



## Blood-Based Biomarkers for Detecting Military-Related Head Injuries

Mild traumatic brain injuries (TBIs) and concussions may be associated with long-term neurological issues. In military service member populations, over 460,000 TBIs have been reported since 2000<sup>1</sup>. While many TBIs are reported in deployed settings, the vast majority occur in non-combat settings. For instance, military service academy cadets represent a group of healthy, young individuals at an increased risk of mild TBI due to combative training exercises, sports, and recreational activities. Aside from long term neurological impacts, TBIs also impact mission readiness and deployment short-term. Blood-based biomarkers may be critical to informing diagnosis of TBI/concussion for immediate decision making such as return to unit decisions, as well as long-term treatment and prevention methods.

### Quanterix Potential Biomarkers of Interest

**Glial fibrillary acidic protein (GFAP)** is a class-III intermediate filament expressed in astrocytic glial cells in the central nervous system, and often serves as a marker of astroglial injury. GFAP is a promising biomarker of post-blast related injury, with studies showing lower GFAP levels being related to more severe psychopathology, such as PTSD and depression<sup>4</sup>. GFAP levels were negatively correlated with cumulative blast exposure, and with duration of military service<sup>6</sup>.

**Interleukin-6 (IL6)** is an inflammatory cytokine that is associated with acute concussion in military combat members. Studies have shown an increase in IL6 as early as 8 hours post-injury<sup>3</sup> and this increase is associated with acute inflammatory responses<sup>7</sup>. In particular, increased IL6 has been associated with poor sleep quality in veteran populations<sup>9</sup>, and preliminary studies aim to decrease circulating IL6 in veterans<sup>8</sup>. There is a need for further study into the correlation between increased inflammatory cytokine levels and risk of developing long-term neurological complications due to blast exposure.

**Ubiquitin C-terminal hydrolase-L1 (UCH-L1)** is one of the most abundant brain proteins, representing between 1 – 2% of total soluble brain protein. More recently, UCH-L1 has been proposed as a potential biomarker for brain injury, as it is released from injured neurons into the CSF and peripheral blood. Studies have shown UCH-L1 levels (along with GFAP, tau, and A $\beta$ -40, and A $\beta$ -42) were significantly increased in law enforcement and military personnel, and elevated UCH-L1 can be detected several hours after exposure to low-level overpressure (such as blast and gunfire)<sup>10</sup>.

**Neurofilament light (NfL)** is a cytoskeletal intermediate filament protein that is expressed in neurons and can be released into the cerebrospinal fluid and bloodstream after neuroaxonal injury. NfL has been shown to be associated with traumatic brain injury as well as neurodegeneration. Studies using Simoa® technology have identified elevated circulating plasma and exosomal NfL increases in service members who suffered from mild TBI, both immediately following and several years post-injury<sup>2</sup>.

**Tau** is a microtubule-stabilizing protein primarily localized in central nervous system neurons, but also expressed at low levels in astrocytes and oligodendrocytes. Repetitive TBI has been associated with elevations of exosomal tau<sup>5</sup> and may be a good indicator of cognitive and somatic post-concussive outcomes.



## References

1. DoD Worldwide Numbers for TBI | DVVIC. <https://www.health.mil/Military-Health-Topics/Centers-of-Excellence/Traumatic-Brain-Injury-Center-of-Excellence/DOD-TBI-Worldwide-Numbers>
2. Exosomal neurofilament light: A prognostic biomarker for remote symptoms after mild traumatic brain injury? *Neurology* 2020 10.1212/WNL.0000000000009577
3. Interleukin-6 is associated with acute concussion in military combat personnel. *BMC Neurology* 2020 <https://doi.org/10.1186/s12883-020-01760-x>
4. Plasma biomarkers associated with deployment trauma and its consequences in post-9/11 era veterans: initial findings from the TRACTS longitudinal cohort. *Translational Psychiatry* 2022 <https://doi.org/10.1038/s41398-022-01853-w>
5. Higher exosomal phosphorylated tau and total tau among veterans with combat-related repetitive chronic mild traumatic brain injury. *Brain Injury* 2018 <https://doi.org/10.1080/02699052.2018.1483530>
6. Assessing a Blast-Related Biomarker in an Operational Community: Glial Fibrillary Acidic Protein in Experienced Breachers. *Journal of Neurotrauma* 2020 <http://doi.org/10.1089/neu.2019.6512>
7. Moderate blast exposure results in increased IL-6 and TNFalpha in peripheral blood. *Brain Behav Immun.* 2017 <https://doi.org/10.1016/j.bbi.2017.02.015>
8. Feasibility and preliminary efficacy for morning bright light therapy to improve sleep and plasma biomarkers in US Veterans with TBI. A prospective, open-label, single-arm trial. *PLOS ONE* 2022 <https://doi.org/10.1371/journal.pone.0262955>
9. Poor Sleep Quality is Linked to Elevated Extracellular Vesicle-Associated Inflammatory Cytokines in Warfighters With Chronic Mild Traumatic Brain Injuries. *Front. Pharmacol.* 2022 <https://doi.org/10.3389/fphar.2021.762077>
10. Neurotrauma Biomarker Levels and Adverse Symptoms Among Military and Law Enforcement Personnel Exposed to Occupational Overpressure Without Diagnosed Traumatic Brain Injury. *Neurology* 2021 10.1001/jamanetworkopen.2021.6445



## Simoa® Technology Enables Best-in-Class Research to Advance Scientific Breakthroughs

Below represents a curated list of peer-reviewed publications where the Quanterix Simoa® assays were used as part of TBI/concussion studies.

Extracellular vesicle neurofilament light is elevated within the first 12-months following traumatic brain injury in a U.S military population

Scientific Reports 2022

[doi.org/10.1038/s41598-022-05772-0](https://doi.org/10.1038/s41598-022-05772-0)

Active duty service members who sustain a traumatic brain injury have chronically elevated peripheral concentrations of A $\beta$ 40 and lower ratios of A $\beta$ 42/40

Brain Injury 2016

[doi.org/10.1080/02699052.2016.1219054](https://doi.org/10.1080/02699052.2016.1219054)

Assessment of Blood Biomarker Profile After Acute Concussion During Combative Training Among US Military Cadets: A Prospective Study From the NCAA and US Department of Defense CARE Consortium

JAMA Network Open

[doi.org/10.1001/jamanetworkopen.2020.37731](https://doi.org/10.1001/jamanetworkopen.2020.37731)

Blood biomarkers of traumatic brain injury and cognitive impairment in older veterans

Neurology 2020

[doi.org/10.1212/WNL.00000000000010087](https://doi.org/10.1212/WNL.00000000000010087)

Inflammation Relates to Chronic Behavioral and Neurological Symptoms in Military Personnel with Traumatic Brain Injuries

Cell Transplantation 2017

[doi.org/10.1177/0963689717714098](https://doi.org/10.1177/0963689717714098)



Scan the QR code with your smart phone camera to be directed to an archive of publications.