

REVIEW

# Optimal Diagnostic Strategies for Concussion-Related Vision Disorders: A Review

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**Abstract:** Concussions are a mild form of traumatic brain injury (TBI) that is typically self-limited and transient with a high prevalence within our communities. Due to the vast visual network interconnectivity, visual symptoms secondary to a concussion occur about 90% of the time. A gold standard to confirm concussion acutely has not been well established. Visual function testing based on symptoms remains the standard of care in off-site evaluation for diagnosis of oculomotor dysfunction. This review covers the current diagnostic strategies for vision based disorders post-concussion for sideline testing, off-site testing, and research driven testing.

Keywords: visual disorders, concussion, oculomotor dysfunction

# Introduction

As a subset of mild traumatic brain injuries (mTBIs), concussions are defined as a self-limited and transient brain trauma. In the United States, mTBIs account for at least 75% of TBI related hospitalizations. Causes of concussions are varied including head injury resulting from motor vehicle accidents, assault, or injury from recreational sports. Amongst combat military members, the prevalence of mTBI ranges from 15.2% to 22.8%. Incidence estimates of sports-related concussions in the United States range from 1.6 to 3.8 million annually. However, the exact incidence of concussions is likely severely underestimated as those in the outpatient settings are not captured and athletes may underreport the presence of concussive symptoms. Reporting may also be affected by the age of the patient and the varying motivations accompanying return to full activity. This underestimation of concussions has drawn scrutiny in recent years. The Centers for Disease Control (CDC) is currently refining plans for a National Concussions Surveillance System (NCSS). Given the extensive research and public interest in this topic, there is a significant enthusiasm to develop the best diagnostic strategy to identify and categorize the presenting symptoms of a concussion.

# Pathogenesis and Symptoms

Concussions are caused by axonal injury via neuronal disruption due to rapid acceleration, deceleration, or rotation of the head.<sup>6</sup> The sudden neuronal disruption results in an increased release of stored neurotransmitters thus causing vast activation of postsynaptic membranes. The cascade of events following the indiscriminate release of neurotransmitters causes a greater demand for energy resulting in an energy crisis, thus disrupting cerebral glucose metabolism. Acute symptoms can last for 7–10 days and are typically transient with recovery within a few weeks post-injury, although in a subset of patients persistent symptoms can occur for months or years.<sup>7</sup> Post-concussion symptoms most frequently include headaches, migraine, slow processing and reaction times, and can lead to long term neurodegenerative changes.<sup>8</sup>

Unsurprisingly, visual manifestations with concussions tend to occur frequently given the extensive integration of the visual system within the cortex. Common visual symptoms associated with concussions include blurry vision, difficulty focusing, reading, or tracking, double vision, and photophobia. Some of these symptoms occur due to abnormalities in

eye movements and focus (the oculomotor system) which includes accommodation, vergences, smooth pursuits and saccades, and is referred to as an oculomotor dysfunction. Oculomotor dysfunction is not equivalent to an oculomotor (third nerve) palsy. Up to 90% of adults have been shown to have oculomotor dysfunctions post-TBI. Military personnel with mTBIs were found to have significant early visual dysfunction with impairments in binocularity, eye fatigue, and photophobia, which can persist as long as 2 years post-injury. In adolescents (11–17 years old) with concussion, including those with sports related concussions, oculomotor dysfunction was reported in 60% to as high as 60-88% of patients as early as 4–12 weeks following injury. Immediate oculomotor dysfunction has also been noted in collegiate athletes who suffer concussions, and can persist beyond one month. Therefore, there is a need for objective vision based diagnostic tools for immediate concussion assessment to be used in various settings for healthcare providers. In this review, we focus on the assessment of visual function within 12 weeks of a concussive injury.

# **Visual Function Deficits**

The effect of a concussion on the visual system is multifaceted and variable. Visual symptoms can occur due to direct damage in the visual system or as a secondary effect from abnormalities in executive function, attention, and memory. The oculomotor pathways involved in smooth pursuits, saccades, and fusional vergences are especially vulnerable to concussive trauma. A complex interplay between the oculomotor pathways, executive functions (such as attention, memory, inhibition, and problem-solving) and the vestibular system is required for optimal visual functioning. Given their interconnection, deficits in any one particular visual task may not reliably identify which of these functions is the primary cause of the poor performance.

Visually tracking objects at near requires accommodation, smooth pursuit, saccades and vergence movements of the eyes. <sup>21</sup> Master et al (2016) reported accommodative insufficiency or accommodative infacility in 51% of adolescents in various stages of recovery from concussion. <sup>14</sup> Scheiman et al reported that 57% of adolescents have accommodative dysfunction within 4–12 weeks post-concussion, with the majority of them having accommodative insufficiency. <sup>15</sup> Reduced accommodation has also been reported in up to 67% of adult patients with mTBI. <sup>22</sup> Similar findings of significantly reduced monocular accommodation have been seen in adult patients with blast-induced concussions. <sup>23</sup> Smooth pursuit errors are reported as eye position errors during testing. <sup>24</sup> Saccade abnormalities in concussion include increased latency, diminished accuracy, and abnormalities of amplitude. <sup>25</sup> Vergence dysfunction categorized as convergence insufficiency was diagnosed in 49% of adolescent post-concussion patients <sup>14</sup> and any vergence disorder was found in up to 60% of adolescent patients in another study. <sup>15</sup> Raghuram et al reported that the concurrence of accommodative and vergence disorders in adolescents was as common as disorders of one system in isolation, 41% of patients with dysfunction of accommodation alone and 43% combined with disorder of vergence. <sup>26</sup> Convergence disorders have been reported in 20.4% of adult post-concussion patients. <sup>27</sup> Other abnormalities reported include reduced amplitude of convergence response when beginning a vergence movement, <sup>28</sup> and reduced accommodative peak velocity. <sup>22</sup>

Precise errors in smooth pursuit may be difficult to detect without specialized recording equipment.<sup>24</sup> Simple direct observation of a patient performing a saccadic movement as they alternate gaze from one horizontal or vertical target to another may miss abnormalities.<sup>25</sup> Recordings of saccades on specialized video-oculography equipment can reveal problems with executive function, attention and memory.<sup>25,29–31</sup> For example, antisaccades are elicited by asking a participant to look away from a newly presented target.<sup>25</sup> They require inhibition of the reflexive saccade movement to the target and may be sensitive indicators of frontal lobe function.<sup>25</sup> The gap saccade test requires subjects to look at a central target and then after a set temporal gap, switch to a peripheral target.<sup>31</sup> Patients with a concussion may have difficulty switching to the peripheral target with shorter interval of the gap compared to a longer interval.<sup>31</sup> This is thought to occur due to difficulty in disengaging attention.<sup>31</sup> Memory deficits may be revealed by asking patients to perform memory-guided saccades.<sup>24,25</sup>

Best corrected visual acuity is generally not affected by a concussion. <sup>10</sup> The most common visual symptom following concussion is photophobia. <sup>9</sup> The pathway implicated in photophobia through intrinsically photosensitive retinal ganglion cells and possible dysregulation in the thalamus is not easily measurable. <sup>32</sup> Glare visual acuity is not considered a substitute for photophobia measurement. Pupil abnormalities, such as slowing or quickening of pupil constriction

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and/or dilation has been found in patients with mTBI.<sup>33–35</sup> Decompensation of pre-existing strabismus and new onset microstrabismus have also been reported in up to 30% of patients with a concussion.<sup>36</sup>

Due to the accessibility of the oculomotor system, investigators have tried to identify abnormalities in vergences, accommodation, smooth pursuits and saccades to diagnose a concussion, make predictions about persistent post-concussive syndrome occurrence, and monitor progress of recovery. 14,37

### **Immediate Concussion Assessment**

# Sideline Assessment

Various "sideline" assessments have been developed to efficiently assess the affected individual given the immediate impact and symptomology of a concussion. Some of these tests include a vision assessment, such as the Sport Concussion Assessment Tool (SCAT) 6, which includes a "Coordination & Ocular/Motor Screen" with questions about photophobia, diplopia, and extra-ocular movements.<sup>38</sup> Other components of the SCAT6 include the Glasgow Coma Scale, Standard Assessment of Cognition (SAC), Post Concussion Symptom Scale (PCSS), Balance Error Scoring System (BESS), and the Tandem Gait test. A pediatric version of the SCAT, Child SCAT, has shown good test–retest reliability of behavioral symptoms in 9–12 year olds.<sup>39</sup> The most reliable portion of the SCAT seems to be the PCSS.<sup>39</sup> The SCAT6 can be administered on the sidelines and also used in post-concussion analysis in an office-based setting. Side-line versions are abbreviated for ease of use and available in an application format. SCAT6 is most reliable within 72 hours of injury.<sup>39</sup> Baseline testing may improve the validity of the SCAT6 to diagnose concussion, but test–retest reliability for all components of the SCAT6 remains limited with a Pearson's r = 0.48.<sup>39</sup>

One of the most widely used immediate concussion vision-based assessment tools is the King-Devick (KD) test. As a timed, rapid automized naming (RAN) task, the KD test requires a patient to rapidly read different patterns of numbers aloud from test cards or a tech-based application over the course of two minutes. 40 The KD test does not specifically test for convergence or accommodation, but involves various parts of the efferent visual pathways that are involved in saccades, convergence, and accommodation movements, and integration with the higher cortical attention and language function. Coordinated integration from the brainstem, cerebellum, and cortex (frontal eye fields, dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex, middle temporal area, and striate cortex) is required to successfully pass this test. The KD test has been validated and tested for reliability in various environments from military personnel<sup>41</sup> to concussed athletes. 40 such as professional ice hockey players, mixed martial arts athletes, high school level football and youth athletes. Galetta et al (2015) performed a meta-analysis on concussed athletes and showed high sensitivity (86%) and specificity (90%) in identifying those concussed from non-concussed, and worsening time to completion (increased time of 4.8s) when compared to an individual pre-season baseline. 40 Given the validity and reliability of the test as well as the ease of administration on the sideline, KD test should be considered gold standard in vision-based immediate concussion assessment. Yet, proper use of the KD test requires a pre-concussion baseline for each athlete and is dependent on the age of the athlete. Baseline testing may also need to be repeated throughout the sports season for this test to remain valid.

Another sideline vision-based assessment to consider is the Mobile Universal Lexicon Evaluation System (MULES). Similar to the KD test, MULES is a random automized naming task and relies on similar visual network structures, such as the DLPFC, to integrate saccadic movement. However, instead of recognition of single digit numbers, MULES shows 54 photographs of objects, fruits, and animals to test saccadic movement with color perception and contextual object identification. Due to a greater processing requirement, this test may rely on a wider cortical network and increased activation of other cortical areas, such as the bilateral fusiform gyri. Similar to KD test results, those with sports related concussions had significant worsening of MULES scores when compared to individual preseason baseline testing, and were correlated with worsening symptom severity scale score of the SCAT5.

Each of these three sideline tests have improved reliability if baseline data are obtained. This makes these test vulnerable to developmental influences, learning curves, and volitional influences. Eye tracking algorithms are currently in development as discussed in Research Tools section below. A commercially available device, EYE-SYNC®, has been tested on the sidelines with good test–retest reliability without need for baseline data (ICC = 0.86). 45

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# Off-Site Testing

The 6th International Conference on Concussion Consensus statement recommends physicians utilize the Sport Concussion Office Assessment Tool (SCOAT6/Child SCOAT6) which is an age-adjusted tool that provides a standardized assessment of immediate and delayed word recall, gait assessment, vestibular-ocular motor screening (VOMS), neurologic examination, cervical spine evaluation and lability of blood pressure with postural changes. OMS assesses oculomotor function in combination with vestibular and neurocognitive function. The presence of vestibular ocular dysfunction on VOMS testing has a four times increased risk for long term persistenc of concussion symptoms. NOMS begins with a baseline assessment for the following symptoms: headache, dizziness, nausea and fogginess on a scale from 0–10. These same symptoms are then subjectively reassessed following each of seven vestibulo-oculomotor tasks: horizontal and vertical saccades (10 movements each, respectively), smooth pursuits, horizontal and vertical vestibular ocular reflex (10 rotations of the head, respectively), NPC, and vision motion sensitivity testing (focusing on thumb held arms-width distance from body and rotating body horizontal through 80 degree are 5 times while focusing on the thumb). VOMS scores have been correlated to the PCSS, and a score >2 increased the probability of identifying concussed patients. Another tool for neuropsychological testing is the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) which is a computerized test assessing verbal memory, visual memory, and visual motor processing speeds.

There is no ophthalmic test that is diagnostic for all visual complaints. Screening protocols have included non-ophthalmic personnel assessing NPC and accommodative amplitudes, <sup>15</sup> but NPC abnormality alone is not diagnostic of convergence insufficiency as proven by a full oculomotor assessment in the article by Raghuram et al. <sup>26</sup> Surveys to detect patients with oculomotor dysfunction even in combination with NPC measurements cannot replace a complete oculomotor evaluation as demonstrated by Scheiman et al who reported sensitivity of NPC as only 63% in identifying any oculomotor abnormality in adolescent patients. <sup>15</sup> Additionally, the Convergence Insufficiency Symptoms Survey (CISS) although validated for non-concussion associated convergence insufficiency has not shown tremendous reliability in concussion associated convergence insufficiency due to high false positives. <sup>15</sup>, <sup>18</sup>, <sup>50</sup> Scheiman et al showed the combination of distant NPC, accommodative amplitude reduction and CISS score >16 identified only 76% of the adolescents found to have oculomotor dysfunction due to a concussion. <sup>15</sup> The specificity of all three tests was only 61%, highlighting the need for full ocular assessment for all adolescents. <sup>15</sup>

A full ocular assessment of concussed individuals could include evaluation of subtle pupillary abnormalities of slowed constriction and dilation, in addition to minimal anisocoria that may be detected using infrared pupillometry. A complete assessment of accommodation and vergence should include positive vergence (convergence) amplitudes at near and distance targets, NPC evaluation, evaluation of convergence facility at near, accommodative amplitude and facility, motility evaluation in all gazes for microstrabismus, and stereoacuity assessment. 51

Accommodative amplitude has been assessed monocularly in distance optical correction using the push up method with an accommodative target brought towards the patient.<sup>28,51</sup> The distance with sustained blur is recorded in centimeters.<sup>26,52</sup> Accommodative facility has been measured monocularly by presenting an accommodative target at 40 cm and recording the speed at which clarity can be achieved when alternating between a +2D and -2D lens in cycles per minute.<sup>52</sup> Accommodative disorders consist of both accommodative deficiency and poor accommodative facility.<sup>14</sup>

Vergence disorders can be assessed with near point of convergence (NPC) tests, near convergence amplitude break and make points, and vergence facility testing at near.<sup>52</sup> Raghuram et al defined disorders of vergence to include convergence insufficiency, convergence deficit, convergence excess, vergence amplitude deficit, or vergence facility deficit.<sup>26</sup> Although small variations in technique exist, most studies measured NPC as the position at which an accommodative target doubled as brought towards the patient from a distance of 40–50 cm.<sup>14,15,26</sup> Vergence amplitudes were reported as the break point of fusion in prism diopters. Vergence facility was measured as the speed in cycles per minute at which clarity of image could be achieved binocularly when alternating a 3 PD Base in prism with a 12 PD Base out prism at near fixation.<sup>52</sup> Video-oculography may assist with detecting abnormalities with saccades and smooth pursuits which may not be detectable on routine ophthalmic exam.<sup>12</sup> Eye tracking algorithms may detect attention and memory deficits by their impact on normal saccade and smooth pursuit motions.<sup>53</sup> There is a correlation of predictive visual tracking abnormalities with symptomatology.<sup>21</sup>

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In repetitive mTBI, testing of peripheral visual fields may be informative as well.<sup>54</sup> Optical coherence tomography (OCT) has demonstrated neural degeneration associated with repetitive mTBI by thinning of the retinal nerve fiber layer (RNFL) in the chronic setting.<sup>55,56</sup>

# Research Tools for Vision Based Assessment

Other acute concussion assessments for visual symptoms have been developed and are used within the research setting to assess saccades, smooth pursuits, and fixations.<sup>57</sup>

Within screening metrics, modifications to standardized tests have sought to give more objective findings to the oculomotor assessment by quantifying cycles of tasks completed in a set interval. For example, Iring-Sanchez et al modified the VOMS to count the cycles of horizontal and vertical saccades, vergence jumps, horizontal and vertical vestibular ocular reflex movements in 60 second intervals, respectively.<sup>13</sup> By adding NPC and an assessment of accommodative amplitude, they defined a new screening tool, oculoMotor and Vestibular Endurance Screening (MoVES).<sup>13</sup> After establishing normative data, their study showed return to baseline number of eye movements occurred in 14–21 days post-concussion.<sup>13</sup> The integration of this quantitative tool into concussion assessments may require baseline data and is under investigation. Arbogast et al similarly modified VOMS to include a tandem-gait assessment called as visio-vestibular exam.<sup>16</sup> The study showed a peak in visio-vestibular dysfunction at one week following concussive injury with differentiation in symptoms by sex, with females having worse scores and taking longer to recover.<sup>16</sup> Haensel et al quantify accommodation by moving a projected screen closer and further to patients as they watched content.<sup>58</sup> Accommodation was measured with an accommodative meter device.<sup>58</sup> Concussed individuals had lower monocular accommodative scores, but not in binocular settings, indicating the accommodative deficiency could be overcome by fusional disparity cues.<sup>58</sup> The incorporation of these newer examination methods into clinical care will require more investigation.

Video-oculography techniques and devices can be used to detect subtle deficits in saccades and smooth pursuits. <sup>59</sup> Hunfalvay et al demonstrated significant increase in fixation time and deficits in smooth pursuit in patients within 7 days of concussive injury using an eye tracking device and the commercialized RightEye® tests. <sup>57</sup> The concussion group in particular demonstrated poor performance with circular, horizontal, and vertical smooth pursuits. Maruta et al also showed decreased performance in visual tracking of circular smooth pursuit. <sup>60</sup> Heitger et al demonstrated deficits in saccades, but not smooth pursuit when using an IRIS infrared limbus tracker, contrary to Hunfalvay et al's findings. <sup>61</sup> Notably, Samadani et al assessed patients with an eye tracker and binocular eye-tracking algorithm in those with head trauma, including concussions. The study found a negative correlation between horizontal conjugacy and total SAC score and a positive correlation between horizontal conjugacy with SCAT 3 symptom severity score. <sup>62</sup> A current FDA approved eye tracking device specific for vision based concussion assessment, EyeBOX®, was demonstrated to have a sensitivity of 80.4% and specificity of 66.1% in determining those who experienced a concussion within the past two years when compared against SCAT3 symptom severity score and SAC. <sup>63</sup> Given the utility and ease in which an eye tracking device and software can be used to detect minutia oculomotor movements, there is currently ongoing research in the utilization of this technology in concert with standardized assessments such as SCAT. One limitation of these technologies is their exclusion of patients with prior strabismus or other ocular pathologies.

Electroretinogram abnormalities have been seen in animal models of mTBI and in human studies with reduced photopic negative response amplitude and alterations in the b-wave amplitudes (principally consisting of bipolar cells) correlated to the presence of photophobia. In one study, patients with a distant history of a concussion had an increase in retinal venule caliber after adjusting for age and other comorbidities than in controls, but validation studies are needed to confirm this result. Further research is needed to understand changes in ERG and retinal vessel findings in concussions.

# Concussion Driven Imaging

Widely known as a process that is more functional than structural, concussions do not typically warrant neuroimaging in healthy children and adults under the age of 65 years per guidelines.<sup>67</sup> A head computed tomography (CT) is only warranted if the patient suffers severe concussion symptoms, such as Glasgow Coma Score less than or equal to 14, loss

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of consciousness greater than 30 seconds to 1 minute, signs of altered mental status, severe headache, seizure activity, focal neurologic deficit, or worsening symptoms.<sup>68</sup> CT imaging is the first line imaging for head injury because of the lower cost, utility, and widespread availability, however, it has variable sensitivity when detecting uncomplicated mTBIs from as low as 3% to as high as 38%.<sup>69–73</sup> Compared to CT scans, magnetic resonance imaging (MRI) has a higher sensitivity in detecting diffuse axonal shear injury (DAI) and small parenchymal contusions.<sup>74,75</sup> Diffusion tensor imaging (DTI) and susceptibility-weighted imaging (SWI) are current MRI techniques that can be utilized to examine microstructural alterations that may be present in an immediate time period post-concussion.

The use of DTI in TBIs is common and has been described in over 100 papers<sup>76</sup> since first described as a tool to detect reduction in anisotropy in mTBI patients within 24 hours of injury by Arfanakis et al in 2002.<sup>77</sup> DTI relies on diffusion properties of water, which examines the magnitude (mean diffusivity (MD)) and directionality of water diffusion (fractional anisotropy (FA)) and can provide information of tissue microstructure.<sup>78</sup> Alterations in these metrics post-concussion have been well-recorded and have demonstrated vast microstructural abnormalities.<sup>75,79–83</sup> Directionality of these metrics vary as some have shown increased in FA and decreased diffusivity<sup>79–82</sup> while others show opposite directionality<sup>83</sup> of these metrics in an acute setting (from 24 hours to 21 days). Despite these promising results, the variability in these metrics make it difficult to use DTI parameters as a prognostic tool with little correlation to the visual track.

SWI takes advantage of different magnetic susceptibilities to enhance contrast between different types of tissue.<sup>84</sup> This makes it possible to identify microhemorrhages that would not be captured in a CT or traditional MRI. SWI has demonstrated increased microbleeds in those with mTBI when compared to controls.<sup>85–88</sup> These results have also been shown to correlate with prognostic outcome.<sup>85</sup> However, similar to DTI, instrument availability, cost, and time all influence the utility of this imaging modality in an acute environment.

Functional magnetic resonance imaging (fMRI) allows the detection of neuronal activation and compensatory changes through mapping of vascular perfusion, based on the blood oxygen level-dependent effect (BOLD). <sup>68,74</sup> When compared to non-concussed individuals, concussed individuals have shown connectivity alterations between various brain regions, which is well described in the literature both with task based fMRIs and resting state fMRIs. <sup>68,74</sup> Most of these studies have found abnormal functionality in the frontal, superior, and parietal lobes focusing on working memory and attentional functioning, occurring even within a month of injury. <sup>68,89–92</sup> Few studies have correlated fMRI findings with the visual network. Johnson et al demonstrated that despite normalization of oculomotor function at the 30 day mark post-injury, fMRI still showed abnormal activation within the visual cortex in the subacute phase of the concussion. <sup>93</sup> Sheth et al found increased connectivity to the left and right superior occipital regions in veterans with a history of mTBI compared non-concussed veterans. <sup>94</sup> However, it remains to be seen if fMRIs can be used diagnostically for vision based concussion symptoms in an acute setting.

#### Conclusion

Given the vast connectivity between the visual network and other cortical structures, visual symptoms are common acutely post-concussion. However, there is no gold standard acute diagnostic test which can isolate the visual system alone on the sidelines, although eye tracking devices are being commercially developed. SCAT6, the presumed gold standard for sideline diagnosis of a concussion, includes a few questions about visual symptoms such as diplopia, photophobia, and an oculomotor screening. These questions are not specific enough in identifying complex visual deficits such as issues with saccades, smooth pursuits, and fusional vergences. Saccades/antisaccades are tested through RAN testing with KD and MULES test. The KD test is the closest to a gold standard sideline test with strong validity and reliability in concussed individuals in an acute setting. These tests combine oculomotor functioning with executive function and memory testing, but need comparison baseline testing, which is not always feasible. There remains a need for a quicker and more comprehensive diagnostic test by non-vision trained professionals.

Off-site testing is most useful in providing a well-rounded picture. This may require a multidisciplinary approach with neurologists or concussion experts evaluating executive function and memory while ophthalmologists/optometrists diagnose visual deficits with a more comprehensive visual exam. This exam may include VOMS or a modified VOMS test to evaluate saccades, smooth pursuit, and the vestibular ocular reflex, but should also include measuring

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pupil size, convergence and accommodation testing, ocular motility, alignment, saccades, smooth pursuits, visual fields, and stereoacuity assessment. Further testing can also be done using video-oculography to identify subtle abnormalities in smooth pursuits and saccades and test for vestibulocular reflex and visual motion sensitivity. These tools are promising for both their prognostic and monitoring capabilities. There is also promise in imaging, however, there is currently little correlation in an acute phase concussion setting and visual tasking.

The standardization of testing will occur as research refines the natural history of mTBI, including identification of prognostic indicators of persistent symptoms in mTBI. As of now, there is not a single diagnostic test that is comprehensive for all visual deficits post-concussions. Instead, patient symptoms should guide specific testing of the components of the visual system.

### **Disclosure**

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