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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

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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, now in an approved no-cost-extension, 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 completed Aim 1 and we have made substantial progress on Aims 2 and 3. For Aim 1: We studied 656 adults with acute mTBI (defined by Glasgow Coma Scale 13-15) and without baseline dementia and 156 demographically similar healthy controls who were enrolled in the multisite 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, and Weschler Adult Intelligence Scale Processing Speed Index). 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 participants with mTBI was 40.2 years, 36.6% were female, and 76.6% were white. At 1-year, 13.5% of participants with mTBI had a poor cognitive outcome versus 4.5% of controls, p=0.003. In univariable analyses, poor 1-year cognitive outcome was associated with non-white race, lower education, lower annual family income, lack of health insurance, hyperglycemia, history of pre-injury depression, and greater injury severity (lower Glasgow Coma Scale score) (all $p<0.05$). Poor-1-year cognitive outcome was also associated with worse 1-year functional outcome, more neurobehavioral symptoms, greater psychological distress, and lower satisfaction with life (all $p<0.05$). The final multivariable prediction model included education, health insurance, pre-injury depression, hyperglycemia, and Rotterdam CT Score >3 and achieved AUC of 0.69 (95% CI=0.62-0.75) for the prediction of a poor 1-year cognitive outcome, with each variable associated with 2-fold or higher increased odds of poor 1-year cognitive outcome. For Aim 2: We developed and refined the PBS scoring system. We established inter- and intra-rater reliability. We are analyzing associations of PBS with post-injury cognition. Preliminary analysis indicates that PBS score is associated with cognitive outcome one year after TBI. For Aim 3: In preliminary analysis, we have added the PBS score to the Aim 1 prediction model and have found that it does indeed improve accuracy of the model, increasing the area under the receiver operating characteristic curve from 0.71 to 0.75.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	**10**	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

Standard Form 298 (Rev. 8-98)
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TABLE OF CONTENTS

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?**

3. Aim 1: Build a prognostic model of risk for cognitive decline 1 year after mTBI - 100% completed
4. Aim 1: Disseminate results: 99% completed (paper about to be accepted to high impact journal)
5. Aim 2a: Establish inter-rater reliability of PBS score - 100% completed for 2 raters; 50% for 3rd rater
6. Aim 2a: Establish intra-rater reliability of PBS score - 100% completed for 2 raters; 50% for 3rd rater
7. Aim 2a: Rate remaining CT scans - 95% completed
8. Aim 2a: Develop final summed PBS score using psychometric methods – 0% completed
9. Aim 2a: Disseminate findings - 0% completed
10. Aim 2b: Determine whether PBS score independently predicts post-mTBI cognitive function and decline 1 year post-injury – 50% completed
11. Aim 3: Determine whether PBS score improves the prognostic value of the model developed in Aim 1 and create final prediction model. – 20% complete

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

1) Major activities: For Aim 1, we have completed all analyses and submitted a manuscript to a high impact journal. We have recently submitted our response to the journal's request for a second round of very minor revisions. We are confident that the manuscript will now be accepted for publication at this journal within a few days to weeks. For Aim 2, while we completed inter-rater and intra-rater reliability of our novel PBS score for 2 raters, to further improve feasibility of other groups adopting the PBS score, we have trained a 3rd rater who was not involved in the initial development of the PBS score, and we are now establishing inter- and intra-rater reliabilithy of this 3rd rater. Ratings of available scans are 95% completed (we are refining our approach to scans that have substantial intracranial trauma) and we are already developing

Aim 2 models evaluating associations of PBS with cognitive function 1 year after mTBI as well as Aim 3 models determining whether PBS improves the Aim 1 model to predict one-year cognitive outcome.

2) Specific objectives: We have completed Aim 1. We are making substantial progress on Aims 2 and 3.

3) Results/Outcomes: For Aim 1: We studied 656 adults with acute mTBI (defined by Glasgow Coma Scale 13-15) and without baseline dementia and 156 demographically similar healthy controls who were enrolled in the multisite 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, and Weschler Adult Intelligence Scale Processing Speed Index). 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 participants with mTBI was 40.2 years, 36.6% were female, and 76.6% were white. At 1-year, 13.5% of participants with mTBI had a poor cognitive outcome versus 4.5% of controls, p=0.003. In univariable analyses, poor 1-year cognitive outcome was associated with non-white race, lower education, lower annual family income, lack of health insurance, hyperglycemia, history of pre-injury depression, and greater injury severity (lower Glasgow Coma Scale score) (all $p<0.05$). Poor-1-year cognitive outcome was also associated with worse 1-year functional outcome, more neurobehavioral symptoms, greater psychological distress, and lower satisfaction with life (all $p<0.05$). The final multivariable prediction model included education, health insurance, pre-injury depression, hyperglycemia, and Rotterdam CT Score >3 and achieved AUC of 0.69 (95% CI=0.62-0.75) for the prediction of a poor 1-year cognitive outcome, with each variable associated with 2-fold or higher increased odds of poor 1-year cognitive outcome. For Aim 2: We developed and refined the PBS scoring system. We established inter- and intra-rater reliability among 2 raters. We have trained a 3rd rater and are establishing inter- and intra-rater reliability of this 3rd rater. We are analyzing associations of PBS with post-injury cognition. Preliminary analysis indicates that PBS score is associated with with cognitive outcome one year after TBI, but only among adults age 40 years or older. For Aim 3: In preliminary analysis, we have added the PBS score to the Aim 1 prediction model and have found that it does indeed improve accuracy of the model, increasing the area under the receiver operating characteristic curve from 0.71 to 0.75.

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. In year 3, we made substantial progress but have requested and received approval for a 12-month no-cost-extension in order to complete all of the aims of this project.

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

Dr. Matthew Pease, neurosurgery resident at University of Pittsburgh, is benefiting from this project. Dr. Pease is collaborating with the PI Dr. Gardner to use machine learning of the baseline TRACK-TBI acute trauma head CTs to predict outcome after mTBI. His plan is to compare the predictive value of his machine learning derived predictors from the acute trauma head CT versus our visually rated PBS score from the acute trauma head CT in the same cohort.

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

Findings were presented at the FY21 Peer Reviewed Alzheimer's Research Program In Progress Review Meeting. Aim 1 findings will imminently be published in a high-impact peer-reviewed journal. The PI has presented the interim findings several times at invited lectures and panel discussions, including an international invited grand rounds lecture at Rabin Medical Center in Israel. The PI was also invited to present findings from this project as part of a symposium proposal that was submitted for consideration for acceptance for the upcoming National Neurotrauma Society meeting in Atlanta in June 2022.

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

Aim 1: We plan to publish the manuscript describing aim 1 findings.

Aim 2-3: We plan to finalize development and validation of the PBS score including associations with cognitive outcome and role in cognitive outcome prediction and submit a manuscript describing this work to a high impact neurology or neurotrauma journal.

3. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

    a. **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 to DoD PRARP in partnership with GryphonBio and Kevin Wang that was funded and 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 was also funded, that seeks to investigate vascular contributions to post-TBI dementia.

    b. **What was the impact on other disciplines?**

The PI recently presented preliminary findings from this project to a group of neurologists and scientists at Rabin Medical Center in Israel. There is interest among this group in using the PBS scoring system to improve prediction of recovery following acute stroke. Thus, it seems that quantifying pre-injury brain structure using widely available clinically obtained head CTs may garner broad interest among clinical neuroscience investigators and providers.

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:**

    a. **Changes in approach and reasons for change**

No significant changes in scope.

    b. **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 restructured our team to facilitate parallel work on Aim 2 and Aim 3 with the goal of making very rapid progress on all aims, including dissemination/publication, during the final no-cost-extension year of this project.

    c. **Changes that had a significant impact on expenditures**

We are on track to spend remaining funds by the end of the no-cost-extension.

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

N/A

e. **Significant changes in use or care of human subjects**

N/A

f. **Significant changes in use or care of vertebrate animals**

N/A

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

N/A

5. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

a. **Publications, conference papers, and presentations**

i. **Journal publications.** Imminent acceptance of Aim 1 manuscript for publication in a high-impact peer-reviewed journal.

ii. **Books or other non-periodical, one-time publications.** Nothing to report.

iii. **Other publications, conference papers, and presentations.**

Findings were presented to the DoD in August 2021, at Grand Rounds at Rabin Medical Center September 2021, and as part of Concussion roundtable discussion at University of Michigan October 2021.

b. **Website(s) or other Internet site(s)**
None.

c. **Technologies or techniques**
None.

d. **Inventions, patent applications, and/or licenses**
None

e. **Other Products**

i. *data or databases:* We will be measuring PBS in our NIH-funded TRACK-GERI study and our recently VA funded TRACK-VA study and these data will ultimately be made publicly available in FITBIR.

ii. *models; Our novel PBS score will inform Dr. Pease's machine learning algorithm that will extract predictors from baseline trauma head CT to predict outcomes after mTBI.*

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name: Raquel Gardner

Project Role: PI

Researcher Identifier: unknown

Nearest person month worked: 25% 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

b. 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 document.

c. What other organizations were involved as partners?

Nothing to report.

7. SPECIAL REPORTING REQUIREMENTS

a. **COLLABORATIVE AWARDS:** N/A.

b. **QUAD CHARTS:** See attached.

8. APPENDICES: None.

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

AZ170057 Year 3 Annual Progress Report W81XWH1810514

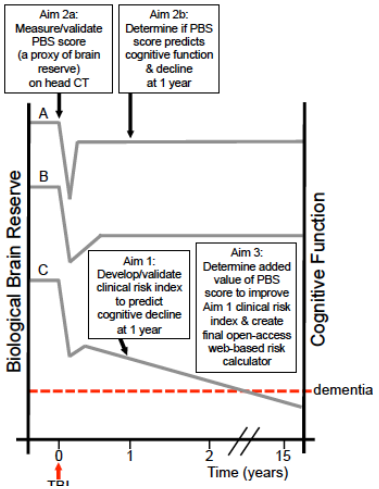
PI: Raquel C. Gardner **Org:** Northern California Institute for Research (NCIRE) **Award Amount:** $344,925.00

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 2021, 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
X Complete Aim 1
☐ Complete Aim 2a – work ongoing
☑ Begin Aim 2b – work ongoing
CY20-21 Goal – Aim 2b and Aim 3
☐ Complete Aim 2b
☐ Complete Aim 3

Comments/Challenges/Issues/Concerns

- Ethics delay, missing outcomes data delay, pandemic staffing challenges

Budget Expenditure to Date as of 10/27/2021
Projected Expenditure: $344,925 (direct & indirect costs)
Actual Expenditure: $256,891 (direct & indirect costs)