BlueCross BlueShield of North Carolina

An independent licensee of the Blue Cross and Blue Shield Association

Corporate Medical Policy

Serum Testing for Evidence of Mild Traumatic Brain Injury AHS – G2151

File Name:	serum_testing_for_evidence_of_mild_traumatic_brain_injury
Origination:	8/2019
Last CAP Review:	5/2021
Next CAP Review:	5/2022
Last Review:	5/2021

Description of Procedure or Service

Traumatic brain injury (TBI) is characterized by pathologic injuries to the brain resulting from external forces or trauma. A broad range of sequela of varying clinical severity include focal contusions and hematomas, diffuse axonal injury, cerebral edema and swelling, and a cascade of molecular injury mechanisms (Williamson & Rajajee, 2021).

Concussion refers to the trauma-induced alteration in mental status, which may or may not involve loss of consciousness, after a mild TBI (Evans & Whitlow, 2021).

Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Serum testing for evidence of mild traumatic brain injury is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When serum testing for evidence of mild traumatic brain injury is covered

Not applicable

When serum testing for evidence of mild traumatic brain injury is not covered

Measurement of blood, saliva, and/or cerebrospinal fluid (CSF) biomarkers for the evaluation of mild traumatic brain injury also known as concussion markers, including S100B, GFAP, and UCH-L1, is considered investigational. This also includes proprietary panel tests and kits, including Banyan BTI™.

Policy Guidelines

Traumatic brain injury (TBI) is a fairly common injury, with an incidence of 1.11 million and a prevalence of 2.35 million in the U.S. in 2016 (Evans & Whitlow, 2021). Although approximately 75%

of TBIs are mild, TBI can adversely affect a person's quality of life in numerous ways, including cognitive functioning, emotional functioning, and physical effects (CDC, 2015; Wright, Kellermann, McGuire, Chen, & Popovic, 2013). As many as 1 in 5 TBI patients have symptoms persisting past 1 month (Silverberg et al., 2020).

Accurate diagnosis of TBI is critical to effective management and intervention but can be challenging due to the nonspecific and variable presentation (Mondello et al., 2017). Tools available to objectively diagnose injury and prognosticate recovery are limited (Mannix, Eisenberg, Berry, Meehan, & Hayes, 2014). Clinical assessment usually includes a neurological exam, followed by a computed tomography (CT) scan of the head to detect brain tissue damage that may require treatment (FDA, 2018). However, as most patients with mild TBI do not have detectable intracranial lesions, like epidural hematomas, on a CT scan (Evans & Whitlow, 2021), this assessment relies heavily on nonspecific symptoms that can vary widely and ignores the mechanistic heterogeneity of TBI (Williamson & Rajajee, 2021).

Brain damage in TBIs is initially caused by external mechanical forces being transferred to intracranial contents, generating shearing and strain forces which stretch and damage axons, and can result in contusions, hematomas, cerebral edema and swelling. Common mechanisms include direct impact, rapid acceleration/deceleration, penetrating injury, and blast waves. However, the pathophysiology of TBI is now understood to include not only the acute event, but also the resulting cascade of molecular injury mechanisms that are initiated at the time of initial trauma and continue for hours or days (Williamson & Rajajee, 2021). The pathophysiology of even mild TBI is complex and may include both focal and diffuse injury patterns. Neuropathological changes found after mild TBI indicate mild multifocal axonal injury, including altered circuit dysfunction and traumatic axonal injury (Truettner, Bramlett, & Dietrich, 2018).

Cell death and the initiation of local metabolic and inflammatory processes resulting from TBI results in the release of a number of inflammatory mediators and damage-associated molecules that are able to cross a dysfunctional blood-brain barrier (Di Battista et al., 2015) or enter the circulation through the glymphatic pathway (Plog et al., 2015). Neurobiochemical marker levels in blood after TBI may reflect structural changes detected by neuroimaging (Mondello et al., 2017). Simpler, sensitive, and specific tests that provide early, quantitative information about the extent of brain tissue damage, identifying and stratifying TBI, would allow rapid and tailored diagnosis of TBI, while minimizing the time, risk, and cost associated with current standards (McMahon et al., 2015). No single ideal TBI biomarker exists (Halford et al., 2017). However, brain-specific markers of neuronal, glial, and axonal damage, identified in the peripheral blood, have shown potential clinical utility as diagnostic, prognostic, and monitoring adjuncts and have been investigated both individually and in combination (Di Battista et al., 2015; Mondello, Jeromin, et al., 2012). Acute-phase biomarkers, including S100 calcium-binding protein B (S100B), glial fibrillary acidic protein (GFAP), and ubiquitin C-terminal hydrolase-L1 (UCH-L1), have shown potential for use in initial screening of patients presenting with head trauma, the vast majority of whom will have normal brain CT findings (Evans & Whitlow, 2021; Maas et al., 2017).

S100 calcium-binding protein B (S100B)

S100B belongs to the calcium binding EF-hand protein group, and it has been associated with cytoskeleton structure, Ca^{2+} homeostasis, cell proliferation, protein phosphorylation and degradation (Chmielewska et al., 2018; Strathmann, Schulte, Goerl, & Petron, 2014). S100B is expressed in the cytoplasm and the nucleus of astrocytes and is present in the bloodstream when the blood brain barrier is disrupted. Several studies indicate that S100B measurement, either acutely or at several time points, can distinguish injured from non-injured patient (Strathmann et al., 2014) and guidelines intended to reduce the need for CT scan using S100B levels in the blood for the initial management of mild TBI have been published (Ingebrigtsen, Romner, & Kock-Jensen, 2000). These guidelines were recently validated in a large multicenter study where S100B was found to have a sensitivity of 97% and a specificity of 34% for the identification of intracranial hemorrhages confirmed by CT scans. The

authors estimated CT scans would have been reduced by 32% with application of these guidelines (Unden, Calcagnile, Unden, Reinstrup, & Bazarian, 2015). However, other investigators have failed to detect associations between S100B with CT abnormalities (Piazza et al., 2007). Additionally, it has limited utility in multiple trauma setting as it is not brain-specific. S100B can be found in non-neural cells, such as adipocytes, chondrocytes, and melanocytes (Chmielewska et al., 2018; Papa et al., 2014), and its levels are also elevated in trauma, specifically orthopedic, without head injury (Anderson, Hansson, Nilsson, Dijlai-Merzoug, & Settergren, 2001: Wang et al., 2018). However, recent data highlight the inclusion of S100B in sets of markers that in combination could contribute to better diagnosis, monitoring, and treatment of CNS conditions (Chmielewska et al., 2018).

Glial Fibrillary Acidic Protein (GFAP)

GFAP is a filament protein that maintains cell shape and structure, coordinates cells' mobility and contributes to the transduction of molecular signals in astrocytes. It is released upon cellular disintegration and degradation of the astrocyte. Concentration of serum GFAP increases after neural trauma and TBI, either as the intact protein or as breakdown products (Chmielewska et al., 2018; Wang et al., 2018). GFAP measurements have provided promising data on injury pathway indication, focal versus diffuse injuries, and prediction of morbidity and mortality (Strathmann et al., 2014). GFAP level was increased in patients with CT-positive scans for intracranial lesions compared to CT-negative scans after mild TBI (Lei et al., 2015). Sensitivities have been reported between 67% and 100% while the specificities ranged from 0% and 89% (Mondello et al., 2017).

McMahon et al (2015) performed a multicenter trial to evaluate GFAP and its breakdown product GFAP-BDP in the diagnosis of intracranial injury. They found that "GFAP-BDP demonstrated very good predictive ability (area under the curve=0.87) and demonstrated significant discrimination of injury severity (odds ratio, 1.45; 95% confidence interval, 1.29-1.64)". The authors concluded that "use of GFAP-BDP yielded a net benefit above clinical screening alone and a net reduction in unnecessary scans by 12-30% (McMahon et al., 2015)."

Ubiquitin C-terminal Hydrolase-L1 protein (UCH-L1)

UCH-L1 is a cytoplasmic enzyme, highly enriched and specifically expressed in neurons, involved in the ubiquitinoylation of abnormal proteins destined for proteasomal degradation (Halford et al., 2017). It is also an important element of axonal transport and, by a strong interaction with cytoskeleton proteins, plays an important role in the axon's integrity (Chmielewska et al., 2018). UCH-L1 has been shown to increase after TBI in serum and CSF as well as correlate with TBI severity and abnormal CT findings (Diaz-Arrastia et al., 2014; Wang et al., 2018). UCH-L1 has also been shown to be significantly elevated in serum among athletes after concussions (Wang et al., 2018). High prognostic value of poor outcome was found at both 3-months (Diaz-Arrastia et al., 2014) and 6-months intervals (Mondello, Akinyi, et al., 2012). Two recent studies report the same sensitivity of 100% and specificities of 21% and 39% (Mondello et al., 2017).

Clinical Utility and Validity

Welch et al (2016) evaluated three serum biomarkers' (glial fibrillary acidic protein [GFAP], ubiquitin C-terminal hydrolase-L1 [UCH-L1] and S100B measured within 6 h of injury) ability to differentiate CT-negative and CT-positive findings. They found that "UCH-L1 was 100% sensitive and 39% specific at a cutoff value >40 pg/mL. To retain 100% sensitivity, GFAP was 0% specific (cutoff value 0 pg/mL) and S100B had a specificity of only 2% (cutoff value 30 pg/mL). All three biomarkers had similar values for areas under the receiver operator characteristic curve: 0.79 for GFAP, 0.80 for UCH-L1, and 0.75 for S100B. Neither GFAP nor UCH-L1 curve values differed significantly from S100B. In our patient cohort, UCH-L1 outperformed GFAP and S100B when the goal was to reduce CT use without

sacrificing sensitivity. UCH-L1 values <40 pg/mL could potentially have aided in eliminating 83 of the 215 negative CT scans (Welch et al., 2016)." However, the authors note that further research is needed.

Wang et al. (2018) reported on the usage of TBI serum and CSF biomarkers as prognostic tools in the ED, neurointensive care unit, and out-of-hospital settings. In the case of mTBI, the researchers stated the similar biomarkers could aid in predicting any development of persistent post-concussive syndrome, including S100B, GFAP, and UCH-L1. Within 12-36 hours from TBI in neurointensive care units, it was found that serum levels of 100B correlate with patient outcomes, and S100B serum levels > 0.7ng/mL correlate with 100% mortality. GFAP modestly correlates with poor outcomes, and "serum GFAP levels were also significantly higher in patients who died or had an unfavorable outcome and have predicted neurological outcome at 6 months." It was also shown in other studies that GFAP and UCHL-1 proteins outperformed S100B in predicting poor outcomes, and the two together "predicate the recovery and unfavorable outcome by distinguishing patients with GOS [Glasgow Outcome Score] 1-3 from patients with GOS 4-5" (Mondello et al., 2016; Takala et al., 2016; Wang et al., 2018).

Gan et al. (2019) evaluated TBI serum biomarkers for four clinical situations; "detecting concussion, predicting intracranial damage after mild TBI (mTBI), predicting delayed recovery after mTBI, and predicting adverse outcome after severe TBI (sTBI)". A total of 200 publications (61722 "observations") were included. For concussion detection, 9 unique publications addressing 15 biomarkers and 946 observations were identified. Four panels ("copeptin, galectin-3, and MMP-9; GFAP and UCH-L1; 10 metabolites; and 17 metabolites") were found to have areas under the curve (AUC) of over 0.9. For evaluation of necessity of CT scan after TBI, 56 publications, 24 biomarkers, and 23316 observations were identified. S-100B (30 publications, 8464 observations) was found to have an AUC of 0.723 and GFAP/GFAP-BDP (16 publications, 2040 observations) was found to have an AUC of 0.831. For evaluation of delayed recovery after mTBI, 44 publications, 29 biomarkers, and 13291 observations were identified. S-100B (24 publications, 2800 observations) had an AUC of 0.691; GFAP's AUC was 0.716 (17 publications, 1959 observations). Finally, for evaluation of poor outcome after sTBI, S-100B (25 publications, 3712 observations) was rated at AUC of 0.762, and GFAP (10 publications, 2448 observations) was rated at AUC of 0.749. Neuron-specific enolase (9 publications, 911 observations) was rated at AUC of 0.715 (Gan et al., 2019).

Banyan BTI™ (Brain Trauma Indicator BTI) from Banyan Biomarkers, Inc. is a proprietary blood test available for clinical measurement of mild TBI. The Banyan BTI is an in vitro diagnostic chemiluminescent enzyme-linked immunosorbent assay (ELISA). The test consists of two kits which provide a semi-quantitative measurement of the concentrations of UCH-L1 and GFAP from serum collected within 12 hours of suspected head injury. Results from the test should be interpreted according to the table provided by the manufacturer. The cut-offs for UCH-L1 and GFAP are 327 pg/mL and 22 pg/mL respectively (Banyan, 2016).

The Banyan BTI test was validated with a sample of 1947 patients. Of these 1947 patients, 120 had positive CT scans, and 117 of these 120 patients tested positive by Banyan BTI (97.5% sensitivity). Of the remaining 1827 patients that tested negative, 666 tested negative by Banyan for a specificity of 36.5%. A total of 669 patients had negative Banyan results, so the negative predictive value was 99.6% (Banyan, 2016).

Another proprietary test for TBI has been designated as a "Breakthrough Device" by the U.S. Food and Drug Administration (FDA). The Tbit platform by BioDirection uses nanowires to detect specific protein molecules that are characteristic of TBI. This platform measures S100B and GFAP in the bloodstream. The manufacturer claimed a sensitivity of 100% and specificity of 41% on a sample of 100 patients (BioDirection, 2015, 2017). However, BioDirection includes a disclaimer saying that Tbit is not FDA-approved, not for use in diagnostic procedures, and only for research use (BioDirection, 2015). They claim, "The Tbit System is designed to measure the body's response to trauma and provide a rapid

point-of-care test result in less than 2 minutes from a single drop of blood, while current technology may run 3-4 hours or more and require serum testing in a central laboratory (Densford, 2019)."

In January 2021, Abbott Laboratories received FDA 510(K) clearance for the i-STAT™ Alinity™ handheld device, which would help evaluate mTBIs. It simultaneously measures UCH-L1 and GFAP in blood and produces results in 15 minutes once a plasma sample is inserted. It has a sensitivity of 95.8% and a >99% negative predictive value. Abbott Laboratories states that this blood test's availability "could help eliminate wait time in the emergency room and could reduce the number of unnecessary CT scans by up to 40%." The company is also working on a whole blood test, and has received breakthrough designation to create a TBI test that runs "on its Alinity™ and ARCHITECT® core laboratory instruments" (Abbott_Laboratories, 2021).

Guidelines and Recommendations

American College of Emergency Physicians (Jagoda et al., 2009) recommended in mild TBI patients without significant extracranial injuries and a serum S100β of level less than 0.1μg/L measured within 4 h of injury, consideration could be given to not performing a CT (Level C).

Centers for Disease Control (CDC, 2016) reaffirmed the 2008 ACEP recommendation in 2016. However, in 2018, the CDC remarked that "Health care professionals should not use biomarkers outside of a research setting for the diagnosis of children with mTBI", noting that there is insufficient evidence to recommend any of the studied biomarkers for mTBI diagnosis in children. The CDC identified S100B, tau protein, autoantibodies against glutamate receptors and oxide metabolites, neuronal ubiquitin C-terminal hydrolase-L1, and glial fibrillary acidic protein biomarker levels as biomarkers that have been studied for concussion evaluation (Lumba-Brown et al., 2018).

The Veterans Administration and Department of Defense (VA/DoD, 2016) Practice Guideline for the Management of Concussion – mild Traumatic Brain Injury states that:

"Excluding patients with indicators for immediate referral, for patients identified by post-deployment screening or who present to care with symptoms or complaints potentially related to brain injury, we suggest *against* using the following tests to establish the diagnosis of mTBI or direct the care of patients with a history of mTBI:

    a. Neuroimaging
    b. Serum biomarkers, including S100 calcium-binding protein B (S100-B), glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal esterase L1 (UCH-L1), neuron specific enolase (NSE), and α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid receptor (AMPAR) peptide
    c. Electroencephalogram (EEG)"

Eastern Association for the Surgery of Trauma (Barbosa et al., 2012) state that "Biochemical markers such as S-100, neuron-specific enolase, and serum tau should not be routinely used in the clinical management of patients with MTBI except in the context of a research protocol."

The consensus statement from **American College of Sports Medicine (ACSM), American Academy of Family Physicians (AAFP), American Academy of Orthopedic Surgeons (AAOS), American Medical Society for Sports Medicine (AMSSM), American Orthopedic Society for Sports Medicine (AOSSM), and the American Osteopathic Academy of Sports Medicine (AOASM) (Herring et al., 2011)** states that: "Investigation in the area of biomarkers (e.g., S-100 proteins, neuron specific enolase, tau protein) is inconclusive for identifying individuals with concussion and represents research that may one day be clinically applicable."

Guidelines from **The Brain Trauma Foundation (Carney et al., 2016; Kochanek et al., 2019),** and the **American Academy of Neurology (Giza et al., 2013)** make no recommendation for or against any serum biomarkers of traumatic brain injury.

Concussion in Sport Group (CISG, 2017)

The Group states that fluid biomarkers are "important research tools" but need further validation and research to determine their clinical utility (CISG, 2017).

Brain Trauma Foundation (2014)

The Foundation states that, although biomarkers are promising, there is not enough conclusive evidence to support their use (Foundation, 2014).

American Academy of Pediatrics (AAP, 2018)

The AAP acknowledges that biomarkers such as "S100β, glial fibrillary acidic protein, neuron-specific enolase, τ, neurofilament light protein, amyloid β, brain-derived neurotrophic factor, creatine kinase and heart-type fatty acid binding protein, prolactin, cortisol, and albumin" have all been investigated in concussion evaluation, but none of these biomarkers have been used in clinical settings (AAP, 2018; Halstead, Walter, & Moffatt, 2018).

National Institute of Care and Excellence (NICE, 2019)

The NICE guidelines regarding "assessment and early management of head injury in children, young people and adults" do not mention any serum biomarkers for evaluation of head injuries (NICE, 2019).

American Medical Society for Sports Medicine (2019)

The Society notes that fluid biomarkers (blood, saliva, and cerebrospinal fluid) in diagnosis of sports-related concussion is under active investigation, but states that overall evidence level is "low". The Society writes that more studies are needed to determine their clinical utility. The Society also acknowledges the FDA approval of the "two-protein brain trauma indicator with glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1 (UCHL1), and clinical use of S100 calcium-binding protein b (s100b) in Europe", but remark that neither of these tests have a role in diagnosis or management of a sports-related concussion (Harmon et al., 2019).

Ontario Neurotrauma Foundation (ONF, 2018),

The ONF published this guideline titled "Guideline for Concussion/Mild Traumatic Brain Injury & Persistent Symptoms", for adults, 3rd Edition in 2018. In it, they state that "Blood-based biomarkers are still considered investigational and therefore are not recommended for use in diagnosing/ assessing patients in the ED or PCP's office" (ONF, 2018).

American Congress of Rehabilitation Medicine Brain Injury Interdisciplinary Special Interest Group Mild TBI Task Force (2020)

This task force published a synthesis of practice guidelines for "Management of Concussion and Mild Traumatic Brain Injury". In it, they note that the Scandinavian Neurotrauma Committee guidelines recommend that "S100B values of <0.10 mg/L, if sampled within 6 hours of injury, can help rule out the need for CT in patients younger than 65 years with a Glasgow Coma Scale score of 14 or a Glasgow Coma Scale score of 15 with loss of consciousness or repeated vomiting". However, they also remark that neither GFAP nor C-terminal hydrolase-L1 have been incorporated into any published clinical

practice guidelines. Further, the task force notes that the biomarkers' incremental value over established clinical decision rules (such as the Canadian CT head rule) is unknown.

The task force also states that "At present, there is no objective biomarker to determine mTBI resolution" (Silverberg et al., 2020).

Applicable Federal Regulations

The FDA has cleared two tests for serum testing for evidence of mTBI as of 04/05/2021 using the search term "TBI," of which one has been approved through the 510(K) process.

On Feb 14, 2018 the FDA approved marketing of the first blood test, Banyan BTI™ (Brain Trauma Indicator BTI) from Banyan Biomarkers, Inc. as part of its Breakthrough Devices Program. This test's purpose is to evaluate mild traumatic brain injury (mTBI), commonly referred to as concussion, in adults. The test is approved to be used, along with other available clinical information, as an aid in the evaluation of patients 18 years of age and older with suspected traumatic brain injury (Glasgow Coma Scale score 13-15). A result from this test is associated with absence or presence of acute intracranial lesions visualized on a head CT (computed tomography) scan (FDA, 2018).

On Jan 8, 2021, with 510(K) clearance, the FDA approved marketing of a second blood test, i-STAT TBI Plasma Cartridge with the i-STAT™ Alinity™ System from Abbott Laboratories. This brain trauma assessment test is intended for in vitro diagnostic use to aid in evaluating patients, 18 years of age or older, with suspected mTBI (Glasgow Coma Scale score 13-15) within 12 hours of injury with other clinical information to assess the need for radiologic imaging (CT, MRI). A result from this test is associated with the absence or presence of acute traumatic intracranial lesions seen on a head CT scan, but is not intended for use in point of care settings (FDA, 2021).

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81479, 84999

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

AAP. (2018). Sport-Related Concussion in Children and Adolescents. Retrieved from http://pediatrics.aappublications.org/content/pediatrics/142/6/e20183074.full.pdf

Abbott_Laboratories. (2021, January 11). Abbott Receives FDA 510(K) Clearance for the First Rapid Handheld Blood Test for Concussions. Retrieved from https://abbott.mediaroom.com/2021-01-11-Abbott-Receives-FDA-510-k-Clearance-for-the-First-Rapid-Handheld-Blood-Test-for-Concussions

Anderson, R. E., Hansson, L. O., Nilsson, O., Dijlai-Merzoug, R., & Settergren, G. (2001). High serum S100B levels for trauma patients without head injuries. Neurosurgery, 48(6), 1255-1258; discussion 1258-1260.

Banyan. (2016). Banyan BTI™. Retrieved from https://www.banyanbio.com/assets/files/000175_vA-IFU-Banyan-BTI.pdf

Barbosa, R. R., Jawa, R., Watters, J. M., Knight, J. C., Kerwin, A. J., Winston, E. S., . . . Rowell, S. E. (2012). Evaluation and management of mild traumatic brain injury: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg, 73(5 Suppl 4), S307-314. doi:10.1097/TA.0b013e3182701885

BioDirection. (2015). Tbit™ Blood Testing Platform. Retrieved from http://biodirection.com/tbit-platform/concussion-and-other-tbi

BioDirection. (2017). BioDirection Announces Results from Pre-Clinical Study of Tbit™ System for Detection of Traumatic Brain Injury. Retrieved from http://www.biodirection.com/news/biodirection-announces-results-from-pre-clinical-study-of-tbit-system-for-detection-of-traumatic-brain-injury

Carney, N., Totten, A., O'Reilly, C., Ullman, J., Hawryluk, G., Bell, M., . . . Ghajar, J. (2016). Brain Trauma Foundation. Guidelines for the management of severe traumatic brain injury, 4th edition. Retrieved from http://braintrauma.org/guidelines/guidelines-for-the-management-of-severe-tbi-4th-ed#/

CDC. (2015). Report to Congress on Traumatic Brain Injury Epidemiology and Rehabilitation | Concussion | Traumatic Brain Injury | CDC Injury Center. Atlanta, GA: Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/traumaticbraininjury/pubs/congress_epi_rehab.html

CDC. (2016). Updated Mild Traumatic Brain Injury Guideline for Adults | Concussion | Traumatic Brain Injury | CDC Injury Center. Retrieved from https://www.cdc.gov/traumaticbraininjury/mtbi_guideline.html

Chmielewska, N., Szyndler, J., Makowska, K., Wojtyna, D., Maciejak, P., & Plaznik, A. (2018). Looking for novel, brain-derived, peripheral biomarkers of neurological disorders. Neurol Neurochir Pol. doi:10.1016/j.pjnns.2018.02.002

CISG. (2017). Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. Retrieved from https://bjsm.bmj.com/content/bjsports/51/11/838.full.pdf

Densford, F. (2019). BioDirection wins FDA breakthrough designation for Tbit concussion detection system. MassDevice. Retrieved from https://www.massdevice.com/biodirection-wins-fda-breakthrough-designation-for-tbit-concussion-detection-system/

Di Battista, A. P., Buonora, J. E., Rhind, S. G., Hutchison, M. G., Baker, A. J., Rizoli, S. B., . . . Mueller, G. P. (2015). Blood Biomarkers in Moderate-To-Severe Traumatic Brain Injury: Potential Utility of a Multi-Marker Approach in Characterizing Outcome. Front Neurol, 6. doi:10.3389/fneur.2015.00110

Diaz-Arrastia, R., Wang, K. K., Papa, L., Sorani, M. D., Yue, J. K., Puccio, A. M., . . . Vassar, M. J. (2014). Acute Biomarkers of Traumatic Brain Injury: Relationship between Plasma Levels of Ubiquitin C-Terminal Hydrolase-L1 and Glial Fibrillary Acidic Protein. In J Neurotrauma (Vol. 31, pp. 19-25).

Evans, R. W., & Whitlow, C. T. (2021, March 17). Acute mild traumatic brain injury (concussion) in adults. UpToDate. Retrieved from https://www.uptodate.com/contents/acute-mild-traumatic-brain-injury-concussion-in-adults

FDA. (2018). FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults [Press release]. Retrieved from https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm596531.htm

FDA. (2021, January 8). I-STAT TBI Plasma Cartridge With The I-STAT Alinity System. Retrieved from https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201778.pdf

Foundation. (2014). Concussion Guidelines Step 1: Systematic Review of Prevalent Indicators. Retrieved from https://braintrauma.org/uploads/07/07/concussion_guidelines_step_1___systematic_review.2-7.pdf

Gan, Z. S., Stein, S. C., Swanson, R., Guan, S., Garcia, L., Mehta, D., & Smith, D. H. (2019). Blood Biomarkers for Traumatic Brain Injury: A Quantitative Assessment of Diagnostic and Prognostic Accuracy. Front Neurol, 10, 446. doi:10.3389/fneur.2019.00446

Giza, C. C., Kutcher, J. S., Ashwal, S., Barth, J., Getchius, T. S., Gioia, G. A., . . . Zafonte, R. (2013). Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology, 80(24), 2250-2257. doi:10.1212/WNL.0b013e31828d57dd

Halford, J., Shen, S., Itamura, K., Levine, J., Chong, A. C., Czerwieniec, G., . . . Wanner, I. B. (2017). New astroglial injury-defined biomarkers for neurotrauma assessment. J Cereb Blood Flow Metab, 37(10), 3278-3299. doi:10.1177/0271678x17724681

Halstead, M. E., Walter, K. D., & Moffatt, K. (2018). Sport-Related Concussion in Children and Adolescents. Pediatrics, 142(6), e20183074. doi:10.1542/peds.2018-3074

Harmon, K. G., Clugston, J. R., Dec, K., Hainline, B., Herring, S. A., Kane, S., . . . Roberts, W. O. (2019). American Medical Society for Sports Medicine Position Statement on Concussion in Sport. Clin J Sport Med, 29(2), 87-100. doi:10.1097/jsm.0000000000000720

Herring, S. A., Cantu, R. C., Guskiewicz, K. M., Putukian, M., Kibler, W. B., Bergfeld, J. A., . . . Indelicato, P. A. (2011). Concussion (mild traumatic brain injury) and the team physician: a consensus statement--2011 update. Med Sci Sports Exerc, 43(12), 2412-2422. doi:10.1249/MSS.0b013e3182342e64

Ingebrigtsen, T., Romner, B., & Kock-Jensen, C. (2000). Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries. The Scandinavian Neurotrauma Committee. J Trauma, 48(4), 760-766.

Jagoda, A. S., Bazarian, J. J., Bruns, J. J., Cantrill, S. V., Gean, A. D., Howard, P. K., . . . Whitson, R. R. (2009). Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury in the Acute Setting. Journal of Emergency Nursing, 35(2), e5-e40. doi:https://doi.org/10.1016/j.jen.2008.12.010

Kochanek, P. M., Tasker, R. C., Carney, N., Totten, A. M., Adelson, P. D., Selden, N. R., . . . Wainwright, M. S. (2019). Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines, Executive Summary. Neurosurgery, 84(6), 1169-1178. doi:10.1093/neuros/nyz051

Lei, J., Gao, G., Feng, J., Jin, Y., Wang, C., Mao, Q., & Jiang, J. (2015). Glial fibrillary acidic protein as a biomarker in severe traumatic brain injury patients: a prospective cohort study. Crit Care, 19, 362. doi:10.1186/s13054-015-1081-8

Lumba-Brown, A., Yeates, K. O., Sarmiento, K., Breiding, M. J., Haegerich, T. M., Gioia, G. A., . . . Timmons, S. D. (2018). Centers for Disease Control and Prevention Guideline on the Diagnosis and Management of Mild Traumatic Brain Injury Among Children. JAMA Pediatr, 172(11), e182853. doi:10.1001/jamapediatrics.2018.2853

Maas, A. I. R., Menon, D. K., Adelson, P. D., Andelic, N., Bell, M. J., Belli, A., . . . Yaffe, K. (2017). Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol, 16(12), 987-1048. doi:10.1016/s1474-4422(17)30371-x

Mannix, R., Eisenberg, M., Berry, M., Meehan, W. P., 3rd, & Hayes, R. L. (2014). Serum biomarkers predict acute symptom burden in children after concussion: a preliminary study. J Neurotrauma, 31(11), 1072-1075. doi:10.1089/neu.2013.3265

McMahon, P. J., Panczykowski, D. M., Yue, J. K., Puccio, A. M., Inoue, T., Sorani, M. D., . . . Vassar, M. J. (2015). Measurement of the Glial Fibrillary Acidic Protein and Its Breakdown Products GFAP-BDP Biomarker for the Detection of Traumatic Brain Injury Compared to Computed Tomography and Magnetic Resonance Imaging. In J Neurotrauma (Vol. 32, pp. 527-533).

Mondello, S., Akinyi, L., Buki, A., Robicsek, S., Gabrielli, A., Tepas, J., . . . Wang, K. K. (2012). CLINICAL UTILITY OF SERUM LEVELS OF UBIQUITIN C-TERMINAL HYDROLASE AS A BIOMARKER FOR SEVERE TRAUMATIC BRAIN INJURY. Neurosurgery, 70(3), 666-675. doi:10.1227/NEU.0b013e318236a809

Mondello, S., Jeromin, A., Buki, A., Bullock, R., Czeiter, E., Kovacs, N., . . . Hayes, R. L. (2012). Glial neuronal ratio: a novel index for differentiating injury type in patients with severe traumatic brain injury. J Neurotrauma, 29(6), 1096-1104. doi:10.1089/neu.2011.2092

Mondello, S., Kobeissy, F., Vestri, A., Hayes, R. L., Kochanek, P. M., & Berger, R. P. (2016). Serum Concentrations of Ubiquitin C-Terminal Hydrolase-L1 and Glial Fibrillary Acidic Protein after Pediatric Traumatic Brain Injury. Sci Rep, 6, 28203. doi:10.1038/srep28203

Mondello, S., Sorinola, A., Czeiter, E., Vamos, Z., Amrein, K., Synnot, A., . . . Buki, A. (2017). Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting with Mild Head Injury to Emergency Departments: A Living Systematic Review and Meta-Analysis. J Neurotrauma. doi:10.1089/neu.2017.5182

NICE. (2019). Head injury: assessment and early management. Retrieved from https://www.nice.org.uk/guidance/cg176/chapter/1-Recommendations#assessment-in-the-emergency-department-2

ONF. (2018). Guideline for Concussion/Mild Traumatic Brain Injury & Persistent Symptoms. Retrieved from https://braininjuryguidelines.org/concussion/fileadmin/media/adult-concussion-guidelines-3rd-edition.pdf

Papa, L., Silvestri, S., Brophy, G. M., Giordano, P., Falk, J. L., Braga, C. F., . . . Robertson, C. S. (2014). GFAP Out-Performs S100β in Detecting Traumatic Intracranial Lesions on Computed Tomography in Trauma Patients with Mild Traumatic Brain Injury and Those with Extracranial Lesions. J Neurotrauma, 31(22), 1815-1822. doi:10.1089/neu.2013.3245

Piazza, O., Storti, M. P., Cotena, S., Stoppa, F., Perrotta, D., Esposito, G., . . . Tufano, R. (2007). S100B is not a reliable prognostic index in paediatric TBI. Pediatr Neurosurg, 43(4), 258-264. doi:10.1159/000103304

Plog, B. A., Dashnaw, M. L., Hitomi, E., Peng, W., Liao, Y., Lou, N., . . . Nedergaard, M. (2015). Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. J Neurosci, 35(2), 518-526. doi:10.1523/jneurosci.3742-14.2015

Silverberg, N. D., Iaccarino, M. A., Panenka, W. J., Iverson, G. L., McCulloch, K. L., Dams-O'Connor, K., . . . McCrea, M. (2020). Management of Concussion and Mild Traumatic Brain Injury: A Synthesis of Practice Guidelines. Arch Phys Med Rehabil, 101(2), 382-393. doi:10.1016/j.apmr.2019.10.179

Strathmann, F. G., Schulte, S., Goerl, K., & Petron, D. J. (2014). Blood-based biomarkers for traumatic brain injury: evaluation of research approaches, available methods and potential utility from the clinician and clinical laboratory perspectives. Clin Biochem, 47(10-11), 876-888. doi:10.1016/j.clinbiochem.2014.01.028

Takala, R. S., Posti, J. P., Runtti, H., Newcombe, V. F., Outtrim, J., Katila, A. J., . . . Tenovuo, O. (2016). Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase-L1 as Outcome Predictors in Traumatic Brain Injury. World Neurosurg, 87, 8-20. doi:10.1016/j.wneu.2015.10.066

Truettner, J. S., Bramlett, H. M., & Dietrich, W. D. (2018). Hyperthermia and Mild Traumatic Brain Injury: Effects on Inflammation and the Cerebral Vasculature. J Neurotrauma. doi:10.1089/neu.2017.5303

Unden, L., Calcagnile, O., Unden, J., Reinstrup, P., & Bazarian, J. (2015). Validation of the Scandinavian guidelines for initial management of minimal, mild and moderate traumatic brain injury in adults. BMC Med, 13, 292. doi:10.1186/s12916-015-0533-y

VA/DoD. (2016). VA/DoD clinical practice guideline for the management of concussion-mild traumatic brain injury. Version 2.0. Washington DC: Management of Concussion-mild Traumatic Brain Injury Working Group Retrieved from https://www.healthquality.va.gov/guidelines/rehab/mtbi/

Wang, K. K., Yang, Z., Zhu, T., Shi, Y., Rubenstein, R., Tyndall, J. A., & Manley, G. T. (2018). An update on diagnostic and prognostic biomarkers for traumatic brain injury. Expert review of molecular diagnostics, 18(2), 165-180. doi:10.1080/14737159.2018.1428089

Welch, R. D., Ayaz, S. I., Lewis, L. M., Unden, J., Chen, J. Y., Mika, V. H., . . . Bazarian, J. J. (2016). Ability of Serum Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase-L1, and S100B To Differentiate Normal and Abnormal Head Computed Tomography Findings in Patients with Suspected Mild or Moderate Traumatic Brain Injury. J Neurotrauma, 33(2), 203-214. doi:10.1089/neu.2015.4149

Williamson, C., & Rajajee, V. (2021, March 29). Traumatic brain injury: Epidemiology, classification, and pathophysiology. UpToDate. Retrieved from https://www.uptodate.com/contents/traumatic-brain-injury-epidemiology-classification-and-pathophysiology

Serum Testing for Evidence of Mild Traumatic Brain Injury AHS – G2151

Wright, D. W., Kellermann, A., McGuire, L. C., Chen, B., & Popovic, T. (2013). CDC Grand Rounds: Reducing Severe Traumatic Brain Injury in the United States. MMWR Morb Mortal Wkly Rep, 62(27), 549-552. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6227a2.htm

Policy Implementation/Update Information

8/27/19   New policy developed. BCBSNC will not provide coverage for serum testing for evidence of mild traumatic brain injury because it is considered to be investigational. BCBSNC does not provide coverage for investigational services. Medical Director review 8/20/2019. Policy noticed 8/27/2019 for effective date 10/29/2019. (sk)

9/10/19   Codes 81479 and 84999 added to Billing/Coding section. Policy remains on notice until 10/29/2019. (sk)

6/23/20   Specialty Matched Consultant Advisory Panel review 5/20/2020. (sk)

7/28/20   Reviewed by Avalon 2nd Quarter 2020 CAB. When not covered section updated, no change to policy statement. Policy Guidelines updated. References updated. Medical Director review 7/2020. (bb)

6/15/21   Specialty Matched Consultant Advisory Panel review 5/19/2021. (sk)

8/24/21   Reviewed by Avalon 2nd Quarter 2021 CAB. Policy Guidelines updated. References updated. Federal Regulations updated. Medical Director review 7/2021. (sk)