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FERNE Clinical Update

MILD TBI BIOMARKERS: LAB NEGATIVE, CT POSITIVE PATIENT CASES

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.

The most important clinical question is "If the biomarker test is negative and the CT is positive for an intracranial lesion, what is the clinical significance of this CT lesion for the patient with mild TBI and a possible concussion?"

PATIENT CARE SUMMARY

It is a rare occurrence that a mTBI patient may present to the ED and have a negative biomarker test and a positive CT, most often a clinically low-risk intracranial injury, typically minor, non-operative, and unlikely to require neurosurgical intervention.

These discordant patient cases are those with small hemorrhages or fractures with minimal clinical impact. These cases represent complicated mild TBI patients. The negative biomarker provides reassurance of low subsequent deterioration risk, supporting selective discharge with appropriate precautions and follow-up for who are otherwise low risk mTBI patients.

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. **If the CT is positive following a negative lab biomarker test, is the missed lesion of clinical significance?** The information provided in this document from the public regulatory document suggests that the missed lesions are of limited clinical severity and significance. None of these patients required subsequent neurosurgical intervention.

Key Clinical Question

In an ED patient with mTBI (GCS 13-15) and a possible concussion, if the brain biomarker test is negative and the CT is positive for an intracranial lesion, what is the clinical significance of this intracranial lesion on the subsequent care and outcome for this patient?

Discordant Patient Cases (Brain Biomarkers Negative, CT Positive)

Key Clinical Concepts

1) These patient cases represent a rare discordant finding where structural injury exists but it is of low clinical significance.
A negative GFAP/UCH-L1 suggests limited astroglial and neuronal injury burden. When CT is positive in this setting, the lesion is typically small and biologically less disruptive.

2) The CT-positive findings in this scenario are overwhelmingly minor, non-operative lesions.
Across regulatory data, these include small subdural hematomas, small subarachnoid hemorrhages, or nondisplaced skull fractures—findings that do not produce mass effect or require neurosurgical intervention.

3) The patient still has a traumatic intracranial injury and must be managed accordingly.
Even if clinically "low-risk," a CT-positive lesion changes disposition, documentation, and follow-up. This is no longer "uncomplicated concussion"—it is **complicated mTBI**.

4) Immediate clinical risk is low, but not zero—observation and judgment still matter.
These lesions have low short-term deterioration risk, but factors such as anticoagulation, age, worsening symptoms, or unreliable follow-up may still necessitate observation or repeat evaluation.

5) The negative biomarker reinforces low likelihood of clinically significant deterioration.
This is the key value: it provides **physiologic reassurance** that the injury is unlikely to progress to a neurosurgical emergency, supporting safe, selective discharge in appropriate patients.

6) This scenario highlights the true role of biomarkers: risk stratification, not diagnosis.
Biomarkers do not "detect lesions"—they estimate **clinical significance of brain injury**. A negative result suggests low-risk biology even when imaging shows minor structural abnormalities.

Publications Included in This Clinical Update (public sources)

- **Banyan BTI (De Novo DEN170045)** — FDA decision memorandum and summary data.
- **Abbott i-STAT TBI (K201778)** — FDA 510(k) summary and validation materials.
- **bioMérieux VIDAS TBI (K240279)** — FDA 510(k) summary and company validation materials.
- **Papa et al., JAMA Network Open (2024)** — open-access biomarker performance data.
- Additional **open validation cohorts and systematic reviews** as available in public domain; I'll add these rows as I locate them.

Extracted Data (from public documents)

- **N (total patients)** and **N with positive NCCT (counts and prevalence %)** where reported in FDA summaries and open papers.
- **Reported Sensitivity, Specificity, PPV, NPV, Accuracy** (as published).
- **Assay platform, cutoffs, and time window** (e.g., ≤12 hours) from regulatory summaries.
- **Verbatim CT wording** for discordant (biomarker-negative / CT-positive) cases when that wording appears in public summaries (FDA memos often include case descriptions).
- In any study row where the public summary lacks verbatim CT wording or raw 2×2 counts, it will be marked **"Full-text required"**.

Clinical Summary from Public Source Descriptions

Public regulatory summaries report that the rare cases with **both GFAP and UCH-L1 below assay cutoffs but a positive NCCT** were **minor, non-operative traumatic findings** (small subdural hematoma, small subarachnoid hemorrhage, nondisplaced skull fracture) rather than large, surgically-treated lesions.

Public Regulatory Documents Statements (Verbatim Summary)

- **Banyan BTI (FDA De Novo DEN170045):** The FDA De Novo decision and review summarize the pivotal data and explicitly note a *very small number* of discordant cases in which serum GFAP/UCH-L1 were below the device cutoffs yet the patient's head CT showed trauma-related findings. Those CT findings are described in the public memorandum as **small subdural hematoma, small subarachnoid hemorrhage, and nondisplaced skull fracture**; the review emphasizes that these were *minor, non-operative* lesions and that the overall negative predictive value was very high. **Limitations:** the De Novo memo paraphrases case descriptions rather than reproducing full case narratives; full verbatim CT report text is in the primary publications or site case reports, not always in the public summary.

- **bioMérieux VIDAS TBI (510[k] K240279) and related 510(k) summaries:** The VIDAS TBI 510(k) summary and device decision documents likewise report high NPV for combined GFAP/UCH-L1 and note that discordant biomarker-negative/CT-positive cases that appear in validation cohorts were **minor intracranial findings or nondisplaced skull fractures**, with no indication of missed neurosurgical emergencies in the public summaries. The 510(k) summary provides performance metrics and describes the intended use window and assay format.

- **Device classification and public 510(k) summaries:** FDA device pages and 510(k) summaries for the various platforms (Banyan, Abbott i-STAT, bioMérieux VIDAS) consistently report **very high NPV** and characterize the small number of false negatives as **clinically minor** in the public documents; the device pages summarize intended use (adults, within 12 hours of injury) and the role of the assays as adjuncts to clinical evaluation rather than replacements for clinical judgment.

Practical Interpretation and Caveats

- **Clinical meaning:** Across public regulatory sources, the discordant cases were *not* described as large, operative bleeds; they were small hemorrhages or nondisplaced fractures that did not require neurosurgical intervention per the summaries.
- **Why full-text matters:** For *exact, word-for-word* CT report text and patient-level detail (timing, symptoms, GCS, anticoagulation status), the primary manuscripts and supplementary case tables (e.g., ALERT-TBI full text) are required; the FDA summaries paraphrase and aggregate for regulatory purposes.

Bottom line: Public regulatory documents consistently report that biomarker-negative / NCCT-positive discordances are *rare* and, in the publicly described cases, *minor* (small SDH, small SAH, nondisplaced skull fracture) rather than clinically important, operative lesions

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What the ALERT-TBI Publication Presents

From the **ALERT-TBI Lancet Neurology paper**, there were **3 false-negative combined-test cases** among **1,959 analyzable patients**; the paper also states that **one of those 3 may not have been a true traumatic CT-positive case**, because follow-up MRI showed an **underlying cavernous malformation** that could mimic a focal hemorrhagic contusion on CT. The paper further reports that the combined GFAP/UCH-L1 test was **100% sensitive for neurosurgically manageable lesions**, so **none of the surgically important lesions were missed** in ALERT-TBI.

What the FDA Summaries Add

The **Banyan De Novo decision memorandum** reports **3 false negatives out of 120 CT-positive cases (2.5%)** and explicitly says **none of the 5 subjects with lesions requiring surgical intervention** had a false-negative result. The later **Abbott i-STAT plasma 510(k)**, using frozen plasma specimens from the ALERT-TBI cohort, found **5 false negatives out of 120 CT-positive cases (4.2%)**, again with **no false negatives among lesions requiring surgical intervention**.

Discordant Lesion Cases

The publicly described **biomarker-negative / CT-positive** lesions were as follows:

- **Small subdural hematoma**
- **Small subarachnoid hemorrhage**
- **Nondisplaced skull fracture**
- **One possible CT mimic later reclassified by follow-up MRI as cavernous malformation rather than true traumatic contusion**

Practical Clinical Interpretation of These Discordant Cases

- **They were rare.**
  In ALERT-TBI, false negatives were uncommon relative to the total cohort and uncommon even among CT-positive patients.

- **They were minor structural findings, not major operative bleeds.**
  The public descriptions point to **small SDH, small SAH, and nondisplaced skull fracture**, not large mass-effect lesions.

- **No neurosurgically manageable lesion was missed.**
  That is the most important safety signal in both the De Novo and Abbott plasma regulatory datasets.

- **One discordant case may not have been a true traumatic intracranial lesion at all.**
  ALERT-TBI reports that follow-up MRI in one false-negative case showed a **cavernous malformation**, suggesting possible CT overcall or mimic.

- **The clinical meaning is low immediate danger, not "no injury."**
  A biomarker-negative / CT-positive patient may still have **complicated mild TBI**, but the publicly described lesions were low-risk and non-operative.

Clinical Summary

The best clinical summary is as follows:

ALERT-TBI identified 3 discordant biomarker-negative / CT-positive cases. One may have been a cavernous malformation mimic. The public regulatory summaries characterize the remaining discordant lesions as small, non-operative abnormalities such as small SDH, small SAH, or a nondisplaced skull fracture. No neurosurgically important lesions were missed. This information supports the role of brain biomarker testing as a reasonable adjunct in the diagnosis of ED mTBI patients who are at low risk based on a favorable clinical history and presentation.

Reference List

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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 the clinical care of mTBI patients.

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