Biomarkers for Traumatic Brain Injury in Pediatrics

Nebraska State Trauma Symposium

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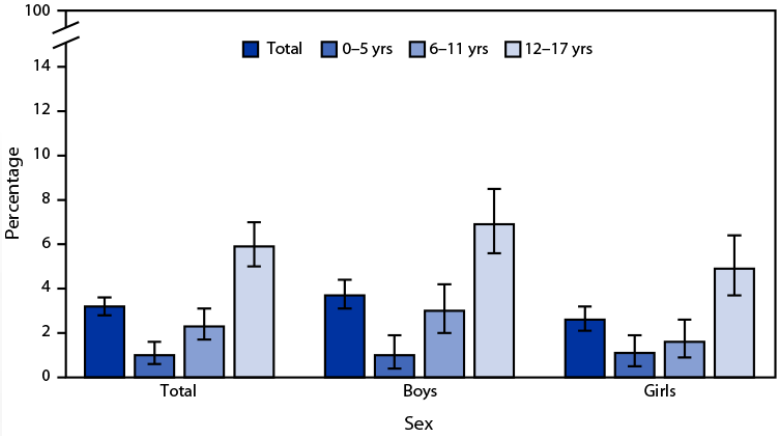
No disclosures

National Center for Health Statistics

In 2022, **2.3 million** (3.2%) children and adolescents aged ≤17 years had ever received a diagnosis of a concussion or brain injury.



National Center for Health Statistics, National Health Interview Survey, 2022.

In 2013, of children <15 years
- 1,500 deaths
- 18,000 hospitalizations
- 640,000 ED visits
- 75% minor, mild, concussion

Surveillance Summaries / March 17, 2017 / 66(9);1–16

CDC Guidelines

Key Recommendations from the CDC Pediatric mTBI Guideline:

1. Do not routinely image patients to diagnose mTBI.
2. Use validated, age-appropriate symptom scales to diagnose mTBI.
3. Assess evidence-based risk factors for prolonged recovery.
4. Provide patients with instructions on return to activity customized to their symptoms.
5. Counsel patients to return gradually to non-sports activities after no more than 1 to 2 days of rest.

PECARN: Imaging

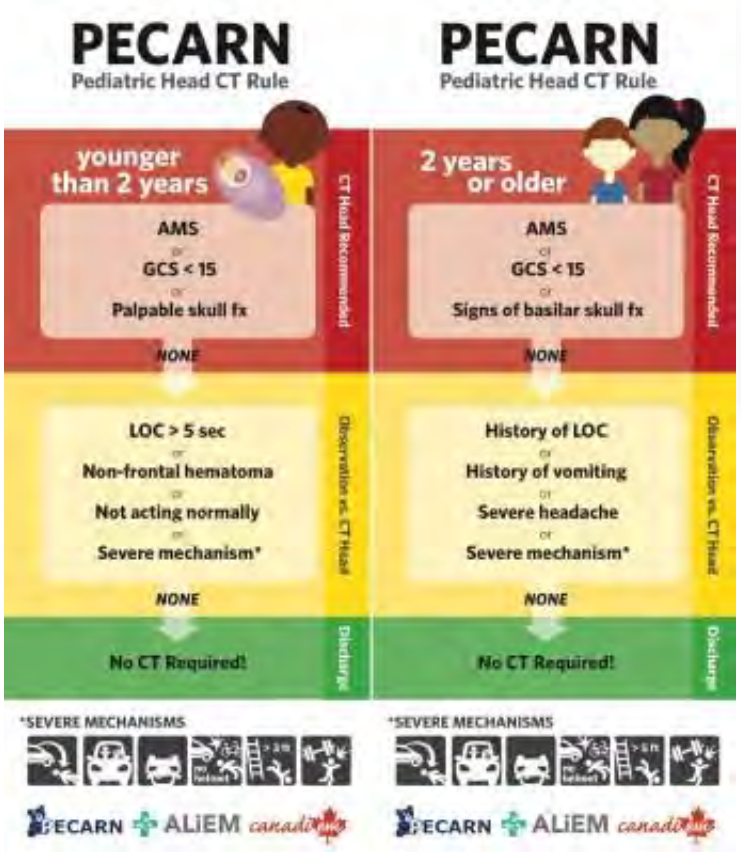
Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study

Lancet 2009; 374: 1160–70

*Nathan Kuppermann, James F Holmes, Peter S Dayan, John D Hoyle, Jr, Shireen M Atabaki, Richard Holubkov, Frances M Nadel, David Monroe, Rachel M Stanley, Dominic A Borgialli, Mohamed K Badawy, Jeff E Schunk, Kimberly S Quayle, Prashant Mahajan, Richard Lichenstein, Kathleen A Lillis, Michael G Tunik, Elizabeth S Jacobs, James M Callahan, Marc H Gorelick, Todd F Glass, Lois K Lee, Michael C Bachman, Arthur Cooper, Elizabeth C Powell, Michael J Gerardi, Kraig A Melville, J Paul Muizelaar, David H Wisner, Sally Jo Zuspan, J Michael Dean, Sandra L Wootton-Gorges, for the Pediatric Emergency Care Applied Research Network (PECARN)**

June 2004-March 2006, 25 EDs
<18 yo, GCS 14-15
42,412 enrolled
35.3% with CT scans

- **5.2%** positive scans
- **0.9%** had clinically significant TBI (death, neurosurgery, intubation >=24h, admission >=2 nights)
- **0.1%** underwent neurosurgery



PECARN Compliance?

Use of CT for Head Trauma: 2007–2015

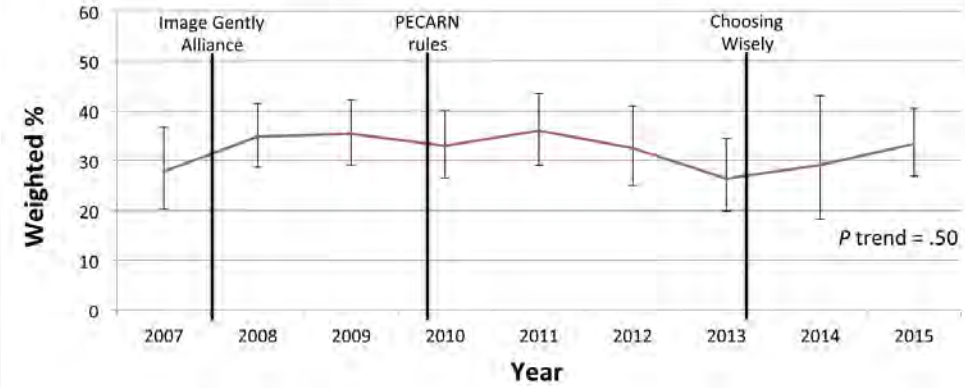
Brett Burstein, MD CM, PhD, MPH,[a,b] Julia E.M. Upton, MD, MPH,[b,c] Heloisa Fuzaro Terra, DDS, MPH,[b,d] Mark I. Neuman, MD, MPH[e]

PEDIATRICS Volume 142, number 4, October 2018:e20180814

National Hospital Ambulatory Medical Care Survey (NHAMCS)

Data on ~30,000 annual visits from 300 randomly selected US EDs

- Inclusion: <18yo, chief complaint or discharge diagnosis of **head injury**
- Outcome: CT use prior to and after publication of PECARN rules (2009)



Factors associated with ↑CT

- Age >= 2 years
- White race
- Higher acuity
- Non-teaching or non-pediatric hospital

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Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

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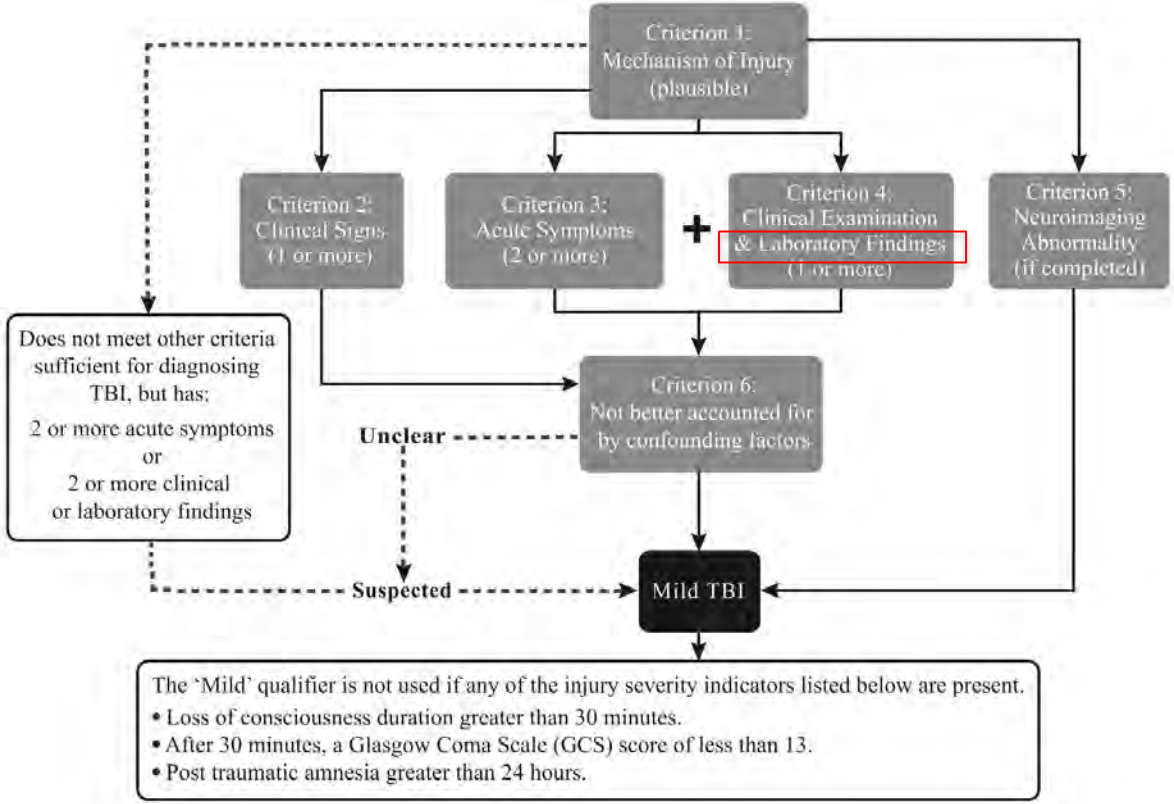
Brain Injury

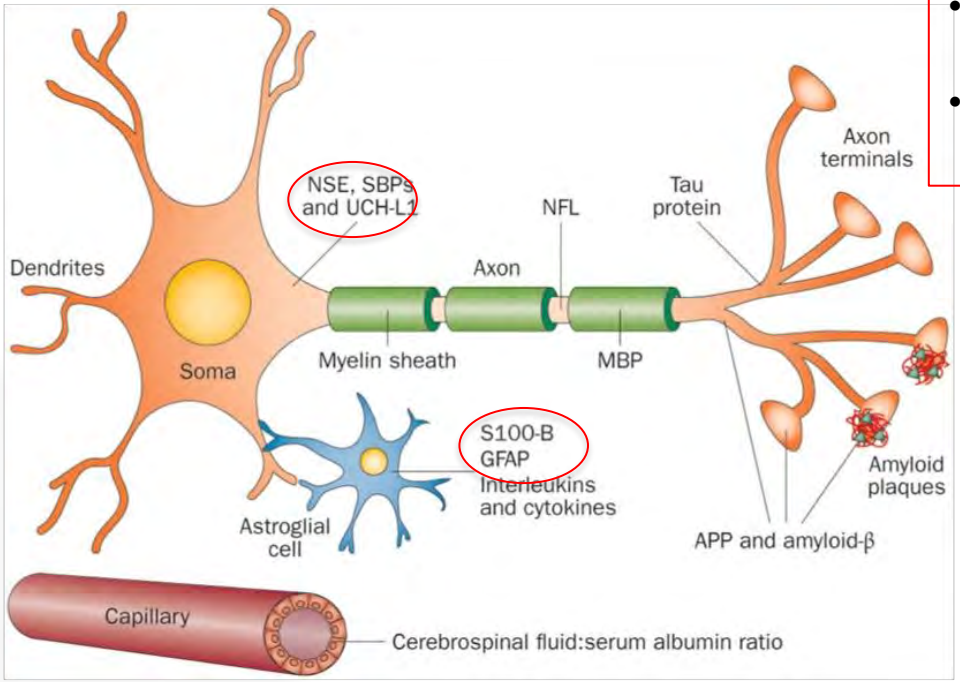


Biomarker platform for prediction of positive CT findings in mild TBI

2018

2024

Biomarkers of TBI?



Ubiquitin C-terminal hydrolase-L1 (UCH-L1)
Cytoplasmic deubiquitinating enzyme

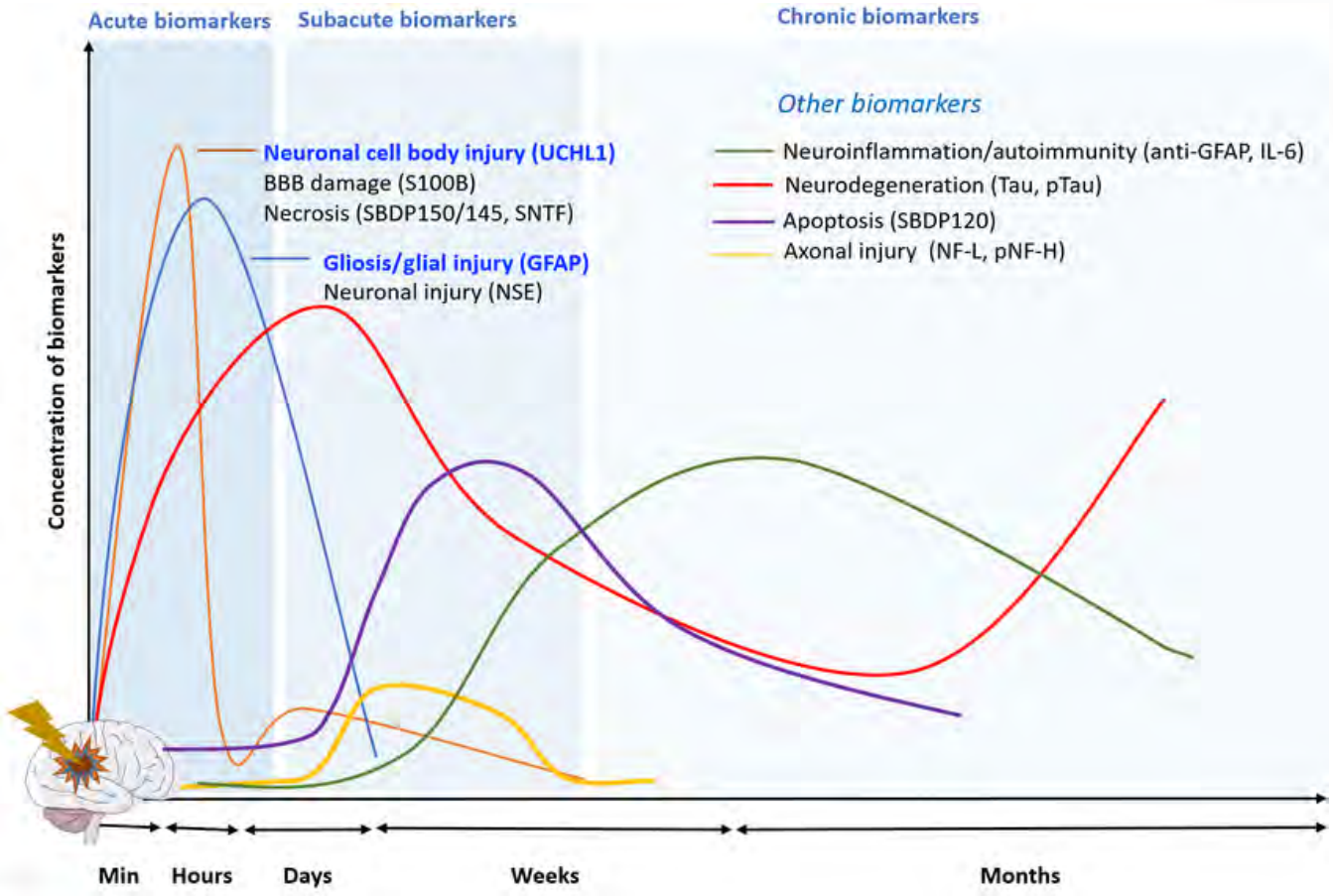
- Removes excessive, misfolded, or oxidized proteins via control of proteasome pathway
- Specific to **neurons**

Glial fibrillary acid protein (GFAP)
Main component of **astroglial** cytoskeleton

- Structure and mechanical strength
- Support of BBB

Upregulated during **astrocyte activation**
Released during **astrocytic death**

Biomarkers - GLIA Diagnostics



Acute Medicine & Surgery 2021;**8**:e622

Adults

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: 782–89

Jeffrey J Bazarian, Peter Biberthaler*, Robert D Welch, Lawrence M Lewis, Pal Barzo, Viktoria Bogner-Flatz, P Gunnar Brolinson, Andras Büki, James Y Chen, Robert H Christenson, Dallas Hack, J Stephen Huff, Sandeep Johar, J Dedrick Jordan, Bernd A Leidel, Tobias Lindner, Elizabeth Ludington, David O Okonkwo, Joseph Ornato, W Frank Peacock, Kara Schmidt, Joseph A Tyndall, Arastoo Vossough, Andy S Jagoda*

22 sites (15 US, 7 EU), N=1959 (+HCT 125)

- Age >18
- GCS 9-15
- HCT within **12 hours of injury**
- Blood within 12 hours of injury

Cut-off values determined from independent group of 334 subjects

	Sensitivity	Specificity	PPV	NPV	LRP	LRN
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)
Neurosurgically manageable lesions (n=8)	1·00 (0·631–1·00)	0·344 (0·323–0·365)	0·006 (0·003–0·012)	1·00 (0·995–1·00)	1·5 (1·447–1·602)	0·0 (0·00–0·093)

Data in parentheses are 95% CIs. PPV=positive predictive value. NPV=negative predictive value. LRP=likelihood ratio positive. LRN=likelihood ratio negative.

Table 3: **Performance of UCH-L1 and GFAP assay for predicting intracranial injury on head CT scan**

Age and normal values

www.thelancet.com/child-adolescent Vol 9 January 2025

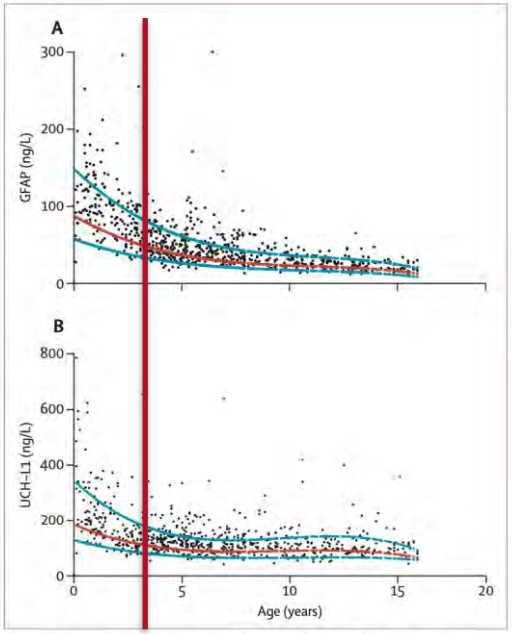
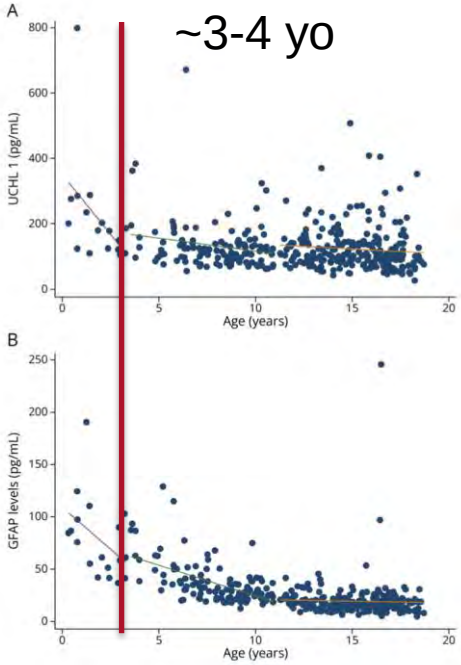


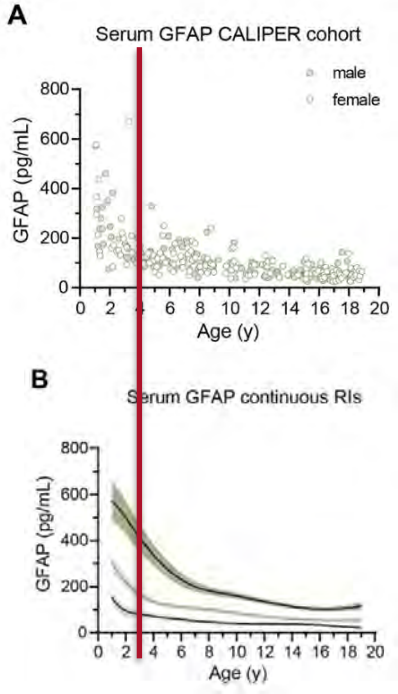
Figure 1: **Quantile regression analysis of serum GFAP (A) and UCH-L1 (B) concentrations in the control group by use of the Alinity (Abbott, Chicago, IL, USA) method**

Serum GFAP and UCH-L1 concentrations were established in a cohort of 718 children without any neurological pathology aged 0–16 years. The blue lines show the 0·25 and 0·75 quantile concentrations. The red lines show the 0·5 quantile concentrations.

~3-4 yo



Neurology | Volume 103, Number 3 | August 13, 2024



Stukas et al.: Pediatric normative serum NF-L and GFAP

Children

ARTICLES · Volume 9, Issue 1, P47-56, January 2025 Download Full Issue

Serum GFAP and UCH-L1 for the identification of clinically important traumatic brain injury in children in France: a diagnostic accuracy substudy

www.thelancet.com/child-adolescent Vol 9 January 2025

Antoine Puravet, PharmD [a,c] · Charlotte Oris, PharmD PhD [a] · Bruno Pereira, PhD [b] · Samy Kahouadji, PharmD [a,c] · Prof Philippe Gonzalo, PharmD PhD [d] · Prof Damien Masson, PharmD PhD [e] · et al. Show more

Children <= 16yo (11 EDs)

- Within **3 hours** of TBI
- GCS 15
- Head CT (intermediate PECARN)

Reference values from 718 control children, >95% percentile for each age group

”Clinically important” TBI

- Positive CT scan with +2 days admission
- Neurosurgery
- PICU admission
- Death

N=531 mTBI
10 ciTBI
14 +HCT

	S100B	GFAP	UCH-L1	GFAP or UCH-L1	GFAP and UCH-L1
Sensitivity (95% CI)	90% (56–100)	100% (69–100)	100% (69–100)	100% (69–100)	100% (69–100)
Specificity (95% CI)	63% (59–67)	50% (45–54)	51% (47–56)	34% (30–38)	67% (63–71)
Positive predictive value (95% CI)	5% (2–10)	4% (2–7)	4% (2–7)	3% (1–5)	6% (3–10)
Negative predictive value (95% CI)	100% (98–100)	100% (99–100)	100% (99–100)	100% (98–100)	100% (99–100)
Area under the curve (95% CI)	0·77 (0·67–0·87)	0·75 (0·73–0·77)	0·76 (0·74–0·78)	0·67 (0·65–0·69)	0·83 (0·81–0·85)
Positive likelihood ratio (95% CI)	2·43 (1·92–3·07)	1·98 (1·82–2·16)	2·05 (1·88–2·24)	1·51 (1·42–1·61)	3·01 (2·67–3·40)
Negative likelihood ratio (95% CI)	0·16 (0·02–1·02)	0	0	0	0

Biomarker concentrations above the threshold value to define a positive test. ciTBI is defined by hospitalisation of more than 2 days with lesions in cranial CT or hospitalisation in intensive care or neurosurgical intervention. ciTBI=clinically important traumatic brain injury.

Table 4: **Performance of biomarker assays for predicting ciTBI**

TBI at Children's Nebraska

January 2020-December 2023

Trauma Quality Improvement Program (TQIP) database (trauma activations and admissions)

894 Admitted with labs

349 Positive cranial imaging for head/face injury

<18 years old
MOI consistent with TBI
HCT and blood test <24h

May 2025 to present

N = 33
+HCT = 14
Mean age = 7.21 +/- 6.66 SD (1 day – 17.9)
Mean GCS = 14.76 +/- 0.56 (13-15)

	GFAP	UCHL1	Either
Sensitivity	**0.93**	0.57	**1.00**
Specificity	0.63	0.68	0.53
NPV	**0.92**	0.68	**1.00**
PPV	0.65	0.57	0.61

Could have saved 10 patients from HCT (**30%**)

Future Directions

- Use of biomarkers for clinical decision making in children (at least in 4-17 year olds)
- Utility of test to predict out-comes and diagnose ”concussion”
- Utility of test to screen for NAT in babies
- Non-TBI applications

Collaborators

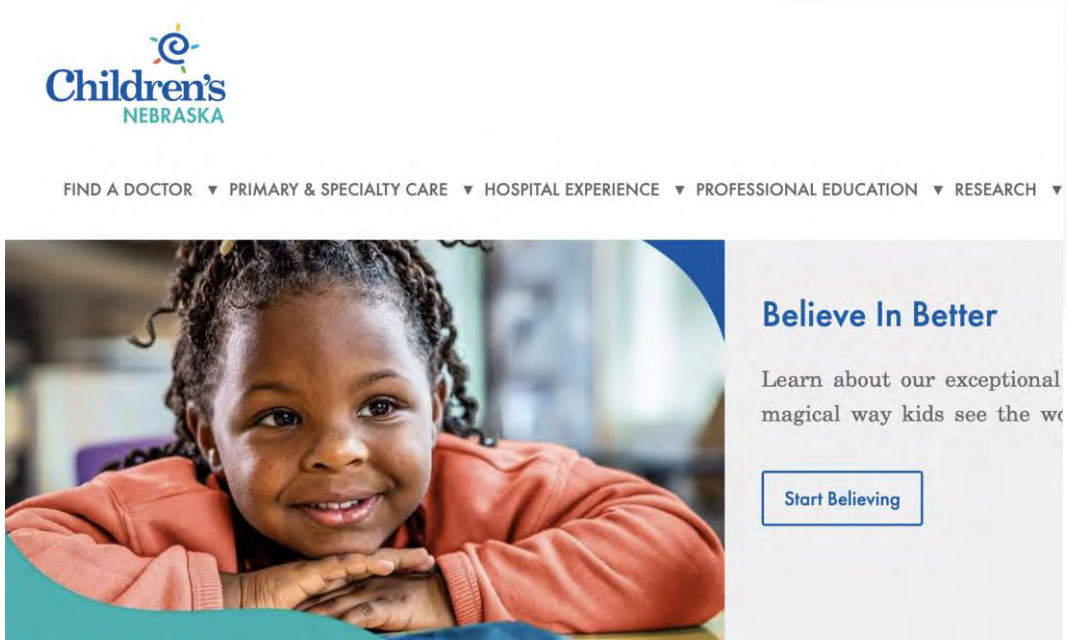
Neurosurgery
Grace Lai, Arnett Klugh
Megan McChesney

ED
Zebulon Timmons, James Buscher
Nursing Staff

Trauma
Patrick Thomas

Child Abuse Pediatrics
Suzanne Haney

Lab
Christopher North
Lab Staff



Child Health Research Institute

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