

JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)



Use of Traumatic Brain Injury Plasma Biomarkers after a Potentially Concussive Event (CPG ID:90)

Provides guidelines for use of plasma biomarkers in the evaluation of casualties with mild TBI (concussion) in a deployed environment.

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PURPOSE

These guidelines are intended to provide a basic management approach after a potentially concussive event using the specific plasma biomarkers for traumatic brain injury (TBI) on the iSTAT Alinity. This guidance does not apply to other brain injury devices or TBI biomarkers. This CPG is intended to complement and build upon the existing [DoD Instruction \(DoDI\) 6490.11 DoD Policy Guidance for Management of Mild Traumatic Brain Injury/Concussion in the Deployed Setting](#).

BACKGROUND

- Between 2000 and 2019 TBI affected over 417,503 service members worldwide, with 88% of those injuries being classified as mild (mTBI), also known as concussion.¹ Common sequelae after mTBI include: headache, visual impairment, Post-Traumatic Stress Disorder (PTSD), depression and cognitive disorders; individuals with a mTBI are at increased risk of post-traumatic stress.²⁻⁴ Secondary to these effects, only 70% of individuals diagnosed with mTBI return to full duty.⁵
- Individuals with mTBI typically have a normal (or negative) head CT. The purpose of head CT in an individual with suspected mTBI is to rule out a more severe injury requiring a higher level of care. For example, intracranial hemorrhage requires inpatient observation and, if severe, neurosurgical intervention. In civilian settings, approximately 6-8% of individuals with suspected mTBI at initial evaluation have evidence of intracranial hemorrhage and 1-2% require neurosurgical intervention.^{6,7}
- CT scanners are typically available in theater at Role 3 facilities and select enhanced Role 2 facilities. The decision to transport a casualty from Role 1 or Role 2 to Role 3 for a head CT can have significant implications for the safety of the flight crew and mission accomplishment. Medical decision making should include an assessment of operational risk.
- An evaluation of the DoD Trauma Registry (DoDTR) suggests 68% of casualties identified as having mTBI were evacuated to the Role 3 for a head CT and 41% to Role 4, with approximately 78% of those Soldiers being returned to duty.⁸ However, it is important to recognize the DoDTR only contains a subset of more severely injured Service Members with an mTBI in theater. Nonetheless, the data suggests that many evacuations for head CT may be avoided.
- The Military Acute Concussion Evaluation 2 (MACE2) provides guidance in the initial evaluation and management of individuals with (GCS score 13-15 in the deployed setting. It includes an assessment of “red flags” to determine the need for head CT and evacuation. In addition, the New Orleans Criteria and the Canadian Head CT rule also aid in identifying individuals most likely to benefit from head CT. None of these rules have been validated in the deployed setting.^{9,10}
- Glial Fibrillary Acidic Protein (GFAP) and Ubiquitin Carboxyl-terminal Hydrolase L1 (UCH-L1) are contained within cells in the central nervous system and released upon neuronal damage. Higher levels indicate worsening neuronal injury.
- In January 2021, the U.S. Food and Drug Administration (FDA) approved a plasma biomarker for TBI, the i-STAT TBI Plasma Cartridge with the i-STAT Alinity System. This semi quantitative assay detects levels of GFAP and UCH-L1 in plasma. A facility with a lab section can perform the TBI plasma biomarker test. A result of “not elevated” on this test has a Negative Predictive Value approaching 100% for determining the absence of acute traumatic intracranial lesions on head

CT imaging. (See Appendix C [Figure 1](#) for further information.) This assay is also known as the *Analyzer, Traumatic Brain Injury (ATBI) System*.

- Since this biomarker is performed on plasma, the test can only be used in a clinical laboratory setting with the capability to produce and test a plasma sample. Key logistical requirements include a centrifuge, refrigerated storage for cartridges, and frozen storage for calibration fluid. Ongoing product development efforts are focused on developing this into a test that can be performed on whole blood which will enable the use of the biomarker in a wider array of settings.

NOTE: Related clinical practice guidelines (CPGs): [VA/DoD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury](#), [JTS Neurosurgery and Severe Head Injury](#)

STRUCTURE TO SUPPORT OPTIMAL USE OF TBI BIOMARKER

To minimize risks associated with use of this novel capability, we recommend a highly controlled rollout of the TBI biomarker. Each theater should restrict interpretation of test results and evacuation decisions to a select number of designated TBI biomarker consultants typically co-located at the Role 3. These individuals possess experience in evaluation, triage, and management of TBI in the acute setting and are knowledgeable in the clinical application of TBI biomarker values. The Theater Trauma Medical Director (TMD) is responsible for directing this overall effort but will normally yield clinical decision-making capacity to the neurosurgeon or other neurospecialist if available. Concurrent and standardized record-keeping using the Biomarker Data Collection Tool ([Appendix D](#)) is a must. This tool succinctly communicates mechanism, signs, symptoms, exam findings, TBI biomarker values, clinical decisions, evacuation priority, and concordant CT results or outcomes. The consultant is responsible for supporting the forward provider in execution of the TBI Biomarker Algorithm ([Appendix A](#)), use of TBI biomarker results, and disposition of the patient. When a negative TBI biomarker test guides a decision to keep the patient at the forward location, the consultant or TMD should remain engaged with that provider until no longer necessary. We recommend the consultants be responsible for completing the Biomarker Data Collection Tools. As the individual responsible for this TBI Biomarker Program, the TMD will ensure the Biomarker Data Collection Tools are submitted to Joint Trauma System (JTS).

INITIAL EVALUATION

Casualties should initially be evaluated and resuscitated based on JTS guidelines, Advanced Trauma Life Support (ATLS) principles, and Tactical Combat Casualty Care (TCCC) protocols after an acute injury, which may include a potentially concussive event (PCE). PCEs are defined in DoDI 6490.11 and include:

- involvement in a vehicle blast event, collision, or rollover;
- presence within 50 meters of a blast (inside or outside);
- a direct blow to the head or witnessed loss of consciousness; and
- exposure to more than one blast event.

The DoD classification of head injury as mild, moderate or severe includes the results of imaging and reports of symptoms for up to 7 days. Thus, for the purposes of initial evaluation in the field, the GCS is the most appropriate initial assessment and also has prognostic implications in the combat environment.

Head injured casualties are initially classified according to their GCS score:

- Mild: GCS 13-15
- Moderate: GCS 9-12
- Severe: GCS 3-8

NOTE: If the casualty has a GCS of 12 or less (moderate or severe TBI), please refer to the [JTS Neurosurgery and Severe Head Injury CPG](#). This Biomarker CPG does not apply.

If the casualty has no other injuries requiring evacuation, has a GCS of 13 or greater, and the TBI plasma biomarker test is not available, the MACE2 and Enclosure 3 of DoDI 6490.11 should guide initial evaluation in addition to these guidelines. (See [Supporting TBI Resources for DoDI 6490.11](#))

This guidance and algorithm ([Appendix A](#)) expands upon the MACE2 and provides initial guidance for locations with access to the new TBI plasma biomarker test. The TBI plasma biomarker test should be used in the place of a “structural brain injury” device as listed on the MACE 2 under “red flags.” However, it is important to note that this device does not provide a definitive diagnosis of a “structural brain injury” and it should be used and interpreted in accordance with the intended use statement in [Appendix B](#). The MACE2 does not delineate which individuals should or should not undergo assessment with a structural brain injury device. This algorithm seeks to expand upon the MACE 2 to assist providers in understanding the most appropriate population for assessment with the TBI plasma biomarker.

RISK EVALUATION FOR BRAIN INJURY & INTRACRANIAL HEMORRHAGE

At locations with access to the TBI plasma biomarker test, a casualty exposed to a PCE should be stratified as high, moderate, or low risk using the [Appendix A Algorithm](#). This is a modification of the MACE2, targeting the population most likely to benefit from the use of the TBI plasma biomarker.

HIGH RISK: DO NOT DELAY CARE FOR TBI PLASMA BIOMARKER

A subset of MACE 2 red flags suggest high risk of brain injury with intracranial hemorrhage. If any one of the following red flag signs or symptoms are present, the casualty should be referred urgently for CT scan. Do not delay evacuation to obtain TBI plasma biomarkers.

- Deteriorating levels of consciousness or a drop in post injury GCS score by 2 or greater
- Combativeness or agitated behavior
- 2 or more episodes of vomiting
- Witnessed seizure activity
- Focal neurologic deficits such as pupil asymmetry, facial weakness/asymmetry, weakness or paralysis on one side compared to the other
- Bleeding disorder or therapeutic anti-coagulation with heparin, low molecular weight heparin, warfarin, or novel oral anticoagulants (direct thrombin inhibitors and direct factor Xa inhibitors)

In addition, casualties with evidence suspicious for a penetrating brain injury, depressed skull fracture, or signs of a basilar skull fracture (e.g., raccoon eyes, battle’s sign, otorrhea) should be referred urgently for CT scan.

MODERATE RISK: TEST TBI PLASMA BIOMARKERS BEFORE EVACUATION

This is the target population for TBI plasma biomarkers. Because of the significant false-positive rate, TBI plasma biomarker testing will be directed to casualties with moderate risk for intracranial hemorrhage. The goal is to allow symptomatic patients who test negative to forego CT scan and remain in place with activity restrictions (i.e. quarters, bed rest) and treatment of symptoms. There are two important caveats to this group:

1. The concussive event must have taken place within 12 hours of testing.
2. The patient should not have other injuries requiring urgent evacuation (fractures, concern for internal injuries, etc.). In this instance, testing should not hold up transport for more urgent issues, but can still be completed.

Casualties without the high risk red flag signs or symptoms described above but exhibit one or more of the following are appropriate candidates for TBI plasma biomarker testing.

- Double vision
- Increased restlessness
- < 2 episodes of vomiting
- Subjective weakness or tingling in arms or legs but no clear focal neurological deficit
- Severe, persistent, or worsening headaches
- Age >60 years
- Anti-platelet drugs (such as aspirin or ibuprofen)
- Drug/alcohol intoxication
- Post traumatic amnesia (inability to recall events for 30 or more minutes before injury)
- Worrisome mechanism of injury: high speed motor vehicle collision or rollover; fall from greater than 3ft; or presence within 50m of a blast inside or outside.

Casualties with any of these findings should be evaluated with the TBI plasma biomarker so long as the test is performed within 12 hours of the initial head injury. Then using the all the clinical details outlined on the Biomarker Data Collection Tool ([Appendix D](#)), the forward provider contacts the TBI Biomarker Consultant and the two come to a decision regarding need for head CT and priority of evacuation. When it is determined that the patient can remain in place with activity restrictions and be treated per the treatment section below, the forward provider and consultant should make a plan to communicate on the patient's progress.

LOW RISK FOR TBI: NO RISK FACTORS PRESENT

If the casualty does not have any of the risk factors described above, the provider should care for the casualty as described in the MACE2. If worsening symptoms develop more than 12 hours after the initial injury, the provider should contact the designated TBI Biomarker Consultant.

Research suggests that some casualties without MACE2 red flags undergo evacuation for head CT despite the MACE2 recommendations. If a provider wishes to obtain a head CT in individuals without the high or moderate risk signs or symptoms described above, a TBI plasma biomarker test should be

performed before referral for a head CT if the casualty is evaluated within 12 hours of injury. Consultation with the designated TBI Biomarker Consultant is strongly recommended to help determine the urgency of referral and evacuation.

LOCATIONS WITH ON-SITE HEAD CT

The TBI plasma biomarkers are a new capability both to the military and the civilian sector. As such, CPGs for the use of TBI plasma biomarkers have not yet been developed by civilian professional societies. When head CT capabilities are available on-site or evacuation is minimal risk, providers may consider performing both the TBI plasma biomarkers and head CT to gain additional experience with the TBI plasma biomarkers in clinical and operational settings. When this happens, it is imperative that a Biomarker Data Collection Tool is completed and forwarded to the consultant or TMD for the purposes of data collection on this emerging technology.

PRIMARY CONCUSSIVE BLAST

The TBI plasma biomarker was validated in civilian blunt trauma patients and it is unknown at this time how the test will perform in casualties sustaining mTBI from a primary blast wave exposure. This underscores the importance of data capture using the processes outlined in this CPG and submission of the Biomarker Data Collection Tool to JTS.

SYMPTOMATIC TREATMENT OF MILD TBI

The hallmark of treatment for service members who sustain an mTBI is relative rest and initial symptom management. Service members with mTBI should be managed in accordance with DoDI 6490.11 and the published [DoD Traumatic Brain Injury Center of Excellence MACE 2](#) and [Progressive Return to Activity Clinical Recommendation](#).

Many casualties with positive (elevated) results with TBI plasma biomarker will not have evidence of brain injury or intracranial hemorrhage on head CT but will have brain injury evident on Magnetic Resonance Imaging (MRI).¹¹ However, a TBI plasma biomarker result of “elevated” is not FDA approved for the diagnosis of mTBI and should not be used as the sole indicator of mTBI diagnosis; a clinical evaluation of the casualty is necessary to make a diagnosis of mTBI. At this time, it is not known whether casualties with positive (elevated) TBI plasma biomarkers but no evidence of injury on head CT should be treated differently from casualties with negative (not elevated) TBI plasma biomarkers. Therefore individuals with elevated biomarkers and a negative head CT should be managed as individuals with mTBI as per DoD guidelines cited in the preceding paragraph.

PERFORMANCE IMPROVEMENT (PI) MONITORING

POPULATION OF INTEREST

Casualties exposed to a potentially concussive event.

INTENT (EXPECTED OUTCOMES)

1. Documented GCS, neurologic exams, MACE2 and symptoms for each service member exposed to a potentially concussive event.
2. TBI Plasma Biomarker performed on moderate risk patients within 12 hours of injury.
3. TBI Biomarker Consultant is informed on all positive and negative TBI Plasma Biomarker tests, resulting in completion of the Biomarker Data Collection Tool ([Appendix D](#)).
4. Biomarker Data Collection Tool is submitted/emailed to JTS: dha.jbsa.healthcare-ops.list.tbi-biomarker@health.mil

PERFORMANCE/ADHERENCE MEASURES

1. MACE2 exams documented on all Service Members diagnosed with mTBI
2. Documented results of the TBI plasma biomarker in the patient's medical record

DATA SOURCES

- Patient Record
- Department of Defense Trauma Registry

SYSTEM REPORTING & FREQUENCY

The above constitutes the minimum criteria for PI monitoring of this CPG. System reporting will be performed annually; additional PI monitoring and system reporting may be performed as needed.

The system review and data analysis will be performed by the JTS Chief and the JTS PI Branch.

RESPONSIBILITIES

It is the trauma team leader's responsibility to ensure familiarity, appropriate compliance and PI monitoring at the local level with this CPG.

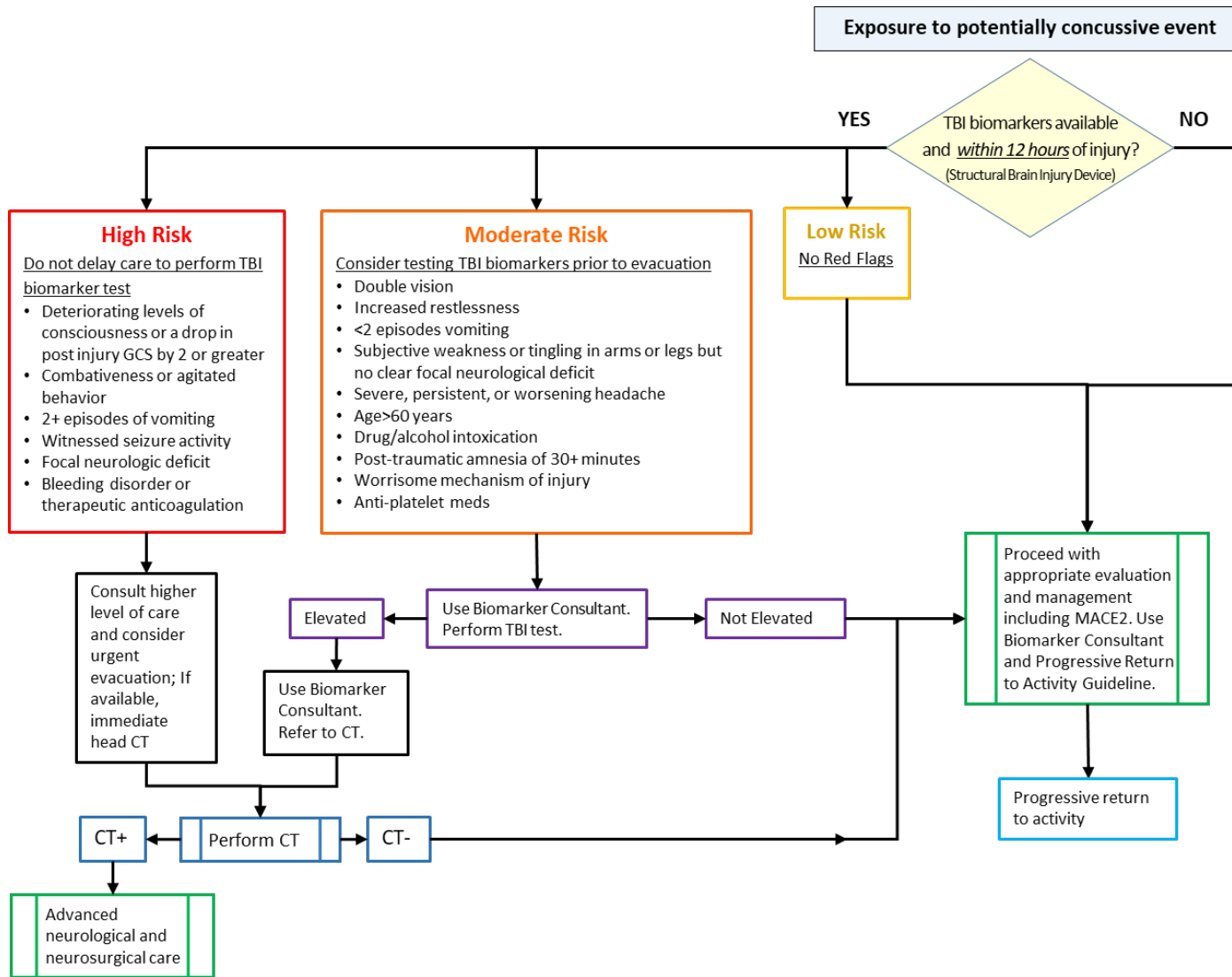
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APPENDIX A: CLINICAL ALGORITHM FOR TBI BLOOD BIOMARKERS USE

Clinical Algorithm for Initial Management of a Potentially Concussive Event using the TBI Blood Biomarkers



APPENDIX B: DETAILED INFORMATION ON THE TBI PLASMA BIOMARKER

NOTE: Information summarized from Abbott Point of Care Inc., 2021, 510(k) Summary: i-STAT TBI Plasma Cartridge with the i-STAT Alinity System (K201778; Approved 8JAN2021).
https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201778.pdf.

Capability Name: Analyzer, Traumatic Brain Injury System

Device Name: i-STAT TBI Plasma Cartridge with the i-STAT Alinity System

Device and Assay Description:

- Semi-quantitative multiplex immunoassay in ethylenediaminetetraacetic acid (EDTA) anticoagulated plasma for:
 - Glial fibrillary acidic protein (GFAP)
 - Ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1)
- Cartridge can only be used on the i-STAT Alinity.
- Will give an error reading if used on i-STAT 1.
- To separate plasma, blood requires processing in clinical laboratory settings with centrifuge capability.
- Cartridges require refrigerated storage; calibration/verification and control fluids require freezer for storage.
- Cannot be used as a point of care test in near patient settings; this may be possible for future products.

Assay Reference Range:

Range derived from n=225 apparently healthy individuals with no history of neurological disease:

- GFAP: Mean 19 pg/mL; Median 15 pg/mL; Reference Interval 2-51pg/mL (2.5th -97.5th percentile)
- UCH-L1: Mean 81 pg/mL; Median 71 pg/mL; Reference Interval 21-204 pg/mL (2.5th -97.5th percentile)

Assay Cut-Off Values and Results:

- Elevated: An elevated result is given if either GFAP OR UCH-L1 is elevated
 - GFAP cut-off: 30 pg/mL
 - UCH-L1 cut-off: 360 pg/mL
- Not elevated: A not elevated result is given if GFAP AND UCH-L1 are below the cut-off
- Not reportable: No result is given if valid results are below the cut-off AND one or more results are not reportable

Assay Performance

There were two studies performed as part of the U.S. Food and Drug Administration (FDA) licensure process.

Study #1: This study was conducted on stored plasma samples and demonstrated performance comparable to the Banyan Biomarkers assay with:

- sensitivity of 95.8% [95% Confidence Interval (CI) 90.6%, 98.2%],
- negative predictive value of 99.3% [95%CI 98.5%, 99.7%], and
- specificity of 40.4% [95%CI 38.2%, 42.7%].

(See [Appendix C](#) for additional details.)

Study #2: This study was conducted on fresh plasma samples and demonstrated comparable sensitivity but lower specificity.

- sensitivity of 100.0 [95% CI 88.3%, 100.0%],
- specificity of 23.7% [95%CI 14.7%, 36.0%].

(See [Appendix C](#) for additional details.)

Intended Use Statement

The i-STAT TBI Plasma test is a panel of in vitro diagnostic immunoassays for the quantitative measurements of GFAP and UCH-L1 in plasma and a semi quantitative interpretation of test results derived from these measurements, using the i-STAT Alinity Instrument. The interpretation of test results is used in conjunction with other clinical information to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (Glasgow Coma Scale score 13-15) within 12 hours of injury, to assist in determining the need for a CT scan of the head. A “Not elevated” test interpretation is associated with the absence of acute traumatic intracranial lesions visualized on a head CT scan. The test is to be used with plasma prepared from EDTA anticoagulated specimens in clinical laboratory settings by a healthcare professional. The i-STAT TBI Plasma test is not intended to be used in point of care settings.

APPENDIX C: SUMMARY OF RESEARCH

Overall Summary of Evidence

Two studies were conducted in support of the FDA licensure request.¹ The first study used frozen plasma samples obtained from the study conducted in support of the Banyan Biomarkers TBI Assay.² This study (n=1901) demonstrated comparable performance to the Banyan Biomarkers assay with a sensitivity of 95.8%, negative predictive value of 99.3%, and specificity of 40.4% [95%CI 38.2%, 42.7%]. There were n=5 false negative test results; none of these were abnormalities requiring surgical intervention.²

The second study used a small sample of fresh plasma samples (n=88) obtained from a small subset of patients a study of TBI at Level 1 Trauma Centers who had head CT performed. In this sample the sensitivity and negative predictive value were 100%, but the specificity was lower - 23.7%. The reason for the lower specificity in this population is not clear but may have been due to the small sample size or due to differences in the study population. For example, only 6% of the population in the first study had findings on head CT as compared to this study where 33% had findings on head CT. The positive predictive values for the two studies were comparable after adjustment for the prevalence of positive head CT.

While the specificity of the assay is low to moderate for brain injury and hemorrhage visible on CT, additional research suggests that many individuals with elevated Glial Fibrillary Acidic Protein using a prototype of the assay have evidence of brain injury on MRI.³ It is important to note the assay is not FDA approved for this purpose.¹

Summary of Study #1

Stored frozen plasma samples were obtained from Bazarian, et al study used for approval of Banyan Biomarkers TBI assay, an early version of this assay.^{1,2}

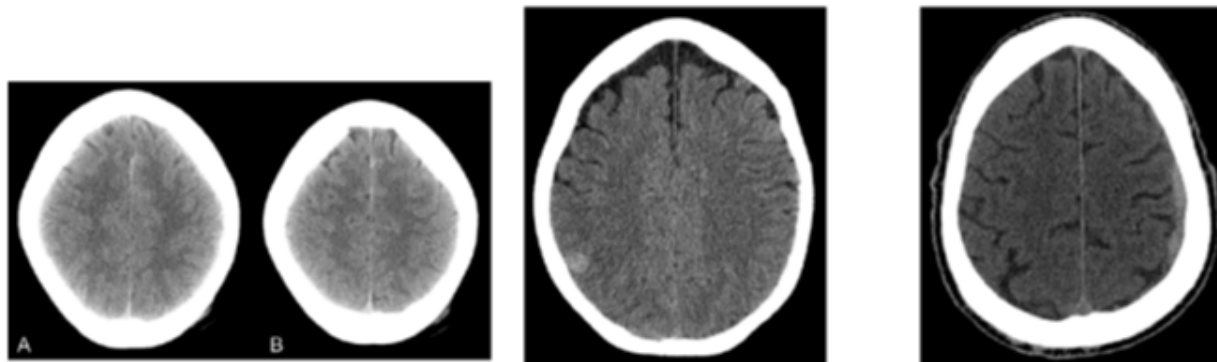
- **Inclusion/Exclusion Criteria:** Adults ≥18 years, presenting to Emergency Department with non-penetrating TBI and GCS 13-15, where the referring provider felt a head CT was indicated, with blood test within 12 hours of injury at 22 sites in the U.S. and Europe
- **The study population** (n=1901) had a median age of 49.0 years and ranged from 18 to 98 years. Over half (56.6%) were male and 70.6% were white and 26.2% were African American.
- Nearly all had a GCS of 15 (94.1%) and around half had Loss of Consciousness (42.2%), Alteration of Consciousness (56.3%), or visible trauma above the clavicle (63.3%). Around one-third reported post-traumatic amnesia (33.0%).
- The median time between injury and blood draw was 3.2 hours with a range of 0.3 to 11.9 hours.

Table 1. Clinical Performance

Clinical Performance			
i-STAT TBI Plasma Test Interpretation	Adjudicated CT Scan Result		Total
	Positive	Negative	
Elevated	115	1061	1176
Not Elevated	5	720	725
Total	120	1781	1901
Clinical Performance Parameters	N=1901	95% Confidence Interval	
Clinical Sensitivity	95.8%	90.6%, 98.2%	
Clinical Specificity	40.4%	38.2%, 42.7%	
Negative Predictive Value (NPV)	99.3%	98.5%, 99.7%	
Positive Predictive Value (PPV)	9.8%	9.2%, 10.2%	
Likelihood Ratio Negative (LRN)	0.10	0.04, 0.23	
Likelihood Ratio Positive (LRP)	1.61	1.15, 1.69	

- There were five individuals with false negative results (i.e. not elevated biomarker result and findings on head CT). None of these individuals required surgical intervention. Findings included a small sub-arachnoid hemorrhage, a small subdural hemorrhage and a venous angioma thought to be a congenital anomaly. See Figure 1 for 3 of the 5 head CT scans from false negative subjects.

Figure 1. Head CT Scans from false negative subjects



Legend: Left (subject 1) – Two non-contrast CT images (A + B) show focal subarachnoid hemorrhage in the anterior, paramedian frontal sulci. Middle (subject 2) – Non-contrast CT image shows a focal area of hyperdensity in the posterior right parietal lobe. On lower slices (not shown), there is a suggestion of some lower attenuation edema which marginates the contusion. Right (subject 3) – Non-contrast CT image shows subdural hemorrhage along the left lateral hemisphere, overlying the frontal and parietal lobes with minimal local mass effect on the brain parenchyma.

Summary of Study #2

Fresh plasma samples were obtained from four clinical sites of the *Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI)* study in the United States.^{1,3}

- Inclusion/Exclusion Criteria:** Adults ≥ 18 years, presenting to Emergency Department with GCS 13-15, who had a head CT performed at 4 sites in the U.S.
- The study population** (n=88) had a median age of 42.5 years and ranged from 18 to 85 years. Nearly three-quarters (71.2%) were male.
- Most had a GCS of 15 (81.8%) and over half had loss of consciousness (68.2%), presence of confusion (67.0%), or post-traumatic amnesia (68.2%).
- The median time between injury and blood draw was 4.3 hours with a range of 2.0 to 11.8 hours.

Table 2. Clinical Performance – Supplemental Fresh Specimen Study

Clinical Performance – Supplemental Fresh Specimen Study			
i-STAT TBI Plasma Test Interpretation	Adjudicated CT Scan Result		Total
	Positive	Negative	
Elevated	29	45	74
Not Elevated	0	14	14
Total	29	59	88
Clinical Performance Parameters	N=88	95% Confidence Interval	
Clinical Sensitivity	100.0%	88.3%, 100.0%	
Clinical Specificity	23.7%	14.7%, 36.0%	
Negative Predictive Value (NPV)*	100.0%	80.2%, 100.0%	
Positive Predictive Value (PPV)*	39.2%	35.9%, 43.4%	
Likelihood Ratio Negative (LRN)	0.00	0.00, 0.50	
Likelihood Ratio Positive (LRP)	1.31	1.14, 1.56	

Legend: *NPV and PPV estimated at 33.0% prevalence of CT scan positive rate for suspected mild TBI subjects. Adjusted NPV and PPV at 6% prevalence (to be comparable to the pivotal study) are 100.0% (95% CI: 96.9%, 100.0%) and 7.7% (95% CI: 6.8%, 9.1), respectively.

Summary of GFAP/MRI Study

Yue JK, Yuh EL, Korley FK, et al. 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(10): 953-961. [https://doi.org/10.1016/s1474-4422\(19\)30282-0](https://doi.org/10.1016/s1474-4422(19)30282-0)

The study enrolled adults with GCS 13-15 between 2014-2018 at 18 participating Level 1 U.S. trauma centers who presented within 24 hours of injury and had a head CT as well as an MRI within 7-18 days post injury.^{1,3}

- Of 1375 individuals enrolled in TRACK-TBI study, 794 had negative head CT and a GCS of 13-15 of whom 450 had an MRI scan performed within 7-18 days. Of these, 27% had positive MRI.
- Individuals with positive head CT had the highest GFAP levels (Median 786.0 pg/mL); followed by those with negative head CT and positive MRI (Median 414.4 pg/mL); followed by those with negative head CT and negative MRI (Median 74.0 pg/mL). Of note, healthy (Median 8.0 pg/mL) and orthopedic trauma (Median 13.1 pg/mL) controls had significantly lower GFAP levels (Table 3/Figure 2).
- From a pathophysiologic perspective, elevated GFAP levels were noted in traumatic axonal injury, diffuse axonal injury, extra-axial and mixed lesions (See Figure 2).
- The sensitivity and specificity of GFAP levels for positive MRI is listed in Table 4. Of note, GFAP levels greater than 282.70 pg/mL has a specificity of 80.3% for positive MRI.

Table 3. Plasma GFAP concentrations by imaging modality and findings

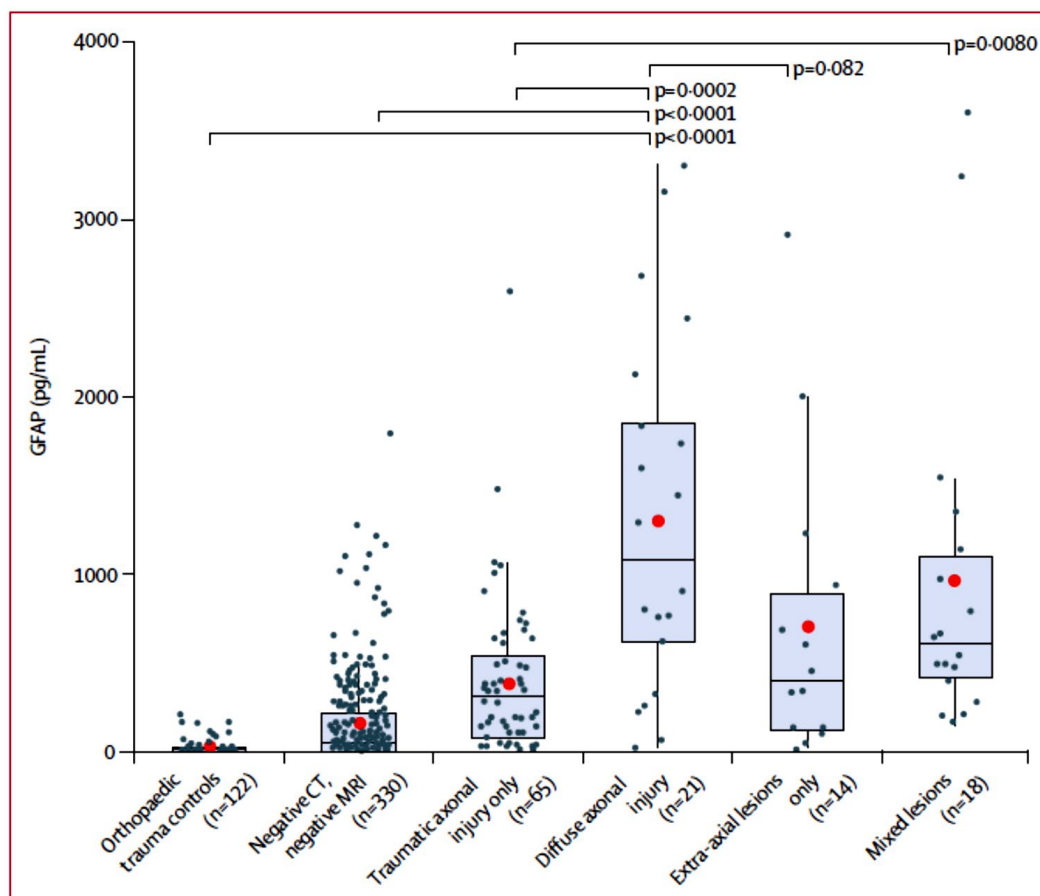
Plasma GFAP concentrations by imaging modality and findings					
	No of patients	Plasma GFAP concentrations (pg/mL)			
		Mean (SD)	Median (25-75 th percentile)	Range	P value
Positive CT	199	1400.9 (1598.6)	786.0 (357.0-1863.3)	0-9409.7	<0.0001*
Negative CT	450	308.0 (530.5)	110.3 (22.7-352.3)	0-4095.1	..
Negative CT & positive MRI	120	692.2 (827.6)	414.4 (139.3-813.4)	5.2-4095.1	<0.00001†
Negative CT & 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‡j
Healthy controls	209	11.0 (12.7)	8.0 (3.0-14.0)	0-98.0	<0.0001‡j

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. j Compared with patients with negative CT and negative MRI findings.

Appendix continued on next page.

References cited in this appendix

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Figure 2. GFAP concentration by MRI pathology

The red dot signifies mean plasma GFAP concentration while boxplots provide range, median, and 25-75th percentiles. Individual dot values are plotted for reference. The Dunn Kruskal-Wallis test for comparisons among different MRI lesion types with a Benjamin-Hochberg correction for multiple comparisons²³ showed that GFAP concentrations are significantly higher in patients with isolated diffuse axonal injury than in those with isolated traumatic axonal injury. Separate Wilcoxon rank sum tests also showed significantly higher GFAP concentrations in patients with isolated diffuse axonal injury than in patients with negative CT and negative MRI findings, and orthopaedic trauma controls. P values are displayed for relevant comparisons. Two patients with isolated intracerebral contusions (GFAP 14.9 pg/mL, 285.4 pg/mL) were not included as boxplot. GFAP=glial fibrillary acidic protein.

Table 4. Cutoff concentrations of plasma GFAP to predict MRI-positive versus MRI-negative findings in patients with negative CT

	Sensitivity	Specificity	NPV	PPV
4.40 pg/mL	1.000 (1.000-1.000)	0.024 (0.009-0.042)	1.000 (1.000-1.000)	0.271 (0.268-0.275)
12.95 pg/mL	0.958 (0.925-0.992)	0.188 (0.148-0.230)	0.925 (0.863-0.981)	0.300 (0.287-0.313)
25.15 pg/mL	0.908 (0.850-0.958)	0.333 (0.288-0.388)	0.910 (0.861-0.957)	0.332 (0.312-0.354)
71.95 pg/mL	0.825 (0.750-0.892)	0.494 (0.442-0.549)	0.888 (0.845-0.924)	0.373 (0.344-0.407)
282.70 pg/mL	0.642 (0.558-0.733)	0.803 (0.758-0.842)	0.861 (0.832-0.890)	0.543 (0.482-0.603)
848.75 pg/mL	0.233 (0.158-0.308)	0.964 (0.942-0.982)	0.775 (0.760-0.793)	0.698 (0.555-0.842)

The k-fold cross validation method was used to select the optimal cutoffs for predicting MRI-positive versus MRI-negative findings in patients with negative CT based on the criteria of adjusted NPV above the level of 0.96, 0.94, 0.92, and 0.90, 0.85, and 0.80, in accordance to data standards for clinical laboratory assays set by the manufacturer. The prevalence of positive MRI scans among patients with negative CT scans was estimated to be 0.27 on the basis of the sample rate to calculate the adjusted NPV. 1000 bootstraps were conducted to determine the optimal cutoffs using the median from each run. The optimal cutoff thresholds were then applied to the full data to calculate the corresponding sensitivity, specificity, NPV, and PPV. GFAP=glial fibrillary acidic protein. NPV=negative predictive value. PPV=positive predictive value.

APPENDIX E: INFORMATION REGARDING OFF-LABEL USES IN CPGS

PURPOSE

The purpose of this Appendix is to ensure an understanding of DoD policy and practice regarding inclusion in CPGs of “off-label” uses of U.S. Food and Drug Administration (FDA)–approved products. This applies to off-label uses with patients who are armed forces members.

BACKGROUND

Unapproved (i.e. “off-label”) uses of FDA-approved products are extremely common in American medicine and are usually not subject to any special regulations. However, under Federal law, in some circumstances, unapproved uses of approved drugs are subject to FDA regulations governing “investigational new drugs.” These circumstances include such uses as part of clinical trials, and in the military context, command required, unapproved uses. Some command requested unapproved uses may also be subject to special regulations.

ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGS

The inclusion in CPGs of off-label uses is not a clinical trial, nor is it a command request or requirement. Further, it does not imply that the Military Health System requires that use by DoD health care practitioners or considers it to be the “standard of care.” Rather, the inclusion in CPGs of off-label uses is to inform the clinical judgment of the responsible health care practitioner by providing information regarding potential risks and benefits of treatment alternatives. The decision is for the clinical judgment of the responsible health care practitioner within the practitioner-patient relationship.

ADDITIONAL PROCEDURES**Balanced Discussion**

Consistent with this purpose, CPG discussions of off-label uses specifically state that they are uses not approved by the FDA. Further, such discussions are balanced in the presentation of appropriate clinical study data, including any such data that suggest caution in the use of the product and specifically including any FDA-issued warnings.

Quality Assurance Monitoring

With respect to such off-label uses, DoD procedure is to maintain a regular system of quality assurance monitoring of outcomes and known potential adverse events. For this reason, the importance of accurate clinical records is underscored.

Information to Patients

Good clinical practice includes the provision of appropriate information to patients. Each CPG discussing an unusual off-label use will address the issue of information to patients. When practicable, consideration will be given to including in an appendix an appropriate information sheet for distribution to patients, whether before or after use of the product. Information to patients should address in plain language: a) that the use is not approved by the FDA; b) the reasons why a DoD health care practitioner would decide to use the product for this purpose; and c) the potential risks associated with such use.