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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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14. ABSTRACT 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: To date, we have made substantial progress on Aim 1. We have obtained all available TRACK-TBI data necessary for our analyses, cleaned the data, and have carefully refined our cognitive outcome of interest that now incorporates performance on both standard pen and paper cognitive tests as well as the computer-based NIH Toolbox cognitive battery. Our preliminary analyses indicate that 13% of individuals presenting acutely with mTBI experience clinically significant cognitive decline within 1 year of injury. We are now poised to begin building our initial prognostic model that will use baseline clinical data to predict poor 1-year cognitive outcome among individuals presenting acutely with mTBI. We presented our preliminary findings as a poster at the Alzheimer's Association International Conference in Los Angeles in July 2019.					
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1. 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.

2. KEYWORDS:

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

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Obtain local IRB approval and HRPO approval for the project.
2. Hire/train our programmer, Dr. Huie.
3. Build REDCap data management system for recording novel CT variables.
4. Obtain, clean, visualize, and quality-check all available TRACK-TBI clinical data on patients who presented within 24h to participating trauma centers with mild TBI (mTBI).
5. Obtain head CT data.
6. Begin building a prognostic model to predict post-TBI cognitive decline using only baseline clinical data.

What was accomplished under these goals?

- 1) Major Activities: We obtained local and HRPO ethics approval. Unfortunately, HRPO ethics approval was quite delayed, however, we were able to achieve rapid progress after approval and have regained most of the lost time. We hired Dr. Huie. We obtained and cleaned the data and refined the definition of poor cognitive outcome for our prognostic models. We presented a poster at the Alzheimer's Association International Conference in Los Angeles in July 2019 reporting preliminary findings. We have weekly team meetings with Dr. Huie, Dr. Boscardin, and Dr. Gardner. We have continued refining the predictor and outcomes variables for the Aim 1 prognostic model. Dr. Gardner has started meetings with Esther Yuh to plan the initial phase of the head CT grading process. We have created the REDCap database to house the novel head CT variables.
- 2) Specific Objectives: We have continued to work on Aim 1 and have begun preparations to begin work on Aim 2.
- 3) Results/Outcomes: Our preliminary estimate is that 13% of mild TBI patients experience poor cognitive outcome 1 year post-injury.
- 4) Other Achievements/Goals Not Met: None.

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

While training was not a goal of this project, we have recently onboarded a VA TBI/Polytrauma Advanced Research Fellow, Michele Diaz RN, onto our team. While Michele's first research project will focus on a different data-set, Michele will join our research team meetings in order to learn from this ongoing project and may contribute to this project in future years.

Additionally, one of our team members, Russell Huie, presented our work as a poster presentation at the annual Alzheimer's Association International Conference in July 2019. Dr. Huie is a TBI researcher and thus had never attended an Alzheimer's meeting before. Thus, this was a unique learning and networking opportunity for Dr. Huie.

How were the results disseminated to communities of interest?

Nothing to report.

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

1. Build and internally validate a prognostic model of risk for cognitive decline 1 year after mTBI using readily available baseline clinical predictors (Aim 1).
2. Disseminate Aim 1 results.
3. Establish inter-rater and intra-rater reliability of CT measures of pre-injury brain structure on a representative sample of ~400 CT exams from these Aim 1 patients.
4. Rate remaining CT exams.
5. Use psychometric methods to develop the final summed PBS score.
6. Disseminate Aim 2a results (development of PBS score).
7. Determine whether PBS score independently predicts post-mTBI cognitive function 1 year after mTBI.

4. IMPACT:

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

During the first year of our project, we have carefully refined a holistic definition of poor cognitive outcome 1-year after mTBI that we believe has substantial relevance to patients and providers. Our novel definition may benefit the field and advance patient-centered research on post-TBI cognitive outcomes once published.

The problem with narrowly defining poor cognitive outcome as “cognitive impairment” alone, is that this approach may miss individuals who are declining cognitively but have not yet dipped below the “impaired” level of cognitive function. On the other hand, a narrow definition of “cognitive decline” may miss those who are simply statically impaired and not recovering who also have a poor cognitive outcome. Thus, our novel definition of poor cognitive outcome includes 1. persistent cognitive impairment relative to normative cognitive scores for age/education on at least 2 different neuropsychological tests OR 2. clinically significant cognitive decline on at least 2 different neuropsychological tests defined using the reliable change index (RCI) which takes into account practice effects and test reliability over time. By using this holistic definition of poor cognitive outcome that includes both impairment and/or decline, we can identify a group of patients with clinically relevant poor cognitive outcome who warrant closer clinical follow-up and rehabilitation.

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.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

1. HRPO approval was very delayed. While we were able to make rapid progress following approval, it is likely that completion of the initial Aim 1 prognostic model will be somewhat delayed from the initial proposed timeline in the SOW.
2. As of today, TRACK-TBI has completed curation and released 12-month longitudinal data for approximately ½ of the total enrolled patients (N= ~1,500). It is unclear when they will complete curation of the other half. We plan to move forward with analyzing all available data and will plan to update our dataset with new data as it becomes available. It is therefore possible that the initial prognostic model for Aim 1 will be developed using the first 1,500 patients and the final Aim 3 model will be completed using the full 3,000.

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

HRPO approval was very delayed. While we were able to make very rapid progress following approval, we are still 2-3 months behind on building our initial Aim 1 prognostic model. We will continue to work to recoup the lost time.

Changes that had a significant impact on expenditures

Nothing to report.

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

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

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

Journal publications.

None.

Books or other non-periodical, one-time publications.

None.

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.

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

None.

- **Technologies or techniques**

None.

- **Inventions, patent applications, and/or licenses**

None.

- **Other Products**

None.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Raquel Gardner

Project Role: PI

Researcher Identifier: unknown

Nearest person month worked: 2 months

Contribution to Project: PI, getting approval, training staff, leading scientific aims

Name: Russell Huie

Project Role: Programmer

Researcher Identifier: unknown

Nearest person month worked: 1 month

Contribution to Project: Meetings with PI to discuss data, approach to initial data management, project goals, 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?

Dr. Gardner was awarded a 5-year R01 from the NIH focused on geriatric TBI. She was also awarded (as multi-PI) another 3-year DoD award focused on neuroimaging phenotypes of post-TBI dementia. There is no overlap between the current project and any of Dr. Gardner's other federally funded projects.

What other organizations were involved as partners?

None.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: None.

QUAD CHARTS: See attached.

9. 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 1 Quarter 4 Report

W81XWH-18-1-0514

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

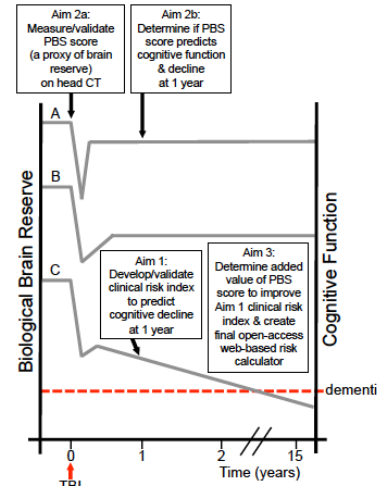


Study/Product Aim(s)

- 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 on building the Aim 1 prognostic model and begun planning for Aim 2 head CT grading of pre-injury brain structure.

Timeline and Cost

Activities	CY	18-19	19-20	20-21	
Planning/Regulatory/Data		█			
Aim 1		█	█		
Aim 2		█	█	█	
Aim 3				█	
Estimated Budget (\$K)		\$85k	\$133k	\$127k	

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
- Complete Aim 2a
- Begin Aim 2b

CY20-21 Goal – Aim 2b and Aim 3

- Complete Aim 2b
- Complete Aim 3

Comments/Challenges/Issues/Concerns

- Refining definition of cognitive decline, incorporating NIH Toolbox

Budget Expenditure to Date

Projected Expenditure: \$86,714

Actual Expenditure: \$69,419

Updated: November 2019, San Francisco, CA