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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, MD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education
San Francisco, CA

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6. AUTHOR(S)
Raquel C. Gardner, Russell Huie, Andrea Schneider, Adam Ferguson, Matthew Pease, Kristine Yaffe, Geoffrey T. Manley, and Esther Yuh

E-Mail: Raquel.gardner@ucsf.edu

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Northern California Institute
for Research and Education
(NCIRE)
4150 Clement Street, 151NC
San Francisco, CA 94121-1563

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Cognitive outcome after mild traumatic brain injury (mTBI, defined as presenting Glasgow Coma Scale 13-15) is extremely heterogeneous. There is an urgent need for better prognostic indicators to guide acute care, rehabilitation, and identify those at highest risk of poor cognitive outcome, cognitive decline, and eventual Alzheimer's Disease/Alzheimer's Disease Related Disorders (AD/ADRD). We hypothesized that biological brain reserve would be an important predictor of cognitive outcome after mTBI. We therefore developed and validated a visually-rated Brain Reserve Score (BRS) to quantify health of the underlying brain parenchyma visible on head CTs routinely obtained to rule out intracranial trauma in adults presenting acutely with mTBI. We leveraged data from 3 prospective cohort studies of acute TBI: Transforming Research And Clinical Knowledge in Traumatic Brain Injury [TRACK-TBI], TRACK-Geriatric TBI Pilot [TRACK-GERI Pilot], and TRACK-Geriatric TBI [TRACK-GERI]). First we developed, refined, and established intra-rater and inter-rater reliability of the BRS in random sub-sets of TRACK-TBI cohort baseline head CTs from adults of all ages. The final BRS ranges from 0 to 10 where 10 is the worst. It includes 3 visually-rated sub-scores that together quantify global brain volume, hippocampal volume, and white matter disease. We established concurrent validity of the BRS by demonstrating that BRS is significantly associated with pre-injury cognitive status in the TRACK-GERI Pilot and TRACK-GERI cohorts comprised of adults age 65y+ in whom informants provide a Clinical Dementia Rating semi-structured interview that permits categorization as pre-injury normal cognition, mild cognitive impairment, or dementia. Next we developed and validated a clinically relevant definition of poor cognitive outcome one year after mTBI and developed a prediction model to predict poor cognitive outcome using only routinely available clinical variables minus BRS score (Schneider et al, J Neurotrauma 2022). Finally, we determined whether BRS score was an independent predictor of poor cognitive outcome one year after mTBI and determined whether it improved the original prediction model. We found that BRS of 6+ was in fact the strongest independent predictor of poor cognitive outcome one year after mTBI, increasing risk by >4-fold (whereas all other predictors examined increased risk by <4-fold). We further found that addition of BRS to the original prediction model did slightly improve model fit. However, there remains substantial residual heterogeneity that deserves further study using additional biomarkers such as blood and follow-up clinical information obtained after presentation. Final results were presented at the National Neurotrauma Society Annual Meeting in Summer 2022.

15. SUBJECT TERMS
Traumatic brain injury, Alzheimer's disease and related disorders, cognitive decline, cognitive outcome, head CT, biomarker

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	20	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

Our study directly addresses the critical need for improved prognostic biomarkers and clinical tools to identify patients at highest risk for poor cognitive outcome, cognitive decline, and eventual Alzheimer's Disease/Alzheimer's Disease Related Disorders (AD/ADRD), after mild traumatic brain injury (mTBI). Briefly, 1) we developed a prognostic model, using only baseline clinical data, to predict poor cognitive outcome 1 year after mTBI. 2) We developed and validated a novel visually-rated CT biomarker of biological brain reserve, the brain reserve score (BRS), that can be efficiently rated on baseline trauma head CT – which we propose is a proxy measure of baseline/pre-injury biological brain reserve. 3) We determined the associated of BRS with one-year cognitive and functional outcome after mTBI and determined the added value of the BRS in our initial prognostic model to predict poor cognitive outcome after mTBI.

2. KEYWORDS:

Traumatic brain injury, Alzheimer's disease and related disorders, cognitive decline, cognitive outcome, head CT, biomarker

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major goals of the project were:

1. Planning/regulatory - 100% complete
2. Aim 1: Build and internally validate a prognostic model to predict one-year cognitive decline post-TBI
    a. Build prognostic model: 100% complete.
    b. Disseminate results: 100% complete – Manuscript published in journal Neurology.
3. Aim 2a: Develop and validate the BBR score
    a. Obtain, store, quality check CT image DICOM data: 100% complete
    b. Establish inter-rater and intra-rater reliability of PBS: 100% complete
    c. Rate remaining baseline CT exams: 100% complete
    d. Use psychometric methods to develop final summed PBS score – 100% complete; still refining approach to scans with intracranial trauma
    e. Disseminate results – 100% complete
4. Aim 2b: Determine whether PBS score independently predicts cognitive outcome
    a. Multiple analyses of PBS score and cognitive outcome – 100% complete
    b. Disseminate results – 100% complete
5. Aim 3: Determine whether PBS score improves prognostic value of Aim 1 model.
    a. Add PBS to Aim 1 model and assess added value. – 100% complete.

What was accomplished under these goals?

1) Major activities: We completed all scientific aims.
2) Specific objectives: All scientific aims.
3) Significant results and key outcomes by Aim:

Aim 1:

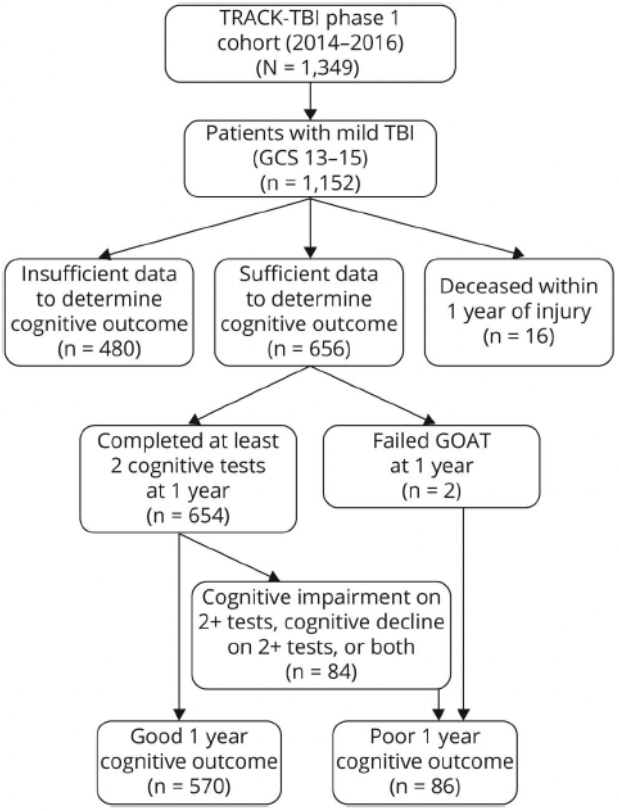
The objectives of this project were to develop and establish concurrent validity of a clinically relevant definition of poor cognitive outcome 1 year after mild traumatic brain injury (mTBI), to compare baseline characteristics across cognitive outcome groups, and to determine whether poor 1-year cognitive outcome can be predicted by routinely available baseline clinical variables.

Methods

Prospective cohort study included 656 participants ≥17 years of age presenting to level 1 trauma centers within 24 hours of mTBI (Glasgow Coma Scale score 13–15) and 156 demographically similar healthy controls enrolled in the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study (**Fig 1**).

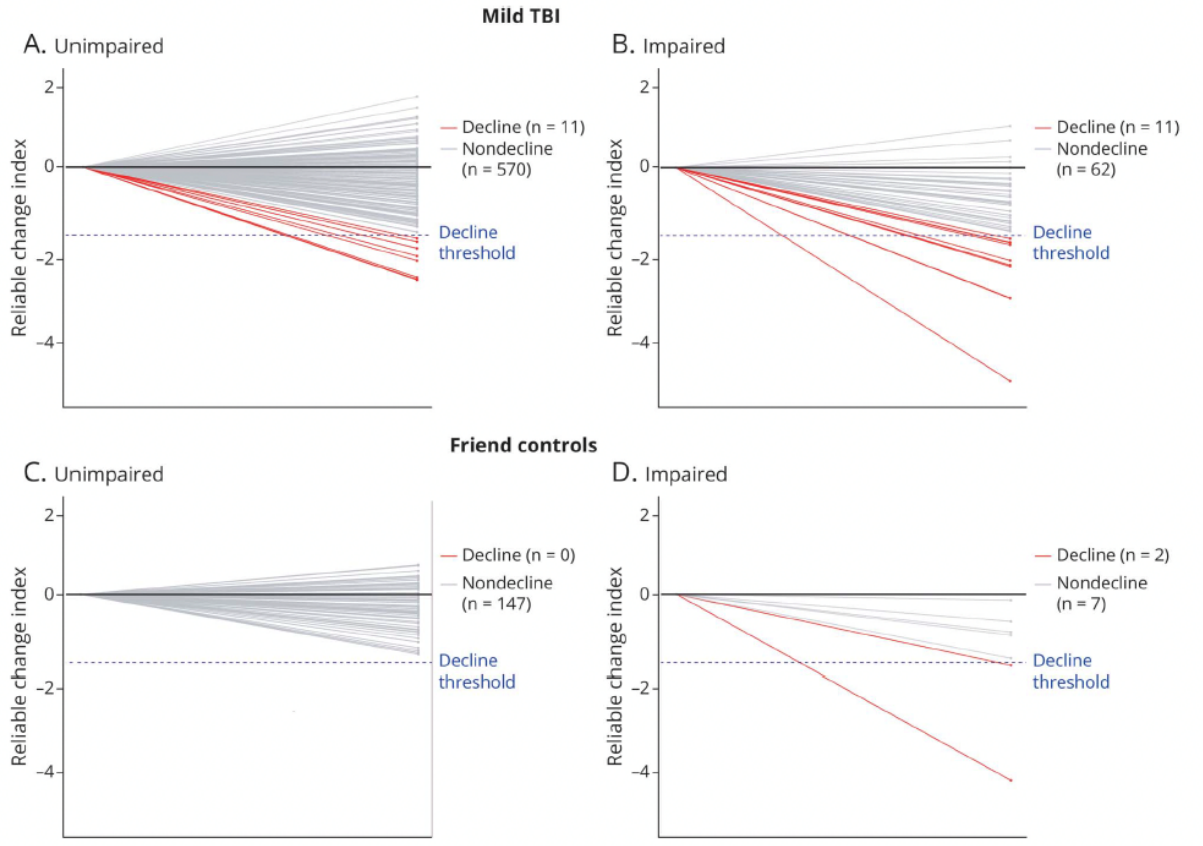
Poor 1-year cognitive outcome was defined as cognitive impairment (below the ninth percentile of normative data on ≥2 cognitive tests), cognitive decline (change score [1-year score minus best 2-week or 6-month score] exceeding the 90% reliable change index on ≥2 cognitive tests), or both (**Fig 2**). Associations of poor 1-year cognitive outcome with 1-year neurobehavioral outcomes were performed to establish concurrent validity. Baseline characteristics were compared across cognitive outcome groups, and backward elimination logistic regression was used to build a prediction model.

Figure 1 TRACK-TBI Participant Flow Diagram



GCS = Glasgow Coma Scale; GOAT = Galveston Orientation and Amnesia Test; TBI = traumatic brain injury; TRACK-TBI = Transforming Research and Clinical Knowledge in Traumatic Brain Injury.

Figure 2 Cognitive Decline Status



Cognitive decline status among participants with mild traumatic brain injury (TBI) (A, without cognitive impairment; B, with cognitive impairment) and controls (C, without cognitive impairment; D, with cognitive impairment). Plots shows each individual patient's 1-year reliable change index (RCI) score that was used to define categorization of cognitive decline (i.e., the RCI from the test with the second greatest decline) after stratification by 1-year cognitive impairment status.

Results

Mean age of participants with mTBI was 40.2 years; 36.6% were female; 76.6% were White. Poor 1-year cognitive outcome was associated with worse 1-year functional outcome, more neurobehavioral symptoms, greater psychological distress, and lower satisfaction with life (all $p < 0.05$), establishing concurrent validity. At 1 year, 13.5% of participants with mTBI had a poor cognitive outcome vs 4.5% of controls ($p = 0.003$). In univariable analyses, poor 1-year cognitive outcome was associated with non-White race, lower education, lower income, lack of health insurance, hyperglycemia, preinjury depression, and greater injury severity (all $p < 0.05$).

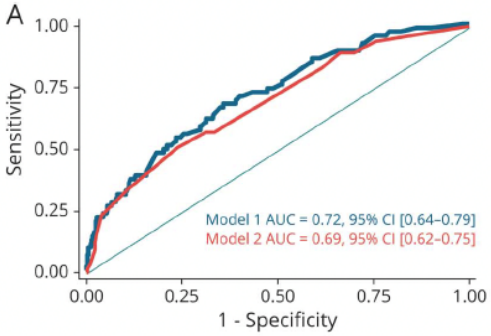
The final multivariable prediction model included education, health insurance, preinjury depression, hyperglycemia, and Rotterdam CT score ≥3 and achieved an area under the curve of 0.69 (95% CI 0.62–0.75) for the prediction of a poor 1-year cognitive outcome, with each variable associated with >2-fold increased odds of poor 1-year cognitive outcome (**Fig 3**).

Discussion

Poor 1-year cognitive outcome is common, affecting 13.5% of patients with mTBI vs 4.5% of controls. These results highlight the need for better understanding of mechanisms underlying poor cognitive outcome after mTBI to inform interventions to optimize cognitive recovery.

Figure 3 Prediction Models of Poor 1-Year Cognitive Recovery* Among Patients With mTBI

A



B

	Model 1		
	Odds ratio	95% CI	*p* value
Race: Non-White	1.33	0.711–2.49	0.37
Education: ≤HS	3.19	1.49–6.83	0.00
Unemployed/retired	1.26	0.64–2.47	0.51
Family income: <$35,0000	1.25	0.63–2.50	0.53
No health insurance	1.90	1.03–3.49	0.04
Depression	2.28	0.94–5.52	0.07
Developmental disability	2.00	0.87–5.52	0.10
Injury: Assault	2.29	0.96–5.47	0.06
Rotterdam score: ≥3	2.21	1.13–4.28	0.02
ED glucose: >200 mg/dL	2.87	0.83–9.89	0.10
Diabetes	0.89	0.29–2.68	0.83
GCS <14	0.79	0.18–3.46	0.75
Anxiety	1.87	0.70–5.01	0.22
Toxicology screen: Positive	0.72	0.28–1.82	0.48

C

	Model 2		
	Odds ratio	95% CI	*p* value
Rotterdam score: ≥3	2.13	1.11–4.05	0.02
Education: ≤HS	3.60	1.79–7.23	0.00
Depression	3.11	1.56–6.12	0.01
No health insurance	2.16	1.17–3.97	0.01
ED glucose: >200 mg/dL	2.79	1.05–7.45	0.04

(A) Receiver operating characteristic curves for models 1 and 2. (B) Model 1 including baseline characteristics that differed between good and poor 1-year cognitive outcome at the $p < 0.2$ level (Tables 2 and 3). (C) Model 2 including baseline characteristics after backward stepwise regression using $\alpha = 0.05$. *Defined as cognitive impairment (≥1 score on ≥2 of 3 tests meeting criteria for impairment), cognitive decline (≥1 score on ≥2 of 3 tests meeting criteria for decline), or both. For the prediction models, baseline characteristics were entered as binary variables with the following reference values as follows: White race, more than a high school (HS) education, working full-time/part-time/students, income ≥$35,000, health insurance, no depression, no developmental disability, nonassault injury, Rotterdam score <3, emergency department (ED) glucose <200 mg/dL or not done, no diabetes, Glasgow Coma Scale (GCS) score ≥14, no anxiety, and negative toxicology screen. AUC = area under the curve; mTBI = mild traumatic brain injury.

Aim 2:

We developed and validated a novel, efficient, visually rated score that can be used to quantify biological brain reserve (BBR) on acute trauma head CT. The final score is comprised of 3 sub-scores and ranges from 0 (healthiest brain) to 10 (least healthy brain): global cortical volume (0-3), white matter changes (0-3), and medial temporal volume (0-4; score the worst side).

Figure 4. Final Brain Reserve Score Visual Rating Guide

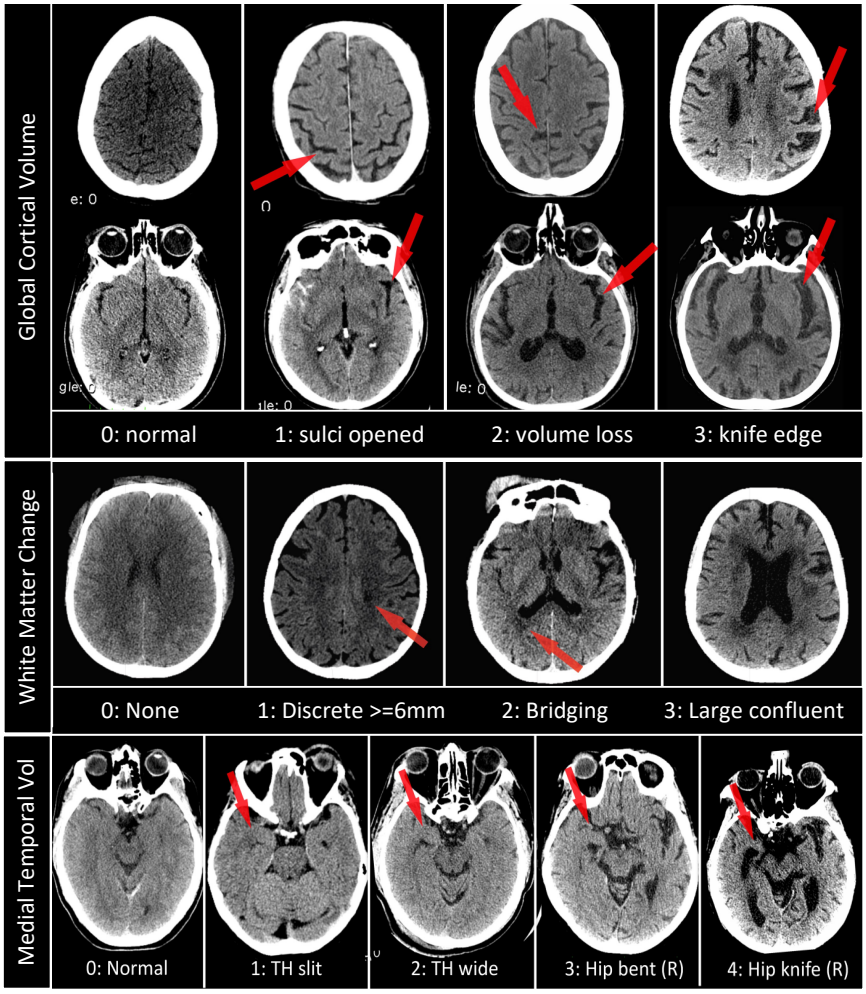
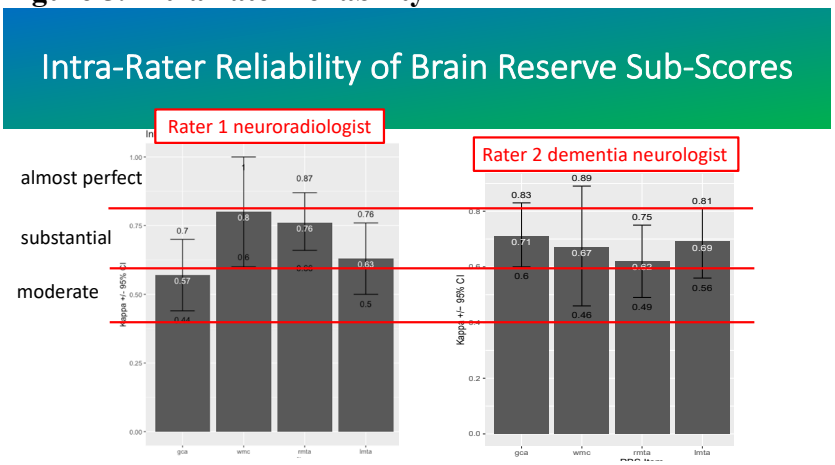


Table 1. Inter-Rater Reliability of Brain Reserve Sub-Scores

Brain Reserve Sub-scores			
	Weighted Kappa IRR (95% CI) rater 1 vs. rater 2	**Weighted Kappa IRR (95% CI) consensus vs. rater 3 (brief training)**	**Weighted Kappa IRR (95% CI) consensus vs. rater 4 (minimal training)**
Global cortical	0.62 (0.49-0.75)	0.66 (0.50-.83)	0.67 (0.52-0.81)
White matter	0.64 (0.40-0.88)	0.58 (0.34-0.83)	0.58 (0.30-0.84)
R Med temp	0.60 (0.47-0.74)	0.63 (0.47-0.80)	0.41 (0.22-0.60)
L Med temp	0.54 (0.40-0.68)	0.54 (0.35-0.72)	0.22 (0.01-0.43)

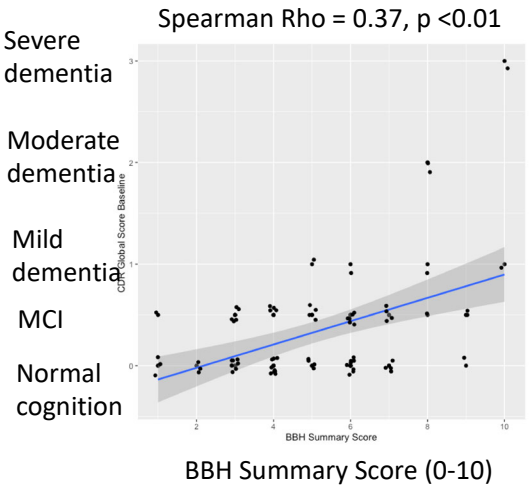
Inter-rater reliability among the 2 expert raters (developers of the rating scale) was moderate to substantial, moderate to substantial in a 3rd rater with several hours of training, and fair to substantial in a 4th rater with only one hour of training (Table 1). Intra-rater reliability among expert raters was moderate to substantial (Figure 4).

Figure 5. Intra-rater reliability



Concurrent validity was established by determining association of BRS with pre-injury clinical dementia rating (CDR) by leveraging data from the ongoing Transforming Research And Clinical Knowledge in Geriatric TBI (TRACK-GERI) study (PI: Gardner) and the completed TRACK-GERI Pilot study (PI: Gardner) that enrolled adults age 65 years plus presenting to Level 1 trauma centers with acute TBI and collected baseline Clinical Dementia Rating (CDR) interviews from informants, thereby permitting categorization of pre-injury cognition as normal, mild cognitive impairment (MCI), or dementia in every participant. Among N=100 geriatric TBI participants from TRACK-GERI, BRS was significantly associated with pre-injury CDR (**Figure 6**; spearman rho 0.37; $p<0.01$). Of note, all patients with a pre-injury diagnosis of dementia had a BRS score of 5 or greater.

Figure 6. BRS is associated with pre-injury cognitive status in older adults



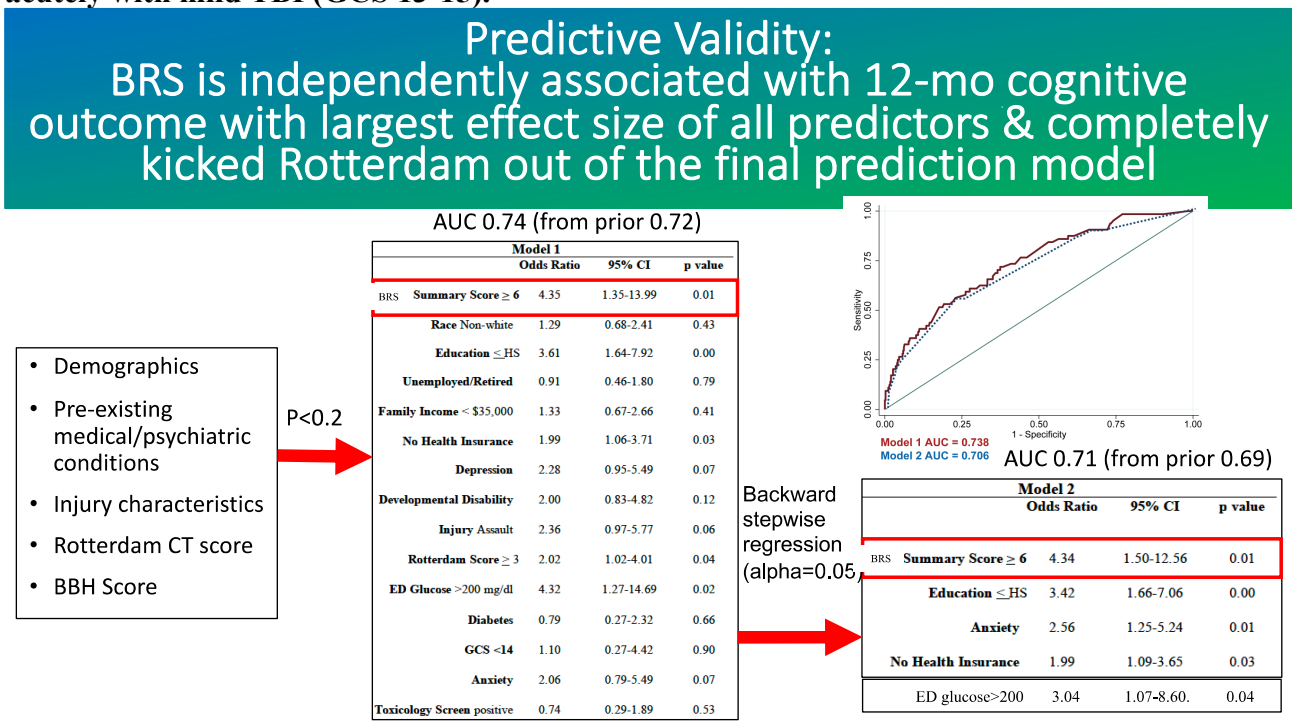
Face validity was established via investigation of the association between BRS and age in the TRACK-TBI cohort versus the TRACK-GERI cohort. While BRS is significantly associated with age in both cohorts, age explains much less of the variance in BRS in the TRACK-GERI (older, sicker) cohort versus the TRACK-TBI (younger, healthier) cohort, providing face validity that BRS provides added value above and beyond age alone (**Figure 7**)

Figure 7. Age explains less of the variance in BRS among older, frailer, adults compared to younger, healthier adults.

Aim 3:

We determined the added value of BRS in the Aim 1 model. In the TRACK-TBI cohort of individuals with acute mild TBI aged 17-90 years, we found that that BRS 6+ is associated with >4 times the odds of having a poor cognitive outcome at one year even after adjusting for demographics, socio-economic status, medical and psychiatric comorbidities, injury features including Rotterdam score on head CT (a measure of TBI seveverity), and toxicology screen results. Furthermore, when we performed backward stepwise regression to identify those predictors that are most predictive of 12-month cognitive outcome (using a $p<0.05$ threshold in the multi-variable model), the model identified just BRS 6+, education, anxiety, lack of health insurance, and ED glucose >200 as the key independent predictors of cognitive outcome at one year. The AUC for the final model was indeed slightly improved to 0.71 (from 0.69 in the final model without BRS). Notably, BRS replaced Rotterdam score in the final model, indicating that in patients presenting with mTBI, BRS may be more important than CT evidence of trauma for predicting cognitive outcome one year later (**Figure 8**)

Figure 8. BRS is an independent predictor of 12-month cognitive outcome in adults presenting acutely with mild TBI (GCS 13-15).



4) Other achievements: With preliminary data from this project, we supported applications for additional grants to the DoD PRARP that were ultimately successful (PRARP award to Andrea Schneider at UPenn and PRARP award to William Haskins at GryphonBio Inc). We have now presented these final results at the National Neurotrauma Society meeting in Atlanta in 2022. We have submitted an abstract about these findings to the 2023 Alzheimer's Association International Conference that will be held in Amsterdam in July 2023. We are preparing a manuscript describing all of these final Aim 2-3 results for submission to a high impact journal that will also incorporate the latest influx of data from the ongoing NIH-funded TRACK-GERI study.

5) Stated goals not met: Because we found that brief training on BRS scoring (as received by our rater #4) resulted in poor inter-rater-reliability, we did not create a website where others can enter in BRS score and other clinical variables to get an estimate of outcome in their specific patient, lest individual providers make erroneous predictions using our model due to errors in BRS scoring. Additional work is needed to develop an efficient, scalable, and effective training module for raters of BRS.

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

Training and professional development were not part of the stated aims of the project. However, the project did provide valuable training and experience to:

1. Andrea Schneider MD PhD, a junior faculty member at UPenn, who led the dissemination of the Aim 1 findings and with this experience and preliminary data successfully competed for her own DoD CDMRP PRARP award.
2. Matthew Pease MD, a neurosurgical resident at University of Pittsburgh, who was trained on the instrument and who subsequently designed an Artificial Intelligence project that seeks to automate our visual ratings of acute trauma head CTs.

How were the results disseminated to communities of interest?

1. Poster presentations at conferences: We presented interim and final results at various conferences over the course of the project including the National Neurotrauma Society Conference and the Alzheimer's Association International Conference.

2. Oral presentations at conferences: We presented final results as an invited oral presentation at the National Neurotrauma Society conference in Atlanta in the summer of 2022.

3. Invited lectures: We have presented interim and final results in invited lectures/Grand Rounds/Research Seminars to various departments/centers at University of California San Francisco, San Francisoc Veterans Affairs Medical Center, Sheba Medical Center Tel Hashomer Israel, Hadassah Medical Center Jerusalem Israel, Ichilov Medical Center Tel Aviv Israel.

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

Nothing to report.

4. IMPACT:

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

We set out to take basic clinical information collected in the ED when patients present with acute mild TBI and to use this data to predict cognitive outcome one year later. To do this, we developed a novel visual rating scale that quantifies brain reserve of the uninjured brain visible on the acute trauma head CT. Remarkably, we found that this new score – that takes 2 minutes for an MD to complete – was indeed an independent predictor of cognitive outcome one year later in a large cohort of adults presenting with mild TBI to trauma centers all over the U.S. In fact, the score was even more predictive of outcome that the Rotterdam score, which is a visual rating of the brain trauma itself (hemorrhage, swelling, brain shift, etc). We anticipate that these findings will contribute to a paradigm shift in how scientists and clinicians think about predicting outcome and forming a prognosis in patients presenting with mild TBI. Specifically, our findings will bring the important concept of brain reserve to the conversation. We further anticipate that others will apply our BRS rating system to their own TBI cohorts and will identify additional valuable uses for this score to predict other important outcomes after TBI such as global functional or psychological recovery. Lastly, we anticipate that this score may prove useful in other acute brain disease such as acute stroke.

What was the impact on other disciplines?

We anticipate that this score may be useful for other acute brain diseases such as acute stroke and several people have asked about this when we have presented these results verbally. Thus, we anticipate that others may apply this score to other acute brain diseases in the future.

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

Nothing to report.

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

Nothing to report.

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.

Schneider ALC, Huie JR, Boscardin WJ, Nelson L, Barber JK, Yaffe K, Diaz-Arrastia R, Ferguson AR, Kramer J, Jain S, Temkin N, Yuh E, Manley GT, Gardner RC; TRACK-TBI Investigators. Cognitive Outcome 1 Year After Mild Traumatic Brain Injury: Results From the TRACK-TBI Study. *Neurology.* 2022;98(12):e1248-e1261.

This article was published alongside a podcast interview with Dr. Gardner about the results which is available on the journal website.

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

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

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

Podcast interview with R. Gardner about the Aim 1 manuscript results, published on the Neurology Journal website and also available directly at this link:

http://traffic.libsyn.com/neurology/Neurology20Podcast_Mar202220Gardner20v2.3.mp3

- **Technologies or techniques**

We developed and validated a novel technique for visually rating brain reserve on trauma head CTs. The detailed scoring guide will be published in our second forthcoming manuscript describing Aim 2+3 results.

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

N/A

- **Other Products**

N/A

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Raquel Gardner, MD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2.2 cal mos
Contribution to Project:	
Funding Support:	

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

No Change.

What other organizations were involved as partners?

None

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:
N/A

QUAD CHARTS:
See attached.

9. APPENDICES:
N/A

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

AZ170057 Final Report W81XWH-18-1-0514

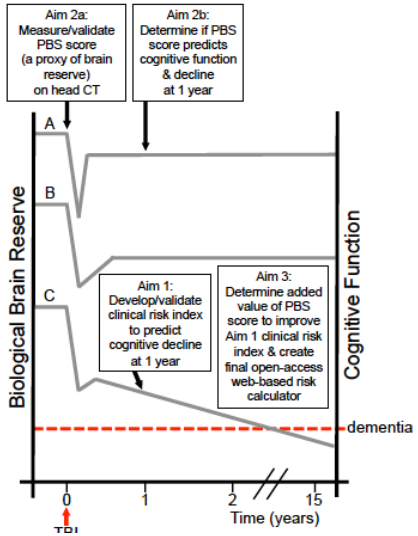
PI: Raquel C. Gardner **Org:** Northern California Institute for Research & Education **Award Amount:** $344,925.00

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	21-22
Planning/Regulatory/Data				
Aim 1				
Aim 2				
Aim 3				
Estimated Budget ($K)	**$97k**	**$133k**	**$127k**	

Updated: January 27, 2023, San Francisco, CA

Goals/Milestones

CY18-19 Goal – Planning/regulatory/data management
X Identify/train staff
X ethics approval
X obtain/prepare data for analysis
X begin Aim 1 and Aim 2a

CY19-20 Goals – Aim 1 and Aim 2a
X Complete Aim 1
X Complete Aim 2a – finalizing rating CTs with extensive trauma
X Begin Aim 2b

CY20-21 Goal – Aim 2b and Aim 3
X Complete Aim 2b
X Complete Aim 3

Comments/Challenges/Issues/Concerns

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

Budget Expenditure to Date

Projected Expenditure: $344,925
Actual Expenditure: $341,427