

ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Biomarker-based brain trauma assessment tests to aid in the evaluation of mild traumatic brain injury in adults

Document Number: HSB-M 05/2025

Date: May 2025



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Summary of Key Points

- Mild traumatic brain injury (mTBI), as categorised by a Glasgow Coma Scale (GCS) score of 13 to 15, is the most common type of head injury, locally.
- In patients suspected of mTBI, a head computed tomography (CT) scan may be needed to rule out intracranial lesions. The necessity of a CT would be dependent on clinical assessments including history taking, physical examination and potentially formal clinical decision rules such as the Canadian CT Head Rule (CCHR).
- Biomarker-based brain trauma assessment tests measure the combination of glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase (UCH-L1) in the blood to determine the need for a CT. This brief includes six FDA-registered devices that are indicated for use in adults (≥ 18 years) suspected of mTBI (GCS score of 13 to 15) within 12 to 24 hours of injury. One of the devices, Alinity i TBI, has been registered locally.
- Based on one HTA report and six diagnostic accuracy studies (total $n=7,025$), no safety data was reported.
 - Using head CT as a reference standard, high sensitivity and negative predictive value (NPV) but low specificity and positive predictive value (PPV) were reported:
 - Sensitivity: 91% to 100%, specificity: 11% to 41%
 - NPV: 95% to 100%, PPV: 7% to 43%
 - Based on one comparative study ($n=1,438$), biomarker-based brain trauma assessment tests appeared to have significantly higher specificity, NPV and PPV, but not sensitivity, compared to clinical decision rules. However, the internal validity of this comparison is questionable, as an adapted version of the clinician decision rules were applied retrospectively.
 - Real-world, 6-month post-implementation data analysis from one HTA report revealed that biomarker tests did not result in expected optimal reduction in CT scans.
- One economic study from France showed that biomarker-based brain trauma assessment tests could potentially result in cost-saving if used before a head CT, with associated cost-savings of €4,150 (SGD\$5,876) per 1,000 patients resulting from reduction of 325 CT scans.
- The costs for most tests are not publicly available. Based on a manufacturer representative (Abbott Laboratories, September 2, 2021), Abbott's i-STAT Alinity system is priced at USD\$10,000 (SGD\$13,603) per analyser (reusable), and the single-use i-STAT TBI Plasma Cartridge costs USD\$16 (SGD\$21.76) per cartridge (single use).
- Key uncertainties include the minimal reporting on the relative performance of the biomarker tests compared to current practice of clinical assessments and the clinical utility of the tests.
- Two ongoing trials due to finish soon may address the gaps on clinical utility and health resource utilisation.
- Current recommendations from clinical practice guidelines (CPGs) on the use of GFAP/UCH-L1-based biomarker-based tests to determine the need for a CT scan in the target population appear to be mixed. Four CPGs recommended biomarker test use while three did not, with NICE (2023) recommending it for research use only.
- Implementation considerations include clinician acceptance of uncertainty concerns when bypassing CT scans based on biomarker-based brain trauma assessment test

results, and clear protocols incorporating the use of the tests including for result interpretation and clinical decision-making.

I. Background

Traumatic brain injury (TBI) refers to alterations in brain function or brain pathology caused by external forces.¹ Common causes include falls, sports-related injuries and motor vehicle accidents. Symptoms include temporary or permanent loss of consciousness (LOC), memory loss, or dizziness, occurring immediately or developing slowly over hours to days.² TBI may be an emergency, as conditions can worsen rapidly without treatment.³

In people with a head injury, the Glasgow Coma Scale (GCS) is a standardised early assessment tool used to evaluate the severity of any associated TBI.⁴ Using the GCS, TBI is broadly categorised into three levels: mild TBI (mTBI) with a score of 13 to 15, moderate TBI with a score of 9 to 12, and severe TBI with a score of ≤ 8 . Globally, more than 90% of patients presenting to hospital with TBI are categorised as mild.⁵ This is supported by local evidence where about 83% of patients admitted for TBI (median age of 67 years) were assessed as mild on the GCS (13 to 15).⁶

mTBI is associated with substantial healthcare utilisation and costs. A European study reported that patients with mTBI required an average of 1.8 days in intensive care, 4.5 days in wards, and 5.8 days in rehabilitation, resulting in a total cost of €3,800 (SGD\$5,510) per patient.⁷ Up to 17% of patients with mTBI do not return to work even 12 months post-injury.⁸ Patients also experience sustained impact on quality of life.⁹

Currently, clinical assessment for patients presenting with head trauma includes medical history, GCS administration, physical examination, and potentially the use of clinical decision rules such as the Canadian CT Head Rule (CCHR) or New Orleans Criteria (NOC).^{4, 6, 10} These decision rules rely on criteria such as age, presence of LOC, and symptoms like headache and vomiting.¹¹ If mTBI is suspected based on the above assessment, a head computerised tomography (CT) scan may be ordered to assess for intracranial lesions,² which commonly include contusions, haemorrhages and axonal injury.^{12, 13}

The current practice to assess the need for head CT has notable limitations such as subjective reports from patients or observers, and lengthy local head CT wait times exceeding four hours (Personal Communication: Head & Senior Consultant from National Neuroscience Institute, 2024). Furthermore, approximately 90% of head CT scans in patients presenting with head trauma are negative for intracranial lesions.¹⁴ These limitations highlight a need for more objective and validated tools to help identify patients presenting with head trauma who may require head CT scans.

II. Technology and Regulatory Status

Biomarker-based brain trauma assessment tests use reagents to detect and measure brain injury biomarkers.¹⁵ Three biomarkers have been extensively studied as tools to aid the decision for a head CT in patients suspected of a mTBI. These are glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase (UCH-L1), and S100B, which are expressed by

various neurons after head injury.¹⁶⁻²⁰ The combination of some of these biomarkers (e.g. GFAP/UCH-L1) has been demonstrated to accurately distinguish between patients with mTBI and healthy controls,^{17, 21, 22} with clinical practice guidelines (CPGs) from some countries recommending the use of either GFAP/UCH-L1 or S100B to identify patients requiring a head CT.²³⁻²⁷

Currently, only tests to quantify GFAP/UCH-L1, have been approved by the US Food and Drug Administration (FDA) in patients with suspected mTBI (summarised in Table 1).²⁷ When used in conjunction with other clinical information, these tests aid in determining the need for head CT in adult patients with suspected mTBI (GCS score of 13 to 15). The tests assess blood samples using various immunoassay methods and can generate results in less than an hour.¹⁶⁻²² These novel devices are primarily intended for clinical laboratory use, with the exception of the i-STAT TBI Cartridge (for whole blood), which is FDA-approved for point-of-care use (Table 1).²⁸⁻³³

Notably, the first FDA-approved device, Banyan BTI, was granted marketing authorisation under the De Novo Classification Request process in 2018, but is no longer commercially available.²⁸ In the past five years, TBI tests based on Banyan technology have been developed by Abbot and VIDAS and approved by the FDA.²⁹⁻³³ These tests have been assessed as substantially equivalent to Banyan BTI with similar indications for use, albeit with slight variations as detailed in Appendix A. The Alinity i TBI, the i-STAT TBI Plasma Cartridge and VIDAS TBI are also CE-marked.^{34, 35} In Singapore, Alinity i TBI is the only Health Sciences Authority (HSA)-registered model, with indications for use (detailed in Table 1) that align with FDA-registered indications.

Table 1: FDA and HSA-registered indications for all six biomarker-based brain trauma assessments.²⁸⁻³³

Product name (Year of approval) FDA	Indication for use
Abbott	
i-STAT TBI Plasma Cartridge (2021) 	The i-STAT TBI Plasma test is a panel of <i>in vitro</i> diagnostic immunoassays for the quantitative measurements of GFAP and UCH-L1 in plasma and a semiquantitative interpretation of test results derived from these measurements, using the i-STAT Alinity Instrument. <u>The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (GCS score 13-15) within 12 hours of injury, to assist in determining the need for a CT scan of the head. A 'Not Elevated' test interpretation is associated with the absence of acute traumatic intracranial lesions visualised on a head CT scan. The test is used with plasma prepared from EDTA anticoagulated specimens in clinical laboratory settings by a healthcare professional. The i-STAT TBI Plasma test is not intended to be used in point-of-care settings.</u>
i-STAT TBI Cartridge (2024) 	The i-STAT TBI test is a panel of <i>in vitro</i> diagnostic immunoassays for the quantitative measurements of GFAP and UCH-L1 in whole blood and a semi-quantitative interpretation of test results derived from these measurements, using the i-STAT Alinity instrument. <u>The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (GCS score 13-15), which may include one of the following four clinical criteria : 1) any period of loss of consciousness, 2) any loss of memory for events immediately before and after the accident, 3) any alteration in mental state at the time of accident, and/or 4) focal neurological</u>

	deficits, within 24 hours of injury, to assist in determining the need for a CT scan of the head. A 'Not Elevated' test interpretation is associated with the absence of acute traumatic intracranial lesions visualised on a head CT scan. The test can be administered in point of care or clinical laboratory settings by a healthcare professional using venous whole blood collected with EDTA anticoagulant.
Alinity i TBI^a (2023)  HSA-registered (DE0508885)	The TBI test is a panel of <i>in vitro</i> diagnostic CMIA used for the quantitative measurements of GFAP and UCH-L1 in human plasma and serum and provides a semi-quantitative interpretation of test results derived from these measurements using the Alinity i system. <u>The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (GCS score 13-15) within 12 hours of injury, to assist in determining the need for a CT scan of the head.</u> A negative test result is associated with the absence of acute intracranial lesions visualised on a head CT scan. The TBI test is intended for use in clinical laboratory settings by healthcare professionals. HSA-registered indication: The TBI test is a panel of <i>in vitro</i> diagnostic CMIA) used for the quantitative measurements of GFAP and UCH-L1 in human plasma and serum and provides a semi-quantitative interpretation of test results derived from these measurements using the Alinity i system. The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (GCS 13-15) within 12 hours of injury, to assist in determining the need for a CT scan of the head. A negative test result is associated with the absence of acute intracranial lesions visualised on a head CT scan. The TBI test is intended for use in clinical laboratory settings by healthcare professionals.
TBI for ARCHITECT (2023) 	The TBI test is a panel of <i>in vitro</i> diagnostic CMIA used for the quantitative measurements of GFAP and UCH-L1 in human plasma and serum and provides a semi-quantitative interpretation of test results derived from these measurements using the ARCHITECT i 100SR System. <u>The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (GCS score 13-15) within 12 hours of injury, to assist in determining the need for a CT scan of the head.</u> A negative test result is associated with the absence of acute intracranial lesions visualised on a head CT scan. The TBI test is intended for use in clinical laboratory settings by healthcare professionals.
bioMerieux	
VIDAS TBI (2024) 	The VIDAS TBI test is composed of two automated assays – VIDAS TBI (GFAP) and VIDAS TBI (UCH-L1) – to be used on the VIDAS 3 instrument for the quantitative measurement of GFAP and UCH-L1 in human serum using the ELFA technique. The results of both assays are required to obtain an overall qualitative test interpretation. <u>The overall qualitative VIDAS TBI (GFAP, UCH-L1) test result is used, in conjunction with clinical information, to aid in the evaluation of patients (18 years of age or older), presenting within 12 hours of suspected mild traumatic brain injury (score 13-15), to assist in determining the need for a (CT) scan of the head.</u> A negative interpretation of VIDAS TBI (GFAP, UCH-L1) test is associated with the absence of acute intracranial lesions visualised on a head CT scan.
<i>Banyan Biomarkers (no longer commercially available)</i>	
Banyan BTI (2018) No longer commercially available, no picture available	The Banyan BTI is an <i>in vitro</i> diagnostic chemiluminescent ELISA. The assay provides a semi-quantitative measurement of the concentrations of UCH-L1 and GFAP in human serum, and is used with the Synergy 2 Multi-mode Reader. <u>The assay results obtained from serum collected within 12 hours of suspected head injury are used, along with other available clinical information, to aid in the evaluation of patients 18 years of age and older with suspected traumatic brain injury (GCS score 13-15).</u> A negative assay result is associated with the absence of acute intracranial lesions visualized on a head CT scan. The Banyan BTI is for prescription use only.
Notes: a. HSA-registered (DE0508885) since January 2024 Abbreviations: CT, computed tomography; CMIA, chemiluminescent microparticle immunoassays; EDTA, ethylenediaminetetraacetic acid; ELFA, enzyme linked fluorescent assay; ELISA, enzyme linked immunosorbent assay; FDA, US Food and Drug Administration; GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; HSA, Health Sciences Authority; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.	

By providing objective biomarker measurements within an hour, these devices may address the limitations of current assessments by providing timely triaging of patients who urgently need CT scans.

III. Subsidy Status

While GFAP/UCH-L1 biomarker-based brain trauma assessment tests are recommended in CPGs from France, Spain, and the US, it is unclear if they are reimbursed publicly in these countries.^{24-26, 36} Among reference jurisdictions, only the National Institute for Care Excellence in the UK has explicitly indicated that these biomarker-based brain assessments are not reimbursed, citing limitations in the clinical evidence base.⁴

IV. Stage of Development in Singapore

- | | |
|---|--|
| ☐ Yet to emerge | ☐ Established |
| ☒ Investigational / Experimental
(subject of clinical trials or deviate from standard practice and not routinely used) | ☐ Established <i>but</i> modification in indication or technique |
| ☐ Nearly established | ☐ Established <i>but</i> should consider for reassessment (due to perceived no/low value) |

V. Treatment Pathway

The current local management pathway for the treatment of head injuries is summarised in Appendix B. This pathway is primarily based on CPGs from the American College of Emergency Physicians and the British Columbia Guidelines and Protocols Advisory Committee.^{26, 37} Local clinician input validated the pathway (Personal Communication: Head & Senior Consultant from National Neuroscience Institute, 2024).

In local practice, a head CT is required for most patients presenting with a GCS score of 13 to 15 (Personal Communication: Head & Senior Consultant from National Neuroscience Institute, 2025). This is unlike other countries such as the US and Canada, where head CTs are typically conducted only in patients who exhibit certain symptoms identified during clinical assessments (e.g. vomiting, amnesia, signs of skull fracture).^{10, 37, 38}

Under the current local pathway, patients are clinically assessed with the GCS scale, across three domains related to eye, verbal, and motor responses. The scores in each element of the GCS are summed to give the overall score, which ranges from 3 (unresponsive in all domains) to 15 (no deficits in responsiveness).⁴ For patients suspected of mTBI based on GCS scores of 13 to 15 and/or other clinical assessments such as CCHR and NOC, the local standard of care (SOC) involves a head CT to determine the presence or absence of intracranial lesions

(specifically haemorrhages) (Personal Communication: Head & Senior Consultant from National Neuroscience Institute, 2024).

Patients without CT-identified intracranial lesions undergo a period of observation before discharge, in 24-hour or short-stay wards. Those who experience clinical deterioration may undergo another CT to reassess for intracranial lesions. Those with identified intracranial lesions may require further observation and/or subsequent neurosurgical intervention.

Local clinicians opined that if adopted, biomarker-based brain trauma assessment tests could help prioritise patients requiring urgent head CT, thereby reducing waiting times (Personal Communication: Head & Senior Consultant from National Neuroscience Institute, 2024). The use of these tests may also allow patients who test negative to undergo observation without a CT scan. (Personal Communication: Head & Senior Consultant from National Neuroscience Institute, 2025).

VI. Summary of Evidence

This assessment of biomarker-based brain trauma assessment tests was conducted using the Population, Intervention, Comparator and Outcome (PICO) criteria in Table 2. Literature searches were conducted in health technology assessment (HTA) databases, Cochrane Library, and Embase.

Table 2: Summary of PICO criteria

Population	Adults (≥18 years) with suspected mTBI, defined as GCS score of 13 to 15
Intervention	FDA-approved biomarker-based brain trauma assessment tests ^a
Comparator ^b	Reference standard: Head CT Comparator: SOC clinical assessment methods to determine the need for a head CT (may include other clinical decision rules such as CCHR or NOC)
Outcome	Safety: AE Clinical effectiveness: Diagnostic accuracy (sensitivity, specificity, PPV, NPV, LR), clinical utility (e.g. intracranial lesion-related morbidity or mortality), changes in health resource utilisation or management Economic outcomes: Cost, cost-effectiveness
Notes: a. FDA-approved biomarker-based brain trauma assessment tests includes Banyan Biomarker's BTI, bioMerieux's VIDAS TBI and Abbott's i-STAT TBI Plasma Cartridge, i-STAT TBI Cartridge (for whole blood), Alinity i TBI, and TBI for ARCHITECT b. The reference standard comparator refers to the diagnostic test used to determine the accuracy of the index test; the clinical comparator is the main alternative treatment or diagnostic strategy, or current clinical practice that are likely to be replaced by or used with the intervention Abbreviations: AE, adverse event; CT, computed tomography; CCHR, Canadian CT Head Rule; GCS, Glasgow Coma Scale; LR, likelihood ratio; mTBI, mild traumatic brain injury; NOC, New Orleans Criteria; NPV, negative predictive value; PPV, positive predictive value; SOC, standard of care.	

The key evidence base comprised one Spanish hospital-based HTA report by Roman (2024), and six additional diagnostic accuracy studies.³⁹⁻⁴⁵

The HTA by Roman (2024) included three observational studies using Alinity i, Banyan BTI or i-STAT Plasma TBI.³⁹ Among the six additional studies, three assessed Alinity i (Welch, 2025⁴⁰; Ladang, 2024⁴²; Legramante, 2024)⁴⁴, while Chayoua (2024)⁴¹ assessed i-STAT Plasma TBI and Lagares (2024)⁴³ assessed VIDAS TBI. The sixth study by Oris (2024) compared diagnostic accuracy performance between i-STAT Plasma TBI and Alinity i.⁴⁵ Only Chayoua (2024)⁴¹ and Lagares (2024)⁴³ reported funding or commercial interests with manufacturers.

The studies generally included patients (≥ 18 years) presenting at healthcare facilities due to a head injury with an initial assessment GCS of 13 to 15. Detailed characteristics of included studies are in Appendix C.

Safety

No studies reported on the safety of these tests. As phlebotomy is a routinely performed procedure, no major safety concerns are expected.

Effectiveness

No studies were identified that assessed the clinical utility of the biomarker-based brain trauma assessment tests. Roman (2024) reported on changes in health resource utilisation six months after biomarker-based brain assessment test implementation.³⁹ All seven studies reported diagnostic accuracy comparing these tests against a head CT as the reference standard.³⁹⁻⁴⁵ Lagares (2024) additionally compared these tests against SOC clinical decision rules and also assessed neurological outcomes at three-month follow-up based on admission biomarker levels.⁴³ The results for the performance of these tests against head CT and SOC clinical decision rules, and neurological outcomes are summarised in Table 3 and Table 4, respectively.

Supplementary analyses not directly addressing the PICO were included as they provided extra information. Three studies additionally reported the diagnostic accuracy of the individual biomarker-specific separately (GFAP and UCH-L1 alone).⁴¹⁻⁴³ Four studies reported on false negativity rate,⁴⁰⁻⁴³ and two of these (Chayoua, 2024; Ladang, 2024) also reported on demographic or clinical factors that could improve the specificity of these tests.^{41,42} Supplementary analysis results are in Appendix D, Appendix E, and Appendix F.

Diagnostic accuracy

Overall, against reference standard head CT, biomarker-based brain trauma assessment tests demonstrated high sensitivity and negative predictive value (NPV), but low specificity and positive predictive value (PPV) across all seven studies (Table 3).³⁹⁻⁴⁵ Combined GFAP/UCH-L1 sensitivity ranged from 91% to 100%, while specificity ranged from 11% to 41%. The HTA also reported Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty ratings of moderate and low certainty for sensitivity and specificity, respectively.³⁹ In addition, PPV ranged from 7% to 43%, NPV 95% to 100%, positive likelihood ratio (LR) 1.19 to 1.61, and negative LR was 0.08.³⁹⁻⁴⁵

Table 3: Diagnostic accuracy of FDA-registered biomarker-based brain trauma assessment tests

Study ID	Device	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Welch (2025) ⁴⁰	TBI for Alinity i	96.7% (91.7% to 98.7%)	40.1% (37.8% to 42.4%)	9.8% (8.2% to 11.6%)	99.4% (98.6% to 99.8%)
Roman (2024) ³⁹	TBI for Alinity i, i-STAT Plasma TBI, Banyan BTI	91.0% to 100.0% ^a	11.0% to 41.0% ^a	29.0% ^b	100.0% ^b

Oris (2024) ⁴⁵	TBI for Alinity i	100.0% (72.0% to 100.0%)	29.7% (23.7% to 36.2%)	6.7% (3.3% to 11.5%)	100% (94.5% to 100.0%)
	i-STAT Plasma TBI	100.0% (75.1% to 100.0%)	28.8% (22.9% to 35.3%)	6.6% (3.3% to 11.5%)	100% (94.3% to 100.0%)
Ladang (2024) ⁴²	TBI for Alinity i	99.1% (NR)	40.6% (NR)	43.1% (NR)	99.0% (NR)
Legramante (2024) ⁴⁴	TBI for Alinity i	100% (64.5% to 100.0%)	27.6% (20.0% to 36.4%)		100% (88% to 100.0%)
Chayoua (2024) ⁴¹	i-STAT Plasma TBI	97.0% (89.0% to 99.0%)	19.0% (14.0% to 25.0%)	27.0% (21.0% to 33.0%)	95.0% (88.0% to 100.0%)
Lagares (2024) ⁴³	VIDAS	98.3% (95.0% to 99.7%)	24.9% (22.6% to 27.4%)	15.7% (13.7% to 17.9%)	99.1% (97.1% to 99.8%)
	CCHR	94.4% (89.9% to 97.1%)	18.2% ^c (16.2% to 20.4%)	14.1% ^c (12.2% to 16.2%)	95.8% ^c (92.4% to 97.8%)
	NOC	95.0% (90.6% to 97.5%)	14.6% ^c (12.8% to 16.7%)	13.7% ^c (11.9% to 15.7%)	95.3% ^c (91.3% to 97.6%)
Notes: a. Based on three primary studies b. Based on one primary study c. Statistically different ($p < 0.05$) for that diagnostic accuracy parameter in comparison to biomarker-based brain trauma assessment test using the McNemar test and Chi-square test Abbreviations: CCHR, Canadian CT Head Rule; CI, confidence interval; GFAP, glial fibrillary acidic protein; NOC, New Orleans Criteria; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; UCH-L1, ubiquitin carboxy-terminal hydrolase					

In addition, Oris (2024) compared the diagnostic accuracy between the i-STAT TBI Plasma Cartridge and Alinity i.⁴⁵ No significant differences in any accuracy measures were reported between the two models.

Lagares (2024) compared the relative performance of biomarker-based brain trauma assessment tests (VIDAS) to clinical decision rules.⁴³ The tests showed significantly higher specificity (25% vs CCHR: 18% [$p < 0.0001$], NOC: 15% [$p < 0.0001$]), PPV (16% vs CCHR: 14% [$p < 0.0001$], NOC: 14% [$p < 0.0001$]) and NPV (99% vs CCHR: 96% [$p = 0.021$], NOC: 95% [$p = 0.022$]). There were no significant difference in sensitivity between the biomarker-based brain trauma assessment tests (98%), CCHR (94%) or NOC (95%).

Exploratory analysis: Neurological outcomes by biomarker levels

Lagares (2024; $n = 1,438$) explored neurological outcomes at seven days and three months post-injury (Table 4).⁴³ At 3 months, both incomplete recovery (25.3% of 1,062 patients) and post-concussion syndrome (24.3% of 1,012 patients) were significantly associated with elevated admission of GFAP and UCH-L1 levels, after adjusting for age, sex, and admission GCS score.

Table 4: Prediction of neurological outcomes by admission biomarker levels

Follow-up	Outcome measure	Results	Median GFAP (IQR) (pg/mL)	Median UCH-L1 (IQR) (pg/mL)
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7 days	Neurological deterioration ^a (n=NR)	11 TBI-related deterioration with no ICU admissions or neurosurgical interventions required	With deterioration: 320.0 (42.5 to 630.0) Without deterioration: 39.8 (20.0 to 80.5) p=0.004 ^d	No association between UCH-L1 level and deterioration
3 months	GOSE score ^b (n=1062)	269 patients (25.3%) had incomplete recovery (GOSE <8)	Incomplete recovery: 54.9 (27.9 to 145) Complete recovery: 39.0 (18.2 to 77.6) p<0.001 ^e	Incomplete recovery: 327.0 (194.0 to 552.0) Complete recovery: 248.0 (160.0 to 412.0) p<0.001 ^e
	Rivermead scale ^c (n=1012)	246 patients (24.3%) had PCS-related symptoms	With PCS: 47.4 (27.0 to 84.6) Without PCS: 39.3 (18.7 to 84.6) p=0.004 ^e	With PCS: 280.0 (181.0 to 511.0) Without PCS: 260.0 (162.0 to 431.0) p=0.001 ^e
Notes: a. Neurological deterioration was a decrease in GCS score of >2 points from the initial GCS, or a neurological deterioration sufficient to warrant intervention b. GOSE assesses global outcome after TBI. The scale ranges from 1 (dead) to 8 (no disability); scores <8 indicate incomplete recovery with varying degrees of disability ⁴⁶ c. Rivermead Post-concussion scale assesses presence and severity of post-concussion symptoms. PCS was determined using ICD criteria: score ≥2 on at least three symptoms (headache, dizziness, fatigue, irritability, sleep disturbances, poor concentration, forgetfulness, poor memory, frustration, or depression) ⁴⁷ d. Unadjusted p-values, as per Mann-Whitney U-test, comparing levels of biomarker (at admission) between those with outcome vs those without outcome e. Adjusted (for age, sex, GCS score at admission) p-values, as per multivariable logistic regression, comparing levels of biomarker (at admission) between those with outcome vs those without outcome Abbreviations: GFAP, glial fibrillary acidic protein; GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale Extended; ICD, International Classification of Diseases; ICU, intensive care unit; IQR, interquartile range; NR, not reported; PCS, post-concussion syndrome; pg/mL, picograms per millilitre; TBI, traumatic brain injury; UCH-L1, ubiquitin carboxy-terminal hydrolase L1				

Changes in management

Roman (2024)³⁹ reported that six months after the implementation of biomarker-based brain trauma assessment tests in their hospital, clinicians frequently performed parallel testing, ordering both biomarker and CT regardless of biomarker results. This was contrary to the intended sequential testing (biomarker then CT if positive), Specifically, among patients with negative biomarker results (n=140), the majority (80%) still underwent CT scanning.

Limitations of evidence

Key limitations include the limited comparative evidence on the relative performance of the biomarker tests to SOC methods, as well as studies reporting on clinical utility of the tests of interest.

The findings should be interpreted with caution for several reasons. Firstly, heterogeneity between studies arising from variability in biomarker cut-offs (GFAP: 22 to 67 pg/mL; UCH-L1: 189 to 400 pg/mL). Secondly, CT scans were only being performed on patients meeting specific clinical decision rules rather than for all patients enrolled in certain studies (Chayoua, 2024; Lagares, 2024), potentially leading to an overrepresentation of more severe cases. Thirdly, when comparing results of biomarker-based brain trauma assessment tests to SOC (clinical decision rules), an adapted version of the decision rules was applied retrospectively,

and patients were categorised accordingly. This could have affected the diagnostic accuracy of the clinical decision rules. Furthermore, NOC is only validated in patients with a GCS score of 15,¹¹ while the patient population used for comparisons included patients with GCS scores of 13 to 15.

Cost-effectiveness

In the identified HTA, Roman (2024) included two studies (Zimmer, 2023 and Su, 2019) that assessed the cost-effectiveness of biomarker-based trauma assessment tests in patients suspected of mTBI.^{48, 49} The details are summarised in Appendix G.

Zimmer (2023)⁴⁸ was a cost-effectiveness analysis (CEA) from the French healthcare system perspective, evaluating the use of biomarker-based trauma assessment tests as a decision tool before a CT versus a universal CT approach. They showed cost savings of €4,150 (SGD\$5,876) per 1,000 patients tested due to reduced CT scans performed, from 1,096 to 771. Additional break-even analysis showed the biomarker test could cost up to €36.55 (SGD\$51.75) before becoming more expensive than the CT-only strategy. The model was most sensitive to intracranial lesion prevalence, GFAP/UCH-L1 test specificity, and proportion of patients discharged immediately due to negative test results.

Su (2019)⁴⁹ was a US cost-utility analysis (CUA) from a societal perspective, evaluating multiple strategies (biomarker-based brain trauma assessment tests alone, CCHR alone and sequential combinations) to determine the need for head CT in patients with mTBI. They found that initial biomarker-based brain trauma assessment tests followed by CCHR for test negative patients would be cost-effective at a willingness to pay threshold of USD\$50,000 (SGD\$68,015) per quality-adjusted life year (QALY), if the unit cost of the tests was ≤USD\$308.96 (SGD\$420.27). The model was most sensitive to probability of intracranial lesions, probability of lesions requiring surgery, and cost of biomarker-based brain trauma assessment tests. Of note, the study used the Banyan BTI biomarker test, which is no longer commercially available.

The generalisability of these results is unclear due to the potential difference in probabilities of intracranial lesions and those requiring surgery, and the cost of the tests. This study was modelled on a 20-year-old male population, whereas in Singapore, the median age of patients experiencing a TBI is 67 years.

Ongoing clinical trials

Based on a search conducted in March 2025, there are currently six ongoing trials across Europe and the US assessing the diagnostic accuracy of GFAP/UCH-L1 biomarker-based brain trauma assessment tests as detailed in Table 5. Most of these trials (five of six) are industry-sponsored or industry-led. Three of the trials appear to involve VIDAS TBI, two are i-STAT TBI, and one trial did not specify the model used.

While several ongoing trials will provide additional diagnostic accuracy data, two trials (NCT06766435 and NCT05425251) may address key evidence gaps by assessing the use of these tests on clinical utility (neurological symptoms) and health resource utilisation. Results from these trials will become available before 2027. Comparisons of diagnostic accuracy

performance against SOC clinical assessment methods to determine need for CT remains unaddressed.

One additional trial (NCT04032509) was identified, involving patients (≥ 18 years) with a GCS score of 13 to 15 and with blood collected within 12 hours of injury. This trial was completed in September 2021, however as of March 2025, no published results were identified.

Table 5: Ongoing trials

Study (Trial ID)	Model evaluated	Population and estimated enrolment (country conducted)	Brief description	Estimated study completion date
Evaluation of the Abbott i-STAT TBI Biomarker Test (NCT06766435)	i-STAT TBI	Adults (≥ 18 years) with GCS score of 13 to 15 and with blood collected within 24 hours of injury n=450 (USA)	Open-label RCT to assess number of head CTs cancelled as a result of i-STAT TBI test, A&E length of stay, as well as other health resource utilisation, and physician-reported Stress of Uncertainty Scales and Malpractice Fear Scales.	October 2025 Sponsored by manufacturer
Glial Fibrillary Acidic Protein (GFAP) and Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-L1) to Exclude Lesions Linked to Significant Traumatic Brain Injuries (GUEST) (NCT05885529)	VIDAS TBI	Adults (≥ 18 years) with GCS score of 13 to 15, blood collected within 12 hours of injury, and meeting one of the following four criteria: 1. >65 years and treated with anti-platelet therapy 2. GCS <15 two hours after trauma if intoxicated 3. Trauma with high kinetics 4. Amnesia of facts >30 mins before trauma n=1,500 (France, Monaco)	Prospective study to assess diagnostic accuracy of GFAP and UCH-L1 combined tests ^a	March 2026 Collaborated with manufacturer
BRAINI-2 Elderly Mild TBI European Study ^a (BRAINI2ELDER) (NCT05425251)	VIDAS TBI ^a	Elderly adults (≥ 65 years) with GCS score of 13 to 15, blood collected within 12 hours of injury, and CT scan within 6 hours of blood sample <i>Study also accepting elderly adults with no mTBI as reference</i> n=2,850 (France, Germany, and Spain)	Prospective cohort study assessing diagnostic accuracy of VIDAS, potential of GFAP and UCH-L1 in predicting neurological symptoms and outcomes post-TBI, reference biomarker values in healthy populations,	March 2025 Collaborated with manufacturer

VIDAS® TBI Real Life Performance in Subjects with Mild Traumatic Brain Injury (mTBI) (NCT06449183)	VIDAS TBI	Adults (≥18 years) presenting at an A&E with GCS score of 13 to 15 and with blood collected within 12 hours of injury n=900 (USA)	Prospective study assessing diagnostic accuracy of VIDAS	November 2025 Sponsored by manufacturer
Use of Cerebral Biomarkers in Minor Traumatic Brain Injury in the Emergency Unit (CerBio-mTBI) (NCT06069674)	Model not specified	Adults (≥18 years) presenting at an A&E within 4 hours of injury and reporting mTBI with risk factors for delayed intracranial bleeding n=1,510 (Italy)	Prospective study assessing diagnostic accuracy of biomarker test (model NR) in patients at risk of delayed intracranial bleeding	March 2024 Not sponsored and no collaborations with manufacturer Indicated as recruiting
Correlation and Rapid Analysis of Neurological Injury Using Markers (NCT06834659)	i-STAT TBI	Adults (18 to 65 years) with suspected TBI n=200 (Italy)	Prospective real-world study assessing concordance between i-STAT TBI Plasma test with CT scans	January 2027 Sponsored by manufacturer
Notes: a. Model not reported, but collaboration with bioMerieux, manufacturer of VIDAS TBI Abbreviations: A&E, Accident and Emergency; CT, Computed Tomography; GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; mTBI, mild traumatic brain injury; NR, not reported; RCT, randomised controlled trial; TBI, traumatic brain injury; UCH-L1, ubiquitin carboxy-terminal hydrolase L1				

Summary

The overall evidence base comprised an HTA (with three observational studies) and six additional diagnostic accuracy studies totalling 7,025 patients. Current evidence is limited to mainly test accuracy data, with minimal evidence comparing biomarker tests to SOC (including assessment with clinical decision rules such as CCHR or NOC), and assessing clinical utility or health resource utilisation. The evidence base was also limited by heterogeneity in biomarker cut-offs applied and CT interpretation.

In comparison to the reference standard of a head CT, the combined tests with GFAP and UCH-L1 demonstrated a high sensitivity (91% to 100%) and high NPV (95% to 100%). However, this is at the expense of a high false positive rate, given their poor specificity (11% to 41%) and PPV (7% to 43%). Currently, there is insufficient evidence to determine the relative performance of these tests to clinical decision rules (CCHR and NOC). Early real-world implementation data in Europe shows limited impact on CT utilisation, with only 20% of patients with negative biomarker tests avoiding CT scans. Two economic analyses showed the potential of the biomarker tests to be cost-saving or cost-effective under specific conditions. However, the generalisability of these findings to Singapore is unclear.

Six ongoing trials were identified, with two trials addressing health resource utilisation, and clinical utility (e.g. neurological symptoms). However, diagnostic accuracy comparisons with SOC remain unaddressed.

VII. Estimated Costs

The costs of most of these tests are not publicly available. Abbott has quoted the i-STAT Alinity system, which can run both their plasma and whole blood cartridges, at approximately USD\$10,000 (SGD\$13,603) per unit¹ presumably for the US market. The single-use i-STAT TBI Plasma Cartridge costs USD\$16 (SGD\$21.76) per cartridge.⁵⁰

For comparison, clinical decision tools are free, as they are simple checklists without copyright restrictions. Regarding head CT costs in local public healthcare institutions (PHIs), 2005 data shows outpatient charges ranging from SGD\$312 to SGD\$790 and inpatient charges from SGD\$312 to SGD\$956.⁵¹ When adjusted for inflation based on the Monetary Authority of Singapore, these ranges would be SGD\$483.45 to SGD\$1,481.34 in 2024.^{52, 53}

VIII. Implementation Considerations

Several key implementation issues need consideration for the local setting. From an organisational perspective, PHIs would need to invest in capital equipment such as laboratory analysers or point-of-care analysers, noting that each biomarker test is compatible only with specific analysers from their respective manufacturers. The current capacity for simultaneous analysis of multiple patient's samples is unclear for the point-of-care and laboratory analysers.

Healthcare provider training and considerations are also crucial. Given the possibility of false negatives, clinician's risk appetite needs assessment. Real-world implementation data from Roman (2024)³⁹ showed that, contrary to intended sequential testing (biomarker test, then CT if positive on biomarker test), clinicians frequently performed parallel testing. Data from an earlier identified ongoing trial (NCT06766435) measuring clinician Stress of Uncertainty Scales and Malpractice Fear Scales could inform local implementation strategies.^{54, 55} Clear protocols incorporating the use of biomarker-based brain trauma assessment tests, including for result interpretation and clinical decision-making would need to be developed.

Accessibility considerations include strategic placement of these devices in trauma centres and community-based hospitals that serve elderly populations, given that the local median age for TBI is 67 years and falls are the predominant cause.⁶ This would ensure the technology is available where it is most needed.

IX. Concurrent Developments

Several other biomarker-based brain trauma assessment tests are either in development or approved by some regulatory authorities such as Health Canada. These include immunoassays for alternative biomarkers such as S100B and aldolase isoenzyme.⁵⁶

Table 6: Other biomarker-based brain trauma assessment tests in development

Device	Biomarker used	Regulatory availability
Tbit System	GFAP and serum S100B	No FDA or approval from other regulatory authorities ^b
BRAINBox TBI	Aldolase isoenzyme, or trauma-specific breakdown of this enzyme ^a	
Elecsys S100	Serum S100B	Not FDA-approved

¹ Based on Monetary Authority of Singapore's 2024 to 2025 exchange rate: USD\$1=SGD\$1.3603 and €1=SGD\$1.4160

	Approval by Health Canada
Notes: a. Breakdown molecule not specified b. Regulatory authorities including Health Canada or Therapeutic Goods Administration Abbreviations: GFAP, glial fibrillary acidic protein; FDA, US Food and Drug Administration	

Other FDA-approved non-biomarker-based tests used for TBI assessment are also available, and included in Appendix H.²⁷

X. Additional Information

Currently, there appears to be mixed recommendations from CPGs on the use of GFAP/UCH-L1 biomarker tests to determine the need for a CT scan in patients presenting with mTBI. Four CPGs (American College of Surgeons, French Society of Anaesthesia and Resuscitation, the Spanish Society of Emergency Medicine and US Department of Defence) recommended use of GFAP/UCH-L1 biomarkers.^{24-26,36}

Three other guidelines, British Columbia (2024), NICE (2023) and the American College of Emergency Physicians (2023) did not recommend the use of any biomarkers for routine clinical practice, instead NICE stated they may be used for further research on their utility to predict of acute complications like intracranial lesions, as well as for prognostic purposes.^{4, 10, 37}

All CPGs recommended testing within 12 hours post-injury. Details of the recommendations are in Appendix I.

Separately, the Scandinavian Neurotrauma Committee, the American College of Emergency Physicians and French Society of Anaesthesia and Resuscitation also recommended the use of S100B.^{10, 23, 25}

Based on clinician comments, this rapid, quantitative assessment could help emergency departments prioritise patients with mTBI who need urgent CT scans, ensuring those at higher risk receive care sooner. There are plans for local adoption by the National Neuroscience Institute (Personal Communication: Head & Senior Consultant and Consultant from National Neuroscience Institute, 2024 to 2025, Senior Consultant).

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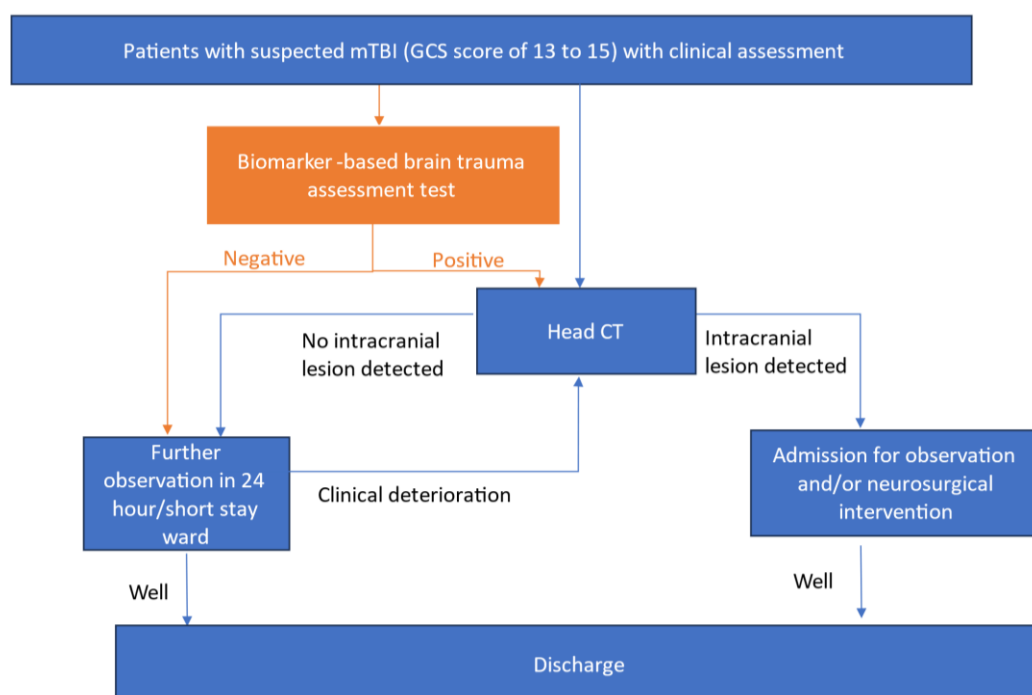
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Appendix

Appendix A: Variations between the six biomarker-based brain trauma assessment tests^{28-33, 57-61}

Product name	FDA registration mode and number	Immunoassay type	Intended use setting	Compatibility with laboratory devices	Specimen type	Cut-offs (pg/mL)	Time to result
Abbott							
i-STAT TBI Plasma Cartridge	Pre-market notification (510k) based on Banyan BTI K201778	Enzyme linked immunosorbent assay	Clinical laboratory	i-STAT Alinity	Plasma	GFAP: 30 UCH-L1: 360	15 minutes
i-STAT TBI Cartridge	Pre-market notification (510k) based on i-STAT TBI Plasma Cartridge K234143	Enzyme linked immunosorbent assay	Point of care and clinical laboratory	i-STAT Alinity	Venous whole blood	GFAP: 65 UCH-L1: 360	15 minutes
Alinity i TBI	Pre-market notification (510k) based on Banyan BTI K223602	Chemiluminescent microparticle immunoassay	Clinical laboratory	Alinity i system	Plasma and serum	GFAP: 35 UCH-L1: 400	18 minutes
TBI for ARCHITECT	Pre-market notification (510k) based on TBI for Alinity i K232669	Chemiluminescent microparticle immunoassay	Clinical laboratory	ARCHITECT i1000SR System	Plasma and serum	GFAP: 35 UCH-L1: 400	NR
Banyan Biomarkers							
Banyan BTI (No longer commercially available)	De Novo pathway DEN170045	Enzyme linked immunosorbent assay	Clinical laboratory	Synergy 2 Multi-mode Reader	Serum	GFAP: 22 UCH-L1: 327	4 hours
bioMérieux							
VIDAS TBI	Pre-market notification (510k) based on Banyan BTI K240279	Enzyme linked fluorescent assay	Clinical laboratory	VIDAS 3	Serum	GFAP: 22 UCH-L1: 327	39 minutes
Abbreviations. BTI, Brain Trauma Indicator; GFAP, glial fibrillary acidic protein; NR, not reported; pg/mL, picograms per millilitre; TBI, traumatic brain injury; UCH-L1, ubiquitin carboxy-terminal hydrolase L1							

Appendix B: Illustration of current treatment pathway (blue) and new treatment pathway (orange) with the introduction of biomarker-based brain trauma assessment tests^a



Abbreviations: CT, computed tomography; GCS, Glasgow Coma Scale; mTBI, mild traumatic brain injury.
Notes:

- a. The CCHR and NOC are clinical decision rules used to aid in determining the need for head CTs to assess for intracranial lesions, for patients with GCS score of 13 to 15 and 15, respectively.¹² Patients are typically indicated for a head CT if they present with any of the following: advanced age (≥ 60 or ≥ 65 years, depending on the specific rule), headache, vomiting, signs of intoxication, amnesia, trauma above the clavicle, seizures, or signs of skull fracture. Both rules demonstrate similar sensitivity (100% sensitivity) for detecting clinically important brain injury and need for neurosurgical intervention in patients with a GCS score of 15.¹²

Appendix C: Characteristics of included studies

Study ID	Study type	Population and follow-up	Intervention (Model, biomarkers and cut-offs)	Comparator	Window of blood sample after injury
Welch (2025) ⁴⁰	Retrospective cohort study	Patients ≥ 18 years presenting to A&E or other healthcare facility at 15 US sites, 5 German sites, and 2 Hungarian sites, with non-penetrating head injury and initial GCS of 13 to 15 (n=1,899)	TBI for Alinity i GFAP ≥ 35 pg/mL UCH-L1 ≥ 400 pg/mL	CT ^a administered for all patients with suspected mild TBI	≤ 12 hours
Roman (2024) ³⁹	HTA, from hospital's perspective	Patients ≥ 18 years with initial GCS of 13 to 15 and loss of consciousness for < 30 mins	TBI for Alinity I, Banyan BTI, i-STAT Plasma TBI	CT ^b administered for all patients with suspected mild TBI	≤ 12 hours

		(n=2,713)	GFAP 22 to 67 pg/mL UCH-L1 189 to 327 pg/mL		
Oris (2024) ⁴⁵	Retrospective cohort study	Patients ≥18 years presenting to A&E at 1 site in France with initial GCS of 13 to 15 and on antiplatelet monotherapy, loss of consciousness, or post-traumatic amnesia of facts for <30 mins (n=230)	TBI for Alinity I, i-STAT Plasma TBI GFAP ≥30 pg/mL UCH-L1 ≥360 pg/mL	CT ^c administered for all patients with suspected mild TBI	≤12 hours
Ladang (2024) ⁴²	Prospective cohort study	Patients ≥18 years presenting to A&E in 1 site in Greece, with initial GCS of 13 to 15 (n=362)	TBI for Alinity i GFAP ≥35 pg/mL UCH-L1 ≥400 pg/mL	CT ^b administered for all patients with suspected mild TBI	≤12 hours
Legramante (2024) ⁴⁴	Retrospective cohort study	Patients ≥18 years presenting to A&E in 1 site in Italy, with initial GCS of 13 to 15 (n=130)	TBI for Alinity i GFAP ≥35 pg/mL UCH-L1 ≥400 pg/mL	CT ^b administered for all patients with suspected mild TBI	≤12 hours
Chayoua (2024) ⁴¹	Prospective cohort study	Patients ≥18 years presenting to A&E at 2 sites in the Netherlands with initial GCS of 13 to 15 and LOC for <30 mins and/or post-traumatic amnesia lasting no more than 24 hours (n=253)	i-STAT Plasma TBI GFAP ≥30 pg/mL UCH-L1 ≥360 pg/mL	CT ^d , administered only in patients meeting the CHIP-decision rule	≤24 hours
Lagares (2024) ⁴³	Prospective cohort study	Patients ≥15 years presenting to A&E or a community hospital at 12 sites in France and 4 sites in Spain, with initial GCS of 13 to 15 (n=1,438)	VIDAS TBI GFAP ≥22 pg/mL UCH-L1 ≥327 pg/mL	CT ^e , administered only in patients meeting the CCHR-decision rule or other risk factors ^f	≤12 hours

Notes:

- Positivity on head CT: Presence of acute epidural haematoma, acute subdural haematoma, intraventricular haemorrhage, parenchymal haemorrhage/contusion, petechial haemorrhage or bland sheer injury, subarachnoid haemorrhage, brain oedema/herniation or ventricular compression/trapping
- Definition of positive test result NR
- Positivity on head CT: Evidence of intracranial pathology such as haematoma, air or contusion
- Positivity on head CT: Marshall score >1, indicating lesions, compressed cisterns, or midline shifts
- Positivity on head CT: Presence of one or more of the following injuries: epidural haematoma, acute subdural haematoma, subarachnoid haemorrhage, intraventricular haemorrhage, intraparenchymal contusion, petechial haemorrhage or any finding related to diffuse axonal injury, and depressed skull fracture
- Neurological focal deficit; anterograde amnesia; GCS <15 after 2 hours post TBI; suspicion of vault depression fracture; fracture of the basal skull; persisting nausea, vomiting or headache; post-TBI seizures; preinjury treatment with

antithrombotic drugs; loss of consciousness or amnesia in patients over 65 years of age; fall more than 1 metre or hit pedestrian; and any other condition requiring a CT according to the in-charge physician.

Abbreviations: A&E, Accidents and Emergency; ALERT-TBI, Prospective Clinical Evaluation of Biomarkers of Traumatic Brain Injury; CCHR, Canadian CT Head Rule; CHIP, CT in Head Injury Patients; CT, computed tomography; GCS, Glasgow Coma Scale; LOC, loss of consciousness; mL, millilitres; NR, not reported; pg, picograms

Appendix D: Diagnostic accuracy of individual biomarkers

Study ID	Device	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)
GFAP alone						
Ladang (2024)	TBI for Alinity	96.5% (NR)	42.6% (NR)	43.3% (NR)	96.4% (NR)	
Chayoua (2024)	i-STAT Plasma TBI	95.0% (86.0% to 98.0%)	28.0% (22.0% to 35.0%)	29.0% (22.0% to 35.0%)	95.0% (89.0% to 100.0%)	1.33 (1.21-1.50)
Lagares (2024)	VIDAS	98.3% (94.9% to 99.7%)	31.3% (28.8% to 33.9%)	16.8% (14.7% to 19.2%)	99.2% (97.7% to 99.9%)	
UCH-L1 alone						
Ladang (2024)	TBI for Alinity i	82.3% (NR)	74.3% (NR)	59.2% (NR)	90.2% (NR)	
Chayoua (2024)	i-STAT Plasma TBI	71.0% (69.0% to 81.0%)	46.0% (39.0% to 53.0%)	29.0% (21.0% to 36.0%)	84.0% (77.0% to 91.0%)	1.32 (1.08-1.65)
Lagares (2024)	VIDAS	57.0% (49.7% to 64.0%)	63.0% (60.3% to 65.7%)	18.0% (15.0% to 21.4%)	91.1% (89.1% to 92.9%)	
Abbreviations: CI, confidence interval; GFAP, glial fibrillary acidic protein; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NR, not reported; PPV, positive predictive value; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.						

Appendix E: Characteristics of patients who had false negatives on the biomarker-based brain trauma assessment tests

Study ID	Proportion of patients with false negatives	Sex	Age (years)	Time to blood draw (hours)	GCS	GFAP (pg/mL)	UCH-L1 (pg/mL)	Diagnosis via head CT
Welch (2025)	4/1,899	2 Females, 2 males	41 to 62	3 to 9	All scored 15	21 to 30	72 to 98	1 Acute subdural haematoma 2 Subarachnoid haemorrhages 1 Parenchymal haematoma
Chayoua (2024)	2/253	2 Males	20 to 55	1 to 3	Both scored 15	<30	<200 to 320	2 Acute subdural haematomas

Ladang (2024)	1/362	1 Male	27	NR	NR	31	312	Objectivating a skull fracture
Lagares (2024)	3/1,438	1 Female, 2 males	31 to 53	3 to 10	14 in 1 patient, 15 in 2 patients	NR	NR	3 Subarachnoid haemorrhages
Abbreviations: CT, computed tomography; GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; NR, not reported; UCH-L1, ubiquitin carboxy-terminal hydrolase L1,								

Appendix F: Approaches to improve specificity

Across two studies, in patients ≥ 65 years it was found that considering LOC, time of sampling and modifying cut-offs to 115 pg/mL for GFAP and 335 pg/mL for UCH-L1 increased specificity from 19% to 46% and 15% to 31%, respectively, while maintaining a high level of sensitivity (95% to 99%).^{41, 42}

Appendix G: Details of health economic studies

Study ID, Country, type of analysis	Model approach, perspective, discount rates, time horizon	Population	Intervention (I) Comparator (C)	Total costs	Total effectiveness	Incremental differences and conclusions
Zimmer (2023) France CEA	Decision-analytic model, French healthcare perspective 2.5% first 30 years and 1.5% thereafter Lifetime horizon	Adults (≥ 18 years) presenting at A&E with suspected mTBI with a GCS score of 13 to 15 within 12 h of injury	(I): Biomarker-based brain trauma assessment test ^{a,b} , (C): CT only	(I): €564.28 (SGD\$799.02) (C): €568.43 (SGD\$804.90)	<i>Per 1,000 patients</i> (I): 770.88 scans (C): 1,096.30 scans -Similar number of A&E visits (1,000) -Similar number of years with GCS score of >3 : 35,284 -Similar number of QALYs: 30,698	Initial screening with biomarker-based brain trauma assessment tests, and subsequent CT for patients testing positive versus CT for all patients results in: Cost saving and reduced number of CT scans per 1,000 patients: -€4,150 (SGD\$5,876) -771 vs 1,096 CT scans

Study ID, Country, type of analysis	Model approach, perspective, discount rates, time horizon	Population	Intervention (I) Comparator (C)	Total costs	Total effectiveness	Incremental differences and conclusions
Su (2019) USA CUA	Decision tree of 4 management strategies (I), Societal perspective 3% Lifetime horizon	Base-case: 20-year-old male with suspected mTBI with a GCS score of 14 to 15	(I1) Biomarker-based brain trauma assessment test only (Banyan BTI) ^{b,c} (I2: CCHR ^b (I3) CCHR then biomarker-based brain trauma assessment test ^b (I4) biomarker-based brain trauma assessment test, then CCHR ^b	NR	QALYs per patient (I1): 28.2935 (I2): 28.2915 (I3): 28.2898 (I4): 28.2952	No incremental differences reported. Authors concluded that biomarker-based brain trauma assessment test, followed by CCHR (I4) is cost-effective at a WTP of USD\$50,000 (SGD\$68,015) per QALY at ≤USD\$308.96 (SGD\$420.27)

Notes:

a. Model not specified, but assumed to be VIDAS TBI based on study authors

b. Patients testing positive will then undergo CT scans

c. No longer commercially available

Abbreviations: A&E, Accident and Emergency; CCHR, Canadian CT Head Rule; CEA, cost-effectiveness analysis; CT, computed tomography; CUA, cost-utility analysis; GCS, Glasgow Coma Scale; mTBI, mild traumatic brain injury; SGD, Singapore Dollar; QALY, quality-adjusted life year; USD, United States Dollar; WTP, willingness-to-pay threshold

Appendix H: Non-biomarker-based devices available or in development for assessment of brain trauma

Device	Mechanism of action	Regulatory availability
BrainScope One	Electroencephalogram	FDA-approved Approval by Health Canada
Automated Neuropsychological Assessment Metrics	Computerised neurocognitive assessment	FDA-approved
Immediate Post-concussion Assessment and Cognitive Testing		Not FDA-approved Approval by Health Canada
DANA		FDA-approved
EyeBOX	Eye tracking	
Eye-SYNC		
Infrascanner 2000 & 2500	Near-infrared spectroscopy	

Abbreviations: FDA, U.S. Food and Drug Administration

Appendix I: Recommendations for the use of biomarkers for assessment of patients suspected with mTBI

Professional Body	Recommendation
American College of Surgeons (2024)	Brain injury biomarkers such as GFAP, UCH-L1, and S100B <u>can be used</u> to rule out the need for brain CT imaging for patients with suspected TBI who meet the following criteria: • GCS of 13 to 15 • Clinical criteria for brain CT imaging based on brain CT imaging decision rules • The clinician assesses a low but nonzero risk for traumatic ICH The extent of GFAP, UCH-L1, and S100B elevation on the day of injury provides clinicians with an estimate of the underlying structural brain injury severity.
British Columbia Guidelines (2024)	While common in research settings, advanced neuroimaging, fluid-based biomarkers, and genetic testing are <u>not indicated for a standard clinical concussion assessment</u> .
Spanish Society of Emergency Medicine (2024)	GFAP and UCH-L1 are helpful for making decisions about adults with GCS scores between 13 and 15 in the first 12 hours after head injury. These biomarkers <u>can indicate the need for CT or help rule out unnecessary imaging</u> . The NPV of negative findings for GFAP/UCH-L1 within 12 hours of trauma allows CT to be ruled out in patients with GCS 15 scores who have symptoms and/or risk factors. CT can also be avoided or in patients with GCS scores of 13 or 14. Such patients can be discharged to home observation if they have recovered sufficiently and are asymptomatic. If more than 12 hours have passed since the head injury or if one of the biomarkers is positive, a scan should be obtained and the usual protocols followed in accordance with the CT findings and clinical picture.
American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Mild Traumatic Brain Injury (2023)	Serum biomarkers, such as S-100 calcium binding protein or brain-specific glial fibrillary acidic protein, may add additional information. The addition of biomarker information may then be combined with patient history and examination features or components of existing clinical decision tools, with the potential for increased specificity and decreased CT utilization. However, at this point, <u>strong data on biomarker use with or without other decision tools is lacking and limited by the availability of these tests</u> . Additionally, more recent work with EEG-based artificial intelligence derived algorithms may lead to improved diagnostic capabilities. Future studies should also investigate whether subsets of patients with coagulopathy, advanced age, NOAC, or newer antiplatelet agent treatments or intoxication may safely avoid imaging after minor blunt head trauma.
National Institute for Care Excellence (2023)	<u>Using biomarkers for predicting acute complications after a traumatic brain injury</u> Evidence from diagnostic accuracy studies suggested that there were high sensitivity values for some biomarkers at certain thresholds for predicting acute complications after a traumatic brain injury, but the specificity values were not high enough across the evidence. Also, many biomarkers were only tested in small samples, which led to imprecise estimates. The committee noted that accuracy differed quite widely between different studies looking at the same biomarker test measured with different assays on different platforms. Also, the evidence was heterogenous, with variable thresholds and time points for different biomarkers. Most people with a head injury present to hospital within 3 hours, and the manufacturers recommend this timeframe for optimal test results. Many of the studies assessed biomarkers beyond this time point. The committee <u>agreed that the specificity values were equally as important as the sensitivity values, given the consequences of unnecessary radiation from CT scans</u> . They thought this was particularly important in people under 16. But, <u>after considering the limitations of the evidence, the committee were unable to make recommendations for using biomarkers to predict acute complications after a mild traumatic brain injury</u> . They did think that biomarker tests had promise, <u>so they proposed a recommendation for research on using biomarkers for predicting acute post-traumatic brain injury complications</u> . Post-concussion syndrome

	The committee agreed that high specificity is needed for brain injury biomarkers for post-concussion syndrome. This was because the population with a mild head injury is large but only a small proportion go on to develop post-concussion syndrome. So, false positives would have a negative effect on resources if biomarkers were to be used to direct everyone towards interventions or monitoring. Overall, the committee agreed that the evidence was too limited to be able to make recommendations for using biomarkers (including fluid biomarkers or MRI) to predict post-concussion syndrome in people with mild traumatic brain injury. There was no evidence from prognostic test-and-treat studies comparing clinical outcomes, so the committee agreed to highlight the criteria for doing a CT head scan.
French Society of Anaesthesia and Resuscitation (2022) (Translated)	Experts propose to perform blood testing combining UCH-L1 and GFAP when available, within 12 hours following mild head trauma, in <u>intermediate-risk^a patients to limit the number of brain scans</u>. Experts propose to perform blood testing of S100B protein, when available, within 3 hours following mild head trauma, in intermediate risk patients^a to limit the number of brain scans.
US Department of Defence (2021)	GFAP and UCH-L1 testing recommended for "moderate risk" patients within 12 hours of mTBI with GCS 13-15 who have any of these factors: double vision, increased restlessness, <2 episodes vomiting, subjective weakness/tingling without clear focal deficit, severe/persistent/worsening headaches, age >60, antiplatelet drugs, drug/alcohol intoxication, post-traumatic amnesia >30 min, or concerning mechanism (high speed MVC/rollover, fall >3ft, blast within 50m). Testing should not delay evacuation in "high risk" patients with: deteriorating GCS (drop ≥2), combativeness, ≥2 episodes vomiting, seizures, focal deficits, or bleeding disorders/anticoagulation. A "not elevated" result has high NPV for ruling out need for CT scan.
Scandinavian Neurotrauma Committee (2013)	S100B analysis in adult patients with mild head injury is recommended in patients meeting the following criteria: • Less than 6 hours have elapsed following trauma, AND • Either GCS 14 and no risk factors (such as anticoagulant therapy or coagulation disorders, posttraumatic seizures, clinical signs of depressed or basal skull fracture, and focal neurological deficits), OR • GCS 15 with LOC or repeated vomiting (≥ 2) and no other risk factors. If S100B is <0.10 mcg/L, the patient may be discharged without a brain CT
Notes: a. Age ≥65 on single antiplatelet therapy, OR GCS <15 at 2h post-trauma with intoxication, OR High-energy mechanism trauma as defined above, OR Amnesia >30 minutes pre-trauma Abbreviations: CT, computed tomography; EEG, electroencephalogram; GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; ICH, intracranial haemorrhage; LOC, loss of consciousness; MRI, magnetic radiation imaging; mcg/L, microgram per litre; mTBI, mild traumatic brain injury; MVC, motor vehicle collision; NOAC, novel oral anticoagulant; NPV, negative predictive value; NR, not reported; RCT, randomised controlled trial; TBI, traumatic brain injury; UCH-L1, ubiquitin carboxy-terminal hydrolase L1; US, United States	