Defense Health Research Programs
Relevance to National Security and Military Families
April 10, 2019

- **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[1]. Most recently, researchers found an increased risk of ALS among those who served in Iraq and Afghanistan[2]. The VA has recognized the connection between ALS and military service by establishing a presumption of service connection for ALS[3]. 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.[4] 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.[5] 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.[6] 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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[1] 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.

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

[3] 38 CFR 3.318 – Presumptive service connection for amyotrophic lateral sclerosis.

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

[5] 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.

[6] 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/.

- **Autism**: According to the Centers for Disease Control and Prevention, 1 in 59 children have an autism spectrum disorder (ASD)[7]. The Department of Defense reports that 18,452 active duty family members had a diagnosis of ASD at the end of fiscal year 2013.[8] This reflects a 77% increase in ASD diagnoses in just four years from fiscal year 2009.[9] 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.[10] Research supported by the Autism Research Program has addressed current needs such as difficulties accessing care associated with mobile military families[11] and gastrointestinal (GI) disorders which are among the most common medical conditions associated with autism.[12] 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.

[7] 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

[8] Report to Congressional Defense Committees, The Department of Defense Enhanced Access to Autism Services Demonstration, July 2014 Semiannual Report to Congress.

[9] Report to Congressional Defense Committees, pp 1.

[10] Dawson, G. et. al. 2009. Randomized, Controlled Trial of an Intervention for Toddlers with Autism: The Early Start Denver Model: Pediatrics.

[11] 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.

[12] 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.[13] [14] 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.[15] Smoking prevalence in the veteran population is reported to be 27% compared to 21% in the non-veteran population.[16] 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 [17]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.[18] Inorganic arsenic compounds have been linked to cancer of the bladder.[19] 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.[20]

[13] American Cancers Society. Bladder Cancer Statistics. Retrieved from http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics, accessed March 9, 2016.
[14] 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.
[15] Joseph, Anne M.; et al. (2005). "The Cigarette Manufacturers' Efforts to Promote Tobacco to the U.S. Military". Military Medicine170: 874–880.
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[17] 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.
[18] H.R.2519 - Victims of Agent Orange Relief Act of 2013113th Congress (2013-2014).
[19] NCI Cancer Trends Progress Report, Retrieved March 9, 2016 from https://progressreport.cancer.gov/prevention/arsenic.
[20] 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.[21][22][23] 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. [24][25][26] 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.[27] 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.

- **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.[28] 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.[29] 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).[30]

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[21] 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.
[22] 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
[23] 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.
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[27] http://www.benefits.va.gov/COMPENSATION/claims-postservice-exposures-camp-lejeune-water.asp
[28] http://download.militaryonesource.mil/12038/MOS/Reports/2016-Demographics-Report.pdf
[29] Cancer Epidemiol Biomarkers Prev. 2009 Jun;18(6):1740-5. doi: 10.1158/1055-9965.EPI-09-0041.
[30] http://cdmrp.army.mil/bcrp/pbks/bcrppbk2018.pdf

- **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 identity molecularly targeted therapies that may be effective in these cancers."[31] 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.[32] Nearly 90% of servicemembers, their spouse, and children fall within the NCI definition of an adolescent or young adults impacted by cancer.[33]

- **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[34], CA111002[35], CA100879[36], CA100512P1[37], CA093176[38])

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[31] https://www.cancer.gov/types/aya

[32] https://www.ncbi.nlm.nih.gov/pubmed/25568146

[33] https://s3.amazonaws.com/rallywebcollateral/wp-content/uploads/2017/03/08143634/DODCDMRPFY17Request_whitepaper_2.pdf

[34] Feng Z, Liu L, Zhang C, et al. 2012. Chronic restraint stress attenuates p53 function and promotes tumorigenesis. PNAS 109:7013-7018.

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- **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.[39] [40] 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.[41] 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.

- **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.[42] 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.

[39] Hoffman JL, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-1900.
[40] 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.
[41] http://www.dtic.mil/dtic/tr/fulltext/u2/1048533.pdf
[42] 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.

- **Epilepsy**: According to 2015 estimates, a staggering 3.4 million Americans suffer from epilepsy.[43] 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). [44] TBIs can take the form of bumps, blows to the head, blasts or penetrating injuries,[45] such as those seen so often in the line of duty. In fact, 4.2% of all troops (Army, Air Force, Navy and Marine Corps combined) who served from 2000 to 2011 were diagnosed with a TBI.[46] These injuries can have a devastating impact on troops; for example, a reported 53% of Vietnam veterans who suffered from severe TBI that required neurosurgery subsequently developed epilepsy,[47] and within a group of veterans of Afghanistan and Iraq, those with TBI had 18.77% greater odds of developing epilepsy than those without TBI.[48] The development of epilepsy can also reduce the pool of potential military enlistees: DOD regulations prohibit anyone currently suffering from seizures from admission into the armed services.[49] Currently, there is no known prevention for PTE following TBI and treatments for PTE are only partially effective and can have severe drawbacks.[50] There is also no known treatment or cure for many other types of epilepsy that afflict our troops and the general population.[51] 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.

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[44] Pitkänen A and Bolkvadze T. Head Trauma and Epilepsy. Jasper's Basic Mechanisms of the Epilepsies [Internet] 4th Edition 2012. Noebels JL, Avoli M, Rogawski MA, et al., editors.
[45] 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.
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[50] Szaflarski JP, Nazzal Y, Dreer LE. Post-traumatic epilepsy: Current and emergent treatment options. Neuropsychiatr Dis Treat 2014; 10:1469-1477.
[51] Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine* 2000;342(5):314-9.

- **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."[52] Studies reviewed in the report found an elevated incidence of Lou Gehrig's disease (ALS)[53] among Gulf War veterans as well as significantly elevated rates of death due to brain cancer[54] 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.[55]

[52] 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.
[53] Research Advisory Committee on Gulf War Veterans' Illnesses, pp. 23-25.
[54] Research Advisory Committee on Gulf War Veterans' Illnesses, pp. 23-26.
[55] 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.[56] Over 35,000 are at risk of developing hydrocephalus due to the severity of the injury.[57] [58] [59] [60]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.[61] [62]

[56] Defense Medical Surveillance System. Theater Medical Data Store provided by the Armed Forces Health Surveillance Center. http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi.
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[62] The Veteran Population Projection Model 2014. U.S. Department of Veterans Affairs. 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.[63] 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.[64] 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.[65]

- **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.[66]

[63] 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

[64] 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

[65] 2014 CDC Camp Lejeune Contaminated Drinking Water Report

[66] 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. [67] [68] [69] [70] 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 up to three times more common among African Americans, Hispanics and Native Americans and it affects over one-and-a-half million persons in the U.S. --90 percent of whom are women. The disease 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. 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 almost 15 percent of active duty Service Members, almost 20 percent of Reserves and 15.5 percent of the National Guard.[71] A recent Pew Research Center report found that the active-duty female force is racially diverse –nearly one-third (31%) of active-duty women are black (including black Hispanics).[72] Twelve percent of women in the Armed Forces report their ethnicity as Hispanic, whether white or black. Our nation now has over 2 million women veterans, about 9 percent of the total veteran population, a figure expected to rise to 15 percent by 2035.[73] [74]

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[67] 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

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[70] 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

[71] http://www.cnn.com/2013/01/24/us/military-women-glance/ Accessed March 4, 2016.

[72] Women in the U.S. Military: Growing Share, Distinctive Profile. Pew Research Center. http://www.pewsocialtrends.org/files/2011/12/women-in-the-military.pdf Accessed March 4, 2016.

[73] Women Veterans Population. Department of Veterans Affairs. http://www1.va.gov/womenvet/docs/WomenVeteransPopulationFactSheet.pdf Accessed March 4, 2016.

[74] Projected Veteran Population 2013 to 2043. Department of Veterans Affairs. http://www.va.gov/vetdata/docs/quickfacts/Population_slideshow.pdf Accessed March 4, 2016.

- **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.[75] 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!"[76] Nearly eighty years later, malaria remains the number one infectious disease threat to U.S. military forces deployed worldwide.[77] 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.[78] 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.[79]

[75] 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.
[76] Paul F Russell, 'Introduction', in Preventive medicine in World War II, op. cit., note 1 above, p. 2.
[77] Moss, Kellie and Josh Michaud. 2013. The U.S. Department of Defense and Global Health: Infectious Disease Efforts. Kaiser Family Foundation pg. 17
[78] Lezaun, J. (2018). The deferred promise of radical cure: pharmaceutical conjugations of malaria in the global health era. Economy and Society, 1-25.
[79] 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.

- **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.[80] 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.[81] [82] [83]

- **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.[84] 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.[85] 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."[86] 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.[87] 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.[88] By studying this population, scientists might be able to understand the cause and triggers of MS and develop effective treatments.

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[80] Annals of Epidemiology, Vol. 10, Issue 3, April 2000, pages 192-195.
[81] 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
[82] Melanoma of the Skin, Cancer Fact Sheets, National Cancer Institute, SEER database, 2007. http://seer.cancer.gov
[83] Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesa, MD: National Cancer Institute; http://seer.cancer.gov/csr/1975_2009_pops09/; Accessed August 22, 2012.
[84]Veterans Health Administration Claim Database. FY 1998-FY2014.
[85]Veterans Health Administration Claim Database. FY1998- FY2014.
[86] 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.
[87] 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
[88] 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[89], NF120087[90], NF110052[91] and NF110052[92]

- **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[93], 120839[94], 130776[95])

[89] Elefteriou, Florent. Neurofibromin Function in Chondrocytes.
[90] 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.
[91] Plotkin, Scott. Phase 2 Study of Bevacizumab in Children and Young Adults With NF 2 and Progressive Vestibular Schwannomas.
[92] North, Kathryn. A Randomized Placebo-Controlled Study of Lovastatin in Children with Neurofibromatosis Type 1 (STARS)
[93] McKinley, Todd O. Mitochondrial Based-Treatments that Prevent Post-Traumatic Osteoarthritis in a Translational Large Animal Intraarticular Fracture Survival Model.
[94] Deane, Kevin D. Pathogenesis and Prediction of Future Rheumatoid Arthritis
[95] 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[96], approximately 11,800 will be diagnosed with ovarian cancer over the course of their lifetimes. [97] 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. [98] 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.

[96] Military Demographics for 2012. Available here: http://www.militaryonesource.mil/12038/MOS/Reports/2012_Demographics_Report.pdf

[97] 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

[98] 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. [99][100] 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. [101][102] Further, the link between type 2 diabetes and pancreatic cancer is well-established[103] and type 2 diabetes is recognized by the VA as an Agent Orange-associated presumptive disease.[104] 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.[105]

[99] 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
[100] Kang, HK et al, HealthVIEWS: Mortality Study of Female US Vietnam Era Veterans, 1965-2010, Am J. Epidemiol 179: 721-30, 2014
[101] Barone E et al, Environmental risk factors for pancreatic cancer: an update. Arch Toxicol 90: 2617-2642, 2016.
[102] 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
[103] 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
[104] http://www.publichealth.va.gov/exposures/agentorange/conditions/index.asp
[105] 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

- **<u>Parkinson's research program</u>**: 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.[106] In 2012, the Department of Veterans' Affairs (VA) made PD presumptive for TBI-connected with military service[107] and secondary service connection for diagnosable illnesses associated with traumatic brain injury.[108] 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.[109] 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.

[106] Ritz et al., Neurology 2012;79:2061-6.
[107] 38 CFR Part 3 Department of Veterans Affairs.
[108] *Federal Register* 2013;78:76196–209.
[109] Tanner et al., Alz Dementia 2014;10:213-225.

- **Prostate Cancer**: Prostate cancer is the second deadliest cancer among American men, killing more than 29,000 men annually,[110] 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,[111] 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.[112] Research funded by the Prostate Cancer Research Program (PCRP) advances treatments; PCRP funding was responsible for accelerating the development of the three new treatments for advanced disease in the last seven years,[113] [114] [115] [116] [117]bringing them to patients faster than typical development of new drugs. Moreover, the program focuses on not only developing more effective therapeutics but also on improving diagnosis to reduce over treatment and accurately distinguish life-threatening disease from indolent tumors,[118] [119] which is likely to have its greatest impact on active duty servicemen who can be confidently monitored through active surveillance,[120] rather than compromising their service to undergo treatment.

[110] American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society; 2018.
[111] 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.
[112] Chamie K1, DeVere 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.
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[114] 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.
[115] 2011 Prostate Cancer Research Highlights. http://cdmrp.army.mil/pcrp/research_highlights/2011
[116] 2012 Prostate Cancer Research Highlights. http://cdmrp.army.mil/pcrp/research_highlights/2012#7
[117] http://cdmrp.army.mil/cdmrp_timeline/oz/pdf/PCRP.pdf
[118] http://cdmrp.army.mil/pcrp/default.shtml
[119] http://comptroller.defense.gov/Portals/45/Documents/defbudget/fy2015/budget_justification/pdfs/09_Defense_Health_Program/DHP_PB15_Vol_I-II.pdf
[120] 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. [121] [122] [123] [124] [125] 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.[126] 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. [127] 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.

[121] Ford ES, Li C, Wheaton AG, Chapman DP, Perry GS, Croft JB. Sleep duration and body mass index and waist circumference among US adults. Obesity2014;22:598-607.
[122] 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.
[123] 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.
[124] 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.
[125] Fang J, Wheaton AG, Ayala C. Sleep duration and history of stroke among US adults. J Sleep Research 2014;23(5):531-537.
[126] 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.mm6506al
[127] 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.[128] 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.[129] The Department of Veterans Affairs considers stomach cancer to be a service connected malignancy for service members who experienced hazardous exposure to ionizing radiation.[130] Additionally, studies suggest that the risk of H. pylori infection increases among military personnel during long-term deployment.[131] This is significant because, according to the National Cancer Institute, infection with H. pylori is the primary identified cause of stomach cancer.[132] 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.[133]

[128] 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
[129] 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/
[130] National Cancer Strategy, Department of Veterans Affairs, Veterans Health Administration, VHA Directive 2003-34. June 20, 2003.
[131]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
[132] 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.
[133] 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

- **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. TB is currently endemic (incidence rate greater than 20 cases per 100,000 population) in 145 countries across the world[134] and 98 of these 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.[135] During deployment, the warfighter could be exposed to M tuberculosis bacteria and could develop either latent or active TB in either drug sensitive (DS) or, much more ominously, drug resistant (DR) forms. In 2014, an estimated 1.7 billion individuals worldwide were thought to be carriers of latent TB bacteria.[136] Over a lifetime, around 10 percent of LTBI cases will progress to infectious TB.[137] LTBI's pervasiveness in the global population should be a primary concern for TB diagnoses in the US military. Already, between 2008 and 2012, most active TB cases (57.9 percent) diagnosed at accession in the US military were associated with an existing LTBI.[138] While the healthy warfighter may not activate a latent TB infection immediately, risk increases for people under significant stress and for immunocompromised individuals.[139] 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 $17,000 for drug-susceptible TB, $150,000 for MDR-TB, and $482,000 for XDR-TB. Further, the lasting side effects of present DR-TB treatment can be devastating, including deafness, kidney damage, depression or psychosis.[140] An increase in the number of patients with MDR-TB or XDR-TB would have a devastating financial impact on state and local health-care systems and on the ever-growing cost of DoD personnel and veteran's care.[141]

[134] World Health Statistics 2015. "Tuberculosis Incidence." http://www.who.int/tb/country/en/
[135] DMDC. Military and Civilian Personnel by Service/Agency by State/Country, December 2016. Defense Manpower Data Center. https://www.dmdc.osd.mil/appj/dwp/dwp_reports.jsp
[136] Houben RMGJ, and Dodd PJ."Challenges in tuberculosis drug research and development". PLOS Medicine. 2016; 13(10): e1002152. doi:10.1038/nm0307-290.
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[141] Zarembo A. "The rising cost of veterans' healthcare and benefits." Los Angeles Times. 2014; Jul 28.

- **Tuberous Sclerosis Complex (TSCRP)**: Research supported by the TSCRP 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 TSCRP award W81XWH-12-1-0190[142] 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.[143] 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 TSCRP 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[144], W81XWH-04-1-0309[145], W81XWH-06-1-015[146], W81XWH-09-1-0088[147], W81XWH-10-1-0861[148], W81XWH-13-1-0040[149].

- **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).[150] The VHA reports 202,000 OEF/OIF veterans with eye injuries since 2000 [151], 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 2018 study using published data from 2000-2017 estimated that deployment-related eye injuries and blindness have cost the U.S. a total of $41.57 billion, driven primarily by the present value, estimated at $40.2 billion, of long-term benefits, lost wages, and family care.[152]

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[142] Wong, Michael. *The Role of Brain Inflammation in Epileptogenesis in TSC*
[143] 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
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[147] Yoshii, Akira. *Studying Protein Synthesis-Dependent Synaptic Changes in Tuberous Sclerosis*
[148] Manning, Brendan. *Defining the Therapeutic Implications of the Integrative Stress Response in TSC*
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[97] 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)
[152] Kevin D. Frick, 2018, "Cost of Military Eye Injury, Vision Impairment, and Related Blindness and Vision Dysfunction Associated with Traumatic Brain Injury (TBI) without Eye Injury"