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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Diffusion tensor imaging in the courtroom: Distinction between scientific specificity and legally admissible evidence

Jennifer Christine van Velkinburgh, Mark D Herbst, Stewart M Casper

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Abstract

Interest and uptake of science and medicine peer-reviewed literature by readers outside of a paper's topical subject, field or even discipline is ever-expanding. While the application of knowledge from one field or discipline to others can stimulate innovative solutions to problems facing modern society, it is also fraught with danger for misuse. In the practice of law in the United States, academic papers are submitted to the courts as evidence in personal injury litigation from both the plaintiff (complainant) and defendant. Such transcendence of an academic publication over disciplinary boundaries is immediately met with the challenge of application by a group that inherently lacks in-depth knowledge on the scientific method, the practice of evidence-based medicine, or the publication process as a structured and internationally synthesized process involving peer review and guided by ethical standards and norms. A modern-day example of this is the ongoing conflict between the sensitivity of diffusion tensor imaging (DTI) and the legal standards for admissibility of evidence in litigation cases of mild traumatic brain injury (mTBI). In this review, we amalgamate the peer-reviewed research on DTI in mTBI with the court's rationale underlying decisions to admit or exclude evidence of DTI abnormalities to support claims of brain injury. We found that the papers which are critical of the use of DTI in the courtroom reflect a primary misunderstanding about how diagnostic biomarkers differ legally from relevant and admissible evidence. The clinical use of DTI to identify white matter abnormalities in the brain at the chronic stage is a valid methodology both clinically as well as forensically, contributes data that may or may not corroborate the existence of white matter damage, and should be admitted into evidence in personal injury trials if supported by a clinician. We

also delve into an aspect of science publication and peer review that can be manipulated by scientists and clinicians to publish an opinion piece and misrepresent it as an unbiased, evidence-based, systematic research article in court cases, the decisions of which establish precedence for future cases and have implications on future legislation that will impact the lives of every citizen and erode the integrity of science and medicine practitioners.

Key Words: Diffuse axonal injury; Mild brain injury; Magnetic resonance imaging; Neuroimaging; Medicolegal; Litigation; Medical jurisprudence; Ethics; Peer review; Publishing

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Core Tip: Transcendence of an academic publication over disciplinary boundaries faces the challenge of application by a group that inherently lacks in-depth knowledge on the scientific method, the practice of evidence-based medicine, or the peer-reviewed publication process. A modern-day example of this is the ongoing conflict between diffusion tensor imaging (DTI) publications and legal standards for admissibility of evidence in personal injury litigation cases in the United States. We have amalgamated the peer-reviewed research on DTI in mild traumatic brain injury with the court's rationale underlying decisions to admit or exclude evidence of DTI abnormalities to support claims of brain injury.

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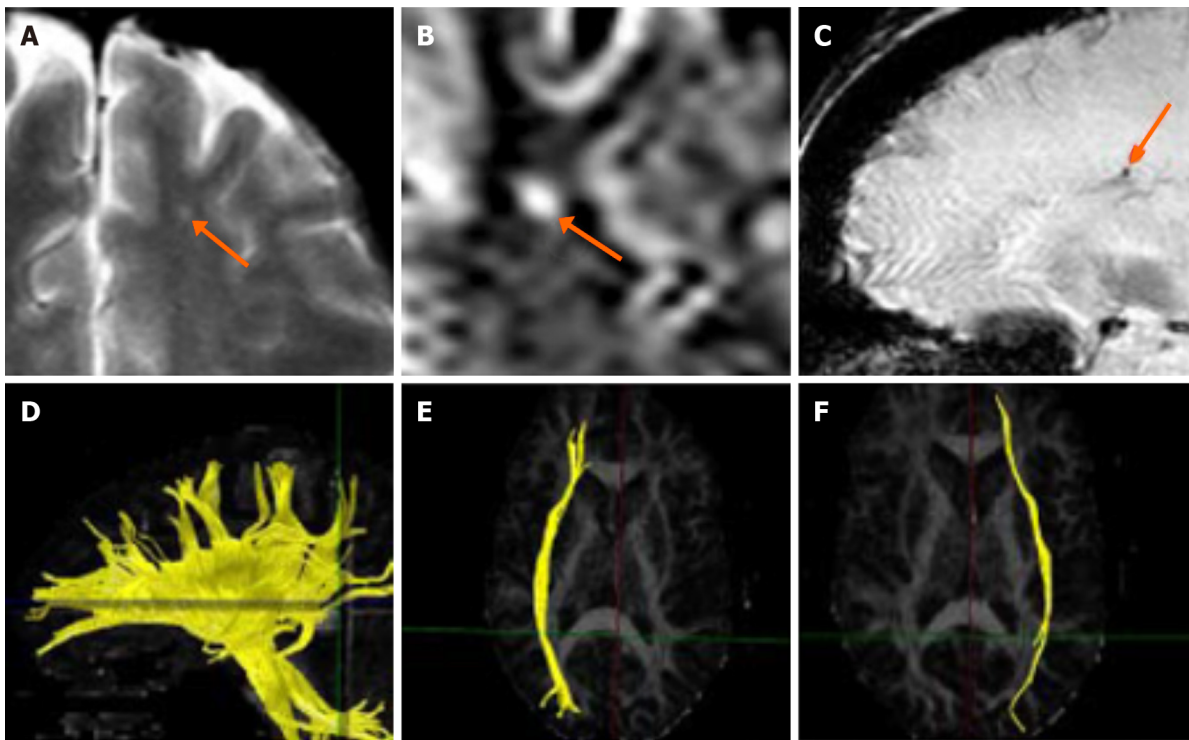
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INTRODUCTION

In 2013 and 2014, the number of emergency department visits, hospitalizations, and deaths related to traumatic brain injury (TBI) approached 2.9 million per year[1,2]. Unsurprisingly, a significant portion of those injuries lead to lawsuits. In addition, such accidents also result in an incalculable number of TBIs, which are characterized by non-specific early symptoms (*e.g.*, amnesia, confusion, dizziness, headache, nausea), no loss of consciousness, and initial imaging studies interpreted as normal. While such patients can later suffer a spectrum of lifelong disabilities, application of the poorly defined label of “mild TBI (mTBI)” complicates both diagnosis and prognosis.

The determination of whether there was a concussive blow revolves around the mechanism of injury and the body's response to the injury. In turn, those issues can be illuminated by input from witnesses. Unfortunately, there are many unwitnessed injuries. Aside from any issues related to the mechanism of injury, in litigated matters involving mTBI, there are two primary areas of controversy: (1) Was there a concussion/mTBI? and (2) Is there a natural course and recovery for the injury? The latter topic implicates the issue of structural brain damage during the chronic stage. The aggregation and evaluation of all data points that go into the complex mosaic of information that is the clinical diagnosis of an mTBI[3] is beyond the scope of this paper. However, those determinations can be made by treating healthcare providers along the course of injury and recovery. Alternatively, a diagnosis and course of recovery might be assessed retrospectively by clinical consultants, researchers, and/or expert witnesses in the context of litigation. The contested field in these cases that has generated the greatest controversy over the last decade is advanced neuroimaging, and diffusion tensor imaging (DTI) in particular. DTI is widely recognized as the most sensitive method to identify white matter disruption in the brain[4] (Figure 1), and the structural neuropathology identified by DTI is positively associated with cognitive dysfunction in attention, memory, processing speed, and executive function[5]. In concussion, DTI plays a complementary role in understanding the physical, cognitive, and emotional disruption in the post-injury chronic stage[6]. Yet, conflict has emerged in the litigation setting by those fearful that the weight of sensitivity will be confused for scientific specificity.

Recently, Shenton *et al*[7] argued that because the data generated by DTI might be misconstrued or misinterpreted, it should not be admitted into evidence. However, this perspective obfuscates the difference between scientific standards and legal standards, possibly based on a simple misunderstanding of the manner in which evidence is actually offered and admitted into evidence in civil litigation. Regardless, it is important to initially recognize that one cannot equate degrees of proof required by law with the statistical probabilities about the number of patients who have sustained a TBI or the number of patients who suffer from persistent post-concussion symptoms (PPCS). As has been demonstrated from contemporary longitudinal outcome studies, the probability of PPCS in a head injury patient hover around 50%[8].



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Figure 1 Imaging evidence of a traumatic brain injury in a representative patient. A: Bright spot on T2-weighted images near the gray-white junction, consistent with traumatic axonal injury (orange arrow); B: Close-up of lesion shown in Panel A (orange arrow); C: Microhemorrhage near the gray-white junction shown on a microhemorrhage-sensitive magnetic resonance image (orange arrow); D: Gaps in the normally continuous distribution of tracts that pass through the corpus callosum; E: Diffusion tensor imaging (DTI) tractography of the relatively normal right fronto-occipital fasciculus; F: DTI tractography of the left fronto-occipital fasciculus showing decreased tracts compared to the right side shown in Panel E.

Undoubtedly, clinical assessments are influenced by the expertise and/or biases of clinicians. The opinions of treating providers often acquire the imprimatur of reliability. That stamp lasts only so long as it remains unchallenged or the appearance of objective evidence influences those opinions. All clinical data collected following a head injury should be considered in an evolving diagnostic process, where the diagnostic impression can change. While head injury is classified at the time of injury by a system that largely depends upon loss of consciousness and/or the length of post-traumatic amnesia[9], the outcome of the condition does not necessarily correspond with the initial classification[10]. The fact that some symptoms and findings are non-specific[11] does not alter their utility, particularly if they can be contextualized (*i.e.*, used not as a pathognomonic sign but within the context of a larger clinical profile). Medicine does not disregard non-specific symptoms but instead considers and attempts to reconcile them.

Because many TBIs are the result of actionable wrongful conduct and because TBI is heterogeneous, the types of evidence gathered are very important for both care of the injured party and the objective benefits of litigation. Individual outcomes following TBI can range from recovery of clinical symptoms to long-term disability, lasting months to years, related to underpinning physical, cognitive, emotional/behavioral and sleep disturbances[11]. DTI abnormalities correlate positively with post-concussion symptoms and severity[12], including self-reported quality of sleep and depression[13]. DTI abnormalities may also account for mTBI-related headache[14,15]. In cases where there are persistent symptoms, a challenge, like Shenton's, to an arguably objective basis for assessing injury poses a serious threat to the welfare of an injured party, and can deprive that person of meaningful and legally authorized compensation.

QUANTITATIVE DTI

Neuroscience has recognized that structural white matter damage, known as traumatic axonal injury (formerly or alternatively called shear injury or diffuse axonal injury), often follows TBI at all levels of severity including mTBI. This has been documented in human histological[16] and postmortem[17] and in animal[18] histological studies. Reliance on histology is necessary because of, among other reasons, the low rate of confirmation using standard clinical neuroimaging such as computed tomography (CT) scan and standard magnetic resonance imaging (MRI)[19,20].

DTI is the most sensitive technology available for drawing compelling inferences about the structural integrity of damaged axons *in vivo*, based upon quantitative assessment of water molecule diffusivity within white matter fibers[21]. When fully intact inside the axonal membrane and the surrounding myelin sheath, water molecules are restricted to intra-axonal movement. When those structures are disrupted through injury, the water molecules become free of spatial restriction and diffuse randomly. Thus, DTI reveals disturbances from the normal patterns of water dispersion consequent to shearing or other damage[22]. Importantly, DTI reveals microstructural pathology that may or may not be visible on routine MRI scans[23,24]. Relying on the metric of fractional anisotropy (FA)[19], neuroscientists have been able to measure whole-brain and regions of interest (ROIs), voxel-wise, and tract-based spatial statistics white matter architecture in mTBI[23,25]. It has been suggested that comparing individual mTBI patients to group norms may lead to “overlook[ing] individual profiles of injury, which are inherently more subtle and heterogeneous across individuals”[26]. However, pre-morbid DTI imaging is rare. To address these issues, a “subject-specific approach” has been proposed[19]. However, given the general absence of pre-morbid DTI data, other clinical diagnostic factors serve as subject-specific markers.

As recently noted in a paper published in *Neurology*[27] on serum biomarker findings related to the neurofilament light chain polypeptide, a marker of axonal damage, DTI is not part of the common imaging protocols following TBI because it has “limited availability, high cost, and cumbersome image processing.” It is not at all surprising that the clinical use of this potential diagnostic technique revolves, at least in part, around cost and reimbursement. Validating microstructural brain damage is not likely to change patient care in most circumstances, so there is little incentive for major medical insurers to pay the expense. While the defense in TBI litigation has popularized a mantra that quantitative DTI “is not in clinical use,” that statement is not only flatly incorrect but overlooks the fact that there is also no legal requirement for clinical use as a prerequisite for the admission of an expert opinion under either the Daubert or Frye standards that will be addressed below.

ADMISSIBILITY OF EVIDENCE

In the law, several types and forms of evidence can be admitted into the record over objection when the evidence is considered “relevant.” Conceptualizing the conflict that arises in the face of competing expert opinions on scientific matters by merely reading the case law without practical experience can be challenging for neuroscientists, even those with a law degree. More than two centuries of common law have taught us that to highlight a potential weakness in otherwise relevant evidence, it should be framed as a challenge to the weight to be given to that evidence by the jury, and not to the admissibility of the evidence[28]. The evidence should be relevant to such questions as: Did the plaintiff suffer a brain injury? Is there any structural evidence of that brain injury?

Rule 401 of the Federal Rules of Evidence provides that evidence is relevant if: it has any tendency to make a fact more or less probable than it would be without the evidence; and the fact is of consequence in determining the action. The same language is mirrored in the rules of evidence in many states. State courts are not bound by the Federal Rules of Evidence (FRE) but many states have adopted the FRE. For example, the North Carolina Code of Evidence mirrors the Federal Rules of Evidence and its Rule 401 provides: “Relevant evidence” means evidence having any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence”[28]. Abnormalities in brain white matter that are consistent with the injury would be considered relevant evidence. A jury’s belief that there is white matter damage consistent with the injury, even if inferred, makes the fact-brain injury-more probable than it would be without the evidence. Whether the same evidence (white matter damage) can be attributed to other causes depends on the specific facts and circumstances of the case. Thus, there are a constellation of factors that may be considered, including but not limited to: The patient’s age; the patient’s prior medical history, including previous concussive events; co-morbidities including co-occurring injuries; pre-existing abuse of drugs, alcohol, and other substances; and the imaging and post-processing techniques employed. In the courtroom, these factors relate to the weight of the evidence.

THE DIAGNOSTIC KEY

Some health care providers claim, without evidence, that the consequences of an mTBI/concussion resolve within 3 mo of injury and that an injury, if there was one, has no lasting consequences[29,30]. Some neuropsychologists still testify about and perpetuate the 3-mo recovery myth[31]. By contrast, other healthcare providers and neuroscientists believe that some constellation of post-concussion symptoms can and do last beyond the unproven 3-mo period, extending to 6 mo and 12 mo[8], and beyond. Often, a patient undergoes advanced neuroimaging, including DTI, well into the chronic stage of recovery at 2 or more years post-injury, and the observed white matter lesions may be viewed as consistent with the original injury. Litigated cases can be reduced to a battle among expert witnesses

who rely upon some objective findings, self-reports, and collateral opinions about whether there is or was a TBI.

Given the above paradigm, there is little wonder that reliance on any data generated through diagnostic testing, including MRI and DTI, can take on great importance in aggregating the evidence of injury. However, to support a claim of neural structure damage, even if standing alone, the test and the results are not considered diagnostic like a pathognomonic biomarker. Rather, DTI evidence of white matter damage (reduced FA) in certain patterns and/or in certain structures tends to make the existence of brain injury more or less likely. Thus, while DTI evidence is not a stand-alone diagnostic test (*i.e.*, a biomarker) for brain damage, the DTI results do provide data that can be further analyzed (and be the subject of cross-examination), to determine if the damage is more likely than not consistent with trauma. Indeed, the spatial pattern of white matter abnormalities may vary among patients with similar presenting symptoms (*e.g.*, nausea, vomiting, headache, disrupted sleep, or neurocognitive disorder) based upon the nature of the mechanical perturbation that caused the injury, the manner in which the patient's brain responded to the perturbation, and genetic vulnerabilities. Also, there are recognized patterns of low FA that are consistent with traumatic axonal injury[26,32]. By addressing and analyzing the actual or potential non-specific signs and/or symptoms, including patterns consistent with traumatic injury, clinicians engage in substantially the same differential diagnostic process that is routinely used in medicine.

There has been ongoing legal conflict between proponents of the use of quantitative DTI to aid not only in the diagnosis of mTBI but also as admissible evidence for the fact-finder (usually a jury), and the opponents who claim that although DTI is the most sensitive technique currently available to assess the structural integrity of white matter in the brain, DTI should not be admitted into evidence in TBI trials. It is the latter position that was most recently advocated by Shenton *et al*[7] in a paper published in the *International Journal of Law and Psychiatry*, titled "Mild traumatic brain injury: Is DTI ready for the courtroom?" As Shenton's paper is a more contemporary reiteration of an opinion previously stated by others including Wortzel *et al*[26] but without new science to support their position, it has not been well embraced by the vast majority of courts (> 90%) that have considered efforts to exclude DTI evidence. Unfortunately, such papers always raise new controversy, with defense experts citing Shenton's paper in their efforts to exclude DTI evidence for reasons that benefit the defense (*i.e.* lowering or eliminating damages of the responsible party)[7]. At minimum, Dr. Shenton should have disclosed, but did not, the parameters of her "conflict of interest" as she has, in the past, served as an expert witness for the defense in opposition to admission of DTI evidence.

The earliest contribution to this debate cited in Shenton's paper was from Wortzel *et al*[26], who advanced the argument (without the benefit of a legal expert as co-author) that DTI should not be used in TBI litigation because, in their opinion, it might fail the standards of admissibility in federal court (*i.e.*, the Daubert admissibility test), the putative findings are non-specific, and group norms should not be used to diagnose an individual patient. Unaware of efforts to reduce the costs of DTI analysis[33], at the North American Brain Injury Society's conference in New Orleans on September 20, 2013, Dr. Wortzel, a forensic neuropsychiatrist, who failed to disclose his conflicts of interest in his mTBI litigation paper, admitted that one reason the defense in DTI cases does not obtain their own competing DTI assessments is because it is "expensive"[34]. Of course, obtaining a second study commissioned by the defense using a different imaging venue with laboratory-specific protocols and controls would afford an opportunity to determine whether the contest is legitimate or whether the effort to preclude the plaintiff's evidence is simply a ruse. At least, a second study might either confirm or purport to refute the claimed damage to white matter. In any case, Wortzel's paper, like Shenton's paper, failed to distinguish between evidence that contributes to the diagnostic formulation and evidence that is a diagnostic biomarker, failing to recognize that no litigant has claimed that DTI results standing alone are diagnostic for TBI.

PUBLICATION ALONE DOES NOT CONVEY RELIABILITY

Great care should always be taken to determine the reliability of opinions expressed in any publication. Shenton's paper, for example, does not reflect new or novel bench science, as would a systematic review that adheres to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) standards[35] and reports the basis of inclusion/exclusion criteria, nor does it purport to reflect the analyses from any of the 70-plus court decisions denying efforts to exclude DTI evidence. Beyond the documented DTI decisions, it is difficult to speculate on the number of similar decisions that have been made but for which transcript evidence was not obtained and/or reported. Because the supporting documents for DTI decision have been filed in multiple cases around the country as part of a public record, those records are available to anyone desiring to inspect them.

From a scientific perspective, the paper is not a systematic review or meta-analysis, an inception cohort study, a cross-sectional study with consistently applied reference standards and blinding, a randomized trial, or even a case series. From the standpoint of evidence-based medicine, it ranks at the bottom of the weighted system (Level 5) established by the Oxford Centre for Evidence-Based Medicine (OCEBM) (2011) because it is a position paper involving "mechanism-based reasoning"[36]. Like the

subject article, other papers cited by Shenton *et al*[26,30,33,37-40] are also the lowest level under ratings of evidence-based medicine. Some authors, such as Drs. Shenton and Wortzel, work as defense forensic witnesses on this or similar issues, embodying potential bias for the non-evidence-based opinions they are publishing[26]. Other citations have included articles by neuropsychologists with similar conflicts of interest (based upon personal experience[37]), but that topic is beyond the scope of this paper. Those papers have not explored or considered the potential bias that favors limiting the use of DTI for research with attendant funding of grants and/or remuneration with expert witness fees.

Moreover, while the list of co-authors for Shenton *et al*[7] includes Judith G. Edersheim, MD, JD, who is both a psychiatrist and a law school graduate, analyses of the applicable rules of evidence do not reflect how the issues have actually been addressed by at least 70 trial courts that have rendered decisions favorable for admitting DTI evidence in mTBI cases.

The court rules that govern admissibility of the portion of an expert's opinion involving new, recent, novel, or innovative science fall primarily under either the Frye[41] or Daubert[42] standard, depending upon the jurisdiction in which the case is pending and whether the matter is in state or federal court. Frye largely governed the admissibility of expert opinions dealing with new or allegedly novel science in the United States prior to adoption of the Daubert rules for application to the Federal Rules of Evidence[31] and which has been largely incorporated, to some extent, in roughly 40 states. For purposes of this paper, the discussion will focus upon the Daubert standard.

The decision in Daubert was originally heralded as a sea-change in the rules of evidence but it was really an unmuted and flexible way for a trial judge, acting as a gatekeeper, to address the factors that render a scientific methodology valid. In cases that started with Daubert, the courts have made clear that the gatekeeper's assessment is not to substitute the judge's views for that of the expert, choose the more persuasive expert, or penalize the proponent because the science is new or still evolving. In fact, the Daubert court emphasized that issues challenging the application of the science relate to the weight of the evidence that can be explored on cross-examination.

THE CASE FOR EXCLUDING DTI EVIDENCE IN THE COURTROOM

Shenton *et al*[7] argued that factors that should justify excluding admission of DTI evidence under the Daubert rule in mTBI cases include standardization, individual comparison to group norms, specificity of findings, and qualifications of the expert. The authors asserted that the concerning issues about DTI have generated various professional responses, including a 2012 conference held at Emory University (Atlanta, GA, United States) and purportedly summarized in the "Meltzer paper"[40]. Unfortunately, this paper was riddled with inaccurate characterizations of the Emory meeting, if one credits the sworn deposition testimony of one of its co-authors, Gordon Sze, MD[43]; one of the attendees, neurologist Randall Benson, MD[44]; as well as a published paper written by an attorney in attendance, William G Jungbauer, Esq[45]. Contrary to the implication of the paper's title, no consensus was reached at the meeting, no actual votes were taken, and the only opinions considered for the paper were those of the neuroradiologists in attendance. Moreover, no minutes were taken, and opposing views expressed during the conference were not described. Unfortunately, invitation and attendance at the meeting were based upon a somewhat randomized and preferential approach that excluded recognized luminaries, such as Michael Lipton, MD, PhD (whose attendance was precluded because the conference conflicting with the Jewish Sabbath), Erin D Bigler, PhD[43,44] who then resided in Utah, and other neuroradiologists who incorporate DTI into their clinical practices. Of note, and also disregarded, is the fact that DTI has also been used clinically by the United States military[46]; neither the Department of Defense nor the Department of Veterans Affairs were represented at the Emory conference.

Meltzer, the lead author, was deposed in 2017 concerning, among other issues, the meeting at Emory, and she verified that DTI is useful for identifying white matter irregularities in the brain; although, she stated that it is not diagnostic but "shows any kind of disruption of the alignment of white matter tracts...[that may be] reported to be abnormal in many diseased states." Meltzer testified that DTI is not a "disease marker" for any condition[47] and that the "Guidelines" article is not a "scientific paper"[47]. To resolve any possible ambiguity, the proponents of using DTI in mTBI cases do not contend that DTI standing alone is "diagnostic". Meltzer later clarified her view that "DTI is not appropriate on an individual basis for diagnosing mTBI"[47]. She also admitted that none of the co-authors of the paper, including herself, had any experience using DTI in the TBI population and she was unable to provide a justification for excluding Randall Benson, MD from the authorship group although he was in attendance, perhaps because he was a behavioral neurologist who routinely employs quantitative DTI in his clinical practice and not a neuroradiologist[47].

With regard to the Consensus Conference outcome, Meltzer conceded that the attendees refused to even consider voting on whether DTI should be admitted into evidence in individual cases of head trauma, almost certainly because there was no consensus. Of the six co-authors of the paper, four were affiliated with Emory University's Center for Ethics and were not neuroradiologists, neuropsychiatrists, neurologists (like Benson), or neuropsychologists[47], and two were neuroradiologists-Meltzer and Gordon Sze, MD of Yale University (New Haven, CT, United States). Dr. Sze testified at his deposition

that he did not write any part of the Meltzer paper; this is itself a problematic issue, in violation of the International Committee of Medical Journal Editors standards and norms of science publication[48]. That leaves Meltzer as the sole composing author, despite having no experience working with DTI, although she may have supervised some researchers who did. The combination of the process that gave rise to the Meltzer paper and the deposition testimony of Drs. Meltzer and Sze raises concern about important issues related to the publication, not the least of which is whether the paper should have been designated a consensus report in the first place.

THE REAL ACCOUNT OF DTI IN THE COURTROOM

Shenton *et al*[7] minimize the history of the use of DTI in the courtroom because they report only five cases involving DTI and mTBI. The early scientific history of using DTI in mTBI was documented in 2013 by Hulkower *et al*[49] in “A decade of DTI in traumatic brain injury: 10 years and 100 articles later.” The courtroom history of the use of advanced neuroimaging is less formal but verifiable, in that there are several “unofficial” reports of decisions on the admissibility of DTI (or other advanced neuroimaging) evidence. Members of the Traumatic Brain Injury Litigation Group (TBILG) of the American Association for Justice have created and maintained a databank for court decisions on the subject, which have been documented in a written order, written decision, or transcript of the proceedings. That documentation remains accessible to members of the TBILG and the contents have been filed in a number of cases throughout the United States. Beyond the documented DTI decisions, it is difficult to speculate on the number of similar decisions that have been made but for which transcript evidence was not obtained and reported. A recent decision denying a motion to preclude the use of DTI in a mTBI case was in *Amidon v. The Goodyear Tire & Rubber Company*, No: 1:18-CV - 02138 (September 3, 2021)[50]. Those files are publicly available. To date, there are approximately 70 documented trial court decisions either admitting DTI evidence or denying a motion to exclude DTI evidence in mTBI cases; by contrast, there have been only four decisions excluding DTI evidence on the basis of methodology (Table 1).

As will be noted hereafter, the most probable points of confusion relate to the role of DTI evidence and misplaced reliance on published papers that do not accurately describe the science. For the former, it must be emphasized that quantitative DTI, standing alone, is not sufficient to diagnose traumatic brain damage. Rather, it is but one item to be considered by a clinician in the diagnostic process. For the latter, the published papers that criticize the use of DTI[7,51,39] are themselves not scientific, as will be the subject of analysis in this paper hereafter. Moreover, those papers conflict with the great weight of scientific authority that validates DTI’s sensitivity to white matter damage, a crucial and relevant factor in these cases.

OTHER STANDARDS

One of Shenton *et al*’s critiques of DTI in the courtroom is that the process lacks adequate standardization[7]. Since the global population of researchers and clinicians who use DTI employ a systematic approach to their assessments, Shenton is referring to a formalized consensus standard. This opinion, however, confuses recommendations for uniform standards by implying that systems that have been and are currently in use are faulty or unreliable. While the existence of multiple platforms and protocols confound the direct comparison of results obtained by different DTI scanners and software, as does the use of different subject and control groups and pre- and post-processing techniques in research studies, these can be controlled for (or minimized) in a properly designed comparative analysis. Indeed, such a study is ongoing, involving multiple centers and TBI subjects[52] assessed with different scanners at each site.

There are at least 16 different manufacturers of 3T MRI machines, but GE Healthcare (Chicago, IL, United States), Siemens Healthineers (Erlangen, Germany), and Philips Healthcare (Amsterdam, The Netherlands) account for a lion’s share of the market. In all, the hardware settings include those required for each sequence of software. Post-processing software allows for the quantification of data and generation of images. While in a perfect world, universal or consensus standards would be based upon a large population studied in a strictly controlled analysis (*i.e.*, identical scanners, software sequences, computational settings, and post-processing software techniques), such a goal seems unrealistic. It is more realistic to expect that there might be publication of standardized MRI sequences (*e.g.*, “Common Data Elements in Radiologic Imaging of Traumatic Brain Injury”)[53], research with protocols standardized among multiple institutions [*e.g.*, TRACK-TBI studies[52] and Enhancing Neuroimaging Genetics through Meta Analysis (ENIGMA)[54]] or accessible databases [*e.g.*, CARE Consortium maintained at the National Institute of Health (NIH) Federal Interagency Traumatic Brain Injury Research Information System[55] the Laboratory of Neuro Imaging[56], or the data community of the Mind Research Network, Collaborative Informatics and Neuroimaging Suite[57], the last of which charges a royalty to use its control group]. Importantly, even before the Emory meeting in late 2012, DTI

Table 1 Diffusion tensor imaging orders by state courts

State	Cases	Date	Court	Ruling	Documents	Frye/Daubert
CA	Gutcher <i>vs</i> Toyota Motor Sales, UNITED STATES, Inc.	8/26/2013	CA Superior Court - County of Kern	Supportive	Reporter's transcript of testimony and proceedings denying MIL to preclude Dr Wu	Daubert
CO	Whilden <i>vs</i> Kimberly Cline, Elmer Dudden & Colorado Cab Company, LLC	5/10/2010	USDC - Jefferson County	Supportive	Order - Denying MIL to preclude DTI evidence - Dr Orrison	Daubert
	Woods <i>vs</i> Ruth	2/14/2014	USDC - County of Arapahoe	Supportive	Order - Motion to Strike Opinions of Plaintiff's Expert Dr Benson - denied (Brimmer, DJ)	Daubert
	White <i>vs</i> Deere & Company, John Deere Limited & John Does 1-5	2/08/2016	USDC - CO	Supportive	Order - Denied Motion to Exclude Dr Benson's opinions	Daubert
	Siewald <i>vs</i> Flores	5/17/2019	DC - Larimer County	Supportive	Denial Notice to Strike/Preclude Snyder, Omnibus Order - Motions to strike expert testimony	Daubert
CT	Vizzo <i>vs</i> Fairfield Bedford, LLC	11/2/2016	Superior Court - Judicial District of Stamford/Norwalk - CT	Supportive	Transcript - Motion to Preclude Daubert/Porter denied	Daubert
FL	Hammar <i>vs</i> Sentinel Insurance Company, LTD	9/27/2010	FL Circuit Court - 13 th Judicial Circuit - Hillsborough County Civil Division	Supportive	Order - Denying Defendant's Frye challenge	Frye
	Sworin <i>vs</i> Harris	4/04/2014	FL Circuit Court - 20 th Judicial District - Collier County	Supportive	Order - Defendant's Motion to Exclude Opinions and Expert's Report of Plaintiff's expert Dr Benson	Daubert
	Marsh <i>vs</i> Celebrity Cruises, Inc.	12/15/2017	USDC- Southern District of FL	Supportive	Order - Daubert Motion denied (Ungar, DJ)	Daubert
	Sutter <i>vs</i> Youngman	2/25/2019	Florida Circuit Court - 7 th Judicial Circuit - Volusia County	Supportive	Order - Defendant's Frye Motion, Hearing Transcript, Plaintiff's Opposition to Defendant's Frye Motion, Deposition of Dr Wintermark	Frye
	Ward <i>vs</i> Carnival Corp.	3/14/2019	USDC - SD - FL	Supportive	Written opinion denying defendant's motion to strike DTI expert (Andrew Walker, M.D.)	Daubert
	Caslow <i>vs</i> Orange Christian School	3/26/2018	Circuit Court, 8 th Judicial District	Unsupportive	DTI precluded	Daubert
IL	Weyer <i>vs</i> SAIA Motor Freight Line, LLC	6/02/2019	USDC- NDIL	Supportive	Motion <i>in limine</i> to preclude Benson DTI evidence denied	Daubert
	Snyder <i>vs</i> Vital	11/2021	Third Judicial Circuit, Madison County	Supportive	Order - DTI & 3D Tractography (Dr Ammar Chaudhry)	Frye
IN	Ruppel <i>vs</i> Kucanin		USDC - Norther District - IN	Supportive	Order - Motion to Exclude Dr Benson's opinions denied (Moody, DJ)	Daubert
IA	Lamphier <i>vs</i> Schlee Masonry	4/16/2012	IA - Worker's Compensation	Supportive	Order for 3T DTI Dr Benson (approved)	DTI approved; test not specified
	Henrickson <i>vs</i> Department of Human Services, State of Iowa	8/14/2012	IA - Worker's Compensation	Supportive	Order for 3T DTI Dr Benson (approved)	DTI approved; test not specified
KY	Roach <i>vs</i> Hughes	3/09/2016	USDC - W.D.KY; 2016 U.S. Dist. LEXIS 192835	Supportive	Order denying to preclude "DTI" Analysis and causation opinion	Daubert
LA	Leboeuf <i>vs</i> B&K Contractors, Inc	5/27/2009	Court of Appeal of LA, 4 th Circuit - 10 So. 3D 897	Supportive	Judgment of trial court affirmed	DTI not contested

	Andrew, <i>et al</i> vs Patterson Motor Freight, Inc., <i>et al</i>	10/23/2014	USDC – Western District of LA - Lafayette Division - 2014 WL 5449732	Supportive	Motion to preclude DTI evidence denied	Daubert
	Barnett vs National Continental Insurance Co.	1/08/2019	USDC – Middle District of LA, 2019 WL 126732	Supportive	Motion to preclude DTI evidence denied	Daubert
	Hall vs Landstar Ranger Inc, <i>et al</i>	12/26/2019	USDC – Western District of LA - Lafayette Division - No. 6i18-CV-0410	Supportive	Magistrate Judge, Minutes of Court & Order 12/26/19	Daubert
	Meadors vs D'Agostino	10/29/2020	USDC – Middle District LA	Supportive	Daubert challenge to non-MD testimony and all DTI issues denied	Daubert
	Hernandez vs Scales	12/15/2021	Court of Appeal of La, 1 st Circuit cert denied by SCT	Supportive	Reversing decision of trial court to preclude DTI & QEEG	LSA-C.E. Art. 702
MA	Zawaski vs Gigs, LLC & Wendell Lee Zorman	11/04/2010	Superior Court - Commonwealth of Ma	Supportive	Notice to Preclude denied	Daubert
	Wu vs Lauriat	9/05/2012	Superior Court - Middlesex County	Supportive	Plaintiff's Opposition to Defendant's Motion, partial transcript	Daubert
	Chiulli vs Newbury Fine Dining d/b/a Sonsie's Restaurant	10/17/2012	USDC - Massachusetts	Supportive	Denied MIL to preclude DTI (Benson) (Tauro, DJ)	Daubert
	Irwin vs Eclectic Dining Inc., d/b/a Atlantica's Olde Salt House	6/23/2015	USDC - MA - Daubert	Supportive	Defense Motion to preclude Dr Benson, Plaintiff's Opposition to Motion to Preclude, Defense Reply Brief	Daubert
	Malagic vs Suffolk Construction	8/05/2022	Superior Court - Middlesex County	Supportive	Oder (Benson) - not diagnostic but consistent	Daubert
	Craffey vs Embree Construction Group, Inc.	10/26/2015	Superior Court - Commonwealth of MA	Supportive	Order - MIL to preclude DTI denied (Benson)	Daubert
MI	Rye vs Kia Motors America, Inc.	2/16/2010	Circuit Court - Wayne County	Supportive	Order - Defendant's MIL to preclude testimony of Dr Benson	Daubert
	Ikola vs Matthew Wright, R&L Trainer, Inc & R&L Carriers Shared Services, LLC	6/23/2015	Circuit Court - County of Berrien	Supportive	Order - Denying Defendant's MIL to Exclude evidence regarding Dr Benson's quantitative DTI	Daubert
MN	Wills vs Benjamin Vincent Sullivan & Pan-O-Gold Baking CO.	9/13/2010	3 rd Judicial District - County of Wabasha	Supportive	Motion to Exclude or limit testimony of [Joseph] Wu denied	Frye
	Hansen vs Crain	4/04/2011	2 nd Judicial District - County of Ramsey	Supportive	Transcript, Motion to preclude Dr Wu on PET and DTI denied	Frye
	Nelson vs BNSF Railway Company	10/01/2013	4 th Judicial District - County of Hennepin	Supportive	MIL barring Dr Wu denied	Frye
	Nordstrom vs Fleet & Farm of Menomnie, Inc.	1/7/2014	10 th Judicial District - County of Washington	Supportive	Motion to preclude DTI denied	Frye
	Hyman vs David T. Chang, M.D.	7/18/2014	2 nd Judicial District - County of Ramsey	Supportive	Order - Defendant's MIL (context)	Frye
	Peddycoart vs Lombardo	2/13/2018	1 st Judicial District - County of Dakota	Supportive	Order denying Motion to Exclude Dr Benson	Frye
MT	Kreiman vs C & CB LLC	10/17/2021	MT Seventh Judicial District Court	Supportive	Cross MIL re DTI; Dr Wortzel barred from testifying DTI not generally accepted	Daubert
NJ	Ferrante vs City of Atlantic City	5/29/2014	Superior Court of NJ - Mercer County - Law Division	Supportive	MIL to bar Dr Benson's testimony on DTI denied	Daubert
NM	Booth vs Kit, Inc.	3/23/2009	USDC- NM	Supportive	Order - Denying Joint Motion to Strike/Limit – Orrison (Parker DJ)	Daubert

	Ebel <i>vs</i> Joe F. Apache, Turner Enterprises, Inc.	12/11/2013	State of NN County of Santa Fe, 1 st Judicial District	Supportive	Order - Denying Defendant's Motion to Exclude DTI	Daubert
NY	LaMasa <i>vs</i> Bachman	11/20/2008	Supreme Court, Appellate Division First Department, NY	Supportive	Judgment affirmed, DTI evidence - 56 A.D. 3d 340, 869NYS (2008)	Frye
	Girgs <i>vs</i> Snapple Distribution Corp. <i>et al</i>	5/22/2014	Civil Court of The City of New York - County of Queens: Part 30	Supportive	Decision and Order - MIL to preclude Lipton, DTI and discovery dispute denied	Frye
	Sullivan <i>vs</i> Daniel I. Walters	7/09/2014	Supreme Court of The State of NY; County of Nassau	Supportive	MIL to preclude DTI (Dr Lipton) denied, Notice of Motion, Affirmation in Opposition, Affirmation in Reply	Frye
	Velez <i>vs</i> Merejo	11/06/2014	Supreme Court of The State of NY - County of NY	Supportive	Request for Frye DTI hearing denied	Frye
	Klipper <i>vs</i> Liberty Helicopters, Inc.	1/12/2015	Supreme Court of The State of NY - County of NY	Supportive	Cross motions under Frye, DTI evidence permitted	Frye
	Melendez <i>vs</i> Patrick McCrowell, <i>et al</i>	11/30/2015	Supreme Court of The State of NY - County of Rockland	Supportive	Hearing and denial of Defendant's Motion to preclude Dr Lipton	Frye
	Jean-Francois <i>vs</i> The Port; Authority of New York and New Jersey	3/16/2016	New York	Supportive	Supreme Queens; Normative data not in Dr Lipton's control; No showing that normative data needed	Frye
	Betty Casas as Guardian of Luis Casas <i>vs</i> Consolidated Edison	3/24/2017	Supreme Court of The State of NY - County of New York	Supportive	Decision and Order - MIL DTI denied (Dr Lipton)	Frye
	Brouard <i>vs</i> Convey	2/09/2018	Supreme Court of The State of New York - Suffolk County	Unsupportive	DTI precluded	Frye
	Aravindakshan <i>vs</i> Martello	3/15/2018	Supreme Court of The State of NY - County of Nassau	Supportive	DTI admitted (Dr Lipton) and Frye	Frye
	Caramanica <i>vs</i> Rhim	3/23/2018	NY State Supreme Court - NY County	Supportive	Defendant's experts testimony limited	Frye
	Barney-Yeboh <i>vs</i> Metro-North Commuter Railroad	4/08/2018	NY State Supreme Court - NY County	Supportive	Cross motions re: DTI preclusion denied	Frye
	Konstantinov <i>vs</i> MTLR Corp., Mehadrin Dairy Corp., & Joel Daskal	1/02/2019	Civil Court of The City of NY - County of Kings: Part 30	Supportive	Cross motions re: DTI preclusion denied	Frye
	Davis <i>vs</i> U-Haul of Arizona	7/30/2019	NY State Supreme Court - Bronx	Supportive	Motion to preclude DTI (Dr Lipton) denied	Frye
	Reichmann <i>vs</i> Whirlpool Corporation	5/20/2020	USDC - Eastern District of New York - 2:16-CV-05151 - AYS	Supportive	Magistrate judge, Order - Denying Motion for Disclosure	Daubert
	Blake <i>vs</i> New York Central Mutual Fire Ins. Co.	12/3/2021	NY State Supreme Court - Westchester County	Supportive	Cross Motions (Dr Lipton) - Plaintiff's motion for general acceptance granted; Defense motion denied	Frye
	Lee <i>vs</i> Troge	2/22/2022	NY State Supreme Court - Dutchess	Supportive	Defense Motion to Preclude Dr Lipton Frye hearing; Denied; Wintermark white paper found not to be peer reviewed	Frye
	Tardif <i>vs</i> City of New York	6/17/2022	Southern District NY 13-CV-4056 (KMW)	Supportive	MIL to Preclude DTI denied	Daubert
	Fall <i>vs</i> Greyhound Lines, Inc.	3/9/2023	NY State Supreme Court - NY County	Supportive	Summary judgment on no-fault threshold denied; Lee <i>vs</i> Troge cited over the Brouard decision	Frye
PA	Barbara Rotunda <i>vs</i> Susan Petruska, DMD	4/2013	Court of Common Pleas - Allegheny County	Supportive	DTI, Frye hearing (Dr Wu)	Frye

	Amidon <i>vs</i> Goodyear Tire & Rubber Company	9/2021	USDC – Middle District of PA Civil No. 1:18-CV-02138	Supportive	Daubert - Motion to Preclude DTI testimony and to preclude Dr Benson denied	Daubert
	Malone <i>vs</i> Taylor	5/7/2019	Tennessee Circuit Court; 2019 WL 6456250	Unsupportive	MIL to preclude DTI; DTI excluded	Daubert
	Williams <i>vs</i> Crawford	3/02/2018	TX Court of Appeals, 2018 WL 1124306	Supportive	Opinion affirming the trial court judgment subject to a remittitur unrelated to DTI	Daubert
	Gregg <i>vs</i> Covert	11/2021	USDC – ED TX; 2021 WL 5140799	Supportive	MIL denied except for causation not addressed by expert	Daubert
UT	Andrus <i>vs</i> Fulgham & Standard Plumbing Supply, Inc.	7/17/2006	District Court of the 3 rd Judicial District - Salt Lake County	Supportive	MIL DTI denied	Frye
WA	Shannon <i>vs</i> Columbia River Basin Railroad	01/23/2013	USDC – Western District of Washington at Tacoma	Supportive	Order – MIL – reserving on preclusion of DTI witness	Daubert
	Peach <i>vs</i> RLI Insurance Company	5/2019	Superior Court of WA for King County	Supportive	Order - Denying Defendant's Motion to Exclude testimony of Dr Raji	Frye
WI	Lewis <i>vs</i> Wisconsin Bell, Inc., d/b/a AT&T Wisconsin	12/2014	WI Circuit Court – Milwaukee County	Supportive	Order - Hearing MIL to ban Dr Benson (DTI) denied	Daubert
	Hoerth <i>vs</i> Allmerica Financial Benefit Insurance Co	3/2023	WI Circuit Court - Winnebago County	Supportive	Order - Hearing MIL to ban Dr Benson (DTI) denied	Daubert
WY	Wagoner <i>vs</i> Schlumberger Technology Corp	6/20/2008	WY; USDC - WY	Supportive	Order limiting defense neuroradiology witness testimony because he lacked experience with DTI	Daubert

Dates are presented as month/day/year. CA: California; CO: Colorado; CT: Connecticut; DTI: Diffusion tensor imaging; FL: Florida; IL: Illinois; IN: Indiana; IA: Iowa; KY: Kentucky; LA: Louisiana; MA: Massachusetts; MD: Medical doctor; MI: Michigan; MIL: Motion in limine; MN: Minnesota; MT: Montana; N/A: Not applicable; NJ: New Jersey; NM: New Mexico; NY: New York; PA: Pennsylvania; PET: Positron emission tomography; QEEG: Quantitative electroencephalogram; TN: Tennessee; TX: Texas; USDC: United States District Court; UT: Utah; VA: Virginia; WA: Washington; WI: Wisconsin; WY: Wyoming.

guidelines for clinical application had been published (March 8, 2012) by the American Society of Functional Neuroradiology, titled “ASFNR Guidelines for Clinical Application of Diffusion Tensor Imaging”[58]. The recognition of such among TBI researchers and clinicians is highlighted by the Meltzer paper and the White Paper (to be discussed below). It is important to note that while both papers are primarily used in litigation (and heavily relied on by the defense), the latter is a White Paper and not a peer-reviewed systematic review or research article. Both papers discuss the goal of improving DTI standards (particularly of the specificity or diagnostic capabilities). That goal, however, is universal among imaging modalities, both solidly established and newly emerging, and did not negate the findings of white matter abnormalities using the ASFNR guidelines.

The Wintermark White Paper[39] was followed by publication of another opinion piece, titled “Traumatic Brain Injury Imaging Research Roadmap”[24]. This Research perspective fomented during a workshop that followed the American Society of Neuroradiology[58] convention in Montreal, Canada (May 2014) and dealt with several advanced imaging processes, including DTI. It provided an exposition of available databases, recommendations for imaging protocols, and suggestions for further stratification of both control group participants and subjects.

The Roadmap article summarized the acute stage imaging methods commonly used for the assessment of patients following TBI at that time, including CT and MRI with “conventional” imaging sequences. The authors distinguished the conventional sequences from the “advanced” methods including DTI, stating they “do not yet play a central standardized role in diagnosis and management of mild TBI because they require further validation.” The language stops short of contending that quantitative DTI provides no data that can be useful for clinicians.

The Roadmap authors advocated the development of “well-characterized methods for quantitative analysis of advanced imaging data,” “well-accepted, uniform, cross-platform, and user-friendly analysis tools,” and “a large data base of normal individuals to which patients with mild TBI could be compared” that includes “standard variation of normal values in an age-stratified fashion and sufficient representation of abnormal.” The authors also recommended stratification by age, sex, handedness, race, ethnicity, socioeconomic status, and academic achievement, as well as core and preferred imaging protocols. They did not, however, determine that existing advanced neuroimaging data acquisition

failed to provide any relevant data, but rather that whether for research purposes or for clinical purposes, by standardizing the data acquisition, neuroscientists could facilitate data sharing across platforms and enhance the collective scientific efforts.

CONFLICTING EVIDENCE

For the past several years, the defense in mTBI cases has complained that quantitative DTI is an unreliable methodology that should not be used in personal injury lawsuits because the findings (generally reduced FA) are non-specific, and the comparison of a single individual to group normative data is unreliable. Notwithstanding these complaints, and despite suggestions to the contrary in the White Paper and the Roadmap paper, quantitative DTI is widely used clinically for mTBI in multiple locations in the United States and for various other neurologic conditions including multiple sclerosis, Alzheimer's disease, dementia, Parkinson's disease[59,60], and planning for brain tumor surgery in both adults and children[61]. Certainly, the quantitative DTI methodologies currently in use can be improved through widespread collaborative efforts to refine the analytic process, or by relying upon larger or better stratified control groups. However, there is no reason to believe that the multisequence brain MRI assessments that include DTI generate false or unreliable data to be interpreted by clinicians. In fact, it is impossible to reconcile the clinical use of DTI in the aforementioned neurological conditions and the exclusion of medicolegal use of DTI in TBI cases. Because there does not appear to be a dispute that DTI is the most sensitive technology available to identify white matter abnormalities in the brain *in vivo*, whether there is a legitimate conflict about the existence of a brain injury in any specific case, is anyone's guess.

The Shenton paper[7] references the American College of Radiology (ACR) Appropriateness Criteria (AC). Shenton treats the AC ratings as an argument against using DTI in the context of a litigated matter involving head trauma. There are major questions about whether clinicians actually rely upon the AC, and there is little literature on the topic. In 2008, the *American Journal of Roentgenology* suggested that clinician utilization of the appropriateness criteria is "low"[62]. No follow-up peer-reviewed studies have been published that refute this point.

While the ACR may have originally developed the AC as a service to the medical profession that remains underutilized in clinical practice, the AC may not have been a compelling need until the issue of overutilization came to the forefront[63-66].

THE INTERSECTION BETWEEN LAW AND SCIENCE

Central to understanding the debate about the use of quantitative DTI in personal injury litigation is the distinction between concepts of proof[67] in science and the law and the requisite levels of proof comparing the 95% confidence level widely used in science to the "greater than 50%" standard applicable in civil lawsuits. Confidence level is a function of statistics and represents the frequency, expressed as a percentage, that the target population would produce a result within the specified confidence level and that the finding was not attributable to chance.

Both science and law are focused on evidence that often involves uncovering and exploring facts. Generally, progress in science follows use of the scientific method in research. Research begins with an observation that evolves into a question and further evolves into a hypothesis or "working hypothesis" for an observed condition or event, either naturally or through experimentation. A hypothesis can be proved or disproved and should be accompanied by a "null hypothesis" – the opposite of the hypothesis, that can also be proved or disproved. The research may produce a theory. Using the scientific method, priority is given to research record keeping so that experiments and outcomes can be reproduced and verified. The process must be neutral and free of bias[68,69]. To this end, serious scientific contributions require contributors to fully participate in conflict of interest disclosure mandated by the International Committee of Medical Journal Editors[48]. While meaningful scientific contributions generally find their way into peer-reviewed publications, the rigor of peer review varies journal-to-journal and publisher-to-publisher. Thus, what remains unknown are the studies that did not produce a paper for various reasons including but not limited to the failure to prove the hypothesis or conversely, proving the null hypothesis. Such selective reporting, sometimes referred to as the file drawer effect, can bias the entire trend of reporting on a particular subject[69]. By contrast, in legal matters, opposing parties marshal the evidence using relevant documents, photographs, video and by presenting testimony of fact and expert witnesses. The issues to be resolved in an injury case generally involve liability, causation, and damages. The factuality of something is resolved (*i.e.*, deemed more likely than not) by the fact finder (usually a jury) as a result of evidentiary hearings. The evidence and fact finding that occurs in an individual case generally governs only in that case.

RESOLVING THE ADMISSIBILITY OF DTI EVIDENCE

One of the dangers of a paper like Shenton's, whose title is "Mild Traumatic Brain Injury: Is DTI ready for the courtroom?"[7] is that it takes a somewhat academic approach to the issue while ignoring the practical application of the law and the way trials actually work. Shenton *et al*[7] theorize that DTI evidence does not pass the admissibility tests promulgated by the federal courts with the landmark decision by the U.S. Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals Inc*[42]. They argue that there are questions to be resolved before DTI evidence should be submitted in a personal injury case and considered by a jury. But the law does not defer to science to anticipate and resolve in the laboratory every issue or controversy in a young field of science[42] before the issue is litigated in the courtroom. The distinctions or open issues can be contested through the use of expert preparation, practical experience, and "vigorous cross-examination"[42]. As the Supreme Court stated in *Daubert*: Respondent expresses apprehension that abandonment of "general acceptance" as the exclusive requirement for admission will result in a "free-for-all" in which befuddled juries are confounded by absurd and irrational pseudoscientific assertions...In this regard respondent seems to us to be overly pessimistic about the capabilities of the jury and of the adversary system generally. Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence[42].

Daubert and the federal cases that followed, revised the gatekeeper status of the trial judge, requiring the judge to determine whether the proposed methodology was sufficiently reliable to be a component of the proffered expert's opinion. Because most personal injury cases are heard in state courts, it remained the prerogative of each state jurisdiction to either adopt a *Daubert*-like analysis or to retain its then current standard – usually an iteration of the *Frye* "general acceptance" rule. In Connecticut, for example, the Supreme Court abandoned the *Frye* standard and adopted the essence of the *Daubert* standard in *State v. Porter*[70]. The essential gatekeeper function under *Daubert* is to assess the methodology at issue to determine its reliability but not to interject his or her own opinion about the expert's conclusions. To do so, the *Daubert* court advocated considering a set of non-exclusive factors that include: Whether the theory or technique on which the expert relies has been or could be tested; whether the theory or technique has been subjected to peer review and publication; the known or potential rate of error of the technique or theory when applied; the existence and maintenance of standards controlling the technique's operation; and whether the theory or technique has been generally accepted in the scientific community[31,42]. This test of reliability is a "flexible" one depending on the "nature of the issue, the expert's particular expertise, and the subject of his [or her] testimony," and therefore, no one factor will necessarily be determinative of the reliability of an expert's testimony[70, 71].

The rejection of expert testimony is the exception rather than the rule[71-73]. The Second Circuit Court of Appeals has noted that "*Daubert* reinforces the idea that there should be a presumption of admissibility of evidence," and it has interpreted *Daubert* as having "advanced a bias in favor of admitting evidence short of that solidly and indisputably proven to be reliable"[74]. Other Circuit Courts have found that challenges to the methodology used by an expert are usually adequately addressed by cross-examination rather than exclusion. As scientists, Shenton *et al*[7] overlooked the presumption for the admissibility of such evidence, perhaps throwing out the good for the sake of the perfect. The law does not embrace that philosophy.

Contrary to the suggestion of Shenton *et al*[7], judges need not be trained as scientists. They have historically performed quite well in civil and criminal cases dealing with countless scientific and/or technical evidence issues. The law neither requires nor permits the question of admissibility to turn on whether there is more for science to learn or discover. The arc of science, and neuroscience in particular, will be very long. Indeed, scientists may be frustrated at the "hubris" of the law[75] that has rejected the notion that judges are incapable of becoming sufficiently familiar with complex areas of science to determine which side has the better argument about the reliability of the methodology at issue. Scientists generally do not realize that trial judges are not required to decide the validity of specific scientific proposition but rather whether there are "sufficient indicia of legitimacy"[70] to permit the opinions derived from the methodology to be considered by the trier of fact.

Nor should there be limitations on an attorney's ability to handle cases involving medicine including neuroscience or other complicated matters. Indeed, like in any profession, the roster of trial lawyers includes a broad spectrum of talent, levels of experience, and sophistication. The fact that TBI cases are more complex than a case involving a fractured femur does not demand greater regulation of the practice of law, or a higher level of attorney scientific competency as a pre-condition for a trial lawyer accepting a case. Ethical constraints should suffice to prevent a lawyer from handling a TBI case beyond his or her competency.

WHITE PAPERS ARE NOT PEER-REVIEWED SCIENTIFIC ARTICLES

There is a misconception on the part of Shenton *et al*[7] as to both the position advocated in the White

Paper[39] as well as the way the White Paper should be applied in the courtroom, given that to date, courts have overwhelmingly admitted DTI evidence in mTBI cases. The two compelling reasons that DTI has a nearly unbroken record of admission over defense objections is beyond question: DTI is recognized as the “most sensitive neuroimaging tool available today to detect microstructural integrity and diffuse axonal injury, the most common injury observed in mTBI”[7]. In addition, without much more evidence, the existence of a white matter abnormality causally connected on a more probable than not basis by an expert in the field, should suffice for evidence to reach the jury.

Using the White Paper to anchor the argument that DTI is not ready for the courtroom reflects a lack of insight about publishing in science. First, a White Paper is generally known to be a non-scholarly/unscholarly advocacy publication, frequently issued on behalf of a group. Scholarly/scientific papers, in contrast, present new research or review research conducted by others and contribute new, evidence-based information to the body of scientific knowledge. As such, a major difference between the two types of publications is that a White Paper is biased to a pre-determined conclusion and accomplishes that goal by cherry-picking references to lead to a pre-specified conclusion. A scholarly scientific paper states its objective including the working hypothesis; presents a comprehensive, balanced, and impartial assessment of the published literature including the literature that is inconsistent with the authors position; reports on the methodology employed; discusses the findings; and reports on a reasoned and unbiased conclusion. A scholarly scientific paper is also submitted for rigorous peer review that conforms to the Committee on Publication Ethics (COPE) Ethical Guideline for Peer Reviewers[76]. While some journals and organizations publish standards to govern White Papers, neither the *American Journal of Neuroradiology* nor the American Society of Neuroradiology had such standards when the Wintermark White Paper[39] was published. Whether the White Paper was submitted for anything more than editorial (and not peer-) review became clearer when a subpoena was issued to the journal for any sort of record of peer review, which the journal was unable to supply. In fact, Dr. Wintermark testified in a deposition that the White Paper “is not a scientific paper...It reports evidence and the recommendations, and we are not held to any standard except the peer review process”[77]. Any paper that presents a one-sided view, omitting reference and citation to any peer-reviewed journal articles that validate the opposing perspective such as the sensitivity of DTI, should not be included among the compendium of supporting evidence for a bona fide body of scientific evidence in the field of scientific research, clinical practice, or legal trials.

For these reasons, science shies away from White Papers, and instead uses the systematic review, which minimizes or removes bias from the study design, including in the obtainment and analyses of data/evidence and the interpretation of findings. When properly performed, the systematic review is recognized in science as the gold standard for reporting the current state of the science on a particular issue[78]. While neither the paper by Shenton *et al*[7] nor the White Paper by Wintermark[39] are systematic reviews, both are structurally organized to look like such. However, both papers fail to adhere to PRISMA protocols (see above), including the PRISMA checklist[35]. Furthermore, the best that can be said about the peer review process for the White Paper is that it is superficial. For the Wintermark White Paper[39], in particular, Dr. Wintermark himself testified about how the final version of the paper went to press: “So people who are listed basically got a copy of the article, got an opportunity to suggest edits, addition, deletions. We did our best to integrate as many of those comments as we could knowing that sometimes it is not possible. And the modified version was circulated again and then at the end the author, all the people listed as the authors, mentioned that they were satisfied with the text as it stands, and we submitted it for publication. And then when it was submitted for publication, it underwent another round of peer review. I cannot remember exactly what were the comments we got back, and we did our best to incorporate those, redistributed the paper and the editor of the journal decided to accept it”[77].

The type of review described within this professional group does not qualify as independent peer review[76]. By contrast, a relatively contemporary systematic review of the changes that follow the three most recognized classifications of TBI (mild, moderate, and severe) was published in 2018 (referred to here as the Wallace Paper)[79]. The thrust of that DTI study was to examine the dose-dependent relationship of white matter changes among the three TBI classifications by examining the specific regions of interest, timing of the scans, and effects of the injury. Unlike Shenton *et al*[7] and the Wintermark White Paper[39], the Wallace Paper strictly adhered to PRISMA reporting requirements. The final sample of studies in the meta-analysis included 29 mTBI studies involving DTI. The authors abandoned the effort to combine the mTBI data with the moderate/severe data after it became evident that the majority of the latter classifications were scanned on 1.5 T scanners whereas most of the mTBI scans were performed on 3.0 T scanners.

The Wallace paper reported that 26 ROIs were examined in multiple studies, while 9 ROIs were examined in single studies. For the most part, the authors documented only reduced FA in the ROIs examined, with the exception of slightly increased FA in two ROIs, but with small effect size and results that did not reach the threshold for statistical significance. The Wallace paper reported that the mTBI group had significantly lower FA (*vs* controls) in the cerebrum (centrum semiovale, corpus callosum, and forceps major).

The authors of the Wintermark White Paper[39] declared that the inability of neuroscientists to resolve the matter of crossing white matter fibers posed a problem using DTI for clinical purposes. They noted that there were qualitative differences in the approaches used to address crossing fibers and that “[f]urther studies...were required to determine whether one of these has a clear advantage compared with the others”[39]. Here again, the law requires reasonable probability and not certainty, and any equivocation resulting from areas involving crossing fibers can be minimized by focusing an assessment on alternate regions. The authors also advocated for “[i]mprovements in data quality with high-order eddy current correction, distortion correction, and high-order shimming beyond second order should further improve data fidelity and increase the reliability of subsequent data processing”[39]. Again, there is no doubt there can always be improvements in data control, but such criticism would not render forensic assessments of individual patients compared to group norms invalid based upon this general recommendation.

The authors of the Wintermark White Paper[39] also complained that based upon group data acquired through research, there are conflicting findings about whether FA, can increase and/or decrease in the acute and chronic stages of TBI and for different structures within the brain. Those issues did not appear to be significant in the later Wallace study[79]. For the most part, the issues of increased FA seem to be less prominent in DTI studies during the chronic stage. The authors of the White Paper argued that “DTI metrics including FA are not specific to TBI ...” but may be found in other neurological disorders that affect the white matter[39]. They further asserted that there is “insufficient evidence” to use quantitative DTI for “routine clinical evaluation of TBI at the individual patient level for diagnosis and/or prognostication”[39]. Possible alternative causes can be analyzed as part of the differential diagnostic process. Furthermore, no one has advocated for the use of quantitative DTI on a routine basis in the context of concussion or mTBI. The process should be reserved for the cohort of subjects with persistent post-concussion symptoms.

To the best of our knowledge, no papers have adequately articulated the concerns raised by either Shenton *et al*[7] or Wintermark *et al*[39] about DTI being used to provide imaging evidence to be relied upon for the differential analysis necessary to make a diagnosis of mTBI and/or persistent post-concussion symptoms. Similarly, to the best of our knowledge, no papers have closely examined proper scientific publication standards that can be easily evaded by authors and publishers. Again, it is important to not obfuscate the difference between scientific certainty and legal proof – the fair preponderance of the evidence or > 50%; the former being essentially a diagnostic biomarker, as opposed to the latter describing something more likely true than untrue. The law generally recognizes a hierarchy of burdens of proof ranging from the highest burden in criminal cases; an intermediate burden of proof – “clear and convincing evidence” in a claim of civil fraud; and the lowest level – “fair preponderance of evidence” in civil cases[80]. Second, it is critical to not confound the difference between a test that is diagnostic and one that provides medical evidence for ruling out or confirming a diagnosis – even a diagnosis based upon inferences as permitted by the rules of evidence. Third, by placing a premium on the idea of routine clinical use, the authors paint a bona fide clinical care technology, such as MRI/DTI, as a litmus test for the admissibility of an opinion about such at trial. That which is used routinely in the clinic may vary by clinician, care site management, geographic region, and/or socioeconomic factors. Much of medicine is limited by reimbursement rates. Traditionally, corroboration of white matter damage has aided in fashioning rehabilitation of a patient[81] and provided validation of the diagnosis for the patient and clinician. It has also been recently proposed as informative of the persistent physiological effects of concussion after clinical symptoms have abated. This assertion, if accurate, would aid in decisions about return to play/work as well as inform the period of vulnerability of a second concussion[82]. Fourth, it has been shown that DTI abnormalities persist after recognizable symptoms have abated and may be the precursor for degenerative changes[83]. Sixth, the addition of the DTI sequence to a brain trauma MRI protocol should add nominal cost for the facility. While the cost of post-processing of DTI may require a specially trained radiologist, technologist, or statistician, the patient (or attorney) can elect to incur that cost.

While Shenton *et al*[7] cited Wortzel because of his authorship about advanced neuroimaging, they neglected to cite the post-Emory Conference article by DTI luminaries Lipton and Bigler, titled “Clarifying the Robust Foundation for and Appropriate Use of DTI in mTBI patients,”[84] which was a direct response to Wortzel (*i.e.*, being inexorably linked digitally to the paper in the literature databases). Lipton and Bigler pointed out the same weak underpinnings of Wortzel’s arguments in terms of persistence of symptoms of mTBI in some patients; Wortzel’s “straw man” argument denigrating quantitative DTI because it requires quantification; the fact that despite methodological variance among studies the same conclusion is reached – low FA is consistent with TBI; and that the “diagnosis of mTBI, or any other disorder, is based on integration of clinical information, not the result of one diagnostic test.” The Shenton authors instead offer another “straw man” argument that insinuates DTI should not be used as a standalone definitive diagnostic test, a use for which it has not been proposed[7]. A more systematic response to the problematic issues in the Wortzel and Meltzer papers was presented in Hulkower’s “A Decade of DTI in Traumatic Brain Injury: 10 Years and 100 Articles Later”[49].

CONTEMPORARY DTI PAPERS

It appears that little has altered the overall landscape for DTI in mTBI litigation since Shenton *et al*[7] was accepted for publication. That paper, like the White Paper, was devoid of contributions to the practical field of DTI science that validates the reliability of DTI as a measure of structural abnormalities of white matter in the brain. It is concerning, however, that Shenton failed to acknowledge the problems inherent in demanding the standardization of DTI protocols. While large consortiums of clinicians and researchers, like TRACK-TBI[52] (elaborated below) and ENIGMA[54], can collaborate on brain research projects, independent clinicians and those not affiliated with a consortium are left to their own protocols. That said, the imaging protocols for 3T MRI for head trauma used by those consortiums are available online from both the TRACK-TBI and ENIGMA websites.

Regarding DTI, the peer-reviewed literature has consistently documented its utility in brain injury/concussion and other neurologic conditions in papers such as two in which Dr. Wintermark was a co-author[51,85]. In “White Matter Asymmetry: A Reflection of Pathology” in Traumatic Brain Injury”[30] the authors reported that the symmetry levels among various studied white matter tracts were lower in the mTBI cohort, a finding that can be interpreted as consistent with trauma. Dr. Shenton herself was a co-author of a paper that reported a study, funded by the Veterans Administration and the NIH, which relied upon DTI to assess the microstructure of limbic and paralimbic structures in the context of PTSD severity[83]; again, not as a pathognomonic biomarker but as part of the pathological profile. The assessment of the white matter microstructure can correlate with chronic post-concussive symptom severity[51] and reveals evidence consistent with persistent neurological disruption[82,85,86].

Another example of the bias in the paper by Shenton *et al*[7] is the authors’ failure to include in their review a paper entitled “White matter alterations in youth with acute mild traumatic brain injury”[87]. This was a prospective observational case-control study of previously healthy children ages 11–16, who presented to the emergency department within 6 h of an mTBI between December 2010 and August 2012. The study concluded that “white matter alterations” were identified in the subjects based upon MRI with DTI performed an average of 2 d following injury. The study also concluded that there was a poor correlation between symptoms and diffusion changes. This was a TBI group reported to be healthy and without co-morbidities that could cause white matter alterations prior to injury. The DTI confirmation of damaged axons in a pediatric population lacking in co-morbidities and white matter changes seen in an aging population supports the notion that similar traumatic damage can be caused in an adult population.

The momentum supporting the continued use of DTI as advocated in this paper has not slowed. Last year, the TRACK-TBI study group published recent findings[88]. This appropriately controlled large multicenter cohort study conducted at 11 trauma centers and with a total of 391 mTBI patients (17–60-years-old) at 2-wk to 6-mo post-injury confirmed DTI to be a reliable imaging tool detecting dynamic white matter microinfrastructure following mTBI. In addition, in 2022, Medeiros *et al*[89] published a systematic review related to the construction of a neuroimaging-based profile including DTI detection of white matter organization of the neural correlates of neuropsychiatric complications following TBI (focusing on depression in their study). Their findings again support the practical value of a pathological profile and the absence of a single pathognomonic imaging biomarker for brain injury outcomes. Finally, just this year (2023), Graham *et al*[90] published their findings of a distinct neuroimaging (including DTI) pattern of post-TBI neurodegeneration involving white matter atrophy, with higher shear forces at time of injury correlating to more progressive atrophy many years later.

Of note, while DTI analysis of the brain is superfluous in TBI cases that show more classic evidence of traumatic axonal injury including microhemorrhages or bright T2 foci at or near the gray-white junction [91,92] where aging changes rarely occur[93], DTI abnormalities showing truncated tracts that end at abnormal foci on routine MRI images indicate a strong correlation between these MRI methods. However, DTI abnormalities such as truncated tracts, asymmetrical numbers or volumes of tracts provide evidence of white matter damage even in the absence of abnormalities on standard MRI images. It is true that DTI abnormalities, bright T2 spots, and microhemorrhages may sometimes occur in brains of patients in the absence of trauma. As with all imaging findings, however, a radiologist must consider artifacts, congenital anomalies, infectious diseases, and various other alternative diagnoses before arriving at a diagnosis of TBI. Clinical signs of TBI and positive imaging findings, whether from routine imaging or non-routine methods that indicate brain damage consistent with trauma, should not be disconnected, ignored, or devalued merely because they are presented in a courtroom.

Summary

The undisputed sensitivity of DTI to provide evidence of white matter abnormalities in the brain during the chronic stage of post-concussion symptoms has been the focus of legal conflict for more than 10 years. This article has summarized the technical properties that make DTI one tool available to clinicians seeking to corroborate a brain injury diagnosis and direct rehabilitation. We have discussed how, although papers have criticized the forgoing use of DTI technology, those papers are rife with shortcomings in their publication processes, weakening their integrity among the peer-reviewed literature. As the three fields of science, medicine and law come together to find accurate and valid resolutions to issues that arise in legal proceedings and to guide patient treatment and management, it

is critical to amalgamate the knowledge among the three on how scientific proof differs from proof in a courtroom; indeed, as presented herein for DTI in particular an overwhelming majority of judicial decisions have validated admitting scientific and medical evidence for the purposes advocated.

CONCLUSION

If the concern of Shenton *et al*[7] is merely that the adversarial process that includes trial lawyers, judges, and jurors may get something wrong, then the argument should fail. Their paper accomplished little other than to stir up trouble, obfuscating the topical issue for non-scientists, particularly judges and juries. While science may evolve to provide the means for corroborating trauma-induced white matter damage documented on quantitative DTI, in the meantime, it is likely that judges will continue to execute their gatekeeping responsibilities to distinguish between scientific methods that have been embraced as reliable and conflicts that revolve around the application of those reliable methods. In the interval, hopefully neuroscientists can accept that our federal and state constitutions ensure that resolving claims involving the weight of evidence remains in the hands of the judge and jury.

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FOOTNOTES

Author contributions: van Velkinburgh JC and Casper SM conceptualized the review; van Velkinburgh JC performed the data collection, formal analysis and interpretation in science/medicine communication and publication topical matters; Herbst MD and Casper SM performed the data collection, formal analysis and interpretation in neuroimaging topical matters; Herbst MD generated the figure; Casper SM performed the data collection, formal analysis and interpretation in legal topical matters, drafted the first version of the manuscript, and generated the Table; All authors reviewed and edited each version of the manuscript for important intellectual content and provided approval of the final version.

Conflict-of-interest statement: Dr. van Velkinburgh has been engaged as an expert witness in litigated matters concerning authorship and publication of papers in scientific and science related journals including testimony concerning her extended research on Wintermark M, Sanelli PC, Anzai Y, Tsiouris AJ, Whitlow CT; American College of Radiology Head Injury Institute. Imaging evidence and recommendations for traumatic brain injury: advanced neuro- and neurovascular imaging techniques. *AJNR Am J Neuroradiol.* 2015 Feb;36(2):E1-E11. Dr. Herbst has served as an expert witness in litigated matters interpreting diffusion tensor imaging of the brain in both clinical and forensic settings. Mr. Casper is a trial attorney who represents personal injury plaintiffs alleging various classifications of traumatic brain injury. Some of his clients have undergone advanced neuroimaging ordered by clinicians.

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