Bright prognosis for brain injury biomarkers

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November 2022—The lack of tools for assessing traumatic brain injury has long bedeviled physicians. There's CT. And then?

"This has been an unmet medical need for years," says Ramon Diaz-Arrastia, MD, PhD, the John McCrea Dickson, MD, professor of neurology and director of the Clinical Traumatic Brain Injury Research Center, University of Pennsylvania Perelman School of Medicine. "As many of us know, it's one of the major barriers that has hindered clinically advanced development of new therapies in TBI. And I think it's pretty clear that the clinical evaluation alone leaves a lot to be desired."

"I am always frustrated that we have limited tools," agrees Frederick Korley, MD, PhD, associate professor and associate chair for research in emergency medicine, University of Michigan Medical School, and scientific director, Massey TBI Grand Challenge, Weil Institute, University of Michigan.

That's now on the cusp of changing. Blood-based biomarkers for brain injury may not be bellying up to the bar just yet, but they are starting to raise the bar for how physicians assess TBI.

Two observational cohort studies should help solidify the case for using these biomarkers. Recently published back-to-back in *Lancet Neurology*, they could pass as scientific doppelgängers. The TRACK-TBI study began in the United States in 2014; later that same year a similar study, CENTER-TBI, was launched in Europe. Both are adequately powered, Dr. Korley says, and the recent papers show similar results and echo findings of earlier studies.

It's welcome news, says Geoffrey Manley, MD, PhD, Margaret Liu endowed professor in TBI and professor of neurosurgery, University of California, San Francisco; chief of neurosurgery, Zuckerberg San Francisco General Hospital; and the contact principal investigator of the TRACK-TBI network. It's not so much that the findings are a surprise, says Dr. Manley, who was a coauthor on the TRACK-TBI paper (Korley FK, et al. *Lancet Neurol.* 2022;21[9]:803–813). Rather, "I would say I find it comforting that we are seeing consistent replication and external validation of these results. These are the things that move the needle clinically," he says. "Certainly it provided me personally with more confidence in the clinical utility of these tools."

Change has been a long time coming, says Dr. Korley, noting that for too many years, brain injury was understudied and underfunded. He surmises that was partly because there was little hope in providing successful treatments for patients with TBI. Now, he says, there's renewed interest in bringing novel diagnostics and therapeutics to the field.

Basic biology has also hampered research. Though there are apt comparisons to be made with TBI biomarkers and cardiac troponin, there's one stark difference: The blood-brain barrier makes it difficult for brain proteins to enter the circulation. "But now that technologies for measuring proteins have gotten better, we're able to measure a lot of these proteins in the blood as well,"
Dr. Korley says.

The TRACK-TBI study looked at two proteins, GFAP (found in glial cells) and UCH-L1 (found in neurons), which can be released when glial cells and neurons die.

Previously, the FDA cleared a test for the blood levels of these proteins that help decide which patients with TBI need a brain CT. In the current study, the researchers asked whether the biomarkers could also yield prognostic information.

To find out, they leveraged the ongoing TRACK-TBI study, enrolling patients ages 17 to 90 from 18 level one

trauma centers across the United States. The researchers included 2,552 patients in their cohort; 1,696 had complete GFAP and UCH-L1 measurements and outcome measurements at six months post-injury. Blood samples were collected on the day of injury (within 24 hours). Researchers measured the study participants' post-TBI functional capacity using the Glasgow Outcome Scale-Extended and further divided participants into several subgroups within the scale.

Dr. Frederick Korley at the University of Michigan: "It's an exciting era. For the first time, we're able to measure brain health using blood tests." [Dwight Cendrowski]

Dr. Korley and colleagues asked three questions of the biomarkers measured on day of injury: how well they can predict 1) death within six months; 2) who will be able to function independently outside their home at six months; and 3) whether the patient will have a full recovery at six months.

"We found that these day-of-injury biomarkers were strongly associated with all these outcomes," Dr. Korley says. Biomarker levels were divided into quintiles—those with the highest levels of GFAP had a risk of death seven times higher than those whose biomarkers were in the lowest quintile, he says. Similarly, for UCH-L1, those in the highest quintile had a risk of death 22 times higher than those in the lowest quintile. The biomarkers also showed strong predictive value for whether patients would be able to function independently outside the home.

Given that strong performance, the researchers asked another question: whether the biomarkers added new information to what is already known beyond the IMPACT score, which is used to predict death and unfavorable outcome for TBI.

"In fact it did," Dr. Korley says. The most complex IMPACT score model—one that incorporates bloodwork—had a baseline AUC (without using the markers) for predicting unfavorable outcome, i.e. inability to survive independently outside the home, of 0.86, he says. When the markers were added, it increased to 0.89. Similarly, the AUC for predicting death was 0.90 without the markers; it increased to 0.94 with the markers.

Dr. Korley is clear: “These markers are providing additional prognostic information.”

The researchers also looked at whether the markers worked best solo or in combination. The answers varied. “The kinetics are a little bit different,” Dr. Korley notes. UCH-L1 shows up before GFAP, becoming elevated within about 30 minutes of injury. GFAP rises within an hour and remains elevated longer, peaking at about 24 hours (though it appears to remain elevated for up to two weeks). UCH-L1 peaks at about eight to 12 hours, then drops significantly.

In a similar vein, the European CENTER-TBI study (Retel Helmrich IRA, et al. *Lancet Neurol.* 2022;21[9]:792–802) looked at six biomarkers, including GFAP and UCH-L1, and found they have incremental prognostic value for functional outcome after TBI, with UCH-L1 appearing to be particularly promising.

Says Dr. Diaz-Arrastia (a coauthor on the TRACK-TBI paper), “The conclusions are really, really, highly, highly consistent with one another.”

What might be the implications for patient care?

Dr. Manley works as a frontline trauma neurosurgeon at a level one trauma center one out of every four weeks. With TRACK-TBI and CENTER-TBI, along with previous studies, “What we’re seeing now is validation of these blood-based biomarkers for both their diagnostic and prognostic utility at a scale that in my opinion is clinically actionable.”

GFAP and UCH-L1 are already FDA cleared to be used in a population of Glasgow Coma Scale 13 to 15 within 12 hours to rule out the need for a head CT. “Which is a really big deal,” Dr. Manley says.

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Beyond that, the two studies “say to me, from a practical perspective, that these blood-based biomarkers are starting to look a lot like troponin,” Dr. Manley continues. “They’re going to be sort of a Swiss Army knife-style biomarker” with diagnostic and prognostic performances that will inform patient triage.

The tests are brain injury specific but not TBI specific—the same way troponin is specific for cardiac injury but not myocardial infarction. Dr. Korley sees a wider vista ahead. “This is just the beginning. Down the line, I think we’re going to use these markers to assess other conditions, like hemorrhagic stroke.” Other brain injury markers have shown promise for conditions such as multiple sclerosis. “It’s an exciting era. For the first time, we’re able to

measure brain health using blood tests," he says.

The markers can also guide the conversations physicians have with the families of TBI patients. "Having this ability to predict allows you to better inform the discussion," Dr. Korley says. The information can also be useful for counseling patients who are experiencing symptoms after discharge from the ED, following a negative CT. "I can reassure patients that their symptoms have a real basis—that brain cells have died, though there was no brain bleeding."

Further down the road it's possible the markers can be used for monitoring response to treatment. "We haven't tackled that in an adequately powered way," Dr. Korley says, "but that is going to be the topic of future work."

Some TBI patients are severely injured and come to the ED in a coma or with altered mental status (Glasgow Coma Scale 3–12). Others are less severely injured and may be awake, talking, and moving without difficulty (Glasgow Coma Scale 13–15). Such distinctions are important, Dr. Korley says. "Essentially, we found that these markers are a lot better for predicting prognosis in the most severely injured patients."

One fervent hope is that use of the markers could help reduce unnecessary CT scans.

It's a worthy goal. Dr. Diaz-Arrastia notes that 90 to 95 percent of patients who get a head CT in U.S. emergency departments have normal results. "That tells us we're probably doing too many. They're easy to do, but expensive, and there is some risk from radiation exposure."

At Dr. Diaz-Arrastia's institution, the markers are being used for research, though discussions are underway for adopting GFAP and UCH-L1 for clinical care. There's great interest in reducing unnecessary CTs, and the markers might help. "But that's not an absolute given," he concedes. Even if it's supported by evidence, "You'd have to change the practice style of physicians, which is not always an easy thing to do," he says with a laugh.

The comparison to troponin is apt in this regard too, Dr. Diaz-Arrastia says, given that it took well over a decade for cardiac troponin markers to become widely accepted in EDs. "Boy, I hope it doesn't take that long for these TBI biomarkers," he adds.

The markers might also be useful in triaging patients in mass casualty situations and in low-resource settings, to assess whether someone needs to be evacuated to a higher level of care.

Though the studies show the markers are most useful in predicting outcomes in more severely injured patients (GCS 3–12), there's interest in exploring use for patients with GCS scores 13 to 15.

"There was a little disappointment that in the less severely injured the markers were not as useful in predicting outcomes," Dr. Korley says. "But again, it probably just speaks to the fact that for the less severely injured, maybe it's not about how much brain injury they had; it's more what they brought to the injury in terms of past medical history including mental health conditions and prior brain injury."

"We're still learning about these markers and how they work," he adds. But he's hopeful they may eventually be useful even for less severely injured patients, who don't show high elevations. He offers the example of a patient who is classified as GCS 15, has low biomarker levels, but exhibits many symptoms. "Then the question is: Is it more the anxiety or depression they had prior to the injury that is contributing to symptoms or their extracranial injuries, as opposed to damage of the brain cells? So it could help us with making sure we're treating the patients appropriately."

The truly important question for many clinicians, however, has less to do with CT use and more with helping the 20 to 30 percent who are likely to have disabling and perhaps permanent problems after discharge from the ED. That can help with counseling, Dr. Diaz-Arrastia says. "And it's the only way we're going to develop therapies. Because it's impractical to do a clinical trial when the expected placebo response is 70 to 80 percent."

Traumatic brain injury experts are hoping the markers can help bring about a shift in thinking as well as in patient

care.

CT scanning is most useful for identifying the small fraction—one to two percent—of patients who need a neurosurgical intervention. However, it's not useful for identifying pathologies that result in long-term disabilities after TBI. Dr. Diaz-Arrastia notes the substantial variability in the way patients respond to TBIs, which is in part due to the lack of precise tools to define and measure TBI. "We have many people who appear to have a seemingly mild injury and are told by ED physicians they'll feel better in a few days." While that's often the case, 20 to 30 percent "are still having significant problems months later" after being told they had a mild concussion, such as being unable to return to work or school or to fulfill family responsibilities.

"That's a significant number," Dr. Diaz-Arrastia continues. "Certainly none of us would call that a mild injury by any means. And from a clinical point of view, we have no way of predicting who those people are going to be."

Dr. Korley hesitates to use the term "mild traumatic brain injury" because, he says, it "does a disservice to the people who are going through it." When physicians use the term, "We're just saying it's mild because they're not in a coma," though the impact on patients' lives can be huge, ranging from debilitating headaches to job loss. "So increasingly we're moving toward using the term GCS 15 traumatic brain injury."

Words matter, Dr. Manley agrees. "As a specialty we're working hard to get rid of some of these old terms that don't help patients." Older terminology was based on a coma score developed half a century ago, when coma was the primary marker for identifying those at risk for death. Those who didn't need neurosurgical intervention were "sort of pushed off to the side."

But longitudinal studies have shown that 50 percent of patients with milder forms of acute injury—those who come to level one trauma centers with a GCS 13 to 15—are not fully recovered after one year. "So there's really nothing 'mild' about that at all," Dr. Manley says. On the flip side, moreover, many patients who are labeled as having "severe" injuries do far better than initially thought.

Says Dr. Manley: "These terms are not only outdated, but they create bias. We trivialize patients who show up with higher GCS scores, and we are nihilistic about patients with lower GCS scores."

The new biomarkers could alter such perceptions. If a blood-based biomarker is quite high, that's concerning. "It's the same with troponin, right?" Dr. Manley says. "If your troponin is elevated, that's bad." And if a blood-based biomarker is low, that's not necessarily an all-clear for the patient, so to speak, but it does indicate a lower risk of a bad outcome.

Dr. Manley welcomes the objectivity a laboratory test brings. "To me, because we can see blood-based biomarkers in people with a GCS of 15, we're now getting down to some biology and not a clinical scoring system."

The markers are only now entering the clinical marketplace, but the military has already begun using them (the Department of Defense helped fund the study, along with the National Institutes of Health), and Dr. Manley says early experience suggests they've been helpful in avoiding unnecessary transport of wounded personnel.

He and his laboratory colleagues are considering how the markers might best be used. Right now the focus is on limiting unnecessary head CTs. "The way this is set up currently is to have a very, very high negative predictive value, which means the threshold is low. You don't ever want to miss anybody who has a positive head CT."

Managing resources is critical, he says. On a busy weekend at a level one trauma center, there can be plenty of people waiting for a head CT. "Sadly, some of those people needed to be at the front of the line, but you didn't know that until they decompensated." Thus, the plan is to start with a point-of-care device that will streamline care on the forefront; eventually they plan to bring on a core lab test, which will be useful should the markers be approved for diagnostic use. Ultimately, he says, he'd like to see the markers used for ruling *in* the need for an imaging test. In another study involving a TRACK-TBI cohort (Yue JK, et al. *Lancet Neurol.* 2019;18[10]:953–961), "we looked at GFAP and UCH-L1 levels in patients with normal CTs." Those with elevated GFAP had MRI findings.

It’s likely that companies will develop both point-of-care and large platform assays, says Dr. Diaz-Arrastia, adding that while his own hospital system does not use POC testing in the emergency department, others might find it useful.

TRACK-TBI used Abbott’s point-of-care i-Stat TBI plasma test, as well as Abbott’s Architect core lab test, switching partway through. A previous study looked at GFAP and UCH-L1 values measured on both types of platforms, showing strong concordance between the two, Dr. Korley says. The researchers also developed equations for predicting point-of-care results based on core laboratory results.

When the TRACK-TBI study began, Dr. Korley says, the researchers used the point-of-care device because it was the most robust assay available. “However, we decided to switch to the core lab assay when it became available because it was easier to assay many samples in a single batch. When you’re doing the point-of-care assay, it’s kind of painful to assay one sample at a time.” The switch, then, “was more out of convenience, and we had previously demonstrated that the results from either assay were nearly equivalent.”

Abbott’s i-Stat TBI plasma test has received FDA 510(k) clearance. The company says it is seeking FDA clearance under breakthrough designation for the TBI test on its Alinity i and Architect core laboratory instruments.

Given the interest in and need for these biomarkers, it’s unlikely GFAP and UCH-L1 will have the final words.

Dr. Diaz-Arrastia predicts neurofilament light might soon receive FDA clearance. NfL is an axonal protein that behaves somewhat differently from GFAP and UCH-L1, he says, but might provide complementary information in evaluating TBI.

As useful as GFAP and UCH-L1, and possibly neurofilament light, appear to be, “we are likely going to need additional biomarkers to help with identifying patients likely to have long-term disability,” Dr. Diaz-Arrastia says. Or perhaps a combination of biomarkers will be useful. “At the end of the day, or even the medium of the day, we’re going to need more than two biomarkers.” Given the complexity of the brain and the heterogeneous pathologies that can lead to disability post-TBI, a panel of six to eight biomarkers might be needed.

Dr. Manley agrees: “I can easily see these markers becoming part of a standard trauma panel.”

In the meantime, laboratories should be aware that the already approved biomarkers are likely to be adopted in many of the major neurotrauma centers—at the very least, Dr. Diaz-Arrastia says. And more will be coming in the future.

“I’m convinced we’re in the early days of this story,” Dr. Diaz-Arrastia says. “There’s actually a lot more to come over the next several years.”

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