Canadian Agency for Drugs and Technologies in Health

Issues in Emerging Health Technologies

Serum Biomarkers to Diagnose Mild Traumatic Brain Injury in Adults

Issue 122 • March 2014

Summary

- ✓ **Traumatic brain injury (TBI) is a significant public health issue. Mild TBI (mTBI) makes up about 80% of cases and can have long-term adverse effects. However, mTBI poses a diagnostic challenge, as imaging is often unhelpful and patient history may be unreliable. Objective measures are being sought to aid in diagnosis, including serum biomarkers. The most commonly reported biomarkers in the literature are serum protein S-100B, neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), and ubiquitin C-terminal hydrolase-L1 (UCH-L1).**
- ✓ **Although serum biomarkers for TBI are in limited use in Europe and Asia, there has been little uptake in North America to date.**
- ✓ **Five recent studies of serum biomarkers for the diagnosis of mTBI were identified. Two examined S-100B, two examined a combination of S-100B and GFAP, and one examined a combination of S-100B and apolipoprotein AI (apo AI). Study results showed that biomarkers will identify most patients with mTBI and will rule out most patients without mTBI; however, a significant number of patients will have false-positive results; i.e., they will be labelled as being affected when they are not and could undergo unnecessary testing and treatment.**
- ✓ **The search for suitable serum biomarkers continues in an effort to identify useful, accurate, and minimally invasive tests to identify patients affected by mTBI.**

The Technology

TBI is a major public health concern. Mild TBI (mTBI), also known as concussion, makes up 70% to 90% of cases of TBI[1-5] and results from rapid acceleration or deceleration (e.g., due to motor vehicle accidents and falls); direct impact (e.g., during sports); or explosions (e.g., military blast injuries). The morbidity associated with mTBI is considerable, as about 50% of patients are left with a residual disability.[6,7]

The diagnosis of mTBI is challenging because the injury-related symptoms are often not associated with any specific findings on imaging (computed tomography [CT] or magnetic resonance imaging [MRI]), and most patients are neurologically intact with a normal Glasgow Coma Scale (GCS) score.[1,2,8] Also, diagnosis may be based on patient self-report, which may be unreliable.[8] (See Current Practice on page 2 for issues concerning the definition of mTBI.)

The accuracy of mTBI diagnosis could be increased with the use of objective indicators that augment clinical and radiological assessment.[4] Biomarkers in body fluids are cellular components related to injury or disease; for TBI, brain-specific biomarkers are released into the bloodstream after cellular damage.[7] An ideal biomarker should appear only in the pathological state of interest and should not be present under normal conditions. [5]

A number of biomarkers, both singly and in combination, are under investigation for early and accurate diagnosis (and prognosis) of mTBI, to overcome the fact that CT and MRI are often unhelpful for mTBI and to decrease unnecessary imaging for patients unlikely to have positive results (Table 1).[1,7] Cerebrospinal fluid and peripheral blood samples are the most common sources of biomarkers, the latter being preferred, as blood sampling is much more accessible and does not involve an invasive process. The goal of research in this area is to identify a specific test that can be routinely performed in emergency departments for mTBI diagnosis and prognosis.

Reagents and other supplies for biomarker testing are available from a number of companies, including Aviva Systems Biology (California, United States [US], and Beijing, China), Banyan Biomarkers (California and Florida, US), Roche Diagnostics (Quebec, Canada, and Mannheim, Germany), and Sino Biological Inc. (Beijing, China).

Table 1: Commonly Cited Serum Biomarkers Being Explored for mTBI Diagnosis	
Serum Biomarker (Listed Alphabetically)	**Description**
Apo AI)	A negative marker of inflammation, decreasing more than 25% during sepsis and burns
BDPs	Products of protein breakdown, including SBDP 145 and SBDP 150 (found in presynaptic terminals and axons)
GFAP	Brain-specific protein found in glial cells
MBP	Abundant protein found in myelin
NSE	Protein found in neurons but also in other cell types
S-100B	Astrocyte protein; most extensively studied biomarker
UCH-L1	Cytoplasmic protein found specifically in neurons

Apo AI = apolipoprotein; BDP = breakdown product; CNS = central nervous system; GFAP = glial fibrillary acidic protein; MBP = myelin basic protein; NSE = neuron-specific enolase; S-100B = serum protein S-100B; SBDP = spectrin breakdown product; UCH-L1 = ubiquitin C-terminal hydrolase-L1.
From Bazarian et al. (2013),[9] Di Battista et al. (2013)[1], and Jetter et al. (2013).[8]

Regulatory Status

Some laboratory tests enter clinical practice directly; however, the biomarkers S-100 and NSE have received Health Canada regulatory approval (licence numbers 69534 and 38986, respectively). (Mr. Steve Lambert, Roche Diagnostics, Laval [QC]: personal communication, 2014, Feb. 14).

Patient Group

The annual incidence of TBI (mild, moderate, and severe) is estimated to be at least 600 per 100,000 people in North America and Europe, with two-thirds of cases occurring in males; the young and the elderly are most commonly affected.[11] About 80% of TBIs are considered mTBIs. Data from Ontario indicate an incidence of hospital-treated mTBI of 535 per 100,000 if only patients in the care of specialists are included, and 653 per 100,000 if patients who are cared for by family physicians are also included.[12] The Canadian Institute for Health Information reported about 15,300 hospitalizations for all types of TBIs in 2003-2004, representing 9% of all trauma admissions. About one in twelve of these patients died, a mortality rate twice that of patients admitted for non-TBI traumatic injury.[13]

US data report 1.4 million TBIs annually, including 1.1 million emergency department visits, 235,000 hospitalizations, 50,000 deaths, and an annual cost of more than $16 billion; these data underestimate the true burden because they do not include patients treated in outpatient hospital settings, physicians' offices, or military facilities (at home or abroad).[4,7,14]

In the US military, there is growing interest in TBI due to blast injuries sustained in recent conflicts, as well as increasing recognition of mTBI sequelae.[15]

The range of mTBI symptoms is broad and varied:[8]

- Neurological; i.e., headache, vomiting, nausea, dizziness, fatigue, drowsiness, sensitivity to light or noise, tinnitus, sleep disturbances, and problems with balance and vision
- Cognitive; i.e., problems with attention, concentration, memory, processing speed, and executive functions (e.g., working memory and decision-making)
- Behavioural; i.e., anxiety, irritability, aggression, and depression.

Symptoms resolve for most patients within 14 days; however, the symptoms can continue much longer for 25% of those affected.[8]

Current Practice

In order to assess and treat mTBI, a clear definition of the disorder is necessary; however, differences exist in the available diagnostic criteria because of the heterogeneity in trauma mechanism and symptom presentation, difficulties in detecting signs and symptoms of injury, and disputes over the use of the term mTBI versus concussion.[1,8] A number of expert bodies have issued diagnostic criteria. For example, guidance from the American Congress of Rehabilitation Medicine includes one or more of:[7,15,16]

- Loss of consciousness (LOC) of up to 30 minutes
- Loss of memory for events immediately before or after the injury for up to 24 hours

- Alterations in mental status (dazed, disoriented, or confused) at the time of the injury
- Focal neurological deficits that may or may not be transient but where the severity of the injury does not exceed:
  - Thirty minutes of LOC
  - Post-traumatic amnesia longer than 24 hours, or
  - GCS score falling below 13 after 30 minutes.

Diagnostic criteria for mTBI published by the government-funded Ontario Neurotrauma Foundation include (in brief): (a) rapid onset of short-lived impairment of neurological function that resolves spontaneously (may evolve over minutes to hours); (b) often no abnormality on standard structural neuroimaging studies; and (c) a graded set of clinical symptoms that may or may not involve LOC.[17] In Canada, current practice is to diagnose mTBI based on clinical findings augmented by imaging in some cases; i.e., biomarkers are not employed.

Methods

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, Embase, PubMed, and The Cochrane Library (Dec. 2013). Grey literature was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/grey-matters). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2008, and December 11, 2013. Regular alerts were established to update the search until the publication of the bulletin.

Citations were selected if they included adult patients with head injuries who were tested for one or more serum biomarkers to establish the diagnosis of mTBI.

The Evidence

Our literature search identified 21 recent primary studies on serum biomarkers for TBI diagnosis (S-100B, six studies; GFAP, two studies; UCH-L1, two studies; SBDP 150, one study; and combinations, 10 studies). Of the full publications (versus those available only as abstracts), five were limited to patients with mTBI and had a sample size of at least 10.

S-100B:

- Researchers in Spain prospectively tested the screening performance of S-100B six hours post-injury in 143 patients with mTBI (62% male, mean age 49, ± standard deviation [SD] 21 years).[18] All patients had normal GCS scores of 15 but at least one neurological symptom such as LOC, amnesia, or headache. S-100B was used as an early marker, as its half-life is 120 minutes with 98% sensitivity for TBI at three hours.[19] CT scans performed within 24 hours post-injury showed that 15 patients (11%) had some brain damage. Six-hour mean S-100B levels were significantly higher in these patients (0.59 mcg/L [95% confidence interval (CI), 0.36 to 0.81] versus 0.37 mcg/L [95% CI, 0.30 to 0.44]; $P = 0.007$); three-hour testing showed a similar degree of discrimination. Test sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were dependent on the cut-off value for S-100B. At the most common S-100B cut-off of 0.105 mcg/L, test sensitivity and NPV were 100%, although specificity and PPV were 27% and 14%, respectively. The authors concluded that S-100B is an effective biochemical indicator of brain damage due to mTBI within six hours of injury in patients without a decrease in consciousness.
- At a peripheral trauma centre in Switzerland with limited CT resources, researchers explored whether the use of S-100B could help triage patients with mTBI as to the need for CT scanning.[19] Prospectively enrolled in the study were 233 consecutive patients with mTBI (61% male, mean age 48 years [range 11 to 97], mean time from injury 2.3 hours) and GCS scores of 13 to 15. S-100B was elevated beyond the cut-off value of 0.105 mcg/L in 169 patients (73%). CT scans were positive in 22 patients (9%); 19 (86%) had elevated S-100B. Test parameters for S-100B as a selection tool for CT were sensitivity and NPV of 86%, specificity 12%, and PPV 13%. The authors concluded that S-100B could be a useful biomarker for CT triage, thus decreasing radiation exposure and freeing up scarce CT resources.

S-100B and NSE:

- At a trauma centre in Austria, researchers prospectively enrolled 107 patients with mTBI and GCS scores of 13 to 15 within three hours of injury (56% male; mean age 59, SD 23 years).[10] They assessed whether increases in S-100B and NSE plus high-risk clinical factors (nausea, amnesia,

vomiting, or LOC) were associated with abnormal CT results. A step-wise analysis was performed to study the relationships among biomarkers, clinical factors, and CT findings. Results showed that 25 patients (23%) had traumatic lesions on head CT: bleeding in 20 (subarachnoid, subdural, or intracerebral) and cerebral contusion in five. These 25 patients had more nausea and vomiting, as well as significantly higher S-100B and NSE values based on receiver operating characteristic and area under the curve analyses. Sensitivity and specificity were calculated as 72% and 37% for S-100B and 53% and 15% for NSE, respectively. (The diagnostic accuracy of the two biomarkers used in combination was not reported.) The authors noted the use of biomarkers plus assessment of the high-risk factors of nausea, vomiting, amnesia, and LOC is safe and reliable in determining a diagnosis, and S-100B and NSE may serve as interim tools until more brain-specific markers — e.g., GFAP and UCH-L1 — are widely available.

S-100B and GFAP:

- Researchers in the Netherlands prospectively enrolled 94 consecutive patients with mTBI (mean age 34 ± SD 14 years; GCS scores of 13 to 15) to analyze the relationships of S-100B and GFAP with imaging findings.[20] Serum biomarkers were assessed on admission (within three hours of injury), and results showed GFAP values were increased in patients with abnormal versus normal CT scans (mean 1.2 mcg/L [SD 2.65] versus 0.05 mcg/L [SD 0.17], respectively; $P < 0.05$). A significant difference in GFAP was also noted for patients with damage seen on MRI. However, S-100B was not related to results of imaging studies or to patient outcomes. There were no performance results given for the two biomarkers used in combination.

Combination of S-100B and apo AI:

- In a prospective comparative study in six upstate New York hospitals, researchers assessed the classification accuracy of S-100B and apo AI, separately and together, for mTBI and the likelihood of predicting an abnormal initial head CT scan result.[9] The study's lead author was a consultant for Banyan Biomarkers and Roche Diagnostics. The mTBI arm included 787 patients who presented within six hours of injury (mean age 38 years; 63% male, 82% Caucasian, and 15% African-American). A control arm included 467 people who received routine blood work. Test performance varied greatly depending on the biomarker cut-off values. At cut-off values defined by 90% of controls, both S-100B and apo AI exhibited 25% sensitivity and 90% specificity. Combining the biomarkers increased classification accuracy. S-100B was better than apo AI at predicting an abnormal CT scan result, with performance dependent on the chosen cut-off value for S-100B. A 90% sensitivity cut-off would have resulted in avoidance of 31% of CT scans, although six subjects would have been missed, whereas with a 98% sensitivity cut-off, 23% of CT scans could have been avoided with one subject missed. S-100B was more accurate in Caucasians and adults than it was in African-Americans and children.

Adverse Effects

No adverse effects were mentioned in any of the included studies. However, no direct adverse effects of peripheral serum tests would be expected, aside from the potential harms flowing from false-negative and false-positive results. False-negative results may lead to delays in diagnosis and treatment and to increased morbidity and mortality, whereas false-positive results can lead to unnecessary treatment.

Administration and Cost

One economic study was identified in which New York state researchers estimated the economic impact of S-100B as a screening test before head CT on emergency department management of adults with isolated mTBI versus usual care.[2] All patients were assigned a normal GCS of 15 because CT scanning in this group can be controversial. The researchers used a decision-tree model to compare the hospital costs in the first 48 hours that were associated with ordering a head CT based on presenting symptoms versus the costs of patients receiving a head CT only if the S-100B level was abnormal (> 0.1 mcg/L).

It was assumed that patients not triaged to CT were discharged (thus freeing up emergency beds), S-100B test cost was $20, additional hours spent awaiting results were valued at $380 per hour, and CT results were delayed by at least one hour beyond laboratory test results. For the usual care arm, it was assumed, based on a literature review, that 45% to 77% (mean 61%) of adult patients were triaged to CT.

For the S-100B arm, proceeding to CT was based on literature-reported test sensitivity and specificity of 97% and 30%, respectively. Sensitivity analyses explored differences due to rates of CT scanning, length of waits for results, and waiting time costs.

Results showed that S-100B screening would cost a mean of $281 per patient-case, while current practice (i.e., CT based on symptoms and physician discretion) would cost $160. However, sensitivity analyses showed S-100B became cost-lowering when the proportion of mTBI patients being scanned based on symptoms and physician discretion was very high (> 78%) or when CT scan results were delayed 1.5 hours more than S-100B results. The authors concluded that the low specificity and poor positive predictive value of S-100B limited its ability to reduce the number of CT scans performed or to lower hospital costs. However, the use of S-100B could result in lower costs if the turnaround time was lower than for CT, or if CT scan rates for mTBI patients were relatively high as part of usual care.

Concurrent Developments

A number of serum biomarkers are being explored to aid in the diagnosis of mild, moderate, and severe TBI, both alone and in combination.[21] There is also interest in the ability of biomarkers to aid in prognosis. For example, a prospective Canadian study examining the added value of S-100B and NSE measurements on patient outcomes after mTBI showed that elevated S-100B on admission, along with other indicators, was predictive of poor outcome at one week; whereas elevated NSE, along with other indicators, was predictive of poor outcome at six weeks.[22] The authors concluded that these biomarkers, in conjunction with patient testing and questionnaires, as well as clinical and neurological examinations, aided in prognosis, although their stand-alone benefit was limited. In contrast, a Dutch study did not find that S-100B or GFAP levels obtained on admission were predictive of mTBI patient outcomes six months post-injury (i.e., regression analyses did not show significance).[20] A US study also noted that supportive data for biomarkers in mTBI prognosis are sparse, as studies are small and have design issues; therefore, biomarkers are not yet a reliable modality for clinical decision-making.[23]

Genetic characteristics are also under investigation for predicting outcomes following neurotrauma, with the most documented being apoliproprotein E (apo E). For example, in a study of 70 children, those with an apo E epsilon4 genotype were more likely to have severe clinical symptoms and unfavourable neurological outcomes one year post-TBI.[24]

Rate of Technology Diffusion

Reluctance to adopt biomarkers for mTBI is due in part to their low specificity and to reports that non-cranial injuries also contribute to biomarker elevations (e.g., some biomarkers are present in bone marrow and adipose tissue).[22,25] However, several biomarkers are in use for TBI diagnosis and prognosis in European countries (e.g., S-100B, NEP, GFAP, and UCH-L1); in fact, Scandinavian guidelines for management of head injury in adults have recently been updated to include indications for S-100B testing.[25,26] Despite this, serum biomarkers for TBI have not been introduced in the US or Canada, although studies are ongoing in North America.[7,9,22,27,28]

Implementation Issues

Because of the common occurrence of mTBI, increasing recognition of the negative outcomes many patients suffer, the challenges inherent in making a diagnosis, and the high cost of and limitations in access to CT and MRI, the use of serum biomarkers upon presentation of patients with suspected mTBI is an appealing concept.[4] However, despite an international flurry of research activity, the ideal biomarker(s) have not yet been developed. Some candidate tests demonstrate high sensitivity and NPV; however, poor performance with respect to specificity and PPV limits their clinical utility. Widespread implementation of one or more serum biomarkers for mTBI may be unlikely until test performance improves to the point where unaffected patients can be reliably identified.

References

1. Di Battista AP, Rhind SG, Baker AJ. Application of blood-based biomarkers in human mild traumatic brain injury. Front Neurol [Internet]. 2013 [cited 2014 Feb 13];4:44. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3640204

2. Ruan S, Noyes K, Bazarian JJ. The economic impact of S-100B as a pre-head CT screening test on emergency department management of adult patients with mild traumatic brain injury. J Neurotrauma [Internet]. 2009 Oct [cited 2013 Dec 16];26(10):1655-64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2822799

3. Forde CT, Karri SK, Young AM, Ogilvy CS. Predictive markers in traumatic brain injury: opportunities for a serum biosignature. Br J Neurosurg. 2013 Jul 15.

4. Mondello S, Schmid K, Berger RP, Kobeissy F, Italiano D, Jeromin A, et al. The Challenge of mild traumatic brain injury: role of biochemical markers in diagnosis of brain damage. Med Res Rev. 2013 Jun 28.

5. Banyan Biomarkers [Internet]. Alachua (FL): Banyan Biomarkers Inc. About us; 2010 Aug 17 [cited 2014 Feb 13]. Available from: http://www.banyanbio.com/?page_id=207

6. Sharma R, Laskowitz DT. Biomarkers in traumatic brain injury. Curr Neurol Neurosci Rep. 2012;12(5):560-9.

7. Kou Z, Gattu R, Kobeissy F, Welch RD, O'Neil BJ, Woodard JL, et al. Combining biochemical and imaging markers to improve diagnosis and characterization of mild traumatic brain injury in the acute setting: results from a pilot study. PLoS One [Internet]. 2013 [cited 2013 Dec 16];8(11):e80296. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3833898

8. Jeter CB, Hergenroeder GW, Hylin MJ, Redell JB, Moore AN, Dash PK. Biomarkers for the diagnosis and prognosis of mild traumatic brain injury/concussion. J Neurotrauma. 2013;30(8):657-70.

9. Bazarian JJ, Blyth BJ, He H, Mookerjee S, Jones C, Kiechle K, et al. Classification accuracy of serum Apo A-I and S100B for the diagnosis of mild traumatic brain injury and prediction of abnormal initial head computed tomography scan. J Neurotrauma. 2013 Oct 15;30(20):1747-54.

10. Wolf H, Frantal S, Pajenda GS, Salameh O, Widhalm H, Hajdu S, et al. Predictive value of neuromarkers supported by a set of clinical criteria in patients with mild traumatic brain injury: S100B protein and neuron-specific enolase on trial: clinical article. J Neurosurg. 2013 Jun;118(6):1298-303.

11. Research in traumatic brain injury [Internet]. Ottawa (ON): Canadian Institute for Health Information; 2012 Aug 20. [cited 2014 Feb 13]. Available from: http://www.cihr-irsc.gc.ca/e/45665.html

12. Ryu WH, Feinstein A, Colantonio A, Streiner DL, Dawson DR. Early identification and incidence of mild TBI in Ontario. Can J Neurol Sci. 2009 Jul;36(4):429-35.

13. Head injuries in Canada: A decade of change (1994-1995 to 2003-2004) [Internet]. Ottawa (ON): Canadian Institute for Health Information; 2006 Aug. [cited 2014 Feb 13]. (Analysis in Brief). Available from: https://secure.cihi.ca/free_products/ntr_head_injuries_2006_e.pdf

14. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006 Sep;21(5):375-8.

15. The Management of Concussion/mTBI Working Group. Management of concussion/mild traumatic brain injury (mTBI) [Internet]. Washington (DC): U.S. Department of Veterans Affairs; 2009; Apr. [cited 2014 Jan 16]. (Va/DoD Clinical practice guideline). Available from: http://www.healthquality.va.gov/mtbi/concussion_mtbi_full_1_0.pdf

16. Marshall S, Bayley M, McCullagh S, Velikonja D, Berrigan L. Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Can Fam Physician [Internet]. 2012 Mar [cited 2014 Jan 16];58(3):257-40. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3303645

17. Ontario Neurotrauma Foundation. Guidelines for concussion/mild traumatic brain injury & persistent symptoms [Internet]. 2nd ed. Toronto: The Foundation; 2013; Sep. [cited 2014 Jan 15]. Available from: http://onf.org/system/attachments/223/original/ONF_mTBI_Guidelines_2nd_Edition_COMPLETE.pdf

18. Egea-Guerrero JJ, Revuelto-Rey J, Murillo-Cabezas F, Muñoz-Sánchez MA, Vilches-Arenas A, Sánchez-Linares P, et al. Accuracy of the S100b protein as a marker of brain damage in traumatic brain injury. Brain Inj. 2012;26(1):76-82.

19. Muller B, Evangelopoulos DS, Bias K, Wildisen A, Zimmermann H, Exadaktylos AK. Can S-100B serum protein help to save cranial CT resources in a peripheral trauma centre? A study and consensus paper. Emerg Med J. 2011 Nov;28(11):938-40.

20. Metting Z, Wilczak N, Rodiger LA, Schaaf JM, Van Der NJ. GFAP and S100B in the acute phase of mild traumatic brain injury. Neurology. 2012 May 1;78(18):1428-33.

21. Kovesdi E, Luckl J, Bukovics P, Farkas O, Pal J, Czeiter E, et al. Update on protein biomarkers in traumatic brain injury with emphasis on clinical use in adults and pediatrics. Acta Neurochir (Wien). 2010 Jan;152(1):1-17.

22. Topolovec-Vranic J, Pollmann-Mudryj MA, Ouchterlony D, Klein D, Spence J, Romaschin A, et al. The value of serum biomarkers in prediction models of outcome after mild traumatic brain injury. J Trauma. 2011 Nov;71(5 Suppl 1):S478-S486.

23. Kalanuria AA, Geocadin RG. Early prognostication in acute brain damage: where is the evidence? Curr Opin Crit Care. 2013 Apr;19(2):113-22.

24. Brichtova E, Kozak L. Apolipoprotein E genotype and traumatic brain injury in children--association with neurological outcome. Childs Nerv Syst. 2008 Mar;24(3):349-56.

25. Astrand R, Undén J, Romner B. Clinical use of the calcium-binding S100B protein. Methods Mol Biol. 2013;963:373-84.

26. Unden J, Ingebrigtsen T, Romner B, Scandinavian Neurotrauma Committee (SNC). Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med [Internet]. 2013 [cited 2014 Feb 13];11:50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3621842

27. Ferguson I, Lewis L, Papa L, Wang K, Mondello S, Hayes R. Neuronal biomarkers may require age-adjusted norms [abstract]. Ann Emerg Med. 2011;58(4 Suppl 1):S213. (Presented at American College of Emergency Physicians, ACEP 2011 Research Forum; San Francisco, CA. Conference start: 20111015 conference end: 20111016.).

28. Hayes R, Mondello S, Wang K. Clinical studies of the utility of serum biomarkers for the diagnosis, prognosis, and management of traumatic brain injury [abstract]. J Neurotrauma. 2011;28(5):A24. (Presented at 10th International Neurotrauma Symposium, INTS; Shanghai, China. Conference start: 20110427 conference end: 20110430.).

Cite as: Foerster V. *Serum biomarkers to diagnose mild traumatic brain injury in adults* [Issues in emerging health technologies, Issue 122]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014.

A clinical expert in traumatic brain injury was consulted by CADTH in preparing this report.

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CADTH is funded by Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. CADTH takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

ISSN: 1488-6324 (online)