

# Promise of Salivary MicroRNA for Assessing Concussion

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**Despite the marked increase** in clinical and basic scientific investigation into concussive brain injury in recent years,<sup>1</sup> the diagnosis and assessment of a concussion remains



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largely based on the reporting of symptoms.<sup>2</sup> The symptoms of a concussion are non-specific and can be caused by many etiologies. The biological basis of concussion symptoms has not been well-characterized and concussion symptoms do not always correlate with more objective measures of injury, such as neurocognitive testing. It therefore remains unclear whether persistent symptoms represent the continuation of concussion pathophysiology, are due to other contributing etiologies, or are the result of concussion management strategies that involve restricting activity.<sup>3</sup> However, most children demonstrate persistent symptoms of a concussion 1 month after their injury.<sup>4,5</sup> Given this large disease burden, objective measures of injury would be highly useful for making the diagnosis of a concussion, monitoring recovery, and identifying those at risk for prolonged symptoms after an injury.

In this issue of *JAMA Pediatrics*, Johnson et al<sup>6</sup> report the results of a prospective cohort study that was designed to evaluate the efficacy of salivary microRNA in identifying children who were at risk for experiencing prolonged symptoms after a concussion. In a sample of 52 patients between the ages of 7 and 21 years who experienced a concussion within 2 weeks before enrolling in the study, the authors identify 5 potential candidate microRNAs that demonstrated utility in identifying those at risk of experiencing persistent symptoms 4 weeks after injury, defined as a Standardized Concussion Assessment Tool 3 score of 5 or more on a child report and/or parent report. Furthermore, the study showed that the test characteristics of a model using these 5 microRNA candidates were superior to using the initial symptom inventory, both child-reported and parent-reported, of the Standardized Concussion Assessment Tool 3.

The use of salivary microRNA in this study is both novel and clinically relevant. To our knowledge, no single biomarker or biomarker panel has demonstrated adequate test characteristics to be widely used as an objective measure for diagnosing or monitoring recovery from a concussion or for predicting those who are at highest risk for a prolonged recovery. If validated in larger, multisite clinical trials, using this salivary microRNA panel to diagnose and manage concussions could be a major advancement to the field. Moreover, the relative ease and speed of obtaining saliva makes this mode of testing especially attractive for pediatric patients. Salivary sampling could be widely used in diverse care settings. Salivary

concentrations of microRNA might be used to identify those who are at highest risk of experiencing prolonged symptoms, determine which patients might be most amenable to available treatments, and further delineate the pathophysiology of concussions.

As the authors note, further investigation will be required before determining the clinical use of salivary microRNA in concussion management.<sup>6</sup> The relatively small sample size in this study requires larger-scale studies to determine the reliability of these associations in diverse care settings, controlling for potential confounding factors, such as sex, mechanisms of injury, predisposing conditions, and treatments. In this study, there were clear differences in several variables (besides microRNA concentrations) between those who experienced prolonged symptoms and those who recovered more quickly. Specifically, a higher proportion of those who experienced prolonged symptoms were girls and used nonsteroidal antiinflammatory medications. A smaller proportion of those who experienced prolonged symptoms sustained their injuries during sports participation and experienced a loss of consciousness with their injuries. Previous literature suggests that girls are more likely to have longer symptoms after sustaining a concussion.<sup>7</sup> The speeds and forces that are involved in collisions that result in sport-related concussions may differ from those that are involved in collisions outside of sports, such as motor vehicle collisions.<sup>5</sup> Although loss of consciousness is sometimes described as a predictor of intracranial hemorrhage, a brief loss of consciousness is not consistently a predictor of a worse outcome after a concussion.<sup>8-11</sup> The use of nonsteroidal antiinflammatory medications may be more common among those with a more severe injury. It is possible that each of these factors is associated not only with symptom duration, but also with microRNA concentrations, thereby representing potential confounding variables. Although the authors are correct in stating that there is no statistical difference in these characteristics between those who recovered quickly and those who experienced prolonged symptoms, given the large effect size associated with each variable, it is possible that the lack of statistical significance was due to the small sample population. It is also possible that there were differences in baseline levels of microRNAs between those who experienced prolonged symptoms than those who recovered more quickly, or that these microRNAs represent susceptibility rather than injury markers.

Still, this work represents an advance in the science of sport-related concussions. The findings are promising, representing potential biomarkers for the diagnosis, recovery, and prognostic assessment of a sport-related concussion. Salivary microRNAs could also offer insights into the under-

lying biological mechanisms of injuries, potentially identifying specific targets to modify disease. Future and ongoing large prospective cohort studies of those who are at risk for concussions, particularly athletes, should consider includ-

ing these microRNA candidates as well as other potential biomarkers, as an objective measure of concussion would be highly useful for those who are caring for patients who have experienced concussions.

#### ARTICLE INFORMATION

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