

Advancing Precision Medicine in TBI: Emerging Role of Blood-Based Biomarkers and the NIH-NINDS CBI-M Framework



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Wisconsin Institute of Neuroscience (WINS)



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DISCLOSURES

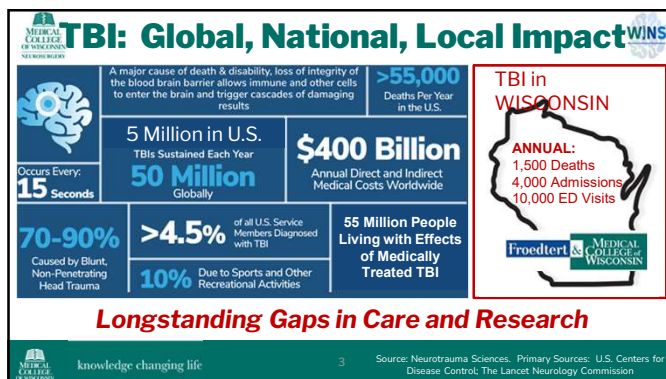
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 - Private foundations and philanthropic support
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- Travel support and speaker honorariums for professional activities.



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LEADERS IN NEUROTRAUMA RESEARCH & CARE

Neurosurgery Research Programs

Research from the Department of Neurosurgery includes multimodal investigations into the generation and treatment of brain injury, biomechanics and spinal cord injury.



Brain Injury Research

The Brain Injury Research Program in MCW's Department of Neurosurgery includes investigations into the acute and chronic effects of traumatic brain injury.



Biomechanics Research

Neurosurgery Biomechanics research is carried out at the ZVAMC Labs and includes investigations into the biomechanics of trauma and biomechanics of the spine.



Spinal Cord Injury Research

Investigations into Spinal Cord Injury at the MCW Department of Neurosurgery seek to improve the recovery and quality of life for patients affected by acute and chronic SCI.

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LEADERS IN BRAIN INJURY RESEARCH

Top 10 Institutions with Largest Total Collaborative Strength in TBI-Concussion Research

MCW

When Trauma Strikes Brain Injury Research, Prevention & Care

WINS

Rank	Institution	Total Link Strength
1	Medical College of Wisconsin	615
2	University of Michigan	505
3	University of North Carolina	498
4	University of Washington	390
5	University of Calgary	342
6	Princeton University	325
7	University of Pittsburgh	300
8	Harvard Medical School	280
9	University of Ottawa	245
10	University of Toronto	245

WORLD NEUROSURGERY 166: e263-e277, October 2022

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Building Destination Programs for Specialized Care

Avalon Action Alliance Donates \$12.5 Million to Create Traumatic Brain Injury Program in Partnership with the Neuroscience Institute

April 27, 2023



Medical College team leads brain injury treatment study

Complex care needed, but often out of reach

Simple solutions

Medical College team leads brain injury treatment study



Greg Burck, MD
Medical Director

Jenna Haberkorn
Physician Director

AVALON ACTION ALLIANCE



May 2024

August 2026

Medical College team leads brain injury treatment study

Complex care needed, but often out of reach

Simple solutions

Medical College team leads brain injury treatment study

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CHALLENGES IN BRAIN INJURY MEDICINE




LACK OF OBJECTIVE MARKERS OF INJURY & RECOVERY

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THE CASE OF TROPONIN:
Rome Wasn't Built in a Day (or a Decade)

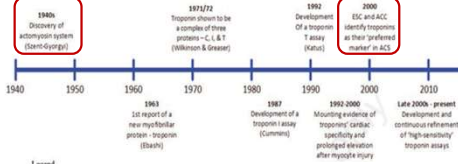
History of Troponin, From Discovery to Modern Day Use

Cardiogenetics 2016; volume 6:6306

Measurement of troponin in cardiomyopathies

Andrew Connelly,¹ Iain N. Findlay,² Caroline J. Coats^{2,3}

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



In Pursuit of the "Troponin for Brain Injury"

Legend:
- ESC: European Society of Cardiology
- ACC: American College of Cardiology
- ACS: Acute Coronary Syndrome

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Advancing Precision Medicine in TBI



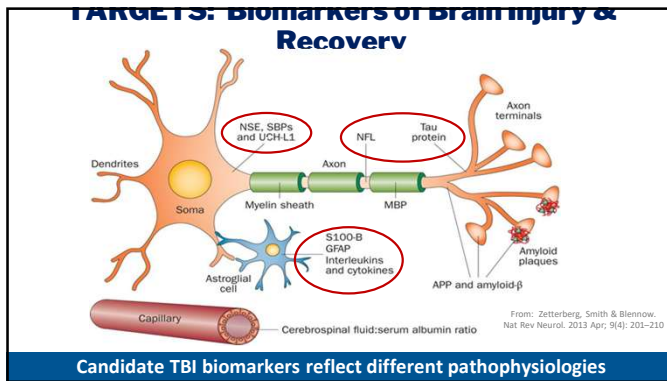
MACE2
Military Acute Concussion Evaluation

Use MACE 2 as close to time of injury as possible.

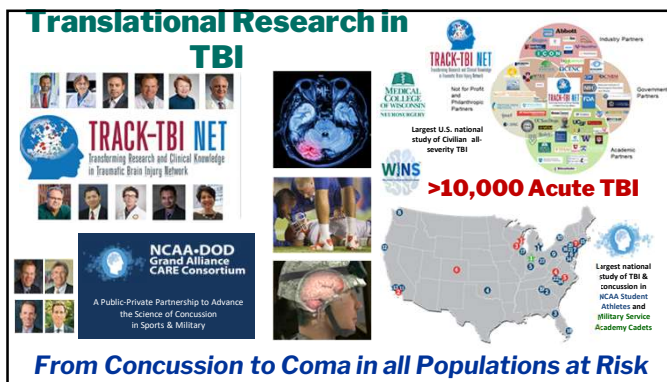
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Time of Evaluation: _____

Tools to Aid in Diagnosis, Management,

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TBI BIOMARKERS: CONTEXTS OF USE

- Acute Triage: Rapid Assessment to Inform Emergency Care
- Injury Management: Neurosurgical Emergency vs. Routine Care
- Aid in Diagnosis: Maximizing Accurate Injury Detection
- Resource Utilization: Inform level of need for Head CT
- Cross-Cutting Utility: Full continuum of severity, populations
- **All Necessitate Pathways to Clinical Translation**
- Prognosis: Predicting Recovery and Outcome

Biological Recovery: Readiness to Return to Activity (Work, Duty, Play)

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BREAKTHROUGHS IN BRAIN INJURY MEDICINE

**U.S. FOOD & DRUG ADMINISTRATION**

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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

**Abbott** CONTACTS HEALTHCARE PROFESSIONALS CUSTOMERS ABOUT ABBOTT

ABBOTT RECEIVES FDA CLEARANCE FOR WHOLE BLOOD RAPID TEST TO HELP WITH ASSESSMENT OF CONCUSSION AT THE PATIENT'S BEDSIDE

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



CORE LAB: PLASMA/SERUM

POC: PLASMA/SERUM

POC: WHOLE BLOOD

CLINICAL PATHWAY: EM & TRAUMA

DRIVING INNOVATION TOWARD CLINICAL TRANSLATION

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POINT OF CARE BIOMARKER TESTING IN ALL SEVERITY TBI



GFAP & UCH-L1 <15 minutes

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

Lancet Neurol 2019; 18: 953-61

David T. Koepsell, Robert A. Gentry, Frederick A. J. Kirkpatrick, William A. Winkler, Shuang Sun, David P. Finkelstein, Steven D. Weisberg, David A. Hirsch, Charles S. Suber, R. Taylor, Adam K. Ferguson, (David H. Lee, Wei Fu, Robert A. Gentry, Anna M. Kucenas, Patrick M. Hynes, Mary T. Davis, David H. Wang, Andrew H. Berman, Harold H. Hoffman, Susan J. Gandy, Henry, and the TRACK-TBI Investigators)

	Number of patients	Plasma GFAP concentration (pg/mL)	p value	
	Mean (SD)	Median (25-75th percentile)	Range	
Positive CT	395	1400.9 (1598.6)	786.0 (52.0-1853.3)	0-9499.7 <0.0001*
Negative CT	459	388.0 (1339.5)	120.3 (23.7-353.3)	0-4095.1
Negative CT and positive MRI	120	652.2 (827.6)	424.4 (139.3-813.4)	5.2-4095.1 <0.0001*
Negative CT and negative MRI	339	168.3 (259.9)	74.0 (17.5-214.4)	0-5864.5
Orthopaedic	122	23.7 (37.7)	13.1 (0.9-30.0)	0-238.8 <0.0001*
Healthy controls	209	13.0 (12.7)	8.0 (1.0-14.0)	0-98.0 <0.0001*

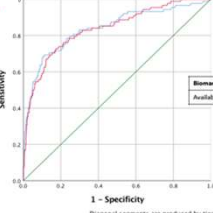
GFAP: glycoprotein acidic protein. P values were calculated from the Wilcoxon rank-sum test for the comparisons, which compares the distributions of the two groups. *Compared with patients with negative CT. †Compared with patients with negative CT and negative MRI findings. ‡Compared with patients with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

Table 2: Plasma GFAP concentrations by imaging modality and findings

UTILITY ACROSS TBI SPECTRUM

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Outcome Prognosis: 12 Months Post TBI



Source of the Curve

- GFAP in pg/mL
- UCH-L1 in pg/mL
- Reference Line

Biomarker	GOSE 1-4	GOSE 5-8	Missing
Available	88 (3.2%)	869	438

Predicting Favorable vs. Unfavorable Outcome

AUC

GOSE 1-4 vs 5-8 @ 12 Mos

GFAP = 0.84

UCH-L1 = 0.84

GOSE 1-4 (12-month)

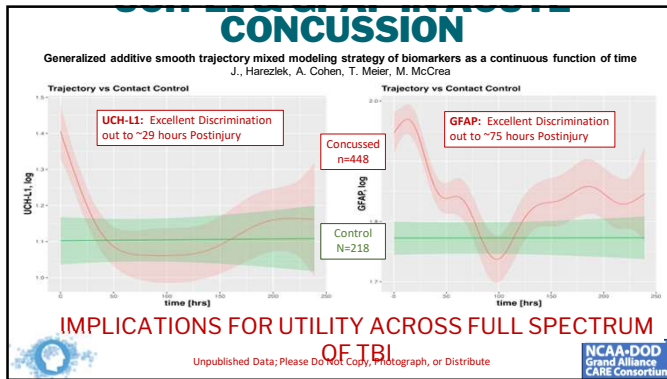
Biomarker	AUC	SE	95% CI Low	95% CI High
GFAP	0.839	0.026	0.788	0.890
UCH-L1	0.838	0.024	0.790	0.886

GOSE score

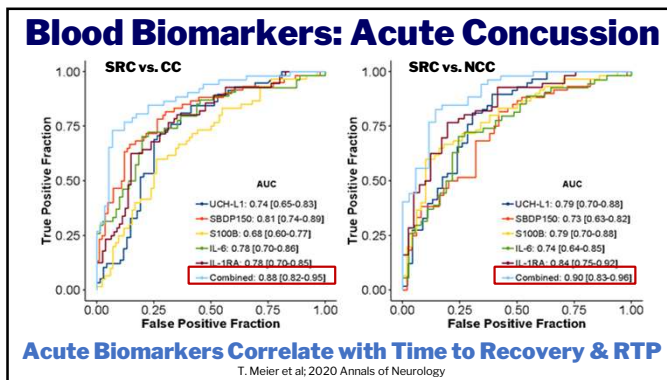


Adapted from Geoff Manley, MD, PhD with permission

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ADVANCING PRECISION MEDICINE

TRAUMATIC BRAIN INJURY

**WE'VE COME A LONG WAY FROM
"HOW MANY FINGERS?"**

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I: IMAGING PILLAR

Neuroimaging Characterization of Acute Traumatic Brain Injury with Focus on Frontline Clinicians: Recommendations from the 2024 National Institute of Neurological Disorders and Stroke Traumatic Brain Injury Classification and Nomenclature Initiative Imaging Working Group

Christine L. Ma, David C. L. et al. (2024). Front. Neurol.

Basic imaging components

☒ Clinically not indicated

☒ CT

☒ MRI

☒ No abnormalities detected

☒ Intracranial injury (epidural, subdural, or intraparenchymal hemorrhage)

☒ Diffuse axonal injury

☒ Skull fracture

Acute TBI pathophysiology

☒ Epidural hemorrhage

☒ Subdural hemorrhage

☒ Intracranial hemorrhage

☒ Contusion

☒ Intracranial hematoma

☒ Traumatic axonal and white matter injury

☒ Intracranial hemorrhage

Mass effect

☒ Midline shift

☒ Herniation

Skull fracture

☒ Evidence of recent contusion

☒ Penetrating traumatic injury

☒ Intracranial injury

☒ Skull fracture

Expected imaging components

☒ Lesion

☒ Location

☒ Volume (quantitative)

☒ Tissue characteristics

☒ Mass effect

☒ Skull fracture

☒ Time to peak

☒ Time to resolution

☒ Time to recurrence

Brain injury

☒ Tissue characteristics

☒ Mass effect

☒ Skull fracture

☒ Time to peak

☒ Time to resolution

☒ Time to recurrence

Skull fracture

☒ Evidence of recent contusion

☒ Penetrating traumatic injury

☒ Intracranial injury

☒ Skull fracture

Brain injury

☒ Tissue characteristics

☒ Mass effect

☒ Skull fracture

☒ Time to peak

☒ Time to resolution

☒ Time to recurrence

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☒ Intracranial injury

☒ Skull fracture

Brain injury

☒ Tissue characteristics

☒ Mass effect

☒ Skull fracture

☒ Time to peak

☒ Time to resolution

☒ Time to recurrence

Skull fracture

☒ Evidence of recent contusion

☒ Penetrating traumatic injury

☒ Intracranial injury

☒ Skull fracture

Leveraging Modern AI Tools & Informatics Platforms in Clinical

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Toward More Holistic Early Traumatic Brain Injury Evaluation and Care: Recommendations from the 2024 National Institute of Neurological Disorders and Stroke Traumatic Brain Injury Classification and Nomenclature Initiative Psychosocial and Environmental Modifiers Working Group

Lindsay D. Nelson, Lindsay Wilson, Jennifer S. Albrecht, David B. Aronowicz, Ernest J. Bartholomew, Sarah A. Berman, Rachel C. Gardner, Shannon B. Jernigan, Monique R. Pappalardo, Jennie Penfold, David C. Thomas, Keith Owen Yeates, Susan Quast, C. Dennis, Geoffrey T. Marney, Andrew L. Ma, Michael A. McCrea, Huh D. Anwar, Abbie Degenhardt, and Hui Lin

Basic modifier components

Injury factors

☒ Mechanism of injury

☒ Comorbid extracranial injury

☒ Secondary insults

☒ Early post-traumatic seizure

☒ Stressful circumstances

Patient factors

☒ Age

☒ Sex

☒ Medical history and medication

☒ Mental health condition

☒ Developmental history

☒ TBI history

☒ Language or communication barrier

Community and society factors

☒ Social disadvantage or deprivation

☒ No or partial health-care insurance

Journal of Neurotrauma

☒ Open access or QR reader and scan code to access the article and other resources online

It's About Injury, Who Comes to Injury, & Response to Injury

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CBI-M: REAL WORLD DATA

DIAGNOSTIC CHARACTERIZATION & PROGNOSTIC UTILITY:

Associations Between CBI Pillar Components in CENTER-TBI and TRACK-TBI

Clinical (GCS) Biomarkers (GFAP) Imaging (CT)

Clinical & Functional Outcome

Blood-based biomarkers and imaging

GFAP TRACK-TBI

2365

GFAP CENTER-TBI

3115

CT detectable intracranial injury

6326

Clinical decision-making

Hospital admission

6817

ICU admission

6817

ICU monitoring

3108

Major craniotomies within 72h

6808

Clinical outcomes at 6 months

Mortality

5330

Unfavorable outcome

5330

Incomplete recovery

5330

Median scaled GFAP level per score

9.3

9.0

8.7

Percentage with endpoint per score

100

75

50

25

0

GCS Score

3

4

5

6

7

8

9

10

11

12

13

14

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Foundational Utility of GCS, Enhanced by Biomarkers &

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CBI-M: REAL WORLD DATA

Beyond mild, moderate, and severe traumatic brain injury: modelling severity from clinical, neuroimaging, and blood-based indicators

Lindsay D. Nelson^{1,2}, Brooke E. Magna³, John K. Yue⁴, Saverio Babiloni⁵, Christopher J. Pettko⁶, Nancy Terkin⁷, Esther L. Yau⁸, Ramona Day-Anastasi⁹, Eli Dwyer¹⁰, Andrew I. R. Moss¹¹, David K. Menon¹², Lindsay Wilson¹³, and Geoffrey T. Manley¹⁴ the TRACK-TBI Investigators¹⁵, on behalf of the CENTER-TBI Participants and Investigators¹⁶

¹Department of Neurosurgery & Neurology, Medical College of Wisconsin, Milwaukee, WI, USA
²Department of Psychology and Neuroscience, Boston College, Boston, MA, USA
³Department of Neurosurgery, University of California, San Francisco, CA, USA
⁴Department of Psychology, University of Massachusetts Lowell, Lowell, MA, USA
⁵Department of Psychology, Florida State University, Tallahassee, FL, USA
⁶Department of Neurological Surgery and Biostatistics, University of Washington, Seattle, WA, USA
⁷Department of Radiology and Biomedical Imaging, University of California, San Francisco, USA
⁸Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
⁹Department of Neurosurgery, University of Antwerp, and Antwerp University Hospital, Edegem, Belgium
¹⁰Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom
¹¹Division of Psychology, School of Natural Sciences, University of Exeter, Exeter, United Kingdom

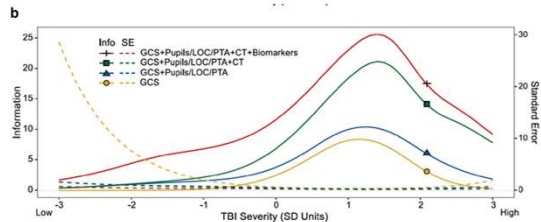
Item response theory (IRT) to develop a new method for quantifying TBI severity using 24 clinical, head CT, and blood-based biomarker variables familiar to clinicians and researchers.

IMPROVING PRECISION IN TBI CHARACTERIZATION & CLASSIFICATION

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CBI-M: REAL WORLD DATA

CUMULATIVE VALUE OF THE CBI-M



ADDED VALUE OF MULTI-DIMENSIONAL CHARACTERIZATION OF TBI

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CBI-M: REAL WORLD DATA

IMPROVED OUTCOME PREDICTION

General severity
 Original research
 Long-term prediction of traumatic brain injury outcome using the CBI-M framework

Gershon Spitz¹, Marina Downing^{2,3}, Megan Carthy⁴, Jennie L. Ponsford⁵

CBI-M framework predicts functional and vocational outcomes up to 10 yrs post-TBI.

ADDED VALUE OF MULTI-DIMENSIONAL CHARACTERIZATION OF TBI

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UTILITY OF CBI-M IN INJURED WORKERS

- AID in DX: Is there brain injury? Beyond CT+/-
- OBJECTIVITY: Beyond subject, self-reported symptoms
- SEVERITY: Multiple indicators (beyond single GCS score)
- CARE PATHWAY: Individualized to facilitate recovery, RTW
- PROGNOSIS: Expected course for recovery, RTW
- RECOVERY: Multiple indicators of fitness to RTW
- NON-INJURY FACTORS: Modifiers influencing recovery, outcome, RTW
- INFORMED REHABILITATION: Take into account injury, non-injury factors to facilitate recovery, outcome, RTW

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CBI-M: A New Era in TBI Treatment

C CLINICAL
B BIOMARKERS
I IMAGING
M MODIFIERS

NATIONAL ACADEMIES Sciences Engineering Medicine
AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
ACS AMERICAN COLLEGE OF SURGEONS
NASSEM TBI Forum
American College of Emergency Physicians
BARD
Medical Countermeasures.gov

Moving Beyond Limitations of "Mild, Moderate, Severe"!

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POWER OF TEAM SCIENCE

MEDICAL COLLEGE OF WISCONSIN NEUROSURGERY
WINS
CENTR
MEDICAL COLLEGE OF WISCONSIN NEUROSCIENCE RESEARCH CENTER
MEDICAL COLLEGE OF WISCONSIN EMERGENCY MEDICINE
MEDICAL COLLEGE OF WISCONSIN NEUROLOGY
Froedtert & MEDICAL COLLEGE OF WISCONSIN
Children's Wisconsin
CS

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