

# **Defense Health Research Programs**

## **Relevance to National Security and Military Families**

### **Updated May 20, 2021**

- **ALS:** According to studies by the Department of Defense (DoD), Department of Veterans Affairs (VA), National Institutes of Health (NIH) and Harvard University, people who have served in the military are approximately twice as likely to develop ALS as the general population<sup>1</sup>. Most recently, researchers found an increased risk of ALS among those who served in Iraq and Afghanistan<sup>2</sup>. The VA has recognized the connection between ALS and military service by establishing a presumption of service connection for ALS<sup>3</sup>. The VA presumes that ALS was incurred in or aggravated by service in the military. Moreover, the presumption applies to any veteran who served, from any branch of the military, regardless of where or when a veteran served (home or abroad, during a time of peace or conflict) and regardless of when they were diagnosed with the disease following discharge (eg, 1 year after service or 50 years). The DoD ALS Research Program is supporting translational research and has developed four potential treatments for the disease, for which there is no cure.
  
- **Arthritis:** According to the Centers for Disease Control and Prevention, over 1 in 3 veterans have arthritis, compared to 1 in 4 in the general population.<sup>4</sup> Arthritis carries with it enormous physical, financial and societal costs, but for veterans and service members, the costs are multiplied. One study found osteoarthritis (OA) rates to be 26 percent higher in service members aged 20 to 24 compared with the same age group in the general population. From the same study, individuals over age 40 were twice as likely to develop OA after returning to civilian life.<sup>5</sup> Data from the U.S. Army's Physical Evaluation Board reveals that among permanently disabling conditions, arthritis was the most common unfitting condition, with 94.4 percent of cases attributed to combat injury.<sup>6</sup> Arthritis is responsible for rising DoD and VA health care costs stemming from joint pain, loss of function, and joint replacement surgery. Research can help identify better joint injury management to reduce the effects of joint degeneration in this population, and help identify ways to prevent joint injury during military training and service.

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<sup>1</sup> Horner, R. D. et. al., 2003, 2008. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans; Haley, R. et. al. 2003. Excess incidence of ALS in young Gulf War veterans; Weisskopf, M. G. 2005, 2009. Prospective study of military service and mortality from ALS; Institute of Medicine, 2006. Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature.

<sup>2</sup> Zivkovic, S. et. al., 2014. Increased Prevalence of ALS in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans.

<sup>3</sup> 38 CFR 3.318 – Presumptive service connection for amyotrophic lateral sclerosis.

<sup>4</sup> Centers for Disease Control and Prevention. Arthritis Help for Veterans. Retrieved from <https://www.cdc.gov/features/arthritis-among-veterans/index.html>.

<sup>5</sup> Cameron KL, et al. Incidence of Physician-Diagnosed Osteoarthritis Among Active-Duty United States Military Service Members. *Arthritis and Rheumatology*. 2011. 62(10); 2794-2982. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/21717422>.

<sup>6</sup> Rivera, J. D., Wenke, J. C., Buckwalter, J. A., Ficke, J. R., & Johnson, A. E. (2012). Posttraumatic Osteoarthritis Caused by Battlefield Injuries: The Primary Source of Disability in Warriors. *The Journal of the American Academy of Orthopaedic Surgeons*, 20(0 1), S64–S69. <http://doi.org/10.5435/JAAOS-20-08-S64>. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3689418/>.

- **Asbestos Diseases:** For more than a century, military service members have been exposed to asbestos. According to the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), all types of asbestos are classified as Class I Carcinogens.<sup>7</sup> Asbestos exposure can cause many diseases including mesothelioma, cancers of the lung, larynx, and ovaries, and lung and pleural diseases such as asbestosis.<sup>8</sup> Asbestos has been widely used in manufactured goods and can still be found in shipyards, existing structures such as military barracks, vehicles, airplanes, and aboard ships.<sup>9</sup> There is no "safe" level of asbestos exposure for any type of asbestos fiber.<sup>10</sup> Inhaling or ingesting asbestos can cause fatal disease. The latency from exposure to diagnosis is commonly 10 - 50 years. Among non-smokers, asbestos exposure increased the rate of lung cancer 5-fold.<sup>11</sup> In addition to the military, family members of service members have also been exposed when fibers are carried home on clothing into military housing which may also be constructed with asbestos-containing materials. Recent asbestos exposures have been reported in the branches of the military serving in Iraq, the Middle East, and Southeast Asia. According to the Institute for Health Metrics and Evaluation database, 40,764 American workers died from asbestos-caused diseases in 2019.<sup>12</sup>

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<sup>7</sup> American Cancer Society, *Known and Probable Human Carcinogens*, 2021. <<https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-carcinogens.html>>

<sup>8</sup> Center for Disease Control, *Occupational Safety and Health Guideline for Asbestos: Potential Human Carcinogen*. 1988. <<https://www.cdc.gov/niosh/docs/81-123/pdfs/0041.pdf>>

<sup>9</sup> U.S. Department of Veteran Affairs. *Public Health: Asbestos*. December 17, 2017. <<https://www.publichealth.va.gov/exposures/asbestos/index.asp>>

<sup>10</sup> United States Department of Labor. *Asbestos*. Occupational Safety and Health Administration. 2014. <<https://www.osha.gov/asbestos>>

<sup>11</sup> Markowitz, Steven; Levin, Stephen; Miller, Albert, et. al. American Journal of Respiratory and Critical Care Medicine/AJRCCM. *Asbestos, Asbestosis, Smoking and Lung Cancer: New Findings from the North American Insulator Cohort*. March 22, 2013. <<https://www.thoracic.org/newsroom/press-releases/resources/Markowitz>>

<sup>12</sup> Asbestos Disease Awareness Organization, *The Irrefutable Fact: Over 40,000 American Workers Died from Preventable Asbestos-Caused Diseases in 2019/ February 15, 2021* <https://bit.ly/2N0yANd>

- **Autism:** According to the Centers for Disease Control and Prevention, 1 in 59 children have an autism spectrum disorder (ASD)<sup>13</sup>. The Department of Defense reports that 18,452 active duty family members had a diagnosis of ASD at the end of fiscal year 2013.<sup>14</sup> This reflects a 77% increase in ASD diagnoses in just four years from fiscal year 2009.<sup>15</sup> Military families are affected substantially by the financial and emotional costs of raising a child with autism and this impact extends to the performance and readiness of service members and their units. It is well known that children with autism, if they receive prompt treatment and early intervention services, can improve their long-term functional prospects dramatically.<sup>16</sup> Research supported by the Autism Research Program has addressed current needs such as difficulties accessing care associated with mobile military families<sup>17</sup> and gastrointestinal (GI) disorders which are among the most common medical conditions associated with autism.<sup>18</sup> Additional research will help to improve treatment and intervention directly serving the interests of service members and DoD families impacted by autism as well as the medical, educational, healthcare and service professionals who serve the needs of the autism community within and beyond.

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<sup>13</sup> Baio, John et. al. 2018. Prevalence of Autism Spectrum Disorder among Children Aged 8 Years – Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014

<sup>14</sup> Report to Congressional Defense Committees, The Department of Defense Enhanced Access to Autism Services Demonstration, July 2014 Semiannual Report to Congress.

<sup>15</sup> Report to Congressional Defense Committees, pp 1.

<sup>16</sup> Dawson, G. et. al. 2009. Randomized, Controlled Trial of an Intervention for Toddlers with Autism: The Early Start Denver Model: Pediatrics.

<sup>17</sup> Ingersoll, B. and Wainer, A. 2013. Initial efficacy of project impact: A parent-mediated social communication for young children with ASD. J Autism Dev Disord 43:2943-52.

<sup>18</sup> Bornstein, Joel. et. al, 2015. The Gut-Brain Interaction and Autism Spectrum Disorder.

- **Bladder Cancer:** Bladder cancer is the 6th most common cause of cancer in the United States, and the 4th most common cancer within the U.S. veteran population.<sup>19</sup> <sup>20</sup> Smoking is a leading risk factor associated with bladder cancer, but male sex, advancing age, and white race are also strong risk factors. Despite mounting evidence in the 1950s of the adverse health effects of smoking and tobacco use, the military continued to include cigarettes in rations until 1975.<sup>21</sup> Smoking prevalence in the veteran population is reported to be 27% compared to 21% in the non-veteran population.<sup>22</sup> It has also been estimated that the prevalence of smoking is 43% higher in the population treated by VA hospitals compared to age matched controls <sup>23</sup>From 1961 to 1971, approximately 1,000,000 gallons of Agent Blue, containing high levels of arsenic were sprayed over the southern region of Vietnam.<sup>24</sup> Inorganic arsenic compounds have been linked to cancer of the bladder.<sup>25</sup> In addition, from the 1950s through the 1980s, people serving or living at the U.S. Marine Corps Base Camp Lejeune, North Carolina, were potentially exposed to drinking water contaminated with industrial solvents, benzene, and other chemicals. This chemical exposure may have led to adverse health conditions, including bladder cancer.<sup>26</sup>

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<sup>19</sup> American Cancers Society. Bladder Cancer Statistics. Retrieved from

<http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics>, accessed March 9, 2016.

<sup>20</sup> Zullig et al, 2013, Cancer Incidence among Patients of the United States Veterans Affairs (VA) Healthcare System, *Mil Med.* 2012 June ; 177(6): 693–701.

<sup>21</sup> Joseph, Anne M.; et al. (2005). "The Cigarette Manufacturers' Efforts to Promote Tobacco to the U.S. Military". *Military Medicine* 170: 874–880.

<sup>22</sup> Brown, D.W., 2010 Smoking Prevalence among US Veterans, *J Gen Intern Med.* Feb; 25(2): 147–149.

<sup>23</sup> Office of Quality and Performance, Veterans Health Administration. Health behaviors of veterans in the VHA: tobacco use. 1999 Large Health Survey of Enrollees. Washington, DC, Veterans Health Administration, 2001.

<sup>24</sup> H.R.2519 - Victims of Agent Orange Relief Act of 2013 113th Congress (2013-2014).

<sup>25</sup> NCI Cancer Trends Progress Report, Retrieved March 9, 2016 from <https://progressreport.cancer.gov/prevention/arsenic>.

<sup>26</sup> US Department of Veterans Affairs, July, 2015, CAMP LEJEUNE: PAST WATER CONTAMINATION, IB 10-449.

- Bone Marrow Failure Disorder:** Myelodysplastic Syndrome (MDS) is rare bone marrow failure disorder that increase risk of developing AML, a fast growing cancer of the blood. Exposure to benzene, historically used extensively by the military, has been well established as a risk factor for myeloid malignancy, and is significantly associated with development of MDS and AML.<sup>272829</sup> Both ground troops and onboard support personnel have been at risk for significant exposure to dioxin, benzene and Agent Orange herbicide during the Vietnam war.<sup>303132</sup> More recently, veterans stationed at Camp Lejeune between 1953 and 1987 were found to have potential exposure to industrial solvents in well water, inclusive of benzene, as recognized by the VA.<sup>33</sup> The Bone Marrow Failure Research Program supports critical research into disease etiology and therapy development pathways. Continued research into bone marrow failure etiology and molecular genomics is essential to saving lives.
- Brain Cancer and Pediatric Brain Tumors:** Today, an estimated 700,000 people in the United States are living with a primary brain tumor, and approximately 85,000 more will be diagnosed in 2021. Brain cancer is the deadliest form of childhood cancer, which is the number one disease-related killer of children under 15. Brain cancer does not discriminate, inflicting men, women, and children of all races and ethnicities, including members of the armed services. This connection was illustrated in a 2014 report by the PRCRP to Congress, linking brain cancer with exposure to ionizing radiation during military service.<sup>34</sup> The report also pointed to a study by Hicks et. al indicating children of men in the Air Force having higher incidence rate of pediatric brain tumors.<sup>35</sup> A subsequent report published by the PRCRP in 2015 highlighted environmental hazards including radiation and insolvents as increasing the risk of brain cancer development. Specifically, high risk exposure related to a brain cancer diagnosis can include but are not limited to chemical weapons, or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, biological agents, and ultraviolet radiation.<sup>36</sup>

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<sup>27</sup> Irons, R. D. and P. J. Kerzic (2014). "Cytogenetics in benzene-associated myelodysplastic syndromes and acute myeloid leukemia: new insights into a disease continuum." *Ann N Y Acad Sci* 1310: 84-88.

<sup>28</sup> Poynter, J. N., M. Richardson, M. Roesler, C. K. Blair, B. Hirsch, P. Nguyen, A. Cioc, J. R. Cerhan and E. Warlick (2017). "Chemical exposures and risk of acute myeloid leukemia and myelodysplastic syndromes in a population-based study." *Int J Cancer* 140(1): 23-33

<sup>29</sup> Smith, M. T., L. Zhang, C. M. McHale, C. F. Skibola and S. M. Rappaport (2011). "Benzene, the exposome and future investigations of leukemia etiology." *Chem Biol Interact* 192(1-2): 155-159.

<sup>30</sup> Armitage, J. M., M. E. Ginevan, A. Hewitt, J. H. Ross, D. K. Watkins and K. R. Solomon (2015). "Environmental fate and dietary exposures of humans to TCDD as a result of the spraying of Agent Orange in upland forests of Vietnam." *Sci Total Environ* 506-507: 621-630.

<sup>31</sup> Landgren, O., Y. K. Shim, J. Michalek, R. Costello, D. Burton, N. Ketchum, K. R. Calvo, N. Caporaso, E. Raveche, D. Middleton, G. Marti and R. F. Vogt, Jr. (2015). "Agent Orange Exposure and Monoclonal Gammopathy of Undetermined Significance: An Operation Ranch Hand Veteran Cohort Study." *JAMA Oncol* 1(8): 1061-1068.

<sup>32</sup> Ross, J. H., A. Hewitt, J. Armitage, K. Solomon, D. K. Watkins and M. E. Ginevan (2015). "Exposure to TCDD from base perimeter application of Agent Orange in Vietnam." *Sci Total Environ* 511: 82-90.

<sup>33</sup> <http://www.benefits.va.gov/COMPENSATION/claims-postservice-exposures-camp-lejeune-water.asp>

<sup>34</sup> <https://cdmnp.army.mil/prcrp/reports/14prcReport.pdf>

<sup>35</sup> Hicks N, Zack M, Caldwell GG, Fernbach DJ, and Falletta JM. 2006. Childhood cancer and occupational radiation exposure in parents. *Cancer* 53:1637-1643.

<sup>36</sup> <https://cdmnp.army.mil/prcrp/reports/15prcReport.pdf> (pg. 7-11)

- Breast Cancer:** According to recent demographic reports, active duty and select reserve females and female spouses under the care of the United States military health system total approximately 1.3 million women.<sup>37</sup> Assuming normal risk of developing breast cancer across a woman's lifetime (1 in 8), 162,500 cases of breast cancer are expected to be diagnosed within that population. Furthermore, a 2009 study suggested that active duty females have a higher incidence of breast cancer than the general population, which would increase the expected number of breast cancer cases.<sup>38</sup> Therefore, breast cancer is a significant issue for the United States military health system. Additionally, military families are affected substantially by the financial and emotional costs of breast cancer and this impact extends to the performance and readiness of service members and their units. The Breast Cancer Research Program has invested in research to better understand how and why breast cancer is initiated, factors that increase risk, and more advanced ways to detect and treat this disease including innovative treatments for breast cancer that are both more effective and less toxic (e.g. sentinel lymph node biopsy, trastuzumab and palbociclib for HER2+ breast cancer, ribociclib and abemaciclib for HR+ breast cancer, vaccines and immunotherapies for breast cancer, nanoparticle-based drug delivery systems).<sup>39</sup>
- Cancer in Adolescents and Young Adults:** Approximately 70,000 adolescents and young adults between the ages of 15 and 39 are diagnosed with cancer each year in the United States. In fact, cancer is the leading cause of disease-related death for this age group. The National Cancer Institute has found that "evidence suggests that some cancers in adolescents and young adults may have unique genetic and biological features. Researchers are working to learn more about the biology of cancers in young adults so that they can identify molecularly targeted therapies that may be effective in these cancers."<sup>40</sup> Unfortunately this age population is not recognized as a unique oncology care group. Adolescents and young adults have no medical "home." Providers must make care and treatment decisions using research and facilities designed for pediatric or older adult patients. This has led to a lack of improvement in survival rates since the War on Cancer began more than 40 years ago.<sup>41</sup> Nearly 90% of servicemembers, their spouse, and children fall within the NCI definition of an adolescent or young adults impacted by cancer.<sup>42</sup>

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<sup>37</sup> <http://download.militaryonesource.mil/12038/MOS/Reports/2016-Demographics-Report.pdf>

<sup>38</sup> Cancer Epidemiol Biomarkers Prev. 2009 Jun;18(6):1740-5. doi: 10.1158/1055-9965.EPI-09-0041.

<sup>39</sup> <http://cdmrp.army.mil/bcrp/pbks/bcrppbk2018.pdf>

<sup>40</sup> <https://www.cancer.gov/types/aya>

<sup>41</sup> <https://www.ncbi.nlm.nih.gov/pubmed/25568146>

<sup>42</sup> [https://s3.amazonaws.com/rallywebcollateral/wp-content/uploads/2017/03/08143634/DODCDMRPFY17Request\\_whitepaper\\_2.pdf](https://s3.amazonaws.com/rallywebcollateral/wp-content/uploads/2017/03/08143634/DODCDMRPFY17Request_whitepaper_2.pdf)

- **Celiac disease:** Celiac disease is recognized as one of the world's most common genetic autoimmune disorders, affecting 1% of the population. Despite this recognition, most cases remain undiagnosed.<sup>43</sup> Prevalence has increased markedly (4-5-fold) since 1950 for reasons not understood. Incidence has also increased in the general population and in active service military personnel<sup>44</sup>, with a peak onset in the second or third decades of life. Currently, there is no medication or cure for celiac disease. Nor is there an effective method for prevention. The only course of action is to follow a strict gluten-free diet. Studies show from 30 to 50 percent of celiac disease patients on a gluten-free diet continue to report symptoms and/or have intestinal damage. There is a wide range of both gastrointestinal and extraintestinal symptoms, and some patients are asymptomatic entirely.<sup>45</sup> Fatigue and chronic abdominal pain are common symptoms. Increased fracture risk, anemia, and other consequences of malabsorption can have substantial impact on patients' quality of life. Not only is living with celiac disease a daily struggle, it is a disease that dramatically increases the mortality risk for other diseases -- 6x increased risk for death from non-Hodgkin's lymphoma; 3x increased risk for death from liver disease; 2.6x increased risk for death from pneumonia<sup>46</sup>; and, 4x risk for small bowel cancer.<sup>47</sup> Demographics support the estimate that thousands of active, Guard, and Reserve service members are currently suffering from celiac disease or are in danger of developing the disease, making them eligible for service-connected disability. Based upon TRICARE covered lives, it is estimated that an additional 77,000 retirees and family members may also suffer from celiac disease. Further research will benefit those suffering from celiac disease by generating strategies to prevent the disease and providing critical guidance on mitigation efforts effecting readiness.

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<sup>43</sup> Caio G, Volta U, Sapone A, Leffler DA, De Giorgio R, Catassi C, Fasano A. Celiac disease: a comprehensive current review. *BMC Med.* 2019 Jul 23;17(1):142. doi: 10.1186/s12916-019-1380-z. PMID: 31331324; PMCID: PMC6647104.

<sup>44</sup> Rubio-Tapia A, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, Brantner TL, Kim WR, Phelps TK, Lahr BD, Zinsmeister AR, Melton LJ 3rd, Murray JA. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology.* 2009 Jul;137(1):88-93. doi: 10.1053/j.gastro.2009.03.059. Epub 2009 Apr 10. PMID: 19362553; PMCID: PMC2704247.

<sup>45</sup> Leonard MM, Sapone A, Catassi C, Fasano A. Celiac Disease and Nonceliac Gluten Sensitivity A Review. *JAMA.* 2017;318(7):647-656. doi:10.1001/jama.2017.9730. PMID 28810029

<sup>46</sup> Holmes GKT, Muirhead A. Mortality in coeliac disease: a population-based cohort study from a single centre in Southern Derbyshire, UK. *BMJ Open Gastroenterol.* 2018 Apr 17;5(1):e000201. doi: 10.1136/bmjgast-2018-000201. PMID: 29686881; PMCID: PMC5911148.

<sup>47</sup> Ilus T, Kaukinen K, Virta LJ, Pukkala E, Collin P. Incidence of malignancies in diagnosed celiac patients: a population-based estimate. *Am J Gastroenterol.* 2014 Sep;109(9):1471-7. doi: 10.1038/ajg.2014.194. Epub 2014 Jul 22. PMID: 25047399.

- Colorectal Cancer:** According to a study published in the June 2009 issue of *Cancer Epidemiology, Biomarkers & Prevention*, researchers found that colorectal cancer was one of the most common forms of cancer among active duty military personnel. Yet, screening rates among military personnel for colorectal cancer remain low. As published in the 2009 Humana Military's Clinical Quality Report Card, only 58 percent of those in the military were up to date with screening in 2008. The Peer Reviewed Cancer Research Program (PRCRP) has supported research into treatments for colorectal cancer, including research into treatments that would block the growth of metastatic colorectal cancer. CA093415<sup>48</sup>, CA111002<sup>49</sup>, CA100879<sup>50</sup>, CA100512P1<sup>51</sup>, CA093176<sup>52</sup>)
- Congenital Heart Disease:** Congenital heart disease (CHD) is the most common class of birth defects and the leading cause of birth defect-related infant mortality. Nearly 1 in 100 babies are born with a CHD and more than five percent will not live to see their first birthday.<sup>53 54</sup> Even those who receive successful intervention are not cured. Children and adults born with CHD require ongoing, costly, specialized cardiac care, and face a lifelong risk of permanent disability and premature death. As a result, healthcare utilization among the CHD population is significantly higher, and health care costs are estimated to be 10 to 20 times greater for this community than the general population. There are higher rates of birth defects, including CHD, for children born in military families. Research conducted through the Department of Defense has found high altitudes play a role. There are some suggestions that the reduced oxygen at high elevations [such as in the mountains of Afghanistan] may adversely affect the pregnancy and the growth of the fetus, but there is little understanding of the effect on the developing fetus of travel to high altitudes.<sup>55</sup> This is especially true early in the pregnancy when the heart and other organs are just forming (8-12 weeks) and the Service member may not yet know or have not verbalized that she is pregnant. Other studies have suggested higher prevalence of CHD among infants conceived in Gulf War veteran families. Further research in these areas will benefit the children conceived of military families and will have broader implications for all American families.

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<sup>48</sup> Feng Z, Liu L, Zhang C, et al. 2012. Chronic restraint stress attenuates p53 function and promotes tumorigenesis. *PNAS* 109:7013-7018.

Hu W, Feng Z, and Levine A. 2012. The regulation of multiple p53 stress responses are mediated through MDM2. *Genes Cancer* 3:199-208. (PMC3494373).

Yu H, Yue X, Zhao Y, et al. 2014. LIF negatively regulates tumor suppressor p53 through Stat3/ID1/MDM2 in colorectal cancers. *Nat Comm* 5:5218.

<sup>49</sup> Lightfoot YL, and Mohamadzadeh M. 2013. Tailoring gut immune responses with lipoteichoic acid-deficient *Lactobacillus acidophilus*. *Front Immunol* 6;4:25.

Lightfoot YL, Yang T, Sahay B, et al. 2013. Targeting aberrant colon cancer-specific DNA methylation with lipoteichoic acid-deficient *Lactobacillus acidophilus*. *Gut Microbes* 4(1):84-88.

Owen JL, and Mohamadzadeh M. 2013. Macrophages and chemokines as mediators of angiogenesis. *Front Physiol* 5(4):159.

<sup>50</sup> Lu J, Ye X, Fan F, et al. 2013. Endothelial cells promote the colorectal cancer stem cell phenotype through a soluble form of Jagged-1. *Cancer Cell* 23(2):171-185.

<sup>51</sup> Pitts TM, Newton TP, Bradshaw-Pierce EL, et al. 2014. Dual pharmacological targeting of the MAP Kinase and PI3K/mTOR pathway in preclinical models of colorectal cancer. *PLoS One* 9(11):e113037.

<sup>52</sup> Song BP, Jain S, Lin SY, et al. 2012. Detection of hypermethylated vimentin in urine of patients with colorectal cancer. *J Mol Diagn* 14(2):112-119.

<sup>53</sup> Hoffman JL, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890-1900.

<sup>54</sup> Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in Atlanta, 1998-2005. *J Pediatr*. 2008;153:807-13.

<sup>55</sup> <http://www.dtic.mil/dtic/tr/fulltext/u2/1048533.pdf>

- **Crohn's Disease and Ulcerative Colitis (Inflammatory Bowel Diseases):** The prevalence of Crohn's Disease and Ulcerative Colitis (collectively known as inflammatory bowel diseases-IBD) increased by two to threefold among veterans from 1998 to 2009. Researchers found nearly 17,000 unique incident cases of Crohn's Disease and over 26,000 cases of Ulcerative Colitis within the military population during this time. Due to the population studied, 94% of the cases were in men. In 2009, the age and gender standardized prevalence rate of Crohn's Disease was 287 per 100,000 VA users and the prevalence rate for Ulcerative Colitis was 413 per 100,000 VA users.<sup>56</sup> Despite having a large population study, much is yet to be known about etiology or cause of these diseases, therefore continued research in this area is necessary to advance knowledge about IBD.
- **Epilepsy:** According to 2015 estimates, a staggering 3.4 million Americans report living with epilepsy.<sup>57</sup> Individuals who serve in the military are especially susceptible to developing a type of epilepsy called post-traumatic epilepsy (PTE), defined as a recurrent seizure disorder following traumatic brain injury (TBI).<sup>58</sup> TBIs can take the form of bumps, blows to the head, blasts or penetrating injuries,<sup>59</sup> such as those seen so often in the line of duty. In fact, over 400,000 active-duty service members were diagnosed with a TBI from 2000-2019.<sup>60</sup> These injuries can have a devastating impact on troops; for example, a reported 53% of a group of Vietnam veterans with penetrating brain wounds developed epilepsy,<sup>61</sup> and within a group of veterans of the Afghanistan and Iraq conflicts, those with TBI were almost 19x more likely to develop epilepsy than those without TBI.<sup>62</sup> Furthermore, people with epilepsy including that which is a result of head injury are largely prohibited from admission into the armed services according to DoD regulations, reducing the pool of eligible recruits.<sup>63</sup> Currently, there is no known prevention for PTE following TBI, and treatments for PTE are only partially effective and can have severe drawbacks.<sup>64</sup> There is also no known treatment or cure for many other types of epilepsy that afflict our troops and the general population.<sup>65</sup> Therefore, the continuation of epilepsy research is critical to the health of our troops, our national security and to the well-being of the population as a whole.

<sup>56</sup> Hou JK, Kramer JR, Richardson P, Mei M, El-Serag HB. The Incidence and Prevalence of Inflammatory Bowel Disease Among U.S. Veterans: A National Cohort Study. *Inflamm Bowel Dis*. 2013 Feb 27. [Epub ahead of print] PubMed PMID: 23448789.

<sup>57</sup> Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy — United States, 2015. *MMWR*. 2017;66:821–825.

<sup>58</sup> Pitkänen A and Bolkvadze T. Head Trauma and Epilepsy. *Jasper's Basic Mechanisms of the Epilepsies* [Internet] 4<sup>th</sup> Edition 2012. Noebels JL, Avoli M, Rogawski MA, et al., editors.

<sup>59</sup> Marr A, Coronado V, editors. *Central Nervous System Injury Surveillance: Annual Data Submission Standards for the Year 2002*. Atlanta: U.S. Department of Health and Human Services, CDC, National Center for Injury Prevention and Control; 2004.

<sup>60</sup> DoD Worldwide Numbers for TBI, Defense and Veterans Brain Injury Center, 2020

<sup>61</sup> Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. *Neurology* 1985; 35(10): 1406-1414.

<sup>62</sup> Pugh MJ, Orman JA, Jaramillo CA, Salinsky MC, Eapen BC, Towne AR, Amuan ME, Roman G, McNamee SD, Kent TA, McMillan KK, Hamid H, Grafman JH. The prevalence of epilepsy and association with traumatic brain injury in veterans of the Afghanistan and Iraq wars. *J Head Trauma* 2015; 30(1):29-37.

<sup>63</sup> DoD Instruction 6130.03, Volume 2, Medical standards for military service: retention. <https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/613003v2p.pdf?ver=2020-09-04-120013-383>

<sup>64</sup> Szaflarski JP, Nazzal Y, Dreer LE. Post-traumatic epilepsy: Current and emergent treatment options. *Neuropsychiatr Dis Treat* 2014; 10:1469-1477.

<sup>65</sup> Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine* 2000;342(5):314-9.

- **Esophageal Cancer:** Esophageal cancer is the seventh leading cause of cancer-related death among American men in both the military and the general population. In addition, four out of five patients (more than 80 percent) die within five years of receiving an esophageal cancer diagnosis. It is one of America's deadliest cancers, largely because little effective treatment, scarce early detection and no screening guidelines exist for this disease. Further, those at greatest risk for esophageal cancer are men over the age of 55 who have a history of gastro-esophageal reflux disease (GERD), tobacco and/or alcohol use, and/or obesity<sup>66</sup> – all risks that are higher in the country's veteran population compared to the general population.<sup>67</sup> Our military personnel and veterans also have additional risks. In fact, the VA has already established that there is a presumption of service connection for esophageal cancer. One reason for this step is that the radiation some veterans have been exposed to has been shown to be linked to the disease.<sup>68</sup> There is also a link to the contaminated drinking water at U.S. Marine Corps Base Camp Lejeune, North Carolina from the 1950s to the 1980s.<sup>69</sup> Veterans and their families who were stationed there were potentially exposed to drinking water contaminated with industrial solvents, benzene, and other chemicals that have been linked to esophageal cancer. Finally, some of the burden of esophageal cancer is linked to military-encouraged smoking. It is well documented that the military continued to include cigarettes in rations until 1975<sup>70</sup> and overall, veterans are more likely to be smokers than the general population.<sup>71</sup>

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<sup>66</sup> Cancer Facts & Figures 2021, American Cancer Society, cancer.org, 1/2021 accessed 2-18-2021.

<sup>67</sup> Using Health Factors Data for VA Health Services Research, Paul G. Barnett, Adam Chow and Nicole E. Flores February 2014, p. 28; VA/DoD Clinical Practice Guideline for SCREENING AND MANAGEMENT OF OVERWEIGHT AND OBESITY, Department of Veterans Affairs, Department of Defense, 2014, p. 3; Research Letter, JR Kramer, Shakhathreh, AD Naik, Z Duan, HB El-Serag, JAMA Internal Medicine, January 2014, Use and Yield of Endoscopy in Patients With Uncomplicated Gastroesophageal Reflux Disorder, p E1.

<sup>68</sup> <https://www.law.cornell.edu/cfr/text/38/3.309>

<sup>69</sup> <https://www.va.gov/disability/eligibility/hazardous-materials-exposure/camp-lejeune-water-contamination/>

<sup>70</sup> Joseph, Anne M.; et al. (2005). "The Cigarette Manufacturers' Efforts to Promote Tobacco to the U.S. Military". *Military Medicine* 170: 874–880.

<sup>71</sup> Brown, D.W., 2010 Smoking Prevalence among US Veterans, *J Gen Intern Med.* Feb; 25(2): 147–149.

- **Fibrous dysplasia/McCune-Albright syndrome (FD/MAS)**: The mutation that causes FD/MAS is located in a very important gene (GNAS) that is necessary for the maintenance of healthy bone. For that reason, the study of FD/MAS has a track record of yielding broad insights about bone biology, like the discovery that bone is the body's source of a key kidney-regulating hormone.<sup>72</sup> FD/MAS provides a unique natural experiment to study key signaling pathways that have implications for treatments of DoD-prevalent conditions, like blast-induced heterotopic ossification, chronic bone pain, skeletal fractures, osteoporosis, and osteoarthritis. Heterotopic Ossification (HO) is a condition where bone forms in soft tissue where bone does not normally exist. Studies have found that blast-induced HO affects approximately 65% of combat-wounded warriors, resulting in obstacles to mobility, use of prostheses, recovery, and returns to service.<sup>73</sup> HO can be caused by the inverse of the gene mutation that causes FD/MAS.<sup>74</sup> The study of the basic biology of FD/MAS could increase understanding of HO because FD/MAS is caused by the activating mutation of GNAS and HO can be caused by the inactivating mutation of the very same gene. Studying FD/MAS can also provide a window into the mechanisms of pain. Because people with FD/MAS transition to chronic pain in a predictable time frame, and exhibit both major forms of pain (nociceptive and neuropathic), this population a convenient sample to track the biochemical, physiological, and neurological emergence of chronic bone pain, from beginning to end.<sup>75,76</sup>

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<sup>72</sup> Riminucci M, Collins MT, Fedarko NS, Cherman N, Corsi A, White KE, Waguespack S, Gupta A, Hannon T, Econs MJ, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. *J Clin Invest.* 2003;112(5):683-92.

<sup>73</sup> Alfieri KA, Forsberg JA, Potter BK. Blast injuries and heterotopic ossification. *Bone Joint Res.* 2012;1(8):192-7.

<sup>74</sup> Brewer N, Fong JT, Zhang D, Ramaswamy G, Shore EM. Gnas Inactivation Alters Subcutaneous Tissues in Progression to Heterotopic Ossification. *Front Genet.* 2021;12:633206.

<sup>75</sup> Kelly MH, Brillante B, Collins MT. Pain in fibrous dysplasia of bone: age-related changes and the anatomical distribution of skeletal lesions. *Osteoporos Int.* 2008;19(1):57-63.

<sup>76</sup> Tucker-Bartley A, Lemme J, Gomez-Morad A, Shah N, Veliu M, Birklein F, Storz C, Rutkove S, Kronn D, Boyce AM, et al. Pain Phenotypes in Rare Musculoskeletal and Neuromuscular Diseases. *Neurosci Biobehav Rev.* 2021;124:267-90.

- **Food Allergies:** Food allergy affects approximately 7.6 percent of children<sup>77</sup> and 10.8 percent<sup>78</sup> of adults in the United States. Active duty service members with a history of food-allergy anaphylaxis or a systemic reaction to food do not meet military accession or retention standards. In spite of this, the incidence rate of food-allergy anaphylaxis among active component service members approximates that found in the general population and appears to be increasing.<sup>79</sup> Inadequate knowledge or misconceptions of current military-specific standards regarding food allergy and how these apply to enlistment, induction, and retention in the US military can lead potentially to inaccurate counseling because each military service has specific regulations that affect the evaluation and decision-making process. Both civilian and military allergists play an essential role in the evaluation, counseling, and management of patients with a food allergy history. Understanding the service-specific language and regulations regarding food allergy will improve the allergist's awareness, counseling, and management of these individuals.<sup>80</sup> Further, in the military, an IgE-mediated food allergy can be disqualifying for entry and specific career specialties. However, given the increasing numbers of service members affected by this condition, the military may wish to consider new policies to allow applicants and members with avoidable food allergies to serve successfully. Future studies are needed to evaluate whether food allergies have any unique consequences in this population.<sup>81</sup>

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<sup>77</sup> Gupta RS, Warren CM, Smith BM, et al. The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States. *Pediatrics*. 2018;142(6):e20181235. (2019). *Pediatrics* March 2019, 143 (3) e20183835; DOI: <https://doi.org/10.1542/peds.2018-3835>.

<sup>78</sup> Gupta, R. S., Warren, C. M., Smith, B. M., Jiang, J., Blumenstock, J. A., Davis, M. M., ... Nadeau, K. C. (2019). Prevalence and Severity of Food Allergies Among US Adults. *JAMA Network Open* 2019; 2(1): e185630. doi:10.1001/jamanetworkopen.2018.5630

<sup>79</sup> Clausen S, Stahlman S. Food-allergy anaphylaxis and epinephrine autoinjector prescription refills, active component service members, U.S. Armed Forces, 2007-2016.

<sup>80</sup> Food allergy guidance in the United States Military: A work group report from the American Academy of Allergy, Asthma & Immunology's Military Allergy and Immunology Assembly. *J Allergy Clin Immunol* 2018; 141(1):54-59

<sup>81</sup> Lee RU, Stahlman S. Increasing incidence and prevalence of food allergies in the US Military 2000-2017. *J Allergy Clin Immunol-Practice* 2020; 8(1):361-63.

- **Gulf War Illness**: According to a 2014 update report of the Congressionally-mandated Research Advisory Committee on Gulf War Veterans' Illnesses (RAC), "Scientific research [since 2008] . . . supports and further substantiates . . . that Gulf War illness is a serious physical disease, affecting at least 175,000 veterans of the 1990-1991 Gulf War, that resulted from hazardous exposures in the Gulf War theater."<sup>82</sup> Studies reviewed in the report found an elevated incidence of Lou Gehrig's disease (ALS)<sup>83</sup> among Gulf War veterans as well as significantly elevated rates of death due to brain cancer<sup>84</sup> among those who were most exposed to the release of nerve gas by the destruction of the Khamisiyah Iraqi arms depot. In addition to improving the health of Gulf War veterans, important discoveries made by the GWIRP will also help protect current and future American servicemembers who are at risk of similar toxic exposures.<sup>85</sup>

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<sup>82</sup> Research Advisory Committee on Gulf War Veterans' Illnesses, *Gulf War Illness and the Health of Gulf War Veterans: Research Update and Recommendations, 2009-2013*, p. 1. U.S. Government Printing Office, Washington, D.C., 2014.

<sup>83</sup> Research Advisory Committee on Gulf War Veterans' Illnesses, pp. 23-25.

<sup>84</sup> Research Advisory Committee on Gulf War Veterans' Illnesses, pp. 23-26.

<sup>85</sup> Research Advisory Committee on Gulf War Veterans' Illnesses, pp. 1; 4; 5; 13; 78; 83. And: Institute of Medicine, N. R. C., 2010. *Gulf War and Health: Volume 8 - Health Effects of Serving in the Gulf War*. The National Academies Press, Washington, DC, pp. 10; 260-64.

- Hydrocephalus**: Hydrocephalus is a chronic neurological condition that affects over one million people in the US. Hydrocephalus has no cure and the only treatment option is brain surgery. Often thought of as a pediatric condition, children can be born with hydrocephalus or develop it after birth, with the premature baby population being at particular risk of post-hemorrhagic hydrocephalus as a result of a brain bleed. Hydrocephalus is the leading cause of brain surgery in children. However, anyone at any time can develop hydrocephalus as it can be caused by a traumatic brain injury, tumor, infection, or as part of the aging process for reasons which are still not understood. This makes hydrocephalus' impact and reach within our military population deep and wide. Families can be affected if their children are born with or develop the condition. Active service members and veterans who have experienced traumatic brain injury are particularly vulnerable to developing hydrocephalus. Since 2000, more than 333,000 U.S. service members have sustained a traumatic brain injury.<sup>86</sup> Over 35,000 are at risk of developing hydrocephalus due to the severity of the injury.<sup>87 88 89 90</sup> The Department of Defense does not currently track the development of hydrocephalus, so, while Normal Pressure Hydrocephalus (NPH) affects elderly adults, it is not known if previous injury, even mild injury, increases the risk of NPH. It is estimated that NPH affects over 700,000 seniors in the United States, including over 180,000 veterans.<sup>91 92</sup>

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<sup>86</sup> Defense Medical Surveillance System. Theater Medical Data Store provided by the Armed Forces Health Surveillance Center. <http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>.

<sup>87</sup> Groswasser, Z., Cohen, M., Reider-Groswasser, I., & Stern, M.J. (1988). Incidence, CT findings and rehabilitation outcome of patients with communicative hydrocephalus following severe head injury. *Brain Inj*, 2, 267-272.

<sup>88</sup> Licata, C., Cristofori, L., Gambin, R., Vivenza, C., & Turazzi, S. (2001). Post-traumatic hydrocephalus. *J.Neurosurg. Sci*, 45, 141- 149.

<sup>89</sup> Marmarou, A., Foda, M.A., Bandoh, K., Yoshihara, M., Yamamoto, T., & Tsuji, O. et al. (1996). Posttraumatic ventriculomegaly: Hydrocephalus or atrophy? A new approach for diagnosis using CSF dynamics. *J.Neurosurg*, 85, 1026-1035.

<sup>90</sup> Mazzini, L., Campini, R., Angelino, E., Rognone, F., Pastore, I., & Oliveri, G. (2003). Posttraumatic hydrocephalus: A clinical, neuroradiologic, and neuropsychologic assessment of long-term outcome. *Arch. Phys. Med. Rehabil*, 84, 1637-1641.

<sup>91</sup> Jaraj D, Rabiei K, Marlow T, Jensen C, Skoog I, Wikkelsø C. Prevalence of idiopathic normal-pressure hydrocephalus. *Neurology*.2014;82:1449–1454. doi: 10.1212/WNL.0000000000000342.

<sup>92</sup> The Veteran Population Projection Model 2014. U.S. Department of Veterans Affairs. [http://www.va.gov/vetdata/Veteran\\_Population.asp](http://www.va.gov/vetdata/Veteran_Population.asp).

- Kidney Cancer:** Kidney cancer affects military personnel and their dependents and veterans. The body insult that causes kidney cancer may occur during active service but may not appear until later in life therefore affecting veterans more frequently than their US civilian counterparts. In a 2012 study identifying cancer incidence among patients of the United States Veterans Affairs Healthcare System kidney cancer was the 6th leading cancer.<sup>93</sup> Vietnam veterans exposed to Agent Orange have had kidney cancer. Exposure to ionizing radiation, chemicals and hazardous materials can cause kidney cancer. Smoking, hypertension and obesity are high kidney cancer risk factors. A cohort of about 210,000 U.S. veterans followed for 26 years was analyzed for a study examining the role of smoking in the development of renal cancer.<sup>94</sup> The follow-up of these military veterans revealed 719 deaths from renal cancer, making this one of the largest studies of renal cancer and cigarette smoking. Current smokers had a 47 percent increase in risk for renal cancer relative to nonsmokers, and the relative risk correlated positively with the number of cigarettes smoked per day. These results were later confirmed by several independent studies showing that about one fifth to one third of renal cancer is associated with smoking. Cigarette smoking generates oxidative stress, which is implicated as one of the direct chemical factors in renal oncogenesis. Most recently, researchers from Oak Ridge National Laboratory demonstrated a near real-time generation of hydrogen peroxide by cigarette smoke. According to a 2014 report issued by the Centers for Disease Control and Prevention US Marines and their families stationed at Camp Lejeune, North Carolina have a 35% higher risk of contracting kidney cancer than their US counterparts due to contaminated drinking water.<sup>95</sup>
- Leukemia/Lymphoma/Multiple Myeloma:** Many of the blood cancers are linked to chemical and radiologic exposure during deployment. Leukemia, non-Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL), and multiple myeloma have all been connected to chemical weapons, or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, etc. The Selected Cancers Cooperative Study Group showed that veterans of the Vietnam War had a 50% increase of risk of HL as compared to subjects who had not served in Vietnam. Evidence associates an increased risk for NHL, HL, and chronic lymphocytic leukemia to Vietnam War service and exposure to herbicides such as Agent Orange.<sup>96</sup>

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<sup>93</sup> Leah L. Zullig, George L. Jackson, Raye Anne Dorn, Dawn T. Provenzale, Rebecca McNeil, Catherine M. Thomas, and Michael J. Kelly. Cancer Incidence among Patients of the United States Veterans Affairs (VA) Healthcare System, *Mil Med.* 2012 June; 177 (6): 693-701

<sup>94</sup> McLaughlin JK, Hrubec Z, Heineman EF, Blot WJ, Fraumeni JF. (1990) Renal Cancer and Cigarette Smoking in a 26-Year Followup of U.S. Veterans. *Public Health Rep.* 105:535-537

<sup>95</sup> 2014 CDC Camp Lejeune Contaminated Drinking Water Report

<sup>96</sup> Frumkin H. Agent Orange and cancer: an overview for clinicians. *CA Cancer J Clin.* 2003;53:245–55.

- **Lung Cancer:** Numerous studies over the years published by the Institute of Medicine, *Cancer*, *Military Medicine*, *Chest* and others have shown that lung cancer incidence and mortality rates, due to much higher smoking rates and exposures to known carcinogens during active duty, are an estimated 25% – 30% higher in the military than in civilian populations.<sup>97 98 99 100</sup> Of growing concern is the lung cancer risk among ground troops deployed during the Gulf Wars whose exposures included asbestos, chromium, diesel exhaust, radon, crystalline silica, pesticides, pollutants and particulate matter from burn pits, oil well fires and the destruction of chemical weapons including sarin gas. Research focused on these veterans is urgently needed. Given lung cancer’s long latency period, and the fact that the average age of Gulf War veterans is now in the mid-fifties, research projects should incorporate CT screening as a platform.
- **Lupus:** Lupus is a debilitating autoimmune disease that causes the immune system to erroneously attack health, living tissue. It is up to three times more common among African Americans, Hispanics and Native Americans.<sup>101</sup> Lupus affects over one-and-a-half million persons in the U.S. --90 percent of whom are women. Defense Department data show that women now make up a much greater share of our armed forces than they have at any time in U.S. history. Women account for 16 percent of active duty Service Members, 19 percent of the Air Force, 18 percent of the Navy, 14 percent of the Army, and 8 percent of the Marines.<sup>102</sup> A 2018 Council of Foreign Relations report found that the active-duty female force is racially diverse—56 percent of female recruits are Hispanic and there are nearly as many black women as white women in the Army.<sup>103</sup> Lupus often strikes young women of childbearing age who experience symptoms such as intense fatigue and exhaustion, joint pains, cognitive and memory problems, and skin rashes. It can also manifest in kidney problems, premature heart disease, strokes, or lung inflammation. Research shows that Lupus is becoming more prevalent among women in the military.<sup>104</sup> In 2009, as many as 20,000 active duty soldiers and veterans were receiving care for lupus through TRICARE or the Veteran’s Administration healthcare system.<sup>105</sup> There are a number of possible reasons that could help to explain the growing rates of Lupus including post-traumatic stress disorder, chemicals and toxins, as well as certain drugs and infectious agents.<sup>106</sup> Research projects are studying these triggers to determine what effect they have on the immune system.

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<sup>97</sup> Stuart Bondurant and Roberta Wedge. *Combating Tobacco Use in Military and Veteran Populations*, , Editors; Committee on Smoking Cessation in Military and Veteran Populations; Institute of Medicine 2009. [http://www.nap.edu/catalog.php?record\\_id=12632](http://www.nap.edu/catalog.php?record_id=12632)

<sup>98</sup> Harris RE, Hebert JR, Wynder EL. Cancer risk in male veterans utilizing the Veterans Administration medical system. *Cancer* 1989;64:1160-8.

<sup>99</sup> *A Study of Cancer in the Military Beneficiary Population*, Guarantor: Raymond Shelton Crawford III, MD MBA, Contributors: Raymond Shelton Crawford III, MD MBA; Julian Wu, MD MPH; Dae Park, MD; Galen Lane Barbour, MD; *Military Medicine*, Vol. 172, October 2007.

<sup>100</sup> Wilson, M.. Prevalence of tobacco abuse in a United States Marine Corp Infantry Battalion Forward Deployed in the Haditha Triad Area of Operations, Al Anbar, Iraq. *CHEST*. 2008;134: s53001

<sup>101</sup> Wallace, D.J., and Hahn, B.H. *Dubois’ Lupus Erythematosus and Related Syndromes*. (8th ed.) Philadelphia, PA: Elsevier Saunders. 2013.

<sup>102</sup> 2015 Demographics: Profile of the Military Community. Department of Defense. Accessed January 21, 2020.

<sup>103</sup> Demographics of the U.S. Military. Council on Foreign Relations. Accessed January 21, 2020.

<sup>104</sup> O’Donovan, et al. Elevated Risk for Autoimmune Disorders in Iraq and Afghanistan Veterans with Posttraumatic Stress Disorder. *Biological Psychiatry*. 2015. Accessed January 21, 2020.

<sup>105</sup> *Lupus, the Prototypical Autoimmune Disease, and the Military*. Lupus Foundation of America, Inc. 2009. Accessed January 21, 2020.

<sup>106</sup> Department of Defense: Lupus Research Program. Accessed January 21, 2020.

- **Malaria:** While malaria has been eliminated from the United States since 1951, it has been and remains a direct threat to members of the United States military serving overseas.<sup>107</sup> During World War II, General Douglas MacArthur was quoted as saying, "This will be a long war if for every division I have facing the enemy, I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease!"<sup>108</sup> Nearly eighty years later, malaria remains the number one infectious disease threat to U.S. military forces deployed worldwide.<sup>109</sup> In 2003, 80 out of 220 or 36% of Marines deployed to Liberia contracted *Plasmodium falciparum* malaria due to low prophylaxis adherence, 46 of which required medical evacuation. Given the threat malaria poses to service members, the Department of Defense, through the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Center (NMRC) conducts malaria-related research and development efforts for drugs, diagnostics and vaccines, helping to establish and enhance partnerships around the world and achieve FDA-approval of new tools in the fight against malaria. WRAIR's role within the DOD is critical, as they are the only institution in the world focused on developing the treatments to prevent malaria in healthy adults.<sup>110</sup> Among its recent successes, the scientists at WRAIR made significant contributions to the development of the RTS,S malaria vaccine which is currently being piloted in Kenya, Malawi, and Ghana, as well as the development of tafenoquine, a single dose cure for *Plasmodium vivax* malaria which was approved by the FDA in July 2018.<sup>111</sup>

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<sup>107</sup> Pages, F., Faulde, M., Orlandi-Pradines, E., & Parola, P. (2010). The past and present threat of vector-borne diseases in deployed troops. *Clinical Microbiology and Infection*, 16(3), 209-224.

<sup>108</sup> Paul F Russell, 'Introduction', in *Preventive medicine in World War II*, op. cit., note 1 above, p. 2.

<sup>109</sup> Moss, Kellie and Josh Michaud. 2013. *The U.S. Department of Defense and Global Health: Infectious Disease Efforts*. Kaiser Family Foundation pg. 17

<sup>110</sup> Lezaun, J. (2018). The deferred promise of radical cure: pharmaceutical conjugations of malaria in the global health era. *Economy and Society*, 1-25.

<sup>111</sup> Hounkpatin, A. B., Kreidenweiss, A., & Held, J. (2019). Clinical utility of tafenoquine in the prevention of relapse of *Plasmodium vivax* malaria: a review on the mode of action and emerging trial data. *Infection and drug resistance*, 12, 553.

- **Mefloquine neurotoxicity/chronic quinoline encephalopathy**: Mefloquine is an antimalarial quinoline drug developed by the U.S. military that had been widely employed until 2013, when the DoD declared it an antimalarial drug of last resort, after research at the Walter Reed Army Institute of Research (WRAIR) identified it as neurotoxic, and the U.S. Food and Drug Administration (FDA) warned that mefloquine may cause long-lasting and even permanent adverse neuropsychiatric effects. The U.S. Department of Veterans Affairs (VA) has recently awarded several disability claims to veterans for permanent neuropsychiatric conditions, including anxiety and insomnia, that the VA has concluded were due to exposure to mefloquine while serving in the military.<sup>112</sup> “Neurotoxicity of mefloquine” was first included as a PRMRP topic area fifteen years ago for one year (FY 2006).<sup>113</sup> DoD has provided other limited funding for toxicity-relevant research, including funding by the Military Infectious Disease Research Program (MIDRP) for a project entitled, Evaluation of Multiple Potential Pharmacogenomic Risk Factors for Chronic Mefloquine Neurotoxicity [i.e. chronic quinoline encephalopathy] Through the Establishment of a Drug Safety Registry.<sup>114</sup> A National Academies of Sciences, Engineering, and Medicine (NASEM) committee, charged “*to assess the long-term health effects that might result from the use of antimalarial drugs by adults, in particular mefloquine, for the prophylaxis of malaria,*”<sup>115</sup> concluded “there is a very limited body of research that directly addresses the pathways by which these drugs might result in persistent changes that produce adverse events that may or may not be reversible.” Consistent with prior PRMP funding and the recommendations of the NASEM committee for further research, support is needed to define persistent and latent central nervous system effects of antimalarial quinoline neurotoxicity, to define the adverse neurophysiological effects of antimalarial quinolines, to disentangle comorbid neuropsychiatric diagnoses confounded by antimalarial quinoline toxicity, and to develop effective treatments.

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<sup>112</sup> Nevin RL, Ritchie EC. FDA Black Box, VA Red Ink? A Successful Service-Connected Disability Claim for Chronic Neuropsychiatric Adverse Effects From Mefloquine. *Federal Practitioner*. 2016;33(10):20–24.

<sup>113</sup> Peer Reviewed Medical, FY06 Topic Areas: <https://cdmrp.army.mil/prmrp/topicareas/topicareas06>.

<sup>114</sup> U.S. Army Medical Research and Materiel Command. Congressionally Directed Medical Research Programs. 2017 Annual Report. <https://cdmrp.army.mil/pubs/annreports/2017annrep/2017annreport.pdf>

<sup>115</sup> National Academies of Sciences, Engineering, and Medicine 2020. *Assessment of Long-Term Health Effects of Antimalarial Drugs When Used for Prophylaxis*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25688>.

- **Melanoma:** A 2000 "Annals of Epidemiology" study comparing mortality among WWII veterans of the Pacific and European Theaters found that Pacific Theater Prisoner of War veterans had an estimated 3-fold higher risk of dying from melanoma than veterans of the European Theater, concluding that exposure to high levels of solar radiation in young adulthood is associated with a higher risk of melanoma mortality.<sup>116</sup> Given this information, U.S. military personnel currently stationed in Iraq and Afghanistan, where the intensity of sun exposure is similar to that of the Pacific, have the potential for a long-term risk of melanoma. According to the American Cancer Society, the American Academy of Dermatology and the Melanoma Research Foundation, skin cancer is the most commonly diagnosed cancer in the United States. Melanoma, the deadliest type of skin cancer, kills an estimated 10,000 Americans each year. Furthermore, people of all ages, races and genders are at risk. Melanoma is the most common form of cancer for young adults 25-29, the second most common form of cancer for young people 15-29 and SEER data suggests that the majority of people diagnosed with melanoma are white men over the age of 50.<sup>117 118 119</sup>
- **Mesothelioma:** There is a long history of asbestos exposure in military service, and a significant elevated risk of mesothelioma in the military population.<sup>120</sup> A study of occupational exposures and subsequent mesothelioma diagnoses found that one third of mesothelioma cases involved Navy and shipyard exposures.<sup>121</sup> Due to disease development latency (i.e., disease of today is caused by exposure from 25-50 years ago) and asbestos' continued presence on US Navy ships (Comptroller General of the United States, 1979), the expectation is that mesothelioma development among service members will not stop. Among other branches of military, recent exposures have been reported among service members engaged across a variety of military interests abroad, particularly in Iraq and Afghanistan. In addition, smoking has been shown to negatively affect survival in mesothelioma patients.<sup>122</sup> The prevalence of tobacco use among military personnel, and specifically smoking, is reported to be significantly higher than that of the general population.<sup>123</sup>

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<sup>116</sup> Annals of Epidemiology, Vol. 10, Issue 3, April 2000, pages 192-195.

<sup>117</sup> Bleyer A, O'Leary M, Barr R, Ries LAG (eds): Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000. Bethesda, MD: National Cancer Institute; 2006

<sup>118</sup> Melanoma of the Skin, Cancer Fact Sheets, National Cancer Institute, SEER database, 2007.

<http://seer.cancer.gov>

<sup>119</sup> Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesda, MD: National Cancer Institute; [http://seer.cancer.gov/csr/1975\\_2009\\_pops09/](http://seer.cancer.gov/csr/1975_2009_pops09/); Accessed August 22, 2012.

<sup>120</sup> Comptroller General of the United States. (1979). Navy's Efforts to Protect Workers From Asbestos Exposure. Comptroller General of the United States.

<sup>121</sup> K. J. BUTNOR, A. S. (2002). Malignant Mesothelioma and Occupational Exposure. The Annals of Occupational Hygiene, 150-153.

<sup>122</sup> Flores, R. M., Zakowski, M., Krug, L., Rosenzweig, K., & Rusch, V. (2007). Prognostic Factors in the Treatment of Malignant Pleural Mesothelioma at a Large Tertiary Referral Center. Journal of Thoracic Oncology, 957-965.

<sup>123</sup> Wilson, M. A. (2008). PREVALENCE OF TOBACCO ABUSE IN A UNITED STATES MARINE CORP INFANTRY BATTALION FORWARD DEPLOYED IN THE HADITHA TRIAD AREA OF OPERATIONS, AL ANBAR, IRAQ. Chest Journal.

- **Multiple Sclerosis:** There are currently over 32,000 veterans with diagnosed multiple sclerosis (MS).and over 11,000 of those veterans have a service connected disability for MS.<sup>124</sup> MS is an unpredictable, often disabling disease of the central nervous system that interrupts the flow of information within the brain, and between the brain and the body. Symptoms range from numbness and tingling to blindness and paralysis. The progress, severity and specific symptoms of MS in any one person cannot yet be predicted. Each year the Veterans Health Administration provides care to more than 28,000 veterans living with MS each year.<sup>125</sup> Currently, there is a presumptive period for a service connected benefit for MS. Individuals who are diagnosed with MS while they are in the military or within seven years of their honorable discharge are eligible for a service-connected disability. A 2003 review found that 5,345 veterans that served in Vietnam and the first Gulf War were diagnosed with MS that was deemed "service-connected."<sup>126</sup> The relative risk for developing MS also was significantly higher for this group of veterans than those who served in World War II and the Korean War.<sup>127</sup> An advisory committee commissioned by the VA has recommended further study into the potential link between combat service and the increased risk of developing MS.<sup>128</sup> By studying this population, scientists might be able to understand the cause and triggers of MS and develop effective treatments.

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<sup>124</sup>Veterans Health Administration Claim Database. FY 1998-FY2014.

<sup>125</sup>Veterans Health Administration Claim Database. FY1998- FY2014.

<sup>126</sup> Wallin, M. T., Page, W. F. and Kurtzke, J. F. (2004), Multiple sclerosis in US veterans of the Vietnam era and later military service: Race, sex, and geography. *Ann Neurol.*, 55: 65–71. doi: 10.1002/ana.10788.

<sup>127</sup> Wallin, M. T., Page, W. F. and Kurtzke, J. F. (2004), Multiple sclerosis in US veterans of the Vietnam era and later military service: Race, sex, and geography. *Ann Neurol.*, 55: 65–71. doi: 10.1002/ana.10788

<sup>128</sup> Wallin, M. T., Page, W. F. and Kurtzke, J. F. (2004), Multiple sclerosis in US veterans of the Vietnam era and later military service: Race, sex, and geography. *Ann Neurol.*, 55: 65–71. doi: 10.1002/ana.10788

- Neurofibromatosis (NF)**: NF research critically addresses areas of great clinical need directly affecting the health of our soldiers. The genetic information learned from NF research holds the key to understanding a number of health issues that affect the war fighter, as well as the general population, including cancer, bone fracture and repair, vascular disease, wound healing and nerve regeneration, deafness, behavioral and psychosocial issues, learning disabilities, muscle weakness, and pain. For example, NF often requires surgical removal of nerve tumors, which can lead to nerve paralysis and loss of function, similar to nerve damage sustained by the war fighter after injury. Understanding how nerves and skin might be regenerated and functionally restored will have significant quality of life value for affected individuals. Current NF research aims to develop a rapid approach for taking a person's skin stem cells and differentiating them into cell types that need replacing after injury. This work will advance skin regeneration research and elucidate the potential of skin derived stem cells to make other cell types such as nerve cells, to restore function after injury. In another example, orthopedists, NF-ologists and tissue engineers are collaborating to investigate innovative technologies that will improve the healing of challenging and recurring bone breaks in NF patients, research that directly benefits war fighters with major bone breakages. Therefore, due to the nature of the wounds and recovery that soldiers are enduring, NF research is of particular benefit to the military mission. Proposals include: NF080017<sup>129</sup>, NF120087<sup>130</sup>, NF110052<sup>131</sup> and NF110052<sup>132</sup>
- Osteoarthritis (OA)**: Current research suggests that stresses placed on joints during military training activities, increased rates of injury, and increased weight of military packs have led active duty soldiers and veterans to have twice the rate of Osteoarthritis (OA) when compared to non-military populations. In fact, OA is the leading cause of disability and medical discharge in active service members under the age of 40. Rheumatoid arthritis (RA) strikes at the peak one's career (mid-late thirties/forties) and often leads to early retirement and disability. CDMRP research funding for OA and RA could help identify arthritis prior to the onset of symptoms. This research could help identify medical and physical interventions to prevent or minimize joint damage and slow or stop the arthritis disease process before joints are permanently damaged. Targeted research efforts would focus on examining genetic factors, ways to improve diagnosis, screening, and treatment options. (Proposals: 101035<sup>133</sup>, 120839<sup>134</sup>, 130776<sup>135</sup>)

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<sup>129</sup> Elefteriou, Florent. Neurofibromin Function in Chondrocytes.

<sup>130</sup> Kim, Aerang. Phase I/II Trial of an Hsp90 Inhibitor in Combination with an mTOR Inhibitor for Patients with Refractory Malignant Peripheral Nerve Sheath Tumors.

<sup>131</sup> Plotkin, Scott. Phase 2 Study of Bevacizumab in Children and Young Adults With NF 2 and Progressive Vestibular Schwannomas.

<sup>132</sup> North, Kathryn. A Randomized Placebo-Controlled Study of Lovastatin in Children with Neurofibromatosis Type 1 (STARS)

<sup>133</sup> McKinley, Todd O. Mitochondrial Based-Treatments that Prevent Post-Traumatic Osteoarthritis in a Translational Large Animal Intraarticular Fracture Survival Model.

<sup>134</sup> Deane, Kevin D. Pathogenesis and Prediction of Future Rheumatoid Arthritis

<sup>135</sup> Hammond, Paula T. Cartilage-Penetrating Chondrogenic Nanoparticles for Early Posttraumatic Osteoarthritis Therapy.

- **Ovarian Cancer:** In the 45 years since the War on Cancer was declared, ovarian cancer mortality rates have not significantly improved. According to the American Cancer Society, it is estimated that in 2017, more than 22,400 American women will be diagnosed with ovarian cancer, and approximately 14,080 will lose their lives to this terrible disease. Ovarian cancer is the fifth leading cause of cancer death in women. Currently, more than half of the women diagnosed with ovarian cancer will die within five years. Of the 850,000 female service members, wives of active duty military and adult daughters of active duty military<sup>136</sup>, approximately 11,800 will be diagnosed with ovarian cancer over the course of their lifetimes.<sup>137</sup> Over a five-year period, nearly 2,600 members of our military or their families may be hospitalized for ovarian cancer or suspected ovarian cancer. The cost of ovarian cancer to our military is great, not only in terms of troop readiness, but also in terms of cancer care costs: treating these cases of ovarian cancer over these patients' lifetimes could cost TRICARE an estimated \$971.2 million.<sup>138</sup> TRICARE's potential costs to care for women with ovarian cancer could fund the Ovarian Cancer Research Program at the Department of Defense for nearly 50 years at its current funding level.

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<sup>136</sup> Military Demographics for 2012. Available here:

[http://www.militaryonesource.mil/12038/MOS/Reports/2012\\_Demographics\\_Report.pdf](http://www.militaryonesource.mil/12038/MOS/Reports/2012_Demographics_Report.pdf)

<sup>137</sup> The lifetime risk of a women developing ovarian cancer is 1.4% according to the SEER Fact Sheet available here: <http://seer.cancer.gov/statfacts/html/ovary.html>

<sup>138</sup> The average cost of frontline ovarian cancer therapy is \$82,000, per the National Institutes of Health. <http://costprojections.cancer.gov/annual.costs.html>

- **Pancreatic Cancer:** Research has shown that there is direct evidence for excessive risk of death from pancreatic cancer in some U.S. veterans. Specifically, nurses serving in Vietnam had a 2 to 5-fold higher risk of pancreatic cancer death compared with non-deployed U.S. military women.<sup>139140</sup> The reasons for this increase may be related to environmental exposures such chemical agents used in the field or in medical facilities, an association with predisposing medical conditions such as diabetes, and/or lifestyle propensities such as smoking, all which include known risk factors for pancreatic cancer.<sup>141142</sup> Further, the link between type 2 diabetes and pancreatic cancer is well-established<sup>143</sup> and type 2 diabetes is recognized by the VA as an Agent Orange-associated presumptive disease.<sup>144</sup> The Peer Reviewed Cancer Research Program has funded a variety of critical research areas since pancreatic cancer was first included in 2011, including investigations into biomarkers to detect pancreatic cancer early or follow response to therapy, targeting the oncogene KRAS, activating the immune system, taking advantage of metabolic differences between normal and malignant pancreas cells, and a variety of highly novel therapeutic approaches. Continued support for this research is critical not only for the potential risks for developing pancreatic cancer associated with military service, but also because pancreatic cancer is currently the nation's third leading cause of cancer-related death and is predicted to surpass colon cancer to become second only to lung cancer by the year 2020.<sup>145</sup>

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<sup>139</sup> Dalager, NA et al, Cancer Mortality Patterns among Women Who Served in the Military: The Vietnam Experience, *J Occup & Environ Medicine* 37: 298-305, 1995

<sup>140</sup> Kang, HK et al, HealthVIEWS: Mortality Study of Female US Vietnam Era Veterans, 1965-2010, *Am J Epidemiol* 179: 721-30, 2014

<sup>141</sup> Barone E et al, Environmental risk factors for pancreatic cancer: an update. *Arch Toxicol* 90: 2617-2642, 2016.

<sup>142</sup> Nyska A et al. Exocrine pancreatic pathology in female Harlan Sprague-Dawley rats after chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin and dioxin-like compounds. *Environ Health Perspect.*112:903–9, 2004

<sup>143</sup> Li D, et al. Diabetes and risk of pancreatic cancer: a pooled analysis of three large case–control studies. *Cancer Causes Control* 22:189–197, 2011

<sup>144</sup> <http://www.publichealth.va.gov/exposures/agentorange/conditions/index.asp>

<sup>145</sup> Rahib L, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer research* 74:2913-2921, 2014

- **Parkinson's research program:** Parkinson's Disease (PD) environmental risk factors overlap common soldier occupational exposures such as traumatic brain injury and neurotoxic chemical exposures. The combination of brain injury and chemical exposure triple Parkinson's risk.<sup>146</sup> In 2012, the Department of Veterans' Affairs (VA) made PD presumptive for TBI-connected with military service<sup>147</sup> and secondary service connection for diagnosable illnesses associated with traumatic brain injury.<sup>148</sup> The Neurotoxin Exposure Treatment (Parkinson's) Research Program (NETPR) is funding studies in biomarkers of TBI and PD. Environmental and occupational chemical exposures, notably pesticides, increase the risk of PD in service members and has also been a focus of NETPR, identifying organochlorine compounds previously used in agriculture, environmental PCBs, and permethrin used in Army uniforms as risk factors for PD.<sup>149</sup> Parkinson's Disease Research, Education, and Clinical Centers (PADRECCs) were established within six leading VA centers to provide treatment to veterans with PD; research in these centers has benefited from NETPR program grants and provides transition between active duty members diagnosed with PD and their state-of-the-art continuity of care for PD in the VA. PD also shares neurological effects of concerns to soldiers such as disrupted sleep, depression, and cognitive impairment. All of these "dual use" aspects that are relevant to soldiers and to the PD community and have been a focus of NETPR.

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<sup>146</sup> Ritz et al., *Neurology* 2012;79:2061-6.

<sup>147</sup> 38 CFR Part 3 Department of Veterans Affairs.

<sup>148</sup> *Federal Register* 2013;78:76196–209.

<sup>149</sup> Tanner et al., *Alz Dementia* 2014;10:213-225.

- **Prostate Cancer:** Prostate cancer is the second deadliest cancer among American men, killing more than 34,000 men annually,<sup>150</sup> and there are more than 2.9 million prostate cancer patients in the U.S. that depend on breakthroughs in research to continue their fight. Prostate cancer significantly impacts both active duty servicemen, veterans, and their families; in fact, active duty males are twice as likely to be diagnosed with prostate cancer as their civilian counterparts,<sup>151</sup> with negative effects on their ability to serve. In addition, soldiers exposed to chemical agents such as Agent Orange in Vietnam are considered to be at increased risk of death from prostate cancer due to its association with high-grade disease in a population-based study of US Veterans.<sup>152</sup> Research funded by the Prostate Cancer Research Program (PCRP) advances treatments; PCRP funding was responsible for accelerating the development of the five new treatments for advanced disease in the last ten years,<sup>153 154 155 156</sup> bringing them to patients faster than typical development of new drugs. Moreover, the program focuses on not only developing more effective therapeutics, but has also led to the development of a new diagnostic tool.<sup>157</sup> By improving diagnosis to reduce over treatment and accurately distinguish life-threatening disease from indolent tumors,<sup>158</sup> the PCRP may have its greatest impact on active duty servicemen who can be confidently monitored through active surveillance,<sup>159</sup> rather than compromising their service to undergo treatment.

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<sup>150</sup> American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021.

<sup>151</sup> Zhu K, Devesa SS, Wu H, et al. 2009. Cancer incidence in the U.S. military population: Comparison with rates from the SEER program. *Cancer Epidemiol Biomarkers Prev* 18:1740-45.

<sup>152</sup> Chamie K1, De Vere White RW, Lee D et al. 2008. Agent Orange exposure, Vietnam War veterans, and the risk of prostate cancer. *Cancer*. Nov 1;113(9):2464-70. doi: 10.1002/cncr.23695.

<sup>153</sup> Ryan CJ, Smith MR, de Bono JS et al. 2013. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013 Jan 10;368(2):138-48. Erratum in: *N Engl J Med*. 2013 Feb 7;368(6):584.

<sup>154</sup> Scher HI, Beer TM, Higano CS et al. 2010. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet*. 2010 Apr 24;375(9724):1437-46.

<sup>155</sup> 2018 Prostate Cancer Research Program Book. <https://cdmrp.army.mil/pcrp/pbks/pcrppbk2018.pdf>

<sup>156</sup> Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. *J Clin Oncol*. 2020;38(32):3763-3772. doi:10.1200/JCO.20.01035

<sup>157</sup> 2018 Prostate Cancer Research Program Book. <https://cdmrp.army.mil/pcrp/pbks/pcrppbk2018.pdf>

<sup>158</sup>

[http://comptroller.defense.gov/Portals/45/Documents/defbudget/fy2015/budget\\_justification/pdfs/09\\_Defense\\_Health\\_Program/DHP\\_PB15\\_Vol\\_I-II.pdf](http://comptroller.defense.gov/Portals/45/Documents/defbudget/fy2015/budget_justification/pdfs/09_Defense_Health_Program/DHP_PB15_Vol_I-II.pdf)

<sup>159</sup> Tosoian JJ, Carter HB, Lepor A et al. 2016. Active surveillance for prostate cancer: current evidence and contemporary state of practice. *Nat Rev Urol*. 2016 Mar 8. doi: 10.1038/nrurol.2016.45. [Epub ahead of print].

- **Sleep:** Insufficient sleep and sleep disorders affect the health of an estimated 70 million Americans across all demographic groups, including military personnel. Sleep disruption, especially insomnia, is a contributing risk factor to the onset and severity of major mental health problems such as depression, bipolar disorder, substance abuse, posttraumatic stress disorder, traumatic brain injury, and suicide.<sup>160 161 162 163 164</sup> An increasingly detrimental condition affecting military troops is sleep-disordered breathing, including obstructive sleep apnea which results in excessive daytime somnolence, poor performance, increased frequency of road traffic accidents, and arterial hypertension.<sup>165</sup> Studies show that 85% of 725 troops returning home from Afghanistan and Iraq had a sleep disorder and the most common was obstructive sleep apnea (51%). If left untreated, obstructive sleep apnea has significant negative impacts on health, including early mortality. By using continuous positive airway pressure (CPAP), a treatment used to combat sleep apnea, military personnel report reductions in pain and fatigue, and improvements in cognitive function.<sup>166</sup> The high prevalence of sleep and circadian disturbances indicates an opportunity for research advances and informed public policy to reduce disease risk across a lifespan and improve the health of our active troops. It is important to accelerate scientific discovery of the relationship between mental health, overall health and sleep and circadian disorders, and strengthen cognitive function and military readiness through the improvement of sleep quality.

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<sup>160</sup> Ford ES, Li C, Wheaton AG, Chapman DP, Perry GS, Croft JB. Sleep duration and body mass index and waist circumference among US adults. *Obesity* 2014;22:598-607.

<sup>161</sup> Ford ES, Wheaton AG, Chapman DP, Li C, Perry GS, Croft JB. Associations between self-reported sleep duration and sleeping disorder with concentrations of fasting and 2-hour glucose, insulin, and glycosylated hemoglobin among adults without diagnosed diabetes. *J Diabetes* 2014;6:338-350.

<sup>162</sup> Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care Survey, 1999-2010. *Sleep* 2014;37:1283-1293.

<sup>163</sup> Wheaton AG, Shults RA, Chapman DP, Ford ES, Croft JB. Drowsy driving and risk behaviors--10 states and Puerto Rico, 2011-2012. *MMWR* 2014;63(26):557-562.

<sup>164</sup> Fang J, Wheaton AG, Ayala C. Sleep duration and history of stroke among US adults. *J Sleep Research* 2014;23(5):531-537.

<sup>165</sup> Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of Healthy Sleep Duration among Adults – United States, 2014. *MMWR Morb Mortal Wkly Rep* 2016;65:137-141. DOI: <http://dx.doi.org/10.15585/mmwr.mm6506a1>

<sup>166</sup> Mysliwiec, Vincent et al. "Sleep Disorders in US Military Personnel: A High Rate of Comorbid Insomnia and Obstructive Sleep Apnea." *Chest* 144.2 (2013): 549–557. PMC. Web. 26 Feb. 2016.

- **Stomach Cancer:** In 2019, 27,500 Americans will be diagnosed with stomach cancer, and more than 11,000 will die from the disease. The initial diagnosis of stomach cancer often is delayed because up to 80 percent of patients are asymptomatic during the early stages.<sup>167</sup> The overall 5-year relative survival rate of stomach cancer in the United States is about 31 percent, according to the American Cancer Society. At Stage IV the 5-year survival rate is just five percent. Survival rates are low because 80-90 percent of patients with stomach cancer present with locally advanced or metastatic tumors.<sup>168</sup> The Department of Veterans Affairs considers stomach cancer to be a service connected malignancy for service members who experienced hazardous exposure to ionizing radiation.<sup>169</sup> Additionally, studies suggest that the risk of *H. pylori* infection increases among military personnel during long-term deployment.<sup>170</sup> This is significant because, according to the National Cancer Institute, infection with *H. pylori* is the primary identified cause of stomach cancer.<sup>171</sup> While treatment of *H. pylori*, when detected, can help prevent cancer, antibiotic resistance is emerging in *H. pylori*. A dedicated research investment is critical to advancing prevention, detection and treatment of stomach cancer and its causal factors.<sup>172</sup>
- **Traumatic Brain Injury, Posttraumatic Stress Disorder, and Psychological Health:** *Traumatic Brain Injury (TBI):* It is estimated that up to a quarter of deployed servicemembers have experienced a TBI, with the Defense and Veterans Brain Injury Center reporting more than 434,000 TBI cases among servicemembers worldwide between 2000 and 2020.<sup>173</sup> <sup>174</sup> Posttraumatic stress disorder (PTSD) often occurs comorbidly with TBI, which can also exacerbate physical health problems and potentially lead to reduced access to health care due to avoidance or other symptoms.<sup>175</sup>

*Posttraumatic Stress Disorder:* Posttraumatic stress disorder (PTSD) is the psychological health condition most commonly associated with military combat deployments.<sup>176</sup> <sup>177</sup>

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<sup>167</sup> Layke JC1, Lopez PP. Gastric cancer: diagnosis and treatment options. *Am Fam Physician*. 2004 Mar 1;69(5):1133-40. <http://www.aafp.org/afp/2004/0301/p1133.html>

<sup>168</sup> Dicken B, Bigam D. Gastric Adenocarcinoma: Review and Considerations for Future Directions. *Ann Surg*. 2005 Jan; 241(1): 27–39. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1356843/>

<sup>169</sup> National Cancer Strategy, Department of Veterans Affairs, Veterans Health Administration, VHA Directive 2003-34. June 20, 2003.

<sup>170</sup> Taylor, DN et al. Second International Workshop on Helicobacter pylori Infections in the Developing World: Helicobacter pylori Infection in Desert Storm Troops. *Clin Infect Dis*. (1997) 25 (5): 979-982 doi:10.1086/516074

<sup>171</sup> Helicobacter pylori and Cancer. National Cancer Institute. <http://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/h-pylori-fact-sheet>. Accessed online Dec. 23, 2015.

<sup>172</sup> Seiji S. Antibiotic Resistance of Helicobacter pylori Among Male United States Veterans. *Clinical Gastroenterology and Hepatology*, Volume 13, Issue 9, September 2015, Pages 1616-1624, ISSN 1542-3565

<sup>173</sup> Lindquist LK, Love HC, Elbogen EB. Traumatic Brain Injury in Iraq and Afghanistan Veterans: New Results From a National Random Sample Study. *J Neuropsychiatry Clin Neurosci*. 2017 Summer;29(3):254-259. doi: 10.1176/appi.neuropsych.16050100. Epub 2017 Jan 25. PMID: 28121256; PMCID: PMC5501743.

<sup>174</sup> DoD TBI Worldwide Numbers, Department of Defense, Defense Health Agency, Military Health System. <https://health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/DOD-TBI-Worldwide-Numbers>. Accessed online May 12, 2021.

<sup>175</sup> Dieter JN, Engel SD. Traumatic Brain Injury and Posttraumatic Stress Disorder: Comorbid Consequences of War. *Neuroscience Insights*. November 2019. doi:10.1177/1179069519892933

<sup>176</sup> Institute of Medicine. (2014). Treatment of posttraumatic stress disorder in military and veteran populations: Final assessment. Washington, DC: The National Academies Press. <https://doi.org/10.17226/18724>

<sup>177</sup> Armed Forces Health Surveillance Center. (2011). Associations between repeated deployments to OEF/OIF/OND, October 2001-December 2010, and post-deployment illnesses and injuries, active component, U.S.

PTSD and TBI have been referred to as the “signature wounds of war”.<sup>178 179</sup> PTSD in combat veterans has been estimated to be about 14%, which equates to over 400,000 service members and veterans who have deployed to Iraq, Afghanistan, and surrounding locations.<sup>180</sup> Over the past decade, DoD-funded PTSD research has contributed to major advancements in the understanding, assessment, diagnosis, treatment, and prevention of PTSD in active duty military personnel. Many of these advancements are the result of leveraging the synergistic power of team science<sup>181</sup> that has occurred through the federal funding of two PTSD research consortia.<sup>182</sup> Although the DoD has continued to fund research consortia for TBI, suicide, and substance used disorders, the funding for a PTSD research consortium ended in 2020. With PTSD recovery rates in active duty military personnel limited to slightly more than 50% of those treated with current evidence-based interventions, and as the incidence of PTSD continues to persist in military populations, there is a critical need for continued funding of DoD PTSD research including support for a PTSD research consortium.

*Psychological Health:* In addition to TBI and PTSD, servicemembers and veterans experience high rates of other mental health conditions, including substance use issues and depression. Servicemembers and veterans face unique stressors compared to the civilian population, through direct combat, mortuary services, moral injury, drone operation, and other defense-specific missions.<sup>183</sup> Many servicemembers are less likely to seek treatment for a mental health condition due to the stigma associated with receiving care in the military community as well as concerns about promotions or security clearance, requiring additional research on how to best reach out to servicemembers experiencing mental health issues.<sup>184</sup>

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Armed Forces. Medical Surveillance Monthly Report (MSMR), 18(9), 2-11. <https://health.mil/Reference-Center/Reports/2011/01/01/Medical-Surveillance-Monthly-Report-Volume-18-Number-9>

<sup>178</sup> Tanielian, T., & Jaycox, L. H. (Eds.). (2008). Invisible wounds of war: Psychological and cognitive injuries, their consequences, and services to assist recovery. Santa Monica, CA: RAND Corporation.

<https://doi.org/10.7249/mg720>

<sup>179</sup> Brundage JF, Taubman SB, Hunt DJ, Clark LL. Whither the "signature wounds of the war" after the war: estimates of incidence rates and proportions of TBI and PTSD diagnoses attributable to background risk, enhanced ascertainment, and active war zone service, active component, U.S. Armed Forces, 2003-2014. MSMR. 2015 Feb;22(2):2-11. PMID: 25734618.

<sup>180</sup> Judkins, J. L., Moore, B. A., Collette, T. L., Hale, W. J., Peterson, A. L., & Morissette, S. B. (2020). The incidence rates of posttraumatic stress disorder over a 17-year period in active duty military service members. *Journal of Traumatic Stress*. Advance online publication. <https://doi:10.1002/jts.22558>

<sup>181</sup> Peterson, A. L., Cifu, D. X., Joiner, T. J., Williams, R. L., Keane, T. M., Hinds, S. R., II, Gutierrez, P. M., & Kosten, T. R. (2018, August). Leveraging the synergistic power of team science: Lessons learned from DoD-funded research consortia. Poster presented at the Military Health System Research Symposium, Kissimmee, FL.

<sup>182</sup> Peterson, A. L., Niles, B. L., Young-McCaughan, S., & Keane, T. M. (2021). Assessment and treatment of combat-related posttraumatic stress disorder: Results from STRONG STAR and the Consortium to Alleviate PTSD. In N. Gorbunov (Ed.), *Military Medicine*. InTech Open.

<sup>183</sup> National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee to Evaluate the Department of Veterans Affairs Mental Health Services. Evaluation of the Department of Veterans Affairs Mental Health Services. Washington (DC): National Academies Press (US); 2018 Jan 31. 6, Department of Veterans Affairs Mental Health Services: Need, Usage, and Access and Barriers to Care. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK499497/>

<sup>184</sup> Acosta, Joie D., Amariah Becker, Jennifer L. Cerully, Michael P. Fisher, Laurie T. Martin, Raffaele Vardavas, Mary Ellen Slaughter, and Terry L. Schell, *Mental Health Stigma in the Military*, Santa Monica, Calif.: RAND Corporation, RR-426-OSD, 2014. As of May 12, 2021: [https://www.rand.org/pubs/research\\_reports/RR426.html](https://www.rand.org/pubs/research_reports/RR426.html)

- **Tuberculosis (TB)**: TB is the single largest infectious disease killer globally and represents 30 percent of deaths from antimicrobial resistant bacteria. TB (and growing drug resistance) presents a serious concern for the US military. Thirty countries are currently classified as having a high TB burden based on the number of incident cases of TB and the severity of the disease (incident per capita).<sup>185</sup> Twenty-six of the thirty countries are areas of interest to the US Department of Defense (DoD)—either locations where US military personnel are already stationed, or regions where deployment probability is high.<sup>186</sup> During deployment, the warfighter could be exposed to TB and could develop either latent or active TB in either drug sensitive (DS) or, much more ominously, drug resistant (DR) forms. In 2018, an estimated 2.3 billion individuals worldwide were thought to be carriers of latent TB bacteria. Over a lifetime, around 10 percent of LTBI cases will progress to infectious TB.<sup>187</sup> LTBI’s pervasiveness in the global population should be a primary concern for TB diagnoses in the US military. Between 2008 and 2012, most active TB cases (57.9 percent) diagnosed in the US military were associated with an existing LTBI.<sup>188</sup> While the healthy warfighter may not activate a latent TB infection immediately, risk increases for people under significant stress and for immunocompromised individuals.<sup>189</sup> Further, veterans will be at increased risk of activating a latent TB infection as they age and develop co-morbid health conditions—creating a public health risk in the US. Perhaps the most serious TB concern facing the US military—and the broader global population—is the increase in drug resistant TB. While there are serious shortcomings in available treatment options for all forms of TB, for DR-TB it is especially problematic and worrisome. Even an MDR-TB outbreak in the US could have serious consequences given the costs associated with treatment. The cost to treat and care for a patient with TB in the US averages \$19,000 for drug-susceptible TB, \$175,000 for MDR-TB, and \$513,000 for XDR-TB.<sup>190</sup>

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<sup>185</sup> World Health Organization. “Global Tuberculosis Report 2019.”

<sup>186</sup> DMDC. Military and Civilian Personnel by Service/Agency by State/Country, September 2019. Defense Manpower Data Center.

<sup>187</sup> WHO. “Latent Tuberculosis Infection.” 2018.

<sup>188</sup> Mancuso JD, and Christopher AL. “Tuberculosis Trends in the U.S. Armed Forces, Active Component, 1998-2012.” Medical Surveillance Monthly Report. 2013; 20(5) 4-8. Available from <https://www.health.mil/Reference-Center/Reports/2013/01/01/Medical-Surveillance-Monthly-Report-Volume-20-Number-5>

<sup>189</sup> Ai JW, Ruan QL, Liu QH, Zhang WH. “Updates on the risk factors for latent tuberculosis reactivation and their managements.” Emerg Microbes Infect. 2016; 5(2): e10. doi: 10.1038/emi.2016.10.

<sup>190</sup> CDC. “The Costly Burden of Drug-Resistant TB in the U.S.” September 2019.

- **Tuberous Sclerosis Complex (TSCR)**: Research supported by the TSCR is paving the way to finding cures and treatments for individuals with TSC as well as those with other neurological disorders like epilepsy and autism spectrum disorder (ASD). Research through TSCR award W81XWH-12-1-0190<sup>191</sup> developed a mouse model for TSC, which in addition to its use for studying epilepsy and autism, is helping understand the consequences and potential treatment for post-traumatic brain injury (TBI) – a disorder of grave concern to the U.S. Armed Services. In 2016, the last year for which complete data are available, there were more than 18,311 documented traumatic brain injuries in the U.S. military.<sup>192</sup> A more recent award, W81XWH-14-1-0061, is testing existing FDA-approved drugs for their ability to treat or prevent epilepsy by regulating the biochemical pathway shared between TSC and TBI. Many other TSCR awards enabled these key studies by generating the knowledge about this shared biochemical pathway. Some of the awards that built this foundation of knowledge include DAMD17-03-1-0073<sup>193</sup>, W81XWH-04-1-0309<sup>194</sup>, W81XWH-06-1-015<sup>195</sup>, W81XWH-09-1-0088<sup>196</sup>, W81XWH-10-1-0861<sup>197</sup>, W81XWH-13-1-0040<sup>198</sup>.

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<sup>191</sup> Wong, Michael. *The Role of Brain Inflammation in Epileptogenesis in TSC*

<sup>192</sup> DoD Worldwide Numbers for TBI, Defense and Veterans Brain Injury Center, <http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>, <http://dvbic.dcoe.mil/files/tbi-numbers/WorldwideTotals2016Nov14-2017508.pdf>

<sup>193</sup> Gutmann, David. *Mouse Models of TSC-Related Epilepsy*

<sup>194</sup> Bernardo, Sabatini. *The Role of TSC1 in the Formation and Maintenance of Excitatory Synapses*

<sup>195</sup> McNeill, Helen. *Genetic and Molecular Analysis of the Mechanisms by which TSC Regulates Neuronal Differentiation*

<sup>196</sup> Yoshii, Akira. *Studying Protein Synthesis-Dependent Synaptic Changes in Tuberous Sclerosis*

<sup>197</sup> Manning, Brendan. *Defining the Therapeutic Implications of the Integrative Stress Response in TSC*

<sup>198</sup> Sahin, Mustafa. *Role of CTGF in White Matter Development in Tuberous Sclerosis*

- VHL:** Von Hippel-Lindau disease (VHL) is a genetic disease caused by a mutation in the *VHL* gene, which normally functions as a tumor suppressor<sup>199</sup>. It affects approximately 1 in 36,000 people, from all nationalities, ethnicities and races.<sup>200</sup> About 80% of people with VHL inherited it from a parent, while the other 20% of people have it as the result of a random genetic mutation. VHL is a chronic disease with no cure and no treatment, other than a lifetime of surveillance and traumatic and expensive surgeries. The manifestations of VHL include the development of tumors throughout a patient's life in up to ten different organs, including the brain, eyes, pancreas, spine and kidneys.<sup>201</sup> These tumors can be benign or malignant. Research into VHL will have a significant impact not just on affected service members and DoD families, but on the broader military community, because the VHL pathway is directly tied to more commonly occurring types of cancer. This could lead to the development of improved diagnostics and treatments, as well as cures, for diseases like kidney cancer and pancreatic cancer<sup>202</sup>, both of which have a higher prevalence in US military and veterans' populations.<sup>203</sup> Several VHL researchers have received CDMRP grants, and VHL research has led to the discovery of at least 8 drugs currently used to treat cancer. Dr. William Kaelin, a VHL researcher, and Dr. Gregg Semenza were CDMRP grant recipients for research projects that contributed toward their 2019 Nobel Prize in Medicine.<sup>204</sup> Dr. Kaelin and another CDMRP grant recipient, Dr. Eric Jonasch, have been directly involved in development of a drug that recently received FDA breakthrough and orphan drug designation and will, hopefully, be used to treat both VHL and kidney cancer.<sup>205</sup>

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<sup>199</sup> Maher ER, et al., von Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet.* 2011 Jun;19(6):617-23. Epub 2011 Mar 9. PMID: 21386872

<sup>200</sup> Varshney, Neha, et al., A Review of Von Hippel-Lindau Syndrome. *J Kidney Cancer VHL.* 2017; 4(3): 20–29. Epub 2017 Aug 2. PMID: 28785532

<sup>201</sup> Chittiboina, Prashant, et al., Von Hippel-Lindau disease. *Handb Clin Neurol.* 2015; 132: 139–156. Epub 2016 Nov 24. PMID: 26564077

<sup>202</sup> Glasker, Sven, et al., Von Hippel-Lindau Disease: Current Challenges and Future Prospects. *Onco Targets Ther.* 2020; 13: 5669–5690. Epub 2020 Jun 16. PMID: 32606780

<sup>203</sup> Zullig, Leah, et al., Cancer Incidence among Patients of the United States Veterans Affairs (VA) Healthcare System, *Mil Med.* 2012 June; 177 (6): 693-701

<sup>204</sup> [https://cdmrp.army.mil/pubs/press/2019/CDMRP\\_Funding\\_Recipients\\_Are\\_Nobel\\_Prize\\_Winners](https://cdmrp.army.mil/pubs/press/2019/CDMRP_Funding_Recipients_Are_Nobel_Prize_Winners)

<sup>205</sup> [https://www.eurekalert.org/pub\\_releases/2020-05/uotm-ntd052820.php](https://www.eurekalert.org/pub_releases/2020-05/uotm-ntd052820.php)

- **Vision:** Vision, the sense most critical for optimal military performance in battlefield and support positions, is vulnerable to acute and chronic injury. Research to effectively treat vision trauma and TBI-related visual disorders can have long-term implications for an individual’s vision health, productivity, and quality of life for the remainder of military service and into civilian life. Traumatic eye injury from penetrating wounds and TBI-related visual disorders ranks second only to hearing loss as the most common injury among “active” military, accounting for upwards of 16 percent of all injuries in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF).<sup>206</sup> The VHA reports 202,000 OEF/OIF veterans with eye injuries since 2000<sup>207</sup>, as well as that upwards of 75 percent of all TBI patients experience short- or long-term visual disorders (double vision, light sensitivity, inability to read print, and other cognitive impairments). A January 2019 *Military Medicine* journal article based on a 2018 study by the Alliance for Eye and Vision Research that used prior published data from 2000-2017 has estimated that deployment-related eye injuries and blindness have cost the U.S. \$41.5 billion in that timeframe, with \$40.2 billion of that cost reflecting present value of a lifetime of long-term benefits, lost wages, and family care.<sup>208</sup>

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<sup>206</sup> VA Office of Public Health and Environmental Hazards, 2010, “Analysis of VA Health Care Utilization among Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) Veterans”

151 Office of Public Health Epidemiologic Report, *Cumulative Frequencies of the Eye and Adnexa Enrollment OIF/OEF/OND* (FY October 2002 to second quarter, FY 2015)

<sup>208</sup> Kevin D. Frick and Eric L. Singman, “*Cost of Military Eye Injury and Vision Impairment Related to Traumatic Brain Injury: 2001–2017*” *Military Medicine*, January 2019