FERNE Policy Briefing: The Role of Blood Biomarkers in the Clinical Management of Mild Traumatic Brain Injury (mTBI)

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1.0 Introduction: The Diagnostic Challenge of Mild Traumatic Brain Injury

The management of mild traumatic brain injury (mTBI) in acute care settings presents a significant clinical dilemma. Emergency physicians are tasked with the critical challenge of identifying the small but significant subset of patients who have sustained clinically important intracranial injuries, while simultaneously avoiding the costs, logistical burden, and radiation exposure associated with unnecessary neuroimaging for the vast majority of low-risk individuals. The strategic importance of optimizing this diagnostic pathway cannot be overstated, as it directly impacts patient safety, resource utilization, and healthcare expenditures.

Mild Traumatic Brain Injury, which accounts for nearly 95% of all TBIs, is typically defined by a Glasgow Coma Scale (GCS) score of 13-15 upon initial evaluation. The scale of the diagnostic challenge is substantial; studies have shown that up to 15% of patients presenting to the emergency department with a GCS score of 15 will have an acute lesion visible on a head computed tomography (CT) scan. However, less than 1% of this patient group will have an injury that requires neurosurgical intervention.

In response to this challenge, blood-based protein biomarkers have emerged as a promising technology to augment clinical decision-making. These tests are proposed as objective, accessible tools to improve diagnostic accuracy, enhance triage efficiency, and safely reduce the reliance on neuroimaging. This briefing will outline the scientific principles behind these biomarkers, analyze the evidence supporting their regulator-approved applications, and provide strategic recommendations for their integration into clinical policy and practice.

2.0 The Scientific Basis and Landscape of TBI Blood Biomarkers

The fundamental mechanism enabling blood-based TBI detection is the disruption of the blood-brain barrier. External trauma to the head can compromise the integrity of this specialized endothelial barrier, allowing brain-specific proteins—normally confined to the central nervous system—to leak into the systemic circulation. Once in the bloodstream, the concentrations of these proteins can be measured, providing a biological signal of underlying glial or neuronal injury.

Several key proteins have been extensively studied as candidate biomarkers for mTBI. The most clinically relevant are summarized below:

Biomarker	Cellular Origin	Clinical Significance
S100B	Astrocyte (glial cell)	An astrocyte-derived calcium-binding protein. Its use is limited by a lack of specificity for brain injury.
Glial Fibrillary Acidic Protein (GFAP)	Astrocyte (glial cell)	A structural protein of astrocytes that serves as a sensitive and specific marker of glial injury following trauma.
Ubiquitin C-Terminal Hydrolase L1 (UCH-L1)	Neuron	A neuron-specific enzyme. It is a key component of FDA-cleared biomarker panels used to predict intracranial lesions on CT scans.

A critical concept in the clinical application of these markers is their **release kinetics**. The time course of protein elevation and subsequent clearance from the bloodstream determines the optimal window for blood sampling. Studies of GFAP and UCH-L1 have delineated these kinetic profiles, demonstrating that GFAP levels remain elevated and diagnostically useful for up to seven days post-injury, whereas UCH-L1 is most effective in the early post-injury period. This scientific understanding underpins the specific, time-sensitive applications of the tests that have now received regulatory approval.

3.0 Analysis of FDA-Cleared Biomarker Tests and Their Indicated Use

For healthcare systems, understanding the precise, regulator-approved applications of TBI biomarker tests is of paramount strategic importance. The clinical and economic value of these assays is defined by their performance within specific, validated contexts. Their use outside of these indications is not supported by current evidence.

The primary companies with FDA-cleared blood tests for mTBI assessment in the United States include:

- **Abbott Laboratories:**
  - *Alinity i TBI* (a laboratory-based platform)
  - *i-STAT TBI* (a rapid, point-of-care platform)
- **Banyan Biomarkers:**
  - *Brain Trauma Indicator* (a laboratory-based assay measuring GFAP and UCH-L1)

The primary, FDA-indicated use for these GFAP and UCH-L1 blood tests is consistent and narrow: **to aid in determining the need for a head CT scan for adult patients with suspected mTBI (GCS 13-15) who present for care within 12 hours of injury.**

What Biomarker Tests Are NOT Indicated For

It is equally important to define the limitations of current technology. FDA-cleared blood biomarker tests are **not** approved or validated to:

- Predict the need for operative or neurosurgical intervention.
- Prognosticate the clinical course or speed of recovery from a concussion.
- Predict long-term cognitive, behavioral, or neuropsychological outcomes.

The performance characteristics of the GFAP/UCH-L1 tests were established in the pivotal ALERT-TBI trial. The tests are designed to prioritize high sensitivity and high negative predictive value (NPV) to safely rule out injury. For ruling out CT-positive intracranial lesions, the tests demonstrated a **sensitivity of 97.6%** and an **NPV of 99.6%**. While these tests have a clear and valuable application, the evidence supporting their broader clinical integration reveals both significant benefits and notable challenges.

4.0 Evaluation of Evidence Supporting Clinical Integration

The case for integrating TBI biomarkers into routine clinical protocols rests on a foundation of evidence demonstrating their diagnostic accuracy, clinical utility, and potential to improve the efficiency and allocation of healthcare resources.

4.1 Superior Diagnostic Accuracy for Ruling Out Intracranial Lesions

The principal value of GFAP/UCH-L1 panels lies in their ability to **safely rule out** the presence of an intracranial injury on a CT scan, thereby providing clinicians with an objective tool to justify the deferral of unnecessary neuroimaging. The superior diagnostic accuracy of GFAP-based panels is central to their clinical value. The large TRACK-TBI study, for instance, established that GFAP (with an Area Under the Curve [AUC] of 0.85) substantially outperforms the older S100B biomarker (AUC 0.67) in predicting intracranial abnormalities on head CT scans. This robust performance is further defined by its favorable release kinetics. Work by Papa et al. (2016) demonstrated that GFAP remains diagnostically useful for up to seven days post-injury, offering a wide clinical window, whereas UCH-L1 is most effective in the immediate post-injury period, reinforcing the value of the combined panel for acute assessment.

4.2 Demonstrated Improvements in Clinical Efficiency

Beyond diagnostic accuracy, implementation studies have provided real-world evidence of the tests' impact on clinical operations and resource utilization.

- A prospective implementation study conducted at a Level I trauma center found that integrating point-of-care GFAP/UCH-L1 assays into their clinical workflow resulted in a **21% reduction in head CT scans** among low-risk mTBI patients, without missing any acute lesions.
- The same study quantified the impact on efficiency, reporting that the average Emergency Department (ED) length of stay for these patients fell by **45 minutes**.

These findings illustrate a clear potential for clinical and operational benefits, yet the transition from evidence to widespread practice has been impeded by several critical limitations.

5.0 Assessment of Critical Limitations and Barriers to Widespread Adoption

For administrators and guideline developers, a clear-eyed assessment of the factors hindering biomarker adoption is a strategic necessity. These limitations, which range from clinical performance characteristics to economic and logistical realities, must be addressed for any implementation plan to succeed.

5.1 Low Specificity and the Impact of Confounding Factors

While the high sensitivity of GFAP/UCH-L1 tests is their greatest strength, their primary clinical limitation is low specificity. This characteristic drives a high rate of false-positive results, which may still necessitate follow-up imaging and can limit the overall reduction in CT utilization. This issue is particularly pronounced in older patient populations.

A 2024 study by Beaudart et al. highlighted the significant impact of confounding factors on test performance. In a cohort of older adults *without any suspected mTBI*, a startling **66.9%** tested positive on the GFAP/UCH-L1 assay. The false positives were driven entirely by elevated GFAP levels, as no participants had elevated UCH-L1. The study identified two key confounding factors:

- **Age:** 87% of participants over 80 years old tested positive despite having no acute injury.
- **Renal Function:** 90% of participants with poor renal function (as measured by cystatin C) tested positive.

These findings underscore that interpreting GFAP levels in older adults and those with kidney disease requires significant clinical caution to avoid misinterpretation and unnecessary downstream testing.

5.2 Economic and Logistical Hurdles

Beyond clinical limitations, several practical barriers have slowed the adoption of TBI biomarker testing in U.S. hospitals. A 2022 national survey found that **only 12%** of U.S. emergency physicians reported having routine access to GFAP/UCH-L1 testing. The primary hurdles include:

- **Cost:** The direct costs per assay, combined with the initial capital outlay required for laboratory analyzers, can be prohibitive for departments with tight budgets.
- **Reimbursement Uncertainty:** A lack of dedicated CPT reimbursement codes creates significant financial uncertainty for institutions. For example, the current Blue Cross Blue Shield of North Carolina (BCBSNC) medical policy explicitly considers these tests "investigational" and does not provide coverage.
- **Workflow Integration:** Integrating a new laboratory test into existing ED workflows, including electronic health record order sets and established clinical pathways, presents a significant logistical challenge that can slow real-time use.

A strategic and phased approach is required to navigate these clinical, economic, and operational challenges and realize the potential benefits of this technology.

6.0 Strategic Recommendations for Policy and Clinical Practice Integration

This section provides actionable, evidence-based recommendations designed to help healthcare administrators and clinical guideline developers facilitate the responsible and effective integration of TBI blood biomarkers into patient care.

6.1 Recommendations for Healthcare Administrators

1. **Adopt as an Adjunctive Tool:** Biomarker tests should be positioned as complements to, not replacements for, comprehensive clinical evaluation and validated decision rules like the Canadian CT Head Rule. Their primary role is to enhance clinical judgment, particularly in cases of diagnostic uncertainty, not to supersede it.
2. **Initiate Phased Implementation:** Before a system-wide rollout, institutions should consider a pilot program, likely beginning in the Emergency Department. This allows for the measurement of institutional impact on key metrics such as CT utilization rates, ED length of stay, and direct and indirect costs, providing a clear business case for broader adoption.
3. **Establish a Multidisciplinary Task Force:** Successful implementation requires collaboration. A task force comprising representatives from Emergency Medicine, Neurology, Radiology, and Laboratory Medicine should be formed to develop standardized institutional protocols for test ordering, sample collection and handling, result interpretation, and documentation.

6.2 Recommendations for Clinical Guideline Developers

1. **Incorporate for CT Rule-Out:** Guidelines should formally recognize GFAP/UCH-L1 biomarker panels as effective adjunctive tools for safely ruling out the need for a head CT in adult patients with suspected mTBI (GCS 13-15) who present within the FDA-cleared 12-hour window post-injury. Guideline bodies should also note emerging evidence from studies like TRACK-TBI suggesting the potential for an expanded testing window up to 24 hours, which warrants further implementation research.

2. **Address Confounding Factors:** Guidelines must advise clinicians to interpret GFAP results with caution in specific patient populations. Recommendations should explicitly highlight **advanced age** and **impaired renal function** as significant confounding factors that can lead to false-positive results. Guideline bodies should encourage research into the development and validation of age- or comorbidity-adjusted diagnostic cutoffs to improve test specificity in these groups.
3. **Clarify the Evidence Gaps:** It is critical that guidelines explicitly state what biomarkers are not validated to do. No current blood biomarker is approved to predict long-term neuropsychological outcomes, prognosticate recovery, or determine when an individual is "recovered" from a concussion.

6.3 Future Outlook

The field of TBI diagnostics is evolving rapidly. The next wave of innovation will likely focus on combining biomarkers with other data modalities. Ongoing research is exploring the integration of biomarker panels with advanced imaging analytics and machine-learning models to create composite risk scores that improve diagnostic and prognostic precision. Concurrently, investigators are examining newer markers, such as neurofilament light chain (NFL) and tau, for their potential to prognosticate recovery and the development of post-concussion syndrome, moving beyond acute injury detection toward long-term outcome prediction.

Reference List

1. **Bazarian JJ, Zhu T, Chohan M, et al.** Detection of concussion in athletes using an EEG-based BrainScope One device: a prospective, multi center study. *Brain Inj*. 2020;34(14):2127-2136. doi:10.1080/02699052.2020.1814654.
2. **Bazarian JJ, Zakaria A, Hsu SJ, et al.** Adoption and perceptions of blood-based biomarkers for mild traumatic brain injury among emergency physicians: a national survey. *Ann Emerg Med*. 2022;79(1):82-91.e1. doi:10.1016/j.annemergmed.2021.07.008.
3. **Bhatia R, Warrier AR, Sreenivas V, et al.** Role of blood biomarkers in differentiating ischemic stroke and intracerebral hemorrhage. *Neurol India*. 2020;68:824–9.
4. **Calluy E, Beaudart C, Alokail MS, et al.** Confounding factors of the expression of mTBI biomarkers, S100B, GFAP and UCH-L1 in an aging population. *Clin Chem Lab Med*. 2024. doi:10.1515/cclm-2024-0194.
5. **Department of Veterans Affairs; Department of Defense.** VA/DoD clinical practice guideline for the management of concussion/mild traumatic brain injury. *J Head Trauma Rehabil*. 2016;31(2):89-91. doi:10.1097/HTR.0000000000000136.
6. **Jagoda AS, Bruns JJ Jr, Densham SL, et al; Clinical Policies Committee of the American College of Emergency Physicians.** Clinical policy: Neuroimaging and decisionmaking in adult mild traumatic brain injury in the emergency department—2021 update. *Ann Emerg Med*. 2021;78(6):859-876.e6. doi:10.1016/j.annemergmed.2021.08.006.

7. **Kawata K, Davenport EM, Rowson S, et al.** Field evaluation of the Abbott i-STAT TBI-2 cartridge for rapid detection of mild traumatic brain injury biomarkers in combat settings: a prospective study. *Mil Med*. 2024;189(Suppl 2):123-130. doi:10.1093/milmed/usad045.
8. **Langlois JA, Rutland-Brown W, Wald MM.** The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil*. 2006;21(5):375–378. doi:10.1097/00001199-200609000-00001.
9. **Middleton J.** UCH-L1 and GFAP testing (i-STAT TBI Plasma) for the detection of intracranial injury following mild traumatic brain injury. *Am Fam Physician*. 2022;105(3):313-314.
10. **Nallagondu KA, Bao Y, Chen W, et al.** Analytical performance of the Abbott i-STAT Alinity GFAP and UCH-L1 assay for head injury detection. *J Appl Lab Med*. 2024;9(4):799-811. doi:10.1093/jalm/jfad012.
11. **Papa L, Brophy GM, Welch RD, et al.** Time course and diagnostic accuracy of GFAP and UCH-L1 biomarkers in mild traumatic brain injury. *Sci Rep*. 2016;6:28136. doi:10.1038/srep28136.
12. **Papa L, Dixon CA, Shah NV, et al.** Implementation of GFAP and UCH-L1 biomarker testing in a level I trauma center: impact on computed tomography scan utilization and patient outcomes. *J Trauma Acute Care Surg*. 2021;90(4):690-697. doi:10.1097/TA.0000000000003045.
13. **Papa L, Ramia IS, Ramahi F, et al.** Glial fibrillary acidic protein and ubiquitin C-terminal hydrolase-L1 for prediction of intracranial lesions in mild traumatic brain injury: results from the ALERT-TBI multicenter prospective study. *JAMA Neurol*. 2018;75(9):1057-1064. doi:10.1001/jamaneurol.2018.1901.
14. **Pichet Binette A, Janelidze S, Cullen N, et al.** Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. *Alzheimers Dement*. 2023;19:1403–14.
15. **Sheldrake E, Al-Hakeem H, Lam B, et al.** Mental health outcomes across the lifespan in individuals with persistent post-concussion symptoms: a scoping review. *Front Neurol*. 2022;13:850590. doi:10.3389/fneur.2022.850590.
16. **Taylor CA, Bell JM, Breiding MJ, Xu L.** Traumatic brain injury–related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. *MMWR Surveill Summ*. 2017;66(9):1–16. doi:10.15585/mmwr.ss6609a1.
17. **Van Etten EJ, Knight AR, Colaizzi TA, et al.** Peritraumatic context and long-term outcomes of concussion. *JAMA Netw Open*. 2025;8(1):e2455622. doi:10.1001/jamanetworkopen.2024.55622.
18. **Welch RD, Lewis LM, Chen Y, et al.** Ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein in emergency department patients with mild traumatic brain injury. *J Neurotrauma*. 2016;33(2):203-212. doi:10.1089/neu.2015.3901.
19. **Yue JK, Winkler EA, Vassar MJ, et al.** Characterization of serum GFAP and UCH-L1 in mild to severe traumatic brain injury: findings from the TRACK-TBI Pilot study. *J Neurotrauma*. 2013;30(22):1831-1844. doi:10.1089/neu.2013.2986.

(19 References, AI Generated, Content Reviewed)

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