Biomarkers for Concussion Susceptibility and Effects

LEGAL IMPLICATIONS

By Betsy Grey, Gary Marchant, and Cory Tyszka

The United States is currently suffering a "concussion epidemic."[1] Concussions, also known as *mild traumatic brain injuries* (mTBI), are a growing public health problem. The frequency and severity of such injuries to young people have increased due to greater participation and competiveness in athletics.[2] Professional sports leagues also face growing concussion concerns as players have gotten bigger, stronger, and faster. Concussive injuries are common in military personnel and victims of car accidents as well. Successive head injuries can be life-threatening and can cause *chronic traumatic encephalopathy* (CTE), a progressive, brain-damaging condition resulting in "memory loss, behavioral and personality changes, speech abnormalities, depression, Parkinson's disease, and Alzheimer's disease."[3]

Currently, no proven way exists to physiologically detect concussion risk or damage. Instead, medicine bases diagnosis of concussive injury mainly on self-reported symptoms. However, when outward clinical symptoms have disappeared, it is even harder to determine whether and when the concussion has fully healed.

To date, physical proof of concussive injuries has been available only in autopsies. Brain autopsies of individuals suspected of having CTE have revealed deposits of aggregates of a protein called tau.[4] The autopsied brains reveal a characteristic tangle of tau, with certain "hot spots" of deposits in the brain. These tangles are also indicators of memory loss, extreme mood swings, and aggressive behavior.[5]

Responding to the growing concerns about concussive injuries in the military, sports, and other activities, scientists have made significant progress in identifying biomarkers of concussion susceptibility and effect. Scientists are now trying to identify people with mTBI or CTE using imaging techniques that identify structural or functional lesions in the living brain.[6] Furthermore, scientists are searching for biomarkers in bodily fluid to diagnose and measure concussive injuries. These biomarkers of effect may interact with biomarkers of susceptibility such as genetics and previous brain injuries as well as confounding factors such as sex, age, and ethnicity. They are also likely to be probabilistic rather than determinative. Regardless, development of these biomarkers of effect and susceptibility raise a number of legal applications and issues, which will be briefly surveyed in this article, focusing on sports-related concussion risks.

Biomarkers of Susceptibility

The presence of the genetic variant Apolipoprotein E4 (APOE4) is well-established as a biomarker for Alzheimer's disease, but researchers believe APOE4 may also be an important biomarker for susceptibility to concussions.[7] Concussion susceptibility is thought to be increased in APOE4 carriers and in those who have suffered previous brain injuries. This finding raises a number of legal implications.

Duty to Screen for and Exclude From Activities Individuals With Increased Concussion Risk

Developing a commercially feasible screen for susceptibility to concussion will likely engender a duty on schools and public and private sports

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organizations to screen athletes for susceptibility, whether screening players of all sports or just high-risk sports.[8] This duty will stem from the duty to provide a relatively safe environment to engage in sports. Because concussions are more common in certain high-risk sports, including football, soccer, and hockey,[9] the duty may vary depending on the type of sport involved. Such screening may also implicate a duty to exclude those individuals with susceptibility biomarkers from high-risk sports activities, monitor them more closely, provide accommodations, and implement additional preventive measures to avoid concussion. An analogous precedent is the obligation of NCAA football teams, pursuant to settlement of litigation, to genetically screen their players for sickle cell trait, which may put players at an increased risk for serious harm from strenuous activity.[10]

Duty to Warn Versus Privacy Interests

Screening results that show an increased susceptibility to concussion will also raise questions surrounding whether and to whom to release that information. The entity performing or ordering the screening will likely be held to a duty to warn the susceptible individual of an increased risk and perhaps also the individual's coach, employer, or parents.[11] However, releasing that information to others may conflict with the susceptible individual's privacy interests in his medical information. Nonetheless, the results may have important implications for family members, and the issue arises whether those individuals have a right to that information as well. Also, use of that information for research in this developing field of medicine may conflict with the individual's privacy interests.[12]

On a related matter, requiring routine screening may result in information that the individual does not want others, such as insurers and employers, to know. If a school, for example, requires wide-scale screening for concussion susceptibility, a number of otherwise healthy students could receive information that has the potential to exclude them from life insurance, disability insurance, and long-term care insurance. Thus, release of test results can have a broad, long-term impact.

Assumption of Risk

Even if an individual is found to be susceptible to concussion, whether by biomarker or because of previous injury, and a school or organization has a consequent duty to monitor or exclude that individual from the high-risk activity, the question remains whether students (or their parents) can validly assume the risk of injury. This may depend on the degree of susceptibility the test indicates. At the same time, the capacity to consent may change over the course of successive injuries, as the cognitive function of the individual potentially can decrease with each injury. Moreover, given the quickly changing circumstances of this area—including the increased competitiveness of student athletics, as well as the related developing science—it is uncertain whether parents and students can ever validly consent to exposure to such an uncertain and changing risk. Indeed, many parents still see concussion as a rite of passage. Even if students can validly assume the risk under some circumstances, there may be a certain level of susceptibility that would always require exclusion. The difficulty is defining the applicable cutoff.

Potential Liability Under Eggshell Skull Doctrine

Under general tort law, the eggshell skull doctrine means that a negligent actor takes his plaintiff as he finds him. Accordingly, someone who is more susceptible to injury nevertheless has a right to be compensated for that injury when he is harmed by someone else's wrongful actions. Even under this doctrine, the question remains whether a susceptible individual has the same right to recovery as a non-susceptible individual, or whether the injured party's compensation would be reduced based on comparative fault or assumption of risk. Further, measuring harm is difficult when the long-term consequences of concussion are so uncertain yet can be so severe.

Potential Application of Idiosyncratic Response Defense

In contrast to the eggshell skull doctrine, a tortfeasor may potentially assert the idiosyncratic response defense when an individual's susceptibility to concussion is rare and unpredictable. Although the eggshell skull doctrine is limited to negligence cases, the idiosyncratic response defense applies in strict liability actions. Borrowing from toxic tort litigation, defendants in such cases have argued successfully that they are not liable for harm from products that affect only genetically hypersusceptible individuals.[13] The difficulty lies in determining what responses are idiosyncratic and the applicable percentage cutoff.

Biomarkers of Effect

Scientists now know that a peptide called amyloid-B that is associated with Alzheimer's starts accumulating in an affected person's brain 15–25 years before memory loss starts. Building on this research, scientists have started using *positron emission tomography* (PET) imaging to identify molecules such as amyloid-B and tau in the living brain. PET scans use radioactive tracers that latch onto specific targets in the brain and emit positrons that are registered by a PET scanner. Scientists have now developed some experimental tau tracers, such as T807 and FDDNP, to detect CTE. They hope that these tracers will be able to track cognitive decline and eventually be used as a CTE diagnostic. In addition, researchers have reported that other brain imaging technologies such as *quantitative electroencephalography* (qEEG) and *functional magnetic resonance imaging* (fMRI) provide promising potential for diagnostic assessment of mTBI and postconcussive damage.[14]

Scientists also have been looking for indicators of concussion injury in bodily fluids. Research shows that in the early stages of Alzheimer's, tau increases and amyloid-B decreases in the fluid around the brain and spinal

cord. Scientists are searching for similar changes in cerebrospinal fluid in acute head injury that could be monitored with a spinal tap. And finally, other scientists report progress in identifying blood-based biomarkers of brain injury that could be used to provide an objective marker of brain damage from concussive hits using only a blood test.[15]

Although the search for TBI and CTE diagnostics is still in its infancy, scientists are hopeful that they will be able to isolate a set of reliable and objective techniques that will detect and assess these injuries while people are alive. This advance will have significant legal implications.

Application in Return-to-Play Determinations Under State Laws

Between 2009 and 2014, all 50 states plus the District of Columbia enacted legislation to address TBI, much of which specifically targets youth sports-related concussions.[16] Frequently, this type of legislation uses the subjective absence of signs of concussion to make return-to-play determinations. That standard is largely inadequate, however, because many concussions are diagnosed based on self-reported symptoms, including headaches, dizziness, and nausea. Moreover, concussion symptoms may evolve for days following the injury and a player may mask his symptoms, whether intentionally to avoid sitting out, or unintentionally as a result of impaired judgment arising out of the injury. Accordingly, relying on an athlete's self-reported symptoms can be inaccurate or even dangerous.

Even when outward symptoms have disappeared, there is no way to determine physiologically when the concussion has fully healed. Due to the difficulty in detection and the reliance on an athlete's own impressions of the seriousness of the harm, many athletes return to play too early, placing them at greater risk for successive injury.[17] Determining when a concussion has healed is crucial because of the severe CTE implications from successive injuries.

Development of biomarkers of effect will have a direct impact on this type of legislation. At the very least, these biomarkers, though not a physical symptom, would likely qualify as a sign of concussion. In any event, these biomarkers will permit more effective return-to-play determinations and a school or organization could be liable for the failure to test for them. To be effective, the biomarkers must first be measured in the students prior to play to create baseline measurements. Then, when there is evidence of a potential concussion, trained personnel can compare the levels of biomarkers postinjury to those baseline measurements.

The hope is that biomarkers will not only signal the presence of a concussion, but also the extent of it, and detect the presence of the concussion after outward symptoms have disappeared. Thus, once the technology is available for widespread use, liability for a successive injury would likely attach when a player is not timely screened or is permitted to return to play with the continued presence of concussion biomarkers.

Medical Monitoring Requirements for Biomarkers

Successive concussive injuries implicate a latent risk for CTE, since CTE may take years to develop. Latent risk claims may seek recovery for the increased risk of CTE, as well as medical monitoring costs. These claims are based on the premise that plaintiff has incurred an injury as a result of a sports-related event and is at increased risk of future disease. Further, this risk is not stable; it increases with more injuries.[18] Courts often limit recovery for latent risks and medical monitoring because of the fear of limitless liability and the speculative nature of the claim. With biomarkers of effect, these claims will become less speculative. Again, effective use of the biomarkers depends upon creating a baseline screening of the players.

Use of Biomarkers to Prove Causation and Injury

Proving injury and causation are two major challenges to bringing a lawsuit to recover for concussive injuries.[19]

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Using self-reported symptoms to show causation of concussive injury is naturally subject to attack as self-interested testimony. [20] Biomarkers of effect may soon be used by both plaintiffs and defendants as objective evidence to prove or disprove injury and causation. Plaintiffs will be able to use biomarkers as an objective diagnostic measure to show concussive injury (in, say, sports or in car accidents). Defendants will also be able to dispute the injury through the absence of biomarkers. Such evidence can also buttress an alternative causation argument—for example, a chemical company accused of causing neurological disorders could show that the plaintiff has biomarkers of concussive injury that could be an alternative cause of the observed symptoms. At the same time, the reliability and medical significance of these biomarkers to prove causation will be open to dispute and likely subject to *Daubert* screening.

Tort Claims for Subclinical Injuries Revealed by Biomarkers

Biomarkers of effect may challenge the concept of legally recognized injury. In asbestos litigation, for example, a minority of courts have concluded that subclinical effects such as pleural thickening are "present injuries" that can support a valid claim.[21] This raises the issue of what constitutes recognizable injury. Biomarkers of effect may reveal subclinical changes even before the outward symptoms begin to manifest, and may open the courthouse doors to more and earlier claims for concussive injuries.

Mandatory Screening Requirements

The development of biomarkers for concussive injury may engender a duty to screen athletes periodically for injury throughout the season. This duty may arise even if the player does not manifest outward symptoms of injury.

Conclusion

Scientists have made significant progress in the development of biomarkers for susceptibility and effect of concussive injury. As these developments continue and biomarkers are applied in a widespread fashion, they will implicate a host of legal issues. Technology allowing for both preliminary susceptibility screening and on-site effect diagnosis will raise questions of duties to screen and to warn, protection of privacy interests, and a change in return-to-play criteria, among others. ◆

Endnotes

1. Erin P. Andrews, *Avoiding the Technical Knockout: Tackling the Inadequacies of Youth Concussion Legislation*, 58 N.Y. L. Sch. L. Rev. 417, 419-21 (2013/2014) (estimated rate of sports- and recreation-related concussions in the United States is 1.6–3.8 million per year).

2. After increasing for many decades, participation in sports such as youth football started to decline in 2010 because of concerns about concussions. *See* Steve Fainaru and Mark Fainaru-Wada, *Youth Football Participation Drops*, ESPN.com (Nov. 14, 2013), available at http://espn.go.com/espn/otl/story/_/page/popwarner/pop-warner-youth-football-participation-drops-nfl-concussion-crisis-seen-causal-factor.

3. Ronald L. Hayes and Stafania Mondello, *The Future of Simple Blood Based Tests to Diagnose Mild TBI*, International Brain Injury Association (2012).

4. Lauren K. Wolf, *Racing to Detect Brain Trauma*, Chem. & Eng. News, July 21, 2014, at 9.

5. *Id.* at 10.

6. *See* Erin D. Bigler, *Mild Traumatic Brain Injury: The Elusive Timing of "Recovery,"* 509 Neurosci. Lett. 1, 2–3 (2012).

7. Kevin E. Gordon, *Apolipoprotein E Genotyping and Concussion: Time to Fish or Cut Bait*, 20 Clinical J. Sports Med. 405, 405 (2010); Jonathan Finnoff et al., *Biomarkers, Genetics, and Risk Factors for Concussion*, 3 Phys. Med. Rehabilit. S452, S454–55 (2011).

8. For example, currently TBI legislation in Arizona requires only that school boards develop and enforce concussion policies for students participating in school district-sponsored activities. There is no complementary requirement for private or professional sports. *See* A.R.S. § 15.341.A.24 (2011).

9. James M. Noble and Dale C. Hesdorffer, *Sports-Related Concussions: A Review of Epidemiology Challenges in Diagnosis, and Potential Risk Factors*, 23 Neuropsychol. Rev. 273 (2013).

10. Vence L. Bonham et al., *Screening Student Athletes for Sickle Cell Trait—A Social and Clinical Experiment,* 363 NEJM 997 (2010). *See also Agu v. Regents of U. of Cal.*, Complaint (Aug. 5, 2014) *available at* http://www.yerridlaw.com/media/Yerrid-Agu-Wrongful-Death-Complaint.pdf (alleging that student athlete who screened positive for sickle cell trait died during a conditioning drill due to insufficient protection of genetically susceptible players).

11. *See Stanley v. McCarver*, 92 P.3d 849 (Ariz. 2004) (holding that the doctor performing the screening owed a duty of care to the patient even in the absence of a doctor-patient relationship because he was in a unique position to prevent future harm).

12. *See Ariz. Bd. of Regents v. Havasupai Tribe*, 204 P.3d 1063 (Ariz. App. 2008).

13. *See* Gary E. Marchant, *Genetic Susceptibility and Biomarkers in Toxic Injury Litigation*, 41 Jurimetrics J. 67, 80–84 (2000).

14. David B. Arciniegas, *Clinical Electrophysiologic Assessments and Mild Traumatic Brain Injury: State-of-the-Science and Implications for Clinical Practice,* 82 Int'l J. PsychoPhys. 41 (2011); Peter G. Gonzalez and Matthew T. Walker, *Imaging Modalities in Mild Traumatic Brain Injury and Sports Concussion*, 3 Phys. Med. Rehabilit. S413, S418–20 (2011).

15. Pashtun Shahim, *Blood Biomarkers for Brain Injury in Concussed Professional Ice Hockey Players,* 71 JAMA Neurol. 684 (2014); Alex P. Di Battista et al., *Application of Blood-based Biomarkers in Human Mild Traumatic Brain Injury,* 4 Frontiers Neurol. Art. 44 at 1 (2013).

16. http://www.ncsl.org/research/health/traumatic-brain-injury-legislation.aspx.

17. *See* Bigler, *supra*, at 1–2.

18. Kaj Blennow et al., *The Neuropathology and Neurobiology of Traumatic Brain Injury*, 76 Neuron 886, 887 (2012).

19. Douglas K. W. Landau, *Proving Damages in Child Concussion Cases,* Trial, Sept. 2014, at 40, 41.

20. Stockard R. Hickey III, *Defending Questionable Mild Traumatic Brain Injury Claims,* For the Defense, June 2014, 14, 17.

21. *See* Note, *Latent Harms and Risk-Based Damages*, 111 Harv. L. Rev. 1505 (1998).