Review Article

Toward development of clinically translatable diagnostic and prognostic metrics of traumatic brain injury using animal models: A review and a look forward

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ABSTRACT

Traumatic brain injury is a leading cause of cognitive and behavioral deficits in children in the US each year. There is an increasing interest in both clinical and pre-clinical studies to discover biomarkers to accurately diagnose traumatic brain injury (TBI), predict its outcomes, and monitor its progression especially in the developing brain. In humans, the heterogeneity of TBI in terms of clinical presentation, injury causation, and mechanism has contributed to the many challenges associated with finding unifying diagnosis, treatment, and management practices. In addition, findings from adult human research may have little application to pediatric TBI, as age and maturation levels affect the injury biomechanics and neurophysiological consequences of injury. Animal models of TBI are vital to address the variability and heterogeneity of TBI seen in human by isolating the causation and mechanism of injury in reproducible manner. However, a gap between the pre-clinical findings and clinical applications remains in TBI research today. To take a step toward bridging this gap, we reviewed several potential TBI tools such as biofluid biomarkers, electroencephalography (EEG), actigraphy, eye responses, and balance that have been explored in both clinical and pre-clinical studies and have shown potential diagnostic, prognostic, or monitoring utility for TBI. Each of these tools measures specific deficits following TBI, is easily accessible, non/minimally invasive, and is potentially highly translatable between animals and human outcomes because they involve effort-independent and non-verbal tasks. Especially conspicuous is the fact that these biomarkers and techniques can be tailored for infants and toddlers. However, translation of preclinical outcomes to clinical applications of these tools necessitates addressing several challenges. Among the challenges are the heterogeneity of clinical TBI, age dependency of some of the biomarkers, different brain structure, life span, and possible variation between temporal profiles of biomarkers in human and animals. Conducting parallel clinical and pre-clinical research, in addition to the integration of findings across species from several pre-clinical models to generate a spectrum of TBI mechanisms and severities is a path toward overcoming some of these challenges. This effort is possible through large scale collaborative research and data sharing across multiple centers. In addition, TBI causes dynamic deficits in multiple domains, and thus, a panel of biomarkers combining these measures to consider different deficits is more promising than a single biomarker for TBI. In this review, each of these tools are presented along with the clinical and pre-clinical findings, advantages, challenges and prospects of translating the pre-clinical knowledge into the human clinical setting.

1. Introduction

In the United States, children ages 0–4 years had the highest estimated annual rates of TBI-related emergency room visits, followed by adolescents ages 15–19 years of age (Faul et al., 2010). The most common causes of TBI are falls and assaults in young children and motor vehicle accidents and sport related injuries in elementary school children and adolescents (Faul et al., 2010). Among pediatric and adolescent, most TBIs are classified as mild, however, there are still many TBI hospitalizations categorized as moderate to severe TBI (Rivara et al., 2011; Asemota et al., 2013). TBI has devastating acute effects and in many cases seems to initiate long-term neurodegeneration (Johnson et al., 2010). It is estimated that 145,000 children and adolescents (ages 0–19 years) are living with lasting cognitive, physical, or behavioral effects of TBI (Zaloshnja et al., 2008). Due to the long-term and potentially detrimental effects of TBI on the young brain, there is

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increasing interest in both pre-clinical and clinical studies to discover diagnostic tools to accurately identify TBI especially concussion/mild TBI in the developing brain. The nature of TBI is complex, often a number of injury mechanisms are simultaneously at play presenting diverse spatial and temporal pathophysiology and injury severities. The heterogeneity in human TBI is an important factor from the clinical perspective in predicting outcomes and injury trajectories which has led to the absence of relevant and validated outcome measures in TBI and are the primary reason for discouraging results from neuroprotective and therapeutic clinical trials over the last four decades (Yue et al., 2013).

Animal models of TBI mimic the neurological deficits of human TBI and offer a unique opportunity to reduce the heterogeneity seen in humans. As such animal studies allow researchers to isolate and investigate the pathological and behavioral changes associated with brain injury in a consistent and reproducible manner. The use of animal models provides a means to explore the underlying reasons for a given outcome, to accelerate preclinical therapeutic findings, and evaluate the efficacy of clinical treatment and management of TBI. In addition, animal models can help to improve correlations with different severities of TBI and to refine the mechanisms of injury involved to develop reliable, efficient and valid classification systems to link specific patterns of brain and neurovascular injury with the appropriate therapeutic interventions. However, there is still a gap between preclinical findings and clinical applications. To take a step toward bridging this gap, in this paper we first present several validated animal models of TBI. We then discuss translatable metrics as potential TBI diagnostic tools including biofluid biomarkers, electroencephalography (EEG), actigraphy, eye tracking, and balance tests. We include metrics that have been explored in both clinical and laboratory studies and can be translated between humans and animals. We will also detail the challenges and research opportunities toward development and evaluation of effort-independent and clinically translatable TBI metrics to advance our understanding and management of TBI in the developing brain.

2. Pre-clinical animal models of TBI

Animal models have been developed that produce different types of TBI such as contusion, diffuse or focal axonal injury, hematomas, and subarachnoid hemorrhage(Pitt and Leung, 2015). Utilizing idealized animal models make it possible to conduct a thorough investigation of pathophysiological mechanisms of TBI, the validation and prognostic value of TBI biomarkers, and the assessment of treatments in a setting of a reproducible phenotype with a known pre-injury exposure. Here we briefly present four specific models that are widely used in animal TBI research: controlled cortical impact (CCI) injury, rapid non-impact rotational injury (RNR), weight-drop impact injury (WDI), and fluid percussion injury (FPI) mainly focusing on pediatric models.

2.1. Controlled cortical impact TBI model

Controlled cortical impact (CCI) TBI models are developed to produce a purely focal cortical/subcortical contusion injury with direct focal damage to the exposed, open or intact dura of the subject and no inertial motion of the head. Contusion injury is one of the most common types of brain injury in children caused by events such as falls, vehicular accident, sport injuries and child abuse (Graham et al., 1989). The CCI model utilizes a blunt indentation device driven by either a loaded spring, a pneumatic piston, or an electromagnetic coil to create a rapid displacement of the cortical surface (Margulies et al., 2015). The severity and functional deficits of CCI injury in animal models can be adjusted by the impact velocity, duration of impact, depth of deformation, and size of the impactor tip. CCI models of infant/pediatric TBI have been developed in the rat (Raghupathi and Huh, 2007; Robinson et al., 2016; Schober et al., 2014), mice (Mannix et al., 2011), rabbit (Zhang et al., 2015), and piglet (Baker et al. (2018); Duhaime

et al., 2000; Missios et al., 2009) typically focusing on moderate to severe injury outcomes.

2.2. Rapid non-impact head rotation TBI model

Rapid non-impact head rotation (RNR) TBI models produce a purely inertial head movement with no head contact, similar to levels experienced in motor vehicle or high velocity trauma that result in unconsciousness, sustained cognitive dysfunction, bilateral diffuse axonal and hemorrhagic injury (Margulies et al., 2015). RNR consists of a pneumatic device that moves a thrust column at controlled acceleration and deceleration levels employing a shaft that is externally coupled to a custom-built linkage assembly to produce the desired kinematics (often rotational motion). The RNR injury model has been mostly studied on pigs (Kilbaugh et al., 2015; Margulies et al., 2015) and primates (Gennarelli et al., 1982), however, there have been limited studies on rats (Xiao-Sheng et al., 2000) and rabbits (Gutierrez et al., 2001). Among those, only the pig studies (Kilbaugh et al., 2015; Margulies et al., 2015) were focused on infant/pediatric TBI.

2.3. Weight drop impact TBI model

Weight drop impact (WDI) injury model consists of a falling weight on the skull to induce focal cerebral contusion and diffuse axonal injury and used to simulate concussion to severe TBI. The diameter, velocity and dwell time of the impactor are adjustable to alter the severity of injury. In Marmarou's WDM (Marmarou et al., 1994), which mainly results in diffuse TBI, a stainless steel disc is mounted to the midline the animal's skull to distribute the force of the impact and prevent skull fracture. Later, WDI was modified to produce disruption in the blood–brain barrier, cerebral edema, and neuronal cell death below the contusion site and remotely in the hippocampus by dropping the weight onto one side of an unprotected skull while resting on a hard surface (Shohami et al., 1988). Another modification to WDI was to support the animal on a fragile aluminum foil support which allows post impact rapid acceleration of the free-moving head and torso (Kane et al., 2012). WDI has been utilized in small animals such as rat (Mychasiuk et al., 2014; Semple et al., 2016) and mouse (Adelson et al., 1996; Chhor et al., 2017) to model pediatric TBI.

2.4. Fluid percussion injury TBI model

The fluid percussion injury (FPI) model employs a rapid fluid pressure pulse delivered to the open dura of an animal causing graded severities of brain injury including contusions, intracranial hemorrhages, brain swelling, grey matter damage, concussion and traumatic axonal injury (McIntosh et al., 1989; Xiong et al., 2013). Injury severity is controlled by the magnitude of the fluid pressure pulse and the location of the craniotomy determines the clinical and pathological effects of injury (O'Connor et al., 2011). Due to the nature of FPI models requiring an opening in the skull, translation of mechanisms and interventions to human head injury is often difficult because the majority of human head injuries involve closed head injury mechanisms (O'Connor et al., 2011). FPI model of TBI have been primarily studied in animals, such as the cat (Stalhammar et al., 1987), sheep (Millen et al., 1985), swine (Fritz et al., 2005), mice (Carbonell et al., 1998; Folweiler et al., 2018; Ogino et al., 2018), and rat (Gorse and Lafrenaye, 2018; Katz and Molina, 2018; McIntosh et al., 1987). Many of these studies typically represent the adult brain, however those employing rats (Prins and Hovda, 2003) and piglets (Fritz et al., 2005; Lafrenaye et al., 2015) have been used to model the newborn and juvenile brain.

3. Translatable metrics

In this section, we reviewed metrics including biofluid biomarkers, electroencephalography (EEG), actigraphy, eye response, and balance
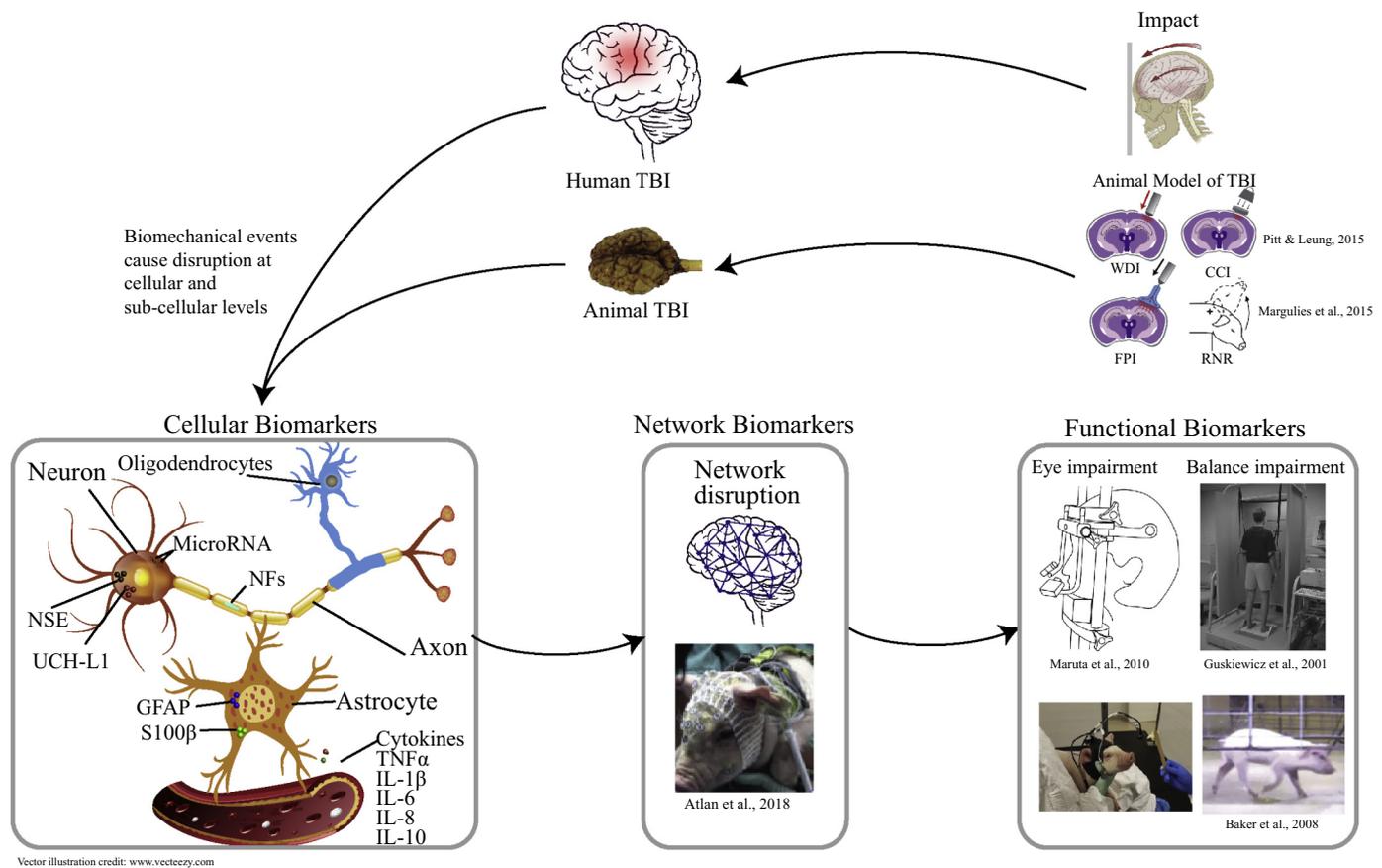
Fig. 1. Schematic of cellular origins and causations of biomarkers and relation between biomechanical event and biomarkers at cellular, neuronal network and functional levels.

tests that have been explored in both clinical and preclinical studies and can be translated between humans and animals. The possible cellular origin, causation and interactions of these biomarkers are illustrated in Fig. 1. In addition, a summary of pediatric clinical and pre-clinical TBI studies that examined the diagnostic and prognostic utility of these translatable biomarkers for TBI is given in Table 1. The main focus of this table was to summarize the literature on the utility of a single or a panel of biomarkers to: (1) detect intracranial lesions to identify patients in need of computed tomography (CT) scan; (2) assess injury severity and prognosis, (3) predict short- or long-term neurological outcomes of TBI; (4) diagnose injured patients (especially concussion/mild TBI) from healthy or non-TBI trauma controls; and/or (5) distinguish between mechanisms of injury, for example, differentiating between inflicted (iTBI) from non-inflicted (nTBI) where abusive head trauma is prevalent in infants and toddlers.

3.1. Biofluid biomarkers

TBI can cause disruption at cellular and sub-cellular levels such as neurons, astrocyte and microglial cells, vasculature and extracellular matrix. These disruptions can initiate a variety of neurotransmitter, metabolomic, mitochondrial, and ionic dysregulations which have been shown to be reflected in affected brain tissues as well as biofluids such as serum, cerebrospinal fluid, saliva and urine (Baker et al. (2018); Gazzolo et al., 2003; Giza and Hovda, 2014; Kilbaugh et al., 2016; Margulies et al., 2015; Smith et al., 2013). The reflections in different biofluids showed to be dynamic, interactive, and dependent on type, severity, and progression of injury. Therefore, biofluids are treasure trove of injury related information and are valuable surrogates to be used as potential diagnostic, prognostic, or monitoring, and even

therapeutic efficacy assessment tools for TBI. Biofluid biomarkers are non/minimally invasive and effort-independent techniques that can be studied in both animals and humans, and thus, they are of great value to serve as a bridge between pre-clinical and clinical findings and advance diagnosis, management and treatment of TBI. Biomarker discovery are particularly invaluable for pediatric and especially neonatal population as radiation from routine CT imaging can be harmful for this group (Brenner and Hall, 2007; Thelin et al., 2017b). Although CSF is in direct contact with the extracellular space of the brain and can more prominently reflect biochemical alternations in brain due to TBI, blood-based biomarkers are less invasive, cost effective, and more feasible and acceptable for patients especially in the pediatric population. Therefore, serum TBI biomarkers have been studied more extensively than CSF biomarkers. There are also limited studies available on the utility of biomarkers in urine (Pickering et al., 2008) and saliva (Hicks et al., 2018) for pediatric TBI. However, it is challenging to utilize urine and saliva to diagnose TBI due to the fact that biomarkers have to cross a number of barriers to appear in these biofluids. In this section, we will mainly focus on TBI biomarkers in serum and briefly review TBI biomarkers in urine and saliva.

To date, numerous clinical and pre-clinical TBI studies have examined several brain-related and injury sensitive biofluid biomarkers that are linked to dynamic changes in metabolism, extracellular matrix, glial, axonal or neuronal damages, and/or neuroinflammation over time following TBI. Among those are S100β and glial fibrillary acidic protein (GFAP) that are related to glial damage; Hyperphosphorylated neurofilaments (NFs: NF-L and NF-H) and Tau that are related to axonal damage; Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-L1) and Neuron-Specific Enolase (NSE) that are related to neuronal cell damage; Interleukins (IL-1β, IL-6, IL-8, IL-10) and Tumor Necrosis Factor-α

Table 1
A summary of pediatric clinical and preclinical studies for TBI biomarkers.

Study	Biomarker(s)	Sample size	Causes and severity of TBIs	Age range	Sampling time	Key findings (e.g. patients vs control, correlation with severity or abnormal CT)	Recommended for diagnostic and prognostic
Clinical studies – biofluid biomarkers							
Fridriksson et al. (2000)	Serum NSE	50	Mild/moderate/severe (n = 50), no control	2 months-16 years	Within 10 h post injury (except one data in 23 h)	– Correlation between NSE level and severity – Serum NSE is capable of predicting ICI with sensitivity of 77% and specificity of 52%, however 25% of ICI patients would have been missed using solely NSE	– Recommended serum NSE as a potential diagnostic tool for predicting ICI in children with blunt head trauma but not to be used as a sole marker
Berger et al. (2002)	Serum S100β	61	Mild (n = 27), moderate (n = 6), and severe (n = 12), control (n = 16)	0–13 years	At 0.5-15.25 h post injury and every 12 h for up to 5 days	– Used NSE cut-off level of 15 ng/mL – Higher serum S100β (H1 > avg. + 2SD of control) after TBI in half of TBI patients (any severity) but the increase lasted > 12 h after injury only in severe TBI patients. – Marginal correlation between serum S100β concentration and GSC score (higher serum S100B for lower GSC) – No relationship between serum S100B elevation and the presence of an abnormal CT	N/A
Spinella et al. (2003)	Serum S100β	163	Mild/moderate/severe (n = 27), control (n = 136)	0–18 years	Within 12 h post injury	– Used S100β cut-off value of 0.25 μg/L. – Higher S100β serum levels (≥2.0 μg/L) in TBI patient with poor 6-months post-injury outcome – Found a mean S100β level of 0.3 μg/L. (0.03–1.47 μg/L) for healthy children	Recommended serum S100β as a potential prognostic tool as its level seems to be associated with long-term outcome
Chiaretti et al. (2005)	Serum and CSD IL-6, IL-1β	26	Severe TBI (n = 14), control (n = 12, obstructive hydrocephalus)	3 months–16 years	2 h and 24 h post-TBI	– IL-1β1 was significantly lower than the IL-6 level both in the CSF and serum – Significant correlation between increase of IL-6 and IL-1β in both CSF and serum from 2 h to 24 h post TBI and severity of TBI and 6 months post-TBI outcomes	– Recommended IL-6 and IL-1β as potential prognostic biomarkers of severe TBI in children
Bandyopadhyay et al. (2005)	Serum NSE	86	Mild (n = 76), moderate (n = 6), severe (n = 4), no control	11 months-18 years	Within 0.4-14.8 h post injury	– Found higher NSE serum levels (mean = 46.4 ng/mL) in TBI patients with poor short-term functional outcomes – Used NSE cut-off level of 21.2 ng/mL	– Recommended serum NSE as a potential prognostic tool as its level seems to be associated with short-term outcomes and maybe useful early predictor of disability in children following closed TBI
Berger et al. (2005)	Serum S100β, NSE (and MBP)	164	TBI (n = 100, including 56 nTB and 44 iTBI), control (n = 64)	0–13 years	Within 12 h post injury, another with 12–24 h, for severe TBI daily up to 5 days	– No difference between serum NSE, S100β and MBP between children with iTBI and nTBI, however iTBI patients had a later peak of all three biomarkers compared with nTBI patients – Higher initial serum NSE and S100β levels for TBI than control	– Recommended time to peak serum NSE, S100β and MBP as a potential tool to discriminate iTBI from nTBI

Table 1 (*continued*)

Study	Biomarker(s)	Sample size	Causes and severity of TBIs	Age range	Sampling time	Key findings (e.g. patients vs control, correlation with severity or abnormal CT)	Recommended for diagnostic and prognostic
Berger and Kochanek (2006)	Serum and urine S100β	29	TBI (n = 111, including 105 without ICI and 6 with ICI), no control	< 13 years	Every 12 h for 3 days post TBI	– Urinary S100β peak later (55 h post TBI) than serum S100β concentrations (14 h post TBI) – Urine S100β was detectable in 80% of TBI patients and 0% of control – TBI patients with undetectable S100β urine as well as TBI patients with normal serum S100β levels were more likely to have good outcomes	– Recommended serum and/or urine S100β as a potential prognostic tool to assist in the prediction of outcome after pediatric TBI
Berger et al. (2007)	Serum S100β, NSE (and MBP)	159	TBI (n = 159), no control	0–13 years	Within 12 h post-TBI, 12–24 h, for severe TBI daily to 5 days	– Correlation between serum S100β, NSE, MBP at all time points and long-term outcomes – Initial and peak NSE concentrations and initial MBP levels more strongly correlated with outcome in children ≤4 years compared with those > 4 years	– Recommended serum NSE, S100β and MBP as a potential prognostic tool for long-term outcomes of TBI (NSE better predictor for children < 4 than > 4 years)
Beers et al. (2007)	Serum S100β, NSE (and MBP)	30	TBI (n = 30, including15 nTB and 15 iTBI), no control	0–13 years	Within 12 h post injury, every12hrs up to 5 days	– Significant difference between time to peak serum NSE, S100β and MBP between children with iTBI and nTBI – Correlation between time to peak serum NSE, S100B and MBP and 6-months post TBI outcomes	– Recommended time course of serum NSE, S100β and MBP as a potential prognostic tool for long-term outcomes of TBI
Piazza et al. (2007)	Serum S100β	15	8 accidental falls, 7 road accidents, mild (n = 9), moderate (n = 2), severe (n = 4), no control	1–15 years	At admission to ER (within 12 h post injury) and after 48 h	– A trend toward correlation between the severity of TBI and serum S100β increase (higher serum S100B for lower GCS score at admission). – CT scans were performed; no data was reported – Used S100B cut-off value of 0.3 μg/L.	– Did not recommend serum S100β to be used as a prognostic tool, particularly when TBI is associated with extracranial lesions
Buttram et al. (2007)	CSF cytokine including IL-6, IL-8, IIβ, IL-10 (, MIP-1α)	46	Severe TBI (n = 36), control (n = 10)	N/A	Serial sampling up to 72 h	– Moderate therapeutic hypothermia did not reduce the elevation of CSF cytokine levels in children after TBI compared to normothermia – Severe TBI in infants and children induces increases in pro- and anti-inflammatory cytokines	none
Pickering et al. (2008)	Urine S100β	35	Mild TBI (n = 17), moderate TBI (n = 1), severe TBI (n = 2), control with limb/fracture injury (n = 15)	< 13 years	Within 12 h post injury,	– Detect S100β in urine in 50% of TBI (0.02–0.07 μg/L) and all extracranial trauma (0.02–0.09 μg/L) patients	Did not recommend urine S100β as an early diagnostic biomarker of TBI
Castellani et al. (2009)	Serum S100β	109	Mild (n = 109), no control	0–18 years	Within 6 h post injury	– Higher serum S100β for patients with positive abnormal CT scans – Used S100β cut-off value 0.16 μg/L	– Recommended serum S100β as a potential diagnostic tool with high sensitivity but low specificity for ICI in mild TBI patients as evidenced by CT scans (raised limitation for children ≤3 years as S100β varied by age a lot at this period)

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Table 1 (*continued*)

Study	Biomarker(s)	Sample size	Causes and severity of TBIs	Age range	Sampling time	Key findings (e.g. patients vs control, correlation with severity or abnormal CT)	Recommended for diagnostic and prognostic
Geyer et al. (2009)	Serum S100β and NSE	148	Mild (*n* = 148), 53 asymptomatic and 95 symptomatic mTBI	0.5–15 years	Within 6 h post injury	– Did not find serum S100β and NSE capable of discriminating between symptomatic and asymptomatic pediatric mTBI – Correlation between S100B and NSE – Negative correlation between both S100β and NSE and age	none
Lo et al. (2009)	Serum S100β, NSE, IL-6, IL-8, IL-10, (SICAM), L-selectin, and endothelin)	28	Mild TBI (*n* = 2), moderate TBI (*n* = 9), severe TBI (*n* = 17) (19 diffuse and 9 focal TBI)	4 months–14 years	At 24 h post-TBI	– 8 biomarkers were measured, and 20 combination of 2-biomarkers were examined, and 5 paired showed high degree of outcome predictability compared to any single biomarker	– Recommended combination of S100β with IL-6, L-selectin, or NSE as a potential prognostic biomarker for predicting poor 6-month post-TBI outcome which outperformed any individual marker
Hallén et al. (2010)	Serum and urine S100β	111	TBI (*n* = 111, including 105 without ICI and 6 with ICI), no control	< 13 years	Within 6 h post injury, and 6 h later	– Significant higher serum S100β in TBI patients with ICI (as evidenced by CT scans) than the ones without ICI – Did not find any difference between urine S100β between group with and without ICI	– Recommended serum (but not urine) S100β as a diagnostic tool for TBI addition to those used in clinical practice today but not as a sole tool
Fraser et al. (2011)	Serum (and CSF) GFAP	27	Severe TBI (*n* = 27), no control	2–17 years	Serums were collected daily for 10 days post TBI	– Serum GFAP on day 1 correlated with 6 months post TBI outcomes but not correlated w/injury severity or CT results – GFAP was dramatically elevated in CSF and serum in children after severe TBI – Hypothermia therapy did not alter serum GFAP levels compared with normothermia after severe TBI in children	– Recommended serum GFAP concentration as a prognostic tool and treatment efficacy assessment for TBI in combined with other biomarkers
Bouvier et al. (2012)	Serum S100β	466	Mild TBI (*n* = 424 including 183 with GSC = 15 and no symptoms), moderate/severe (*n* = 22),no control	0–16 years	Within 3 h post injury	– Found serum S100β to be capable of discriminating between patients with normal and abnormal CT scans with high sensitivity (100%) and relatively low (33%) specificity – S100β cut off values were used: 0.35 μg/L for age 0–9 months,0.23 μg/L for age 10–24 months, and 0.18 μg/L for age > 24 months	– Recommended serum S100β as potential diagnostic tool to reduce the number of required CT scans
Berger et al. (2012)	Serum S100β, NSE, MBP, UCH-L1	49	Mild (*n* = 11), moderate (*n* = 12), severe (*n* = 16), control (*n* = 10)	1 week-12.4 years (4.1 ± 3.8 years)	Within 24 h of hospital admission	– Correlation between serum UCH-L1 (not NSE, MBP, S100β) and GSC scores, suggesting it may have potential in predicting injury severity and outcomes	– Recommended serum UCH-L1 as potential prognostic tool, may be useful in assessing outcome after moderate and severe pediatric TBI

Table 1 (*continued*)

Study	Biomarker(s)	Sample size	Causes and severity of TBIs	Age range	Sampling time	Key findings (e.g. patients vs control, correlation with severity or abnormal CT)	Recommended for diagnostic and prognostic
Žurek and Fedora (2012)	Serum S100β, NSE, GFAP, NF-H (Hsp70)	63	TBI (n = 63), no control	0–19 years	Within 12 h post injury, daily up to 6 days	– NF-H in significant amounts in the blood of children with TBI and grew significantly faster in patients who had worse outcomes or died – Higher initial serum NSE, S100β, GFAP levels in patients who died or had worse outcomes – 2nd peak for GFAP 3-4 days post TBI – Studied temporal profile by serial sampling & found S100β, GFAP peaked within 12 h, NSE peaked later within 1-2 days post-TBI and NFH continued to increase even 6 days post TBI	– Recommended these serum biomarker as potential prognostic tools to predict outcomes of TBI in children as their serum levels seems to correlate with mortality
Babcock et al. (2012)	Serum S100β	109	Mild (n = 94), moderate/severe (n = 15), no control	< 19 years (14.6 ± 4.0)	Within 6 h post injury	– Higher serum S100β for TBI patients with abnormal CT scans than with normal CT – Found serum S100β levels to correlate with TBI severity in children. – S100β was a fair predictor of abnormal cranial CT results for children with all severities of TBI except children with mTBI and a GCS of 15 – Determined S100β cut-off value of 0.006 μg/L	– Recommended serum S100β to be used as diagnostic tool for predicting abnormal cranial CTs in children with TBI except for mTBI with GSC = 15
Babcock et al. (2013)	Serum S100β	76	Mild (n = 76), no control	≥ 5-18 years	Within 6 h post injury	– Did not find an association between S100β levels and post-concussion syndrome (PCS) for children with mTBI	– Did not recommend serum S100β to be used as a prognostic tool for children with mTBI
Mannix et al. (2014)	Serum GFAP	13	Concussion (n = 13), no control	11–17 years	One within 24 h and one withig 24–72 h post-TBI	– Initial GFAP levels (within 24 h) to be correlated with initial and follow-up symptom burden up to 1-month post TBI – Did not find follow-up GFAP levels (within 24–72 h) to be correlated with outcomes – Average GFAP within 24 h post-concussion 0.12 ng/mL and 0.04 ng/mL within 24–72 h post-concussion (no ICI when imaging was obtained)	– Recommended serum GFAP as a potential prognostic tool for objective measure of injury and recovery after pediatric concussion
Manzano et al. (2016)	Serum S100β	73	Mild (n = 73), no control	n = 9 < 2 years, n = 64 2-16 years	Within 6 h post injury	– Found higher sensitivity for serum S100β in predicting abnormal CT scans in children > 2 years in comparison to children < 2 years – Found higher serum S100β for patients with intracranial injury (ICI) as evidenced abnormal CT scans than without ICI – Used S100β cut-off value of 0.14 μg/L	– Recommended serum S100β to be used as diagnostic tool with high sensitivity and poor specificityfor abnormal CT, helpful to rule out CTs but not to be used as a sole marker due to poor specificity performance

Table 1 (*continued*)

Study	Biomarker(s)	Sample size	Causes and severity of TBIs	Age range	Sampling time	Key findings (e.g. patients vs control, correlation with severity or abnormal CT)	Recommended for diagnostic and prognostic
Papa et al. (2015)	Serum GFAP	257	Mild (n = 254), moderate (n = 3), trauma control without head trauma (n = 60)	2 weeks-21 years (n = 56 < 5 years)	Within 6 h post injury	– Found serum GFAP (6 h post-TBI) correlated with injury severity and CT results – Determined GFAP cutoff level of 0.15 ng/mL for detecting ICI – Found higher GFAP serum levels in subjects with ICI on CT scans compared to those without ICI (with TBI-no ICI or with other trauma)	– Recommended serum GFAP as a diagnostic tool for detecting ICI as even for infants and toddlers (< 5 years) and mTBI with GSC = 15
Papa et al. (2016)	Serum GFAP & S100β	155	Mild (n = 112), moderate (n = 2), trauma control without head trauma (n = 41)	6 months-21 years (n = 56 < 5 years)	Within 6 h post injury	– GFAP performed better than S100β in diagnosis of TBI and predicting intracranial lesions on head CT specially for children < 10 years and even better for children < 5 years – Determined GFAP cutoff level of 0.15 ng/mL and S100β cutoff level of 0.020 ng/mL for detecting ICI	– Recommended serum GFAP over S100β as diagnostic tool of TBI particularly for young children
Rhine et al. (2016)	Serum GFAP & UCH-L1	45	Mild TBI (n = 25), orthopedic injury (OI)(n = 20)	11–16 years	Within 6 h post-TBI & 3 more times over 1 moth post-TBI	– GFAP but not UCH-L1 to be significantly higher acutely following mTBI compared to orthopedic injury – Did not find GFAP or UCH-L1 capable of predicting 1 month post-TBI outcomes	– Recommended GFAP (but not UCH-L1 specially in presence of non-TBI trauma) as a potential diagnostic tool for children with mild TB
Mondello et al. (2016b)	Serum S100β, GFAP, UCH-L1 (and MBP)	85	Mild (n = 20), moderate (n = 6), severe (n = 19), control (n = 40)	< 15 years (3.8 ± 3.7 years)	0.5–20.6 h post injury	– Serum UCH-L1 and GFAP performed better than S100β and MBP in prediction of 6-months post-injury outcomes – Found higher GFAP and UCH-L1 serum levels in TBI patient compared with controls – Correlations between serum UCH-L1 and GFAP levels and severity of injury – GFAP and UCH-L1capable of discriminate mild TBI from control – UCH-L1 but not GFAP capable of discriminating patients with and without ICI – Determined UCH-L1 cut-off value of 0.09 ng/mL for ICI detection	– Recommended serum UCH-L1 and GFAP as diagnostic tools to discriminate between TBI vs contol and as potential prognostic tools for predicting long-term outcome – Recommended serum UCH-L1 as a diagnostic tool to detect ICI
Papa et al. (2017)	Serum UCH-L1	256	Mild (n = 253), moderate (n = 3), control (n = 60)	2 weeks-21 years (n = 56 < 5 years)	Within 6 h post injury	– Higher UCH-L1 serum levels in subjects with ICI on CT scans compared to those without ICI (with TBI-no ICI or with other trauma), no significant difference between mild TBI without ICI and non-TBI trauma control – Determined UCH-L1 cut-off level of 0.18 ng/mL for detecting ICI	– Recommended serum UCH-L1 as a diagnostic tool for detecting ICI as evidanced by CT scans, even for infants and toddlers (< 5 years) and mTBI with GSC = 15
Johnson et al. (2018)	Saliva microRNA	59	Concussion (n = 59)	7–21 years	Within 14 days	– Found 5 miRNAs (miR-320c-1, miR-133a-5p, miR-769-5p, let-7a-3p, and miR-1307-3p) levels in saliva capable of identifying concussion prolonged symptom	– Recommended salivary microRNA as a potential tool to identify prolonged concussion symptoms

Table 1 (*continued*)

Study	Biomarker(s)	Sample size	Causes and severity of TBIs	Age range	Sampling time	Key findings (e.g. patients vs control, correlation with severity or abnormal CT)	Recommended for diagnostic and prognostic
Park et al. (2018)	Serum S100β and NSE	10	mild/moderate TBI (*n* = 5), moderate/severe TBI (*n* = 5), no control	6–18 years	within 6 h post injury, and 1-week post-injury	– Elevated serum S100β and NSE levels within 6 h after TBI decreased at 1 week after trauma – Found serum S100β level at 1 week after TBI to be correlated to the severity of brain damage	– Recommended S100β and NSE serum biomarker as potential peognostic tools to predict and monitor outcomes of TBI in children
Park and Hwang (2018)	Serum S100β, NSE, and IL-6	15	TBI (*n* = 15), no control	4–18 years	Within 6 h post injury, and 1-week post-injury	– Levels of S100β and NSEwithin 6 h post TBI were related to injury severity and at 1 week after TBI were related to 6-month post TBI outcomes – Elevated serum S100β, NSE, and IL-6 levels within 6 h after TBI decreased at 1 week after trauma	– Recommended serial sampling of serum S100β and NSE (but not IL-6) as potential prognostic tools for assesing injury severity and predicting long-term outcomes in pediatric TBI
Hicks et al. (2018)	Saliva and CSF microRNA	129	Severe TBI (*n* = 8 for CSF), mild TBI (*n* = 61, for saliva), control (*n* = 60, for saliva)	4–21 years	Saliva sampled within 14 days post-TBI, CSF sampled: 1, 4–7, & 8–17 days post TBI	– Six miRNAs showed parallel alternation in saliva after mild TBI and in CSF after severe TBI (miR-182-5p, miR-221-3p, mir-26b-5p, miR-320c, miR-29c-3p, miR-30e-5p) – microRNA in saliva were capable of distinguish mild TBI from control – Found 135 microRNA in saliva after mild TBI	– Recommended Salivary microRNA as a potential diagnostic biomarker for TBI but more studies are required
Clinical studies – EEG							
Mizrahi and Kellaway (1984)	EEG measures	660	Concussion with LOC	3 mos.-15 years	At least 6 months post injury	Resting EEG abnormalities correlated with severity of concussion	– Recommend the use of EEG as a tool to measure and monitor pediatric concussion
Gaetz et al. (2000)	EEG measures	60	Sport related concussion (*n* = 15 one concusison, *n* = 15 two concussions, *n* = 15 with 3+ concussions), Control (*n* = 15)	16–21 years	At least 6 months post injury	Longer P3 latency for 3+ concussion groups in comparison to control for visuall oddball task	– Recommend P3 as an EEG feature of increased severity of injury
Kiefer et al. (2015)	EEG measures	1	Sport related concussion	15 years	36 h before injury, 18 h, 21d, 50d, 116d	Brain Network Activation algorithm demonstrated improved scores over time and after subject returned to play during auditory oddball task	– Recommend multivariate EEG measures as a potential tool to evaluate brain function over time
Moore et al. (2015)	EEG measures	30	Sport related concussion (*n* = 15), Control (*n* = 15)	8–10 years	At least 6 months post injury	Decreased N1 amplitude and prolonged N2 latency for Switch Task, decreased P3 amplitude and prolonged N2 for Go-NoGo	– Recommend N1, N2, and P3 features for EEG analysis of concussed children
Howell et al. (2018)	EEG, Gait parameters	20	Sport related concussion	8–18 years	7 ± 2.5 days after injury	Using a visual Go/No-Go, Brain Network Activation score for relative time between visual events found to be moderately correlated with average walking speed	– Recommend analyzing EEG with dual task gait schemes
Jacquin et al. (2018)	EEG, SCAT-3, Reaction time	364	Sport related concussion (*n* = 177), Control (*n* = 187)	13–25 years	Day 0 (time of injury), Day 5, Return To Play date, 45 days after RTP	Multimodal Brain Function Index (eBFI) able to detect differences between control and concussed group during resting EEG	– Recommend multivariate, multimodal analysis combining EEG and other measures as a potential tool to detect and monitor concussion
Baillargeon et al. (2012)	EEG measures	96	Sport related concussion (*n* = 48), Control (*n* = 48)	9–27 years	Within 1 year after injury	No differences in P3a amplitude and latency. Main effect of age on amplitude and latency for P3b for visual oddball task	– Recommend age specific P3b as a potential measure for concussion detection and monitoring

Clinical studies – actigraphic measures, gait and eye response

Table 1 (*continued*)

Study	Biomarker(s)	Sample size	Causes and severity of TBIs	Age range	Sampling time	Key findings (e.g. patients vs control, correlation with severity or abnormal CT)	Recommended for diagnostic and prognostic
Kaufman et al. (2001)	Actigraphic measures	34	Mild head injury (n = 19), Control (n = 15)	10–17 years	4 years post injury	Actigraphic recordings were able to detect poorer sleep quality, lower sleep efficiency, and more time awake for the injured group	– Recommend the use of actigraphy as an indicator of sleep quality after concussion
Milroy et al. (2008)	Actigraphic measures	48	Concussion (n = 18), Orthopedic Control (n = 30)	7–12 years	At least 6 months post injury	No significant differences were reported for sleep disturbances between groups	– Actigraphy measures may not be specific to brain injury, and polytrauma may be a cofounding factor when interpreting data
Katz-Leurer et al. (2008)	Gait parameters	48	TBI (n = 24), control (n = 24)	7–14 years (8.7 ± 3.5 years)	3–12 months	– Significantly shorter step length, longer step time, higher hip abductor and knee extensor strength values and higher variability of step length and time post-TBI	None
Tham et al. (2015)	Actigraphic measures	100	Concussion (n = 50), Control (n = 50)	12–18 years	At least 12 months post injury	– Actigraphy measures were able to detect poorer sleep quality, shorter sleep durations, and more active minutes during the night for injured group	Recommend the use of actigraphy
DiCesare et al. (2017)	Eye response	49	Sport related TBI (n = 17 recent and n = 15 days after injury) Control (n = 17)	16.8 ± 1.2 years	7.67 days after injury	– Significant change in saccade latency and fixation error and initial fixation error	– Recommended the eye-tracking analysis scheme can be used for accurate diagnosis and prognosis
Preclinical studies – biofluid biomarkers							
Robinson et al. (2016)	Serum GFAP, serum cytokines including TNFα, IL-1β, IL-6, IL-10, gait parameters	125	CCI TBI model (n = 76), control/sham (n = 49)	P12 rat equivalent to several-month-old infant human age stage	3 days post-TBI or 13–16 days post-TBI (chronic group)	– Functional outcomes post TBI were reflected in serum and imaging biomarkers using P12 rat CCI model of infant TBI – Significant elevation of serum GFAP and TNFα 3 days post-TBI	– Recommended combination of imaging and serum biomarker using pre-clinical models as a potential tool for therapeutic interventions and efficacy assessment tool
Hajiaghamemar et al. (2017)	Serum amino acids (17 amino acids)	25	CCI TBI (n = 12), RNR (n = 13), pre-injury as control (n = 25)	4 weeks piglets equivalent to toddler human stage	Pre injury, at 24 h or 4 days post-TBI	– Combination of Glycine, Taurine, and Ornithine aminoacids as optimal TBI diagnosis for focal-diffuse TBI	– Recommended a panel of biomarker rather than single biomarker as a potential diagnostic tool for TBI
Preclinical studies – EEG							
Ibrahim et al. (2010)	EEG measures	5	Low and moderate level axial plane rapid non impact rotation (RNR)	4 weeks piglets equivalent to toddler human stage	6 h post injury	Suppression of resting EEG activity after moderate injury and remained up to 6 h post injury	– Recommend EEG as a tool to monitor concussion in the piglet model
Atlan et al. (2018)	EEG measures	22	Rapid non impact rotation (RNR), Controlled cortical injury (CCI)	4 weeks piglets equivalent to toddler human stage	Pre, 1, 4 or 5, 7 days	Decreased N40 and P60 amplitude and longer latency on days post injury in comparison to pre injury day for auditory oddball paradigm	– Recommend auditory oddball paradigm for use to study concussion in piglet model of brain injury
Sabir et al. (2015)	Electrocorticoraphic measures	14	Weight drop injury (n = 7), Sham (n = 7)	10–21 weeks mice equivalent to toddler human stage	Day 1 and 2 post injury	Brain injured mice had a decreased ability to stay awake and were reflected in spectral activity measures	Electrocorticographic measures are sensitivity to sleep disruptions post-concussion, however implanted electrodes are invasive
Preclinical studies – actigraphic measures, gait and eye response							
Jaber et al. (2015)	Balance parameters	25	CCI and RNR piglets	4 weeks piglets equivalent to toddler human stage	pre,1–6, 24 h	– Significant increase in the root mean square acceleration in the anterior-posterior and medial-lateral directions	– Recommended bispectral index and postural sway as diagnostic tools to assess brain injury deficits in a piglet model of TBI
Olson et al. (2016)	Actigraphic measures	30	CCI (n = 8), RNR (n = 9), Sham (n = 6), Naïve (n = 7)	3–4 weeks piglets equivalent to toddler human stage	Day 4–6 post injury	Injured piglets had greater periods of inactivity during the day and greater active periods during the night	– Recommended the use of accelerometer based actigraphic measures as an indicator of sleep quality for concussion in piglets

Table 1 (*continued*)

Study	Biomarker(s)	Sample size	Causes and severity of TBIs	Age range	Sampling time	Key findings (e.g. patients vs control, correlation with severity or abnormal CT)	Recommended for diagnostic and prognostic
Baker et al. (2018)	Balance parameters	16	CCI piglets	3- & 6-weeks piglets equivalent to toddler human stage	Pre, 1, 3, 7 days	Significant decrease in stride velocity and 2-limb support	– Recommended gait parameters as diagnostic tool

(TNFα) that are related to inflammation, and amino acids and other metabolites that are related to energy deficits following TBI.

3.1.1. S100β

S100β is a small calcium binding protein expressed mainly in astrocytes and certain neuronal cell types and is the most frequently explored biomarker for TBI diagnosis (Babcock et al., 2012; Bouvier et al., 2012; Castellani et al., 2009; Hallén et al., 2010; Manzano et al., 2016; Pickering et al., 2008) and prognosis (Babcock et al., 2013; Park et al., 2018; Park and Hwang, 2018; Piazza et al., 2007; Spinella et al., 2003; Žurek and Fedora, 2012) in pediatric clinical studies (Table 1). Serial serum sampling in clinical studies showed that S100β elevates and declines quickly following TBI and is present for a short time in serum with a half-life of an hour to a day (Park et al., 2018; Thelin et al., 2017b; Žurek and Fedora, 2012). Pre-clinical studies using different models of TBI such as CCI (Cardinell, 2017), WDI (Ma et al., 2018), and blast (Ahmed et al., 2015) also reported significant alternation of S100β serum concentration following TBI. These studies focused on adult animals and, to our knowledge, none of the pre-clinical studies investigating S100β focused on infant/pediatric TBI.

For diagnostic purposes, most pediatric studies (Table 1) focused on investigating the capability of S100β to detect intracranial lesions as evidenced by abnormal CT scans. Higher serum concentration of S100β were found in patients with abnormal CT scans compared to control cohorts or patients with normal CT. Therefore, it is suggested that serum S100β is a potential diagnostic tool for predicting intracranial lesion and abnormal CT in children with TBI (Babcock et al., 2012; Bouvier et al., 2012; Castellani et al., 2009; Hallén et al., 2010; Manzano et al., 2016). Although S100β serum concentration is limitedly in clinical use for adults as a general screening tool to identify those in need of CT scanning (Thelin et al., 2017b), it has not yet been studied and validated extensively enough to be recommended for clinical use in the pediatric population (Lumba-Brown et al., 2018). The literature on S100β serum biomarker in pediatric TBI is not as rich as it is for adult and the cut-off values for abnormal S100β are diverse in the pediatric literature (0.006–0.35 μg/L, Table 1). These diverse results may be explained by the fact that brain tissue and biofluid expression of S100β are highly age-dependent, particularly in the very young age due to the ongoing central neurodevelopmental process (Modi and Kanungo, 2010; Park et al., 2018; Portela et al., 2002). The large age variation in most current pediatric TBI studies (Babcock et al., 2012; Castellani et al., 2009; Geyer et al., 2009; Lugones et al., 2018; Manzano et al., 2016) (Table 1) is another factor that contributes to the diverse cut-off value results in the literature. Another explanation is that S100β is not a brain-specific biomarker and may be derived from extracranial sources such as musculoskeletal injury and bone fracture (Agoston et al., 2017; Rothermundt et al., 2003). Some of the pediatric TBI studies used healthy subjects as control while some others used patients with limb or fracture injury as control cohort. The S100β threshold value associated with TBI detection is still debated even for adults (Kövesdi et al., 2010) in whom S100β were shown to be less sensitive with age (Modi and Kanungo, 2010). Non-brain specificity and high age dependency of S100β in the young brain make it difficult to determine an optimal cut-off value sensitive and specific enough to reliably diagnose TBI in infant and pediatric populations. The utility of S100β serum biomarker to distinguish iTBI from nTBI has also been investigated in a few pediatric studies (Beers et al., 2007; Berger et al., 2005) and did not find significant difference between peak serum concentration of S100β or NSE in children from either cause. However, Beers et al. (2007) and Berger et al. (2005) found significant longer time to peak for iTBI patients compared to nTBI patients and therefore, suggested time to peak of S100β and NSE as potential tools for discriminating iTBI from nTBI in pediatrics.

For prognostic purposes, many pediatric studies investigated the peak or temporal profile of S100β concentration following TBI to determine the severity of injury and/or predict short- or long-term

outcomes of TBI (Babcock et al., 2013; Berger and Kochanek, 2006; Park et al., 2018; Park and Hwang, 2018; Piazza et al., 2007; Spinella et al., 2003; Žurek and Fedora, 2012) (Table 1). The results of these studies are sometimes conflicting, with some showing correlation between S100β levels early after TBI (within a day) (Berger and Kochanek, 2006; Spinella et al., 2003; Žurek and Fedora, 2012) or 1-week post-TBI (Park et al., 2018; Park and Hwang, 2018) and the long-term TBI outcomes while others did not find any correlation especially in the presence of extracranial injury (Babcock et al., 2013; Piazza et al., 2007). The conflicting results may be explained by the fact that S100β is not a brain specific marker. The elevation of serum S100β following TBI has been shown to be an indication of blood-brain barrier (BBB) disruption, which has a critical role in pathophysiology outcomes of TBI even years later (Blyth et al., 2009; Kanner et al., 2003) that may explain the correlation of serum S100β and the long-term post-TBI outcomes. Studies demonstrated that the rate of decline of serum S100β inversely correlates with severity of TBI, with a slower decline for more severe TBI in both pediatrics (Žurek and Fedora, 2012) and adults (Thelin et al., 2017a).

In addition to serum, S100β urine concentrations has been investigated as diagnostic and/or prognostic TBI biomarker in a few pediatric studies (Berger and Kochanek, 2006; Hallén et al., 2010) but the results are inconclusive. Hallén et al. (2010) found no significant difference in urine S100β concentrations between pediatric TBI patients with and without intracranial complications while they found a significant difference in serum S100β concentrations between these two groups. Contrarily, Berger and Kochanek (2006) found an increase in both urinary and serum S100β concentrations in children with TBI. They reported that peak urinary S100β concentrations occurred significantly later than peak serum S100β concentrations.

In summary, although S100β is the most widely studied biomarker in pediatric TBI, the non-brain specificity and high age-dependency attributes in the young brain suggest that S100β is not an appropriate biomarker to be used as a sole tool for diagnosis of TBI in pediatric population. However, due to its rapid release into blood following TBI, it is a valuable biomarker to be combined with other biomarkers and tools in clinical practice today for early diagnosis of TBI especially in the absence of extracranial injuries.

3.1.2. Glial fibrillary acidic protein (GFAP)

GFAP, a marker of astroglial injury, is another well studied TBI biomarkers explored in many pediatric clinical studies (Fraser et al., 2011; Mannix et al., 2014; Mondello et al., 2016b; Rhine et al., 2016; Žurek and Fedora, 2012) as well as infant/pediatric pre-clinical studies (Robinson et al., 2016) (Table 1) and has been shown to be dramatically elevated in serum following TBI. GFAP showed a rapid influx, but slower than S100β, in serum following TBI and remained elevated for a longer time in comparison to S100β (Thelin et al., 2017b; Žurek and Fedora, 2012), which provides a wider time window for this biomarker to diagnose TBI, and thus, reduces the probability of missing detection due to late blood sampling. Although serum GFAP and S100β are both linked to glial injury, GFAP performs better than S100β in detecting head trauma and predicting intracranial lesions on head CT in pediatric TBI especially in young children (< 5 years) and in presence of extracranial injuries (Papa et al., 2016). This enhanced predictive performance may be attributed to the fact that GFAP, in contrast to S100β, is a CNS specific protein (Mondello et al., 2016b; Papa et al., 2015). Several studies recommended serum GFAP to be used as a diagnostic marker of TBI specially for detecting intracranial hemorrhage (Kou et al., 2013; Mondello et al., 2011; Mondello et al., 2016b). Serum GFAP also found to be capable of discriminating between focal and diffuse TBI in adults as its elevation was shown to be significantly higher in focal and/or hemorrhagic injury than in non-hemorrhagic and/or diffuse brain injury (Kou et al., 2013; Mondello et al., 2011).

On the prognostic applications, serum GFAP concentration was shown to be predictive of TBI-induced brain pathology (Huang et al.,

2015; Mondello et al., 2016a), injury severity and poor long-term post-TBI outcomes (Fraser et al., 2011; Mondello et al., 2016b). All the pediatric studies explored GFAP (Table 1) except one (Rhine et al., 2016) reported that GFAP peak values within 24 h correlated with severity of injury and long-term post-TBI outcomes. Although both acute disintegration of astrocytes and reactive astrogliosis underlie circulating GFAP in serum and CSF after TBI, tissue pathology assessment of pre-clinical TBI models revealed that the acute disintegration of astrocytes is the dominant source of GFAP elevation in serum and CSF following TBI (Huang et al., 2015). This mechanism is consistent with the rapid and high elevation of serum GFAP which peaks within hours to a day following TBI (Fraser et al., 2011; Luoto et al., 2017) and has been attributed to early astrocyte damage that occurs within hours after injury (Huang et al., 2015; Zhao et al., 2003), whereas reactive astrogliosis occurs days post-TBI (Hellewell et al., 2010). A secondary peak in serum GFAP that has been observed a few days post-TBI (Fraser et al., 2011; Žurek and Fedora, 2012) may be due to the increase in reactive microglia.

The brain specificity of GFAP, its rapid and high elevation in serum following TBI, and the consistency of the finding in the literature (Table 1) suggest that serum GFAP is a suitable biomarker to be used as a TBI diagnostic and/or prognostic tool in pediatric population, especially if it combines with other biomarkers with different cellular origins and temporal profiles. However, more studies need to be done to better determine its predictability and characteristics to support the use of it in clinical practice.

3.1.3. Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1)

UCH-L1 is a neuronal injury marker and similar to S100β and GFAP showed a rapid influx and short time availability following TBI; however, UCH-L1 has a faster decline in comparison to GFAP (Huang et al., 2015; Kou et al., 2013; Mondello et al., 2011; Thelin et al., 2017a). Serum UCH-L1 has been explored in several pediatric clinical studies (Berger et al., 2012; Mondello et al., 2016b; Papa et al., 2017; Rhine et al., 2016) (Table 1) and adult pre-clinical studies (Huang et al., 2015; Mondello et al., 2016a) as a potential biomarker of TBI. Mondello et al. (2016b) and Papa et al. (2017) found serum UCH-L1 capable of identifying TBI patients with intracranial lesions as evidenced by abnormal CT from TBI patients with normal CT, uninjured (Mondello et al., 2016b) or non-TBI trauma control subjects for mild to severe TBI and suggested serum UCH-L1 as a potential diagnosis biomarker of intracranial lesions. However, Rhine et al. (2016) and Berger et al. (2012) did not find significant difference in serum UCH-L1 levels between pediatric patients with mild TBI and uninjured/non-TBI trauma controls.

On the prognostic application, Mondello et al. (2016b) and (Berger et al., 2012) found correlation between early elevation of UCH-L1 in serum and injury severity and long-term post-TBI outcomes. Pre-clinical studies using different models of TBI also showed direct relation between lesion volume, neuronal degeneration and astrocyte damage of brain tissue, and temporal profile of GFAP and UCH-L1 biomarkers in serum and CSF post-TBI (Huang et al., 2015). Studies that compared GFAP and UCH-L1 and/or S100β showed that GFAP is a better diagnostic biomarker for TBI in comparison to UCH-L1 and S100β especially in the presence of extracranial lesions as it is a CNS specific protein while UCH-L1 and S100β are not (Huang et al., 2015; Kou et al., 2013; Lewis et al., 2017; Papa et al., 2016; Rhine et al., 2016). For example, serum UCH-L1 showed to be elevated for sham-TBI animals in the presence of anesthesia and surgical procedure while no elevation was observed for GFAP (Huang et al., 2015). However, GFAP and UCH-L1, have different temporal profiles and cellular origins, therefore, multivariate analysis may enhance the predictability of each of them individually.

The utility of UCH-L1 in urine as a biomarker of brain injury has been also explored in adult TBI and no significant difference between controls and patients with white matter lesions in UCH-L1 levels in

urine were reported (Li et al., 2015). To date, no study has been explored urine UCH-L1 for pediatric TBI.

3.1.4. Neuron-specific enolase (NSE)

NSE is a glycolytic enzyme which is localized predominantly in the cytoplasm of neurons. Following TBI, NSE releases passively into the extracellular compartments under pathological conditions during neuronal cell destruction (Kövesdi et al., 2010) and then leaks into CSF and serum following neuronal cell death secondary to traumatic injury (Berger et al., 2002; Žurek and Fedora, 2012). This mechanism makes serum NSE a great biomarker candidate for monitoring ongoing injury after TBI (Park et al., 2018) and have been examined as TBI biomarker in many pediatric (Beers et al., 2007; Berger et al., 2005; Berger et al., 2007; Berger et al., 2012; Fridriksson et al., 2000; Park et al., 2018; Park and Hwang, 2018) and adult clinical studies (reviewed in (Thelin et al., 2017b)) as well as adult pre-clinical studies (Gyorgy et al., 2011). NSE like GFAP has a prolonged serum elevation post-TBI, however, serum NSE elevation has a longer time to peak and slower decline profile especially for more severe cases or cases with poor outcomes (Park et al., 2018; Thelin et al., 2017b; Žurek and Fedora, 2012). NSE with a serum half-life of 24–72 h has a longer temporal profile in comparison to S100β, UCH-L1 and GFAP (Beers et al., 2007; Thelin et al., 2017b; Žurek and Fedora, 2012) which makes it a better prognostic biomarker for possibly predicting outcomes and monitoring treatment effects. Slower elevation to peak NSE values, and appearance of a secondary peak in NSE temporal profiles in patients with progressing injury may also be attributed to delayed neuronal death following TBI (Bandyopadhyay et al., 2005; Park et al., 2018; Žurek and Fedora, 2012). Serial sampling in several pediatric studies showed that peak and time to peak of NSE concentrations correlate with short and long-term post-TBI outcomes in children with varying severity (Bandyopadhyay et al., 2005; Beers et al., 2007; Berger et al., 2007; Park et al., 2018; Žurek and Fedora, 2012). One of these studies showed stronger correlation of peak NSE concentration with outcome in children < 4 years of age (Berger et al., 2007). Many pediatric studies demonstrated the capability of NSE as predictor of intracranial injury and poor outcome following TBI (Bandyopadhyay et al., 2005; Beers et al., 2007; Berger et al., 2007; Park et al., 2018). Like UCH-L1 and S100β, NSE is not CNS specific and is also present in red blood cells and platelets which limits its utility as a predictor of TBI in multi-trauma cases (Johnsson et al., 2000). Although NSE is a marker of neuronal injury, histopathology of damaged brain tissue showed that NSE can also be an effective marker of axonal injury in its early stages (Ogata and Tsuganezawa, 1999). It is reported that after axonal injury, NSE is upregulated to maintain homeostasis, and thus, NSE can be detected in cytoplasm surrounding the disrupted axons (Ogata and Tsuganezawa, 1999; Yokobori et al., 2013). NSE serum levels in children with diffuse brain injury were twice as high as those with focal brain injury (Lo et al., 2009), and thus, this biomarker can discriminate these two types of TBIs. NSE has been shown to be age-independent in the pediatric population (Berger et al., 2005). Žurek and Fedora (2012) reported that NSE serum concentration was much higher and remain elevated for longer time after severe TBI in children compared to adults which may be an indication of more neuronal cell death and higher susceptibility of developing brains to TBI in compare to adults.

3.1.5. Neurofilaments (NFs)

NFs are the most abundant protein components of the axonal cytoskeleton and consists of three subunits NF-L (light), NF-M (medium), and NF-H (heavy) containing 543, 916 and 1020 amino acids, respectively (Petzold, 2005). NFs play an important role in the maintenance of axon caliber, growth of axons during development, and conducting of electrical impulses along axons (Yuan et al., 2012). NFs are proved markers of axonal injury that have been shown to accumulate in discrete regions of the axon following cytoskeleton damage resulting in swollen bulbs, disconnection and additional neuropathologic changes

(Smith and Meaney, 2000). However, there are presently a limited number of studies that have examined serum level of NFs as biomarkers of TBI in adult (Al Nimer et al., 2015) and pediatric clinical studies (Žurek and Fedora, 2012) as well as adult rat pre-clinical studies (Anderson et al., 2008; Shaw et al., 2005). Serum NFs remained elevated days after TBI in mild to severe cases but rose faster in severe cases or those with poor outcomes, suggesting that NFs may be of good prognostic value (Anderson et al., 2008; Žurek and Fedora, 2012). More studies are needed to evaluate the utility of NFs as biomarkers of TBI and to characterize their temporal profile.

3.1.6. Neuroinflammatory and metabolomic biomarkers

Besides biomarkers such as S100β, GFAP, UCH-L1, NSE, NF-L, NF-H that are linked to primary injury because of neuronal, glial, and/or axonal damages, there are biomarkers that are linked to the sequalae of metabolomic and inflammatory events following TBI which lead to energy deficits, brain tissue damages and atrophy evolving over hours, days, months, and even years. Therefore, metabolomic and neuroinflammatory biomarkers are linked to secondary pathology after TBI and underlie some of the acute and chronic neuropathological outcomes of TBI (Nizamutdinov and Shapiro, 2017).

Among neuroinflammatory biomarkers are cytokines that can be released by a wide variety of cells such as microglia, macrophages, and endothelial cells and play an important role in repair and maintenance of brain function after TBI, and thus, influence the secondary injury (Sordillo et al., 2016). Cytokines including TNFα, IL-1β, IL-6, IL-8, IL-10, and L-selectin are some of the common neuroinflammatory biomarkers that explored in a few pediatric clinical TBI studies (Buttram et al., 2007; Chiaretti et al., 2005; Park and Hwang, 2018) and pediatric pre-clinical studies (Robinson et al., 2016). These cytokines showed to be elevated in injured brain tissue, CSF and serum following TBI. IL-1β and IL-6 (Lo et al., 2009) and combination of S100β and IL-6 or L-selectin (Castellani et al., 2009) were found to be corelated with severity of injury and was predictive of poor long-term outcomes. From a therapeutic point of view, pre-clinical studies have illustrated that blockade of these cytokines can reduce brain injury (Sordillo et al., 2016). Given the role of neuroinflammatory cytokines in the secondary injury and long-term pathological outcomes of TBI, more studies are needed to evaluate these biomarkers for pediatric TBI and assess their possible age dependency.

Serum metabolite and metabolomic pathways have also shown to be significantly altered after TBI (Bahado-Singh et al., 2016; Hajiaghamemar et al., 2017; Louin et al., 2007; Yi et al., 2016), and their alternations are shown to be correlated with post-TBI neurodegeneration, neurological and cognitive impairments (Louin et al., 2007; Yi et al., 2016). Among metabolites, amino acids are shown to have an important role in neuronal survival, growth and differentiation as well as neuronal circuitry development and maintenance (Kurbat and Lelevich, 2009). Their role is even more significant in the developing brain as they are crucial to provide energy for all cellular processes required for brain development and function. Hence, the additional high metabolic demands following TBI have a synergistic effect and can intensify the outcomes of TBI in the pediatric population (McKenna et al., 2015). Despite the important role of metabolite biomarkers on post-TBI outcomes in pediatric, to our knowledge, these biomarkers have not yet investigated in any pediatric clinical TBI study. In adult TBI population, Yi et al. (2016) investigated the utility of metabolite biomarkers for diagnosis of TBI and identified a panel of nine serum metabolite biomarkers (serine, pyroglutamic acid, phenylalanine, galactose, palmitic acid, arachidonic acid, linoleic acid, citric acid, and 2,3,4-trihydroxybutyrate) capable of discriminating between TBI patients with and without cognitive impairment, and healthy controls. In a pediatric pre-clinical study, Hajiaghamemar et al. (2017) also found a panel of three amino acids capable of diagnosis of focal and disuse TBI with high sensitivity and specificity. In an adult pre-clinical study, plasma concentrations of the amino acid proline were found to be

correlated with post-TBI neurological deficit as a sign of brain damage severity, and thus, it has been suggested as a potential TBI monitoring biomarker candidate (Louin et al., 2007). The variety of metabolomic biomarkers and their key roles in dysregulating the normal neuronal developmental process after TBI emphasize their prognostic potentials to predict possible long-term neuronal deficits post-TBI, however more studies to be done in pediatric TBI.

3.1.7. microRNA

MicroRNAs are short non-coding endogenous RNA molecules that play key roles in the regulation of cellular processes such as cell signaling, proliferation, differentiation, survival, and death post-trauma. MicroRNAs recently became of great interest in the biomarker field due to their stability and abundancy in biofluids and their tissue-specific expression patterns. So far over 2000 microRNAs have been identified in the human and many studies have used microRNA profiling in different tissues and biofluids with the purpose of biomarker discovery for trauma and disease such as cancer, cardiovascular diseases, diabetes, nervous system disorders, and TBI (Di Pietro et al., 2018). Utility of microRNAs as TBI biomarkers is at very early stage. There are only handful of studies that have examined serum microRNA signatures as biomarkers of TBI and none of them are specific to children (Bhomia et al., 2016; Di Pietro et al., 2017; Redell et al., 2010; Yang et al., 2016). In addition, a couple of studies have recently explored microRNAs in saliva as TBI biomarkers for pediatric (Hicks et al., 2018; Johnson et al., 2018) and adult (Di Pietro et al., 2018). Hicks et al. (2018) examined alternations of CSF and salivary microRNAs after severe and mild TBIs. They found six microRNAs, functionally related to neuronal development, including miR-182-5p, miR-221-3p, mir-26b-5p, miR-320c, miR-29c-3p, and miR-30e-5p, that demonstrate similar alternation trends in CSF after severe TBI and in saliva after mild TBI. They reported that downregulation of miR-320c were directly correlated with attention difficulty post-TBI and it increased to baseline over time after injury. In the other pediatric study, Johnson and collaborators found concentrations of five salivary microRNAs including miR-320c-1, miR-133a-5p, miR-769-5p, let-7a-3p, and miR-1307-3p capable of distinguishing patients with prolonged symptoms of concussion. They also reported that concentrations of miR-320c-1 were correlated with memory difficulty 4 weeks post injury (Johnson et al., 2018). In another study, 21 microRNAs in saliva including two brain specific microRNAs (miR-27b and miR-142-3p) were reported that can discriminate between concussed and non-concussed adult athletes (Di Pietro et al., 2018). There are some pre-clinical studies that explored microRNA expressions in different brain regions after TBI (Di Pietro et al., 2018). Due to the variety of microRNAs that are expressed uniquely within specific brain regions and cell types and their stability and richness in biofluids, microRNAs have the potential to be ideal biomarkers for TBI. With additional pre-clinical and clinical investigations, biofluid microRNAs may be potential biomarkers for diagnosis and prognosis after TBI.

3.1.8. Biofluid biomarker considerations: clinical and preclinical

One of the challenges in clinical and translational studies of serum biomarkers is the development of baseline levels that represent the normal healthy population and the determination of a cut-off value for TBI prediction. The baseline and cut-off values will be even more difficult to determine when the biomarker is age-dependent. Many brain-related biomarkers such as S100β, GFAP and UCH-L1 are shown to be age dependent in the pediatric population and are significantly higher in younger children specially during the first year of age (Mondello et al., 2016b; Sabbatini et al., 1999). Conversely, NSE serum biomarkers did not show age dependency in children (Berger et al., 2006). Most current TBI pediatric studies were conducted over wide range of ages (e.g. up to 18 years) which may explain the diverse serum cut-off values of age-dependent biomarkers such as S100β reported in the literature. Cut-off values of age-insensitive biomarkers such as NSE is more consistent in the pediatric TBI literature, probably due to age

insensitivity of this biomarker (Papa et al., 2015). Overall, age-independent biomarkers have superiority over age dependent ones for pediatric population. For age-dependent biomarkers, normal serum concentrations and TBI cut-off values needs to be determined over a narrow age range to minimize age variability. Age dependency of some serum biomarkers also emphasizes the importance of using age appropriate pre-clinical models in translational biomarker pediatric TBI research to enable discovering compatible and sensitive biomarkers. Within this context, one of important challenges for successful translation of serum biomarkers to clinical diagnostics is difference of the concentration levels and validity of biomarkers cross-species which can be overcome through a direct comparison between animal models and human data (Mondello et al., 2016a).

Another challenge with TBI biomarkers is that many of them such as S100β, UCH-L1, NSE, amino acids and many others are not brain specific. These biomarkers are expressed in other organs and cell types such as endocrine system, endothelial cells, smooth muscle cells, erythrocytes, and peripheral nerves (Agoston et al., 2017) that limits the utility of them as TBI biomarkers in multi-trauma scenarios (Castellani et al., 2009; Geyer et al., 2009; Lugones et al., 2018). In that regard, brain specific serum biomarkers such as NF-L, NF-H and GFAP may perform better in multi-injury events.

All biomarkers discussed in this section showed to pose a distinct temporal profile following TBI which is also dependent on injury type, mechanism and severity. Moreover, many of the biomarkers explored in the literature are not brain specific, however, the temporal profile of these biofluid biomarkers may be different after TBI and injury to other organs. For example, although biofluid S100β elevation was observed in injuries other than TBI, S100β released from an extracerebral origin showed a shorter temporal profile than S100β released due to TBI (Savola et al., 2004). Therefore, coupling the biofluid concentration of these biomarkers with their temporal profiles may enhance the capability of these biomarkers in diagnosing TBI and monitoring the progression of TBI. For example, characteristics of temporal profiles of NSE and S100β serum concentrations such as time to peak and possible secondary peak after TBI were shown to be able to distinguish between children with iTBI and nTBI in mild to severe TBIs (Beers et al., 2007; Berger et al., 2005; Berger et al., 2006). Frequency and time domain of blood sampling have a critical role in determining the accuracy of temporal signatures of biomarkers, especially in translational research where different life spans of animal models and humans need to be taken into consideration.

Unfortunately, longitudinal studies assessing biofluid biomarkers of clinical and pre-clinical pediatric TBI are severely limited, also the sampling frequency and the time points are dispersed among studies (Beers et al., 2007; Robinson et al., 2016; Žurek and Fedora, 2012). Late blood sampling and differences in the time point and frequency of sampling, in part, may explain some of the conflicting results of biomarkers between studies. To overcome these limitations, more longitudinal studies are needed with high frequency sampling in order to characterize the temporal profile of biomarkers so that the underlying molecular and pathological events following pediatric TBI can be elucidated.

3.2. Electroencephalography (EEG)

TBI can disrupt the functional neural processes of the brain resulting in altered electrophysiological states (Rapp et al., 2015). Electroencephalography (EEG) provides a measure of the electrical activity of the brain which can help to monitor the changes in cognitive processing over the course of the TBI, informing on differences between healthy and diseased populations and the time course of recovery (Schmitt and Dichter, 2015). EEG in humans is typically collected non-invasively using surface scalp electrodes capturing the summation of synchronous activity of millions of post-synaptic potentials of the cerebral cortex (Luck, 2014; Rapp et al., 2015). The electrical potential difference

between two electrodes establishes a channel. These channels are arranged in a montage that display patterns of electrical activity across the scalp indicative of regional activity or inactivity (Rapp et al., 2015). Due to the lack of structural abnormalities associated with mild traumatic brain injury, EEG provides a non-invasive indicator of brain functional activity on the millisecond scale. EEG research employs the recording of spontaneous activity or evoked potentials in response to an external stimulus. Event related potentials (ERPs) are segments of the continuous EEG signal that are time-locked with an external event stimulus and have been considered a sensitive measure of brain activity after a concussion (Gosselin et al., 2006).

Typical measurement variables associated with EEG are power frequency bands from continuous measurement and amplitude and latency characteristics associated with ERP waveforms. Power frequency bands include: Delta: 0.5–4 Hz, Theta: 4 − 8 Hz, Alpha: 8–12 Hz, Beta: 12–20 Hz, Gamma: 20–80 Hz, where common findings associated with concussion are increased alpha, increased delta, and decreased theta (Ianof and Anghinah, 2017; Kenzie et al., 2017; Nuwer et al., 2005; Oster et al., 2010; Sandsmark et al., 2017). Common ERP components that have been studied for sports-related concussions in human subjects include: N2, found at 200–350 ms with a frontal central distribution on the scalp (Broglio et al., 2009; Gaetz and Weinberg, 2000; Ledwidge and Molfese, 2016; Moore et al., 2015); the P3, found at 300–800 ms with a midline parietal distribution (Baillargeon et al., 2012; De Beaumont et al., 2009; Dupuis et al., 2000; Gaetz et al., 2000; Gosselin et al., 2006; Lavoie et al., 2004; Moore et al., 2016; Moore et al., 2014; Moore et al., 2017; Nandrajog et al., 2017; Ozen et al., 2013; Parks et al., 2015; Theriault et al., 2009); the error-related negativity (ERN) (De Beaumont et al., 2009; Pontifex et al., 2009), typically occurring at 50–100 ms at the midline frontal and central scalp sites; and the error positivity (eP), which occurs at 200–500 ms following the ERN, typically observed in the midline central and parietal scalp areas (Brush et al., 2018; Lesiakowski et al., 2018). General trends across research studies denote a decrease in amplitude and increase in latency for ERP components associated with concussed cohorts in comparison with healthy controls, furthermore the P3 or P300 is the most widely used for injury (Brush et al., 2018). A few studies have suggested the use of a panel of EEG features as part of a multi-modal analysis of concussion that include behavioral measures such as balance and gait to detect and monitor concussion (Howell et al., 2018; Jacquin et al., 2018); however, more evidence is needed to evaluate the robustness of including a collection of measures. The diverse findings on ERP related components are attributed to variability in the type of cognitive tasks used to elicit the ERP responses (i.e., auditory or visual stimuli). Due to the non-uniformity of tests run across studies, a direct comparison is difficult. Small and heterogeneous study samples are common across research studies, often age, injury mechanism, and outcomes are factors that result in underpowered sample sizes that are susceptible to bias, false and inflated effects (Brush et al., 2018).

To control for the variability in subject sample and characteristics, animal models of TBI are a promising avenue to study the mechanisms of concussive injury from injury causation to changes to neural function, intracranial injury mechanisms, and histopathological changes post mortem. Research employing animal models of TBI combined with EEG measures have primarily used rats under lateral fluid percussion injury (Biswas et al., 2018), projectile concussive impact (Leung et al., 2014; Mountney et al., 2017), high deceleration impact system (Napoli et al., 2012), a weight drop model (Ucar et al., 2006), and mice under blast loading (Liu et al., 2017) and also using the weight drop model (Sabir et al., 2015). While differences observed in the power frequency bands between injured and non-injured animals were demonstrated, the measurement of EEG in these studies involved opening up the cranial vault and implanting electrodes directly on the brain. Due to the smaller size of the rat and mouse brain and the invasive nature of electrode implantation in these studies, translation to human TBI is difficult. In addition, EEG research employing rodent models of TBI are

not specific to the pediatric age range. Research employing a piglet model of pediatric concussion has demonstrated promise in the utility of this model for clinical measures of concussion using EEG. Large animal models better resemble the biomechanics of brain tissue injury because the gross neuroanatomy and relative composition of white and grey matter tissues are similar between the human and pig brain (Cullen et al., 2016). Atlan et al. (2018) conducted a pilot study on 4-week-old piglets subject to two injury conditions (CCI and RNR in the sagittal and coronal directions). EEG was captured using a non-invasive 32 electrode array placed on the surface of the scalp of each animal to measure responses from an auditory oddball paradigm. Unlike previous animal work employing invasive measurement techniques for studying TBI, the piglet model provides a novel means to capture EEG responses with potential translation to pediatric concussion. Atlan et al. (2018) reported a reduction in the P60 amplitude and an increase in the N40 latency were associated with injured animals.

These studies demonstrate the efficacy of EEG as a diagnostic tool able to detect differences between injured and healthy brains in both human and animals. There is still a need to identify relevant features of the EEG signal that consistently indicates an injured brain in addition to those that are sensitive to differing severities and symptoms across species. Human studies provide a subset of potentially relevant features with which to guide and evaluate the experimental animal work, such as the N1 and P3. However, homologous EEG features that represent similar cognitive processes and functioning between the human and animal remains elusive. Such works that have attempted to identify homologues between human and pigs were examined by Arnfred et al. (2004); Arnfred et al. (2003). These authors conducted auditory oddball paradigms to adult male pigs, attempting to describe ERP homologues to human ERPs. The authors concluded that the pig P30 is equivalent to the human P300a in distribution and latency, showing promise of the pig model of TBI for studying injury mechanisms in the human.

3.3. Actigraphy

Mild traumatic brain injury has been documented to result in abnormal sleep and activity patterns in humans and animals (Sandsmark et al., 2017). In the pediatric population, disruptions in the sleeping and waking hours can lead to problems with cognition, chronic pain, and psychological distress, normal neurocognitive development and impaired learning (Tham et al., 2015). The gold standard for measuring sleep quality is through the use of polysomnography (PSG). Patients are often required to stay at a sleep laboratory fitted with a series of electrodes (EEG, electrocardiographic and video) to record physiological patterns during sleep. While these studies provide the ideal laboratory environment with which to observe and take measurements of the patient throughout the stages of sleep, it takes place in an unfamiliar environment (not at home in their own bed), often requiring sophisticated and expensive equipment. A promising alternative to polysomnography is actigraphy to capture sleep disturbances inferred from changes in activity. Actigraphy employs an accelerometer-based device (usually in the form of a watch worn on the non-dominant wrist) to capture time-stamped perturbations in the acceleration signal (Allan et al., 2017).

Kaufman et al. (2001) compared sleep and activity in adolescent subjects whom sustained a mild TBI approximately 4 years prior in comparison with healthy controls. Polysomnographic recordings taken in a sleep laboratory for one night, followed by actigraphic recordings and a sleep diary at home for 5 nights. Both the PSG techniques and the actigraphic recordings combined with sleep diaries were able to detect that the injured group had poorer sleep quality, including lower sleep efficiency and more time spent awake (Kaufman et al., 2001). Furthermore, this study demonstrates persistent sleep disturbances in adolescent children years after head injury. In one study by Milroy et al. (2008) whom compared actigraphic data in a sample of children with

mild TBI (n = 18) in comparison with a non-head injured, orthopedic injury control group (n = 30) using an actigraphic watch for 5 nights. These authors reported no significant differences in sleep disturbances between groups, however, Tham et al. (2015), using larger sample sizes of children with mild TBI (n = 50) and healthy controls (n = 50) found that actigraphy was able to detect poorer sleep quality including shorter sleep durations and more active minutes during the night for the injured group.

Animal research examining the relationship between brain injury with activity patterns and sleep disruptions have primarily used invasive techniques with EEG data captured from an implanted electrode on the surface of the animal brain (Petraglia et al., 2014; Sabir et al., 2015; Sandsmark et al., 2017). Research employing non-invasive techniques used an instrumented cage system that measured pressure on the cage floor to infer on activity in rodents (Rowe et al., 2014a; Rowe et al., 2014b), as well as an accelerometer imbedded harness in piglets (Olson et al., 2016). The animal TBI research employing rats and mice mentioned above often involved invasive techniques either from the injury model itself (FPI and CCI) or from the implanted EEG electrodes in addition to the cage system. In the piglet model of TBI, Olson et al. (2016) instrumented 4-week old piglets with an accelerometer embedded harness jacket to monitor the animal's day and night time activity 4 days after both CCI and RNR. In comparison with naïve piglets, brain injured animals demonstrated longer periods of inactivity during the day time and increased activity during the night time. Overall, animal models of TBI have indicated altered sleep and wake disturbances that are like those reported in humans with TBI (Wickwire et al., 2016).

Actigraphic measurements are a promising tool to non-invasively monitor active and inactive periods in both humans and animals. Actigraphy provides an inexpensive alternative to PSG, and while lacks specificity, it permits an understanding of the behavioral responses affected in mild BTI in comparison to healthy controls. Future research efforts employing actigraphy in an animal model of TBI includes increasing the time points studied to provide an idea of the progression of sleep disturbances over time and their resolution. Correlation of actigraphy with other measures of cognitive functional and behavioral tests, serum biomarkers and EEG, can provide further insight on the interrelation between sleep quality with on-going symptoms and behaviour states. A link between these objective measures and subjective symptoms can inform clinical management and decisions on prognosis with regarding rest and recovery after TBI.

3.4. Gait and balance assessments

Increase in postural instability and vestibulomotor impairment are frequently reported as outcomes of TBI. Reliable balance assessments are essential to identifying balance problems for both diagnostic and rehabilitation purposes. Several balance assessment techniques have been introduced and their reliability have been investigated in the literature. Among those are the Balance Error Scoring System (BESS) which is a low-cost balance assessment that consists of single leg, double leg, and tandem stances on a firm and on a foam surface while hands are on the hips. Errors are tallied to calculate a BESS score. Errors include opening eyes, hands lifted off iliac crest, step, stumble, fall, moving hips > 30 degrees abduction, lifting forefoot or hill and remaining out of test position > 5 s. The BESS has been utilized in several studies as a diagnostic tool for TBI in pediatrics and adults and has shown to detect significant difference between concussed and control groups. (Cushman et al., 2018; Guskiewicz et al., 2001; Quatman-Yates et al., 2014; Riemann and Guskiewicz, 2000). Later, BESS was modified to improve its reliability to three stances on a hard surface only. Modified BESS has also shown significant changes in postural stability for a TBI group (Muir et al., 2014). In a few studies, it was shown that instrumenting BESS with measurement tools such as accelerometers (King et al., 2014) and force plates (Chang et al., 2014) can increase its

reliability to evaluate balance improvements (Shetty et al., 2018). The Berg Balance Scale and the Pediatric Balance Scale are other common balance assessments that can be utilized for school-aged children (Franjoine et al., 2003). These assessments consist of 14 items such as the time for sitting to stand, standing with eyes closed, standing with feet together, turning 360 degrees, and reaching forward with outstretched arm. There are also two simple balance performance assessments: the functional reach test (FRT) that evaluates the reaching ability while standing and Timed Up and Go (TUG) that is the recorded time for a task of standing from a chair, walking 3 m, turning around, walking back and sitting down. Lower FRT values and higher TUG values in children post-TBI in comparison with the controls were reported in the literature (Katz-Leurer et al., 2008). Ghent Developmental Balance Test (GDBT) was developed for younger children from the moment of independent walking until the age of 5 and it consists of 35 balance items such as the time and the ability of bipedal standing, standing on a balance pad, kicking a ball, and standing on a line with eyes closed. Each item is scored from 0, for the case that the child cannot attempt the items, to 2 for the successful performance. The sum of the scores on all items can be converted to a percentile score based on GDBT manual for standardization (De Kegel et al., 2012). Use of force plates and wearable sensors (e.g. accelerometer) have become a key advancement to develop more quantitative balance assessment techniques. In one of the first studies, Lehmann et al. (1990) utilized force plate to assess balance and found significant differences in all balance parameters such as postural sway between TBI patients and controls. Computerized posturography testing (CPT) is a more advance quantitative technique to assess balance in human and has become the gold-standard of balance assessment. CPT utilizes moving force plate and provides 3 test protocols including: 1) "Sensory Organization Test" that assesses the patient's ability to make effective use of visual, vestibular, and proprioceptive information under three visual conditions (eyes open, eyes closed, sway-referenced visual surrounding); 2) "Motor Control Test" that assesses the patient's ability to quickly and automatically recover from unexpected external provocations; and 3) "Adaptation Test" that assesses the patient's ability to modify motor reactions and minimize sway when the support moves unpredictably in the toes-up or toes-down direction. Eye closed tests in CPT assessments showed that patients with severe TBI have more difficulty processing information from their vestibular system to maintain balance in compare to controls (Pickett, 2007) that may be attributable to the fact that TBI subjects are often over reliant on visual compensatory rather than vestibular system strategies to compensate for vestibular dysfunction and maintain balance. Wearable sensors have also been used to quantify clinical balance test results. Gera et al. (2018) quantified postural sway of 38 athletes who had sustained a mild TBI and 81 control athletes using a commercially available wearable inertial sensor that contains a tri-axial accelerometer, a tri-axial gyroscope, and a tri-axial magnetometer. They observed higher postural sway and increased postural sway in the mild TBI group compared to the control group due to a higher dependence on visual cues to maintain balance.

Several studies have explored balance deficits in more dynamic settings (i.e. gait analysis using motion capture systems). Katz-Leurer et al. (2008) performed gait analysis on children diagnosed with severe closed head injury and healthy controls and found significantly shorter step length, longer step time, higher hip abductor and knee extensor strength values as well as higher variability of step length and time in children post-TBI in comparison to controls. In another study, Basford et al. (2003) performed gait analysis using a motion capture system and found lower walking velocity and stride length in adult TBI subjects with complaints of instability in compare to healthy controls.

In pre-clinical research, several techniques have been developed to assess balance in animals. One of the most common assessments of the vestibulomotor system in mice is with the use of a beam balance. Mice are placed on a narrow beam and balance is scored from 0, for no attempt to keep balance, to 5 for a steady posture. Another common

balance test used in mice and rats is the rotarod (Hamm et al., 1994). The rotarod consists of a motorized rotating rod and two large plexiglas discs positioned on each side. The mice walk on the rotating disks at various speeds and the latency until the animal falls is an indicator of balance performance. Inclined plane is another assessment that measures ability of rats to maintain its position at a given angle (Hamm, 2001). There are limited studies in large animal balance assessment for TBI diagnosis. In one study an accelerometer and video camera were used to measure postural sway of piglets subject to sham, CCI and RNR TBI. A significant increase in the root mean square acceleration in the anterior-posterior and medial-lateral directions in both CCI and RNR models in comparison to sham animals (Jaber et al., 2015). In another study, gait parameters of sham and CCI injured piglets were investigated using video analysis. A significant increase in percent stance time, a significant decrease in stride velocity and 2-limb support were reported in the more severe CCI injured animals (Baker et al. (2018)). By reviewing the literature, it is evident that quantitative balance and gait assessments are reliable low-cost tools for TBI diagnosis. However, most of these assessment methods rely on instructional-based assessments rather than non- instructional involuntary movements. A challenge in balance assessment that needs to be addressed is the development of methods that rely on non-instructional involuntary movements that can be implemented for non-verbal populations including animal models and young children.

3.5. Eye response

The cognitive symptoms such as deficits associated with concentration, attention, memory, planning and decision making are associated with microstructural changes in the frontal white matter in TBI (Maruta et al., 2010). These deficits may result from disruption of cerebellar-cortical tracts due to diffuse axonal injury (Suh et al., 2006). On the other hand, measuring eye response is a prominent, cost effective, quantitative diagnostic tool with high reliability. Eye response assessments include a variety of measures such as pupil response to light, fixation, smooth pursuit eye movements, saccades (rapid shifting of gaze to a new area of interest), measuring the point of gaze and visual tracking. Among these measures, visual tracking performance which is tracking of a moving target requires integration of attention and planning. This measure includes smooth and saccadic elements of eye movement (Heitger et al., 2009) that have been widely used to study the cognitive symptoms associated with TBI in pediatrics (Ellis et al., 2015)and adults (Caplan et al., 2015; Heitger et al., 2009; Maruta et al., 2010; Samadani et al., 2016; Samadani et al., 2015). All eye tracking systems either measure the position of the eye relative to the head or the orientation of the eye in space (Duchowski, 2007). In general, eye movement techniques can be categorized into three groups: (1) Electro-OculoGraphy which is based on the electric potential differences of the skin around the eye; (2) scleral contact lens that relies on a search coil embedded in contact lenses; and (3) video-based methods that utilize combined pupil and corneal reflection of the light source (typically infrared) and image processing (Duchowski, 2007). There are numerous studies that have been conducted to investigate the utility of these techniques to diagnose TBI in pediatrics and adults. Significant change in saccade latency and fixation error and initial fixation error have been reported in eye response in pediatric TBI (DiCesare et al., 2017). In an adult TBI studty, Caplan et al. (2015) captured horizontal and vertical binocular gaze data for subjects with post concussive syndrome (n = 60) and asymptomatic control subjects (n = 26). They reported significant differences in a number of eye tracking components including saccades and smooth pursuit eye movements for subjects with symptomatic mild TBI which can discriminate between individuals with mild TBI and the control group. Similar findings were observed in another study (Suh et al., 2006) on adult subjects with mild TBI (20 chronic and 6 acute) and controls (n = 26) using a circular pursuit target-blanking paradigm. Increased

oculomotor deficits during target blanking were reported for the TBI subjects, indicated by earlier generation of saccades, increased oculomotor error, and increased intra-individual variability compared to controls. In another mild TBI study, eye movement function with sensitivity and specificity of nearly 100% was reported as the most effective metric in identifying adult patients with post-concussion syndrome (Heitger et al., 2008). Samadani et al. (2016) developed an eye tracking algorithm to assess eye movements of the adult subjects watching a video clip rather than following instruction. They investigated 89 eye tracking measures and suggested a subset as the best predictor of brain injured subjects. They also reported that the severity of disconjugate gaze in TBI and concussion patients were detectable with their algorithm and was proportionate to the severity of concussion symptoms.

On the pre-clinical side, several eye tracking systems have been developed for animals for different purposes such as peahens to study the process of mate choice (Yorzinski et al., 2013), dogs to measure canine visual behavior (Williams et al., 2011) and rats to study the response to sensory stimuli (Schriver et al., 2018). However, there is a paucity of preclinical studies using eye response in animals as a TBI diagnostic biomarker which is a critical gap in the literature worthy of future consideration in TBI pre-clinical studies. Another area that has not been adequately studied is the effect of TBI on non-voluntary eye response that brings insight to potential biomarkers based on non-voluntary movement and non-instructional cognitive tasks. Therefore, the pursuit of non-voluntary eye response measures of particular interest in translational TBI research.

4. Translational challenges and pathways for exploration

TBI biomarkers are valuable tools for diagnosis of TBI and monitoring its progression as well as evaluation of therapeutic efficacy in TBI patients. In the process of biomarker discovery, animal models are extremely valuable as they can provide unique opportunities to closely explore molecular and cellular pathology in the brain tissue, which is not easily possible in the clinical setting. TBI biomarker studies in animals also play an important role in the development of new therapies, and to quantitate the therapeutic efficiency. However, translation of preclinical outcomes to clinical applications face several challenges. In this section, we review the advantages, challenges and prospects of translating pre-clinical knowledge into the human clinical setting.

4.1. Heterogeneity

Heterogeneity remains the main challenge in the field of clinical TBI. Mechanisms of injury, injury severity, spatial and temporal pathophysiology, and clinical outcomes are just a few examples contributing to variability in clinical data. One approach to address the heterogeneity of human TBI into pre-clinical studies is to integrate several preclinical models to find the biomarkers that are applicable to a spectrum of TBI mechanisms and severities (Hajiaghamemar et al., 2017; Margulies et al., 2015; Shultz et al., 2017). Conducting studies across species and over variety of TBI models is also an important step toward identifying preclinical-clinical compatible panel of biomarkers which can help to achieve more translational success. This effort would be possible through large scale collaborative research initiatives between multiple centers.

4.2. Age equivalency of humans and animals

The selection of an appropriately aged animal model to reflect the desired human population under study is based on the stages of development of the animal that closely resembles the human stage of maturation and is not simply based on age after birth (Finnie, 2012). Researchers have proposed that rodent models at 7 days old, 7–11 days, 17–21 days, and adult can be used to represent human birth, infants, and toddlers, and adults respectively (Hagberg et al., 2002; Kochanek

et al., 2017). While rodents tends to be the most commonly used species in research with a large number of published studies available regarding pathophysiology, functional and behavior outcomes, these animals have smaller, lissencephalic brains, composed of less white matter tissue than grey matter than those typically seen in the human brain (Cernak, 2005; Finnie, 2001; Vink, 2018). Adult humans have gryencephalic brains with a 2–4 mm thick grey matter ribbon enclosing the white matter (Dahnke and Gaser, 2018). These characteristics play an important role affecting the movement of the brain within the skull and subsequent patterns of localized mechanical stress culminating on the neural tissues (Duhaime, 2006; Ho and Kleiven, 2009; Xiong et al., 2013). Larger animal models, such as sheep and pigs have distributions of grey matter and white matter tissues that are more similar to the human brain. Additionally, the presence of well-formed gryi and sulci in these large animal models better resemble the pathology of white matter injuries (Duhaime, 2006; Finnie, 2001). More recent efforts employing magnetic resonance imaging techniques for longitudinal assessment of white matter composition of the 3-month old piglet brain demonstrated similar trajectories to the human adolescent brain (ages 10–19 years old), which further supports the piglet model for studying pediatric concussion (Ryan et al., 2018a; Ryan et al., 2018b). Newborn piglets, piglets at 1–5 days, and 3–4 weeks old resemble the newborn human, infant and children brain maturations (Hagberg et al., 2002; Kochanek et al., 2017).

The age-dependency of some of the TBI biomarkers discussed in this review also emphasize the importance of using age appropriate animal models in TBI studies especially with the purpose to translate to the pediatric clinical setting. In addition, utilizing age-independent metrics and/or narrow age groups in study designs are a good path to minimize age dependency of tests and establish robust biomarkers.

4.3. Temporal profile

One of the challenges that prevents successful translation of clinical and pre-clinical studies is the neglect of distinct biomarker temporal profile in human and animal models due to different life span and time scale of biological process, metabolomic rate, pharmacokinetic, pathophysiological responses. The proper selection of the sequential time points is necessary to capture the dynamic progression of biomarkers. This selection is achievable through parallel clinical/pre-clinical studies as well as more precisely characterizing the temporal pattern of biomarkers by more frequent serial sampling. Direct comparison of the temporal profile in pathophysiology response in animals and humans can help to identify appropriate translating time scaling factors, which is an important parameter for the successful translation of biomarkers. On the other hand, most animal TBI models have focused on acute outcomes but the majority of clinical studies concentrate on long term outcomes of TBI. This misalignment is a clear deficiency in the literature and more work needs to be done to assess long term outcomes after TBI in preclinical studies. One of the challenges with animal TBI studies is the difficulty to maintain and house severely injured animals post TBI to mimic the intensive care settings of humans. Often, a human subject diagnosed with TBI receives medication that can affect the assay and trajectory of serum biomarkers as well as long-term outcomes of TBI measured using other indicators (Oli et al., 2009). Overall, increasing the number of studies employing parallel clinical/pre-clinical longitudinal research designs provides the opportunity to directly compare biomarker occurrence between preclinical models and human data and is a promising path toward overcoming some of the challenges in translation of animal data into clinical practice.

4.4. Panel of multi-domain translatable metrics

Many TBI studies in the literature have assessed TBI diagnostic and prognostic capability of one or a few targeted biomarkers individually. However, brain injury is a multifactorial process involving complex

linkage between metabolic evolution, molecular interaction between brain tissue and biofluids, and neuropathological sequelae of injury that can lead to many deficits such as neurodegeneration, neurological, functional and cognitive impairments and many more. Given all the complexity and variation of TBI especially in pediatric population, it is unlikely that a single biomarker will be able to predict TBI with enough sensitivity and specificity. A panel of biomarkers considering different deficits of TBI seems to be more promising to diagnose the diversity of injury and monitor its progression. For example, in biofluid biomarkers, a panel of multiple glial, neuronal, metabolism, inflammatory, and microRNA biomarkers seems to be a more appropriate approach to identify and assess the severity, timing and pattern of injury. The concept of using multivariate biofluid biomarkers for TBI is growing and several clinical studies showed superiority of multivariate biofluid biomarker over single biomarker for TBI (Beers et al., 2007; Diaz-Arrastia et al., 2014; Hajiaghamemar et al., 2017; Lo et al., 2009; Peacock et al., 2017). In addition, a panel of different EEG features or scores have shown promise as a potential tool to detect and monitor concussion (Jacquin et al., 2018; Kiefer et al., 2015).

Ideal translatable biomarkers should be accessible, non-invasive, nonverbal, effort-independent, and rely on objective rather than subjective measures. For example, serum biomarkers are minimally invasive and relatively objective measures and several biofluid biomarkers showed good potential to be used as diagnostic and prognostic tools for TBI. Actigraphy and EEG metrics are also non-invasive, both measure passive responses, and thus require minimal effort from the studied subject. In addition, as discussed in this review, both actigraphy and EEG measures have demonstrated promise in differentiating between healthy controls and brain injured cohorts. Similarly, balance and eye response assessment techniques that are based on involuntary movements also have a high potential of translatability between animals and human outcomes. Especial, conspicuous is the fact that these preclinical biomarkers and techniques can be tailored for nonverbal infants and toddlers. Combining these clinical/pre-clinical translatable measures considering their distinct temporal profiles seems to be a path toward development of comprehensive and unbiased panel of biomarkers capable of diagnosis and monitoring the progression of TBI from different deficit aspects. All of the reviewed metrics showed the capability to be implemented in clinical as well as preclinical studies especially using large animal models of TBI. Measuring multi-domain biomarkers at uniform time points across clinical and preclinical allows for relationships to be established that relate cellular, functional and behavioral processes and identify markers that are more sensitive and specific at different post injury time windows that can relate to prognosis.

5. Conclusion

A large proportion of TBI related emergency department visits are from young children and adolescents where falls, assaults, motor vehicle accidents, and sport related injuries are among the top events leading to injury. The acute and potential long-term effects include cognitive, physical, and behavioral deficits, which may be exacerbated in the developing brain affecting their productivity in academics, contributions to society, and life at home with close family and friends. The nature of TBI is complex, with diverse clinical presentations, causes and mechanisms of injury contributing to challenges associated with diagnosis, treatment, and management practices. In efforts to minimize the detrimental long-terms effects of TBI, an increase in pre-clinical and clinical research have sought to determine translatable diagnostic and prognostic measures of TBI and especially concussion in order to expedite injury resolution and reduce long term risks associated with TBI. Animal models of TBI are necessary in addressing the heterogeneity of TBI by isolating the mechanisms of injury in a reproducible manner, however translation to humans is difficult due to inter-species differences such as brain anatomy, behavior, life-span and time scale of

biological process, metabolomic rate, pharmacokinetic, pathophysiological responses. In this review, we presented the findings, advantages, challenges and prospects of biofluid biomarkers, EEG, actigraphy, eye responses, and balance as potential tools for diagnosis, prognosis and TBI monitoring. These tools are valuable for bridging the gap between animal and human TBI outcomes because they involve effort-independent and non-verbal tasks capturing specific deficits. In addition, they are easily accessible and are non/minimally invasive. TBI causes dynamic, age dependent deficits in multiple domains, and thus, combining a number of biomarkers into a panel may be more suitable to detect these subtleties in deficits across age groups. These techniques can be used in parallel clinical and pre-clinical studies involving both human and animals and help to overcome some of the challenges associated with translation. Direct comparison of the temporal profile in different pathophysiological responses and behavioral and functional deficits in animals and humans can help to identify appropriate translating time scaling factors to enhance translation of biomarkers. Multicenter collaborations and large-scale data sharing will help to close this gap and promote advancements in therapies and interventions.

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