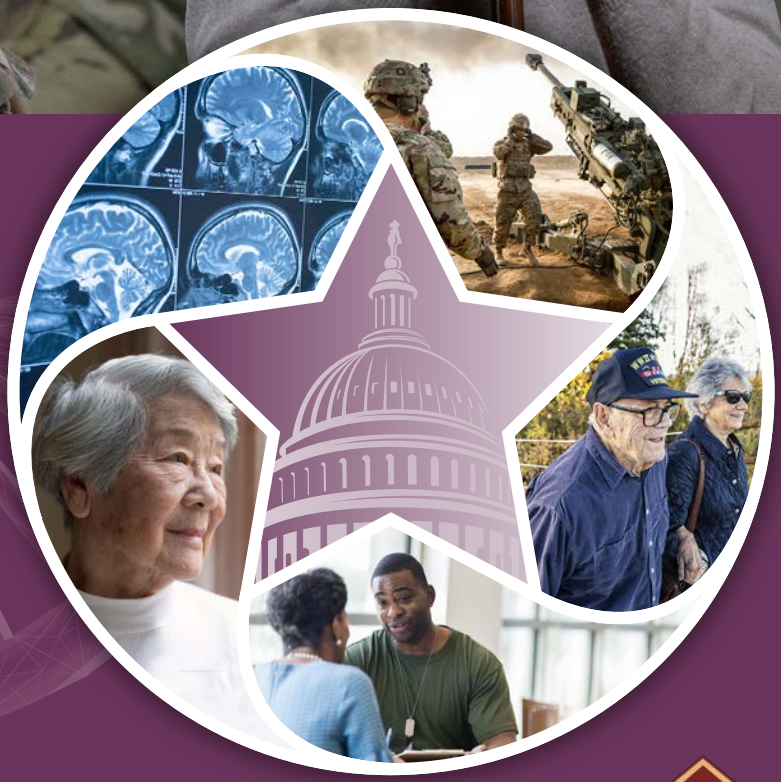
Peer Reviewed Alzheimer's Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense



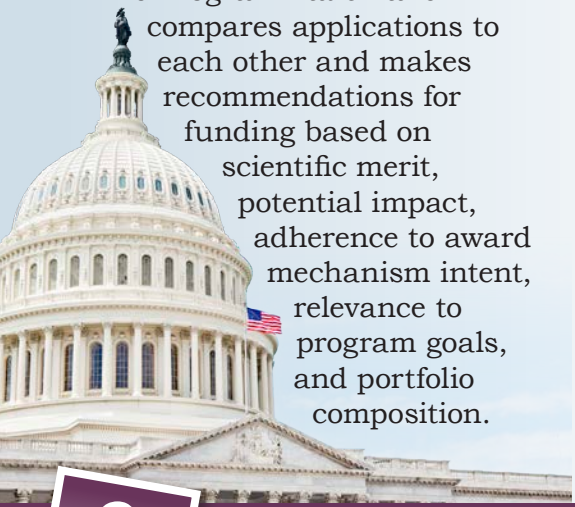
U.S. Army Medical Research and Development Command

Congressionally Directed Medical Research Programs

The Congressionally Directed Medical Research Programs (CDMRP) were created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a Congressional appropriation of funds for breast cancer research. Since then, the CDMRP has grown to encompass over 30 targeted programs and has been responsible for managing over $15 billion since its inception through fiscal year 2020 (FY20).

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for evaluating applications, with both tiers involving dynamic interaction between scientists and disease survivors (consumers). The first evaluation tier is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to award mechanism intent, relevance to program goals, and portfolio composition.



Peer Reviewed Alzheimer's Research Program

VISION: To address the long-term consequences of traumatic brain injury as they pertain to Alzheimer's disease and Alzheimer's disease related dementias

MISSION: Devoted to (1) understanding the association between traumatic brain injury and Alzheimer's disease/Alzheimer's disease related dementias, and (2) reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities

ABOUT THE PROGRAM

Military personnel and other individuals living with Alzheimer's disease (AD) face symptoms such as memory loss, aggression, post-traumatic stress disorder and depression. These symptoms impact individuals living with AD subsequent to Traumatic Brain Injury (TBI), as well as their loved ones and caregivers. The Peer Reviewed Alzheimer's Research Program (PRARP) was initiated in fiscal year 2011 (FY11) to address the long-term consequences of TBI as they pertain to AD in both the civilian and military communities. In FY16, the program expanded to include AD-related dementia (ADRD) research pertaining to TBI. Appropriations for the PRARP from FY11 through FY20 totaled $138 million (M).

FACTS ABOUT TBI AND AD

- Between 2000 and 2018, deaths from AD increased 146%. One in three seniors die with AD or another dementia.[1]
- It is estimated that AD and other dementias will cost the nation $1.1 trillion by 2050.[1]
- While there is likely more than one cause for AD, evidence suggests that closed head injuries may contribute to the number of AD cases.[2]
- TBI is a risk factor for cognitive decline in older adults and is associated with an earlier age of onset of symptoms.[2]
- The Defense and Veterans Brain Injury Center reported more than 400,000 cases of TBI in the U.S. military since 2000.[3]
- In 2014 alone, there were 2.87 million TBI-related emergency department visits, hospitalizations, and deaths in the United States.[4]

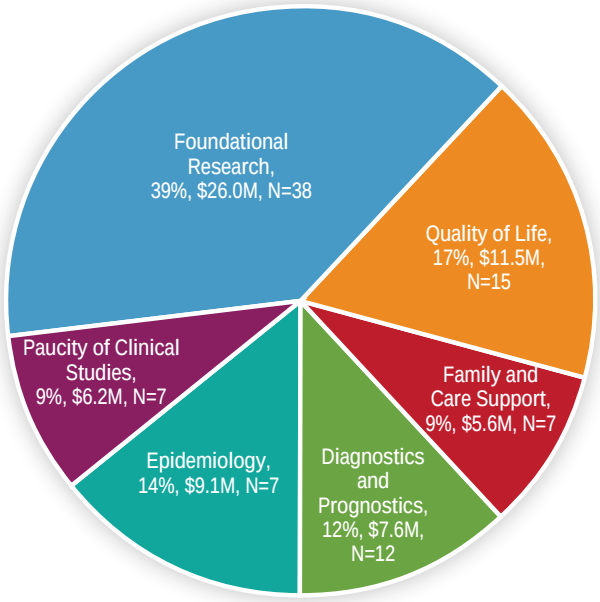
[1] https://www.alz.org/media/Documents/alzheimers-facts-and-figures-infographic.pdf
[2] https://www.alz.org/dementia/traumatic-brain-injury-head-trauma-symptoms.asp
[3] https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi
[4] https://www.cdc.gov/traumaticbraininjury/get_the_facts.html

OVERARCHING CHALLENGES

Each year, the PRARP releases Overarching Challenges that represent long-standing research goals for the program and address the long-term consequences of TBI-related dementias for the military, Veteran, and civilian communities.

- **Foundational Research**: Research to examine the interrelationship between TBI and subsequent AD/ADRD and to translate these findings.
- **Paucity of Clinical Studies**: Clinical studies to examine the interrelationship between TBI and subsequent AD/ADRD.
- **Diagnostics and Prognostics**: Technologies, tests, surveys, questionnaires, devices, biomarkers, or analyses to detect TBI sequelae for AD/ADRD utilizing new and/or pre-existing datasets.
- **Epidemiology**: Epidemiological research to examine the interrelationship between TBI, risk and resiliency factors, and subsequent AD/ADRD.
- **Quality of Life**: Technologies, assessments, interventions, or devices to benefit individuals living with the common symptoms of TBI and AD/ADRD.

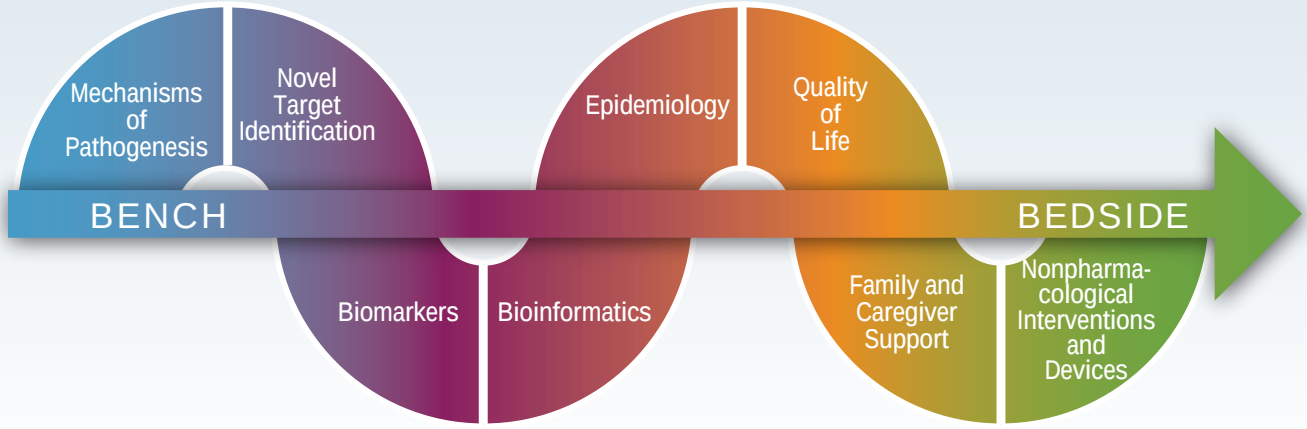
FY15-FY19 PRARP Research Investment by Overarching Challenge



- **Family and Care Support**: 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/or AD/ADRD.

FOCUS AREAS

In conjunction with the broadly focused Overarching Challenges, the PRARP uses Focus Areas, which are more scientifically driven and narrower in research focus, to frame the Program Announcement of each funding opportunity. The Focus Areas cover the entire research spectrum from bench to bedside.

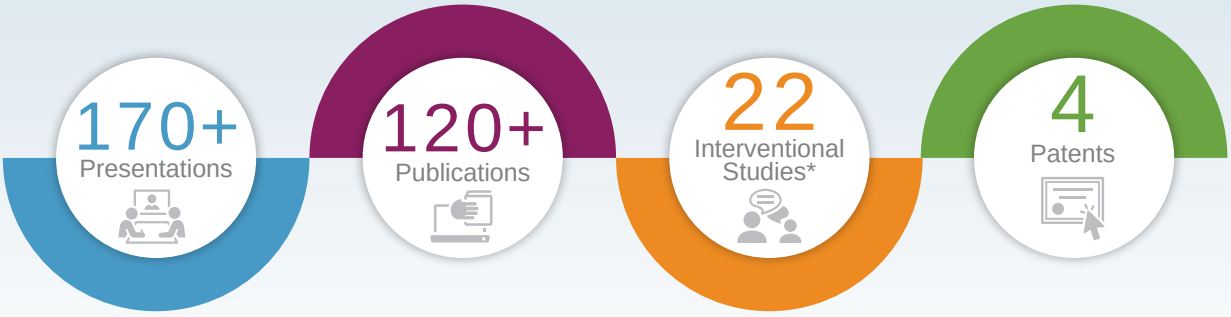


PRARP Portfolio Investment Strategy

In conjunction with the Programmatic Panel, the PRARP continually assesses the state of the science to update the program's research gaps and priorities to achieve the PRARP's Vision and Mission. When the program began in FY11, the PRARP aimed to address research gaps in the paucity of clinical studies, diagnostics, and quality of life. Over time, the program evolved to address research gaps in foundational research, caregiver burden/support, prognostics, and epidemiology. The program continually adapts and modifies its funding opportunities to fill research gaps and priorities identified by the programmatic panel.

	FY14	FY15	FY16	FY17	FY18	FY19
Overarching Challenges	• Paucity of Clinical Studies • Diagnostics • Foundational Research • Quality of Life • Caregiver Support	• Paucity of Clinical Studies • Diagnostics • Foundational Research • Quality of Life • Caregiver Support	• Paucity of Clinical Studies • Diagnostics • Foundational Research • Quality of Life • Caregiver Support • Epidemiology	• Paucity of Clinical Studies • Diagnostics • Foundational Research • Quality of Life • Caregiver Support • Epidemiology	• Paucity of Clinical Studies • Diagnostics • Foundational Research • Quality of Life • Caregiver Support • Epidemiology	• Paucity of Clinical Studies • Diagnostics/ Prognostics • Foundational Research • Quality of Life • Family and Care Support • Epidemiology
Funding Opportunities Developed	• Convergence Science Research Award • Military Risk Factor Research Award • Quality of Life Research Award	• Convergence Science Research Award • Military Risk Factor Research Award • Quality of Life Research Award	• Convergence Science Research Award • Epidemiology od 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 • Innovation in Care and Support Award • Research Partnership Award
	13 awards $12M	16 awards $12M	15 awards $15M	17 awards $15M	21 awards $15M	17 awards $15M

Since FY14, the PRARP has funded over 120 projects that have produced:



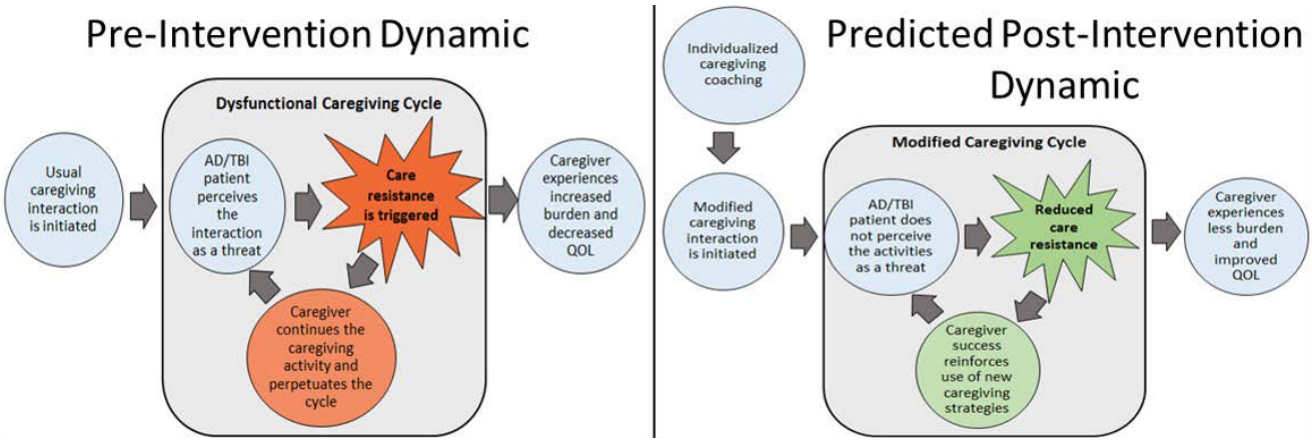
*Includes caregiver, cognitive, and quality of life intervention studies.

Improving Quality of Life Through Training to Reduce Care-Resistant Behaviors

David Geldmacher, M.D., University of Alabama at Birmingham

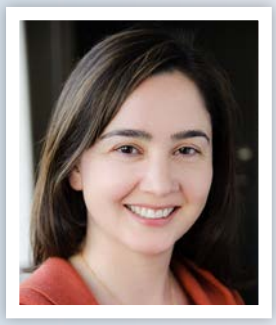
Caring for individuals who live with a neurological impairment such as TBI or AD/ADRD can be challenging. Caregivers must show compassion for individuals with a variety of symptoms that can include memory issues, poor judgement, and depression. Quite often, a caregiver is faced with the challenge of helping an individual eat, get dressed, or shower. That individual may refuse their help and may even not be able to complete that activity. This leads to a declining state of health for not only the person with the impairment, but the caregiver as well. Tools and strategies that enable a caregiver to deal with these significant challenges are truly needed.

Dr. David Geldmacher developed a strategy that prepares caregivers for encounters with care-resistant behaviors. Dr. Geldmacher's approach involved six weekly online coaching sessions conducted by a nurse practitioner. These helped participants set goals for improving how they interact with their family member. The sessions were tailored to individual needs since the personal history of the person affected by the neurological impairments was a factor in the overall intervention. The coaching involved role-playing and script development to guide the caregiver when confronted with a care challenge at home. Using the combination of education, role-playing, and custom-tailoring, the training has shown some success in a small cohort of participants funded by the PRARP; this study is currently ongoing.[5] While outcomes have thus far focused on individuals living with dementia, the study also tests this coaching approach for caregivers for those living with TBI.



Cognitive losses in people with AD or TBI may cause them to perceive caregiving activities as physical or psychological threats. This results in a dysfunctional cycle of resisting care that can increase caregiver burden and decrease quality of life in the family setting. This project coaches caregivers to use individualized strategies to change their approach to care activities, with the intent to trigger less care-resistant behavior. A successful intervention would result in reduced caregiver burden and improved quality of life for the family.

[5] Jablonski R, Winstead V, and Geldmacher D. 2019. Description of process and content of online dementia coaching for family caregivers of persons with dementia. Healthcare (Basel) 7(1):13. doi: 10.3390/healthcare7010013.



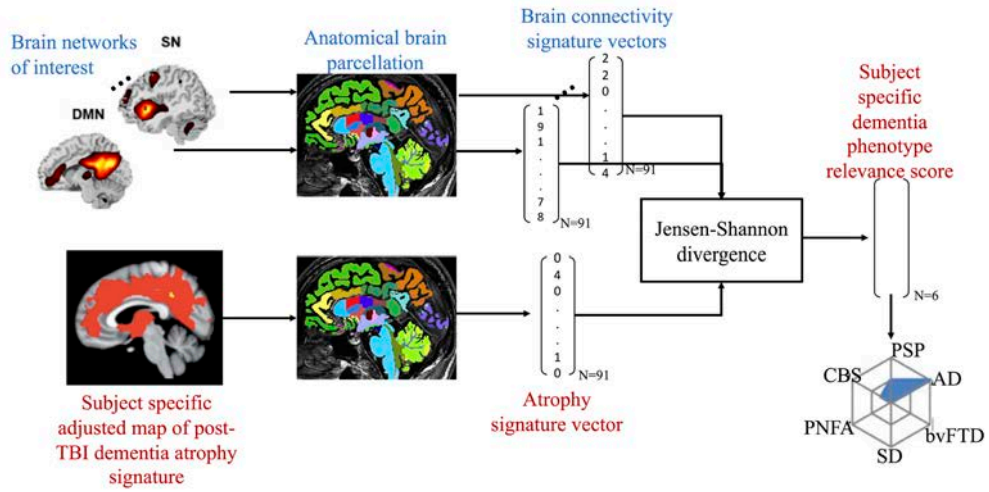
Understanding Long-Term TBI Consequences Using Artificial Intelligence

Duygu Tosun-Turgut, Ph.D., Northern California Institute for Research and Education; U.S. Department of Veterans Affairs (VA), San Francisco VA Health Care System; and University of California San Francisco

The long-term risks of head injuries are poorly understood, with some studies suggesting severe consequences and others no consequence at all. Two major challenges exist when trying to understand the long-term nature of TBIs. First is the lack of large and well-characterized datasets. Large datasets reveal how TBIs exert long-term effects across a population that is truly representative of individuals who experience a TBI. Injuries also need to be well characterized in terms of severity, age of injury, and the overall health of the individual at the time of injury. The second major challenge is finding high quality, objective data, like medical images or blood tests, that can tell us more about the biological nature of an individual TBI. When biology and data science are combined, a precise prognosis can be made within a given population.

These two challenges each separately represent daunting tasks, and combining them into a single study would seem to be impossible. Information technologies, such as artificial intelligence, now make bringing together and analyzing large, disparate types of data feasible. Dr. Duygu Tosun-Turgut is working with a large dataset that includes magnetic resonance imaging (MRI) data of more than 1.6 million Veterans with and without a TBI. As the MRI data from these Veterans is verified and processed, it will be used to test an algorithm that can predict 5+ year risk of developing post-TBI dementia. Dr. Tosun-Turgut anticipates building a database of 200,000 patient records with as many as 12,000 structural MRIs used to inform the algorithm. The algorithm may predict a dementia or another outcome based on MRI data years before signs of cognitive decline. Understanding TBI-dementia at its earliest stages may lead to improved study designs for future clinical trials.

Stratification of Network-Based Neurodegeneration Subtypes



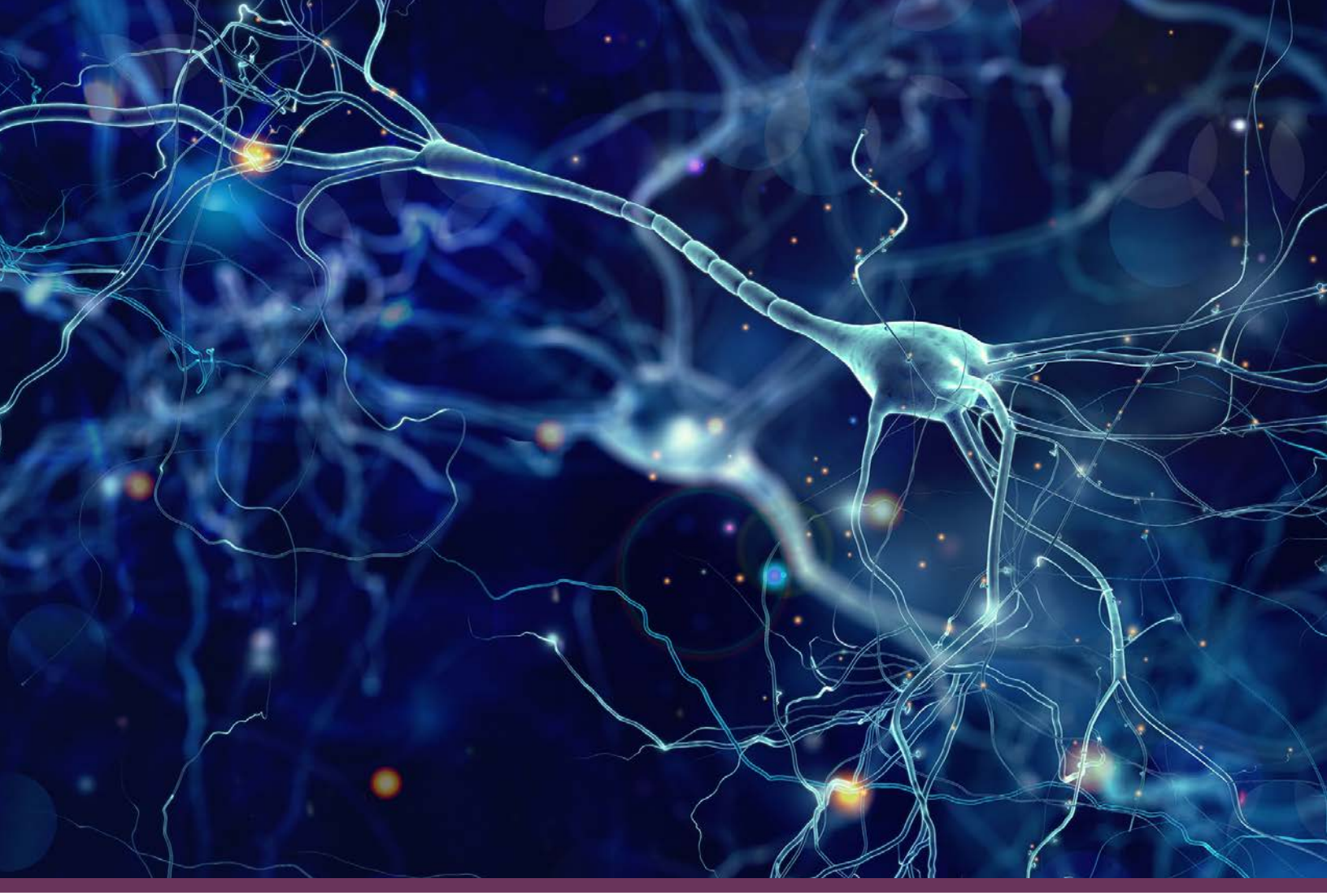
Subject stratification to network-based neurodegeneration subtypes of post TBI-dementia by quantifying topographic similarity (i.e., Jensen-Shannon divergence) between dementia atrophy signature and networks of interest implied in related neurodegenerative diseases including AD, behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), progressive nonfluent aphasia (PNFA), corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP).

Nancy Meserve, PRARP Consumer Reviewer

At age 62, with a family history of dementia in very old age, I learned that I carry the ApoE 4 allele. Even worse, I learned that conventional wisdom predicted my own diagnosis of Alzheimer's in 2020 at age 68! Not being able to see a path to my currently healthy 68-year-old self, I visualized my relatives' fates as my own. It took reading research, participating in a clinical trial, peer networking, and participating as a consumer reviewer in the PRARP to realize that failure gives rise to discoveries and creates novel targets to prevent, mitigate, and treat TBI and AD/ADRD.

As a former special educator who worked with parents to improve outcomes for students with TBI and other special needs, I used that roadmap for my own uncertain outcome: Find the best available resources and learn from others. I learned how to critically read ApoE 4 studies on prevention, resilience, and predictions of my future. I found peer support and warm friendships in ApoE4.info, an online community of Apoe4 carriers who cherish competing voices and strategies in the face of uncertainty. I lived the truth of my earlier observation of acute stress disorder in parents facing TBI in their children: When we validate acute distress after a life-altering medical diagnosis, we empower that person and their family, professionals, and the community to build a future with purpose and joy.

The ApoE4 Board of Directors has encouraged my role as a PRARP consumer reviewer, recognizing that populations beyond ApoE4 should be represented through my participation. I admit to worrying that I knew far too little to be a consumer reviewer! What I discovered instead was that, while my individual critique is valid, it is the dynamic discussion as a group that we ALL need to reach a strong consensus at the end of the PRARP process. I have left each panel energized by the passion of researchers, the respect for my contributions, and the confidence that we can achieve the mission of the PRARP for those we represent.



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