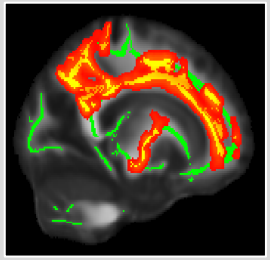
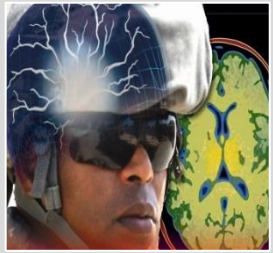
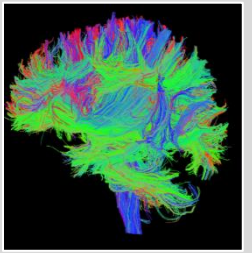
EMERGING BIOMARKERS IN TBI & CONCUSSION:

PROGRESS TOWARD CLINICAL TRANSLATION



Michael McCrea, PhD, ABPP

Professor & Vice Chair of Research

Co-Director, Center for Neurotrauma Research (CNTR)

Department of Neurosurgery

Medical College of Wisconsin

BIOMARKERS IN MODERN MEDICINE

SCIENTIFIC:

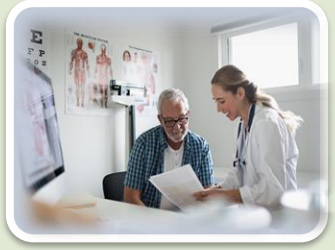
INFORMING PATHO-PHYSIOLOGY OF INJURY & DISEASE

DIAGNOSTIC:

DETERMINE PRESENCE & DEGREE OF INJURY & DISEASE

STRATIFICATION:

ENRICHMENT FOR TREATMENT & CLINICAL TRIALS



PROGNOSTIC:

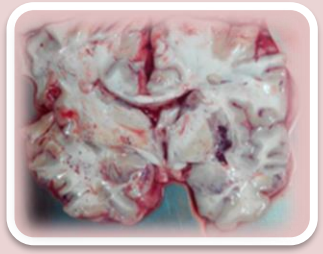
PREDICTING PATIENT RISK, RECOVERY & OUTCOME

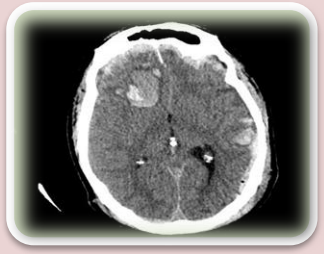
OUTCOME:

MEASURING RESPONSE TO TREATMENT, DISEASE MODIFICATION

TOWARD INDIVIDUALIZED MEDICINE

LAY OF THE LAND: TBI





SCIENTIFIC: MAJOR ADVANCES IN PATHO-PHYSIOLOGY OF INJURY & RECOVERY

DIAGNOSTIC: CLINICAL DX AND HEAD CT THE STANDARD; GCS FOR SEVERITY

STRATIFICATION: LITTLE BEYOND CT+/- AND GCS, OFTEN INDEPENDENT OF PATHOLOGY

PROGNOSTIC: PRIMARILY CLINICAL AND DEMOGRAPHIC PREDICTORS, LITTLE BIOLOGICAL

OUTCOME: BLUNT, GLOBAL OUTCOME (GOSE); PROGRESS IN COA'S

MAJOR GAP IN PRECISION MEDICINE

(non)Precision Medicine in TBI

Uzma Samadani, MD, PhD, FAANS; Samuel R. Daly | Features
AANS Neurosurgeon: Volume 25, Number 3, 2016

- Lack of stratification, phenotyping
- One size fits all approach
- Inability to match Rx to phenotype
- Inclusion/ exclusion
- Blunt outcome measurement

LACK OF OBJECTIVE BIOMARKERS

ROME WASN'T BUILT IN A DAY (OR DECADE)

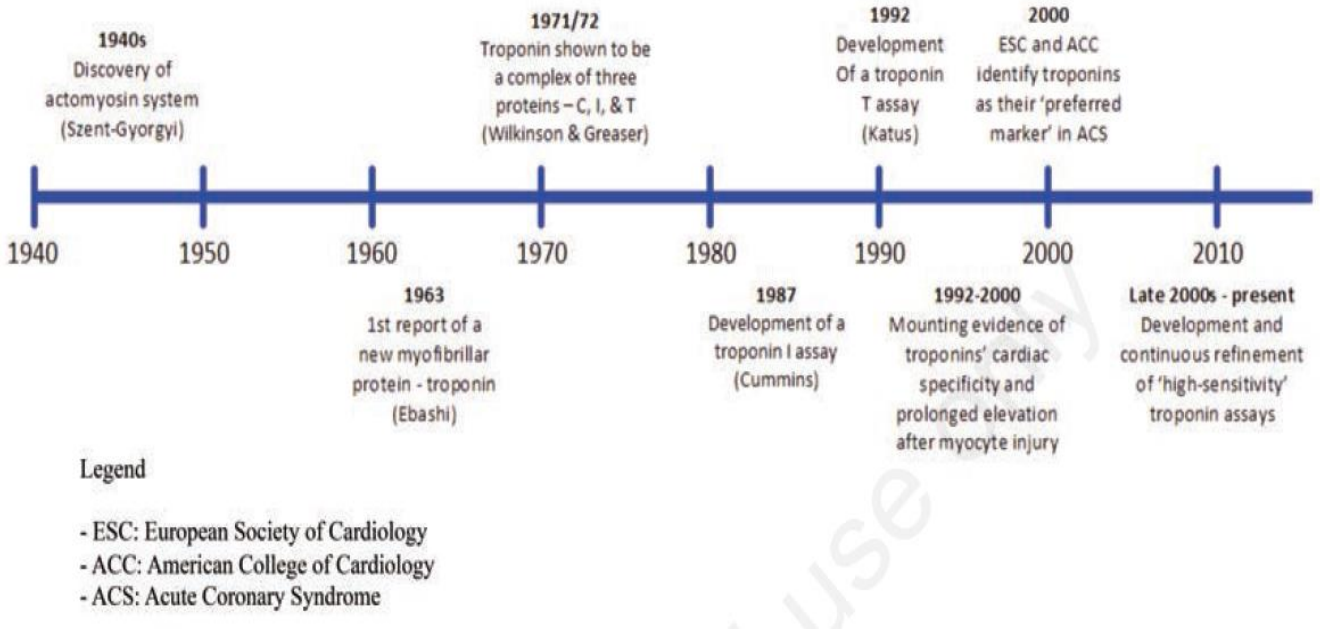
Cardiogenetics 2016; volume 6:6306

Measurement of troponin in cardiomyopathies

Andrew Connelly,[1] Iain N. Findlay,[2] Caroline J. Coats[2,3]

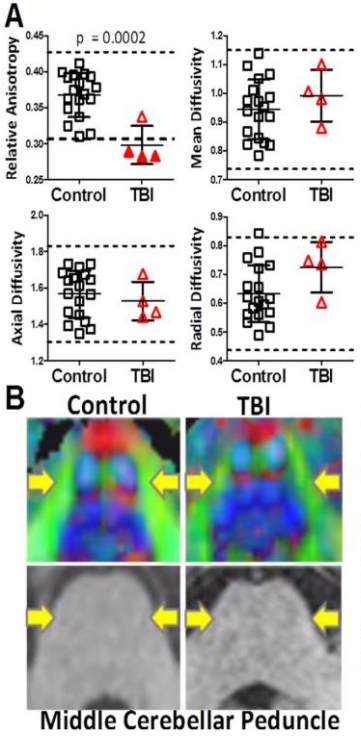
[1]School of Medicine, University of Glasgow; [2]Inherited Cardiac Conditions Clinic, Queen Elizabeth University Hospital, Glasgow; [3]Department of Cardiology, Golden Jubilee National Hospital, Glasgow, UK

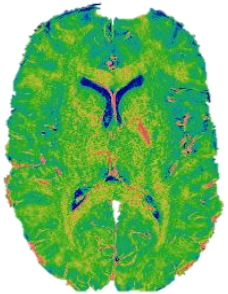
History of Troponin, From Discovery to Modern Day Use

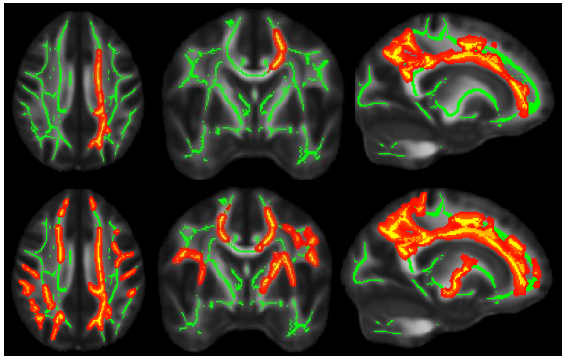


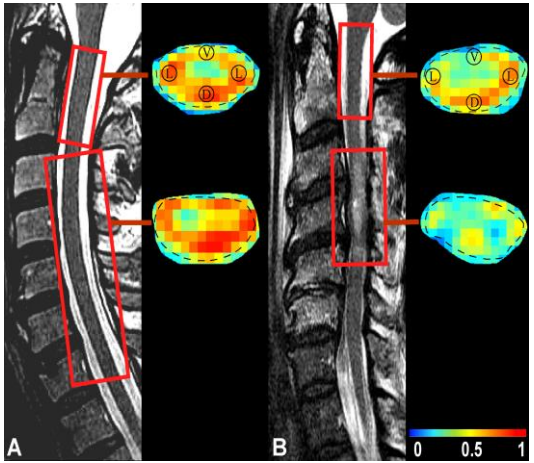
MEDICAL COLLEGE OF WISCONSIN
NEUROSURGERY

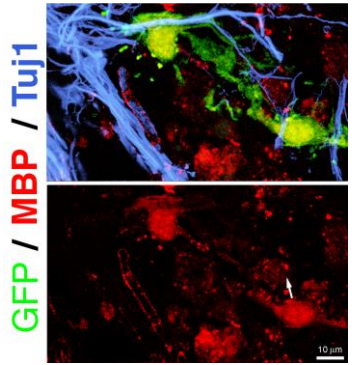
ROLE OF NEUROTRAUMA BIOMARKERS





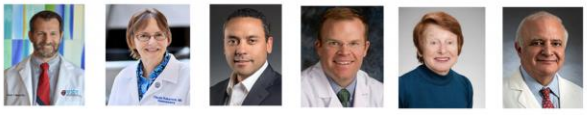






Diagnosis, Prognosis, Enrichment, Outcome

Modern "BIG SCIENCE" in TBI



TRACK-TBI NET

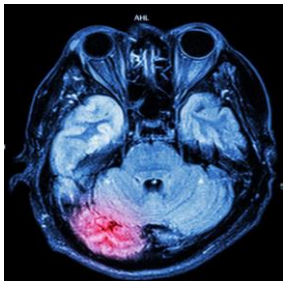
Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network

TBI Endpoints Development

A Collaborative for Advancing Diagnosis and Treatment of TBI

NCAA•DOD Grand Alliance CARE Consortium

A Public-Private Partnership to Advance the Science of Concussion in Sports & Military

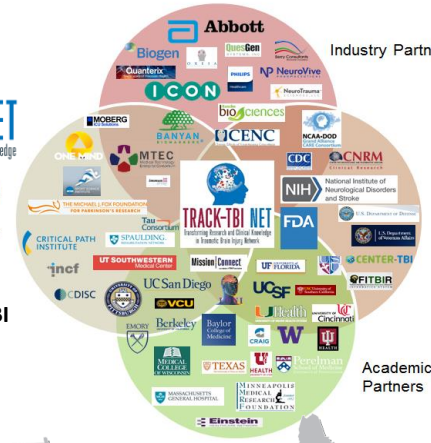


TRACK-TBI NET

Transforming Research and Clinical Knowledge in Traumatic Brain Injury Network

Not for Profit and Philanthropic Partners

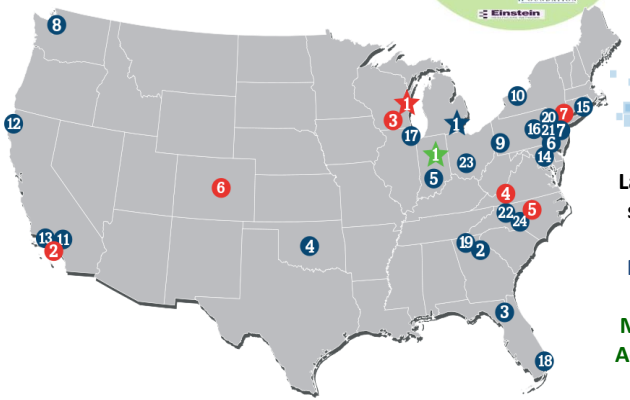
Largest national study of Civilian TBI



Industry Partners

Government Partners

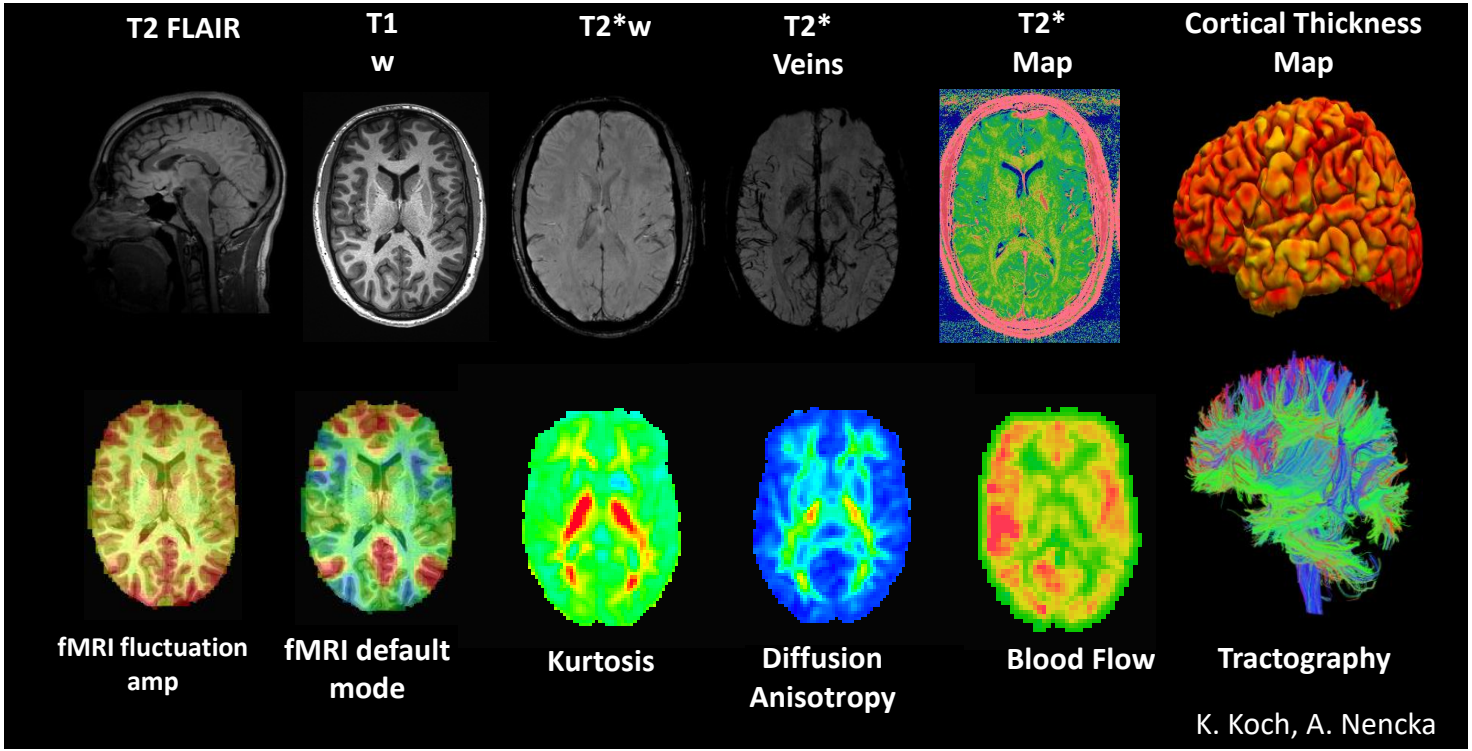
Academic Partners



Largest national study of TBI & concussion in NCAA Student Athletes and Military Service Academy Cadets

Informing the Science of TBI in all Populations at Risk

Sharper Image: Advanced MRI & TBI



TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

Protocols Aligned for Study of Civilian, Military, Sport TBI

NCAA•DOD Grand Alliance CARE Consortium

IMAGING PATHOPHYSIOLOGY OF INJURY & RECOVERY

MRI & TBI: Not So "Uncomplicated"

ORIGINAL ARTICLE

Magnetic Resonance Imaging Improves 3-Month Outcome Prediction in Mild Traumatic Brain Injury

Esther L. Yuh, MD, PhD,[1,2] Pratik Mukherjee, MD, PhD,[1,2] Hester F. Lingsma, PhD,[3] John K. Yue, BS,[1,4] Adam R. Ferguson, PhD,[1,4] Wayne A. Gordon, PhD,[5] Alex B. Valadka, MD,[6] David M. Schnyer, PhD,[7] David O. Okonkwo, MD, PhD,[8] Andrew I. R. Maas, MD, PhD,[9] Geoffrey T. Manley, MD, PhD,[1,4] and the TRACK-TBI Investigators

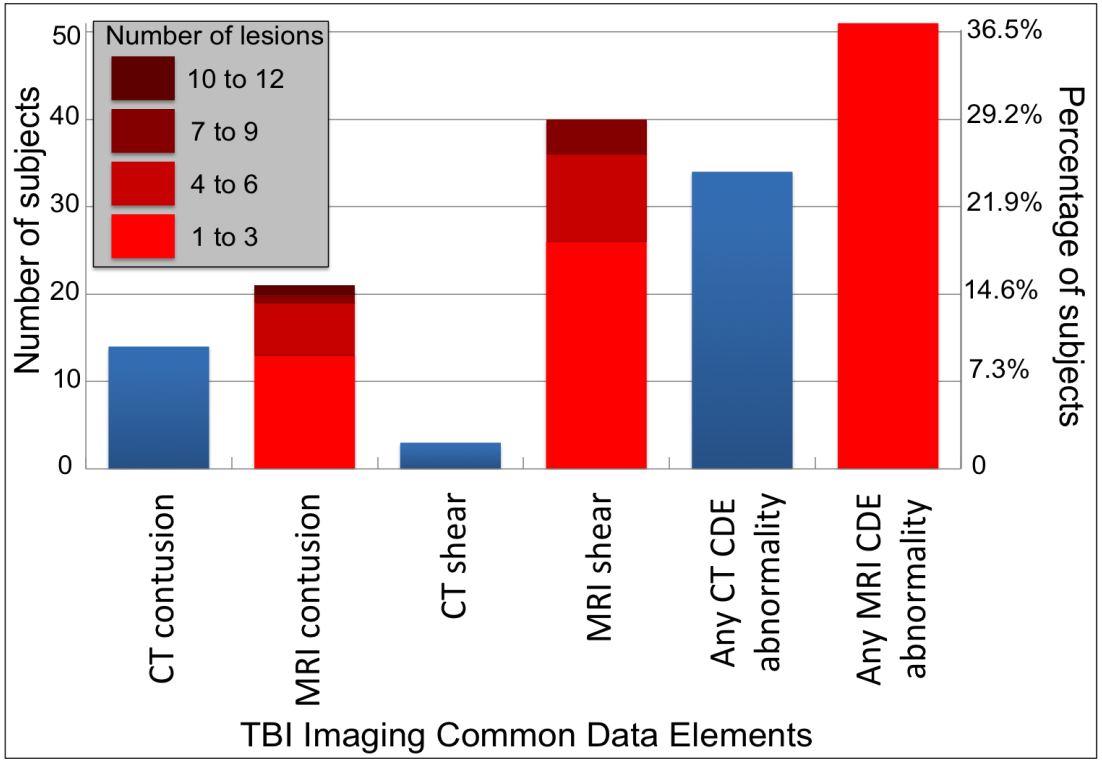
Objective: To determine the clinical relevance, if any, of traumatic intracranial findings on early head computed tomography (CT) and brain magnetic resonance imaging (MRI) to 3-month outcome in mild traumatic brain injury (MTBI).

Methods: One hundred thirty-five MTBI patients evaluated for acute head injury in emergency departments of 3 LEVEL I trauma centers were enrolled prospectively. In addition to admission head CT, early brain MRI was performed 12 ± 3.9 days after injury. Univariate and multivariate logistic regression were used to assess for demographic, clinical, socioeconomic, CT, and MRI features that were predictive of Extended Glasgow Outcome Scale (GOS-E) at 3 months postinjury.

Results: Twenty-seven percent of MTBI patients with normal admission head CT had abnormal early brain MRI. CT evidence of subarachnoid hemorrhage was associated with a multivariate odds ratio of 3.5 ($p = 0.01$) for poorer 3-month outcome, after adjusting for demographic, clinical, and socioeconomic factors. One or more brain contusions on MRI, and ≥4 foci of hemorrhagic axonal injury on MRI, were each independently associated with poorer 3-month outcome, with multivariate odds ratios of 4.5 ($p = 0.01$) and 3.2 ($p = 0.03$), respectively, after adjusting for head CT findings and demographic, clinical, and socioeconomic factors.

early brain imaging after MTBI is demonstrated. The addition of early CT and MRI markers to a prognostic model based on previously known demographic, clinical, and socioeconomic predictors resulted in a >2-fold increase in the explained variance in 3-month GOS-E.

ANN NEUROL 2013;73:224–235



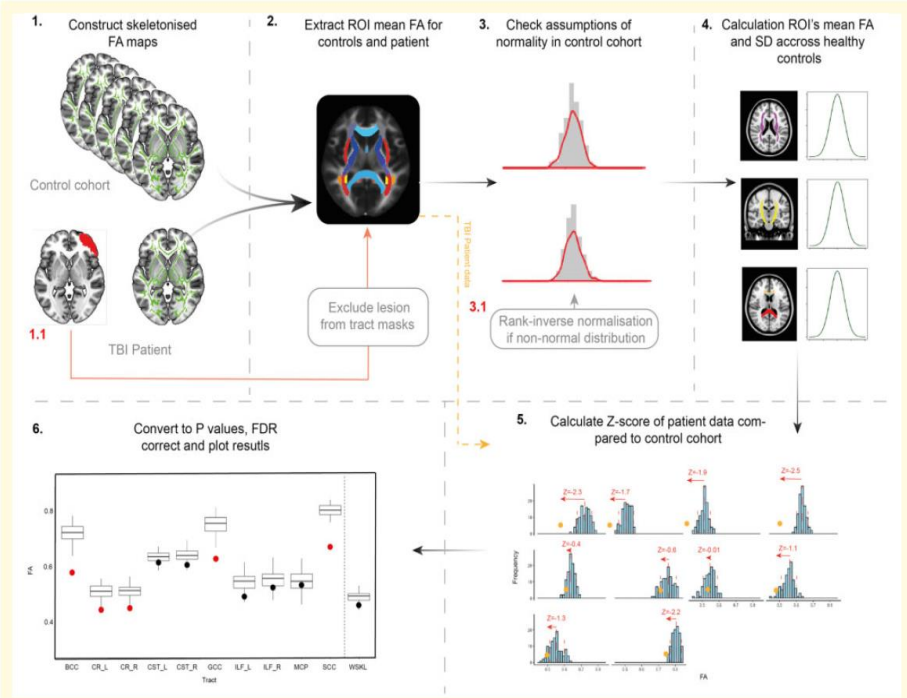
27% With Negative CT Have Positive MRI

PATHWAY TO PATIENT CARE

Detecting axonal injury in individual patients after traumatic brain injury

Amy E. Jolly,[1,2] Maria Bălăeț,[1] Adriana Azor,[1] Daniel Friedland,[1] Stefano Sandrone,[1]
Neil S. N. Graham,[1] Karl Zimmerman[1] and David J. Sharp[1,2]

BRAIN
A JOURNAL OF NEUROLOGY



- Pipeline for DTI analysis to Dx Axonal Injury
- FA calculated in high performing tracts
- 117 msTBI patients (92 chronic, >6 mos; 25 subacute 10d-6w), 103 controls
- DIAGNOSTIC: AI detected in 52% of chronic, 28% of subacute TBI patients
- SENSITIVITY: 1/3 of TBI with normal standard MRI had evidence of AI
- PHENOTYPIC: 40% with visible microbleeds had no AI on DTI
- PROGNOSTIC: AI associated with poorer cognitive, functional outcome
- LONGITUDINAL COURSE: More DTI abnormality further out from TBI

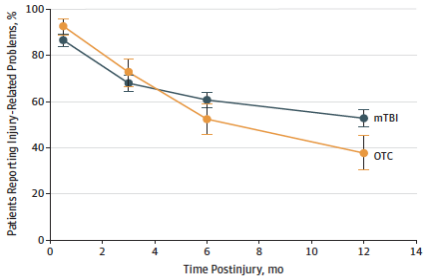
Predicting Outcome in TBI

JAMA Neurology | Original Investigation

Recovery After Mild Traumatic Brain Injury in Patients Presenting to US Level I Trauma Centers
A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study

Lindsay D. Nelson, PhD; Nancy R. Temkin, PhD; Sureyya Dikmen, PhD; Jason Barber, MS; Joseph T. Giacino, PhD; Esther Yuh, MD, PhD; Harvey S. Levin, PhD; Michael A. McCrea, PhD; Murray B. Stein, MD, MPH; Pratik Mukherjee, MD, PhD; David O. Okonkwo, MD, PhD; Claudia S. Robertson, MD; Ramon Diaz-Arrastia, MD, PhD; Geoffrey T. Manley, MD, PhD; and the TRACK-TBI Investigators

Figure. Percentage of Patients in the Mild Traumatic Brain Injury (mTBI) and Orthopedic Trauma Control (OTC) Groups Reporting Injury-Related Limitations With Day-to-Day Functioning From 2 Weeks to 12 Months Postinjury on the Glasgow Outcome Scale–Extended Score Interview



Rates decreased from 87% (mTBI) and 93% (OTC) at 2 weeks to 53% (mTBI) and 38% (OTC) at 12 months postinjury. Group differences were nonsignificant at 2 weeks (RR, 0.93; 95% CI, 0.89-0.98), 3 months (RR, 0.92; 95% CI, 0.84-1.02), and 6 months (RR, 1.14; 95% CI, 0.99-1.31) postinjury. At 12 months postinjury, the mTBI group reported significantly higher rates of continued limitations with day-to-day functioning (RR, 1.38; 95% CI, 1.12-1.71).

Key Points

Question How common are persistent, injury-related functional limitations following mild traumatic brain injury vs orthopedic trauma?

Findings In this cohort study of 1154 patients with mild traumatic brain injury and 299 patients with orthopedic trauma serving as controls, 53% of participants with mild traumatic brain injury reported impairment 12 months postinjury vs 38% of those with orthopedic trauma. Patients with intracranial abnormalities had the poorest outcomes; however, patients without abnormalities also reported problems at 12 months.

Meaning Many patients who present to level I trauma centers with mild traumatic brain injury experience difficulties at 12 months postinjury, suggesting that this injury is not always benign; better follow-up and treatment appear to be needed.

IMPORTANCE Most traumatic brain injuries (TBIs) are classified as mild (mTBI) based on admission Glasgow Coma Scale (GCS) scores of 13 to 15. The prevalence of persistent functional limitations for these patients is unclear.

OBJECTIVES To characterize the natural history of recovery of daily function following mTBI vs peripheral orthopedic traumatic injury in the first 12 months postinjury using data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, and, using clinical computed tomographic (CT) scans, examine whether the presence (CT+) or absence (CT–) of acute intracranial findings in the mTBI group was associated with outcomes.

DESIGN, SETTING, AND PARTICIPANTS TRACK-TBI, a cohort study of patients with mTBI presenting to US level I trauma centers, enrolled patients from February 26, 2014, to August 8, 2018, and followed up for 12 months. A total of 1453 patients at 11 level I trauma center emergency departments or inpatient units met inclusion criteria (ie, mTBI [n = 1154] or peripheral orthopedic traumatic injury [n = 299]) and were enrolled within 24 hours of injury; mTBI participants had admission GCS scores of 13 to 15 and clinical head CT scans. Patients with peripheral orthopedic trauma injury served as the control (OTC) group.

EXPOSURES Participants with mTBI or OTC.

MAIN OUTCOMES AND MEASURES The Glasgow Outcome Scale Extended (GOSE) scale score, reflecting injury-related functional limitations across broad life domains at 2 weeks and 3, 6, and 12 months postinjury was the primary outcome. The possible score range of the GOSE score is 1 (dead) to 8 (upper good recovery), with a score less than 8 indicating some degree of functional impairment.

RESULTS Of the 1453 participants, 953 (65.6%) were men; mean (SD) age was 40.9 (17.1) years in the mTBI group and 40.9 (15.4) years in the OTC group. Most participants (mTBI, 87%; OTC, 93%) reported functional limitations (GOSE <8) at 2 weeks postinjury. At 12 months, the percentage of mTBI participants reporting functional limitations was 53% (95% CI, 49%-56%) vs 38% (95% CI, 30%-45%) for OTCs. A higher percentage of CT+ patients reported impairment (61%) compared with the mTBI CT– group (49%; relative risk [RR], 1.24; 95% CI, 1.08-1.43) and a higher percentage in the mTBI CT–group compared with the OTC group (RR, 1.28; 95% CI, 1.02-1.60).

CONCLUSIONS AND RELEVANCE Most patients with mTBI presenting to US level I trauma centers report persistent, injury-related life difficulties at 1 year postinjury, suggesting the need for more systematic follow-up of patients with mTBI to provide treatments and reduce the risk of chronic problems after mTBI.

Acute White-Matter Abnormalities in SRC: A DTI Study from the NCAA-DoD CARE Consortium

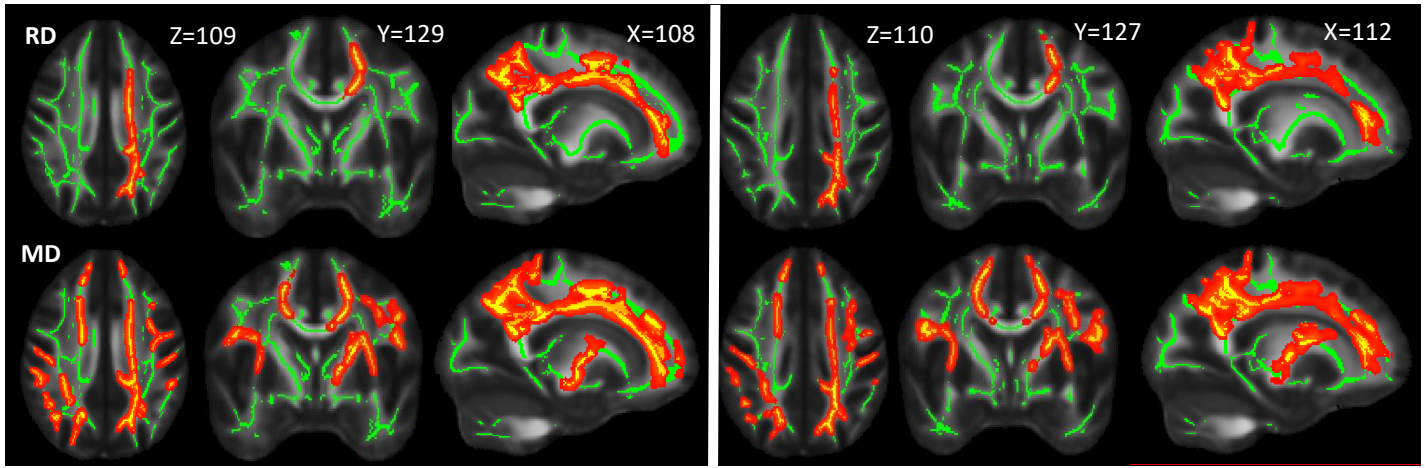
S. Mustafi, J. Harezlak, K.M. Koch, A.S. Nencka, T.B. Meier, J.D. West, C.C. Giza, J.P. DiFiori, K.M. Guskiewicz, J.P.Mihalik, S.M. LaConte, S.M. Duma, S.P. Broglio, A.J. Saykin, M.McCrea, T.W. McAllister, and Y.C Wu

J Neurotrauma. 2018 Nov 15;35(22):2653-2664.

ACUTE DIFFUSION MRI (24-48 hrs PI)

Concussed vs. Contact Control

Concussed vs. Non-Contact Control

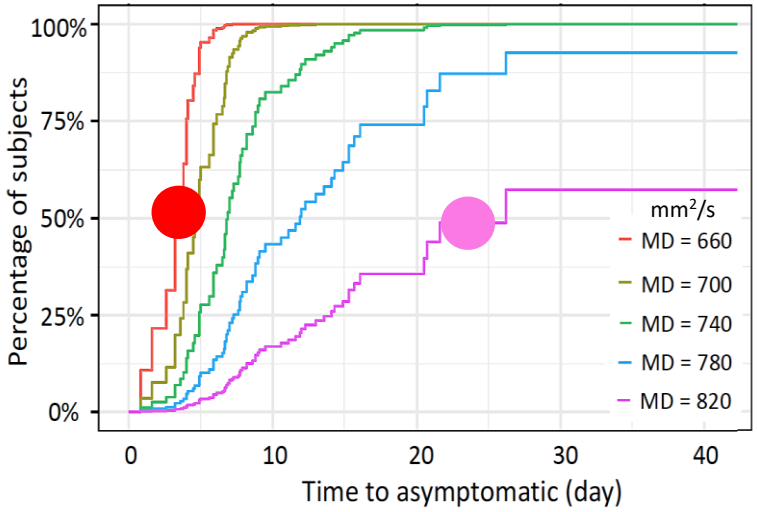


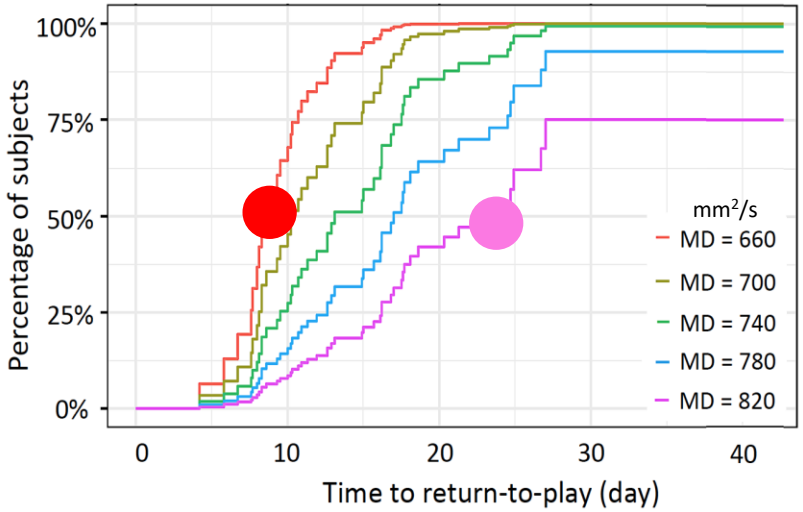
Corrected $p < 0.05$, **Location**: Anterior and posterior corona radiata and corpus callosum

Widespread elevations in mean diffusivity relative to controls

Longitudinal White Matter Abnormalities in SRC: A Diffusion MRI Study of the NCAA-DOD CARE Consortium

Y.C. Wu, J. Harezlak, N.M.H. Elsaid, Z. Lin, Q., Wen, S.M. Mustafi, L.D. Riggen, K.M. Koch, A.S. Nencka, T.B. Meier, A.R. Mayer, Y. Wang, C.C. Giza, J.P. DiFiori, K.M., Guskiewicz, J.P. Mihalik, S.M. LaConte, S.M. Duma, S.P. Broglio, A.J. Saykin, M. McCrea, T.W. McAllister (**NEUROLOGY 2020**)

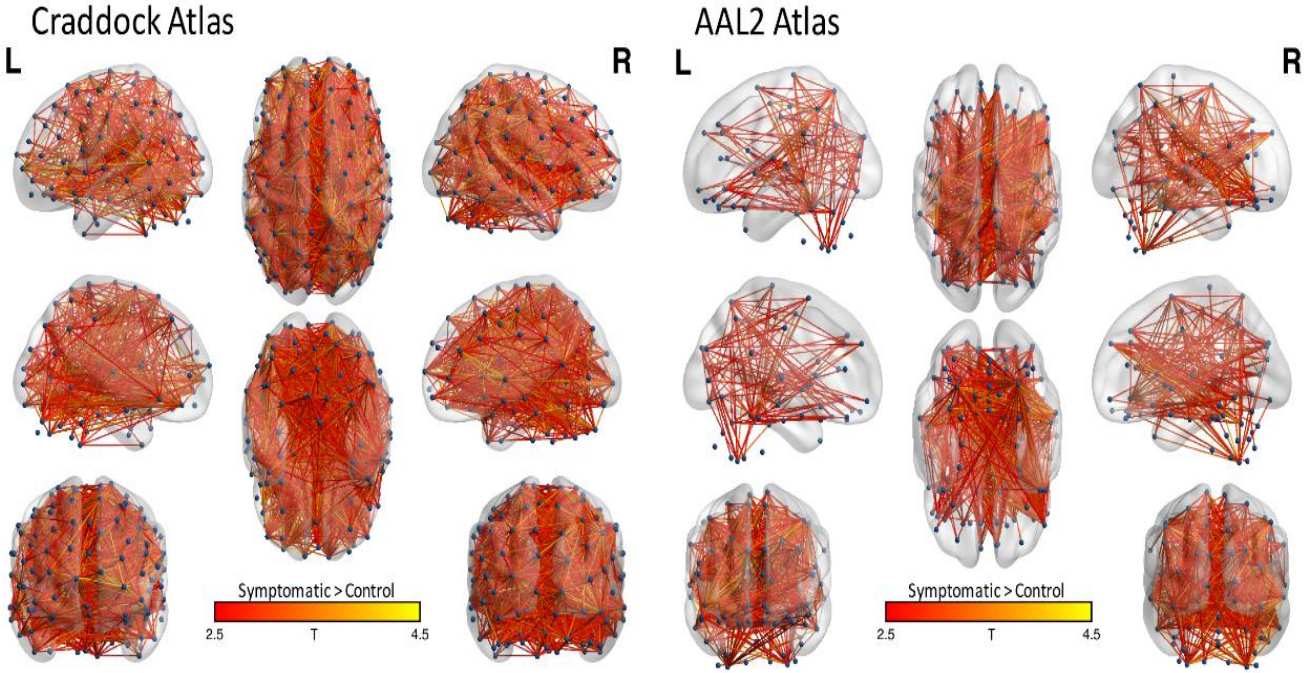


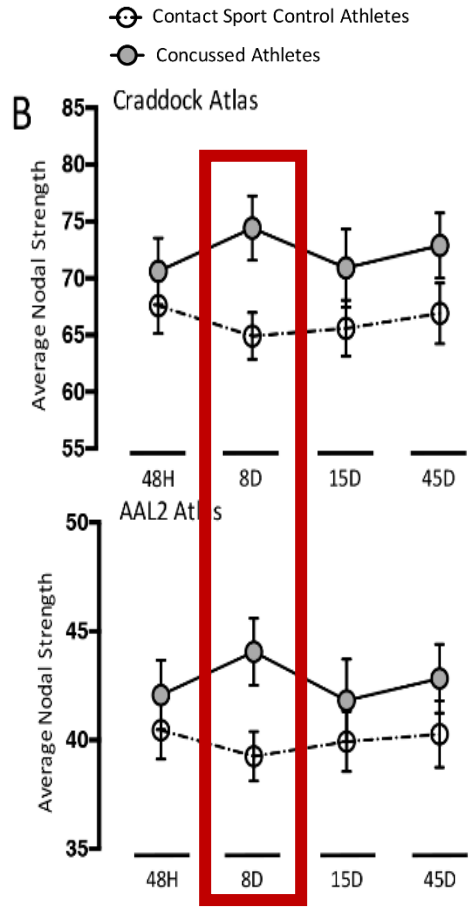


Burden of acute MD abnormality associated with symptoms, recovery & RTP time

Acute Changes in Functional Connectivity: rs-fMRI

(Kaushal, Meier et al; **HBM 2019**)

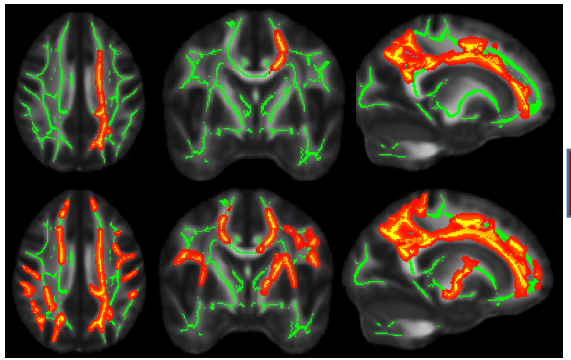




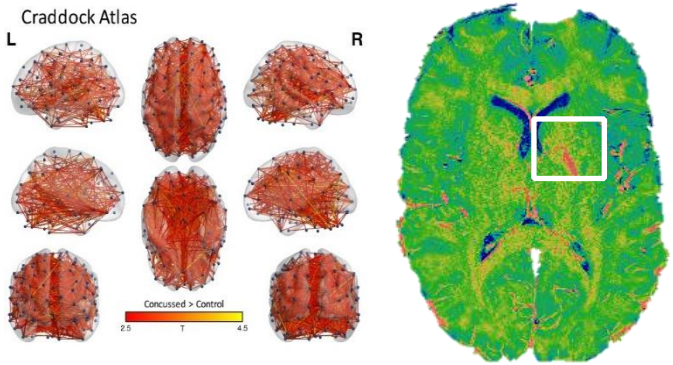
Delayed Onset of Functional Injury

MRI Biomarkers of Injury & Recovery

STRUCTURAL CHANGES
(Central White Matter Regions)



FUNCTIONAL CHANGES
(Diffuse White+Gray Matter)

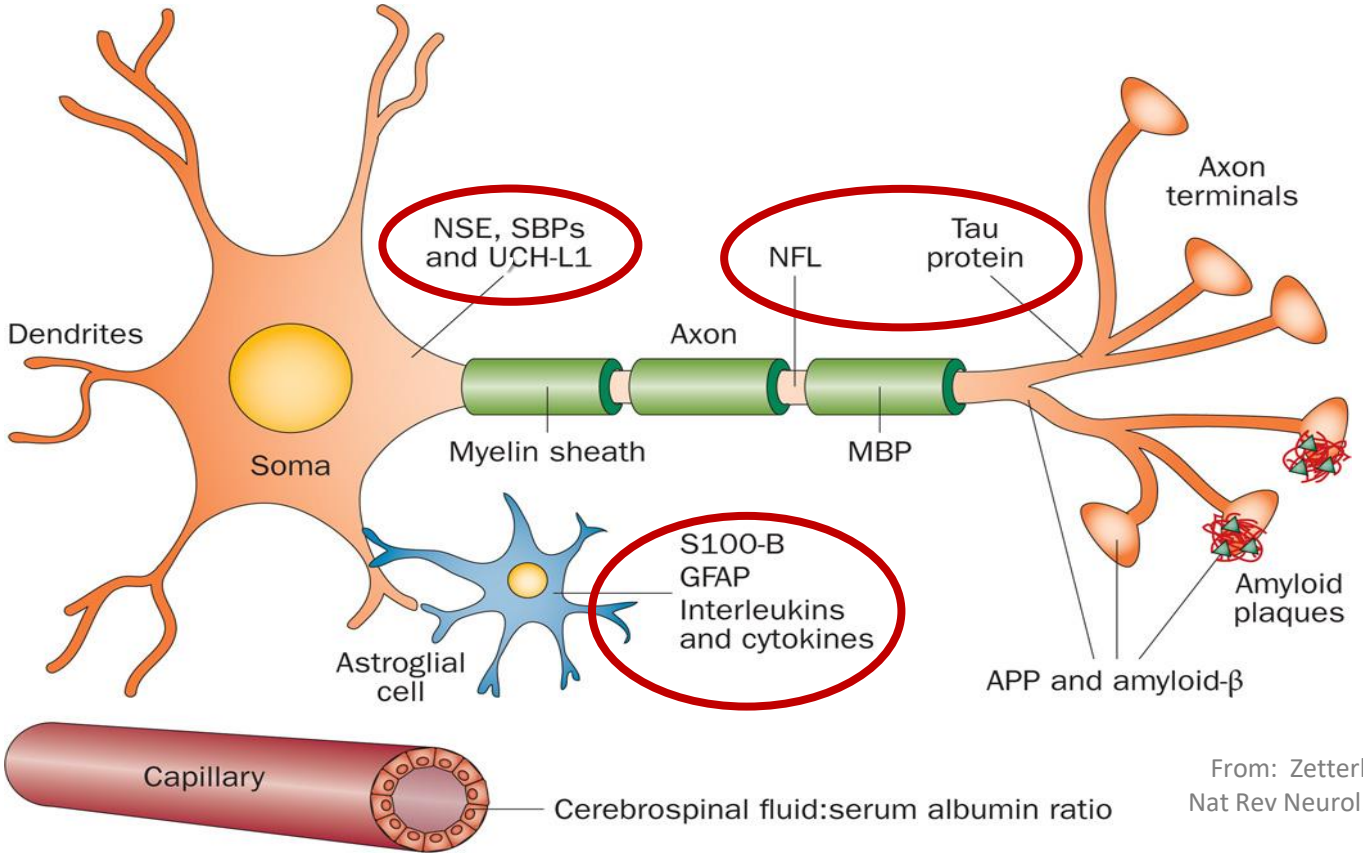


Pathophysiological Hypotheses:

Axonal strain/injury, glial injury, white matter integrity, dysregulation of CBF, changes in brain metabolism/energy, altered neurotransmission, inflammation, edema, other

M. McCrea 2020

Blood Biological Markers of Injury & Recovery



From: Zetterberg, Smith & Blennow. Nat Rev Neurol. 2013 Apr; 9(4): 201–210

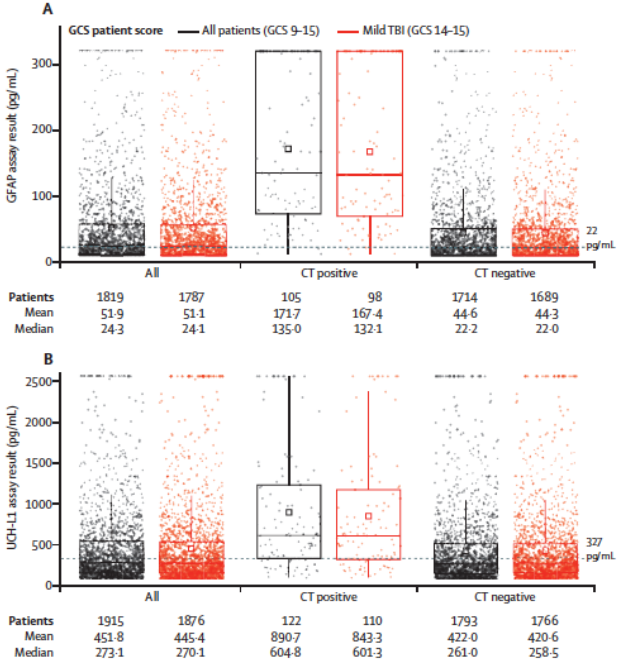
Candidate TBI biomarkers reflect different pathophysiologies

Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study

Lancet Neurol 2018

Published Online
July 24, 2018

Jeffrey J Bazarian, Peter Biberthaler*, Robert D Welch, Lawrence M Lewis, Pal Barzo, Viktoria Bogner-Flatz, P Gunnar Brolinson, Andras Büki, James Y Chen, Robert H Christenson, Dallas Hack, J Stephen Huff, Sandeep Johar, J Dedrick Jordan, Bernd A Leidel, Tobias Lindner, Elizabeth Ludington, David O Okonkwo, Joseph Ornato, W Frank Peacock, Kara Schmidt, Joseph A Tyndall, Arastoo Vossough, Andy S Jagoda*



	Sensitivity	Specificity	PPV	NPV
GCS 9–15 (n=1959)	0·976 (0·931–0·995)	0·364 (0·342–0·387)	0·095 (0·079–0·112)	0·996 (0·987–0·999)
GCS 14–15 (n=1920)	0·973 (0·924–0·994)	0·367 (0·345–0·390)	0·088 (0·073–0·105)	0·995 (0·987–0·999)
Neurosurgically manageable lesions (n=8)	1·00 (0·631–1·00)	0·344 (0·323–0·365)	0·006 (0·003–0·012)	1·00 (0·995–1·00)

Data in parentheses are 95% CIs. PPV=positive predictive value. NPV=negative predictive value. LRP=likelihood ratio positive. LRN=likelihood ratio negat

Table 3: Performance of UCH-L1 and GFAP assay for predicting intracranial injury on head CT scan

Limitation: core lab test that requires 3-4h to return result

= barrier to broad clinical adoption or fielded use

Adapted from Geoff Manley, MD, PhD with permission

GFAP for Aid in Diagnosis of TBI

Journal of Neurotrauma, Ahead of Print | Original Article

Full Access

Point-of-Care Platform Blood Biomarker Testing of Glial Fibrillary Acidic Protein versus S100 Calcium-Binding Protein B for Prediction of Traumatic Brain Injuries: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study

David O. Okonkwo, Ross C. Puffer, Ava M. Puccio, Esther L. Yuh, John K. Yue, Ramon Diaz-Arrastia, Frederick K. Korley, Kevin K. W. Wang, Xiaoying Sun, Sabrina R. Taylor, Pratik Mukherjee, Amy J. Markowitz, Sonia Jain, Geoffrey T. Manley, The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Investigators ... See all authors

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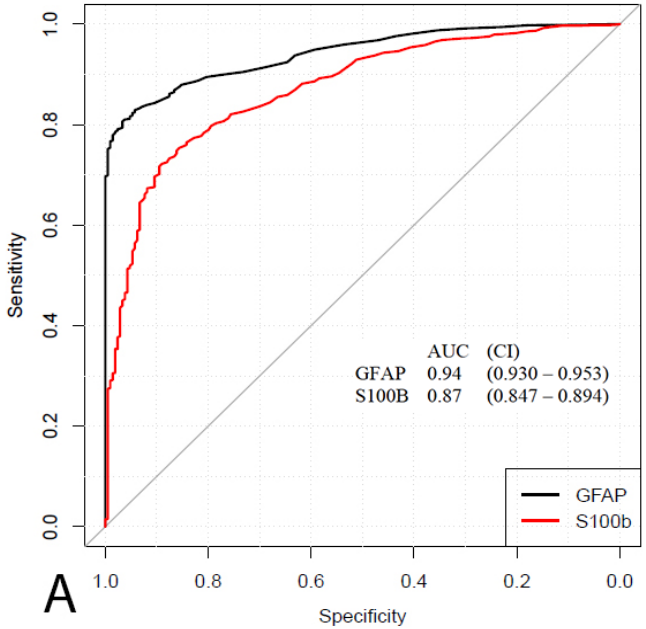
For aid in diagnosis of TBI, **POC GFAP** significantly outperformed core lab S100B

GFAP AUC 0.94 **95% CI 0.93-0.95**

S100B AUC 0.87 95% CI 0.85-0.89

p<0.001



- GFAP (plasma) cutoffs for TBI vs Healthy Controls

Cutoff	Sensitivity	Specificity	NPV	PPV
14.05	0.902 (0.884, 0.918)	0.775 (0.713, 0.828)	0.544 (0.502, 0.594)	0.963 (0.954, 0.972)
11.15	0.928 (0.913, 0.941)	0.646 (0.579, 0.708)	0.576 (0.524, 0.63)	0.945 (0.935, 0.955)
10.05	0.943 (0.932, 0.955)	0.632 (0.56, 0.694)	0.626 (0.573, 0.683)	0.944 (0.933, 0.953)
8.05	0.962 (0.952, 0.972)	0.536 (0.469, 0.603)	0.685 (0.623, 0.748)	0.932 (0.922, 0.941)
5.1	0.984 (0.977, 0.991)	0.402 (0.335, 0.474)	0.793 (0.717, 0.867)	0.915 (0.907, 0.925)

Adapted from Geoff Manley, MD, PhD with permission

Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study

John K Yue*, Esther L Yuh*, Frederick K Korley*, Ethan A Winkler, Xiaoying Sun, Ross C Puffer, Hansen Deng, Winward Choy, Ankush Chandra, Sabrina R Taylor, Adam R Ferguson, J Russell Huie, Miri Rabinowitz, Ava M Puccio, Pratik Mukherjee, Mary J Vassar, Kevin K W Wang, Ramon Diaz-Arrastia, David O Okonkwo, Sonia Jain, Geoffrey T Manley, and the TRACK-TBI Investigators†

Lancet Neurol 2019; 18: 953–61

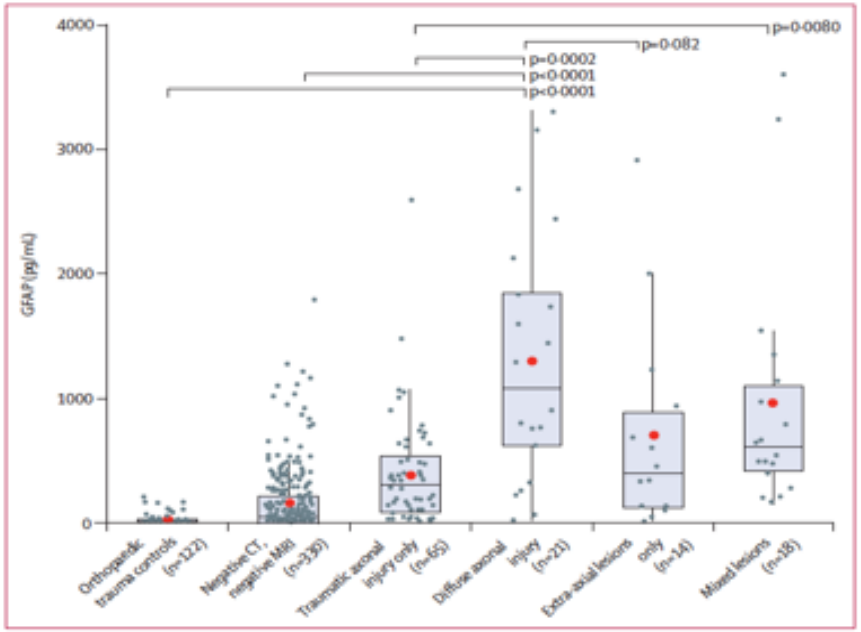
Summary

Background After traumatic brain injury (TBI), plasma concentration of glial fibrillary acidic protein (GFAP) correlates with intracranial injury visible on CT scan. Some patients with suspected TBI with normal CT findings show pathology on MRI. We assessed the discriminative ability of GFAP to identify MRI abnormalities in patients with normal CT findings.

	Number of patients	Plasma GFAP concentration (pg/mL)			p value
		Mean (SD)	Median (25–75th percentile)	Range	
Positive CT	199	1400·9 (1598·6)	786·0 (357·0–1863·3)	0–9409·7	<0·0001*
Negative CT	450	308·0 (530·5)	110·3 (22·7–352·3)	0–4095·1	..
Negative CT and positive MRI	120	692·2 (827·6)	414·4 (139·3–813·4)	5·2–4095·1	<0·0001†
Negative CT and negative MRI	330	168·3 (250·9)	74·0 (17·5–214·4)	0–1864·5	..
Orthopaedic trauma controls	122	23·7 (37·2)	13·1 (6·9–20·0)	0–216·8	<0·0001‡§
Healthy controls	209	11·0 (12·7)	8·0 (3·0–14·0)	0–98·0	<0·0001‡§

GFAP=glial fibrillary acidic protein. P values were calculated from the Wilcoxon rank sum test for the comparisons, which compares the distributions of the two groups. *Compared with patients with negative CT. †Compared with patients with negative CT and negative MRI findings. ‡Compared with patients with negative CT and positive MRI findings. §Compared with patients with negative CT and negative MRI findings.

Table 2: Plasma GFAP concentrations by imaging modality and findings



- **Blood-based biomarkers are more sensitive than CT**
- **Potential to improve diagnosis and triage of TBI patients**

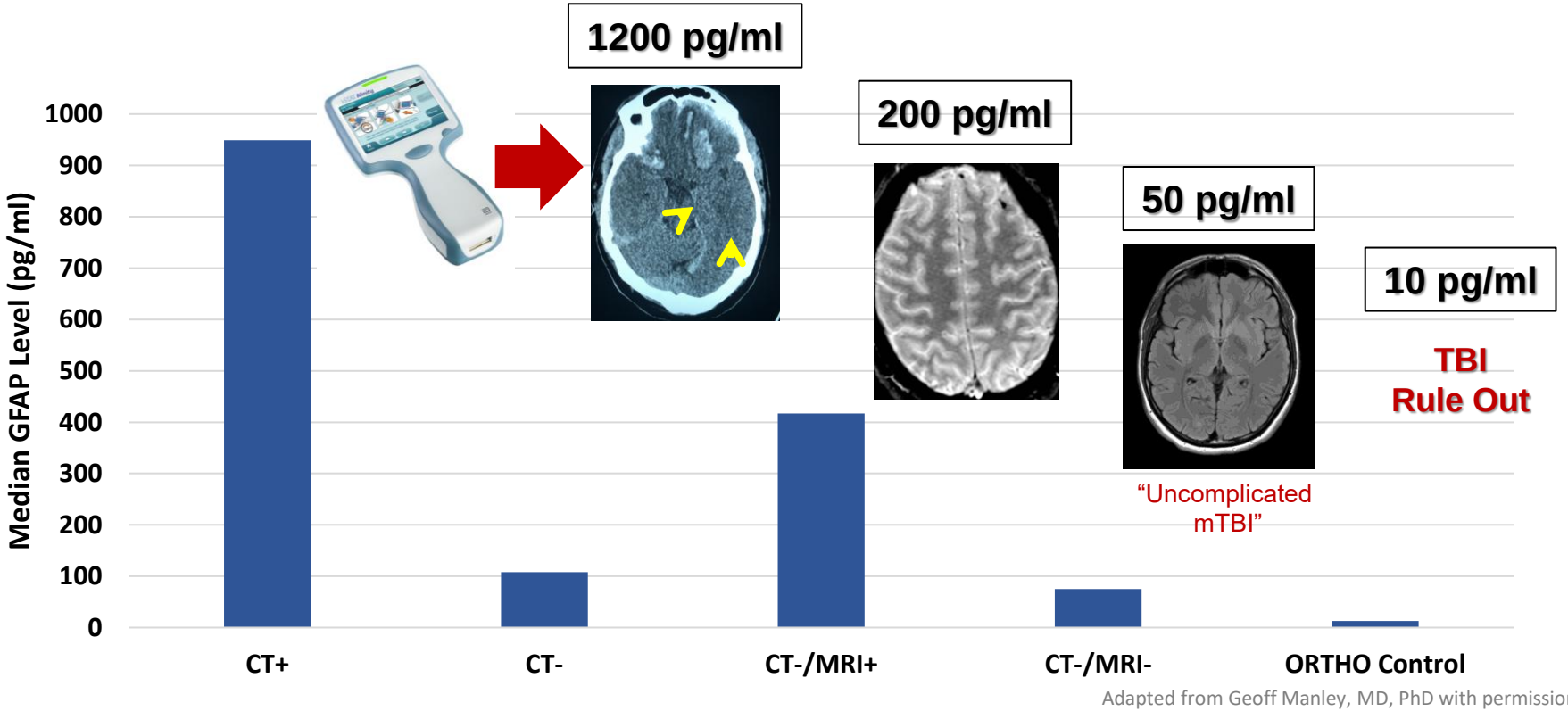
ACUTE BIOMARKERS PREDICT FAVORABLE VS. UNFAVORABLE RECOVERY AT 12 MONTHS POSTINJURY:

AUC FOR GOSE 1-4 vs 5-8:

GFAP = 0.84, UCH-L1 = 0.84

Adapted from Geoff Manley, MD, PhD with permission

ACUTE GFAP LEVELS AFTER TBI



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POTENTIAL VALUE: Diagnostic, Prognostic, Enrichment

Blood Biomarkers of Acute SRC

JAMA Network Open

Original Investigation | Neurology

Association of Blood Biomarkers With Acute Sport-Related Concussion in Collegiate Athletes

Findings From the NCAA and Department of Defense CARE Consortium

Michael McCrea, PhD, ABPP; Steven P. Broglio, PhD; Thomas W. McAllister, MD; Jessica Gill, PhD; Christopher C. Giza, MD; Daniel L. Huber, MPH; Jaroslaw Harezlak, PhD; Kenneth L. Cameron, PhD; Megan N. Houston, PhD; Gerald McGinty, DPT; Jonathan C. Jackson, MD; Kevin Guskiewicz, PhD; Jason Mihalik, PhD; M. Alison Brooks, MD, MPH; Stephan Duma, PhD; Steven Rowson, PhD; Lindsay D. Nelson, PhD; Paul Pasquina, MD; Timothy B. Meier, PhD; and the CARE Consortium Investigators

Abstract

IMPORTANCE There is potential scientific and clinical value in validation of objective biomarkers for sport-related concussion (SRC).

OBJECTIVE To investigate the association of acute-phase blood biomarker levels with SRC in collegiate athletes.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, prospective, case-control study was conducted by the National Collegiate Athletic Association (NCAA) and the US Department of Defense Concussion Assessment, Research, and Education (CARE) Consortium from February 20, 2015, to May 31, 2018, at 6 CARE Advanced Research Core sites. A total of 504 collegiate athletes with concussion, contact sport control athletes, and non–contact sport control athletes completed clinical testing and blood collection at preseason baseline, the acute postinjury period, 24 to 48 hours after injury, the point of reporting being asymptomatic, and 7 days after return to play. Data analysis was conducted from March 1 to November 30, 2019.

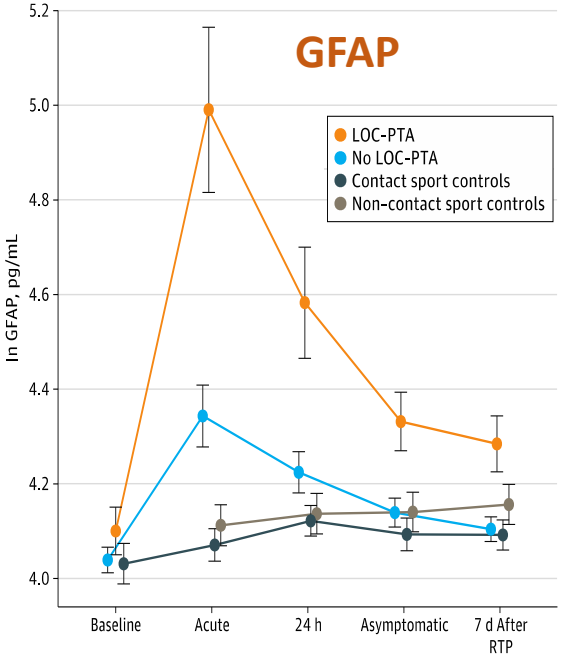
MAIN OUTCOMES AND MEASURES Glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain, and tau were quantified using the Quanterix Simoa multiplex assay. Clinical outcome measures included the Sport Concussion Assessment Tool-Third Edition (SCAT-3) symptom evaluation, Standardized Assessment of Concussion, Balance Error Scoring System, and Brief Symptom Inventory 18.

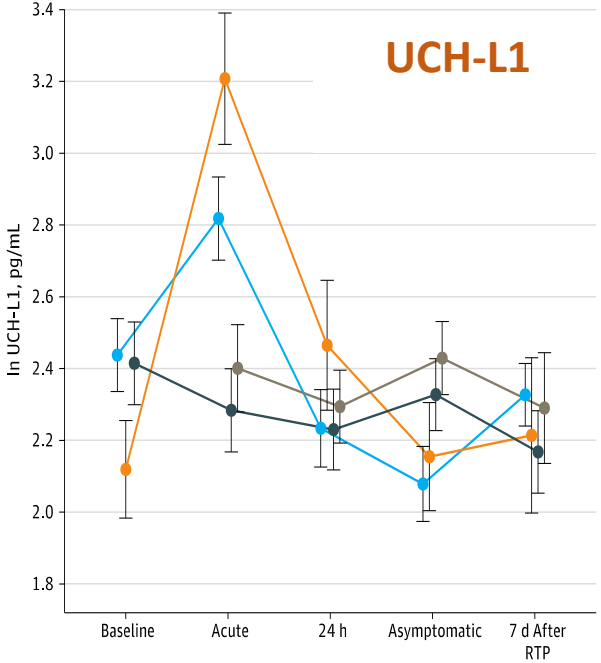
Key Points

Question Is sport-related concussion associated with levels of traumatic brain injury biomarkers in collegiate athletes?

Findings In this case-control study of 504 collegiate athletes with concussion, contact sport control athletes, and non–contact sport athletes, the athletes with concussion had significant elevations in multiple traumatic brain injury biomarkers compared with preseason baseline and with 2 groups of control athletes without concussion during the acute postinjury period.

Meaning These results suggest that blood biomarkers can be used as research tools to inform the underlying pathophysiological mechanism of concussion and provide additional support for future studies to optimize and validate biomarkers for potential clinical use in sport-related concussion.





JAMA Network Open

Plasma Biomarker Concentrations Associated With Return to Sport Following Sport-Related Concussion in Collegiate Athletes—A Concussion Assessment, Research, and Education (CARE) Consortium Study

Elevated Biomarker Levels ≤ 24 Hours After SRC Associated with Longer Time to Recovery & RTP

Blood Biomarkers of "Uncomplicated" mTBI

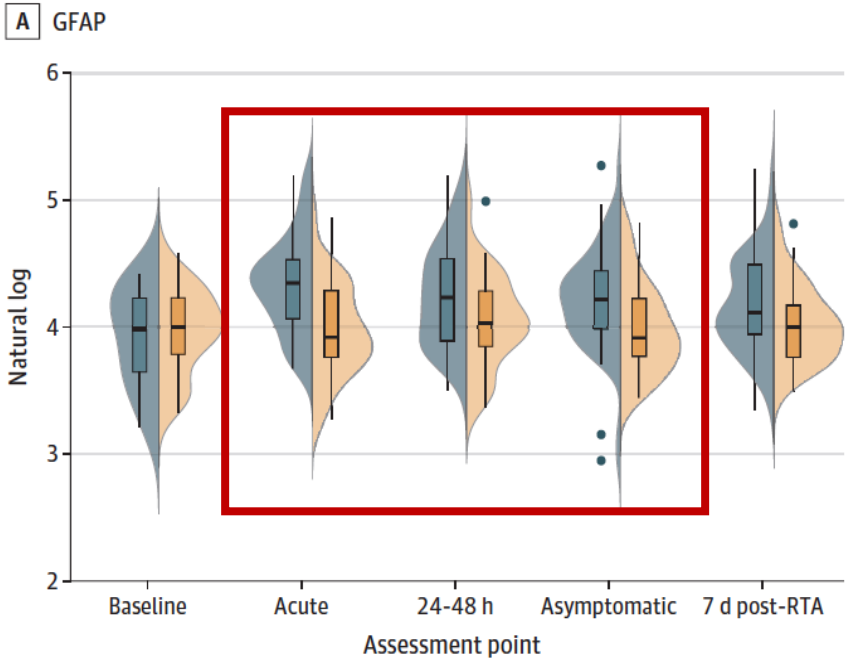
Original Investigation | Neurology

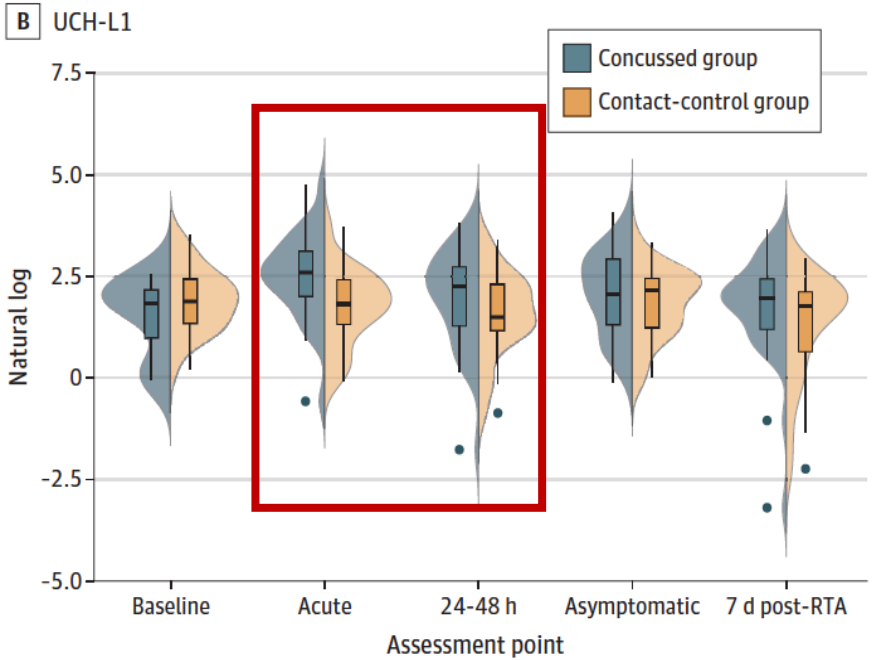
Assessment of Blood Biomarker Profile After Acute Concussion During Combative Training Among US Military Cadets

A Prospective Study From the NCAA and US Department of Defense CARE Consortium

JAMA Network Open™

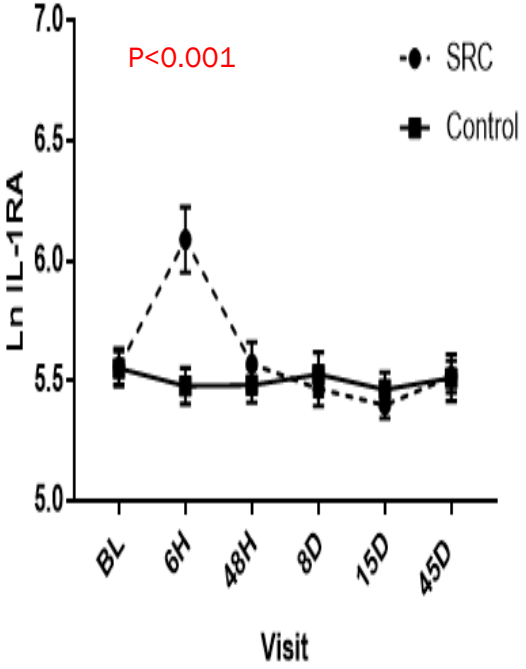
Christopher C. Giza, MD; Michael McCrea, PhD; Daniel Huber, MPH; Kenneth L. Cameron, PhD; Megan N. Houston, PhD; Jonathan C. Jackson, MD; Gerald McGinty, DPT; Paul Pasquina, MD; Steven P. Broglio, PhD; Alison Brooks, MD; John DiFiori, MD; Stefan Duma, PhD; Jaroslaw Harezlak, PhD; Joshua Goldman, MD; Kevin Guskiewicz, PhD; Thomas W. McAllister, MD; David McArthur, PhD, MPH; Timothy B. Meier, PhD; Jason P. Mihalik, PhD; Lindsay D. Nelson, PhD; Steven Rowson, PhD; Jessica Gill, PhD; and the CARE Consortium Investigators

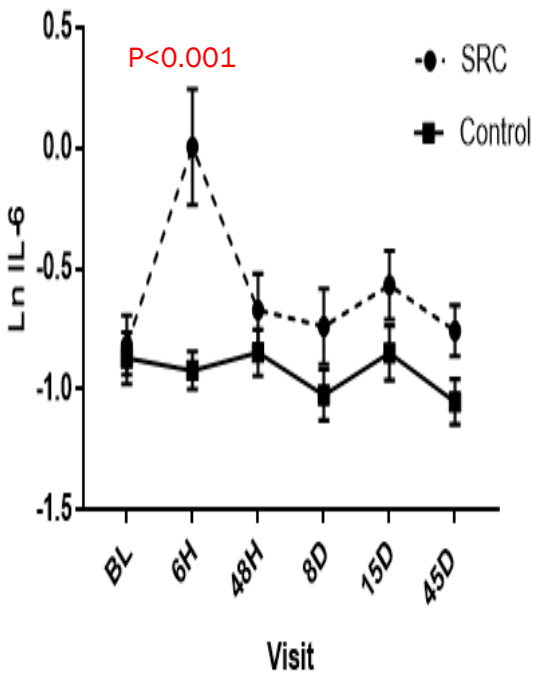


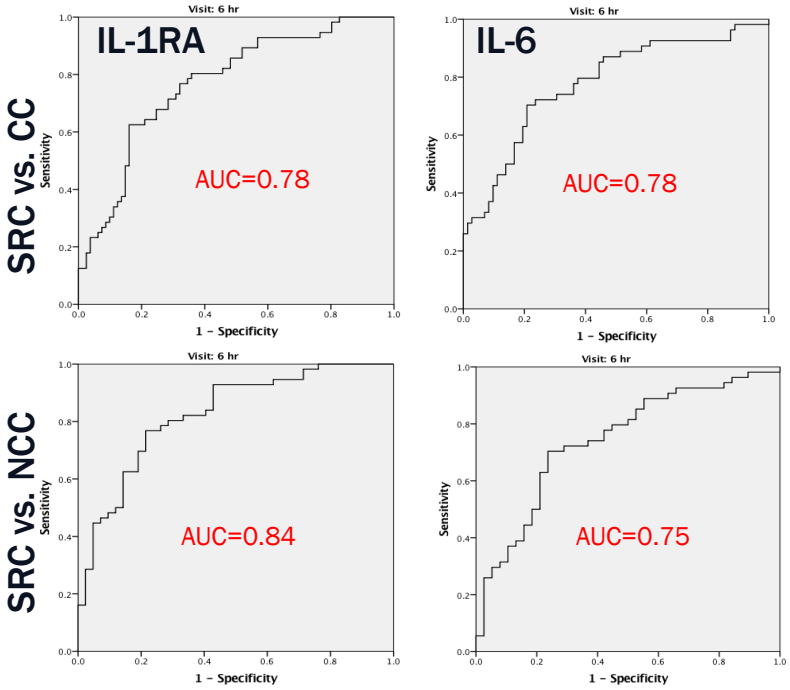


JAMA Network Open. 2021;4(2):e2037731. doi:10.1001/jamanetworkopen.2020.37731

Inflammatory Markers of Acute SRC



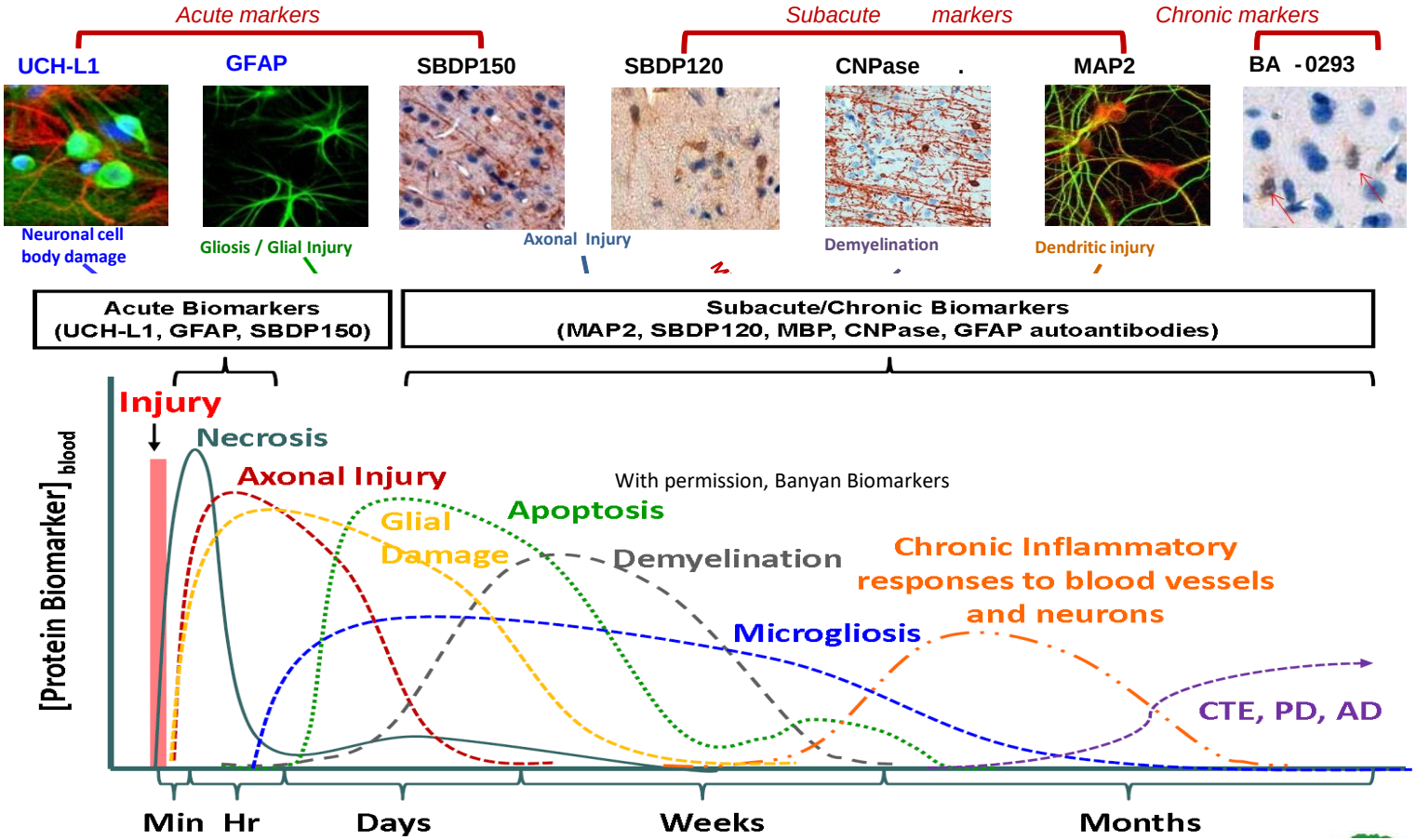




Acute IL-1RA & IL-6 levels predict recovery time

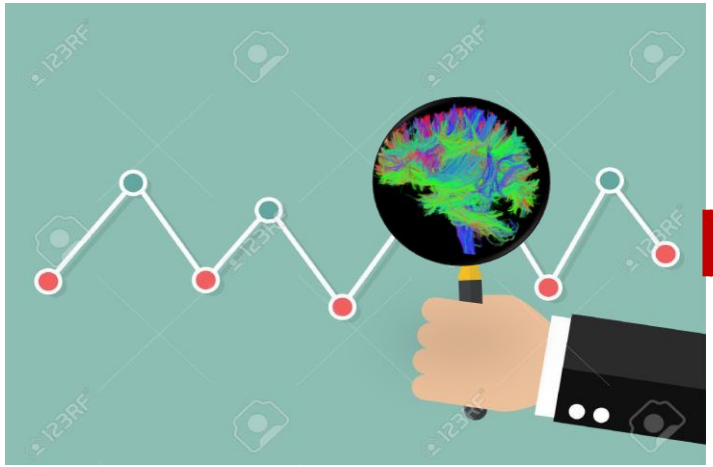
Nitta et al. 2019, Neurology; Meier et al., 2020, Annals of Neurology

CAUTION: No Singular Solution



BIG PICTURE: TBI Biomarkers

Scientific Research



Provide valuable insight into neurobiology of injury & recovery

Clinical Application

Require further validation for clinical use in SRC

Long Road to Clinical Translation

BIOMARKERS: *TRANSLATION PATHWAY*

DEMONSTRATION

Discovery & Optimization of Candidate Biomarkers

VALIDATION

Clinical Studies on Diagnostic & Prognostic Utility

IMPLEMENTATION

Operationalize (commercialize) for POC Use in Trauma Care

Additive Value in Diagnosis, Evaluation, Prognosis, Management

FROM BENCH TO BEDSIDE

FDA U.S. FOOD & DRUG ADMINISTRATION

February 14, 2018

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FDA News Release

FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults

New quick testing option to help reduce need for CT scans, radiation exposure for patients

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For Immediate Release February 14, 2018

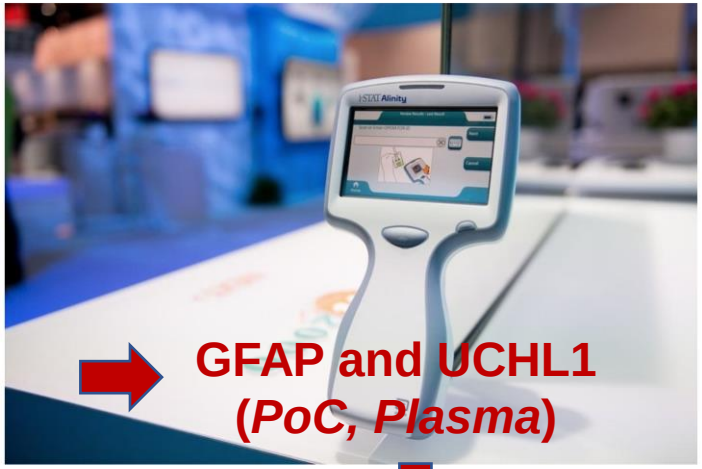
GFAP and UCHL1 (*Core Lab*)

January 12, 2021

MedTech

FDA clears Abbott's hand-held blood test for TBIs, concussions

by Conor Hale | Jan 12, 2021 7:35am



Abbott's handheld i-STAT Alinity test aims to provide a result in 15 minutes. The com currently developing a version that could be used outside the healthcare setting, such as on the sideline of a sporting event. (Abbott)

GFAP and UCHL1 (*PoC, Plasma*)

ABBOTT, THE U.S. DEPARTMENT OF DEFENSE AND TRACK-TBI PARTNER TO STUDY POINT-OF-CARE BLOOD TEST FOR CONCUSSIONS

-- Academic, military and healthcare leaders have come together to conduct a scientifically rigorous clinical trial of a blood t

-- Research could lead to the first point-of-care blood test of its kind to help evaluate concussions within minutes

GFAP and UCHL1 (*PoC, WhBlood*)

Real Life: Value of Prognostic Biomarkers

JAMA Neurology | Original Investigation

Functional Outcomes Over the First Year After Moderate to Severe Traumatic Brain Injury in the Prospective, Longitudinal TRACK-TBI Study

Michael A. McCrea, PhD; Joseph T. Giacino, PhD; Jason Barber, MS; Nancy R. Temkin, PhD; Lindsay D. Nelson, PhD; Harvey S. Levin, PhD; Sureyya Dikmen, PhD; Murray Stein, MD, PhD; Yelena G. Bodien, PhD; Kim Boase, BA; Sabrina R. Taylor, PhD; Mary Vassar, RN, MS; Pratik Mukherjee, MD, PhD; Claudia Robertson, MD; Ramon Diaz-Arrastia, MD, PhD; David O. Okonkwo, MD, PhD; Amy J. Markowitz, JD; Geoffrey T. Manley, MD, PhD; and the TRACK-TBI Investigators

Figure 1. Glasgow Outcome Scale–Extended (GOSE) Total Score Distribution for Patients With Severe Traumatic Brain Injury at 2 Weeks and 3, 6, and 12 Months Postinjury

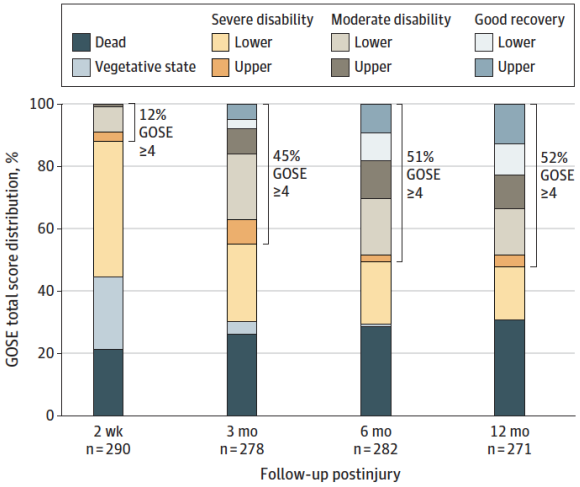
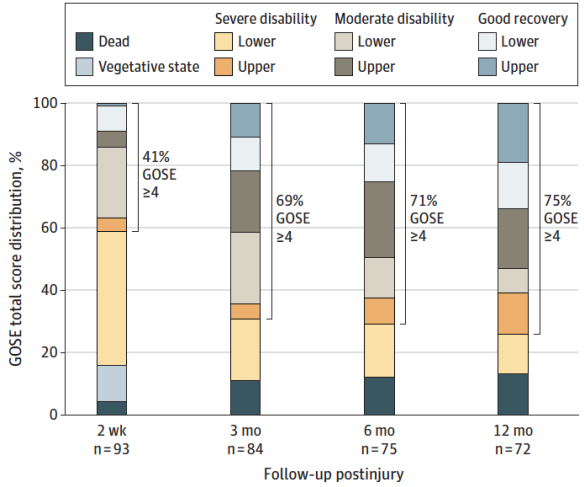


Figure 2. Glasgow Outcome Scale–Extended (GOSE) Total Score Distribution for Patients With Moderate Traumatic Brain Injury at 2 Weeks and 3, 6, and 12 Months Postinjury



Key Points

Question How do functional outcomes change from the acute to chronic phases of recovery after moderate to severe TBI (msTBI)?

Findings In this cohort study of 484 participants with msTBI, by 12 months postinjury, approximately half of those with severe TBI and three-quarters of those with moderate TBI recovered the ability to function independently at home for at least 8 hours per day. Among participants in a vegetative state at 2 weeks, 77% recovered consciousness and 25% regained orientation by 12 months.

Meaning In this study, the presence of acute severe impairment did not universally portend poor functional outcomes after msTBI; clinicians should refrain from making early, definitive prognostic generalizations about the likelihood of poor functional outcomes following moderate and severe TBI.

TBI BIOMARKERS: FUTURE DIRECTIONS

SCIENTIFIC:

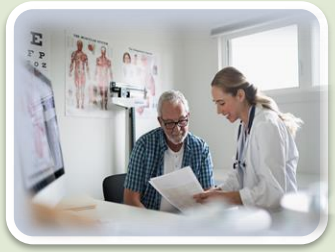
INFORMING PATHO-PHYSIOLOGY OF INJURY & DISEASE

DIAGNOSTIC:

DETERMINE PRESENCE & DEGREE OF INJURY & DISEASE

STRATIFICATION:

ENRICHMENT FOR TREATMENT & CLINICAL TRIALS



PROGNOSTIC:

PREDICTING PATIENT RISK, RECOVERY & OUTCOME

OUTCOME:

MEASURING RESPONSE TO TREATMENT, DISEASE MODIFICATION

AIM TOWARD PRECISION NEUROTRAUMA CARE

MEDICAL COLLEGE OF WISCONSIN
NEUROSURGERY

Center for Neurotrauma Research
Medical College of Wisconsin

TEAM SCIENCE

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