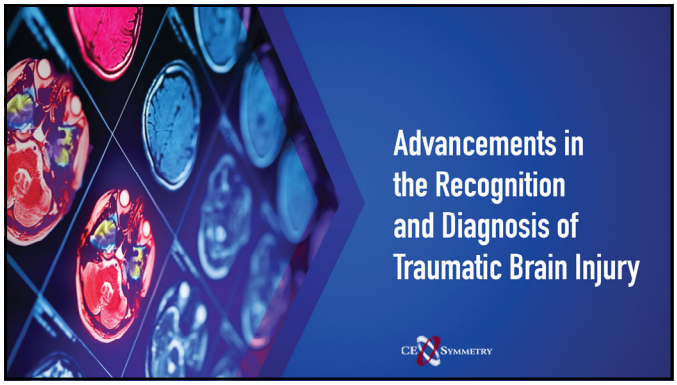
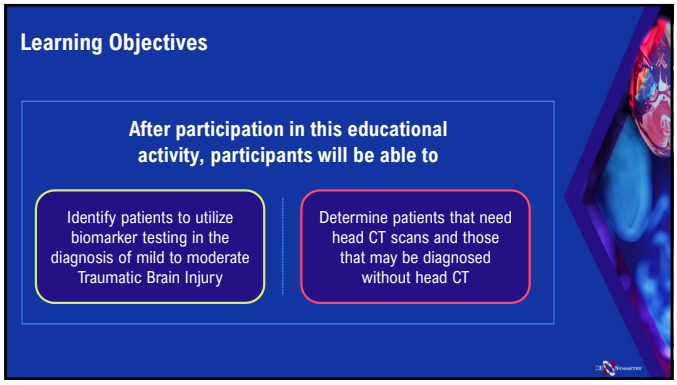
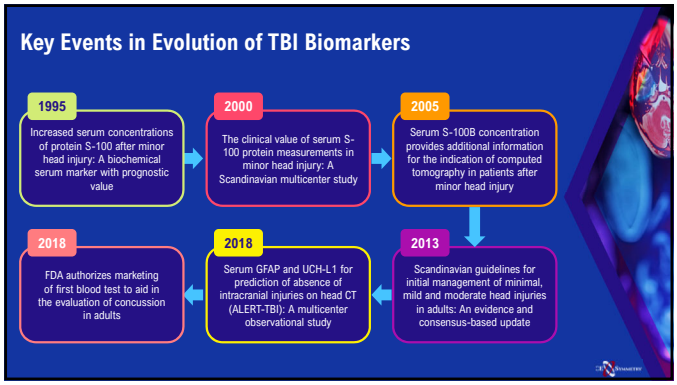

Advancements in the Recognition and Diagnosis of Traumatic Brain Injury
CE Symmetry

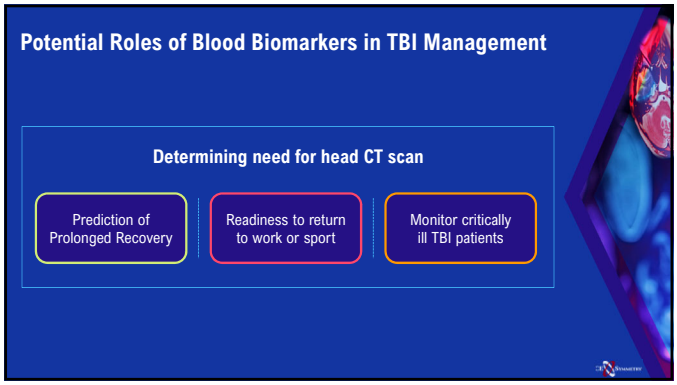

Mild Traumatic Brain Injury:
It's in the Blood
Deborah B. Diercks, MD, MSc
Professor and Chair, Department of Emergency Medicine
University of Texas Southwestern Medical Center


Learning Objectives
After participation in this educational activity, participants will be able to
Identify patients to utilize biomarker testing in the diagnosis of mild to moderate Traumatic Brain Injury
Determine patients that need head CT scans and those that may be diagnosed without head CT

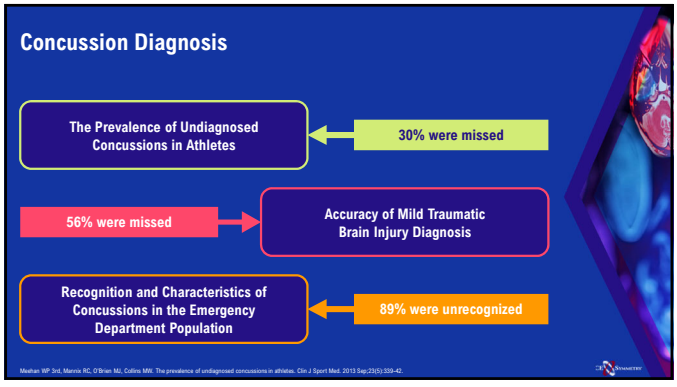
Key Events in Evolution of TBI Biomarkers



Potential Roles of Blood Biomarkers in TBI Management



Concussion Diagnosis

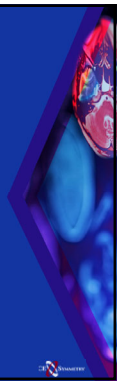


Diagnostic Issues

Reference standard for diagnosis is problematic		
	Disease	**No Disease**
Index Test+	TP	FP
Index Test-	FN	TN

Acute symptoms neither sensitive nor specific for concussion	
False +	**False -**
Syncope	Purposeful under-reporting
Seizure	Dementia
Acute stress disorder	Drug use
Migraine HA	
Cervical injury	
Drug use	

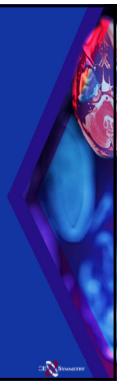
More objective reference standard needed – FDA Requirement / DOD Needs



Current ED Clinical Evaluation of Patients with Suspected Mild TBI

- Head CT Scan most everyone
- Selective head CT scanning
  - Clinician gestalt
  - Clinical guidelines (ACEP, Scandinavian Guidelines)
  - **Clinical decision rules**

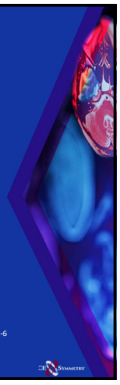
Goal: Reduce CT use without affecting patient outcomes



Clinical Decision Rules - CCTH Rule (2001)

- 3121 enrolled (only 67% scanned)
- 98·4% sensitive (96% – 99%) for "clinically important" brain injury
- 92·0% (88% - 94%) for any injury on CT
- For "clinically unimportant injury" the rule identified 70/94
  - Sensitivity 74.5% (64.4% - 82.9%)
- CT scans now higher resolution
- What about those not scanned?

Lancet. 2001 May 5;357(9266):1391-6



Canadian CT Head Rule

Instructions

Only apply to:

- Glasgow Coma Scale (GCS) 13–15 with LOC
- Amnesia to the head injury event
- Confusion

Exclusion Criteria:

- Age <16
- Blood thinners
- Seizure after injury

CCTH Rule Interpretation

High Risk Criteria

- GCS <15 (2 hrs post-injury)
- Suspected open or depressed skull fracture
- Signs of basilar skull fracture
- ≥2 episodes of vomiting
- Age ≥65 years

Medium Risk Criteria

- Retrograde amnesia ≥ 30 minutes
- "Dangerous" mechanism
  - Pedestrian struck by motor vehicle
  - Occupant ejected from motor vehicle
  - Fall from >3 feet or >5 stairs)

Canada - 1822 patients with GCS score of 15

Canadian Head CT rule

- Neurosurgical – 100% sensitive
- Clinically important injury
  - **Sensitivity 100%**
  - Specificity 50.6%

New Orleans Head CT rule

- Neurosurgical -100% sensitive
- Clinically important injury
  - Sensitivity 100%
  - **Specificity 12.7%**

Stiell, I. G., Clement, C. M., Rowe, B. H., Schull, M. J., Brison, R., Cass, D., Eisenhauer, M. A., et al., Comparison of the Canadian CT Head Rule and the New Orleans Criteria in patients with minor head injury. Jama, 2005, 294(12):1511-1518.

U.S. (314 Patients with GCS 15)

Canadian Head CT rule
- Neurosurgical – 100% sensitive
- Clinically important injury
  - **Sensitivity 100%**
  - Specificity 36.3%

New Orleans Head CT rule
- Neurosurgical -100% sensitive
- Clinically important injury
  - Sensitivity 100%
  - **Specificity 10.2%**

Pupa, L., Stiell, I. G., Clement, C. M., Pawlowicz, A., Wolfram, A., Braga, C., Draviam, S., et al., Performance of the Canadian CT Head Rule and the New Orleans Criteria for predicting any traumatic intracranial injury on computed tomography in a United States Level I trauma center, Acad Emerg Med, 2012, 19(1):2-10.

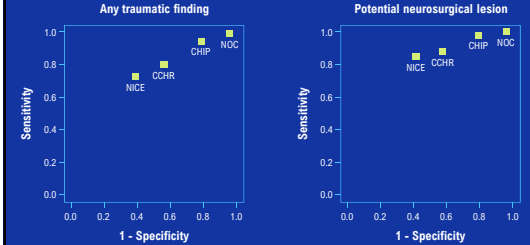
Netherlands - 3181 patients with a GCS score 13 to 15

Canadian Head CT rule
- Neurosurgical – 100% sensitive
- Clinically important injury
  - **Sensitivity 83.4%–87.2%**
  - Specificity 37.2%–39.7%

New Orleans Head CT rule
- Neurosurgical -100% sensitive
- Clinically important injury
  - Sensitivity 97.7%–99.4%
  - **Specificity 3.0%–5.6%**

Smits, M., Dippel, D. W., de Haan, G. G., Dekker, H. M., Vos, P. E., Kool, D. R., Nederkoorn, P. J., et al., External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury, Jama, 2005, 294(12):1519-1525.

Performance of the CT decision rules



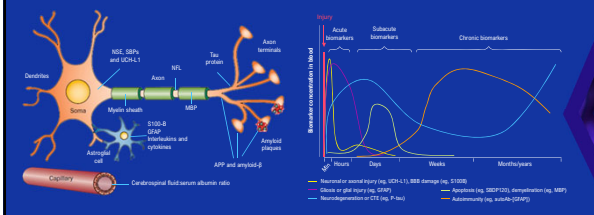
CT = computed tomography; CHIP = CT in head injury patient rule; NICE = National Institute for Health and Care Excellence; NOC = New Orleans Criteria; CCHR = Canadian CT Head Rule.
Foks KA, van den Brand CL, Lingsma HF, van der Naalt J, Jacobs B, de Jong E, et al. External validation of computed tomography decision rules for minor head injury: prospective, multicentre cohort study in the Netherlands. BMJ (Clinical research ed). 2019;362:k3537.

Difficulty Implementing CCTHR

- Intervention and control sites had and INCREASE in imaging (13.3% and 6.7%)
- **Increase 6.7% MORE in intervention sites (p=0.16)**
- 5.3% (95% CI 2.5% to 8.1%) reduction in CT use for given time points **(3.8% average reduction pre- and post-intervention periods)**

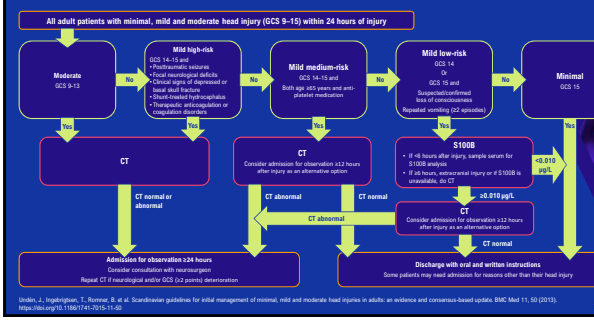
Stiell IG, Clement CM, Grimshaw JM, Brison RJ, Rowe BH, Lee JS, et al. A prospective cluster-randomized trial to implement the Canadian CT Head Rule in emergency departments. Cmaj. 2010;182:1527-32.
Sharp, A. L., Huang, B. Z., Tang, T., Shen, E., Malnick, E. R., Venkatesh, A. K., Kanter, M. H., et al., Implementation of the Canadian CT Head Rule and Its Association With Use of Computed Tomography Among Patients With Head Injury, Ann Emerg Med, 2018, 71(1):54-63.e52.

Origin and kinetics of brain biomarker proteins



Zetterberg, H., Smith, D. & Blennow, K. Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. Nat Rev Neurol 9, 201–210 (2013)
Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, Bragge P, Brazinova A, Büki A, Chesnut RM, Citerio G, Coburn M, Cooper DJ, Crowder AT, Czeiler E, Czosnyka M, Diaz-Arrastia R, Dreier JP, Duhaime AC, Ercole A, van Essen TA, Feigin VL, Gao G, Giacino J, Gonzalez-Lara LE, Gruen RL, Gupta D, Hartings JA, Hill S, Jiang JY, Ketharanathan N, Kompanje EJO, Lanyon L, Laureys S, Lecky F, Levin H, Lingsma HF, Maegele M, Majdan M, Manley G, Marseille J, Mascia L, McFadyen C, Mondello S, Newcombe V, Palotie A, Parizel PM, Peul W, Piercy J, Polinder S, Puybasset L, Rasmussen TE, Rossaint R, Smielewski P, Söderberg J, Stanworth SJ, Stein MB, von Steinbüchel N, Stewart W, Steyerberg EW, Stocchetti N, Synnot A, Te Ao B, Tenovuo O, Theadom A, Tibboel D, Videtta W, Wang KKW, Williams WH, Wilson L, Yaffe K; InTBIR Participants and Investigators. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol. 2017 Dec

Integration of S100B into clinical management guidelines in 2018



Undén, J., Ingebrigtsen, T., Romner, B. et al. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med 11, 50 (2013). https://doi.org/10.1186/1741-7015-11-50

Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): A multicentre observational study

Jeffrey J Bazarian[1], Peter Biberthaler[2], Robert D Welch[3], Lawrence M Lewis[4], Pal Barzo[5], Viktoria Bogner-Flatz[6], P Gunnar Brolinson[7], Andras Bukí[8], James Y Chen[9], Robert H Christenson[10], Dallas Hack[11], J Stephen Huff[12], Sandeep Johar[13], J Dedrick Jordan[14], Bernd A Leidel[15], Tobias Lindner[16], Elizabeth Ludington[16], David O Okonkwo[17], Joseph Ornato[18], W Frank Peacock[19], Kara Schmidt[20], Joseph A Tyndall[21], Arastoo Vossough[22], Andy S Jagoda[23]

Abstract

Background: More than 50 million people worldwide sustain a traumatic brain injury (TBI) annually. Detection of intracranial injuries relies on head CT, which is overused and resource intensive. Blood-based brain biomarkers hold the potential to predict absence of intracranial injury and thus reduce unnecessary head CT scanning. We sought to validate a test combining ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP), at predetermined cutoff values, to predict traumatic intracranial injuries on head CT scan acutely after TBI.

Methods: This prospective, multicentre observational trial included adults (≥18 years) presenting to participating emergency departments with suspected, non-penetrating TBI and a Glasgow Coma Scale score of 9–15. Patients were eligible if they had undergone head CT as part of standard emergency care and blood collection within 12 h of injury. UCH-L1 and GFAP were measured in serum and analysed using prespecified cutoff values of 327 pg/mL and 22 pg/mL, respectively. UCH-L1 and GFAP assay results were combined into a single test result that was compared with head CT results. The primary study outcomes were the sensitivity and the negative predictive value (NPV) of the test result for the detection of traumatic intracranial injury on head CT.

Findings: Between Dec 6, 2012, and March 20, 2014, 1977 patients were recruited, of whom 1959 had analysable data. 125 (6%) patients had CT-detected intracranial injuries and eight (<1%) had neurosurgically manageable injuries. 1288 (66%) patients had a positive UCH-L1 and GFAP test result and 671 (34%) had a negative test result. For detection of intracranial injury, the test had a sensitivity of 0·976 (95% CI 0·931–0·985) and an NPV of 0·996 (0·987–0·999). In three (<1%) of 1959 patients, the CT scan was positive when the test was negative.

Interpretation: These results show the high sensitivity and NPV of the UCH-L1 and GFAP test. This supports its potential clinical role for ruling out the need for a CT scan among patients with TBI presenting at emergency departments in whom a head CT is felt to be clinically indicated. Future studies to determine the value added by this biomarker test to head CT clinical decision rules could be warranted.

Funding: Banyan Biomarkers and US Army Medical Research and Materiel Command.

Bazarian JJ, Biberthaler P, Welch RD, Lewis LM, Barzo P, Bogner-Flatz V, et al. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. Lancet Neurol. 2018;17:782–9.

Study Design

- Non-penetrating head injury
- 18 years or greater with GCS 9 to 15 (n=1959)
- Subset GCS 14 to 15 (n= 1920)
- CT done as standard of care
- Blood sample obtained within 12 hours of injury
- Pre-specified cutoffs – (positive if either or both above)
  - UCH-L1 - 327 pg/mL
  - GFAP - 22 pg/mL

GFAP/UCH-L1 ELISA Platform (ALERT-TBI)

All Subjects, GCS 9-15 (n=1959)		
	CT+	CT-
Test+	122	1166
Test-	3	668

Mild TBI Subjects, GCS 14-15 (n=1920)		
	CT+	CT-
Test+	110	1144
Test-	3	663

Subjects	Sensitivity	Specificity	PPV	NPV	LR+	LR-
GCS 9–15 (n=1959)	0.976 (0.931–0.995)	0.364 (0.342–0.387)	0.095 (0.079–0.112)	0.996 (0.987–0.999)	1.5 (1.455–1.616)	0.07 (0.00–0.153)
GCS 14–15 (n=1920)	0.973 (0.924–0.994)	0.367 (0.345–0.390)	0.088 (0.073–0.105)	0.995 (0.987–0.999)	1.5 (1.457–1.618)	0.07 (0.00–0.159)

Bazarian JJ et al. Lancet Neurology 2018; 17(9):782-789

GFAP+UCH-L1: Hand-Held Device

Subjects w GCS 13-15 (n=1901)	CT+	CT-
Test+	115	1061
Test-	5	720

Subjects w GCS 15 (n=1798)	CT+	CT-
Test+	90	999
Test-	4	696

	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR-
GCS 13-15 (n=1901)	95.8 (90.6, 98.2)	40.4 (38.2, 42.7)	9.8 (8.2, 11.6)	99.3 (98.4, 99.7)	1.61 (1.51, 1.69)	0.10 (0.04, 0.23)
GCS 15 (n=1798)	95.7 (89.6, 98.3)	41.1 (38.7, 43.4)	8.3 (6.8, 9.8)	99.4 (98.5, 99.8)	1.63 (1.51, 1.71)	0.10 (0.04, 0.26)

Biarnian JJ et al. Acad Emerg Med 2021; 28(11):1308–1317

Main Study Population (GCS 14 and 15)

All study-defined CT findings

Table of CCTHR by CT	CT		
CCTHR	**CT+**	**CT-**	**Total**
Yes	47	379	426
No	**20**	473	493
Total	67	852	919

CCTHR

Sensitivity: 70.1% (57.7%–80.7%)

Specificity: 55.5% (52.1%–58.9%)

NPV: 5.5% (93.8%–97.5%)

Table of Assay by CT	CT		
Assay	**CT+**	**CT-**	**Total**
Positive	64	521	585
Negative	**3**	331	334
Total	67	852	919

Biomarker Assay

Sensitivity: 95.5% (87.5%–99.1%)

Specificity: 38.8% (35.6%–42.2%)

NPV: 99.1% (97.4%–99.8%)

Evaluation of Glial and Neuronal Blood Biomarkers Compared with Clinical Decision Rules in Assessing the Need for Computed Tomography in Patients with Mild Traumatic Brain Injury

Papa L, Laddie JG, O'Brien JF, et al. Evaluation of Glial and Neuronal Blood Biomarkers Compared With Clinical Decision Rules in Assessing the Need for Computed Tomography in Patients With Mild Traumatic Brain Injury. JAMA Netw Open. 2022;5(3):e221302. doi:10.1001/jamanetworkopen.2022.1302

Clinical Decision Rules vs GFAP and UCH-L1

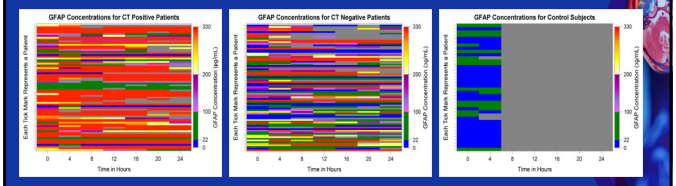
	CCHR + GFAP	NOC + GFAP
AUC	0.88	0.85
95% CI	[0.81-0.95]	[0.77-0.94]

Papa L, Ladde JG, O'Brien JF, et al. Evaluation of Glial and Neuronal Blood Biomarkers Compared With Clinical Decision Rules in Assessing the Need for Computed Tomography in Patients With Mild Traumatic Brain Injury. JAMA Netw Open. 2022;5(3):e221302. doi:10.1001/jamanetworkopen.2022.1302

	CCHR (n=346) (%)	NOC (n=344) (%)	NEXUS II (n=345) (%)
How comfortable would you be in following this rule for this patient?			
Very comfortable	49 (14)	46 (13)	52 (15)
Comfortable	162 (47)	158 (46)	140 (41)
Neutral/Unsure	83 (24)	93 (27)	67 (19)
Uncomfortable	31 (9)	36 (11)	68 (20)
Very uncomfortable	21 (6)	11 (3)	18 (5)

	CCHR (n=338) (%)	NOC (n=324) (%)	NEXUS II (n=341) (%)
Do you use this rule on a regular basis when evaluating MTBI patients for a head CT?			
I use this rule regularly	**89 (26)**	54 (16)	166 (49)

- 86% felt a blood test might or would be useful
- Only 13% not useful



Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study

John K Yue[1], Esther L Yuh[2], Frederick K Korley[3], Ethan A Winkler[1], Xiaoying Sun[4], Ross C Puffer[5], Hansen Deng[6], Winward Choy[1], Ankush Chandra[1], Sabrina R Taylor[1], Adam R Ferguson[1], J Russell Huie[1], Mitri Rabinowitz[2], Ava M Puccio[5], Pratik Mukherjee[2], Mary J Vassar[1], Kevin K W Wang[7], Ramon Diaz-Arrastia[8], David O Okonkwo[5], Sonia Jain[3], Geoffrey T Manley[3], TRACK-TBI Investigators

450 patients were CT negative:

- 120 MRI positive
- 330 MRI negative

Yue JK, Yuh EL, Korley FK, Winkler EA, Sun X, Puffer RC, et al. Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study. Lancet Neurol. 2019;18:953-61.

Where Now – ACEP Clinical Policy mTBI 2023

- **Level A recommendation** – "Use the Canadian CT Head Rule (CCHR) to provide decision support and improve head CT utilization in adults with a minor head injury."
- **Level B recommendations** – "Use the National Emergency X-Radiography Utilization Study (NEXUS) Head CT decision tool (NEXUS Head CT) or the New Orleans Criteria (NOC)… however, the lower specificity of the NEXUS Head CT and NOC compared with CCHR may lead to more unnecessary testing"

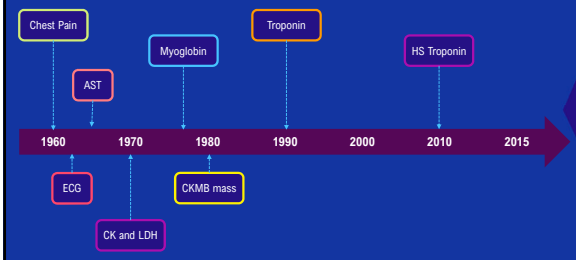
ACEP

- Serum biomarkers such as S-100, or GFAP may add additional information.
- "However, at this point, strong data on biomarker use with or without other decision tools is lacking and limited by the availability of these tests".
- EEG-based algorithms (artificial intelligence) may offer improved diagnostic capabilities (future)

Clinical Adoption in ED

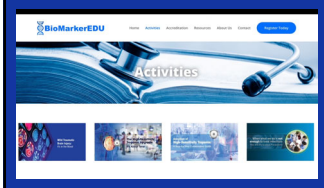
- Will providers order the test?
- Does testing impact ED operations & patient throughput?
- Are test results available in timely fashion (point-of-care whole blood)?
- Do patients accept the test (shared decision making)?
- Is the test cost effective?
- What to do with biomarker + patients with normal head CT scan?
  - Lack of expert mTBI clinics
- The "so what" factor
  - "Non-clinically important" CT findings
  - Nihilistic view of mTBI therapy in general

Timeline of the development of cardiac biomarkers for the diagnosis of acute myocardial infarction



Garg P, Morris P, Fazlanie AL, Vijayan S, Dancso B, Dastidar AG, et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. Intern Emerg Med. 2017;12:147-55.

Additional BioMarker Educational Content – BioMarkerEDU.com



- Extensive collection of additional BioMarker content
  - TBI,
  - HS Troponin
  - Sepsis
- More than 8 hours of content in short, independently accredited sessions
  - 6 TBI videos
  - 14 hs cTn videos
  - 1 procalcitonin video
- No fee to obtain CME credit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