The Honorable Adam Smith  
Chairman  
Committee on Armed Services  
U.S. House of Representatives  
Washington, DC 20515

Dear Mr. Chairman:


The report presents CTE-relevant research expenditures totaling $138,890,862.00 during FY 2014–FY 2019, based on funding level data reported at the March 2020 National Research Action Plan Review and Analysis. The Department of Defense (DoD) and the Department of Veterans Affairs also allocated monies for the National Research Action Plan portfolio in support of CTE research through the Chronic Effects of Neurotrauma Consortium and the Long-Term Impact of Military-Relevant Brain Injury Consortium Awards. Since CTE is currently diagnosed via post-mortem neuropathological examination, development of CTE-specific treatment is not yet achievable. Due to current gaps in CTE research and detection methodologies, an accurate projection of the number of Service members with CTE is not possible at this time. However, in addition to the efforts described in this report, the DoD is pursuing a Comprehensive Strategy for Warfighter Brain Health to optimize Warfighter brain health and performance in order to maximize Joint Force superiority and lethality in all operating environments. The DoD remains committed to continued CTE research to address the outlined gaps between CTE and traumatic brain injury research, and ultimately, to assist Service members and their families.

Thank you for your continued strong support for our Service members, civilian workforce, and families.

Sincerely,

Matthew P. Donovan

Enclosure:
As stated
The Honorable William M. “Mac” Thornberry
Ranking Member
Committee on Armed Services
U.S. House of Representatives
Washington, DC  20515

Dear Representative Thornberry:


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Thank you for your continued strong support for our Service members, civilian workforce, and families.

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Enclosure:
As stated
Report to Congress

Chronic Traumatic Encephalopathy

August 2020


The estimated cost of this report for the Department of Defense (DoD) is approximately $2,810.00 for Fiscal Year (FY) 2019–FY 2020. This includes $0.00 in expenses and $2,810.00 in DoD labor.

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I. PURPOSE

This report is in response to House Report 116–120, pages 158–159, accompanying H.R. 2500, the National Defense Authorization Act for Fiscal Year (FY) 2020, which requests the Secretary of Defense to provide a report to the Committee on Armed Services of the House of Representatives no later than March 1, 2020 on Chronic Traumatic Encephalopathy (CTE) related issues.

II. POTENTIAL GAPS IN CTE RESEARCH AND DETECTION METHODOLOGIES
(Projected Number of Service Members Potentially Afflicted with CTE)

CTE is a progressive neurodegenerative disease suspected to be associated with repeated brain trauma. Currently, a CTE diagnosis can only be made through a neuropathological examination post-mortem. Although pre-mortem manifestations attributed to CTE are similar to those of Alzheimer’s disease (AD), CTE appears to be a pathologically distinct entity. The potential relationship between CTE and multiple sub-concussive events or more substantial head injuries, including blast-related traumatic brain injury (TBI), is an important area of study for the Department of Defense (DoD). Accordingly, in 2015, the DoD Blast Injury Research Program Coordinating Office organized a State-of-the-Science Meeting on CTE. This meeting convened subject matter experts from DoD, other Federal agencies, academia, industry, international partners, and the sports community, and resulted in identified clinical and research knowledge gaps. CTE is a high priority for Federal agencies that significantly collaborate on interagency research activities. An example of this is evident by the November 6–7, 2019 conference hosted by the National Institutes of Health (NIH) on “The Neuropathological Diagnosis of Chronic Traumatic Encephalopathy (CTE): Next Steps.” Attendees included the leading international experts in CTE neuropathology, and they did not reach agreement on the specific histologic characteristics of CTE. The consensus view of these experts was that there is no clear or proven association between the histologic findings, specifically p-tau, with any specific mechanism of injury or any specific pre-morbid clinical disease or syndrome. Additionally, CTE-related research published in peer-reviewed journals and ongoing efforts presented at major scientific meetings have further delineated key knowledge gaps regarding the relationship between CTE and TBI. These gaps are summarized as follows:

- The incidence and prevalence of CTE, including in Service members and veterans, are currently unknown. Due to current gaps in CTE research and detection methodologies, an accurate projection of the number of Service members with CTE is currently not possible.

- At present, CTE is diagnosed via post-mortem neuropathological examination, and **no reliable means exists to diagnose CTE prior to death.** Development of fluid and imaging biomarkers, including positron emission tomography (PET) ligands for tau and other aberrant proteins associated with CTE, are needed for the pre-mortem diagnosis of CTE and subsequent treatment of those diagnosed with CTE.

- The most commonly cited peer-reviewed publication on CTE is a case series limited by
methodological biases, incompletely validated pathological criteria, limited availability of clinical data, and a reliance on inherently biased postmortem data (Mez et al).

- With the possible exception of head trauma, substantiated risk factors for CTE are unknown due to the absence of any longitudinal or prospective studies with broad recruitment strategies, reliable diagnostics, and a robust neuropathological component.

- Clear and standardized clinical criteria for CTE are lacking: There is an ongoing NIH-funded process that is attempting to define provisional consensus clinical criteria which can be used in research studies to assess correlations with CTE. The work of the consensus group is ongoing as of this report.

- Therapeutics development cannot occur if clear and standardized criteria for CTE are lacking.

- Symptoms and mood disorders attributed to CTE are non-specific. For example, aggressive behaviors, depression, or suicide, often linked to CTE, have also been attributed to narcotics and alcohol abuse and behavioral health disorders without evidence of CTE.

- It remains unknown whether there exists a dose response relationship between CTE and brain trauma. For example, evidence is unavailable regarding the potential for CTE following prolonged exposure to a large number of sub-concussive blows (e.g., repetitive low level blasts) versus the potential after sustaining a single or multiple symptomatic mild TBIs.

- There is a lack of blast-exposed clinical tissue, with well-annotated medical and blast exposure histories, available for neuropathological analysis.

Due to the current gaps in CTE research and detection methodologies, an accurate projection of the number of Service members with CTE is not possible at this time.

### III. DOD MEDICAL RESEARCH FUNDING FOR CTE/TBI: FY 2014–FY 2019

Expenditures for CTE-relevant research is presented based on the funding level data reported at the National Research Action Plan (NRAP) Review and Analysis in March 2020. The total FY 2014–FY 2019 expenditure for CTE-relevant research is $138,890,862.00 across the NRAP portfolio (much of this research is also relevant to other important aspects of TBI in addition to CTE). In addition, DoD and the Department of Veterans Affairs (VA) allocated monies for the NRAP portfolio through the Chronic Effects of Neurotrauma Consortium (CENC) and the Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) Awards, in support of CTE research. The NRAP was published in August 2013, in response to a White House

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Directive for DoD, VA, the Department of Health and Human Services, and the Department of Education to outline coordinated research efforts focused on the causes and mechanisms underlying TBI, posttraumatic stress disorder, and other co-occurring conditions. To address the objectives outlined in the NRAP, the NIH, VA, and DoD have many joint initiatives, including research targeting the acute and chronic effects of neurotrauma and the relationship of CTE and TBI. Details of the recent CTE and TBI research-related efforts included in the DoD medical research budget are incorporated in the following lists of projects, which are separated by primary funding source. The total FY 2014–FY 2019 expenditure for CTE-relevant research from the below tables is $138,890,862.00.

A. Combat Casualty Care Research Program (CCCRP)/Joint Program Committee 6 (JPC-6)

The neurotrauma portfolio (NTP) of the CCCRP focuses on closing military relevant gaps across a broad range of research areas to improve the prevention, diagnosis, management, and treatment of TBI and related sequelae from point-of-injury to acute hospitalization. The NTP’s goals are to: (1) decrease morbidity and mortality from neurotrauma; (2) mitigate secondary brain injury across all TBI severities; (3) provide cutting-edge medical solutions for the Service member injured in multi-domain operations; and (4) advance materiel and knowledge development. Ultimately, these efforts intend to expand and develop new clinical practice guidelines, care algorithms, therapies, devices, and procedures that enhance the decision-making capabilities of medical personnel, thus enabling earlier intervention and improvement in outcomes. **Reference source not found.** provides a summary of the JPC-6/CCCRP FY 2014–FY 2019 investments in CTE-related research, totaling $58,732,746.00.

<table>
<thead>
<tr>
<th>NRAP Category</th>
<th>Study Title</th>
<th>Lead Site</th>
<th>Total Funded Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundational Science/Etiology</td>
<td>Mechanism and Biomarkers of Degenerative Conditions After Repeated Mild TBI</td>
<td>Uniformed Services University of the Health Sciences (USUHS)</td>
<td>$765,022</td>
</tr>
<tr>
<td>Prevention and Screening</td>
<td>Early Recognition of CTE Through FDDNP PET Imaging</td>
<td>Cleveland Clinic Foundation</td>
<td>$746,068</td>
</tr>
<tr>
<td>Prevention and Screening</td>
<td>Tau Imaging Of CTE</td>
<td>Brigham and Women's Hospital, Inc.</td>
<td>$849,403</td>
</tr>
<tr>
<td>Prevention and Screening</td>
<td>In Vivo Neuroimaging Biomarker Panel For CTE</td>
<td>University of Pittsburgh</td>
<td>$631,733</td>
</tr>
<tr>
<td>Prevention and Screening</td>
<td>PET Ligands For Measuring Tau In The Brains Of Combatants After TBI</td>
<td>University of California, San Francisco</td>
<td>$2,863,058</td>
</tr>
<tr>
<td>Foundational Science/Etiology</td>
<td>Tau Accumulation In TBI: Mechanisms And Treatment</td>
<td>University of Pennsylvania</td>
<td>$2,769,876</td>
</tr>
<tr>
<td>Treatment</td>
<td>Novel Mechanism for Reducing Acute and Chronic Neurodegeneration After TBI</td>
<td>University of California, Davis</td>
<td>$763,828</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------</td>
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</tr>
<tr>
<td>Prevention and Screening</td>
<td>Development of in Vivo Biomarkers for Progressive Tau Pathology after TBI</td>
<td>Washington University</td>
<td>$2,985,400</td>
</tr>
<tr>
<td>Prevention and Screening</td>
<td>Development of in Vivo Biomarkers for Progressive Tau Pathology after Traumatic Brain Injury</td>
<td>Texas, University of, Southwestern Medical Center at Dallas</td>
<td>$1,448,083</td>
</tr>
<tr>
<td>Prevention and Screening</td>
<td>Biomarker Signatures in Blood for Acute and Chronic mTBI Using the SOFIA Technology</td>
<td>New York, State University of, Downstate Medical Center</td>
<td>$1,983,210</td>
</tr>
<tr>
<td>Foundational Science/Etiology</td>
<td>Degenerative Conditions After Repeated Mild Traumatic Brain Injury (mTBI)</td>
<td>Uniformed Services University of the Health Sciences (USUHS)</td>
<td>$765,022</td>
</tr>
<tr>
<td>Prevention and Screening; Foundational Science; Treatment; epidemiology</td>
<td>*Chronic Effects of Neurotrauma Consortium (CENC)</td>
<td>Virginia Commonwealth University (VCU)</td>
<td>$37,175,000</td>
</tr>
<tr>
<td>Prevention and Screening; Foundational Science; Treatment; epidemiology</td>
<td>*Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) Award</td>
<td>VCU</td>
<td>$4,987,043</td>
</tr>
</tbody>
</table>

* Indicates funds also received from the VA.
+ FDDNP is the acronym for 2-{1-[6-{[fluorine-18] fluoroethyl}(methyl)amino]-2-naphthyl}- ethylidene)malononitrile

B. Office of Naval Research (ONR)

The ONR was established by law as the U.S. Government’s first permanent agency devoted to funding civilian scientific research during peacetime. It manages and funds basic and applied science and advanced technology development with an array of partners in academia, industry, and government in the United States and around the world. The ONR is not conducting CTE research directly, as CTE is neither in the title nor in the subject of research on TBI diagnosis, treatment, and prevention. Since some CTE may be exacerbated by TBI, some research that contributes to the understanding of TBI, may also contribute to the understanding CTE over time. Therefore, the ONR reports funding for FY 2014–2019 as zero.

C. The Peer Reviewed Alzheimer’s Disease Research Program (PRARP)

The PRARP, supported by the DoD Congressionally Directed Medical Research Programs, was
initiated in 2011 to address the long-term consequences of TBI as they pertain to AD. In FY 2016, the program was expanded to include AD-related dementias research as it pertains to TBI. Consistent with this mission, the PRARP has invested a total of $4,288,485 in FY 2014–FY 2019 in CTE related research projects (Table 2).

Table 2. PRARP Supported CTE Research

<table>
<thead>
<tr>
<th>NRAP Category</th>
<th>Study Title</th>
<th>Lead Site</th>
<th>Total Funded Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundational Science/Etiology</td>
<td>The Role of Inflammation in Development of AD Following Repetitive Head Trauma</td>
<td>Indiana University School of Medicine</td>
<td>$658,533</td>
</tr>
<tr>
<td>Prevention and Screening</td>
<td>Rapid Seeded Amyloid Amplification Assay to Assess TBI and Its Potential Linkage to CTE or AD</td>
<td>Colorado State University</td>
<td>$748,055</td>
</tr>
<tr>
<td>Foundational Science/Etiology</td>
<td>Glial Cell Dysfunction in Neurodegenerative Sequelae of Repetitive Mild Traumatic Brain Injury</td>
<td>The Roskamp Institute Inc.</td>
<td>$703,489</td>
</tr>
<tr>
<td>Foundational Science/Etiology</td>
<td>Role Of Non-neuronal Cells In Tauopathies After Brain Injury</td>
<td>University of California, Los Angeles</td>
<td>$629,525</td>
</tr>
<tr>
<td>Foundational Science/Etiology</td>
<td>Is Failure of Glymphatic Tau Clearance a Critical Pathophysiological Event in CTE?</td>
<td>University of Rochester</td>
<td>$769,000</td>
</tr>
<tr>
<td>Prevention and Screening; Foundational Science/Etiology</td>
<td>Application of Proteomics and Electrophysiology to Identify Biomarkers and Targets for CTE Therapeutics</td>
<td>Emory University</td>
<td>$779,883</td>
</tr>
</tbody>
</table>

D. Uniformed Services University of the Health Sciences (USUHS)

As part of its mission to educate, train, and prepare uniformed services health professionals and scientists to support the Military Health System and the readiness of the Uniformed Services, USUHS supports CTE research that is innovative and relevant to DoD. Specifically, the USUHS has invested $75,869,631.00 in FY 2014–FY 2019 in support of CTE-related research projects (Table 3).

Table 3. USUHS Supported CTE Projects

<table>
<thead>
<tr>
<th>NRAP Category</th>
<th>Study Title</th>
<th>Lead Site</th>
<th>Total Funded Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>UCSF/USUHS Partnership To Develop Tau Prion Therapeutics For CTE</td>
<td>USUHS; University of California, San Francisco</td>
<td>$75,459,631</td>
</tr>
<tr>
<td>Prevention and Screening</td>
<td>CTE and Posttraumatic Neurodegeneration: Neuropathology and Ex Vivo Imaging</td>
<td>Boston; USUHS</td>
<td>$410,000</td>
</tr>
</tbody>
</table>
IV. DOD GRADUATE MEDICAL EDUCATION PROGRAMS THAT INCORPORATE CTE INTO CURRICULA

The military medical and graduate health sciences school, USUHS, provides DoD graduate medical education programs within the Neuroscience Graduate Program and the Department of Anatomy, Physiology, and Genetics; these programs incorporate CTE (e.g., tau pathology/neurochemistry) into the curricula. The study of neuropathology of a variety of neurodegenerative disorders, such as AD, Parkinson’s disease, and CTE, is routinely included as a part of medical education.

V. PLAN AND METHODOLOGIES TO DETECT SERVICE MEMBERS AND COVERED BENEFICIARIES: CTE-RELATED INITIATIVES

Currently, the state of the science has not established clear relationships between particular causes and clinical manifestations of CTE. No pre-morbid diagnostic tools to identify or track progression of potential CTE-like pathology yet exist. The relationship between CTE and the mechanism of injury, pre-morbid clinical deterioration, or pre-disposing factors can only be firmly established through large brain tissue repositories that include complete and comprehensive clinical records of the donors. The Veterans Administration-Boston University-Concussion Legacy Foundation (VA-BU-CLF) Brain Bank and the Center for Neuroscience and Regenerative Medicine (CNRM) Brain Tissue Repository are two existing brain tissue repository programs. Both programs emphasize outreach to ensure public awareness of the brain tissue repositories, and sufficient staffing and technology to facilitate rapid access to the fresh tissue and medical records. Two large epidemiological studies are tracking the long-term effects of TBI in Service members and veterans, and working with these brain tissue repositories to enhance understanding of the natural history of TBI. Moreover, Deputy Secretary of Defense Memorandum, “Comprehensive Strategy and Action Plan for Warfighter Brain Health,” dated October 1, 2018 directs the Under Secretary of Defense for Personnel and Readiness to develop a comprehensive strategy and plan of action focused on promoting warfighter brain health and countering TBI. On February 1, 2019 the Acting Deputy Assistant Secretary of Defense for Health Readiness Policy and Oversight expanded the strategy to specify six lines of effort (LOEs). Of particular relevance to CTE, LOE 5 focuses on the long-term effects of TBI, and awareness and support for the CNRM Brain Tissue Repository. Below, each brain tissue repository initiative is further described:

- The VA-BU-CLF Brain Bank, established in 2009, focuses on understanding any potential relationship between brain trauma and CTE (http://www.bu.edu/cte/our-research/brain-bank/). The VA-BU-CLF Brain Bank contains more than 600 brains, of which over 325 brains (including those of veterans) have been diagnosed with CTE according to the National Institute of Neurological Disorders and Stroke criteria. Bio specimens are acquired via a brain donor registry and hotline, with standardized protocols in place to ensure that tissue and data are acquired and readily available to investigators. Beyond brain tissue, comprehensive retrospective clinical data (e.g., clinical symptoms, history of TBI, history of substance abuse) are available.
• In 2018, the DoD and the VA have each committed up to $5M per year for 5 years to fund a program entitled, “The Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC).” The intent of this program, an extension of the previously funded 2012 CENC study, is to support a consortium of clinical sites conducting a large longitudinal study and associated sub-studies of Service members and veterans who sustained a TBI or are otherwise at risk for chronic TBI related health issues to include CTE. The knowledge gained through the proposed studies will inform TBI pathways of care, illuminate specific target areas to improve TBI care, and lay the foundation for a clinical trial network. This award was granted (October 1, 2019) to VCU and will extend the study cohort to include U.S. veterans of any war. It is not yet known how much of this award will focus specifically on CTE.

• In 2011, the USUHS established the CNRM Brain Tissue Repository, and neuropathologists are examining those brains to enhance our understanding of the potential causes and risk factors for CTE in the military (http://www.researchbraininjury.org/our-team/). The CNRM Brain Tissue Repository currently contains brain specimens of about 168 Service members or veterans. An outreach awareness program has also been developed to build a registry for individuals interested in brain donation.

VI. THERAPEUTICS UNDER DEVELOPMENT FOR COVERED BENEFICIARIES AFFLICTED WITH CTE

Clear and standardized criteria for the pre-morbid diagnosis of CTE do not currently exist and remain a research gap. Therefore, it is not yet possible to develop CTE specific treatment.

VII. CONCLUSION

The DoD is committed to continued research in CTE to address the outlined gaps between CTE and TBI research, and ultimately assist Service members and their families.