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Review Article

Point-of-care Biosensing for Mild Traumatic Brain Injury Triage: From S100B to GFAP/UCH-L1, Analytical Validation, and Clinical Benchmarking

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Abstract

Mild traumatic brain injury (mTBI) represents the majority of head injury presentations in emergency departments (EDs), yet only a minority of patients have acute intracranial lesions on computed tomography (CT). This leads to widespread use of unnecessary CT scans. Point-of-care (POC) biosensing, defined as analytical testing performed at or near the site of patient care, offers a promising solution to this dilemma by enabling rapid biomarker quantification to inform CT decision-making. This review aims to evaluate POC-compatible biosensing strategies for ultra-early mTBI triage, with emphasis on platforms, matrix effects, and benchmarking aligned with CT-based decision-making. Two key precedents support this approach: (1) the integration of S100B into Scandinavian Neurotrauma Committee guidelines, which has demonstrated the potential for safe reduction of CT scans, and (2) the regulatory clearance of glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) testing to rule out the need for head CT in adults with suspected mTBI (Glasgow Coma Scale 13–15) when serum is collected within 12 hours of injury. Accordingly, this review focuses on the most implementable use case for mTBI, namely CT triage/rule-out. It synthesizes the current biomarker landscape (S100B, GFAP, UCH-L1), analyzes POC-suitable sensing modalities, and proposes a practical validation and benchmarking framework aligned with this intended use. A critical component is interference testing and real-world sample robustness, including vulnerabilities such as hemolysis-related elevation of UCH-L1. In conclusion, the most reliable path for biosensor translation in mTBI is to anchor development and validation to the ED CT-triage use case, emphasizing decision-point robustness and resilience to real-world sample variability over pure analytical sensitivity.

Introduction

Mild traumatic brain injury (mTBI) represents the majority of head injury presentations in emergency departments (EDs); however, only a minority of patients exhibit acute intracranial lesions on head computed tomography (CT).[1] This discrepancy creates a persistent clinical dilemma: clinicians must maintain high sensitivity for clinically significant intracranial injuries while avoiding unnecessary CT, which entails costs, radiation exposure, and workflow burdens, particularly during overcrowding or in resource-limited settings. From a translational and regulatory perspective, the most stable and implementable biomarker use case is not long-term prognosis but early triage/rule-out of acute intracranial lesions on head CT within a clearly defined time window and population. Two clinical precedents illustrate that biomarker-guided pathways can significantly influence CT utilization and patient flow: (1) Scandinavian guideline pathway incorporating S100B. In a large validation study of the Scandinavian Neurotrauma Committee (SNC) guidelines, applying the guideline algorithm would have resulted in an estimated CT reduction of 32% (211/662), while only one low-risk patient with S100B below the recommended cutoff had a small traumatic CT abnormality that resolved on follow-up imaging.[2] (2) Real-world implementation and discharge impact. In a prospective cohort evaluating implementation of updated SNC

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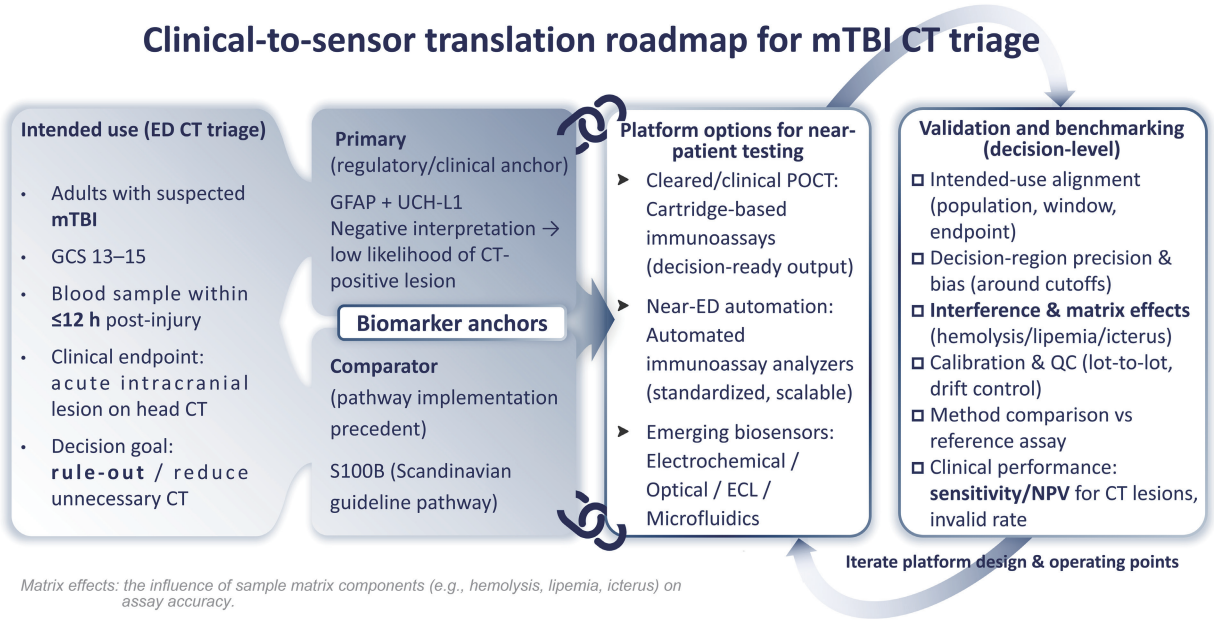

Fig. 1. Clinical-to-sensor translation roadmap for mTBI CT triage. The framework starts from a clearly defined intended use (adults with suspected mTBI, GCS 13–15, sampling within ≤12 h) and a CT-based endpoint (acute intracranial lesion on head CT). Biomarker anchors (GFAP/UCH-L1 as the primary CT-triage anchor and S100B as an implementation comparator) guide selection of near-patient testing platforms, ranging from cleared cartridge-based POCT and near-ED automation to emerging biosensors. The rightmost panel summarizes the decision-level analytical validation and clinical benchmarking requirements, which must address matrix effects to ensure reliability, emphasizing robustness to matrix effects and interference, calibration/QC, method comparison, and clinically meaningful performance metrics (sensitivity/NPV and invalid rate). CT, computed tomography; ECL, electrochemiluminescence; ED, emergency department; GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; mTBI, mild traumatic brain injury; NPV, negative predictive value; POCT, point-of-care testing; QC, quality control; UCH-L1, ubiquitin C-terminal hydrolase-L1.

guidelines, more than one third of mild TBI cases were directly discharged without further observation or CT, and one in five of these discharges was attributed directly to S100B testing; importantly, compliance was reported as suboptimal (guideline followed in ~40%), underscoring that workflow integration and training are central to achieving benefit.[3]

In parallel, biomarker-guided CT triage is supported by an explicitly defined regulatory framing for GFAP/UCH-L1. The U.S. Food and Drug Administration (FDA) decision documentation for the Banyan Brain Trauma Indicator specifies use in adults with suspected traumatic brain injury (Glasgow Coma Scale (GCS) 13–15) with serum collected within a defined time window and states that a negative assay result is associated with the endpoint-linked CT rule-out visualized on head CT.[4] These precedents collectively imply a concrete target product profile for next-generation point-of-care testing (POCT) biosensors intended for ED triage:

In this context, "point-of-care biosensing" refers to analytical devices that perform biomarker detection at or near the site of patient care (e.g., in the ED), with the defining attributes of workflow-compatible time-to-answer, high sensitivity at clinically relevant decision thresholds, robustness to real-world sample quality, and standardization across devices and operators.

1. Time-to-answer compatible with ED flow, such that results are available early enough to influence CT ordering and disposition (observation vs discharge).
2. High sensitivity at prespecified decision thresholds aligned to the clinical endpoint (CT-visible acute intracranial lesion), with transparent handling of borderline zones.
3. Robustness to real-world sample quality (hemolysis/lipemia/icterus) and standardization across devices, lots, and operators.
4. Benchmarking against reference assays and clinically meaningful operating points, not merely the lowest limit of detection (LOD) in buffer.

Accordingly, this review provides a critical evaluation of point-of-care compatible biosensing strategies for the ultra-early triage of mTBI, with a specific focus on sensing platforms, matrix effects and interference, and benchmarking, all anchored to CT-based decision-making. To illustrate this framework, Figure 1 provides a clinical-to-sensor translation roadmap for mTBI CT triage.The scope of this review is defined as follows: it encompasses adult patients (Glasgow Coma Scale 13–15) with an emphasis on CT triage/rule-out within the early post-injury sampling window. Pediatric populations, moderate-to-severe TBI management, and long-term prognostic applications are beyond the primary scope.

Biomarkers for ED triage: strengths, constraints, and practical kinetics of S100B, GFAP, and UCH-L1

Why focus on the "triad" (S100B, GFAP, UCH-L1)?

A wide range of candidate biomarkers have been investigated in TBI, but for fast, reliable clinical translation, the most defensible strategy is to focus on biomarkers with (i) pathway-level implementation precedent and/or (ii) a clear intended-use anchor for ED decision-making. S100B has been incorporated into SNC guideline algorithms and tested in validation and implementation studies demonstrating potential CT reduction and discharge impact.[2] GFAP/UCH-L1 have a regulatory-defined CT triage (rule-out) intended-use anchor, offering a stable operating point for biosensor development and benchmarking.[4]

S100B: Implementation maturity with specificity caveats

S100B is an astrocyte-enriched calcium-binding protein that can rise after brain injury.[5] Its strongest clinical value has been demonstrated when embedded within a strict algorithm (e.g., SNC guidelines) with defined inclusion/exclusion criteria and sampling windows, where validation work suggests meaningful CT reduction potential.[2] However, S100B is vulnerable to reduced specificity due to extracranial sources and contextual confounders; therefore, it is best viewed as a rule-out adjunct rather than a standalone diagnostic marker.[6] This has direct engineering implications: a POCT system targeting S100B must prioritize classification stability near the decision threshold and minimize false positives driven by matrix artifacts, rather than optimizing only for ultra-low LOD.

GFAP: A strong astroglial marker aligned to lesion detection

GFAP is an astroglial intermediate filament protein released with astroglial injury and has consistently shown a strong association with intracranial lesions. For ED triage, GFAP is attractive because it supports the "CT-lesion discrimination" objective central to the intended use case. In practice, GFAP is commonly positioned as the dominant marker for lesion detection, with UCH-L1 providing complementary information. GFAP/UCH-L1 are the biomarker pair used in cleared CT-triage assays and therefore represent the most practical clinical anchor for ED rule-out benchmarking.[7,8]

UCH-L1: Complementary neuronal injury signaling and a major interference concern

UCH-L1 is a neuron-enriched protein reflecting neuronal injury processes. Its translational value is strongest when used in combination with GFAP under an intended-use framework anchored to CT outcomes.[4] For sensor developers, UCH-L1 also highlights why pre-analytical robustness is not optional. A head-to-head evaluation reported the first evidence that hemolysis significantly elevates UCH-L1 concentrations from 400 mg/L of hemoglobin, which can directly bias interpretation in acute trauma samples where hemolysis is common.[9] This single finding has outsized implications for POCT design and validation: interference testing must include graded hemolysis panels, and systems should incorporate either (i) automated hemolysis indices, (ii) built-in QC flags/invalid rules, or (iii) calibration strategies resilient to hemolysis-related bias.

Practical takeaway for "steady" ED triage development

For a stable, high-probability-of-acceptance Sensors review and for real-world POCT development, the biomarker triad supports a pragmatic hierarchy:

1. Primary ED triage anchor: GFAP/UCH-L1, because it aligns with the regulatory-defined ED CT rule-out intended-use anchor.[4]
2. Implementation comparator: S100B, because guideline-based studies provide a concrete benchmark for CT reduction and workflow effects and serve as a real-world comparator for new POCT systems.[2]
3. Non-negotiable validation focus: matrix effects and interference, especially hemolysis for UCH-L1, because these factors determine whether a "good-in-buffer" sensor is clinically deployable.[9]

While the GFAP/UCH-L1 pair is the most clinically anchored dual-marker strategy for ED CT rule-out, emerging multi-marker approaches have been explored to address heterogeneity in injury biology and to stabilize decisions near clinical cutoffs. In practice, adding a systemic stress or metabolic marker (e.g., lactate) has been proposed as a pragmatic extension that may help interpret borderline biomarker profiles in patients with extracranial injury, variable kinetics, or complex physiological derangements. These extensions may also support prognostic enrichment in selected contexts; however, for ED implementation, the key requirement is not the number of markers but whether the added marker measurably improves decision-level safety (sensitivity/negative predictive value (NPV)) and reduces ambiguous or invalid calls within the prespecified sampling window. Therefore, multi-marker panels should be evaluated using the same cutoff-anchored validation logic emphasized in this review (matrix robustness, interference control, and comparator benchmarking), rather than being justified solely by analytical sensitivity.

Point-of-care biosensing modalities for mTBI triage: Technical feasibility and deployment constraints

Cleared POCT systems as reference targets: GFAP/UCH-L1 cartridges and intended use

For ED CT triage, the most stable engineering target is not an experimental LOD in buffer but a workflow-compatible assay that preserves high sensitivity at clinically meaningful operating points. Two regulated/near-patient implementations clarify this target. Regulatory-cleared intended use in adult ED mTBI CT rule-out provides a stable anchor for defining operating points and validation expectations.[10]

In parallel, handheld cartridge testing has moved into routine point-of-care form factors. Abbott's i-STAT TBI Plasma cartridge is explicitly positioned as an aid to determining the need for head CT in adults with suspected mTBI (GCS 13–15), and the product documentation describes a multiplex immunoassay for UCH-L1 and GFAP that yields a semi-quantitative interpretation in approximately 15 min, using a small plasma sample volume.[11] The methodological review literature likewise describes i-STAT as producing results 15 min after loading plasma and summarizes its CT-triage interpretation logic.[12]

These "clinical-grade" POCT systems are important in a Sensors review for two reasons. First, they anchor biosensor development to a validated intended use and an operational constraint set that includes speed, robustness, and standardized interpretation rather than purely analytical novelty. Second, they define a practical benchmark for emerging biosensing modalities: any new platform must either match the analytical and clinical utility of such systems or provide a compelling advantage in portability, cost per test, multiplex expansion, or resilience to pre-analytical variability (Table 1).[2,7,8,13–22]

Electrochemiluminescence (ECL) and chemiluminescence: multiplex-friendly signal generation with POCT prototypes

ECL occupies a strategically useful middle ground between central laboratory immunoassays and field-deployable biosensors. Its strengths are high sensitivity, low background, and multiplexing potential, and recent work has focused on translating these properties into compact devices. A POCT prototype system has been reported for simultaneous ECL sensing of multiple TBI biomarkers, demonstrating a concrete engineering path toward multi-analyte panels rather than single-marker assays.[22] Related platform-level work in Lab on a Chip discusses the design logic of compact ECL immunoassay devices and notes the prevalence of multiplex ECL strategies in both academic and established platforms.[23]

For mTBI CT triage, the relevance of ECL/CL is not only signal strength. It is the ability to package a multi-step sandwich immunoassay into a controlled cartridge workflow where incubation, washing, and readout variability can be standardized. This aligns closely

Table 1. Representative clinically used tests and emerging sensing platforms for blood-based biomarkers in mTBI

Category	Example (status)	Biomarker (s)	Sample matrix	Readout/format	Typical time-to-result (as described)	Why it matters for "sensor" translation	Key reference
Regulatory/clinical translation	Banyan Brain Trauma Indicator (BTI) (FDA De Novo; predicate for later clearances)	GFAP, UCH-L1	Serum	Chemiluminescent immunoassay (ELISA-like workflow)	Not positioned as rapid POC; historically limited by turnaround/automation in ED workflows	Landmark regulatory path for GFAP+UCH-L1; illustrates that "clinical utility" alone is insufficient without workflow-compatible speed and automation	7,8
Regulatory/near-patient testing	Abbott i-STAT TBI Plasma (FDA 510(k))	GFAP, UCH-L1	Plasma	Handheld cartridge-based immunoassay	~15 min (POC)	Benchmarks what "ED-usable" looks like: cartridge workflow, short TAT, minimal sample handling	13
Regulatory/automated immunoassay	VIDAS TBI (GFAP, UCH-L1) on VIDAS 3 (FDA 510(k) K240279)	GFAP, UCH-L1	Serum (quantitative automated assays)	Automated immunoassay on benchtop analyzer	Instrument-based rapid testing (workflow depends on lab/ED setup)	Shows the "near-ED lab automation" route: less portable than handheld POC, but scalable and standardized	14
Clinical validation evidence	ALERT-TBI multicenter observational validation (clinical evidence base for GFAP+UCH-L1)	GFAP, UCH-L1	Blood-based sampling within early window	Biomarker panel to predict CT-negative intracranial injury	Designed for use within 12 h of injury (study design window)	Establishes the clinical "use case": rule-out CT-positive injury; supports performance targets for sensors	15
Guideline-based clinical use (Europe/Scandinavia)	Scandinavian Neurotrauma Committee guideline incorporating S100B (validated)	S100B	Serum	Laboratory assay integrated into decision rule	Used for early triage (guideline-defined time window)	Demonstrates real-world pathway where a single biomarker can reduce CT use when paired with strict clinical criteria	2
Health-economic/implementation	S100B added to mTBI guideline pathways (cost and CT reduction potential)	S100B	Serum	Lab assay + guideline algorithm	Depends on local lab turnaround	Implementation barrier is often compliance/logistics, not only analytical performance—relevant when arguing for true POC sensors	16
Research prototype (portable electrochemical)	TBISTAT (open-source wireless portable EIS potentiostat; proof-of-concept in plasma)	S100B	Human plasma (spiked)	Electrochemical impedance spectroscopy (EIS)	Platform intended for POC-style use; demonstrates quantitative range and LOD	A concrete example of "instrument miniaturization + impedance assay" pathway; links directly to portable reader design choices	17
Research sensor (electrochemical immunosensor)	Cysteamine-modified electrochemical immunosensor (Sensors, 2021)	S100B	(Demonstrated at clinically relevant levels; matrix depends on experiment)	Electrochemical immunosensing on modified electrode surface	Not inherently POC unless paired with simplified prep/reader	Good for Table 1 because it is published in Sensors and provides a "within-journal" exemplar of electrochemical routes	18
Research sensor (label-free EIS)	Label-free EIS biosensor for UCH-L1 (Biosens. Bioelectron., 2022)	UCH-L1	Human serum (TBI patients)	Label-free EIS immunosensing	Rapid sensing demonstrated at biosensor level	Strong example of clinically relevant matrix (patient serum) for UCH-L1, highlighting fouling/interference and calibration needs	19

(continued)

Table 1. *(continued)*

Category	Example (status)	Biomarker (s)	Sample matrix	Readout/format	Typical time-to-result (as described)	Why it matters for "sensor" translation	Key reference
Research sensor (transistor-based)	Graphene GFET biosensor for GFAP in patient plasma (ACS Sensors, 2021)	GFAP	Patient plasma	Graphene field-effect transistor (GFET)	Ultrafast sensing concept (study-specific)	Represents "electronics-first" sensing: potentially fast and sensitive, but needs robust packaging, drift control, and sample conditioning	20
Research prototype (ECL multiplex, POC-friendly)	Multiplex ECL on disposable SPCE + portable reader (Biosensors, 2022)	GFAP, h-FABP, S100β	Human serum (demonstrated)	Electrochemiluminescence sandwich immunoassay	Positioned as POC-friendly via SPCE + portable reader	Demonstrates multiplex ECL immunoassay packaged into a POC-friendly disposable format, indicating a feasible path towards multi-analyte panels at the point of care	21
Research prototype (ECL multiplex system)	Spatially resolved ECLIA prototype for simultaneous multi-biomarker sensing (RSC, 2023)	Multi-biomarker TBI panel (prototype system)	Blood-based concept; system-level prototype	Microarray-type spatially resolved ECL immunoassay	Prototype system direction (study-specific)	Evidence at the "Systems Engineering" level: It is not just about individual sensing components, but rather an evolution toward holdable/integratable devices	22

CT, computed tomography; ECL, electrochemiluminescence; ED, emergency department; EIS, electrochemical impedance spectroscopy; ELISA, enzyme-linked immunosorbent assay; FDA, U.S. Food and Drug Administration; GFAP, glial fibrillary acidic protein; GCS, Glasgow Coma Scale; LOD, limit of detection; mTBI, mild traumatic brain injury; NPV, negative predictive value; POC, point-of-care; POCT, point-of-care testing; PPV, positive predictive value; TAT, turnaround time; TBI, traumatic brain injury; UCH-L1, ubiquitin C-terminal hydrolase-L1.

with ED constraints and supports consistent threshold-based interpretation, which is essential for a rule-out use case. The remaining translational barriers tend to be manufacturability, quality control across lots, and ensuring that multiplexing does not introduce cross-talk or shared failure modes under real-world sample conditions.

Electrochemical immunosensors: Compact hardware, but matrix robustness becomes the decisive bottleneck

Electrochemical biosensing, including amperometric, voltammetric, impedance-based, and transistor-inspired approaches, is attractive for ED and austere settings because it can be implemented with low-power electronics and inexpensive disposable elements. However, the dominant challenge is not detection physics; it is matrix-driven variability. Protein fouling, non-specific adsorption, and lot-to-lot electrode surface differences can shift baseline and slope in ways that are clinically unacceptable near decision thresholds. The practical implication for mTBI triage is that electrochemical platforms must be engineered around anti-fouling strategies, internal referencing, and rigorous interference stress testing rather than only reporting impressive analytical sensitivity in purified buffers. Methodological reviews of TBI biomarker testing highlight that near-patient assays and POCT use cases are inherently tied to CT decision support and thus require reproducibility and interpretation stability as first-class goals.[12]

In a Sensors-focused narrative, electrochemical approaches should therefore be presented as promising for scale and portability, with success criteria tied to decision-level performance, drift control, and robustness under hemolysis and other common ED sample quality issues, rather than as a competition over the lowest numerical LOD.

Optical and imaging-based readouts: multiplexing potential and standardization requirements

Optical biosensing spans absorbance/colorimetry, fluorescence, surface plasmon resonance, and nanophotonic enhancement strategies.[24] In ED triage, the value proposition of optical/imaging readouts is often multiplexing and the practical feasibility of visual or camera-based acquisition (including smartphone-enabled imaging workflows), provided that acquisition variability is controlled and validated.[25,26] Yet optical approaches face a recurring translational trap: performance can look excellent under standardized illumination and clean samples but degrade quickly under real-world variability in turbidity, background chromophores, and acquisition conditions. This is where a Sensors review can offer practical value: it can formalize how optical systems should be validated and benchmarked, and it can explain why algorithmic normalization and reference regions are not "optional AI add-ons" but core components of measurement traceability in camera-based POCT.[27]

In the CT-triage framing, optical platforms are best positioned when they can guarantee controlled acquisition, provide internal references, and demonstrate robust calibration transfer across devices and sites. Without these elements, even strong analytical sensitivity may fail to translate into stable negative/positive calls at clinically meaningful thresholds.

Analytical validation and clinical benchmarking: A practical framework aligned to CT-triage decisions

Intended use defines the analytical targets

For a rule-out test, analytical validation must be designed backwards from the decision endpoint. Consistent with the intended-

use anchor, the clinically decisive region is the concentration range around prespecified cutoffs where classification stability determines patient safety and CT utilization.[10] This framing implies that the most important performance region is not the absolute low end of detection in buffer; it is the concentration range around prespecified decision thresholds where classification stability determines patient safety and CT utilization (Table 2).

Cartridge-based POCT provides a clear template for these constraints. Abbott's i-STAT TBI Plasma documentation describes a multiplex immunoassay for UCH-L1 and GFAP that produces a semi-quantitative interpretation in approximately 15 min and is used to assist in determining the need for head CT in adults with suspected mTBI within a defined time window.[11] The methodological review literature further summarizes that i-STAT results can be used to assist in determining the need for head CT and describes the dual-marker "one or both above cutoff" logic, including example cutoff values reported in the literature.[12]

For emerging biosensors, this means that validation must demonstrate consistent classification performance and acceptable invalid rates in the ED setting, not merely "analytical sensitivity" in idealized conditions.

Core analytical validation domains for POCT biosensors

Regulatory-grade review documents provide a useful blueprint for what reviewers implicitly expect. Regulatory review documents illustrate the evidence package typically expected for reliability claims (analytical characterization plus method comparison), which can be translated into an engineering-facing validation checklist.[10] In a Sensors review, this can be translated into a practical validation framework that prioritizes: detection capability across the reportable range relevant to decision thresholds; precision across runs, days, lots, and operators; linearity and high-dose antigen effects that could cause false negatives; cross-reactivity and non-specific binding; and stability of both reagents and samples under realistic handling conditions.

The key point for mTBI triage is that these elements are not independent. Even modest drift, small lot-to-lot slope differences, or matrix-dependent bias can substantially change classification near the rule-out threshold and therefore can cause unsafe CT reduction or, conversely, loss of CT reduction benefit due to inflated false positives.

Interference testing is decisive and hemolysis is a known vulnerability for UCH-L1

Trauma samples frequently show hemolysis, lipemia, and variable handling times, particularly during high-throughput ED operations. Interference testing must therefore be planned as a primary validation domain rather than as a late-stage "checklist item." This is particularly important for UCH-L1: a head-to-head evaluation reported the first evidence that hemolysis significantly elevates UCH-L1 concentrations beginning at 400 mg/L hemoglobin, a magnitude that can plausibly occur in real ED samples and directly bias interpretation.[9]

This observation has practical consequences for biosensor translation. If a biosensing platform is intended to output a binary or semi-quantitative triage interpretation, then the system must either detect and flag hemolysis-related risk, incorporate internal controls that reveal sample quality degradation, or demonstrate that its calibration and signal processing remain stable under graded hemolysis conditions. Without such evidence, even a technically elegant sensor is likely to be judged clinically fragile.

Matrix consistency is a first-order determinant of POCT transfer-

Table 2. Decision points in ED CT triage for adult mTBI (GCS 13–15) and corresponding performance indicators for biosensor/POCT development

Decision point (clinical)	Intended-use constraints	Specimen & time window	Cutoff source (examples)	Decision-level metrics to report	Operational indicators (ED realism)
Rule-out CT (avoid head CT when safe)	Adult suspected mTBI; GCS 13–15; CT-visible acute intracranial lesion as endpoint	Serum or plasma; within ≤12 h of injury (aligned to cleared tests/ major studies)	IFU/regulatory documents for cleared assays; large validation studies; pre-specified study protocol thresholds	Sensitivity & NPV at the prespecified cutoff(s); confusion matrix; performance near the decision threshold ("decision region")	Repeat/invalid rate ("Repeat test" frequency), turn-around time, rate of hemolysis/lipemia/icterus flags, device/operator reproducibility
Escalate care/ proceed to CT (positive/elevated result)	Avoid false reassurance; ensure borderline handling	Same as above	Same as above	Specificity/PPV (contextual), positive agreement vs reference assay; robustness under interference	Clear "borderline/gray zone" rule; QC failure-mode reporting; workflow integration feasibility
No-result/repeat (test failure or QC flag)	Must not silently output a wrong binary call	Same as above	IFU-defined repeat rules (where applicable)	Invalid rate, causes of invalid (matrix, cartridge, operator), retest success rate	Report invalid reasons; recommended ED action when repeat persists

CT, computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; IFU, Instructions for Use; mTBI, mild traumatic brain injury; NPV, negative predictive value; POCT, point-of-care testing; PPV, positive predictive value; QC, quality control.

ability. Although cerebrospinal fluid can be informative biologically, it is not aligned with routine ED CT rule-out workflows; therefore, serum and plasma are the primary matrices of interest for intended use in triage. Importantly, serum–plasma differences (e.g., anticoagulants, coagulation-related composition, protein partitioning, and background chromophores/turbidity) can introduce systematic assay bias that becomes clinically meaningful near decision thresholds. Accordingly, studies should avoid mixing matrices when defining or applying cutoffs, and biosensor validation should include matrix-matched calibration materials, matrix-specific interference panels, and when cross-matrix claims are made, explicit bridging analyses reporting bias and decision reclassification around the cutoff. In addition to analytical interference (e.g., hemolysis/lipemia/icterus) and matrix effects, biological variability can shift biomarker distributions around decision thresholds and thereby influence rule-out performance. Clinically relevant factors include age, extracranial injury burden (e.g., fractures/polytrauma), comorbid conditions, and post-injury kinetic differences that affect baseline levels and temporal trajectories. Because CT triage decisions are sensitive to small bias near cutoffs, validation plans should prespecify subgroup analyses (e.g., age strata; isolated head injury vs extracranial injury) and report whether sensitivity/NPV are preserved at the intended cutoff within the prespecified sampling window.

Benchmarking against reference methods and against the workflow endpoint

Analytical validation alone is not sufficient for CT-triage adoption because the value proposition is inherently clinical. The Scandinavian guideline validation work provides a useful comparator because it ties biomarker-informed decision rules to expected CT reduction under a defined pathway, while reporting safety-relevant outcomes. In the BMC Medicine validation cohort, applying the SNC guideline algorithm would have resulted in a 32% CT reduction while maintaining high sensitivity for intracranial hemorrhage and documenting the rare discordant case with low S100B and a small, self-resolving CT lesion.[2]

For new POCT biosensors, a "most defensible" benchmarking package therefore includes two linked comparisons. The first is a method comparison against a reference assay in matched clinical samples, because this establishes trueness and identifies systematic bias that would undermine decision thresholds. The second is an endpoint-aligned clinical performance assessment in the intended-use population and time window, because this determines whether the device can safely reduce CT while preserving sensitivity. POCT systems that already market CT-triage use, such as i-STAT TBI Plasma, operationalize this principle by embedding the biomarker interpretation into an explicitly CT-linked clinical claim and a defined time-to-result.[11]

When presented in a Sensors review, this framework helps reconcile the engineering literature, which is often dominated by proof-of-concept sensitivity claims, with the implementation reality that triage decisions demand stable operating points, interference resilience, and clinically anchored benchmarking.

ED deployment considerations: Workflow integration, interpretation, and human factors

The central implementation lesson: Triage value depends on pathway adherence, not only assay performance

In mTBI triage, even a highly sensitive biomarker can fail to reduce CT utilization if clinicians do not trust, understand, or operationally integrate the result into disposition decisions. This is visible in real-world S100B implementation under the updated SNC guideline pathway. In a prospective cohort, implementation was associated with direct discharge of more than one third of mild head injury cases without further observation or CT, and one in five of these discharges was directly attributed to S100B testing; however, nearly half of negative S100B results were ignored, and overall guideline adherence was reported as poor, with the guideline not followed for nearly 40%.[3] These findings are important for sensor developers because they show that "clinical impact" is often bottlenecked by training, workflow friction, and perceived risk rather than by analytical sensitivity alone.

Deployable POCT requirements: Interpretation rules, turnaround time, and failure handling

Current FDA-cleared blood biomarker tests for mTBI CT triage provide a practical reference for what ED adoption tends to require: a defined target population and time window, standardized sample requirements, and a result that is already expressed in clinically interpretable terms. Cleared CT-triage assays specify target population, sampling window, and standardized interpretive outputs, all of which are key requirements that biosensor prototypes should emulate for ED adoption.[4]

Similarly, Abbott's i-STAT TBI Plasma test is positioned as an aid to determining the need for head CT in adults with suspected mTBI (GCS 13–15) within 12 h of injury, with a "not elevated" interpretation associated with the absence of acute traumatic intracranial lesions on head CT; the product materials specify a small plasma sample (20 μL) and a result available about 15 min after applying the sample.[11] The instructions for use describe a semi-quantitative interpretation displayed as "Elevated," "Not Elevated," or "Repeat Test," which is a key design choice because ED workflows often need a decision-ready output rather than a raw concentration alone.[11]

A parallel example is the VIDAS TBI (GFAP, UCH-L1) assay, where the FDA 510(k) review states that a negative interpretation is associated with the endpoint-linked CT rule-out visualized on head CT in adults presenting within 12 h with suspected mild TBI (GCS 13–15), and that results are used with other clinical information to assist CT decision-making.[28]

Evidence anchors for "absence of CT lesions": From clinical studies to cleared test framing

The CT-triage framing for GFAP and UCH-L1 is supported by large clinical evaluation. The ALERT-TBI multicenter observational study reported that a combined serum GFAP–UCH-L1 test had a sensitivity of 97.6% and an NPV of 99.6% for detection of acute intracranial injuries on head CT, supporting its use to rule out the need for CT among patients in whom CT is otherwise considered.[15]

For S100B, guideline-based evidence provides a complementary implementation benchmark. In a validation of the SNC guidelines, applying the guideline algorithm to the cohort would have resulted in an estimated CT reduction of 32% (211/662 patients), with only one low-risk patient below the S100B cutoff showing a small traumatic CT abnormality that resolved on follow-up imaging.[2] This kind of pathway-level evidence is particularly useful for Sensors readers because it translates biomarker testing into the operational endpoints that actually matter in the ED: CT utilization, observation time, discharge rates, and safety events.

Operational robustness and "failure modes" that matter in trauma care

ED deployment imposes stresses that are easy to underappreciate

when developing proof-of-concept sensors. Regulatory submissions for point-of-care devices illustrate the types of robustness evidence that can be persuasive. For the i-STAT TBI system, FDA review documents describe evaluations across operating temperatures, altitude simulation, instrument tilt, and vibration, reflecting how a near-patient system is expected to tolerate non-ideal environments.[13] The earlier 510(k) review also describes analytical studies such as high-dose hook-effect testing, with no hook effect observed within stated high antigen concentrations for GFAP and UCH-L1.[29]

In addition to device robustness, sample quality is a first-order risk in trauma testing. Hemolysis is common in acute settings and can bias certain biomarkers; a recent head-to-head evaluation reported that hemolysis significantly elevates UCH-L1 concentrations from 400 mg/L hemoglobin, which can directly distort interpretation if not detected or mitigated.[9] For developers, this reinforces that the path to "stable ED use" typically requires explicit interference management and clear rules for when to repeat or invalidate a test, not only improved analytical sensitivity.

How to design biosensors

Defining success: Decision-region robustness beyond analytical LOD

The strongest way to make a sensor paper clinically credible is to define success against CT-triage decisions. Accordingly, decision-level validation should prioritize cutoff-adjacent robustness and standardized interpretive outputs (e.g., Not Elevated/Elevated/Repeat) rather than only analytical sensitivity in buffer.[4] That framing implies that developers should concentrate validation around the concentration ranges that determine "not elevated" versus "elevated" interpretations because small biases or drift near these thresholds can flip a decision. In practice, this is why cleared POCT implementations emphasize standardized interpretation outputs such as "Not Elevated/Elevated/Repeat Test" rather than only providing continuous concentrations.[30]

Reporting elements that strengthen clinical credibility

A Sensors review becomes substantially more useful and publishable when it translates regulatory-grade validation logic into an engineering checklist for emerging biosensors. Regulatory reviews for POCT systems provide concrete examples of expected evidence (hook effect, interference, robustness under realistic conditions), which can be mapped to staged reporting for academic prototypes.[29] This does not mean every academic prototype must reproduce every regulatory study, but it does mean the review can propose a staged pathway where early prototypes report not only LOD and dynamic range, but also repeatability across days, device-to-device variability, matrix stress tests, and decision-level performance against an appropriate comparator method.

Human factors and pathway integration as "the missing third pillar" alongside biomarkers and sensors

Real-world S100B experience shows that even when a biomarker pathway can theoretically reduce CT utilization, the realized benefit depends on adherence and clinician behavior. The prospective cohort evidence describing frequent ignoring of negative S100B results and overall guideline non-adherence indicates that training and workflow integration are essential to achieve safe CT reduction.[3] Therefore, a biosensor that aims to improve on the status quo should be designed with deployment in mind: sample collection and preparation must be minimal, invalid/repeat logic must be clear, interpretation must be decision-ready, and the system should anticipate trauma realities such as hemolysis-related bias for UCH-L1.[9]

Recommended additions to strengthen reproducibility and translational relevance

To maximize acceptance probability and speed, Part 7 and Part 8 should convert the above into immediately reusable assets for readers: a platform-by-platform comparative table anchored to CT-triage requirements and a concise validation checklist aligned with the cleared-test logic and known interference risks. The manuscript can explicitly position GFAP/UCH-L1 as the CT-triage anchor supported by large observational evidence such as ALERT-TBI, while presenting S100B as the implementation comparator with guideline-based CT reduction and real-world adherence lessons.[15]

Comparative synthesis for sensors developers: Platform selection, decision-level performance, and a CT-triage–aligned checklist

Using cleared CT-triage tests as the "stability anchor" for any new biosensor

For a review that aims to be both publishable and practically useful, it is helpful to treat cleared CT-triage assays as the reference target profile rather than as distant "clinical lab competitors." The FDA decision memo for the Banyan Brain Trauma Indicator explicitly frames the intended population and endpoint, stating that a negative result is associated with the endpoint-linked CT rule-out visualized on head CT in adults with suspected traumatic brain injury and GCS 13–15.[4] The VIDAS TBI 510(k) review similarly specifies an adult ED CT-triage intended use within 12 h and emphasizes use alongside clinical assessment to support CT decision-making.[28]

Likewise, the i-STAT TBI Plasma program is positioned around a rapid result (approximately 15 min after sample application) and an explicit CT decision-support claim, which is an important engineering constraint because ED workflows require time-to-answer and interpretability as much as analytical sensitivity.[28]

These regulatory and product documents also highlight issues that repeatedly surface in academic prototypes. One example is traceability: the i-STAT cartridge documentation notes the absence of internationally recognized standard reference materials for GFAP and UCH-L1, an important detail because it explains why calibration transfer and lot-to-lot control must be designed as "first-order" features rather than as afterthoughts.[31]

Platform comparison table aligned to CT triage and ED constraints

The following table is intentionally decision-centric. It does not rank platforms by "best LOD in buffer," because CT triage depends more on classification stability around cutoffs, robustness to interference, and operational reliability (Table 3).[32,33]

A CT-triage–aligned validation checklist that avoids overclaiming and speeds acceptance

To keep the checklist stable and decision-relevant, it is anchored to the regulatory-defined ED CT rule-out intended use and prespecified cutoffs.[4] Evidence from large clinical evaluation provides realistic performance anchors; for example, the ALERT-TBI work

Table 3. Comparative analysis of point-of-care biosensing platforms for CT triage in mTBI: Strengths, failure modes, and validation imperatives

Platform family	Typical POCT form	What it does well for CT triage	What usually breaks in real ED samples	What "good validation" must include for publishable credibility
Cleared immunoassay-derived POCT (GFAP/UCH-L1)	Cartridge + reader; standardized interpretation	Intended-use and endpoint are explicit; results can be delivered within an ED-compatible timeframe; negative interpretation tied to absence of acute intracranial lesions on head CT in adults with suspected mTBI (GCS 13–15) within 12 h[32]	Pre-analytical variability still exists; hemolysis remains common in trauma and can bias some biomarkers	Method comparison vs reference, interference panels, lot/operator robustness, invalid/repeat logic, and decision-level metrics (sensitivity/NPV at prespecified cutoffs) supported by endpoint-linked evidence[33]
Electrochemical immunosensors	Disposable electrode + compact reader	Strong portability and cost potential; hardware can be small and field-deployable	Surface fouling and non-specific adsorption shift baseline; drift and batch variability can flip calls near cutoffs	Matrix-matched calibration, drift/lot controls, graded interference studies (hemolysis/lipemia/icterus), and decision-region precision rather than only LOD
Optical/imaging and nanophotonic readouts	Chip + optics/camera; sometimes phone-readable	Multiplex expansion and spatial referencing can be natural; potential for low-cost readout	Illumination and turbidity variability; background chromophores; camera/device differences; algorithmic calibration transfer issues	Controlled acquisition protocol, internal reference regions, cross-device calibration transfer, robustness to turbid/colored matrices, and endpoint-aligned benchmarking
ECL/CL-enabled compact systems	Cartridge/microfluidics + CL/ECL readout	High signal-to-noise; multiplexing is practical; assay physics is clinically familiar	Device complexity and consumable integration; cross-talk and shared failure modes in multiplex workflows	Multiplex cross-talk testing, stability across temperature and handling, and clinically anchored operating points rather than "best analytical sensitivity"

The intent here is not to imply that one platform is universally superior. Instead, the ED triage problem forces each platform to prove the same core claims: rapid turnaround, stable classification near the decision threshold, and resilience to common trauma sample conditions. CL, chemiluminescence; ECL, electrochemiluminescence; ED, emergency department; GFAP, glial fibrillary acidic protein; GCS, Glasgow Coma Scale; LOD, limit of detection; mTBI, mild traumatic brain injury; NPV, negative predictive value; POCT, point-of-care testing; UCH-L1, ubiquitin C-terminal hydrolase-L1.

has been reported as achieving a sensitivity of 97.6% and NPV of 99.6% for ruling out CT-positive lesions using combined GFAP and UCH-L1.[33]

A validation framework that reviewers tend to accept quickly is one that (i) prespecifies operating points, (ii) reports robustness and interference, and (iii) includes at least one comparator method. Because hemolysis can significantly elevate UCH-L1 from a defined hemoglobin threshold, interference testing must be explicitly planned rather than implicitly assumed.[34]

The following table expresses the checklist in "what to report" terms, which is often the fastest way to convert sensor development into a publishable narrative and figures (Table 4).

Future directions

Looking forward, the highest-yield research direction is not simply to add more biomarkers, but to build biosensing systems that can sustain CT-triage–level decision performance across diverse ED environments. Large clinical evaluations such as ALERT-TBI, which report high sensitivity and NPV for ruling out CT-positive lesions using combined GFAP and UCH-L1, offer realistic anchors for what clinical credibility looks like and therefore what next-generation platforms must strive to match or exceed with clear advantages in portability, speed, or scalability. Future work should prioritize (i) decision-region robustness around prespecified cutoffs, (ii) matrix- and interference-resilient designs that reflect real ED samples, and (iii) standardized "camera-to-answer" or cartridge-to-answer pipelines with traceable calibration transfer and explicit failure handling (repeat/invalid rules) to prevent silent misclassification under heterogeneous acquisition conditions.

Limitations

This review is intended as a practical, CT-triage–aligned roadmap rather than a formal systematic review; therefore, included evidence syntheses and examples may not capture all emerging biomarkers or prototype platforms. The scope is intentionally focused on adult ED patients with suspected mTBI (GCS 13–15) in an early post-injury sampling window and on the rule-out (CT reduction) decision context; pediatric populations, moderate-to-severe TBI care, and long-term prognostic applications are not comprehensively covered. In addition, differences across studies in specimen matrix (serum vs. plasma), sampling time windows, and cutoff definitions introduce heterogeneity that can affect apparent performance, particularly near decision thresholds. Finally, many engineering prototypes remain under-validated at the decision region and under real-world workflow conditions, limiting direct cross-platform comparability.

Conclusions

The most reliable path for clinically credible biosensor translation is to frame development and reporting around the ED CT-triage intended use, because it has a clearly defined endpoint and prespecified decision thresholds anchored by cleared systems and major validation studies. The decisive translational barrier is often not analytical sensitivity in controlled conditions but performance stability under real-world sample and workflow variability. Accordingly, clinically persuasive biosensor work should emphasize (i) precision and bias near cutoffs, (ii) explicit interference/matrix

Table 4. A practical validation checklist for the development of point-of-care biosensors aligned with CT-triage decision-making in mTBI

Validation domain	What to report (CT-triage–aligned)	Why it matters for ED adoption	Suggested minimum sample size (planning guidance)	Recommended reporting formats
Intended-use anchoring	Population (adult suspected mTBI, GCS 13–15), time window, endpoint (acute intracranial lesions on head CT), and mapping of negative/positive interpretations to CT triage	Prevents scope drift and makes conclusions defensible	Not applicable (definition-level)	Intended-use statement block; flow diagram of inclusion/exclusion
Decision-region performance	Precision and bias around prespecified cutoffs; repeat/invalid frequency	Small shifts near cutoffs can flip triage decisions	Precision near cutoff: ≥20 replicates per level (low/near-cutoff/high) across ≥3 days (or equivalent repeated runs)	Precision table (CV%/SD); near-cutoff bias summary; invalid/repeat-rate table
Method comparison	Matched-sample comparison to a reference assay with bias analysis	Establishes trueness and identifies systematic error	≥40–100 clinical specimens spanning the decision region (include near-cutoff enrichment)	Passing–Bablok or Deming regression; Bland–Altman/bias plot; slope/intercept with CI
Interference & matrix effects	Graded hemolysis/lipemia/icterus; matrix-matched calibrators; explicit handling of hemolysis for UCH-L1	Trauma samples are often non-ideal; interference is a major failure mode	Interference: ≥3 levels per interferent × ≥3 replicates each; ideally test ≥10 unique clinical matrices near cutoff	Interference bias plot (Δ vs control); acceptance criteria table; "flag/invalid rule" description
Calibration & traceability	Calibration transfer strategy, QC materials spanning low/medium/high, lot-to-lot stability; note lack of international reference materials if applicable	Supports reproducibility across sites and batches	Lot-to-lot: ≥3 lots; QC levels: low/near-cutoff/high with ≥10 replicates/level/lot	Levey–Jennings QC charts; lot-to-lot bias plot; traceability narrative
Clinical benchmarking	Sensitivity/NPV at prespecified operating points; CT reduction/disposition impact where feasible	Demonstrates clinical value beyond analytical novelty	Endpoint benchmarking: ≥100–300 intended-use patients if feasible; otherwise clearly state as future validation need	Confusion matrix; ROC (optional) but emphasize fixed-cutoff metrics; CT reduction estimate with CI
Reporting of failures	Invalid causes (matrix, cartridge, operator), repeat-test outcomes, missingness	Prevents hidden fragility in ED deployment	Report on all tested runs; minimum: ≥100 total tests for stable invalid-rate estimate	Invalid/Repeat rate (%) with reasons; CONSORT-like flow of exclusions

CI, confidence interval; CT, computed tomography; CV, coefficient of variation; ED, emergency department; GCS, Glasgow Coma Scale; mTBI, mild traumatic brain injury; NPV, negative predictive value; QC, quality control; ROC, receiver operating characteristic; UCH-L1, ubiquitin C-terminal hydrolase-L1.

testing (including hemolysis vulnerability for UCH-L1), and (iii) traceable calibration transfer and QC strategy in the absence of universally accepted reference materials. When these decision-level requirements are treated as core scientific deliverables, next-generation POCT platforms can more credibly claim ED relevance and a realistic capacity to reduce unnecessary CT.

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Author contributions

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