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Could an Eye-Tracking Test Aid Clinicians in Making an Autism Diagnosis?:

New Findings and a Look to the Future

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Autism spectrum disorder (hereafter, "autism") affects the ability to socially interact and communicate with others and is diagnosed in 1 in 36 children in the United States. The early course and clinical presentation of autism are variable, and differential diagnosis of young children can be challenging even for autism specialists. For example, one study found that only 60% of autism diagnoses were made with certainty in a sample of 478 toddlers and preschoolers who had been referred to specialists for an autism evaluation.[1] In a 6-site study where diagnostic evaluations were conducted by experienced clinicians with 496 children aged 16 to 30 months referred to specialized centers, only 70.2% of diagnoses were made with a high level of certainty.[2] Thus, approximately 1 in 3 autism diagnostic evaluations of young children are associated with uncertainty. Children with higher cognitive and language abilities and milder autism-related behaviors are more likely to be missed and often receive their diagnoses later than those with greater language delays and more pronounced autism-related behaviors.[2] The high degree of diagnostic uncertainty for young autistic children contributes to delays in access to supports and services. Receiving an autism diagnosis is a first step to qualifying for early behavioral therapies that have been shown to improve outcomes, including language, cognitive, social, and adaptive skills.[3]

The lack of objective, quantitative biomarkers has been a hindrance in progress toward developing better diagnostic tools for autism. Among the most promising autism biomarkers is the use of eye tracking to monitor the child's attentional preferences for social vs nonsocial stimuli.[4,5] Autism is characterized by decreased spontaneous visual attention to social stimuli (social attention), a feature that is apparent early in life.[6] The Autism Biomarkers Consortium for Clinical Trials, a National Institutes of Health multisite study of 6- to 11-year-old autistic and neurotypical (ie, not displaying signs of autism) children, evaluated biomarker properties for a battery of eye-tracking tasks, including acquisition rates, construct validity, stability, and group discrimination. An eye-tracking task indexing social attention showed the strongest performance as a potential autism biomarker and

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consequently was accepted to the Food and Drug Administration's Biomarker Qualification Program.[4] Notably, research has found minimal age and cultural effects on assessments of social attention via eye tracking in autistic individuals of a wide age range(1–17years); however, girls tend to show higher levels of social attention than boys, regardless of diagnostic status.[7]

In this issue of *JAMA*, Jones and colleagues[8] report the results of a multisite, prospective, double-blind study that evaluated an eye-tracking test measuring social attention compared with expert clinical diagnosis for identifying autism in 16-to30-month-old children who were refer red to specialists for an autism evaluation. This study demonstrated that the eye-tracking test was able to accurately classify autism vs non-autism in children with 71.0% sensitivity and 80.7% specificity with a positive predictive value of 76.2. When cases in which the diagnostician was uncertain about the clinical diagnosis were removed from the analysis, sensitivity increased to 78.0% and specificity increased to 85.4% with a positive predictive value of 81.2. Results of the eye-tracking test were also correlated with clinical assessments of the child's level of autism-related behaviors and verbal and cognitive abilities.

The study by Jonesetal[8] represents a significant step forward toward developing more objective tools for early diagnosis of autism. The intended use of the eye-tracking test is to aid clinicians in making an autism diagnosis in young children who have been referred to a specialty clinic for evaluation. By integrating multiple sources of information—including the eye-tracking test, parent report, and clinical observations—the accuracy, certainty, and efficiency of autism diagnostic assessment could potentially be improved, resulting in fewer missed cases and allowing more children to receive empirically validated early therapies from which they couldbenefit.[3] Frazierandcolleagues[9] argued that the use of scalable autism diagnostic biomarkers, such as an eye-tracking test, could potentially improve lifetime outcomes of autistic individuals. This would result from earlier diagnoses and access to behavioral therapy and other services and supports that could improve long-term outcomes and quality of life.

A possible future application of an eye-tracking test is as an autism screening tool, which was not evaluated in the study by Jones et al. Validation of its use for autism screening will require additional studies conducted in primary care or other community settings with nonspecialist pediatricians. The American Academy of Pediatrics recommends universal autism screening at 18 and 24 months by primary care physicians using a parent questionnaire, most often the Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F).[10,11] Although parent report is an essential part of autism screening and has been shown to reduce disparities in access to an autism evaluation, the M-CHAT-R/F has lower accuracy when used in primary care settings, particularly for children of racial and ethnic minority groups, girls, and those from families with lower educational levels.[12] These disparities in accurate screening are particularly noteworthy given documented delays in autism diagnosis for children of racial and ethnic minority groups and girls.[13,14] In a study of 25999 children with a well-child visit aged between 16 to 26 months in a large pediatric network that implemented universal autism screening, Guthrie and colleagues[12] found that the sensitivity of M-CHAT-R/F was 38.8% and its positive

predictive value was 14.6%. Thus, there is a clear need for objective, accurate, and scalable autism screening tools to complement parent report.

Another possible future application of the findings by Jones et al is the use of eye tracking to identify infants younger than 1 year who have a higher likelihood of a later autism diagnosis. Eye tracking is one of several infant autism biomarkers currently being studied, which include brain-based biomarkers measured via magnetic resonance imaging, electroencephalography, and near-infrared spectroscopy.[15] Eye tracking has the advantage of being relatively inexpensive and easy to administer. Research has demonstrated the ability to monitor gaze in young autistic children using only a smartphone or tablet.[5] Differences in social attention based on eye tracking have been found in infants later diagnosed with autism as young as 2 to 6 months of age.[6] Early behavioral signs of autism emerge between 6 and 12 months of age and include reduced attention to people, a lack of orienting when the infant's name is called, reduced communicative babbling and gestures, differences in affect and social engagement, and motordelays.[15] Future studies are needed to examine whether a combination of an eye-tracking test assessing social attention with other early behavioral signs increases accuracy of prediction of a later diagnosis of autism in infants.

Finally, quantitative, objective, and scalable biomarkers, such as the eye-tracking test, could be used as an endophenotype in genetic studies. Such measures could be incorporated into studies using quantitative trait locus analysis to understand genetic contributions to autism.[16] Quantitative, easy-to-administer biomarkers that are feasible in large-scale genetic studies will be useful for parsing the heterogeneity of autism and increasing the diversity and representation of participants in autism research studies.

While the study by Jones et al represents a milestone in the development of autism diagnostic biomarkers, there remains work to be done before an eye-tracking test is used in clinical practice. Demonstrating that an eye-tracking test improves diagnostic certainty would require following children whose diagnosis was uncertain longitudinally to determine whether the test improves prediction of a later definitive autism diagnosis. Future studies will need to assess how feasible, acceptable, reliable, and efficient the eye-tracking test is when used by clinicians as an aid in autism diagnosis in practice. Research will need to assess how information from the eye-tracking test should be weighted and integrated with other sources of information, such as parent report and clinical observation, to arrive at a diagnostic decision. For example, could the time spent on clinical observational assessment of the child be reduced in cases where the eye-tracking test indicated a very high likelihood of autism? If so, this could potentially help address the current long waitlists to see an autism specialist. It will be important to understand the influences of sex, other demographic factors, and co-occurring conditions, such as intellectual disability, on diagnostic accuracy to ensure that potential biases are mitigated. The risks and benefits of incorporating objective biomarkers into standard clinical care should be carefully evaluated based on input from clinicians, care-givers, autistic individuals, health care administrators, and other stakeholders to ensure that this new approach to improving autism diagnostic certainty leads to long-term benefit for autistic individuals and their families.

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