CDMRP
Department of Defense

Peer Reviewed Alzheimer's Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and Department of Veterans Affairs (VA). As part of their final report,[1] the committee recommended that each CDMRP program "… develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future…and that these strategic plans should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

Originally released in 2018, this updated strategic plan presents the 2019 strategy for the CDMRP's Peer Reviewed Alzheimer's Research Program (PRARP). The 2019 PRARP Strategic Plan identifies the high-impact research goals identified as most important to the American public, military and Veteran communities. It highlights an adaptable framework that is responsive to new challenges and scientific breakthroughs across research funded in traumatic brain injuries (TBIs), Alzheimer's disease (AD), and the related dementias (ADRD). This plan provides insights on the program's goals over time for AD/ADRD subsequent to TBIs. Funding for the PRARP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding.

PRARP BACKGROUND AND OVERVIEW

History: The PRARP was initiated in fiscal year 2011 (FY11) per a request and funding from Congress. Experts from the Department of Defense (DoD), VA, NIH, and Alzheimer's Association met and agreed that there was enough evidence to focus the PRARP on the relationship between TBI and AD, while meeting the needs of the civilian community at large. This was based on a variety of inputs, including an Institute of Medicine[2] report that showed an increased risk for dementia in military cohorts.

The Linkage Between TBI and Dementia: The prevalence of AD is estimated to be 2.6 million (M) to 5.2M individuals and is reported to increase with age.[3] The same study notes that the actual prevalence may be even higher, as many cases are missed. According to the Centers for Disease Control and Prevention (CDC), AD/ADRD was the sixth leading cause of death in the United States in 2014.[4] U.S. healthcare costs in 2010 were estimated to range from $157 billion (B) to $215B.[5]

Currently, there are no effective treatments for dementia. Some medications can address the symptoms of AD/ADRD, but their effects are only temporary. The molecular and physiological pathways of dementia are intensely studied, yet many clinical trials have shown little success. Identifying risk factors in the development of AD/ADRD and their associated biomarkers is a necessary means for both improving clinical trial outcomes and preventing initiation of the processes leading to AD/ADRD. As noted in the introduction, TBI is a recognized risk factor associated with development of AD/ADRD. The PRARP studies address a subset of research associated with AD/ADRD, with an emphasis on TBI as a risk factor for AD/ADRD.

The prevalence of TBI has steadily increased over the previous decade[6], with 716 emergency department visits and 92 hospitalizations per 100,000 among the U.S. population in 2010. This was associated with a

reported domestic cost of $76.3B in 2010. TBI is also a recognized risk associated with military Service, with approximately 350,000 documented cases.[7] This number is suspected to suffer from underreporting.

The long-term consequences of TBI as they pertain to AD/ADRD require further study, given the complexity of the pathology and the number of individuals incurring a TBI in both military and domestic settings. In this regard, the PRARP is investigating how other risk factors or comorbidities interplay with TBI to promote or hasten AD/ADRD. Risk factors such as sleep disorders, genetics, depression, traumatic stress and drug use are all under investigation. The PRARP is also focused on sex-based differences to ensure a complete understanding of who is at risk in military populations for AD/ADRD.

Human TBI studies present a number of challenges. Confounders in these studies include self-reported injury, time between injury and first clinic visit, multiple acute or sub-concussive injuries, and the wide array of TBI definitions. In addition to TBI, other factors may influence risk for developing AD/ADRD. These include genetics, sleep, activity, nutrition, hypertension, diabetes, other metabolic disorders, gender, and age. Many or all of them may affect a particular individual with a TBI, but the mechanisms of effect are unknown and require significant study. Some of these may represent modifiable risk factors, the study of which may help address the symptoms of AD/ADRD in the context of TBI.

Early epidemiological studies completed decades before the PRARP's inception anticipated research challenges facing the PRARP. Many early studies showed an unclear TBI-Dementia inter-relationship due to the complexity of the variables in each study[8]. This led the PRARP to take a new approach to epidemiological TBI-AD studies. Some variables in the early epidemiological studies included (1) the quality of TBI data (e.g., severity, time after injury before report); (2) unknown risk and resiliency factors for both TBI and AD/ADRD, and (3) limited or no validation by autopsy or other markers indicative of AD/ADRD subsequent to TBI. It's important to state that validation of AD/ADRD pathology (by autopsy or other means) is critical, since some symptoms may represent another neurological disorder; this is still a gap in the PRARP.

Newer PRARP-funded prospective and retrospective studies are showing a trend toward a higher risk of AD/ADRD from TBI exposures. These studies also show a linkage of TBI to other comorbidities or risk factors[9] that drive cognitive decline forward, making future mechanistic studies possible based on these findings. The complexity of these findings also requires more rigorous study to truly understand the TBI-AD/ADRD connection, and its true extent.

In FY16, the PRARP was expanded to include ADRD research as it pertains to TBI. This was done to highlight the complexity of the TBI-dementia connection and the need for an expanded scope into other areas outside of traditional AD research to include Lewy body, frontotemporal, and vascular dementias. It is hoped that the revised focus will expand our knowledge of the complex pathology of TBI as it pertains to AD/ADRD.

It is well known that TBI and AD/ADRD share a variety of common symptoms including memory disorders, aggression, depression, and executive functioning deficits. The PRARP therefore funds research that looks at patient symptoms in order to explore more effective diagnostic strategies to understand the progression of symptoms. This helps us understand TBI-AD/ADRD as well as what makes a person vulnerable to chronic TBI effects and outcomes such as AD/ADRD. The PRARP also funds research to help us understand the mechanisms and pathophysiology of progression to AD/ADRD following TBI or other military risk factors.

Given the challenges of understanding the TBI-AD/ADRD interrelationship, the PRARP additionally funds research to prevent progression of initial symptoms to ensure they do not worsen. In milder cases, it may even be possible to alleviate some acute symptoms. Since its inception, the PRARP has emphasized the importance of Quality of Life research as a means of alleviating the impact of deleterious symptoms and reducing their impact on both patients and caregivers. The PRARP continues to invest in this area as well as in research that facilitates caregiving by family members. Examples of research in this latter area highlight the complexity of funding and executing such initiatives.

The Role of the Programmatic Panel: The PRARP Programmatic Panel is key to executing a strategy that matures from basic research toward translation and beyond. The CDMRP funding cycle is shown in **Figure 1**, which captures both tiers of application review. Essentially Peer Review is a technical assessment of an application. It measures the quality of an application in terms of the science and response to the intent of a particular Program Announcement (funding opportunity).

In the second-tier of project selection, the Programmatic Panel recommends peer-reviewed applications for funding. The Programmatic Panel has multiple roles at Programmatic Review, including ensuring a balance between the scientific priorities listed in the Program Announcements and moderating the overall balance between basic, translational, and human validation. The panel is composed of individuals from academia and the DoD, NIH, VA, and the Alzheimer's Association.

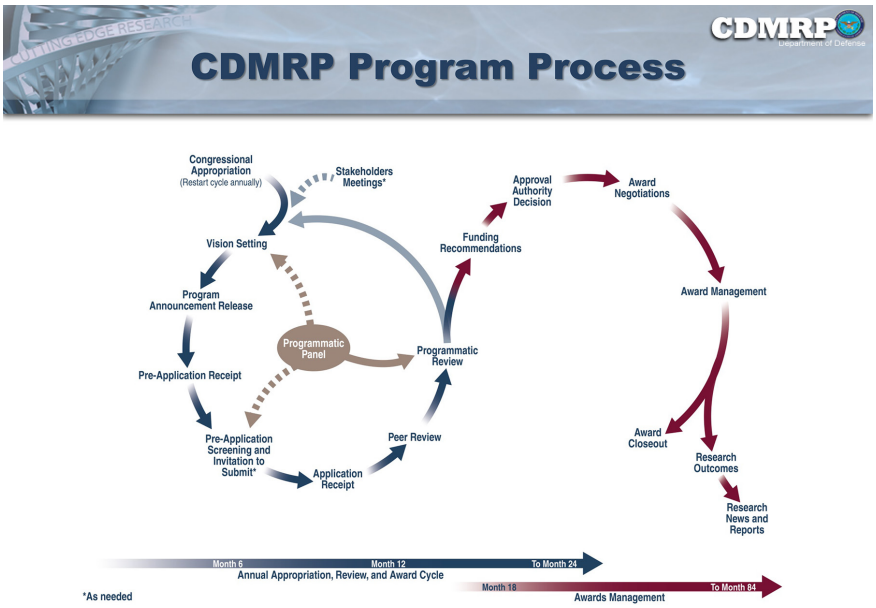

Figure 1: The CDMRP funding cycle, or program process.

In addition to this essential role of strategically selecting research, during Vision Setting, the Programmatic Panel works with the Program Manager to assess the PRARP's overall performance during the last several years, and sets and revises the PRARP's Mission and Vision. This is an essential exercise, since it identifies forthcoming research priorities and the types of funding opportunities/Program Announcements the PRARP will subsequently offer, should funding become available. The FY19 Vision and Mission statements provide a succinct description of the PRARP:

Vision: To address the long-term consequences of TBI as they pertain to AD and ADRD

Mission: The PRARP's mission is devoted to (1) understanding the association between TBI and AD/ADRD, and (2) reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities

The Mission and Vision are expanded upon through the identification of Overarching Challenges and Focus Areas, which essentially provide the foundation for the PRARP's requests for applications (Program Announcements). These are captured in the Strategic Direction section of this document.

FUNDING HISTORY AND NUMBER OF AWARDS

The program received a total of $108M in funding from FY11 through FY18. During this period, 112 projects were funded by the PRARP. Awards (21) for FY18 will be made by no later than September 30, 2019. The FY19 PRARP appropriation is $15M.

RESEARCH PORTFOLIO OVERVIEW AND ACCOMPLISHMENTS BY FY19 PRARP OVERARCHING CHALLENGE

For a full description of each Overarching Challenge, please see the Strategic Direction section of this document.

Diagnostics and Prognostics: Research funded by the PRARP produced novel proteomic investigations leading to the development of potential diagnostics and prognostics. Nanobodies, for example, are small antibody fragments with the ability to recognize a wider variety of substrates than are recognized by antibodies. These characteristics make them interesting candidates for detecting plaques or tangles, or their smaller precursors. Nanobodies can target amyloid and tau, the respective plaque and tangle forming proteins commonly seen in AD. Subsequent findings showed that nanobodies can also target other proteins such as alpha synuclein (A-Syn) and TDP-43. This highlights the utility of these molecules for use across AD/ADRD. (A-Syn is commonly seen in Lewy body dementia, and TDP-43 is associated with multiple types of dementia, but notably frontotemporal dementia). Recently, these basic research findings were extended into a patient cohort with PRARP funding that showed that nanobodies can discern individuals with a history of TBI exposure from individuals with no history of TBI. The nanobodies showed high specificity using easily obtainable blood samples. More specifically, the research showed differences in the levels of amyloid, tau, TDP-43, and A-Syn in the TBI cohort.[10] It is important to note that these injuries occurred more than 25 years before the testing, demonstrating the potential of these nanobodies to track putative markers of TBI and AD/ADRD over long periods of time. Nanobodies represent one of many alternatives to conventional antibodies the PRARP is exploring.

Paucity of Research Resources: Multiple animal models of TBI have shown a key relationship between TBI and neuroinflammation. Although mechanistic details are incomplete, the developed research resources and findings can be used by other researchers to extend knowledge of the interrelationship between TBI and AD/ADRD. PRARP-funded research showed a potential role for amyloid in regulating TBI-neuroinflammation.[11] Preliminary evidence indicates that amyloid may be responsible for an initially impaired immune response to injury, as animals overexpressing amyloid subsequently revealed a chronic and persistent neuroinflammatory response months later compared to controls. This chronic response appears to delay healing. One plausible mechanism is that amyloid initially impairs the brain's innate immune response regulated by microglia and perhaps the peripheral monocytes that cross the blood-brain barrier after injury. It is possible that these cells interact with amyloid to modulate their response at all stages after injury. This finding and others like it have led to a dramatic increase in interest in understanding how the immune response is altered after TBI. The research is beginning to translate into humans and extends our understanding of more subtle elements such as how the vascular (blood-brain barrier) disruptions lead to an immune cascade and subsequent neuroinflammatory response. The PRARP is also focused on the long-term consequences of these vascular alterations and continues to support newer animal models for TBI so that a complete understanding of the long-term consequences of these injuries can be appreciated. It is, however, important to note that the prudent use of larger animals is necessary. As basic findings with smaller animals become clearer, careful confirmation will likely be required in a larger animal model before human research can safely begin. Experiments in animals larger than rodents will expand our knowledge of neuroinflammation and vascular insult and help characterize how white matter injuries contribute to TBI.

Epidemiology: The PRARP funded a large number of prospective and epidemiological human studies looking at the interplay between TBI and AD/ADRD. A recently completed study of retired Veterans revealed a number of findings that showed the complexity of the TBI-AD/ADRD connection. The study revealed that "remote" TBI is common in older Veterans with a predominance of mild injuries. That is, while many of these injuries occurred during their military Service, some occurred before or after their Service. These individuals displayed worsening executive function and processing speed even decades after their injuries. Furthermore, the prevalence of comorbid psychiatric conditions (depression, anxiety, post-traumatic stress disorder, bipolar disorder, and substance abuse) all increased as a function of TBI severity. Another study funded by the PRARP suggests that depression in women is a risk factor for dementia, but this population also had a high prevalence of TBI.[12] More work is needed to fully understand how these comorbidities impact risk of TBI for AD/ADRD.[4] Perhaps, as the interaction of comorbidities is better understood, it may be possible to identify them as independent risk factors for dementia.

Paucity of Clinical Studies: The PRARP also funded a number of clinical studies to understand and quantify the relationship between TBI and AD/ADRD, including a large, multi-institutional study of Vietnam-era Veterans using the Alzheimer's Disease Neuroimaging Initiative (ADNI) model. The DoD ADNI effort standardizes a number of different nuclear, magnetic resonance imaging (MRI), and cerebrospinal fluid-based biomarkers across more than a dozen research sites. Vietnam-era Veterans with and without mild cognitive impairment (MCI) are enrolled in Phases I and II of the multi-year study. Given the complexity of the study, analyses of available data are still in progress and may require significant further investigation to fully understand the richness of the cohort and the generated data.

In the interest of addressing the challenges of current human imaging studies, the PRARP funded additional studies that are developing next-generation imaging biomarkers that promise to have increased sensitivity and specificity for AD/ADRD. The PRARP is building a robust portfolio of Positron Emission Tomography (PET) biomarkers that are currently being tested in humans. PET biomarkers are used in PET scans and promise a minimally invasive way to understand protein deposition after TBI. When used in conjunction with MRI, these markers provide a complete "picture" of the brain's anatomy. This can be used to track changes due to TBI over time. PRARP investments continue to look at novel and advanced MRI techniques, such as functional MRI imaging, which can be used to look at how networks in the brain are altered by cognitive impairments.

Quality of Life and Caregiving: Individuals living with cognitive impairments have diverse needs. These cognitive impairments affect not only the individual, but their caregivers, families and other loved ones as well. The PRARP is funding work to understand what can be done to alleviate or stabilize cognitive impairments as a means of increasing quality of life for patients and caregivers (thus reducing caregiver burden, bad behaviors, and less reliance on emergency room visits) or for long-term care.

The PRARP is therefore growing a large portfolio of nonpharmacological interventions for cognitive impairments. This includes nonpharmacological interventions for caregivers, which are particularly needed as there are few tools available to reduce their stress and help them manage the symptoms of a loved one with a memory impairment. Some of the research in this area focuses on the concept of "aging in place." This is the concept that lifestyle adjustments can maintain or improve overall mental and physical health, which is particularly important for our Veterans, as there is a need to promote a continuum of care once the Service member leaves active duty and begins to age. As behavioral symptoms of advancing dementia closely resemble symptoms of both acute and chronic TBI, PRARP research also benefits the general population despite the program's primary focus on the effects of TBI and neurodegenerative dementia in Service members and Veterans.

One example of PRARP-funded research in this space examined the role of exercise in alleviating or stabilizing memory impairments. Exercise has long been proposed as a component of aging in place, yet many questions about the role of exercise in healthy aging remain unanswered. One of the key challenges in understanding how exercise can benefit aging individuals is characterizing the types of exercise that are most beneficial to aging individuals, especially those showing signs of memory impairments. One PRARP-funded study compared aerobic versus balance/flexibility exercises in Veterans diagnosed with cognitive impairments. The study showed evidence that aerobic exercise resulted in positive cognitive outcomes, but there were benefits to the balance/flexibility training as well. The balance/flexibility training arm of the study had better participant retention and resulted in improved overall physical health of Veterans with MCI. While interventions such as exercise, memory notebooks, and mindfulness therapies are showing efficacy, biomarkers to objectively assess these therapies represent a gap toward translation.

The PRARP also funds research to understand how activities of daily living (ADLs) are impacted by cognitive impairments. In addition to looking at individuals with cognitive impairments, some of this research explores what caregivers do most efficiently to help their loved ones. Other projects assess how living with memory impairments can impact financial decisions and training opportunities for caregivers. Training for caregivers can help them cope with stressful situations and behaviors and build resilience. One challenge is accessibility to the training for individuals in remote areas or with limited travel options. Strategies to remotely disseminate this training have the potential to provide access to caregivers who may have challenges in receiving traditional, in-class training and allow caregivers to learn at their own pace. The PRARP is funding a number of internet-based interventions to address the above concerns. In conclusion, the PRARP seeks and continues to fund projects that increase compassion for caregivers, as well as the vitality of all individuals living with cognitive impairment.

RESEARCH FUNDING LANDSCAPE

Dementia is a domestically and internationally recognized public health concern. In addition to the cost of care for individuals living with AD/ADRD, the emotional toll on the individual and their family is staggering. Research funding is predominantly provided by the NIH. Other federal partners, such as the VA, provide additional funding, as shown in **Table 1**.

	NIH	DoD	VA
FY11	$448M	$15M	$12.4M
FY12	$503M	$12M	$13.4M
FY13	$504M	$12M	$11.6M
FY14	$562M	$12M	$11.2M
FY15	$631M	$12M	$13.7M
FY16	$986M	$15M	$12.8M
FY17	$1423M	$15M	$11.8M
FY18	$1915M	$15M	$11.8M

Table 1. NIH, DoD, and VA dementia funding by FY.

In 2011, Congress established the National Alzheimer's Project Act, which is intended to create and maintain an integrated national plan to overcome AD via federal funding (e.g., the CDC, Administration on Aging [AoA], and Centers for Medicare and Medicaid Services) and non-federal participation (e.g., state health departments, academicians, and caregivers). The plan requires regular compilation of information and coordination of AD research and services across all federal agencies. The PRARP regularly provides data and updates to the NIH and Department of Health and Human Services (HHS) as part of the plan, including descriptions of all PRARP research projects. The International Alzheimer's Disease Research Portfolio (IADRP) uses a common ontology and contains data provided by more than 25 national and international funders. **Table 2** provides a snapshot of research funding using the IADRP ontology. While the PRARP has a similar proportion of

	NIH (N=6368 Projects*)	PRARP (N=70 Projects)	All IADRP Partners* (Non-DoD) (N=8202 Projects*)
Category A. Molecular Pathogenesis and Physiology of Alzheimer's Disease	3342 (52.5%)	20 (28.6%)	4218 (51.4%)
Category B. Diagnosis, Assessment, and Disease Monitoring	1314 (20.6%)	22 (31.4%)	1715 (20.9%)
Category C. Translational Research and Clinical Interventions	1006 (15.8%)	4 (5.7%)	1401 (17.1%)
Category D. Population Studies (Epidemiology)	408 (6.4%)	7 (10.0%)	431 (5.2%)
Category E. Care, Support, and Health Economics of Alzheimer's Disease	298 (4.7%)	17 (24.3%)	437 (5.3%)

Table 2. Comparison of NIH and PRARP Funding Using IADRP Data, FY12-FY16.

*Data are only for categories used by the DoD PRARP. * = Roughly 5% of projects may have been categorized twice.*

projects compared to the NIH in each category, the PRARP has a higher proportion of research in Category E: Care, Support, and Health Economics of Alzheimer's Disease. It is important to note that, in addition to the NIH, other agencies within the HHS (e.g., the AoA) fund such research, so the proportional difference may be smaller when all of HHS is considered.

The PRARP also partners with the NIH by centralizing data from human prospective TBI studies into the Federal Interagency Traumatic Brain Injury Registry (FITBIR). The FITBIR is a central repository for phenotypic, genomic, and imaging data from TBI studies that is accessible as a web-based application to securely contribute and access shared data. FITBIR is a trans NIN-DoD partnership.

PRARP Scientific Landscape Surveys: The PRARP surveys the academic community each year to better understand the needs and perceived gaps of the PRARP research community. The PRARP research community is defined as individuals registered via eBRAP.org who note interest in the program. The survey is voluntary and open to the general public so long as they register in eBRAP.org. The PRARP Programmatic Panel uses the data as a tool to assist in the development of funding opportunities to meet the needs of Service members, Veterans and the general public. The survey focuses on future design of funding opportunities, translational research hurdles, and how some of the Overarching Challenges can be addressed. Questions include:

Question 1: What would be an ideal granting mechanism to accelerate research in TBI-related AD/ ADRD (e.g., Translational Research or New Investigator targeted)?

A total of 138 responses were recorded for this question. Almost half of the respondents (N=54) felt that the solicitations the program offered for FY18 met the needs of the research community. About 25% (N=39) of respondents indicated an interest in translational research. They defined translational research as having preclinical and/or risk factor foci. An equally robust response (N=35) highlighted the need to continue to bring New Investigators into the field, citing the need for fresh thoughts into both TBI and AD/ADRD. Less emphasis was placed on research partnerships and high-risk/high-reward initiatives (N=9 and 6, respectively). Trends among those who thought research partnerships were desirable indicated a need for multi-partnered awards that could support infrastructure and develop research resources. Those who highlighted a desire for a high-risk/high-reward mechanism thought that an emphasis on basic research would strengthen the PRARP's research pipeline.

Question 2: What are some of the basic or translational research hurdles needed to understand how TBI becomes AD/ADRD?

A total of 129 responses were recorded for this question. Three key areas identified. Many researchers identified a need for better animal and cellular models (N=42). Respondents noted that not enough researchers are transitioning their models from TBI into AD/ADRD or vice versa. Better models would empower cross-comparisons between researchers, thereby accelerating novel discoveries. Some researchers also highlighted a need for a specific TBI model for AD/ADRD. Other significant gaps included a need for more novel research into the pathology of AD/ADRD after TBI (N=45). Specific input was received regarding inflammation, amyloid, tau, novel proteinopathies, vascular biology, roles of specific cell types, and elimination/accumulation of proteins, genetics, and epigenetics. The need for continued support of longitudinal studies was also identified (N=23). Questions remain about how to address slow disease progression, how symptoms lead to disease, and the role of imaging and other diagnostics. Additionally, the research community identified a need for more study endpoints. Interest was also expressed for specifically studying how TBI works with other unknown risk factors (N=11). Respondents noted that understanding these risk factors may lead to disease modification or prevention. They also noted that diverse populations need to be studied further, resiliency factors are understudied, and the accuracy of patient-level TBI exposure data is questionable despite recent strides. Other responses included support for data/tissue registries (N=6), partnership with the Food and Drug Administration (N=1), and the need for investigators from outside TBI or AD/ADRD (N=1).

Question 3: How do we better image or diagnose AD/ADRD in living individuals years after TBI? What would a roadmap for this look like?

A total of 109 responses were recorded for this question. Responses to this question robustly supported focusing on longitudinal studies (N=80). Support for ADNI infrastructure was noted, since the ADNI already has a large research infrastructure. Investigators noted that nuclear imaging (e.g., PET scans); advanced MRI techniques (diffusion tensor imaging; functional and metabolomic imaging) were all needed. Confirmation via autopsy and longitudinal scans were also mentioned. Some respondents also noted that a brute force approach may not be efficient or feasible. They noted that an ideal strategy needs to take advantage of the state of the art as well as be multi-tiered, so that the study is robust enough to characterize patient sub-populations most at risk. A focus on surveillance was also suggested (N=25), with an overall strategy of "cheaper" diagnostic testing (smell, salivary, and ocular) and online longitudinal surveys. This could be done in older individuals, as the need for routine cognitive screening is becoming more apparent. A small number of respondents (N=4) also indicated that more databases are needed, mainly in order to facilitate new and novel ways to characterize TBI exposure and cognitive decline.

STRATEGIC DIRECTION

Since the Program's inception in 2011, the PRARP has worked with its Programmatic Panel to fund research that would benefit both the military and civilian communities at large. The PRARP Programmatic Panel continually assesses the state of the science, available technologies, and identified capital research projects that impact the PRARP's Vision and Mission. These efforts have driven the development of the PRARP Overarching Challenges, which represent the major gaps that need to be addressed to achieve the PRARP's Vision and Mission. In FY11, the Overarching Challenges were limited to Paucity of Clinical Studies, Diagnostics, and Quality of Life. Over time, the program evolved to add gaps in Research Resources, Caregiver Burden/Support, and Epidemiology. The Diagnostics category was also expanded to include new technologies, tests, biomarkers, and devices.

The PRARP continues to balance its funding priorities (**Figure 2**) based on research outcomes in TBI and AD/ADRD. The PRARP also considers the level of investment in each Overarching Challenge as part of the process for future scientific planning. The PRARP further segments the technical aspects of the Overarching Challenges into Focus Areas that are used to target specific types of research to those funding mechanisms that are most likely to achieve success. These Focus Areas are also intended to help investigators think about the types of science needed to address the program's Overarching Challenges.

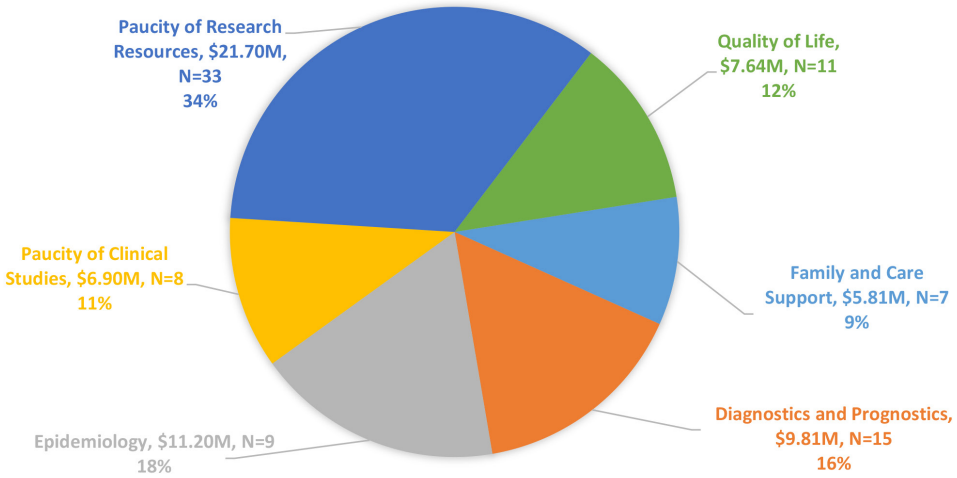

Figure 2: PRARP Portfolio balance by Overarching Challenge for FY14-FY18

The PRARP Programmatic Panel revisits the definition of each Overarching Challenge and Focus Area annually. For FY19, the PRARP's Overarching Challenges are as follows:

- **Paucity of Research Resources:** The paucity of research resources and models to examine the interrelationship between TBI and subsequent AD/ADRD for the military, Veteran, and civilian communities and to translate these findings.
- **Paucity of Clinical Studies:** The paucity of clinical studies to examine the interrelationship between TBI and subsequent AD/ADRD for the military, Veteran, and civilian communities.
- **Diagnostics and Prognostics:** The need for technologies, tests, surveys, questionnaires, devices, biomarkers, or analyses to detect TBI sequelae for AD/ADRD utilizing new and/or pre-existing datasets.
- **Epidemiology:** The paucity of epidemiological research to examine the interrelationship between TBI, risk and resiliency factors, and subsequent AD/ADRD for the military, Veteran, and civilian communities.
- **Quality of Life:** The need for technologies, assessments, interventions, or devices to benefit individuals living with the common symptoms of TBI and AD/ADRD.
- **Family and Care Support:** The need for technologies, assessments, interventions, or devices that enhance the lives of those providing care and families of individuals living with the common symptoms of TBI and AD/ADRD.

For FY19, the PRARP's Focus Areas are as follows:

- **Mechanisms of Pathogenesis:** Identification of contributing mechanisms to include circuit dysfunction associated with TBI and subsequent AD/ADRD.

- **Biomarkers:** Development of methods to diagnose, prognose, or characterize neurological changes or risk/resiliency factors associated with TBI and subsequent AD/ADRD.
- **Quality of Life:** Research intended to alleviate, stabilize, or characterize the symptoms, or deficits, common to TBI and AD/ADRD.
- **Family and Caregiver Support:** Research intended to reduce the burden of care on the caregivers or families of individuals living with the common symptoms or deficits of TBI and AD/ADRD.
- **Epidemiology:** Utilize new and existing studies and datasets to examine the relationships between risk and resiliency factors for TBI and subsequent AD/ADRD.
- **Novel Target Identification:** Basic research (non-human) directly leading to identification of new targets for the development of existing or new investigational medicines, drugs, or agents for TBI and subsequent AD/ADRD.
- **Nonpharmacological Interventions and Devices:** Research into non-medication-based interventions and devices to improve quality of life or caregiving for those living with the common symptoms of TBI and AD/ADRD.
- **Bioinformatics:** Tools, including machine learning, to access, annotate, curate, store, and visualize large existing or novel datasets, e.g., multimodal magnetic resonance imaging (MRI), other imaging techniques, surveys, questionnaires, and diagnostics for TBI and subsequent AD/ADRD.

Given the challenges associated with the state of the science in TBI and AD/ADRD research, the PRARP research portfolio is targeted toward near- and medium-term goals. Ideally, the ultimate long-term goal is to prevent and/or effectively treat TBI-AD/ADRD. As there are no effective AD/ADRD treatments, it is currently difficult to plan for long-term goals. Data from epidemiological and longitudinal studies may provide insights into unknown risk and resiliency factors for TBI-associated dementia. As these risk factors are uncovered and rigorously validated, they may provide new insights into the biological processes that link TBI with dementia and AD/ADRD. Subsequent studies in both humans and animals will be required to fully characterize these risk and resiliency factors and identify how they exert their effects within the context of TBI pathology. This knowledge could ultimately be used to develop new biomarkers and study endpoints for clinical interventions. However, at this time, much remains to be discovered before the program can embark in studies such as pharmacological interventions. Efficacious interventions such as these would ultimately be the long-term goal of the program.

The technology revolution also helped shape the PRARP's near- to medium-term goals. Given the large increases in computing power and social media presence, new technologies that empower both individuals living with TBI and their caregivers are a research priority. The PRARP is funding development of new technologies in these areas to ameliorate the common symptoms of TBI and dementia. Symptoms such as cognitive impairment and challenges such as daily care may be greatly impacted by these new technologies. The PRARP will continue to invest in these areas in an effort to make newer technologies available to both Veterans and the afflicted general public.

INVESTMENT STRATEGY

NEAR TERM

The PRARP investment strategy began at the PRARP's inception. **Table 3** shows the overall investment strategy for the PRARP over the past 5 years of PRARP funding. While the definitions for each gap evolved over the years, the gaps themselves represent key areas of research that still require further investigation. The gaps are equivalent to the PRARP's Overarching Challenges. In order to solicit the right types of research to address these gaps, the funding mechanisms/Program Announcements have changed. In FY15, research was solicited through three mechanisms. These mechanisms called out the need for more basic research, an emphasis on quality of life, and support of continued investments into longitudinal studies via the Military Risk Factor Research Award (MRFA). In FY16, a pivotal year for the program, the funding mechanisms evolved significantly toward translational research. The MRFA was shifted from its prospective focus to an epidemiological focus. In place of the MRFA and its epidemiology-based derivative, a translational focus began to emerge as the Translational Research Partnership Award (TRPA). FY16 also the first year the PRARP addressed the need for related dementia research, AD/ADRD. FY17 saw the continued emphasis on translation, with the TRPA reoffered as the Research Partnership Award (RPA). The minor revisions between the TRPA and RPA widened the pool of applicants who could apply to the program while retaining a general focus on multi-partnered and impact-based research. FY17 also represented the first year a New Investigator Award was offered. Overall, these changes were made to reinvigorate the research pipeline ahead of large patient-centered cohort studies.

The PRARP is committed to a robust, patient-centered approach to TBI and AD/ADRD. FY19 encouraged applications not only to think about the research impact, but also potential research innovations. While the number of mechanisms decreased, a commitment

	FY15	FY16	FY17	FY18	FY19
Gaps/Priorities	Paucity of Clinical Studies; Diagnostics; Research Resources; Quality of Life; Caregiver Support	Paucity of Clinical Studies; Diagnostics; Research Resources; Quality of Life; Caregiver Support; Epidemiology	Paucity of Clinical Studies; Diagnostics; Research Resources; Quality of Life; Caregiver Support; Epidemiology	Paucity of Clinical Studies; Diagnostics; Research Resources; Quality of Life; Caregiver Support; Epidemiology	Paucity of Clinical Studies; Diagnostics and Prognostics; Research Resources; Quality of Life; Family and Care Support; Epidemiology
Funding Opportunities	Convergence Science Research Award Military Risk Factor Research Award Quality of Life Research Award	Convergence Science Research Award Epidemiology of Military Risk Factors Research Award Quality of Life Research Award Translational Research Partnership Award	Convergence Science Research Award Quality of Life Research Award Research Partnership Award New Investigator Award	Convergence Science Research Award Quality of Life Research Award Research Partnership Award New Investigator Award	Convergence Science Research Award Innovations in Care and Support Award Research Partnership Award

Table 3. PRARP Funding Opportunities, FY15-FY19

to new investigators remained, as the newer innovation/impact-based mechanisms included a funding level for young researchers. Perhaps the most monumental change for FY19 was revision of the Quality of Life Research Award (QLRA), which was replaced by the Innovations in Care and Support Award (InCASA). The InCASA encourages innovative research that improves the quality of life and care for individuals living with the common symptoms of TBI and/or AD/ADRD and/or their families and care providers. It also challenges researchers to propose work that should challenge existing research paradigms or exhibit high levels of creativity.

MEDIUM TO LONG TERM

The medium to long-term outlook involves developing the tools and knowledge to support cutting-edge clinical trials in preventing dementia subsequent to TBI. The PRARP is funding several avenues of research to accomplish this. The PRARP will continue to restock its basic and translational research pipelines through its current mechanisms. In addition, the PRARP funds caregiving and quality of life research, two important topic areas that allow the PRARP to (1) understand the symptoms of TBI and dementia, (2) understand what can be done to alleviate or stabilize symptoms, and (3) provide information on what types of new study endpoints can be developed for cognitive or executive functioning deficits. These new study endpoints present a unique nexus between symptom management and potential diagnostics that develop through basic research. It is hoped that researchers that characterize symptomatology will ultimately work with individuals interested in diagnostics. New survey tools or innovative study designs will help us to better quantitatively understand the populations living with cognitive and executive functioning impairments and to better determine how to more efficiently help these individuals live as full a life as possible. The PRARP's RPA mechanism provides a key toward bringing individuals interested in these separate areas together in research with richer outcomes. When successful, larger longitudinal studies can begin that will stretch out into interventional clinical trials with next-generation quantitative biomarkers. While the PRARP does not support pharmacological interventions, the body of evidence gathered from our holistic approach will support and inform clinical trials that consider all aspects of patient care, including their caregivers.

MEASURING PROGRESS

NEAR TERM

The PRARP will monitor the response and number of funded applications for each of its Overarching Challenges. It will monitor the progress of awardees according to their statement of work, track a broad range of research outcomes (e.g., publications, presentations, patents), and share this information with the PRARP Programmatic Panel. These tools will be used to adjust the PRARP's portfolio direction and investment strategy on a yearly basis.

MEDIUM TO LONG TERM

The PRARP will continue to closely monitor the TBI and AD/ADRD research landscapes, continue to capture key research accomplishments funded by the PRARP (e.g., patents and publications), and use this data to measure progress toward addressing its strategic goals and the program's overall vision and mission. The PRARP will also continue working to be cognizant of other funded

research outcomes and initiatives in both AD/ADRD and TBI that may drive the PRARP's overall investment strategy. Based on research outcomes, both within and outside the PRARP, next-generation clinical trials will be developed that take advantage of new diagnostics and ways to measure recovery from cognitive decline.

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