blame of self or others, persistent inability to experience positive emotions, inability to remember key aspects of the traumatic event); and Arousal (e.g. aggressive, self-destructive or reckless behavior, exaggerated startle response, hypervigilance, problems with concentration, and sleep disturbances).[16]

The lifetime prevalence of PTSD in the U.S. general population is estimated at 6.8%.[17] However, the prevalence among service members is generally higher; for example, researchers estimate that 10% of Gulf War veterans[18] and 13.8% of Operation Enduring Freedom and Operation Iraqi Freedom veterans experience PTSD.[19] As one might

14. *National Center for PTSD: DSM-5 Criteria for PTSD*, U.S. DEP'T VET. AFF. (Jan. 3, 2014), http://www.ptsd.va.gov/professional/PTSD-overview/dsm5_criteria_ptsd.asp; AM. PSY. ASS'N, POSTTRAUMATIC STRESS DISORDER: DSM-5 CHANGES IN PTSD CRITERIA 1 (2013), http://www.psychiatry.org/File%20Library/Practice/DSM/DSM-5/DSM-5-PTSD.pdf.

15. *See DSM-5 Criteria for PTSD*, *supra* note 11.

16. *Id.*

17. Ronald C. Kessler et al., *Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication*, 62 ARCHIVES GEN'L PSYCHIATRY 593, 596 (2005).

18. Han Kang et al., *Post-Traumatic Stress Disorder and Chronic Fatigue Syndrome-like illness among Gulf War Veterans: A population-based survey of 30,000 Veterans*, 157 AM. J. EPIDEMIOL. 141, 145 (2003).

19. RAND, INVISIBLE WOUNDS OF WAR: PSYCHOLOGICAL AND COGNITIVE INJURIES, THEIR CONSEQUENCES, AND SERVICES TO ASSIST RECOVERY 97 (Terry Tanielian & Lisa Jaycox eds., 2008) [hereinafter INVISIBLE WOUNDS REPORT]; *see generally* INST. MED. NAT'L ACADS., TREATMENT FOR POSTTRAUMATIC STRESS DISORDER IN MILITARY AND VETERAN POPULATIONS: INITIAL ASSESSMENT (2012) (stating that the percentage of veterans that served in Afghanistan and Iraq that suffer from PTDS is between 13% and 20%).

expect, the incidence of PTSD among service members is closely associated to traumatic events experienced during combat exposure.[20] Therefore, due to the nature of their jobs, service members are particularly at risk of being impacted by PTSD. In fact, PTSD was the third-most common disability for veterans receiving compensation in fiscal year 2012, after tinnitus and hearing loss.[21]

The economic cost of mental health services is another aspect of the burden of PTSD and other mental health disorders. The estimated two-year cost of PTSD and major depression for 1.6 million service members returning home from Afghanistan and Iraq is between $4.0 billion and $6.2 billion, depending on whether that statistic includes the value of lives lost to suicide mortality.[22] Furthermore, the number of veterans needing mental health services increased from 927,052 to 1.46 million over the last eight years, which led the Department of Veterans Affairs (VA) to increase its mental health care budget 39% from 2009 to 2013.[23]

PTSD symptoms not only lead to a large degree of suffering for service members, but it also leads to suffering and difficulty for their families.[24] In particular, PTSD often leads to impairments in occupational functioning, which can limit service members' effectiveness on the job and force them to take time off work for treatment.[25] One concern among some military leaders is that PTSD

20. Tyler C. Smith et al., *New Onset and Persistent Symptoms of Post-Traumatic Stress Disorder Self Reported After Deployment and Combat Exposures: Prospective Population Based US Military Cohort Study*, 336 BRIT. MED. J 366, 366 (2008); *see* Naomi Breslau, *The Epidemiology of Trauma, PTSD, and Other Postrauma Disorders*, 10 TRAUMA, VIOL. & ABUSE 198, 203 (2009).

21. Richard J. McNally & B. Christopher Frueh, *Why are Iraq and Afghanistan War Veterans Seeking PTSD Disability Compensation at Unprecedented Rates?*, 27 J. ANXIETY DISORDS. 520, 520–21 (2013).

22. INVISIBLE WOUNDS REPORT, *supra* note 15, at 200.

23. U.S. DEP'T VET. AFF., 2013 PERFORMANCE AND ACCOUNTABILITY REPORT I-2 (2013), http://www.va.gov/budget/report/ [hereinafter VA P&A 2013 Report].

24. Lisa Gorman et al., *National Guard Families After Combat: Mental Health, Use of Mental Health Services, and Perceived Treatment Barriers*, 62 PSYCHIATRIC SERVS. 28, 31 (2011); Abigail H. Gewirtz et al., *Posttraumatic Stress Symptoms Among National Guard Soldiers Deployed to Iraq: Associations With Parenting Behaviors and Couple Adjustment*, 78 J. CONSULT. & CLIN. PSYCHOL. 599, 603 (2010); *see* Suzannah K. Creech et al., *Impact of Coping Style and PTSD on Family Functioning After Deployment in Operation Desert Shield/Storm Returnees*, 26 J. TRAUM. STRESS 507, 507 (2013).

25. Paula P. Schnurr & Carole A. Lunney, *Work-Related Outcomes Among Female Veterans and Service Members After Treatment of Posttraumatic Stress Disorder*, 63 PSYCHIATRIC SERVS. 1072, 1077–78 (2012); David A. Adler et al., *Psychiatric Status and Work Performance*

can affect military readiness and effectiveness by decreasing available manpower and military duty performance.[26] These issues, combined with the economic cost of PTSD, make PTSD prevention an important undertaking for DoD. A potential way to prevent or minimize the economic and biopsychosocial burden of PTSD in the military is to identify those service members who are at high genomic risk for developing PTSD and assign them to missions that will minimize their combat exposure or develop interventions that may help to decrease their chances of developing PTSD. When considering this possibility, one of the first steps should be to examine whether genome-based PTSD risk prediction is currently possible, and if not, to identify the scientific questions that remain to be answered before that goal can be realized.

III. SCIENTIFIC CHALLENGES FOR PTSD PREVENTIVE GENOMIC SEQUENCING

PTSD is a significant problem for the military, and in theory, genomics holds much promise for improving PTSD risk prediction.[27] However, in order to use genomics for PTSD risk prediction and make important personnel decisions based on this information, the military needs a solid scientific foundation that will allow it to reliably predict these risks. Recent developments in genomic technologies and psychiatric genomics research may eventually provide the military the genomic intelligence necessary to more reliably predict the risk of PTSD among service members. But, the field of psychiatric genomics cannot currently provide this robust scientific foundation, and it will probably not be able to do this for a number of years.

A. Psychiatric Genomics

To understand why reliable PTSD risk prediction based on genomics is not currently possible, and may not be for some time, we need to briefly examine the recent development and current state of psychiatric genomics. Uncovering the genomics of psychiatric disorders such as PTSD has proven to be a challenge.[28] Psychiatric

of Veterans of Operations Enduring Freedom and Iraqi Freedom, 62 PSYCHIATRIC SERVS. 39, 40 (2011).

26. *See* Michael P. Fisher, *PTSD in the U.S. Military, and the Politics of Prevalence*, 115 SOC. SCI. & MED. 1, 5 (2014).

27. *See* Nadia Solovieff et al., *Genetic Association Analysis of 300 Genes Identifies a Risk Haplotype in SLC18A2 for Post-traumatic Stress Disorder in Two Independent Samples*, 39 NEUROPSYCHOPHARM. 1872, 1876 (2014).

28. *See generally* Steven A. McCarroll et al., *Genome-Scale Neurogenetics: Methodology and Meaning*, 17 NAT. NEUROSCI. 756, 761 (2014) (concluding that while finding genomic markers for psychiatric disorders

disorders are complex diseases in which numerous genes and environmental factors play a role. In fact, even though the contribution of genomics is substantial,[29] environmental factors, such as exposure to stress or traumatic events, are believed to play a more prominent role in determining the risk for psychiatric disorders.[30]

Part of the difficulty in uncovering the genomics of psychiatric disorders stems from the fact that numerous genes are involved and each of these genes contributes only a small amount to the overall risk of developing a psychiatric disorder.[31] In addition, individuals can have different combinations of genes that put them at risk, and these genes interact with other genes and environmental factors to shape overall risk.[32] The small contribution of individual genes to the overall risk of developing a psychiatric disorder means that researchers need to examine very large samples of subjects with psychiatric disorders. Then, they need to compare their genetic profiles to carefully selected controls in order to obtain the statistical power necessary to detect the contribution of these genes (hereafter referred to as the "statistical power" problem).[33]

As a further complication, there are more than 20,000 protein-coding genes in the genome. Thus, in the pursuit of genes that are associated with psychiatric disorders, researchers face a challenging needle-in-a-haystack problem as well. For years, researchers tried to formulate informed hypotheses about which genes could contribute to the overall risk for a psychiatric disorder in order to focus their research on those genes that they believed were more likely to play a

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has progressed since 2009, when a more complete human genome was finally mapped, this is still in a nascent stage); *see* Stephen B. Manuck & Jeanne M. McCaffery, *Gene-Environment Interaction*, 65 ANN. REV. PSY. 41, 61 (2014); *see* Karestan Koenen et al., *From Candidate Gene to Genome-wide Association: The Challenges and Promise of Posttraumatic Stress Disorder Genetic Studies*, 74 BIOL. PSYCHIATRY 634, 635 (2013).

29. *See* Patrick F. Sullivan et al., *Genetic Architectures of Psychiatric Disorders: The Emerging Picture and its Implications*, 13 NAT. REVS. GEN. 537, 538 (2012); *see* Roger K. Pitman et al., *Biological Studies of Post-Traumatic Stress Disorder*, 13 NAT. REVS. NEUROSCI. 769, 777 (2012).

30. Teri A. Manolio, *Bringing Genome-Wide Association Findings Into Clinical Use*, 14 NAT. REVS. GEN. 549, 551 (2013).

31. *See id.*; *see* McCarroll et al., *supra* note 25, at 761; *see* Manuck & McCaffery, *supra* note 25, at 42.

32. *See* Manuck & McCaffrey, *supra* note 25, at 42.

33. Aiden Corvin et al., *Genome-Wide Association Studies: A Primer*, 40 PSYCHOL. MED. 1063, 1070–72 (2010).

role.[34] Unfortunately, this *candidate gene* approach has proven inefficient and generated numerous inconsistent and contradictory findings.[35]

B. How are Psychiatric Genomics Addressing these Challenges?

In recent years, researchers have begun to perform large-scale genome-wide association studies (GWAS) to address the statistical power and needle-in-a-haystack problems.[36] GWAS studies address the needle-in-a-haystack problem because, unlike candidate gene studies, they follow a hypothesis-free approach by examining large numbers of genes without an *a priori* determination of which genes might have any predictive value for psychiatric disorders. [37]

Even though GWAS help address the needle-in-a-haystack problem, this approach involves a great number of statistical tests,[38] which exacerbate the statistical power problem in psychiatric genomics. This means that GWAS for psychiatric disorders require even larger samples than candidate gene studies. Therefore, in order for GWAS to detect the many genes that make a small but significant contribution to the overall risk for psychiatric disorders, GWAS need samples that can be in the order of thousands of case and control subjects—perhaps even into the tens or hundreds of thousands.[39] Conducting these large-scale GWAS involves a great amount of resources and coordination that single research projects are often unable to achieve and therefore progress in psychiatric genomics can be slow.

In recent years, psychiatric genomics researchers have begun developing conglomerates, such as the Psychiatric Genomics Consortium in order to pool resources and datasets.[40] This approach

34. See Koenen et al., *supra* note 25, at 634–35; *see* McCarroll et al., *supra* note 25, at 756–57; *see* Pitman et al., *supra* note 26, at 769-70.

35. *See* Pitman et al., *supra* note 26, at 777; Marylin C. Cornelis et al., *Genetics of Post-Traumatic Stress Disorder: Review and Recommendations for Genome-Wide Association Studies*, 12 CURR. PSYCHIATRY REPS. 313, 314 (2010).

36. Corvin et al., *supra* note 30, at 1063; Anna C. Need & David B. Goldstein, *Schizophrenia Genetics Comes of Age*, 83 NEURON 760, 760–61 (2014).

37. *See* Corvin et al., *supra* note 30, at 1072.

38. *Id.* at 1071.

39. *See id.*; *see* Koenen et al., *supra* note 25, at 634; Schizophrenia Working Grp. Psy. Genomics Consortium, *Biological Insights from 108 Schizophrenia-Associated Genetic Loci*, 511 NATURE 421, 421 (2014) [hereinafter PGC Schizophrenia Nature 2014].

40. *Psychiatric Genomics Consortium*, UNIV. N. CAR. SCH. MED. (2014), http://www.med.unc.edu/pgc.

has allowed researchers to combine sets of GWAS data in order to conduct mega-analyses for a number of psychiatric disorders.[41] The result of this large-scale GWAS and GWAS mega-analyses approach has been unprecedented advances in uncovering some of the genetic bases of schizophrenia[42] and to a lesser extent bipolar disorder, major depressive disorder, attention deficit hyperactivity disorder, and autism.[43] They have also identified a number of genes that play a role across numerous psychiatric disorders.[44] However, these large-scale GWAS and mega-analyses approaches have not yet been applied to PTSD genomics.

C. What about PTSD Genomics?

Genomic influences account for 30%[45] to 70%[46] of the risk for PTSD, but PTSD genomics research has confronted the same statistical power and needle-in-a-haystack problems described above for research with other psychiatric disorders, together with a number of other complications particular to PTSD.[47] For example, PTSD studies are not consistent in the way they define cases of PTSD or the characteristics of the control groups, some researchers use trauma-exposed controls while others do not.[48]

To date, PTSD genomics research has relied mostly on candidate gene studies.[49] Although these studies have identified more than twenty genes associated with PTSD such as SLC6A4 (also known as 5HTTLPR), DRD2, FKBP5, and PACAP, many consider these findings suspect because of how difficult it has been to replicate

41. Sullivan et al., *supra* note 26, at 543.

42. *See* Need & Goldstein, *supra* note 33, at 762; PGC Schizophrenia Nature 2014 *supra* note 36, at 424.

43. *See* Psychiatric Genomics Consortium: Results, UNIV. N. CAR. SCH. MED. (2014), http://www.med.unc.edu/pgc/results.

44. Cross-Disorder Grp. Psy. Genomics Consortium, *Identification of Risk Loci with Shared Effects on Five Major Psychiatric Disorders: A Genome-Wide Analysis*, 381 LANCET 1371, 1375–78 (2013).

45. Murray B. Stein et al., *Genetic and Environmental Influences on Trauma Exposure and Posttraumatic Stress Disorder Symptoms: A Twin Study*, 159 AM. J. PSY. 1675, 1675 (2002).

46. Carolyn E. Sartor et al., *Common Genetic and Environmental Contributions to Post-Traumatic Stress Disorder and Alcohol Dependence in Young Women*, 41 PSYCHOL. MED. 1497, 1502–03 (2011).

47. *See* Solovieff et al, *supra* note 24, at 1876–77; *see* Koenen et al, *supra* note 25, at 635–36; *see* Pitman et al, *supra* note 26, at 780, 783; *see* Cornelis et al., *supra* note 32, at 323.

48. *See* Solovieff et al., *supra* note 24, at 1873.

49. *See* Stein, *supra* note 42, at 1675.

candidate gene PTSD studies.[50] In contrast, large-scale GWAS and GWAS mega-analyses studies of schizophrenia have identified more than 350 genes that are reliably implicated in schizophrenia.[51] Some PTSD GWAS studies have begun to emerge in the literature.[52] These studies have identified some new genes and provided evidence for the association of others that had been reported in candidate gene studies.[53] However, PTSD GWAS studies have used relatively small samples, which as recognized by the authors of these studies is a limitation that needs to be addressed in order to advance the field of PTSD genomics.[54]

Fortunately, efforts are underway by prominent researchers to develop large-scale GWAS and mega-analyses for PTSD within the Psychiatric Genomics Consortium. [55] These efforts should help speed the process of uncovering the genomics of PTSD and these are not the only ongoing large-scale efforts. The VA is currently taking advantage of developments in MPS technologies, which have decreased the cost of WES, to help lead the charge towards uncovering the genomics of PTSD. In 2011, the VA launched the Million Veteran Program (MVP) "a ground-breaking genomic medicine program, [which] endeavors to collect genetic samples and general health information from 1 million Veterans in the next 5-7 years."[56] MVP's goal is "to study how genes affect health…[d]ata collected from MVP will be stored anonymously for research on diseases like diabetes and cancer, and military-related illnesses, such as post-traumatic stress disorder."[57] As of September 30, 2013 more than 200,000 veterans have enrolled in MVP and the project has begun sequencing of the first samples.[58]

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50. *Id.*

51. *See* Need & Goldstein, *supra* note 33, at 761.

52. *See* Solovieff et al., *supra* note 24, at 1877; Pingxing Xie et al., *Genome-Wide Association Study Identifies Susceptibility Loci for Posttraumatic Stress Disorder*, 74 BIOL. PSYCHIATRY 656, 661 (2013); *see* Guia Guffanti et al., *Genome-Wide Association Study Implicates a Novel RNA Gene, the lincRNA AC068718.1, as a Risk Factor for Post-Traumatic Stress Disorder in Women*, 38 PSYCHONEUROENDOCRINOLOGY 3029, 3030 (2013).

53. *See* Solovieff et al., *supra* note 24, at 1877.

54. *See id.*; Xie et al., *supra* note 49, at 661; *see* Guffanti et al., *supra* note 49, at 3036.

55. *See* Koenen et al., supra note 25, at 634.

56. VA P&A 2013 Report, *supra* note 20, at Part I-19.

57. *Million Veteran Program*, *supra* note 4.

58. VA P&A 2013 Report, *supra* note 20, at Part I-19.

While the identification of genomic variants that reliably predict high risk for PTSD or the integration of genomic information into risk prediction models for PTSD is probably a few years away, efforts such as the Psychiatric Genomics Consortium's PTSD Working Group, and the VA's MVP, are helping pave the way. Furthermore, given that the prospect of implementing a PTSD-PGS program in the military is currently being considered, it is important to begin examining some of the most relevant legal and ethical challenges these programs may generate. The following sections examine these issues.

IV. LEGAL CHALLENGES FOR IMPLEMENTING A PTSD-PGS PROGRAM IN THE MILITARY

Many of the legal and ethical considerations in establishing a PTSD-PGS program are dependent on the way such program would be implemented and how the military would use the information collected. To discuss this, one should assume, with the JASON report,[59] that: such a program would employ DNA sequencing technologies such as MPS at the whole genome or whole exome (WGS or WES) levels; that participation in the program would be a requirement for all service members; and that the resulting genomic information about PTSD risks would be used for determining service assignments for military personnel. Each of these initial assumptions bears explanation before proceeding.

We assume that a PTSD-PGS program in the military would employ WGS or WES, instead of more limited targeted sequencing, because of the number of genes the military would need to examine to offer useful predictions and the range of phenotypes that the military would be interested in examining.[60] For example, given that PTSD is a complex disorder, predicting the risk of PTSD is likely to involve sequencing a large number of genes in different regions of the genome. Furthermore, in addition to PTSD, the JASON Report suggests that the military would be interested in a wide range of other phenotypes that would be relevant for military duty such as "the ability to tolerate conditions of sleep deprivation, dehydration, or prolonged exposure to heat, cold, or high altitude, or the susceptibility to traumatic bone fracture, prolonged bleeding, or slow wound healing."[61] Although panels of specific genes implicated in PTSD and all of these phenotypes could be created for targeted sequencing, on a mass scale, it will be much more cost efficient to sequence entire

59. JASON Report, *supra* note 3, at 4 (recommending that the DoD Military Health System should "[p]lan for the eventual collection of complete human genome sequence data from all military personnel.").

60. JASON Report, *supra* note 3, at 43.

61. *Id.*

genomes or exomes at once, even if the resulting data is only queried for PTSD risk variants.

Second, we assume that a PTSD-PGS would be a requirement for all service members because, as with a universal vaccination scheme, an overcompensation strategy would likely be the most effective method for minimizing the risk of PTSD. Identifying high risk personnel that could face environments where there is a high likelihood of experiencing traumatic events would be useful, and it would be relatively harmless to discover that personnel in low stress environments are at low genomic risk for PTSD.

Finally, in the absence of effective biomedical prophylaxis or treatment for PTSD, one of the principal reasons for establishing a PGS program would be to use genomic information to make service assignments by determining which service members are most likely to succeed in a particular mission and less likely to suffer harms such as PTSD.[62] The military already uses information about genetic conditions such as sickle cell and G6PD deficiency to determine assignments so a PTSD-PGS program would likely be used to extend this practice.[63]

The most serious legal concerns raised by a PTSD-PGS program are issues related to genetic discrimination and invasion of privacy. We will first examine the concerns about genetic discrimination. While the goal of using genomics to minimize the risk of PTSD may be noble, achieving this goal may involve discriminating against asymptomatic service members on the basis of their genomic information. For example, if the PTSD-PGS identified Private Williams as being at high risk for developing PTSD, his superiors could decide to assign him to duties where he would not be exposed to combat or to missions in which combat exposure was expected to be low. While this would likely minimize Private Williams' risk of developing PTSD, it would also negatively impact his prospects of getting promotions. This may be particularly difficult to accept for Private Williams, and others like him, because they would be denied certain opportunities based on genomic risks that may never materialize, and not the presence of actual symptoms that limit their capacity to perform their job.

In the civilian context, of course, the Genetic Information Nondiscrimination Act of 2008 ("GINA") prohibits employers from using genomic information to assign employees to certain jobs.[64] In

62. *Id.*

63. *See* Nunes *supra* note 5.

64. Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881 [hereinafter GINA]; Mark A. Rothstein, *GINA, the ADA, and Genetic Discrimination in Employment*, 36 J. L. MED. & ETHICS 837–38 (2008); Mark A. Rothstein, *Genetic Discrimination in Employment is Indefensible*, HASTINGS CTR. REP., Nov.-Dec. 2013, at 3,

fact, GINA prohibits employers from even requesting that employees undergo any kind of genetic testing or that they disclose the results of genetic tests.[65] However, GINA does not apply to the United States military. [66] Therefore, if the military implemented a PTSD-PGS program, service members like Private Williams would not be able to assert the protections afforded to civilians under GINA. Nevertheless, Private Williams may be able to argue that this practice violates the Constitution, by appealing to the Equal Protection clause.

A. Equal Protection

Service members who are denied certain assignments based on their genomic information could claim that these genome-based decisions constitute genetic discrimination that violates the equal protection principles found in the due process clause of the Fifth Amendment.[67] Service members could claim, for example, that the program has a discriminative motive, that of either identifying and terminating service members with supposedly inferior genomes from service, or denying them certain opportunities. If the information generated by the program is used to determine assignments, service members could also claim that the application of the program discriminates against service members who are physically and emotionally fit for assignments, but have some genomic variants that indicate that in the future they might develop certain conditions such as PTSD. In that sense, the program would treat similarly situated individuals (at least in terms of phenotype) differently based solely on their genomic profiles. Finally, service members could argue that there is no justification or rational basis for denying them certain opportunities because they currently have no symptoms, and the genetic contribution to the risk of complex diseases like PTSD is relatively small compared to the contribution of environmental factors. Therefore, their genomic information does not allow the military to make the reliable predictions necessary to protect its interests in minimizing health risks for service members and improving or maintaining military readiness.

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3 (2013); *but see* Noah Levin, *A Defense of Genetic Discrimination*, HASTINGS CTR. REP., Jul.-Aug. 2013, at 33 (2013) (arguing that genetic discrimination in employment should be allowed in some cases).

65. GINA, *supra* note 61, at § 202(b).

66. *See* Baruch & Hudson, *supra* note 6, at 439.

67. See United States v. Windsor 133 S. Ct. 2675, 2695–96 (2013) (ruling that the federal government could not discriminate against state-recognized same-sex marriages and, by extension, the individuals in such marriages); Bolling v. Sharpe 347 U.S. 497, 500 (1954) (extending the prohibition on racial discrimination to the federal government by striking down racial discrimination in District of Columbia Public Schools).

While some of these arguments may be persuasive, particularly if they were made in a civilian context, it may be difficult to convince courts to restrict the military's collection and use of genomic information. Traditionally, courts have been highly deferential to the military (a practice known as the *military deference doctrine*) regarding regulations and practices that may impinge on service member's constitutional rights, but the military considers important for military readiness.[68] This deference is generally based on three arguments:

> (1) military authorities are uniquely able to determine the unique needs of the armed forces in crafting military regulations; (2) courts are ill-equipped to determine the impact upon discipline that any particular intrusion upon military authority might have; and (3) military commanders have been charged by Congress and the President with carrying out the national military policy, and both of those branches have been conferred that power explicitly by the Constitution.[69]

B. Invasion of Privacy: Lessons from DoD DNA Registry

If the military established a PGS program, service members could also argue that the collection and analysis of their genomic information constitutes a violation of their privacy rights. In order to evaluate this claim it is important to consider relevant precedents. In 1991 DoD initiated a DNA Registry to collect and store blood and saliva samples from all service members for the purposes of remains identification.[70] Soon after the program began, two servicemen refused

68. *See generally* John F. O'Connor, *The Origins and Application of the Military Deference Doctrine*, 35 GA. L. REV. 161 (2000) (characterizing the Supreme Court's traditional military deference as rooted in a reading of the Constitution that allowed the military to act as needed under the president's Art. II authority as commander-in-chief of the military); *see generally* Steven B. Lichtman, *The Justices and the Generals: A Critical Examination of the U.S. Supreme Court's Tradition of Deference to the Military, 1918-2004*, 65 MD. L. REV. 907 (2006) (analyzing the Supreme Court's deference to the military through the lens of affirmative action); *but see* John F. O'Connor, *Statistics and the Military Deference Doctrine: A Response to Professor Lichtman*, 66 MD. L. REV. 668, 672 (2007) (arguing, inter alia, that although the Supreme Court does give deference to the military in its decisions, the deference is rooted in a reading of the separation of powers rather than a general policy of always deferring to military leadership when the articulate their opinions on the outcome of a case).

69. *See* O'Connor, *supra* note 65, at 270.

70. Mayfield v. Dalton 901 F. Supp. 300, 302 (Haw. 1995); *see also Armed Forces Repository of Specimen Samples for the Identification of Remains (AFRSSIR)*, ARMED FORCES MED. EXAMINER SYS. (Aug. 21, 2014), http://www.afmes.mil/index.cfm?pageid=doddr.afrssir.overview.

to provide specimen samples for the DNA Registry and challenged the constitutionality of the program.[71] While the district court's decision was eventually vacated as moot because the servicemen were honorably separated from active duty, the plaintiffs' arguments are illustrative of the kinds of challenges a more comprehensive genomic sequencing program could face if implemented in the military.

The servicemen's strongest argument in *Mayfield v. Dalton* was that the specimen collection constituted an unreasonable seizure for the purposes of the Fourth Amendment.[72] However, the court held that the collection of specimens "for the military's DNA registry, though undoubtedly a "seizure," is not an *unreasonable* seizure and is thus not prohibited by the Constitution."[73] The court favorably cited cases noting that military personnel have a diminished expectation of privacy; found that specimen collection is a relatively limited invasion; and considered that the restricted purpose of the program (i.e. remains identification), and the compelling interest protected (in the instance of remains identification, "confirm which of its members has fallen in battle[,] . . . may have been taken prisoner or are otherwise unaccounted for [and being able to provide] solace [to the relatives of fallen servicemen, via the] speedy and definite identification of the remains of their loved ones"[74]) make the specimen collection a reasonable seizure under the Fourth Amendment. [75]

Interestingly, one of the plaintiffs' claims in *Mayfield* was that the military could expand its use of the specimens collected. They argued that at some point the military could "use the DNA samples for some less innocuous purpose, such as the diagnosis of hereditary diseases or disorders."[76] The court found that the plaintiffs presented no evidence that the military had used or planned to use the samples for any purpose other than remains identification, thus "[a] challenge to such hypothetical future use, or misuse . . . does not present a justiciable case or controversy." [77]

C. Unreasonable Seizure of Genomic Information

Twenty years after the plaintiffs in *Mayfield* raised concerns about other potential uses of genetic information, military advisors, such as the authors of the JASON Report, are discussing the possibility that

71. *Mayfield*, 901 F. Supp. 300, *vacated as moot*, 109 F. 3d 1423 (9th Cir. 1997).

72. *Id.*

73. *Mayfield*, 901 F. Supp., at 304 (emphasis from original).

74. *Id.*

75. *Id.*

76. *Id.*

77. *Id.*

the DoD might establish a genomic sequencing program, which could potentially be used for predicting a service member's risk for developing PTSD. This type of program would be more challenging from a Fourth Amendment standpoint because it could be argued that the broader kind of information sought and the multiple potential uses of this information would make the unconsented seizure of a blood or saliva sample for the genomic sequencing program unreasonable. As with DoD's DNA Registry, the PTSD-PGS would involve the collection of blood or saliva samples, thus in this sense the physical intrusion upon service members would not be any worse than what the DNA Registry program requires. However, in this nascent era of genomics, limiting any Fourth Amendment analysis that involves genetic or genomic testing to whether the collection of blood or saliva is a reasonable seizure given the government's interests, would completely ignore the core issue that is really at stake: the seizure of genomic information.

What would make the collection of samples for the PTSD-PGS program more invasive than the DNA Registry—and perhaps unreasonable in terms of the Fourth Amendment—is the kind of information extracted from these blood or saliva samples and how the military is expected to use that information. PTSD-PGS would likely employ WGS or WES, meaning that DoD would collect DNA sequencing data from the entire genome (WGS) or all-protein coding genes in the genome (WES). Either way, the raw DNA data collected by WGS or WES would be much broader than the genetic information extracted from blood or saliva samples for the purposes of remains identification. WGS or WES data would allow the military to determine all of a service member's medical genomic risks known in the scientific literature, including risks and predispositions that are unrelated to his or her fitness for military duty.

Furthermore, the purpose of the PTSD-PGS program would be to determine health risks and the likelihood of phenotypes and traits relevant for military duties in order to decide whether a service member is fit for duty or at least how equipped the service member may be for particular assignments from a genomic standpoint.[78] This information would have much broader implications for a service member's entire military career than the identification of his or her remains. The information could be used to determine assignments, which could limit the ways in which service members could serve, and negatively impact their opportunities for getting promotions and advancing their military careers.

On the other hand, regardless of how invasive WGS/WES may be, the military can argue that it has some very compelling interests to protect with PSTD-PGS, primarily concerning the health and well

78. JASON Report, *supra* note 3.

being of service members, and military readiness. These compelling interests, combined with the military deference doctrine, may mean that in practice the only viable option for service members looking to significantly limit the scope of a military genomic sequencing program and the way this information is used would not be through the courts. Rather, they may need to convince Congress to regulate the collection and use of genomic information in the military.[79]

D. Unreasonable Search of Genomic Information

Interestingly, even if courts held that the seizure of samples for a military genomic sequencing program was reasonable, service members may be able to argue that certain searches within their genome would be unreasonable. For instance, service members could argue that the genomic information sought and analyzed by a military's WGS/WES program should be limited to sequencing information directly related to military readiness or the minimization of health risks that may be prompted or exacerbated by military duty. Even when WGS or WES is performed, laboratories have the bioinformatics capacity to determine which genes are analyzed and interpreted in order to determine specific health risks. Therefore, it is possible to restrict the information sought and analyzed by the military to that relevant to military duty and readiness. One problem with this could be finding an adequate way to define which genomic information is sufficiently related to military readiness. If defined too broadly, it may intrude into elements of the service member's health that have little bearing on their ability to perform their mission. However, it seems like the search and analysis of genes such as those closely associated with colon cancer (e.g. MLH1, MSH2, MSH6, and PMS2) or hereditary breast and ovarian cancer (e.g. BRCA 1 and BRCA 2) could be considered an unreasonable invasion of service members' intimacy unless consented.

V. ETHICAL CHALLENGES

The prospect of a PTSD-PGS program also raises a range of ethical and social challenges that will require consideration by DoD, if the agency is to comply with the JASON Report's prescriptions for military genomics. These range from questions about the impact of implementing such a program on the units to which individual service people belong, to issues at the interfaces of the military with civilian society, to challenges in the design and implementation of the research necessary to develop evidence-based PGS programs in the first place.

79. See GINA, *supra* note 61.

A. Unit Cohesion and Fair Distribution of Combat Risk

One of the interesting features of the military is that it is one of the few American social spheres where the rights and interests of the individual do not come first. As William Rhodes articulates in his introduction to military ethics:

> As a result, militaries put tremendous emphasis on an ethical requirement to value the needs of one's group above personal desires. Sometimes this is referred to, as in military "core values" statements, as the virtue of selflessness. In its highest manifestation, an individual's identification with his unit is so thoroughgoing that he sees little distinction between the unit's well-being and his own . . . . Fear of failing one's subordinates or failing to accomplish the mission that others are depending on become predominant ethical worries.[80]

On one hand, this means that many of the usual autonomy-based bioethical worries over preventive genomic sequencing (the need for adequate individual informed consent to sequencing, rights to know or not know sequencing results and incidental findings, the privacy of these findings, etc.) are, if not moot in the active duty context, at least relocated from individuals to the commanders responsible for their best interests. If the chain of command concurs that the privacy costs and discrimination risks of PGS are proportionate to the mission-oriented benefits that relevant military cohorts could garner, our civilian fixation on personal freedoms of opportunity and self-determination would not stand in the way.

On the other hand, as Rhodes stresses, privileging the interests of the cohort over the individual also generates a commitment, on the part of both commanders and subordinates, to the cohesion of the unit and a mutuality of effort within it. Teamwork is prized and its opposite is castigated as "shirking": contriving to relieve oneself of duty to avoid one's group obligations. As sympathetic as Corporal Klinger's cross-dressing efforts gain a psychiatric "Section 8" discharge from his M.A.S.H. duties were for his American TV audience in the 1970's, he was not behaving like a good soldier. Moreover, his vice was not cowardice: it was that his group needed him to fulfill their mission, which would suffer from his departure.

In this context, a commander contemplating a PTSD-PGS in an otherwise asymptomatic cohort faces an ethical challenge: would it be fair to the unit to reassign soldiers to noncombat roles on the basis of probabilistic, but unproven, risk of downstream PTSD? First of all, if genetic markers for PTSD risk are as common in the population as the incidence of the disorder suggests, this could itself have a

80. WILLIAM RHODES, AN INTRODUCTION TO MILITARY ETHICS 54 (2009).

destabilizing effect on the unit as whole. Should all cases of PTSD risk be treated alike for reassignment purposes, or could key personnel – e.g. the Tank Commander, the Demolitions Expert, the IT Expert-- be kept in their combat roles on other grounds of military necessity regardless of their genomic status? These decisions are exacerbated, secondly, by the fact that the benefits of PTSD-PGS to any particular cohort or unit are never going to be directly mission-related. To the extent that PTSD is a most often a delayed onset condition, a preventive screening program may be in at-risk individuals' eventual health interests, and could certainly benefit the military veterans health care system by saving downstream costs. But it is not clear how it can help a unit meet its primary military objectives. In fact, since the ordinary and expected risks of combat are more severe and predictable than a genomic risk of PTSD, a program that allows (or forces) soldiers to avoid the former in the name of avoiding the latter may look more like a shirkers' lottery than a humane service, at least to those left to face the trial of combat. In sum, by disrupting unit cohesion and relieving asymptomatic soldiers of their ordinary risk-taking obligations, such a program may appear to commanders like a disproportionate risk to their unit's functionality, even if its risks to its individual recipients are negligible. If commanders are to take the morale and mission-readiness of their units as their primary concern, this may simply relocate what might be considered "autonomy-based" ethical challenges to mounting universal PTSD-PGS upwards within chains of command as issues of professional integrity for unit commanders.[81]

B. During Active Duty, Training, or Recruitment?

Perhaps the foregoing concerns indicate that active duty personnel who already belong to mission-oriented military units are simply the wrong target for PTSD-PGS. If PTSD risk information was collected and used earlier in a service person's military life, during training, for example, units themselves could be composed of either high and low risk personnel from the start, depending on their missions, in the way that aptitude tests are already used to assign new recruits to different kinds of military vocations. Or, to take a step further back, why not employ the PGS during recruitment, to pursue a "PTSD-free" military across the board?

Conducting PTSD-PGS during military training has attractions similar to newborn genetic screening in the public health context.[82]

81. Maj. William. H. Margerum, *Integrity: the military professional and society*, AIR UNIV. REV.(Sept, 1983), http://www.airpower.maxwell.af.mil/airchronicles/aureview/1983/sep-oct/margerum.html.

82. See generally Mary Ann Baily & Thomas Murray, *Ethics, Evidence, and Cost in Newborn Screening*, HASTINGS CTR. REP., May-Jun. 2008, at 23

Detected early enough, the long-term harms of a recruit's genomic vulnerabilities could be taken into account even in developing their military life-plan, by putting them on a low-stress diet of stateside desk jobs and support missions that would avoid the environmental triggers of their (possible) predisposition. This approach would take the program's risk/benefit calculations out of the (benignly paternalistic) hands of unit commanders, avoid the unit cohesion and shirking issues, and make it easier to justify implementing PTSD-PGS universally across the military, rather than just for those most likely to encounter the environmental triggers of PTSD.

On the other hand, this would create a bifurcated military, with a class of behind-the-lines support units composed heavily of PTSD-vulnerable recruits, and a combat class composed of recruits of unknown PTSD risks. In the hierarchical and specialized world of the military, this bifurcation in itself may be no cause for moral alarm. But it could run afoul of two important military moral values that would make it problematic. The first is the principle of military advancement through merit.[83] If one's genomic classification places a permanent bar on certain military career paths, it compromises the ability of service people to "work themselves up from the ranks" to leadership positions. The perception that the military embraces and empowers personal initiative by its members to overcome their own limitations, and "be all they can be" despite the vagaries of their social backgrounds is important both to its members sense of solidarity and its external recruitment efforts. Mandatory genomic sorting could damage that perception on both fronts, especially if people thought that only those on the "high stress track" would have important opportunities to demonstrate military virtues like courage, self-sacrifice, leadership and strength, in ways that count as military heroism.[84] This risk, in turn, reflects the other value at stake: the opportunity that the military offers recruits to leave the unjust prejudices of civilian society behind, in favor of a system without systematically favored groups defined on mission-irrelevant grounds. The military's internal sense of fairness demands that no one should be denied the opportunity to prove themselves if they can "pass muster" for the job at hand, regardless of their biological

(describing the history, current practice, and suggested limitations on neonatal genetic screening).

83. DARLINE ISKRA, BREAKING THROUGH THE BRASS CEILING: STRATEGIES OF SUCCESS FOR ELITE MILITARY WOMEN (2008).

84. SHANNON FRENCH, THE CODE OF THE WARRIOR: EXPLORING WARRIOR VALUES PAST AND PRESENT (2004).

background.[85] Doing so on the basis of their genomic foreground, the argument would go, seems just as discriminatory.

One possible way out of these conundrums is suggested by the newborn screening analogy. For the case of phenylketonuria risk screening in newborns, at least, the idea is to follow the early detection of PKU risk with a special diet designed to protect the patient's brain from a poisonous accumulation of phenylketones during its postnatal development, after which a normal diet can be resumed. If a sequence-informed service assignment were *not* permanent, but capable of being "tested out of" by doing well with regimen of hypothetical PTSD "challenges," perhaps its threat to the military's meritocractic ethos could be avoided. But even such a regimen of special vetting could endanger another important military ethical commitment if it came to reflect negatively on "low stress" service careers themselves.

A corollary of the military values of opportunity and fairness is that, in (military ethical) theory, low stress but critical military support operations should enjoy the same prestige as combat units, and afford equally honorable opportunities for leadership and heroism.[86] Given the military's veneration of warrior heroes, it is a continuing psychosocial challenge to inculcate and promote this principle of equity, both within military circles and in the wider society. It would undermine that effort if a genomic sorting program early in a military career carried a perceived stain of weakness to those in non-combatant military career paths. But unlike other disabilities, such as an amputation, or even other genetic vulnerabilities, like Long Q-T syndrome, PTSD is about a soldier's resilience in the face of the kinds of trauma strong soldiers are expected to face. It has a direct connection to core mission-related military virtues that makes it particularly potent as a vulnerability and stigmatizing to the service assignments with which it becomes associated.

One way to try to avoid all these worries would be to use PGS even earlier during recruitment, to help build a military that has as few personnel at high risk for PTSD as possible. If targeting PTSD-PGS to trainees is like newborn screening, this approach could be analogized to prenatal screening: its goal would be to select out only those recruits who do not show the PTSD markers, and reject those who do from military service altogether, in a genomic version of the old 4F exclusion.

85. ISAAC HAMPTON, THE BLACK OFFICER CORP: HISTORY OF BLACK MILITARY ADVANCEMENT FROM INTEGRATION THROUGH VIETNAM (2012)

86. LAWRENCE ROCK, THE TOOTH AND THE TAIL: AN ORAL HISTORY OF SUPPORT TROOPS IN VIETNAM (2012).

As appealing as this approach appears from inside the military, however, it does face significant social challenges. Now we are in the situation of performing genomic sequencing on individuals who are not yet part of the military and still retain their full panoply of autonomy rights. Even if the armed services could, in the face of the ADA and the Equal Protection clause, legally make the absence of genomic markers for PTSD risk a prerequisite for recruitment into military employment, the moral case for genetic discrimination against would-be volunteers who carry the risk markers would be strong, given the many military occupations in which such recruits could excel without risk to the military's mission. Moreover, in performing PTSD-PGS on civilians, recruiters would face all the challenges now being encountered in clinical and public health settings in which WGS/WES is being implemented.[87] Fully informed consent to the sequencing would be morally required, including disclosures concerning the psychosocial risks as well as the benefits of identifying PTSD markers and other genomic information that may be examined. Plans for managing incidental and secondary target findings, especially medically actionable findings, would need to be in place. Questions about the storage and disposition of their sequence data would need to be addressed, especially for those who are rejected or decline to join the military for other reasons. Would their data be expunged, or placed under their control in some other way? What privacy protections would it enjoy during its analysis and use by the military recruiters? Those who currently aspire to use sequencing technologies in civilian clinical and public health settings are already besieged by the complexity of these challenges. If the attempt to manage them for the purposes of military recruitment simply compounds the public relations challenge of proposing to use genomic screening to insure a military without PTSD, the whole approach begins to look doubtful.

C. Genetic Essentialism and Post-Service Stigmatization

The problem with using PTSD-PGS as a recruitment screen is that it has to happen at the interface of the civilian and military moral spheres, where civilian values still have purchase. Another set of related issues arise at the other end of a military career, after a discharge from the armed services. As the VA exemplifies, the military's ethical obligations to its personnel extend well beyond their active service. Conscientious military planners will have to consider the implications of PTSD-PGS for veterans in their post-military civilian lives. If carrying PTSD risk markers is a serious enough

87. *See generally* PRESIDEN'L COMM. FOR STUDY BIOETHICAL ISSUES, PRIVACY AND PROGRESS IN WHOLE GENOME SEQUENCING (2012) (recommending twelve ways in which whole genome sequencing can be improved while also respecting privacy & security issues).

vulnerability to warrant exclusion from core military assignments—or, more crucially, from military service itself—what should civilian institutions make of that fact when assessing the merits of veteran applicants for high stress positions? In civilian life, the prudential over-determinism of PTSD-PGS could easily be misinterpreted as a strong genetic essentialism, allowing all the individual's qualities to be eclipsed by their genomic markers in a scientifically inappropriate overinterpretation of their significance in civilian life. Even if the applicants' individual genomic marker results are undisclosed, a military record of low stress assignments, or a genomic 4F designation could come to exacerbate the social burden that veterans already face when they are stigmatized as "unstable" or unreliable under stress. [88] The military could join other efforts within the genomics community to *demythologize* genomic information though public education, but it would have to face the challenge that the humbler interpretations of PTSD genomics required to counteract those invidious misinterpretations will also cut against the rationale for conducting PTSD-PGS for personnel assignments in the first place.

D. Research Ethics Issues

Finally, how should a PTSD-PGS program be developed and tested? To be ethically justified, it would have to be well grounded in the best evidence available that its candidate markers were robust predictors of PTSD risk, that assigning high risk personnel to low stress roles would reduce that risk, and that the psychosocial sequelae of being labeled at high PTSD risk—both during active duty and after discharge—do not outweigh its benefits.[89] Unlike pharmacogenomic trials involving clear physiological pathways and discrete outcomes, it is almost impossible to imagine a controlled, scientifically rigorous study that could produce this evidence without amounting to the widespread implementation of the program and its longitudinal follow-up. Biomedical research with service personnel is sometimes excused from the usual requirements of voluntary informed consent, free withdrawal, and confidentiality out of military necessity, but usually in the face of some imminent threat to an overriding military mission objective. Would the prevention of PTSD in veterans and the accompanying health care cost savings merit such an exemption?[90] If not, the program's (large) exploratory phase would

88. Dinesh Mittal et al., *Stigma Associated with PTSD: Perceptions of Treatment-Seeking Combat Veterans*, 36 PSYCHIATRIC REHAB. J. 86, 88, 90(2013).

89. *See* M.J. Khoury, *Dealing with the Evidence Dilemma in Genomics and Personalized Medicine*, 87 CLIN. PHARMACOL. & THERAPEUTICS 635, 635 (2010).

90. Patrick Moran, *A Military Exception to "Informed Consent":* Doe v. Sullivan, 66 ST. JOHN'S L. REV. 847, 863 (1992) (asserting, *inter alia*,

have to be accompanied, like other military health services research, with a version of the usual protections for human research participants in place. [91] That would, again, bring the military back to many of the same ethical challenges that genomic sequencing research is currently facing in other clinical and public health settings.

VI. CONCLUSIONS

Despite current scientific enthusiasm over preventive genomic sequencing, the deference of American law to military necessity, and the unique features of military morality, the prospect of a military PTSD-PGS program may be more challenging than the JASON Report suggests. In fact, the three sections of this tour of the scientific, legal and ethical considerations involved in mounting such a program come together to effectively dissolve the rationales that might have insulated a military program from the complexities of the ongoing debates over PGS in our individualistic civilian context, in four ways.

First, it is clear that the state of PTSD genomics is far from being robust enough to support a meaningful PGS program. Under that scientific uncertainty, commanders will not have the evidence they need to make responsible decisions about their subordinates' best interests in this context, given the possible harms of PTSD risk labeling in both active duty and post-discharge settings. Since it is unlikely that any individual's downstream risks for PTSD will jeopardize a unit's immediate functionality except through the destabilizing effects of reassignment, commanders who are given a choice are likely to forego the program for those under their command, despite the risk of increased costs to the military health care system. If commanders are not given a choice but are unable to endorse the program, military ethics prescribes that they share their inability with their troops and relinquish their paternalistic authority by calling for volunteers.

Second, while legal doctrine might support the military's authority to create a PTSD-PGS program, such a program's interfaces with the civilian lives of either new recruits or discharged veterans reintroduce legal and civil rights challenges that strictly internal military interventions can avoid. If PTSD-PGS is used as a recruiting screen, it faces both constitutional challenges and the ethical complexities of civilian genomic sequencing. If it is limited to

that the military regulations regarding informed consent exist solely to protect military members on the battlefield, and that the current rules preclude genuine experimentation, as had occurred with LSD).

91. *See* John McManus et al., *Informed Consent and Ethical Issues in Military Medical Research*, 12 ACAD. EMERGENCY MED. 1120, 1123–25 (2005).

active duty personnel, its planners must develop ways to mitigate the potentially adverse impact of PTSD risk labeling on veterans opportunities and the lives of their families.

Third, the practice of segregating personnel with high genomic PTSD risk into low stress assignments may run afoul of the military's own ethical commitment to a level playing field for meritocratic advancement, and its disinterest in stigmatizing critical non-combat vocations. As a result, even the military's internal morality may push planners to make room for informed choices by volunteers who are willing, like the ship's cook manning the anti-aircraft gun at Pearl Harbor, to take on additional PTSD risks in their unit's interest.

Fourth**,** since PTSD-PGS does not address any imminent military necessity beyond the long-term health and health care costs of individual personnel, its development should be governed by the research ethics that regulates other health service research in the military. If PTSD-PGS is to eventually gain the evidence base it will require to be ethically justifiable as a universal military program, it will require testing in longitudinal cohort studies that will have to offer their participating personnel the standard autonomy-oriented protections.

Discussions of workplace genetic screening in the 1980's often ended with a recommendation that represented a compromise between those who would use genetic testing to involuntarily exclude the hypersusceptible from occupational exposures to toxins and those who criticized such proposals as paternalistic and potentially discriminatory. [92] The compromise was to have companies offer the genetic testing as a health service to their workers, and to allow individual employees to decide whether or not to avail themselves of the service or follow up on its findings. While some declined such services, those that used them and discovered themselves to be hypersusceptible to the workplace toxins overwhelmingly took voluntary steps to minimize their risks. It may be that this is where the challenges in PTSD-PGS in the military are pointing as well. From the legal and ethical perspectives the least problematic way of establishing an PTSD-PGS program for military personnel may be to make it a voluntary program for service members and to offer targeted sequencing of those loci that are known to be most relevant to the phenotypes most closely associated with a given individual's military duties. Under this personalized approach to PTSD-PGS, individual service members would decide whether to learn their own risk status as a matter of personal health planning beyond their military responsibilities rather than as a matter of professional military duty. Those that learned they were at increased genomic risk

92. ELAINE DRAPER, RISKY BUSINESS: GENETIC TESTING AND EXCLUSIONARY PRACTICES IN THE HAZARDOUS WORKPLACE (1991).

for PTSD could be given the opportunity to decide whether they want to report this information in order to request reasonable accommodation, similar to the way the American's with Disabilities Act works in civilian contexts. This degree of autonomy may be at odds with military tradition. But, the probabilistic information that PTSD-PGS will be able to provide for the foreseeable future is so uncertain, can have such profound implications for service members' social success within and beyond the military, and could be misinterpreted and misused in so many ways detrimental to military values, that repositioning PGS as an optional perk of military service, like subsidized PX prices or the G.I. Bill, rather than using it as a weapon, an element of a new genomic arms race, may be the better part of valor.