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TITLE: **A Novel Visually Graded CT Biomarker of Preinjury Brain Structure to Improve Prediction of Cognitive Decline After Mild Traumatic Brain Injury**

PRINCIPAL INVESTIGATOR: Raquel C. Gardner

CONTRACTING ORGANIZATION: San Francisco VA Medical Center / Northern California Institute for Research and Education

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14. ABSTRACT

Purpose: Mild traumatic brain injury (mTBI) is a signature injury of modern warfare and affects an estimated 42 million people worldwide each year. MTBI may lead to chronic cognitive problems (in memory and thinking ability) in up to half of patients. Even more concerning is that mTBI may lead to progressive cognitive decline and eventual Alzheimer's dementia (AD) and AD related disorders (ADRD), increasing risk by up to 3-fold. There are currently no practical tools to accurately predict who will suffer from chronic or progressive cognitive consequences of mTBI and who will recover uneventfully. Our project will directly address the overarching challenge of the need for biomarkers and tools to prognose cognitive decline and subsequent progression to AD/ADRD after mTBI.

Scope: We are conducting a 3-year project that will cost-efficiently harness existing data from more than 1,260 adults age 16 years and older presenting to 18 trauma centers across the U.S. within 24 hours of mTBI who participated in the DoD/NIH-funded Transforming Research And Clinical Knowledge in TBI (TRACK-TBI) study. Our aims are as follows: **Aim 1:** Use state-of-the-art modeling techniques to develop and validate a practical prediction tool to identify which patients will develop early cognitive decline 1 year after mTBI using only information that is easily and routinely collected in the acute trauma setting (e.g. demographics, military and prior TBI history, clinical and CT measures of TBI severity, lab values, and pre-existing medical/psychiatric comorbidities). **Aim 2:** Develop and validate a novel CT biomarker of pre-injury brain structure (PBS), the PBS score, and determine whether PBS score predicts cognitive function and early cognitive decline 1 year after mTBI.

Aim 3: Determine whether the PBS score improves the prediction tool developed in Aim 1 and then create a final, optimized, open-access, web-based, "clinical risk calculator" appropriate for use in an acute trauma setting to predict risk for cognitive decline 1 year after mTBI in individual patients.

Findings: We have made substantial progress on Aims 1 and 2. We studied 657 adults with acute mTBI (defined by Glasgow Coma Scale 13-15) and without baseline dementia who were enrolled in the multisite trauma center-based prospective TRACK-TBI Study. Participants underwent cognitive testing at 2-weeks, 6-months, and 1-year post-mTBI (Rey Auditory Verbal Learning Test, Trails A/B, Processing Speed Index, NIH-Toolbox Fluid Cognition Composite and Picture Vocabulary Test). Poor cognitive outcome was defined as cognitive impairment, cognitive decline, or both. Cognitive impairment was defined as having a score falling below the 9th percentile on age-specific cognitive norms on ≥2 two tests. Cognitive decline was defined as having a change score (defined as best 2-weeks or 6-months score minus the 1-year score) exceeding the 90% confidence interval of the reliable change index on ≥2 tests. T-tests and chi-square tests were used to assess univariate associations of demographic, socioeconomic, medical comorbidity, and injury-related factors with poor cognitive outcome. Missing outcome data was accounted for using propensity weighting. Mean age of patients was 41 years, 35% were female, 19% were black, and 15% were Hispanic. At 1-year post-TBI, 18% of participants had a poor cognitive outcome. Of those with poor cognitive outcome, 62% met criteria for cognitive impairment alone, and 14% met criteria for cognitive decline alone, and 24% met criteria for both cognitive impairment and cognitive decline. Those with poor cognitive outcome were older and had greater injury on initial head CT. We completed individual rater and consensus ratings of PBS on initial trauma head CT for N=299 patients in this cohort. Inter-rater reliability of sub-scores and summary score achieved our goal. We are currently establishing intra-rater reliability, the final component of development of the PBS score. Preliminary analysis indicates that PBS score is associated with cognitive outcome at one year post-injury.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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INTRODUCTION:
Subject: Prediction of poor 1-year cognitive outcome after mild traumatic brain injury (mTBI).
Purpose: MTBI is a signature injury of modern warfare and affects an estimated 42 million people worldwide each year. MTBI may lead to chronic cognitive problems (in memory and thinking ability) in up to half of patients. Even more concerning is that mTBI may lead to progressive cognitive decline and eventual Alzheimer's dementia (AD) and AD related disorders (ADRD), increasing risk by up to 3-fold. There are currently no practical tools to accurately predict who will suffer from chronic or progressive cognitive consequences of mTBI and who will recover uneventfully. Our project will directly address the overarching challenge of the need for biomarkers and tools to prognose cognitive decline and subsequent progression to AD/ADRD after mTBI.
Scope: We are conducting a 3-year project that will cost-efficiently harness existing data from more than 1,260 adults age 16 years and older presenting to 18 trauma centers across the U.S. within 24 hours of mTBI who participated in the DoD/NIH-funded Transforming Research And Clinical Knowledge in TBI (TRACK-TBI) study. Our aims are as follows: **Aim 1:** Use state-of-the-art modeling techniques to develop and validate a practical prediction tool to identify which patients will develop early cognitive decline 1 year after mTBI using only information that is easily and routinely collected in the acute trauma setting (e.g. demographics, military and prior TBI history, clinical and CT measures of TBI severity, lab values, and pre-existing medical/psychiatric comorbidities). **Aim 2:** Develop and validate a novel CT biomarker of pre-injury brain structure (PBS), the PBS score, and determine whether PBS score predicts cognitive function and early cognitive decline 1 year after mTBI. **Aim 3:** Determine whether the PBS score improves the prediction tool developed in Aim 1 and then create a final, optimized, open-access, web-based, "clinical risk calculator" appropriate for use in an acute trauma setting to predict risk for cognitive decline 1 year after mTBI in individual patients.

1. KEYWORDS:

Mild traumatic brain injury, cognitive decline, cognitive impairment, prognosis, prediction model

2. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

Aim 1: Build a prognostic model of risk for cognitive decline 1 year after mTBI - 50% completed
Aim 1: Disseminate results: 25% completed
Aim 2a: Establish inter-rater reliability of PBS score - 100% completed
Aim 2a: Establish intra-rater reliability of PBS score - 0% completed
Aim 2a: Rate remaining CT scans - 25% completed
Aim 2a: Develop final summed PBS score using psychometric methods – 0% completed
Aim 2a: Disseminate findings - 0% completed
Aim 2b: Determine whether PBS score independently predicts post-mTBI cogntiive function and decline 1 year post-injury – 10% completed

- **What was accomplished under these goals?**

1) Major activities: For Aim 2, we spent several months refining our approach to dealing with the unexpectedly large amount of missing cognitive outcomes data. We finalized our definition of the primary cognitive outcome, and established prevalence of poor cognitive outcome at one year post-injury in the cohort. We are preparing our initial paper describing prevalence and predictors of poor one year cognitive outcome for publication. In parallel, we have made steady progress on the development and validation of the PBS score for Aim 2 and completed independent and consensus ratings on N=299 scans. We have established intra-rater reliability and are now investigating inter-rater reliability of PBS score.

2) Specific objectives: We continue to make progress on Aim 1 and Aim 2a.

3) Results/Outcomes: We studied 657 adults with acute mTBI (defined by Glasgow Coma Scale 13-15) and without baseline dementia who were enrolled in the multisite trauma center-based prospective TRACK-TBI

Study. Participants underwent cognitive testing at 2-weeks, 6-months, and 1-year post-mTBI (Rey Auditory Verbal Learning Test, Trails A/B, Processing Speed Index, NIH-Toolbox Fluid Cognition Composite and Picture Vocabulary Test). Poor cognitive outcome was defined as cognitive impairment, cognitive decline, or both. Cognitive impairment was defined as having a score falling below the 9th percentile on age-specific cognitive norms on ≥2 two tests. Cognitive decline was defined as having a change score (defined as best 2-weeks or 6-months score minus the 1-year score) exceeding the 90% confidence interval of the reliable change index on ≥2 tests. T-tests and chi-square tests were used to assess univariate associations of demographic, socioeconomic, medical comorbidity, and injury-related factors with poor cognitive outcome. Missing outcome data was accounted for using propensity weighting. Mean age of patients was 41 years, 35% were female, 19% were black, and 15% were Hispanic. At 1-year post-TBI, 18% of participants had a poor cognitive outcome. Of those with poor cognitive outcome, 62% met criteria for cognitive impairment alone, and 14% met criteria for cognitive decline alone, and 24% met criteria for both cognitive impairment and cognitive decline. Those with poor cognitive outcome were older and had greater injury on initial head CT. We completed individual rater and consensus ratings of PBS on initial trauma head CT for N=299 patients in this cohort. Inter-rater reliability of sub-scores and summary score achieved our goal. We are currently establishing intra-rater reliability, the final component of development of the PBS score. Preliminary analysis indicates that PBS score is associated with cognitive outcome at one year post-injury.

4)Other achievements/Goals Not Met: Ethics approval delays in Y1 translated into delays in Y2. Additional challenges in Y2 that led to further delays include unexpected large amount of missing cognitive outcomes data and global pandemic leading to reduced efficiency of research team. This led to delays in Aim 1 and Aim 2 components on which subsequent aims are contingent. We are currently restructuring our team with the goal of making very rapid progress on all aims, including dissemination/publication, during the final year of this 3 year project.

- **What opportunities for training and professional development has the project provided?**

We recently added Andrea Schneider as an other significant contributor (without support) to our project team. Dr. Schneider is an outstanding new junior faculty at Upenn with training in epidemiology, neuro-critical care, and cognitive aging research. She is new to the TRACK-TBI Network and has less experience studying acute TBI. This project is providing valuable training opportunities for Dr. Schneider to learn more about studying cognitive outcomes after acute TBI and to learn more about the TRACK-TBI research network and data. Dr. Schneider's work with our team led directly to her application for an independent grant from DoD PRARP in the latest funding cycle.

- **How were the results disseminated to communities of interest?**

Findings were presented at the FY20 Peer Reviewed Alzheimer's Research Program In Progress Review Meeting on 9/9/20. We had intended to present our findings at the annual Neurotrauma meeting, however, this was cancelled due to the pandemic. We have presented our interim findings several times at TRACK-TBI Investigator meetings.

- **What do you plan to do during the next reporting period to accomplish the goals?**

We plan to restructure our team and specifically add additional outstanding biostatistical and programming support (with remaining funds) in order to rapidly complete all Aims. We are planning 3 publications. Paper 1: Prevalence and predictors of poor cognitive outcome one year after mild TBI. Paper 2: Pre-injury brain structure on acute trauma head CT predicts cognitive outcome one year after mild TBI. Paper 3: Prediction of poor cognitive outcome one year after mild TBI.

3. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

We developed a novel approach to definition of poor cognitive outcome after TBI (that includes both impairment and decline) and this definition informed a new collaborative grant application to DoD PRARP in partnership with GryphonBio and Kevin Wang that will seek to use our novel definition to study biomarkers of

post-TBI AD across varied, heterogeneous, cohorts. Our work also directly informed a new collaborative grant application to DoD PRARP in partnership with Andrea Schneider that seeks to investigate vascular contributions to post-TBI dementia.

- **What was the impact on other disciplines?**

Nothing to report.

- **What was the impact on technology transfer?**

Nothing to report.

- **What was the impact on society beyond science and technology?**

Nothing to Report.

4. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

No significant changes in scope.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

Ethics approval delays in Y1 translated into delays in Y2. Additional challenges in Y2 that led to further delays include unexpected large amount of missing cognitive outcomes data and global pandemic leading to reduced efficiency of research team. This led to delays in Aim 1 and Aim 2 components on which subsequent aims are contingent. We are currently restructuring our team with the goal of making very rapid progress on all aims, including dissemination/publication, during the final year of this 3 year project. Specifically, we are hiring additional biostatistical and programming consultants to more rapidly complete Aim 1 and Aim 3 prediction models.

- **Changes that had a significant impact on expenditures**

Because progress was delayed due to ethics approval and missing data and the pandemic, we have under-spent our budget. However, in order to catch-up, we now plan to allocate those funds to increase biostatistical and programming support to support more rapid completion of aims during Y3.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

N/A

- **Significant changes in use or care of human subjects**

N/A

- **Significant changes in use or care of vertebrate animals**

N/A

- **Significant changes in use of biohazards and/or select agents**

N/A

5. **PRODUCTS:**

- **Publications, conference papers, and presentations**

  - **Journal publications.** Nothing to Report.
  - **Books or other non-periodical, one-time publications.** Nothing to Report.
  - **Other publications, conference papers, and presentations**.

*Gardner et al. Cognitive Decline One Year After Mild Traumatic Brain Injury: A TRACK-TBI Study. Poster presentation at Alzheimer's Association International Conference, Los Angeles. July 2019. This paper is in preparation and will be submitted to a high impact journal. We anticipate submission of an additional 2 papers during Y3. We hope to present our findings at the National Neurotrauma Meeting this summer. Dissemination at conferences was impacted by the pandemic. We have presented our findings several times at TRACK-TBI Investigator meetings.

- **Website(s) or other Internet site(s)**

  None

- **Technologies or techniques**
  None

- **Inventions, patent applications, and/or licenses**
  None

- **Other Products**
  None

6. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name: Raquel Gardner
Project Role: PI
Researcher Identifier: unknown
Nearest person month worked: 14% effort over 12 months
Contribution to Project: PI, rating head CTs, data analysis, leading scientific aims

Name: Russell Huie
Project Role: Programmer
Researcher Identifier: unknown
Nearest person month worked: 11% effort over 12 months
Contribution to Project: Meetings with PI to discuss data, data analysis

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

See updated other support. Dr. Gardner's NIH K23 ended and other projects began.

- **What other organizations were involved as partners?**

Nothing to report.

7. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** *N/A*
- **QUAD CHARTS:** See attached.

8. **APPENDICES:** None.

OTHER SUPPORT

GARDNER, RAQUEL

ACTIVE

Title of the Project: *Transforming Research and Clinical Knowledge in Geriatric Traumatic Brain Injury (TRACK-GERI)*
Grant number: R01NS110944-01
Principal Investigator: Gardner
Time commitment: 5.50 calendar months
Supporting Agency: NIH Center for Scientific Review
Grants Management Specialist: Yvonne C. Talley; talleyy@mail.nih.gov
Performance Period: 09/01/2019 – 05/31/2024
Level of Funding: direct/yr
Projects Goals: The goals of this career development award are to assemble a new prospective longitudinal cohort study of acute geriatric traumatic brain injury (TBI) that will establish the natural history and neuropathology, identify age-appropriate blood-based biomarkers, and develop an optimized set of tools for capturing geriatric TBI predictors and outcomes for use in large-scale geriatric TBI clinical trials.
Specific Aims: **Aim 1**: Assemble a prospective cohort of patients age ≥65y presenting to the Emergency Department ≤72h after TBI who underwent CT. Enroll 270 TBI patient/study-partner dyads and 90 controls; perform baseline assessments and blood draws, and assess longitudinal outcomes at 2wk, 3mo, 6mo (primary endpoint) and 12mo; offer enrollment in a brain donation program. **Aim 2:** Develop and validate optimized geriatric TBI predictor and outcome assessments: 2a: Systematically measure apolipoprotein E allele and pre-injury comorbidities/polypharmacy, physical frailty, and multi-domain functional status via detailed patient and study partner interviews using validated geriatric instruments and assess association of these predictors with outcome after TBI. 2b: Describe the natural history of geriatric TBI using validated TBI and geriatric outcomes and then use data-driven analytics to identify the most parsimonious set of measures for longitudinal outcome assessment in this population. 2c (exploratory): Measure pre-injury brain structure (atrophy/white matter disease of uninjured brain visualized on baseline CT) and explore association with outcome after TBI. **Aim 3:** Identify age-appropriate diagnostic and prognostic blood-based biomarkers. This work will directly inform design of large-scale age-appropriate geriatric TBI clinical trials that are urgently needed to improve care and outcomes in this vulnerable population.
Project Overlap: None

Title: A Novel Visually Graded CT Biomarker of Preinjury Brain Structure to Improve Prediction of Cognitive Decline After Mild Traumatic Brain Injury
Grant number*: W81XWH-18-1-0514*
Principal investigator: Gardner
Time Commitment: 1.8 calendar months
Supporting agency: Dept of Defense (DoD)
Performance period: 09/30/2018 - 09/29/2021
Level of funding: direct/yr
Project Goals: The overarching goal of this project center is to determine if evaluation of preinjury brain structure can identify heterogeneity in preinjury brain health that directly contributes to heterogeneity in cognitive recovery after mild traumatic brain injury.
Specific Aims: 1) To develop and internally validate a practical prognostic model using only TBI common data elements (CDEs) that are routinely collected in the acute trauma setting. 2) To develop and validate the PBS score in the same cohort of well-characterized adults with mTBI and to determine whether PBS score independently predicts cognitive function and cognitive decline 1 year after mTBI. 3) To determine whether the PBS score improves the prognostic value of the model developed in Aim 1 and to create a final, optimized, open-access, Web-based clinical risk calculator appropriate for use in an acute trauma setting to predict cognitive decline 1 year after mTBI in individual patients.
Project Overlap: None

Title: Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC): Epidemiological Study

***Grant number**:* W81XWH-18-PH/TBIRP-LIMBIC
Principal investigator: Yaffe
Time Commitment: 1.8 calendar months
Supporting agency: Dept of Defense (DoD)
Performance period: 09/30/2019 - 09/29/2024
Level of funding: direct/
yr
Project Goals: The goal of this project is to leverage a large nationwide cohort of TBI-exposed veterans and the latest machine learning techniques to understand the phenotype and neuropathology of post-TBI dementia.
Specific Aims: Aim 1: To create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data. Aim 2: To use machine-learning to develop and internally validate an MRI-based algorithm for predicting 5+ year risk of post-TBI dementia in all veterans nationwide with a diagnosis of TBI and a MRI as well as specifically among those with mild TBI. Aim 3: To compare neuroimaging features on structural MRI in veterans with post-TBI dementia versus those with dementia without preceding TBI. Specifically, we will identify: TBI-associated patterns of atrophy within previously established neurodegenerative disease-specific neural networks (a proxy for clinical dementia sub-types), and TBI-associated burden and distribution of white matter disease.

Project Overlap: None

Pending:

Title: Neuroimaging Endophenotypes and Predictors of Post-Traumatic Brain Injury Dementia in a Nationwide Cohort of Veterans
***Grant number**: Pending* W81XWH-19-1-0669, AZ180117
Principal investigator: Tosun-Turgut/Gardner/Yaffe
Time Commitment: 1.80 calendar months
Supporting agency: Dept of Defense (DoD)
Performance period: 09/01/2019-08/31/2022
Level of funding: direct/yr
Project Goals: The proposed 3-year project will cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of 1.6 million TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data; (2) predict which TBI-exposed veterans will go on to develop dementia; and (3) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans. We expect that we will (1) produce the largest military-relevant MRI dataset with expertly curated TBI exposure and dementia outcome and up to 12 years of follow-up (with option of continued follow-up via VHA EMR); (2) develop a method for predicting 5+-year risk of post-TBI dementia using routinely collected clinical MRI. This work may directly inform clinical care of veterans and identify a high-risk subset that may be ideal for further studies of underlying mechanisms of post-TBI dementia and clinical trials for prevention; and (2) facilitate discovery of the nationwide epidemiology of neuroimaging biomarker-supported dementia sub-types in TBI-exposed versus unexposed veterans receiving care within VHA. This work may directly inform public health planning within the DoD and VHA and generate testable hypotheses regarding underlying etiology of post-TBI dementia.
Specific Aims: 1) To create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data. 2) To use machine-learning to develop and internally validate an MRI-based algorithm for predicting 5+ year risk of post-TBI dementia in all veterans nationwide with a diagnosis of TBI and an MRI available for analysis (N>70,000) as well as specifically among those with mild TBI (N>33,000). 3) To compare neuroimaging features on structural MRI in veterans with post-TBI dementia (N=3,677) versus those with dementia without preceding TBI (N=8,435). Specifically, we will identify:

a. TBI-associated patterns of atrophy within previously established neurodegenerative disease-specific neural networks (a proxy for clinical dementia sub-types), and
b. TBI-associated burden and distribution of white matter disease.

Project Overlap: None

***THIS IS THE SUBJECT OF THIS SUBMISSION**

Inactive:
Title of the Project: *Traumatic Brain Injury and the Aging Brain: Predictors of Clinical Trajectories*
Grant number: K23NS095755
Principal Investigator: Gardner
Time commitment: 6.00 calendar months
Supporting Agency: NIH/National Institute of Neurological Disorders and Stroke
Grants Management Specialist: Yvonne C. Talley; talleyy@mail.nih.gov
Performance Period: 07/01/2015 – 08/31/2020
Level of Funding: direct/yr
Projects Goals: The goals of this career development award are to provide protected time and dedicated training for the PI to study the effects of traumatic brain injury (TBI) on the aging brain. The PI's long-term career goal is to become a leader in TBI and brain aging research with a focus on clinical predictors and mechanisms of post-TBI neurodegeneration. The specific long-term goal of this research program would be to uncover novel targets for treatment and prevention of post-TBI cognitive, behavioral, motor, and functional decline in high-risk, vulnerable, aging adults. Training goals include (1) advanced training in research methods and biostatistics, (2) advanced training in epidemiology of aging with a focus on inter-disciplinary neurological and geriatric predictors and outcomes, and (3) TBI-focused research. The scientific goals of this project are to describe multi-domain clinical trajectories after acute and remote traumatic brain injury in older adults and also to define clinical predictors of these trajectories.
Specific Aims: (1) to define detailed clinical trajectories and predictors of trajectories after *acute* TBI in older adults, (2) to define detailed clinical trajectories and predictors of trajectories after *remote* TBI in older adults.

Project Overlap: None

OVERLAP
None

A Novel Visually Graded CT Biomarker of Preinjury Brain Structure to Improve Prediction of Cognitive Decline After Mild Traumatic Brain Injury

AZ170057 Year 2 Quarter 3 Progress Report

W81XWH1810514

PI: Raquel C. Gardner **Org:** Northern California Institute for Research (NCIRE) **Award Amount:** $344,925.00

Study/Product Aim(s)

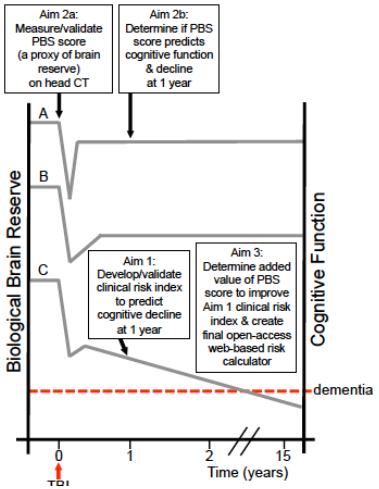
•Aim 1: To develop and internally validate a practical prognostic model to predict cognitive decline 1 year after mTBI.

•Aim 2: 2a: To develop and validate the preinjury brain structure (PBS) score – using validated visually-graded CT measures of brain structure – and 2b: to determine whether PBS score independently predicts cognitive function and cognitive decline 1 year after mTBI.

•Aim 3: To determine whether the PBS score improves the prognostic value of the model developed in Aim 1 and then create a final, optimized clinical risk calculator appropriate for use in an acute trauma setting to predict cognitive decline 1 year after mTBI in individual patients.

Approach

We are harnessing existing data from the 18-site Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study to develop and validate our novel CT biomarker of pre-injury brain structure (PBS score) and determine its prognostic value among >1,260 adults who were enrolled in TRACK-TBI within 24 hours of mTBI and completed 12 months of longitudinal cognitive testing.



Theoretical peri-TBI cognitive trajectories in a patient with high (A), medium (B), and low (C) pre-injury biological brain reserve demonstrate the critical prognostic value of measuring preinjury brain structure (PBS) as a proxy of biological brain reserve.

We have continued work for the Aim 1 prognostic model and have nearly completed development, reliability assessment, and rating of PBS score for Aim 2.

Timeline and Cost

Activities / CY	18-19	19-20	20-21
Planning/Regulatory/Data			
Aim 1			
Aim 2			
Aim 3			
Estimated Budget ($K)	**$97k**	**$133k**	**$127k**

Updated: October 2020, San Francisco, CA

Goals/Milestones

CY18-19 Goal – Planning/regulatory/data management

☑ Identify/train staff

☑ ethics approval

☑ obtain/prepare data for analysis

☑ begin Aim 1 and Aim 2a

CY19-20 Goals – Aim 1 and Aim 2a

☐ Complete Aim 1 – work ongoing

☐ Complete Aim 2a – work ongoing

☐ Begin Aim 2b

CY20-21 Goal – Aim 2b and Aim 3

☐ Complete Aim 2b

☐ Complete Aim 3

Comments/Challenges/Issues/Concerns

- Ethics delay, missing outcomes data delay, staffing challenges

Budget Expenditure to Date as of 10/22/2020:

Projected Expenditure: $229,950 (direct & indirect costs)

Actual Expenditure: $119,448 (direct & indirect costs)