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## Biomarker-Based Point-of-Care Tests for the Evaluation of Mild Traumatic Brain Injury



*iStock Image: Laboratory medical diagnostics, tests for brain and neurological system concept*

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## Methods

CADTH Horizon Scanning bulletins present an overview of the technology and available evidence on a given topic. They are not systematic reviews and do not involve the critical appraisal of all studies or include a detailed summary of study findings. They are not intended to provide recommendations for or against a particular technology.

### Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources including MEDLINE via Ovid, Embase via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were biomarkers and concussion. No methodological search filters were applied to the search. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2015 and April 15, 2020.

### Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was a biomarker-based, point-of-care (POC), brain trauma indicator device or platform and targeted people with mild traumatic brain injury or concussion. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

### Peer Review

Manufacturers were given the opportunity to comment on an earlier draft; manufacturer input was received and addressed in this report.

## Summary

- Mild traumatic brain injury can have subtle signs and symptoms, yet the underlying neuropathology is complex and involves several neurochemical, structural, and functional changes in the brain.<sup>1</sup>
- Currently, in patients who present with mild signs and symptoms, neurologic assessment and mental status testing guide the triage decision for an imaging investigation of potential brain lesions.<sup>2-4</sup>
- Ideally, a portable biomarker-based POC test would contribute information to help health care professionals determine the need for imaging in those suspected of having a mild traumatic brain injury and would safely avoid unnecessary radiation exposure in others, while also saving health care resources.
- Several biomarker-based POC devices are currently in development; however, the identification of a single optimal biomarker has proven to be quite difficult and it is likely that a composite of several biomarkers will be required for optimal assessment results.

## Background

Traumatic brain injuries (TBI) are physical injuries to brain tissue that alter brain function either temporarily or permanently.<sup>3,5</sup> They can have consequences on activities of daily living and, in many cases, appear to initiate long-term neurodegeneration processes.<sup>6,7</sup> Common mechanisms by which a TBI tends to occur include falls, motor vehicle collisions, being struck by or against an object, sports, and blast-related injuries.<sup>7-9</sup> Severity varies from mild concussion to fatal damage.

While moderate and severe cases of TBI have greater objective clinical features, signs and symptoms of mild TBI can be more subtle such as a transient change in mental status or level of consciousness, post-traumatic amnesia, or focal neurologic deficits.<sup>3,10</sup> A few terms have been used in the literature to denote mild TBI, such as mild head trauma and concussion.<sup>4</sup> All concussions are considered to be a mild TBI, but mild TBI is distinguished from concussions when there is imaging evidence of intracranial lesions or if there is a persistent neurological deficit.<sup>4</sup> The majority of mild TBI patients are fully alert and awake,<sup>11</sup> some may be completely asymptomatic by the time they are medically assessed,<sup>4</sup> and some may not even seek medical care.<sup>12</sup> In 2014, a cross-sectional survey of Canadians aged 12 years and older (except those living in a nursing home, on reserves, or members of the Canadian Armed Forces) found that 19% of respondents who experienced a TBI self-reported not seeking medical care within 48 hours of their injury.<sup>12</sup>

Describing the burden of mild TBI in Canada is difficult because of the lack of consistent reporting across Canadian jurisdictions.<sup>13</sup> In 2017, it was estimated there were 162 new cases of mild TBI per 100,000 Canadians,<sup>14</sup> with an estimated national prevalence of 65,678 cases.<sup>14</sup> From a provincial perspective, there were 1,330,336 Ontarians diagnosed with a concussion between 2008 and 2016, with an annual average of 1,153 per 100,000 inhabitants.<sup>15</sup> In British Columbia, there were 11 concussion hospitalizations per 100,000 inhabitants from 2012–2013 to 2016–2017.<sup>16</sup> Because these estimates only reflect those who sought medical care, the true annual figures are likely higher.

Currently, the assessment of an individual with a suspected mild TBI includes a field trauma assessment, a neurological examination incorporating a rapid tool (e.g., the Glasgow Coma Scale [GCS]), and decision rules (e.g., Canadian CT Head Rule)<sup>9</sup> to triage them to imaging or an appropriate next level of care.<sup>3</sup> The GCS, developed in 1974, is a generally accepted system used to assess the level of consciousness of patients with a brain injury by observing their ability to open their eyes spontaneously, to be oriented and respond coherently to verbal questions, and to successfully obey motor commands.<sup>17,18</sup> The GCS scale ranges from the worst score of 3 for complete unresponsiveness, to the best score of 15 for an awake and alert patient.<sup>17,19</sup> Higher scores indicate a better prognosis, and a score of 13 to 15 is consistent with mild TBI.<sup>17,19-21</sup>

While a general categorization of injury severity can be extrapolated from the level of consciousness measured by the GCS, the tool has limitations. For instance, a GCS score of 15 does not necessarily imply an absence of internal damage after a head trauma; further investigation and patient monitoring may still be warranted.<sup>4,19,22</sup> Also, the tool is dependant on the assessment skills of the observer<sup>23</sup> and its interrater reliability has come into question.<sup>24</sup> As well, the GCS is unable to predict the development of complications<sup>25</sup> and it is not appropriate for use in patients with prior neurological conditions.<sup>26</sup> Although imaging via a CT scan is an alternative to bridging some of these shortcomings,<sup>3</sup> approximately 90% of mild TBI cases will not have any evidence of structural abnormalities visible on a CT scan.<sup>4,10,27-31</sup>

These limitations highlight an opportunity to improve the care pathway through the use of objective and quantifiable metrics, which can be obtained as soon as possible after the injury, outside of clinical laboratories, and in close proximity to where the patient is receiving care.<sup>32,33</sup> This has brought about the recent interest in developing biomarker-based POC devices to rapidly and accurately identify TBI. Ideally, the tests take the form of a small hand-held or otherwise portable device, designed to allow the investigation of a patient's condition more rapidly than conventional laboratory-based techniques.<sup>34</sup> Furthermore, they rely on quantifiable characteristics of a biological process (i.e., biomarkers) such as the measurement of proteins, intracellular or extracellular components, even brain electrical activity signatures.<sup>28,35-37</sup>

By offering POC convenience and clinical information at a crucial time for appropriate triage, a specific subgroup of suspected mild TBI patients could be sent for imaging, while others could safely avoid unnecessary ambulance transport, imaging, radiation exposure (thereby reducing long-term cancer risk), and at the same time saving health care resources.<sup>38</sup>

CADTH has done previous work on this topic, including a 2014 report on serum biomarkers used to diagnose mild TBI in adults.<sup>39</sup> The purpose of this Horizon Scan is to provide an overview of the potential use of biomarker-based POC tests for investigating suspected mild TBI.

## The Technology

Myriad biomarkers are being investigated for use in POC devices that detect mild TBI, such as those found in whole blood, serum, plasma, extracellular fluid, cerebrospinal fluid, saliva, as well as eye tracking, electroencephalogram measurements, and imaging findings.<sup>7,20,26,28,34,36,40-56</sup> Table 1 summarizes a selection of biomarker-based POC devices that are currently being developed for TBI.

As the underlying neuropathology of mild TBI is complex and involves several neurochemical, as well as structural and functional, changes in the brain,<sup>1</sup> the identification of an optimal biomarker has proven to be difficult. The following is a description of individual biomarkers relevant to POC devices listed in Table 1.

### Ubiquitin Carboxy-Terminal Hydrolase Isoenzyme L1 (UCH-L1)

Used by the Banyan Brain Trauma Indicator,<sup>57</sup> as well as the i-STAT Alinity,<sup>58</sup> UCH-L1 is expressed in the cytoplasm of neuronal cells and is involved in neuron cell turnover as a response to adverse events that may damage brain tissue.<sup>7,20,21,30,42,45,59</sup> A 2017 systematic review reported the sensitivity of UCH-L1 for the detection of intracranial lesions on CT scans to be 100% (95% confidence interval [CI], 88% to 100%) and with a specificity of 21% (95% CI, 12% to 32%) in one primary study and 39% (95% CI, 33% to 46%) in another.<sup>28</sup> This biomarker was recently granted US FDA clearance for clinical use in identifying the presence of intracranial injury after more severe TBI.<sup>60</sup> However, in mild TBI, the peak UCH-L1 serum concentration is low and rapidly disappears, which may affect its utility and reliability as a biomarker in these cases.<sup>7,26,40,61,62</sup>

### Glial Fibrillary Acidic Protein (GFAP)

Used by the Banyan Brain Trauma Indicator,<sup>57</sup> the i-STAT Alinity,<sup>58</sup> as well as the Tbit system,<sup>63,64</sup> GFAP is expressed from astrocytes (i.e., a type of glial cell) after neuronal injury.<sup>7,20,21,30,42,49,65</sup> Following a TBI, GFAP is released somewhat later than UCH-L1 and remains elevated for a longer time, which provides a wider time window for detection.<sup>7,30,40,42,61,66</sup> The sensitivity of GFAP for the detection of intracranial lesions on CT scans have been reported to be 67% to 100%, with a specificity between 0% to 100%.<sup>28,30</sup> This biomarker was recently granted FDA clearance for clinical use in identifying the presence of intracranial injury after more severe TBI.<sup>60</sup> Nevertheless, GFAP is helpful at differentiating between focal and diffuse brain injury<sup>7</sup> and it is useful for all severities of TBI;<sup>21</sup> however, GFAP's ability to diffuse into the bloodstream is dependant on the blood-brain barrier also being damaged.<sup>41</sup> In one study, the use of this biomarker was shown to reduce the number of CT scans in TBI cases by a range of 12% to 30%.<sup>67</sup>

With a TBI, injury to neighbouring cell types is not surprising and there is a strong association between GFAP and UCH-L1.<sup>66</sup> The combination of these two biomarkers has been reported to have better sensitivity and specificity for identifying TBI patients from healthy controls than either biomarker alone.<sup>45,68</sup>

## Aldolase Isoenzyme C (ALDOC)

Used by the BRAINBox TBI device,<sup>69</sup> the expression of ALDOC increases after astrocytes are injured and can remain elevated for up to five days post injury.<sup>26,70</sup> In mild TBI cases, the biomarker can be present in serum one hour post injury.<sup>70</sup> Here too, the enzyme's ability to diffuse into the bloodstream is dependant on the blood-brain barrier also being damaged.<sup>70</sup>

## Brain Electrical Activity

The BrainScope One device<sup>71</sup> uses non-invasive electroencephalography (EEG) to measure the electrical activity of the brain and monitor changes over the course of a TBI.<sup>1,7</sup> Typical measurements collected include power frequency bands (i.e., alpha, beta, gamma, delta, theta), amplitude, and latency.<sup>7,45</sup> Common findings associated with concussion are changes in power frequencies,<sup>7,37</sup> as well as decreased wave amplitudes.<sup>45</sup> Another measure of brain electrical activity reported to reflect brain injury in mild TBI is based on the complexity of the EEG signal, which drops in concussive injury.<sup>37</sup>

## S100 Calcium-Binding Protein B (S100B)

Used by the Elecsys S100 test kit,<sup>72,73</sup> the Liaison S100 test kit,<sup>72,74</sup> as well as the Tbit system,<sup>63,64</sup> the S100B protein is expressed from astrocytes after neuronal injury.<sup>7,11,21,30,49,53,59,72</sup> However, S100B is not a brain-specific biomarker and may arise from extracranial sources such as musculoskeletal injury and adipose tissue, limiting its specificity in a multi-trauma injury scenario.<sup>7,21,25,42,61</sup> The protein remains in circulation for one hour to one day<sup>7</sup> before being excreted.<sup>11,72</sup> The sensitivity of S100B as a predictor of intracranial lesion on a CT scan has been reported as 72% to 100%, with a specificity of 5% to 77%.<sup>28,31,75</sup> Higher serum concentrations have been linked to abnormal CT findings<sup>7,30,49,76</sup> and there is a proposed lower threshold that could be used, together with additional parameters, to avoid unnecessary imaging in select patients.<sup>76</sup> Nevertheless, S100B is also an indicator of blood-brain barrier disruption rather than just brain damage.<sup>40,49,53</sup> With these shortcomings in mind, it should be highlighted that clinical symptoms and other assessment measures should be considered in addition to S100B levels when assessing a patient with suspected mild TBI.

**Table 1: Characteristics of Biomarker Point-of-Care Devices Used for Traumatic Brain Injury Assessments**

Device, manufacturer, country	Type of biomarker used	Intended use, description of procedure	Regulatory availability
Banyan Brain Trauma Indicator, <sup>57</sup> for use with the Synergy 2 Multi-Mode luminometer (BioTek Instruments Incorporated)  Banyan Biomarkers Inc.  US	Blood sample: <ul style="list-style-type: none"> <li>• UCH-L1</li> <li>• GFAP</li> </ul>	Assessment of TBI in patients 18 years and older <sup>57</sup>  Serum processed from whole blood collected within 12 hours of injury is tested via ELISA for presence of each biomarker.	<ul style="list-style-type: none"> <li>• No active Canadian medical device licence</li> <li>• Received FDA Class II designation on June 14, 2018;<sup>77</sup> however, the company is currently only supplying the United States Department of Defence.<sup>57</sup></li> </ul>
BRAINBox TBI <sup>69</sup>  BRAINBox Solutions, Inc.  US	Blood sample: <ul style="list-style-type: none"> <li>• Astrocyte injury-defined biomarkers, including ALDOC or a trauma-specific breakdown product of ALDOC.<sup>69</sup></li> </ul>	Assessment of TBI  A blood sample is placed on an application pad for ELISA analysis by the device. <sup>78</sup>	<ul style="list-style-type: none"> <li>• No active Canadian medical device licence</li> <li>• No active FDA approval. Received Breakthrough Device designation on June 6, 2019<sup>69</sup></li> </ul>
BrainScope One (formerly known as Ahead 300) <sup>71,79</sup>  BrainScope Company Inc.  US	EEG: <ul style="list-style-type: none"> <li>• Absolute and relative power</li> <li>• Asymmetry</li> <li>• Quantitative EEG coherence</li> <li>• Fractal dimension</li> </ul>	Assessment of TBI in patients aged 18 to 85 years who have a GCS of 13 to 15 <sup>71</sup>  Within 72 hours of injury, a forehead-only electrode headset is placed on the patient to record EEG measurements for five minutes via a hand-held device. <sup>71</sup> The patient then	<ul style="list-style-type: none"> <li>• Received a Canadian medical device licence (103943) on November 25, 2019</li> <li>• The former Ahead 300 device was approved for commercialization in the US in September 2016 and was rebranded to BrainScope One in May 2018<sup>80</sup></li> </ul>



Device, manufacturer, country	Type of biomarker used	Intended use, description of procedure	Regulatory availability
		completes a 10-minute cognitive performance test on the hand-held device before the TBI assessment results are displayed. <sup>71</sup>	
Elecsys S100 test kit for use in the cobas e 601 analyzer <sup>72,73</sup> Roche Diagnostics GmbH Germany	Immunoassay of blood sample: • Serum S100B protein	Assessment of TBI <sup>73</sup>  Serum, collected within three hours of injury, is measured to assess levels of the biomarker. The assay takes approximately 18 minutes. <sup>73</sup>	<ul style="list-style-type: none"> <li>The test kit received a Canadian medical device licence (69534) on November 19, 2005. It was amended on December 9, 2019.</li> </ul>
i-STAT Alinity, <sup>58,81</sup> Abbott Point of Care Inc. US	Blood sample: <sup>82</sup> • UCH-L1 • GFAP	Measures a range of biomarkers for various conditions <sup>81</sup> and it may be used in the assessment of TBI.  A few drops of blood are applied to a cartridge and inserted into the hand-held device for analysis. <sup>81</sup>	<ul style="list-style-type: none"> <li>Received a Canadian medical device licence (69528) on January 27, 2017</li> <li>Not commercially available in the US<sup>58</sup></li> </ul>
LIAISON S100 test kit for use in the Liaison Analyzer <sup>72,74</sup> Diasorin SpA US	Blood sample: • Serum S100B protein	Intended to detect serum S100B protein in malignant melanoma; unclear if it could be applied to TBI  NR	<ul style="list-style-type: none"> <li>The test kit received a Canadian medical device licence (86744) on August 24, 2012</li> </ul>
Tbit System <sup>63</sup> BioDirection, Inc. US	Blood sample: • GFAP • Serum S100B protein	Assessment of concussion and other TBI  A drop of blood is analyzed via a tabletop device and results are returned in 90 seconds. <sup>64</sup>	<ul style="list-style-type: none"> <li>No active Canadian medical device licence</li> <li>No active FDA approval</li> </ul>

ALDOC = aldolase isoenzyme C; EEG = electroencephalography; ELISA = enzyme-linked immunosorbent assay; GFAP = glial fibrillary acidic protein; GCS = Glasgow Coma Scale; NR = not reported; TBI = traumatic brain injury; UCH-L1 = ubiquitin carboxy-terminal hydrolase isoenzyme L1.

## Cost

A 2019 cost-effectiveness study from the US compared the cost-effectiveness of biomarker screening for TBI to the application of clinical decision rules or routine CT scans for mild or moderate TBI.<sup>10</sup> The authors determined, assuming a 0.104 probability of an intracranial lesion in mild TBI, that the biomarker screen was cost-effective if the cost was \$308.96 or below (calculated from a societal perspective and expressed in 2018 US dollars) per test.<sup>10</sup>

## Who Might Benefit?

While the use of biomarker-based POC tests for mild TBI is a developing and evolving area, these technologies are being considered for people with a presumed mild TBI in amateur sports and professional athletic settings, military combat theatres, and other pre-hospital settings. As previously discussed, the assessment of a patient with a presumed mild TBI is complex and the availability of a biomarker-based POC tool would aid in triaging the patient to the appropriate next level of care.<sup>41</sup>

## Current Practice

The current practice for the identification of mild TBI starts with a neurologic assessment and mental status testing.<sup>2-4</sup> Additionally, unconsciousness greater than one minute, mental status changes, or abnormalities upon neurologic examination would indicate the need for urgent imaging and further consultation.<sup>2</sup> Imaging, usually via a head CT without contrast media, is recommended for a subset of patients with mild TBI<sup>2</sup> (e.g., usually those with more than transiently impaired consciousness, a GCS score below 15, focal neurologic findings, persistent vomiting, seizure, a history of loss of consciousness, or a clinically suspected fracture).<sup>3,76</sup> The Ontario Neurotrauma Foundation guidelines on concussion and mild TBI<sup>4</sup> recommend using the Canadian CT Head Rule<sup>9</sup> – a clinical decision-making tool to help determine which patients would benefit from the imaging technique.<sup>9</sup> The purpose of imaging is to identify injuries requiring immediate neurosurgical intervention (e.g., hematomas, contusions, skull fractures, diffuse axonal injury) and to assess the prognosis for long-term management.<sup>2</sup> Although not indicated for the initial examination,<sup>2</sup> MRI may be useful later on in the clinical course of the pathology for the potential prognosis of long-term outcomes,<sup>55</sup> detection of subtle contusions,<sup>3</sup> presence of diffuse axonal injury,<sup>3</sup> and presence of traumatic microbleeds that may persist for years following the initial injury.<sup>54</sup> Plain skull X-rays are not recommended, as they cannot help assess the brain tissue.<sup>3,4</sup>

## Summary of the Evidence

Trials pertaining to biomarker-based POC testing devices for mild TBI were only identified for the BrainScope One and i-STAT Alinity devices. Study characteristics are listed in Table 2.

## Results

The study population in the Hanley et al. (2018) and the Hanley et al. (2017) publications was limited to adults 18 to 85 years of age.<sup>29,37</sup> Therefore the generalizability of the results in pediatric or adolescent populations remains unclear. Furthermore, as the study population was a convenience sample,<sup>29,37</sup> it is possible that a selection bias was present. Notably, the distribution of some baseline characteristics (e.g., mean age, sex, mechanism of injury) were unequal between the group with injuries visible on a CT scan (CT-positive) and the group without visible injuries (CT-negative). Also, it is not clear from the demographics if any of the study participants had a history of previous TBI or existing comorbidities that may have affected the interpretation of their CT scan results.

Correspondingly, the subgroup analysis by Hack et al. (2017) had an unequal distribution of some baseline characteristics (e.g., mean age, sex, mechanism of injury) between the group with injuries visible on a CT scan (CT-positive) and the group without visible injuries (CT-negative).<sup>83</sup> Therefore, it is possible that a selection bias was present. What is more, the clinical observation of loss of consciousness alone as a comparator in determining whether a patient is likely to have an intracranial bleed is not representative of the contemporary standard of care at the time of the study. Therefore, it is possible that this contributed to overstating the favourable outcomes of the device.

The study population in Wilde et al. (2020) was limited to a small group of collegiate athletes aged 17 to 24.<sup>1</sup> Therefore the generalizability of the results in other age groups or non-athletic populations remains unclear. Furthermore, as the study population was a convenience sample,<sup>1</sup> it is possible that a selection bias was present.

The study population in Yue et al. had a mean age of 36.3 years (standard deviation [SD] = 15.0), were 63% male, and mostly injured in road-traffic accidents (68%) or falls (20%);<sup>84</sup> therefore the generalizability of the results in other age groups or other mechanisms of injury remains unclear.



**Table 2: Characteristics of the Trials**

Author, year; name of study; country	Study design, study duration, sample size	Population	Intervention comparator(s)	Outcomes
<b>BrainScope One</b>				
Wilde et al. (2020) <sup>1</sup> US	Case-control study  Sample size: N = 31	Collegiate athletes aged 17 to 24: • concussed n = 18 • non-concussed n = 13	Enhanced BFI score from BrainScope One  DTI MRI	• White matter diffusivity (e.g., fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity)
Hanley et al. (2018) <sup>37</sup> US	Retrospective cohort subgroup analysis of the B-AHEAD III study <sup>29</sup>  Subgroup n= 713	• See Hanley et al. (2017) <sup>29</sup> in the Reference section that follows • Subgroup consisted of patients for which a categorical classification of functional impairment could be determined	BFI score from Ahead 300 <sup>a</sup>	• Severity of functional impairment
Hack et al. (2017) <sup>83</sup> US	Retrospective subgroup analysis of the B-AHEAD III study <sup>29</sup>  Subgroup n = 680	• See Hanley (2017) <sup>29</sup> in the Reference section that follows • Subgroup consisted of patients with known absence or presence of loss of consciousness	Ahead 300 <sup>a</sup>  LOC, LOC plus amnesia	• Prediction of intracranial bleed
Hanley et al. (2017) <sup>29</sup> Validation Of Point-Of-Care TBI Detection System For Head Injured Patients (B-AHEAD III) US	Prospective cohort  Enrolment between February and December 2015  N = 720	• Convenience sample of adults presenting to the emergency department at 11 different sites and within 72 hours of a head injury	Ahead 300 <sup>a</sup>  CT	• Likelihood that a patient was CT-positive (positive predictive value) • Negative predictive value
<b>i-STAT Alinity</b>				
Yue et al. (2019) <sup>84</sup> Subgroup analysis of the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) trials US	Prospective cohort  Enrolment between February 2014 and June 2018 <sup>b</sup>  Subgroup = 450	Patients with TBI who had a clinically indicated head CT scan within 24 hrs of injury and with a negative result. <sup>84</sup> • 330 had negative MRI scans • 120 had positive MRI scans	i-STAT <sup>b</sup> analysis of GFAP within 24 hours of injury <sup>84</sup>  MRI at seven to 14 days post injury <sup>84</sup>	• Ability to identify patients with positive versus negative MRI findings

BFI = brain function index; DTI = diffuse tensor imaging; LOC = loss of consciousness.

<sup>a</sup>The former Ahead 300 device was approved for commercialization in September 2016 and was rebranded to BrainScope One in May 2018.<sup>80</sup>

<sup>b</sup>This study was performed with the former generation of the i-STAT platform, not the proposed i-STAT Alinity device.

## Detecting Intracranial Injury

Hanley et al. (2017) reported that the Ahead 300 device had a sensitivity of 92.3% (95% CI = 87.8% to 95.5%) and a specificity of 51.5% (95% CI, 48.1% to 55.1%) for detecting intracranial injury visible on a CT scan.<sup>29</sup> Furthermore, the authors reported that the device had a negative predictive value of 96.0% (95% CI, 93.2% to 97.9%) and a positive predictive value of 34.5% (95% CI, 30.0% to 39.3%) for intracranial injury visible on a CT scan.<sup>29</sup>

Hack et al. (2017) reported that the Ahead 300 device performed 83% better at determining whether a head injury patient was likely to have an intracranial bleed or not (i.e., CT-positive or CT-negative) over the clinical observation of loss of consciousness alone (area under the receiver operating characteristic [ROC] curve of 0.83 and 0.68, respectively).<sup>83</sup> Hence, the odds ratio for the “loss of consciousness” method of prediction is 4.65 (95% CI, 3.10 to 6.97) and the device method is 16.22 (95% CI, 8.09 to 32.52).<sup>83</sup>

Yue et al. (2019) reported that, within 24 hours of injury, plasma concentrations of GFAP as detected by the i-STAT device was able to discriminate (area under the ROC curve 0.777 [95% CI, 0.726 to 0.829]) between patients with MRI-positive findings and patients with MRI-negative findings of injury.<sup>84</sup>

## Characterization of Severity of Functional Impairment

Hanley et al. (2018) developed a brain function index (BFI) score intended to reflect functional impairment in brain injury and based on measures of brain electrical activity generated by the Ahead 300 device.<sup>37</sup> The higher the BFI, the more severe the impairment. The authors’ analysis demonstrated a sensitivity of 35% that the index score could differentiate between CT-positive (BFI score = 299.4 [±1.2]) and CT-negative patients with mild TBI (BFI score = 247.1 [±0.3]).<sup>37</sup> Similarly, they reported a sensitivity of 62% that the index score could differentiate between the CT-positive and the CT-negative patients with normal function (BFI score = 222.5 [±1.0]).<sup>37</sup>

Wilde et al. (2020) compared diffuse tensor imaging (DTI) MRI metrics to an enhanced BFI score of concussed and non-concussed collegiate athletes.<sup>1</sup> The authors reported that the enhanced BFI score (composed of EEG, clinical, and cognitive findings) was related to DTI alterations in the white matter of multiple regions of the brain, particularly in the frontal and temporal areas.<sup>1</sup> However, none of the group differences in the DTI metric survived the false discovery rate statistical correction.<sup>1</sup> The authors also attempted to standardize DTI scores and correlate them to the enhanced BTI score; however, none were statistically significant.<sup>1</sup>

## Concurrent Developments

Several research groups around the world are working to advance research on biomarker-based POC testing. In many of the examples that follow, the technology is emergent and will need further development before regulatory approval and clinical application.

### US

A research team in Arizona has proposed a detection method that relies on four biomarkers: GFAP, neuron-specific enolase, S100B, and tumour necrosis factor-alpha.<sup>65</sup> The device uses a gold disc electrode to measure microlitre, volume-sized samples of blood and return concentrations of these biomarkers in under 90 seconds.<sup>65</sup> The technology is still experimental while a more cost-effective electrode material is sought, which is also expected to affect the testing time.<sup>65</sup>

Another team in Arizona developed a POC tool that detects the sustained blood elevation of norepinephrine concentrations, known to negatively relate to long-term outcomes in TBI.<sup>34,85</sup> However, the team’s research remains experimental and the researchers are seeking to confirm their findings in human trials.

A group in Arkansas started a phase II trial in 2018 for a portable brain injury biomarker system that detects levels of lactate, pyruvate, and glucose via an integrated microdialysis probe.<sup>86</sup> The group is developing this medical device for the clinical monitoring of patients with severe brain injury.<sup>86</sup>

### Australia

Researchers in Sydney have developed a portable system that uses a smartphone to deliver a visual stimulus while an EEG headset records brain activity signals.<sup>52</sup>

### Canada

A team in London, Ontario reported on the use of a mass spectrometry metabolomic profiling method for concussion.<sup>87</sup> The authors have filed a patent application for metabolomics profiling of central nervous system injury (US patent number 62/135886).<sup>87</sup>

### UK

A research team in Birmingham reported on an assay that detects Cystatin D (CST5), stated to be an ultra-early biomarker with the ability to determine the presence and severity of TBI.<sup>25</sup> The assay is not currently portable, limiting its usefulness for field applications.<sup>25</sup>

Another research team in Birmingham has proposed a lab-on-a-chip for rapid plasma separation from a single drop of blood sample.<sup>88</sup> The chip is inserted into a portable system, which uses a diode laser, for the analysis of N-acetylaspartate (NAA).<sup>88</sup> A decrease in plasma NAA levels occurs in mild TBI because of reduced biosynthesis or its increased utilization.<sup>88</sup> The technology is still experimental and researchers are seeking to confirm their findings in mild TBI cases.<sup>88</sup>

Researchers have also discovered that micro ribonucleic acids (microRNA) play a critical role as regulators in various diseases, including TBI.<sup>41,56</sup> Good diagnostic accuracy for mild TBI detection has been reported using blood levels of multiple immune-related genes.<sup>89,90</sup> However, microRNA can also be sampled from saliva, making it an ideal non-invasive candidate for a POC test.<sup>91</sup> Researchers in Birmingham are seeking to establish a panel of microRNA biomarkers in urine and saliva for the rapid diagnosis of sports-related concussion and to see whether these biomarkers would be clinically useful for diagnostic, prognostic, and return-to-activity decisions.<sup>92</sup>

## Implementation Issues

The nature of TBI is often complex, where a number of injury mechanisms can be simultaneously involved, resulting in varied types and severity of injuries.<sup>7</sup> While TBI is not a new condition, there has been a growing impetus to improve existing assessment tools and develop new ones in the last decade.<sup>93</sup>

In Canada, the issue was recently brought into the public eye when the Minister of Health received a mandate to establish a Pan-Canadian Concussion Strategy and raise awareness for parents, coaches, and athletes on concussion treatment.<sup>94</sup> In addition, there have been increasing calls for ways to safely reduce unnecessary medical imaging, both to reduce radiation exposure (thereby reducing long-term cancer risk) and conserve health care resources.<sup>38</sup> Biomarker-based POC tests, if adequately able to detect intracranial injury, may help in this regard.

While biomarker-based POC tests would help guide the decision to perform further imaging, another aspect to consider in their implementation is that some can take longer to return results than performing a CT scan.<sup>95</sup> This delay may result in an overall lengthier hospital stay, with potential repercussions on other patients waiting for an available bed.<sup>95</sup>

## Final Remarks

While biomarker-based POC testing is a new technology that may allow for the faster triage of patients with suspected TBI, there remains a number of considerations before such devices can be used in clinical practice in the Canadian setting. These include a need for additional well-designed prospective studies to demonstrate that these devices have both the sensitivity and specificity required to correctly identify people with and without mild TBI.

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