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FERNE Clinical Update

MILD TBI BIOMARKERS: CONCLUSIONS AND CLINICAL RECOMMENDATIONS

The Clinical Imperative and Core Concepts

CLINICAL IMPERATIVE

The primary goal of incorporating blood biomarkers (Glial Fibrillary Acidic Protein [GFAP] and Ubiquitin C-Terminal Hydrolase L1 [UCH-L1]) is to **safely reduce unnecessary head Computed Tomography (CT) scans** and associated radiation exposure in the majority of adult mild TBI (mTBI) patients, who rarely have intracranial lesions (CT-positive prevalence typically 5%–12%). FDA-cleared GFAP/UCH-L1 blood tests provide an objective, high-sensitivity adjunct to clinical decision rules to optimize triage and expedite care.

Representative Case

A 35-year-old male presents to the ED 6 hours after a fall from a skateboard, striking his head. He had a momentary loss of consciousness (LOC) at the scene, headache, and one episode of vomiting en route. His GCS is 15, and his neurological exam is non-focal. Based on clinical decision rules (e.g., Canadian CT Head Rule), imaging may be indicated due to LOC and vomiting. Given his low-risk clinical profile and short duration of symptoms, a GFAP/UCH-L1 biomarker test is drawn. **If the test is negative, can we safely defer the CT scan, reduce his radiation exposure, and discharge him sooner?** The answer, based on FDA-cleared technology and clinical trial data, is yes, for carefully selected patients.

8 Essential Clinical Recommendations

No.	Actionable Recommendation	Rationale (Conclusion)
R1. Integrate as Adjuncts	**Use GFAP/UCH-L1 tests only as complements** to clinical decision rules; they are not a standalone diagnostic.	Biomarkers alone may underperform standard clinical evaluation.
R2. Manage Negative Results	Defer CT safely for low-risk adults with a **negative result**, provided they are within the <=12 hour window.	The tests prioritize high NPV (up to 99.6%) for safe CT deferral.
R3. Adjust for Confounders	Exercise heightened caution when testing patients of **advanced age or those with renal impairment**.	These patient factors drive false-positive GFAP results (87% positivity in <=80 years).
R4. Override for Anticoagulation	**Do not defer CT based solely on a negative biomarker** in patients on anticoagulation/antiplatelet agents.	Anticoagulation increases true lesion prevalence (approx 15%–20%), shrinking NPV to approx 97%–98%.
R5. Set Prognostic Expectations	Avoid providing patients with prognostic guidance based on acute biomarker results; the test utility is limited to **acute triage**.	Current FDA-cleared tests are **not approved** to predict recovery or long-term symptoms.
R6. Avoid Pediatric Routine Use	**Do not apply adult protocols to children**; use for pediatric mTBI only within a research setting.	The **CDC recommends against routine use** outside research due to insufficient evidence.
R7. Utilize POC for Throughput	Implement POC testing, if feasible, to leverage rapid turnaround times (15–18 minutes).	Operational data shows integration results in a **21% CT reduction** and shortens LOS by 45 minutes.
R8. Enforce Rigorous Protocols	Ensure strict adherence to **<=12 hour timing** and standardized sample handling protocols.	Following timing and criteria ensures performance metrics (sensitivity >= 95%) are maintained.

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15 Conclusions and Clinical Recommendations

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15 Conclusions

C1. Primary Role and Indication: The FDA-cleared GFAP/UCH-L1 tests are strictly **adjunctive tools** indicated only to aid in determining the need for a head CT scan in adults (GCS 13-15) presenting within 12 hours of injury.

C2. Performance Profile: These multiplex blood tests prioritize **extremely high sensitivity (up to 97.6%) and Negative Predictive Value (NPV, up to 99.6%)** to safely defer imaging, accepting the trade-off of low specificity (around 35%).

C3. Confounding Variables: The interpretation of GFAP results requires significant caution in specific populations, as **advanced age and impaired renal function** are major confounding factors driving false-positive results.

C4. Temporal Constraints: While UCH-L1 peaks early (8 hours) and GFAP lasts longer (up to 7 days), **adherence to the 12-hour window** is mandated for the FDA-cleared rule-out indication to ensure maximal diagnostic reliability.

C5. Prognostic Limitations: Current FDA-cleared blood or EEG tests are **not approved or validated** to predict the speed of concussion recovery, long-term neuropsychological outcomes, or the necessity for neurosurgical intervention.

C6. Comparative Utility in Polytrauma: GFAP demonstrates superior diagnostic accuracy compared to S100B, particularly because S100B lacks specificity and can be elevated by **extracranial injuries or orthopedic trauma**.

C7. Clinical and Economic Impact: Integrating point-of-care (POC) GFAP/UCH-L1 assays demonstrably improves clinical flow by reducing head CT scans (e.g., 21% reduction) and shortening ED length of stay.

C8. Adoption Challenges: Widespread adoption is significantly hampered by **logistical and economic barriers**, including lack of dedicated reimbursement codes, high capital outlay for analyzers, and slow integration into clinical pathways.

C9. Liberal CT Use: Because head NCCT is clinically useful and cost-effective, **liberal use is justified**.

C10. Anticoagulated Patients Are Often Older and At Risk: Anticoagulant use most often causes risk to **exceed the minimal risk** that identifies patients who might optimally be tested with brain biomarkers. Cutoffs might also need to be modified in most of these patients due to advanced age.

C11. Alcohol Use Confounds Biomarker Use: Alcohol levels above 100–150 mg/dL will increase the number of false positives, such that a **doubling of the positive cutoff for both biomarkers is suggested** without causing an increase in false negative biomarker tests.

C12. Key Risk Elements Guide Practice: The **Modified Canadian Head CT Rule for Minor Head Injury** clearly identifies the mTBI patients for whom head NCCT is indicated, making easy the establishment of mTBI patients for whom brain biomarkers is not indicated.

C13. Ongoing Clinician Learning is Facilitated: Clinician learning is made easy in 2026 through the use of organized conferences, remote learning, Internet content, social media, and AI, such that **greater adoption of optimal testing strategies is possible**.

C14. Understand What the Goals Are of These Tests: The **goal of performing tests is to achieve optimal patient outcome**s using tests that are clinically efficacious and cost-effective.

C15. Established Protocols and the EMR Can Justify Medical Decision Making that Optimizes mTBI Outcomes: Optimal mTBI patient diagnostic protocols are constantly being developed and modified. The **clinical factors that make these protocols work to benefit patients can be integrated into the EMR** for consistent medical practice

15 Clinical Recommendations

R1. Integrate as Adjuncts: Utilize GFAP/UCH-L1 tests only as **complements to standard, validated clinical decision rules** (e.g., Canadian CT Head Rule), never as replacements for a comprehensive clinical evaluation.

R2. Manage Positive Results: Since specificity is low, caution patients that a positive result indicates a **need for further imaging (CT scan)**, but often does not mean a severe injury is present.

R3. Interpret Age-Adjusted: Exercise heightened clinical caution when testing patients of **advanced age or those with renal impairment**, as false-positive GFAP results are common in these groups.

R4. Respect the Time Window: Ensure blood samples are collected **within 12 hours of injury** for maximum rule-out certainty, as this adheres to the FDA-cleared performance profile and UCH-L1 kinetics.

R5. Set Expectations: Avoid providing patients with prognostic guidance based on acute biomarker results; explicitly state that the tests' utility is limited to **acute triage for intracranial lesions**.

R6. Favor GFAP in Polytrauma: When evaluating patients with concurrent extracranial injuries, choose GFAP-based panels over S100B, as **GFAP maintains greater brain-specific accuracy**.

R7. Utilize POC for Throughput: Implement point-of-care testing to leverage rapid turnaround times (15–18 minutes) to **speed up triage and reduce ED length of stay**, maximizing the operational benefit.

R8. Develop Institutional Protocols: Form a multidisciplinary task force (EM, Lab, Radiology) to **establish standardized protocols for test ordering**, result integration into the EHR, and managing follow-up.

R9. Accept Any Reasonable CT Reduction: When initiating the use of a clinical protocol for the optimal management of mTBI patients, expect that the **initial reduction in head NCCT will be modest**. Collect data that will track test optimization over time by comparing clinician use and patient outcomes.

R10. Liberally Neuroimage Anticoagulated Patients and Study Results: Collect data that tracks the test results of both brain biomarkers and head NCCT using an **institutional protocol that initially promotes the use of both tests in anticoagulated patients**. Local data, including

positive head NCCT prevalence, will help to determine brain biomarker NPV and the need for ongoing liberal head NCCT use.

R11. Study Biomarkers Use for Intoxicated Head Trauma Patients: Collect data that tracks the test results of both brain biomarkers and head NCCT in intoxicated mTBI patients using an **institutional protocol that initially promotes the use of both tests in intoxicated patients**. Local data, including positive head NCCT prevalence, will help to determine optimal brain biomarker cutoffs and NPV and the need for ongoing liberal head NCCT use in this mTBI subgroup.

R12. Know Risk Elements and Recommendations: Using the Modified Canadian Head CT Rule for Minor Head Injury to **establish a list of mTBI patients for whom head NCCT is indicated** and brain biomarkers are not clinically indicated.

R13. Use AI and more to Change Clinical Practice: When optimal mTBI patient testing strategies are identified going forward, use all the teaching modalities to **educate clinicians on best practices** for these patients.

R14. Utilize an Early Adoption Strategy That Focuses on Best Patients for Biomarker Use: Once a standardized protocol is developed to improve clinical decision making, **encourage clinicians to liberally use head NCCT when clinical gestalt suggests greater than minimal risk**. Use the EMR to collect clinically relevant data and CQI methods to determine the success of biomarker use by monitoring patient outcomes, decrease in head NCCT use, ED throughput, and cost of care.

R15. Use Protocols and the EMR to Minimize Medicolegal Risk: Use established protocols to create a local protocol for your institution or healthcare system. **Integrate your local protocol into your EMR** for automated data collection, facilitated decision making, and facile ongoing CQI activities.

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These conclusions and recommendations are based on review of the relevant publications and work with the AI tools Co-Pilot and Notebook LM. Please refer to the original sources from the reference list and other clinically relevant sources for more information that guides clinical care of mTBI patients.

FERNE 2025 Clinical Update ED Mild TBI Patients Lab Testing

Conclusions and Recommendations Sloan 112625 Final

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