



Early Detection and Diagnosis of Autism Spectrum Disorder: Why Is It So Difficult?

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Autism spectrum disorder (ASD) affects approximately 2% of children in the United States (US). Therapeutic interventions are most effective if applied early, yet diagnosis often remains delayed, partly because the diagnosis is based on identifying abnormal behaviors that may not emerge until the disorder is well established. Universal screening has been recommended by the American Academy of Pediatrics at 18 and 24 months yet studies show low compliance by pediatricians and the US Preventive Services Task Force does not support universal screening. To better understand the limitations of universal screening this article looks at the performance of screening tests given the prevalence of ASD. Specifically, although the sensitivity and specificity of the Modified Checklist for Autism in Toddlers, Revised with Follow-up, the de facto screening tool, exceeds 90%, the relatively low prevalence of ASD in the general population (~2%) results in a positive predictive value of about 33%, resulting in only 1 of 3 children identified by the Modified Checklist for Autism in Toddlers, Revised with Follow-up actually having ASD. To mitigate this issue, the American Academy of Pediatrics has recently recommended the use of a Level 2 screener after failing a Level 1 screener, before referring children on for a full comprehensive evaluation for ASD. In this way, a series of screening tools are used to enrich the population of children referred for further evaluation so fewer without an ASD diagnosis are evaluated. We have developed a program to train pediatricians to utilize these instruments as well as learn to diagnose ASD so children can effectively be referred for appropriate services at the front lines. Given the current burden on the medical system with the diagnosis and evaluation of children with ASD, it is important to create efficient systems for screening children which can best identify those most likely to have ASD. Developing methods to identify those children most at risk for developing ASD, either through consideration of medical or family history or through the use of biomarkers, may be helpful in identifying the children that require increased surveillance and those that do not need screening.

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Introduction

Autism spectrum disorder (ASD) is perhaps one of the most important medical disorders of our era because of the number of people it affects. The prevalence of ASD has

increased significantly over the past 3 decades and now is estimated to affect 1 in 54 children, about 2%,¹ of children in the United States (US). Even more significant is the fact that ASD does not occur in isolation. Children with ASD require significant support from the educational, medical, and social systems that results in a significant economic burden² with the lifetime social costs to date in the US estimated to be more than \$7 trillion.³ In addition, the disability of a child creates a spillover effect, decreasing the quality of life for the entire family.⁴⁻⁶

The only proven therapy for core symptoms of ASD is behavioral therapy, particularly if it is started early in life. Although behavioral therapy is implemented using several

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specific techniques, one common theme for treatment of ASD is that the earlier an intervention is started, the better the long-term outcomes for the child.^{7,8} However, although we know that early intervention, especially if started before the second year of life, is most effective, the mean age of obtaining a diagnosis of ASD is 4 years 3 months and has not improved significantly over the 2 past decades despite efforts to educate the public and health professionals.¹ Although there are several barriers preventing the implemented of intensive behavioral therapy early in life, one of the primary limitations is the timely identification and diagnosis of children with ASD. This article will discuss some of the reason for our failures to achieve the goal of early identification as well as some of the potential solutions.

The Behavioral Diagnosis of Autism and Its Limitations

ASD was first defined in the third edition of the Diagnostic Statistical Manual of Mental Disorders (DSM) in 1980. Since that time it has undergone several revisions, being divided into 3 subcategories in the DSM-IV, only to be redefined as one disorder with a spectrum of severities in the DSM-5.⁹ However, the same specific core features have always defined ASD. These features include (1) a lack of social-communication abilities and (2) the presence of repetitive and/or restrictive interests and/or behaviors.¹⁰

Although the DSM-5 is the ultimate diagnostic reference for ASD, it outlines a criterion for diagnosis including target symptoms but does not provide a formal test for ASD. Thus, a wide variety of instruments have been developed to assist with the diagnosis of ASD, ranging from parental questionnaires, parental interviews, clinical judgments, and direct interactions. The 2 tests that are considered the gold-standard for diagnosing ASD include the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised. The ADOS is essentially a structured play examination in which the examiner systematically implements various social “presses” with the individual being evaluated in order to evoke social interactions. The Autism Diagnostic Interview-Revised is a structured interview with a caregiver in which developmental and behavioral symptoms are reviewed. These tests are believed to be of higher quality because they are structured and require specific training. However, even these gold-standard tests can be biased: unpredictable factors can affect examiner-child interactions and interviews rely on the memory and understanding of the caregiver. Thus it is not surprising that even these gold-standard diagnostic tools show a large variation in their diagnostic capabilities.¹¹

Additionally, there are intrinsic limitations in the clinical behavioral tools used for diagnosing ASD, most notably is the lower age limit at which ASD can be diagnosed. This is due to a combination of factors, including the fact that (1) many social-communication skills do not emerge until after the first year of life; therefore, there is a lower age limit at

which such skills are considered deficient; (2) some behaviors are normal in early infancy and only become abnormal if they persist into later infancy or beyond, and (3) abnormal behaviors such as repetitive behaviors may emerge later, after the disorder is well established. Thus, the ability of diagnostic instruments to identify behaviors that clearly define ASD has a lower age limit.

Screening for Autism Spectrum Disorder and Limitations of Universal Screening

A discussion of the current method for identifying children with ASD is important because it demonstrates the difficulties involved in using screening and diagnostic tests to identify the disorder at a population level. As mentioned above, ASD is, at this point, evaluated by behavioral measurements.

For over a decade, the American Academy of Pediatrics (AAP) has promoted the idea of universal screening for ASD in all children during their well-child checkups with their primary care physicians (PCPs), most commonly pediatricians.¹² The initial algorithm developed by the AAP specified that a child with any developmental concern should be screened for ASD or referred for an extensive workup; the algorithm also suggested that children without any concerns should be screened at 18 and 24 months of age.¹² Seemingly paradoxical, the US Preventive Services Task Force pointed out that there is insufficient evidence to assess the balance of benefit versus harm for screening children for ASD if no concerns for ASD have been raised by parents or clinicians,¹³ essentially creating a controversy over universal screening.¹⁴ To understand this controversy and the nuances, and specifically, the unintended consequences of universal screening, the practical performance of medical tests in the real-world setting are discussed.

In the original position paper, the AAP directed pediatricians to use a variety of screening tools in their practice. The current de facto standard is the Modified-Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F). This tool has been extensively studied, is free to use, has been translated into many languages besides English and can be completed by the parents within 5-10 minutes. Evaluation of the psychometric properties of this test demonstrate that it can attain a high sensitivity (91%) and specificity (96%) using a total score cut-off of 3.¹⁵ The performance of a medical test is commonly judged on the sensitivity and specificity to categorize a patient into the correct category (disease versus healthy). Since sensitivity and specificity of 90% or higher are considered excellent for a medical test, it would appear that the M-CHAT-R/F is an excellent screening test for pediatricians to use.

However, performance of a medical test in real world practice is highly dependent on many factors. The sensitivity and specificity are intrinsic to the medical test irrespective of the prevalence of the disease in the population in which the test is applied. However, the performance of a test in real world

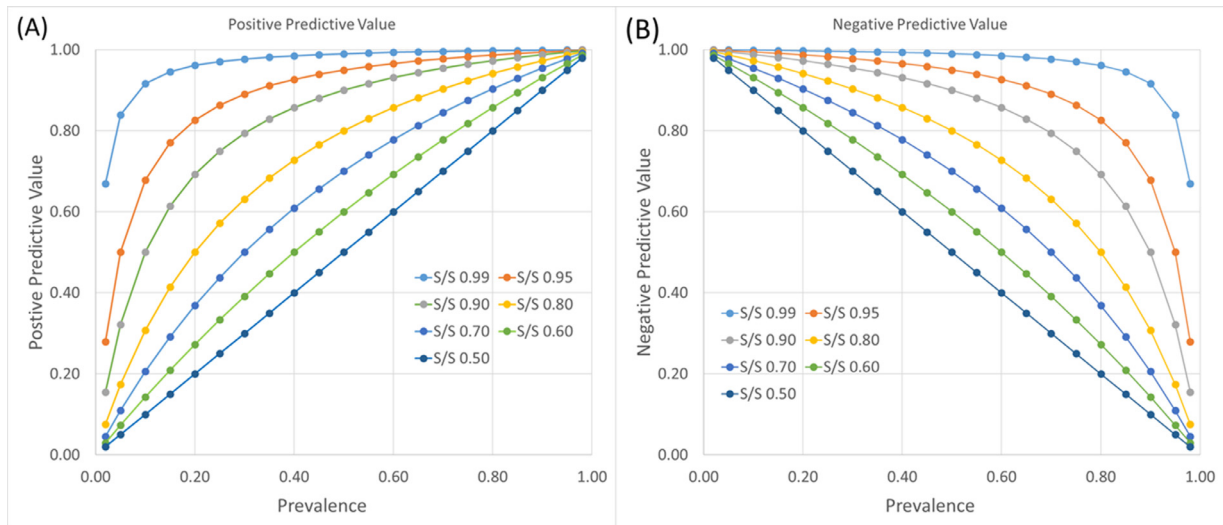


Figure 1 Relationship between real-world medical test performance as indexed by positive and negative predictive values given the sensitivity and specificity (S/S) of the test and prevalence of disease in the target population. For a disease with a low prevalence in the population, even a test with a high sensitivity and specificity (S/S), say 99% (light blue curve) will have modest positive predictive value.

practice is dependent on the prevalence of the disease in the population. When the performance of a medical test is considered in conjunction with the actual population it is being applied, the positive predictive value (PPV) and the negative predictive value (NPV) are considered rather than the sensitivity or specificity of the test. Figure 1 outlines the relationship between disease prevalence and PPV/NPV depending on sensitivity and specificity of a medical test. What is striking is that the PPV and NPV will be limited if the prevalence of the disease is low even if the test has an extremely high sensitivity and specificity, even 99%. For example, given that the ASD prevalence is about 2% of children, applying a test with an extremely high sensitivity and specificity (99%) to the

general population could only provide a PPV of 67% although the NPV would be 100%.

Thus, applying the general childhood population prevalence of ASD at 2% along with the sensitivity and specificity of the M-CHAT-R/F, results in a PPV of 32% and negative NPV of 100%, very close of the empirical values cited in a large M-CHAT-R/F study.¹⁵ From a practical point of view this means that of every 100 children screened in the pediatrician’s office, 6 will screen positive as potentially having ASD but only 2 of the children will actually have ASD (Fig. 2). Thus, essentially, the pediatrician is only 33% accurate when raising concerns about ASD to the family. Most doctors pride themselves on providing solid and accurate

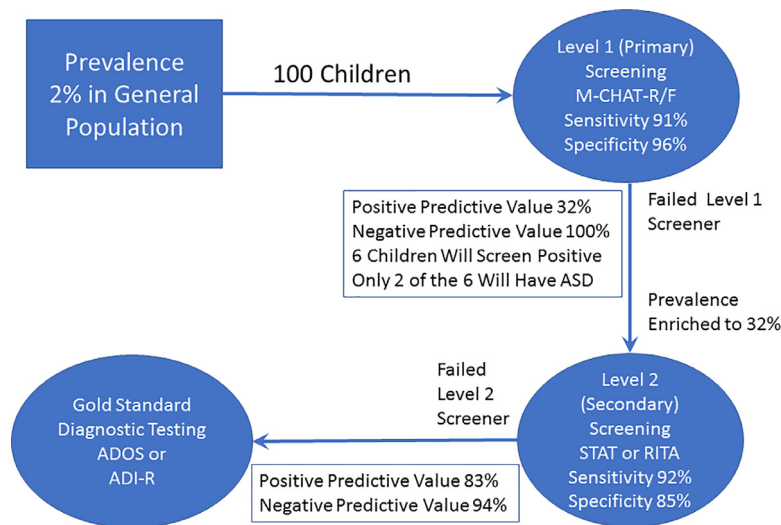


Figure 2 A multilevel screening approach is needed to maximize the predictive value of screening. A primary (Level 1) screener can only provide a modest positive predictive value but it can also enrich the population so a secondary screener (Level 2) can result in a much higher positive predictive value.

advice, so being wrong 67% of the time is somewhat counterintuitive to the practice of medicine. Thus, it is not surprising that studies have shown a low compliance of pediatricians with the AAP recommendations for universal screening¹⁶ and this may explain, in part, the skepticism of the US Preventive Services Task Force.¹³

Screening Needs to Be a Multistep Process

The M-CHAT-R/F provides an excellent example of the limitations of screening tests, why children who screen positive for ASD need to be referred for further evaluation and why a screening test cannot make a diagnosis. However, the initial process (primary or Level 1 screening test) has the purpose of enriching the population of patient referred for further testing so that the prevalence of ASD in the children that screen positive is 32% rather than 2%. Thus, secondary (Level 2) screening tests can be used to accurately identify children at risk for having an ASD diagnosis. In the original guidelines, the AAP did list a large number of “Level 2” screening tests¹² but in the revised, more recent guidelines they recommend a confrontational interactive evaluation of the child to confirm a positive “Level 1” screening test.¹⁷

Now, with an enriched prevalence in the population, a secondary screening test with even a more modest sensitivity and specificity can be used and will result in a better PPV. In addition, the number of individuals that need to be examined has been greatly reduced, making the process much more efficient. For example, centers have utilized secondary screening tests such as the Rapid Interactive Screening Test for Autism in Toddlers (RITA-T)¹⁸ to improve the efficiency of the diagnostic processes.¹⁹ As seen in Figure 2, with a secondary screening test, the PPV is improved to 83%, so approximately 8 of every 10 children referred for gold-standard testing will be diagnosed with ASD, a much better rate than 32%.

Developing a Front-Line Screening and Diagnostic Program

The Early Access for Care – Arizona project at Phoenix Children’s Hospital was started in 2015 to provide training to PCPs for the identification and diagnosis of ASD in order to decrease the time between parental concerns and the time of diagnosis of ASD and to provide diagnostic and comprehensive care for children at the front lines of medicine.[‡] The program includes both in person and webinar meetings as well as training on specific screening and diagnostic tools. Training in the ADOS is also offered for both PCPs and other qualified individuals. In the original program, after failing

screening with the M-CHAT-R/F for children of 18 or 24 months of age (universal screening) or those children noted to have concerns by the parent or PCP, the child would be referred for a ADOS evaluation performed at the PCP office or by a partner trained in ADOS administration and scoring. Simultaneously, the PCP would conduct the Screening for Autism in Toddlers and Young Children (STAT) instrument in their office. If the ADOS and STAT results agreed, the child would be referred for ASD specific treatment. During the first 3 years of the project (2015-2017), 44 PCPs started the project with 16 completing the entire course and becoming certified in the diagnosis of ASD.

In 2019 the project was reviewed and revised based on feedback from the PCPs that completed the project as well as from discussion of an advisory board of experts on ASD in Arizona. A survey of the PCPs that previously completed the Early Access for Care – Arizona program demonstrated some interesting data. The MCHAT-R was always given by 89% of the PCPs, the great majority, with 78% also completing the follow-up. However, only 44% of the PCPs always used the STAT and only 56% of the PCPs had an ADOS evaluator to work with. For diagnosis, the DSM-5 criterion was always documented for diagnosis, but functional limitations were only documented always by 56% of the PCPs. Asking PCPs to rate their competency on various tools on a scale from 1 (not competent) to 5 (extremely competent) resulted in some interesting findings. For the most part, PCPs rated themselves (average competence) as having good competence on using the M-CHAT-R/F (5.0), the STAT (4.6), and the DSM-5 (4.7). However, they rated themselves rather modestly on documenting functional limitations (3.8) and understanding the ADOS (3.7). We also found that the percentage of patients that were able to obtain services through the Department of Developmental Disabilities (DDD) based on the PCP diagnosis of ASD varied widely from 100% to 5% with an average of 66%.

In reviewing the program, we found several areas in which modifications to the program could improve efficiencies and effectiveness. First, the notion of using the STAT in parallel with the ADOS could potentially result in an unnecessary procedure which could result in wasted resources. Specifically, the ADOS is a 90-120 minute examination that requires specialized training and usually a separate appointment. Additionally, the STAT is not designed as a diagnostic tool. Second, the PCPs found the STAT instrument as rather lengthy in its implementation in the office, thus explaining why it was not universally implemented by PCPs despite self-rated competence. Third, it was clear that the PCPs did not feel comfortable documenting functional limitations and thus did not do so as part of the diagnostic workup sometimes. Documenting functional limitations adequately is an especially important finding as we find that many children are rejected from obtaining therapeutic services covered by the DDD of Arizona because of the lack of documentation of functional limitations despite adequate documentation of the diagnosis of ASD.

Thus, we modified the program to integrate a step-wise approach to screening and diagnosing children with ASD

From the [‡]The original program was started by Dr Robin Blitz from a generous grant from the Board of Visitors (Phoenix AZ).

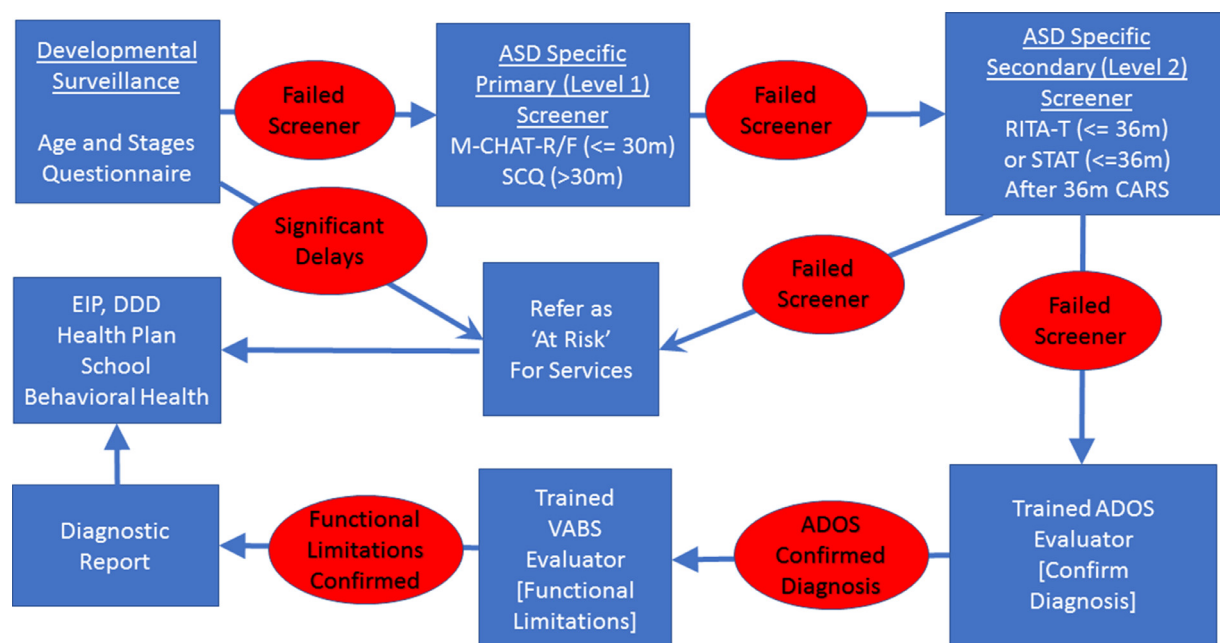


Figure 3 The most recent Early Access for Care – Arizona pipeline. Through a series of screeners and diagnostic instruments, children can be identified and diagnosed with autism spectrum disorder (ASD) as well as have functional limitations documented in order to qualify for treatment. Our philosophy is to refer for evaluation for service early as the diagnostic workup is ongoing in order to most effectively allow children to obtain services early. ADOS, autism diagnostic observation schedule; DDD, Department of Developmental Disabilities; EIP, Early Intervention Program; M-CHAT-R/F, modified-checklist for autism in toddlers, revised with follow-up; RITA-T, rapid interactive screening test for autism in toddlers; SCQ, social communication questionnaire; STAT, screening for autism in toddlers and young children; VABS, Vineland adaptive behavior scale.

that can be implemented in the PCPs office and streamline the initiation of services (Fig. 3). First, we have linked the identification of children at risk for ASD to the normal ongoing developmental surveillance that should be part of standard well-child care. Several straightforward instruments can be integrated into the flow of the PCP office which are sensitive to identifying children with potential developmental delays including delays in social-communication. One of these instruments, the Ages and Stages Questionnaire, has been used with the M-CHAT-R/F to combine screening for developmental delays and ASD.²⁰⁻²² Thus, we recommend that the normal developmental screening process be the first step in screening for ASD. Most importantly, if a child is found to have significant (>50%) delays in development then they should be immediately referred for evaluation for services, especially if they are under 3 years of age. This type of referral differs from state to state; in Arizona a child does not need a definite diagnosis of ASD until 6 years of age, so it is best for the child to be evaluated for therapies if developmental delays are suspected while the workup for ASD is ongoing.

Second, the recommended primary (Level 1) developmental screener with the most evidence, the M-CHAT-R/F, is recommended for those aged 30 months or less. Unfortunately, there is no well-studied screening tool for those older than 30 months, but the Social Communication Questionnaire (SCQ) can be used in this age range and has good correspondence with ADOS scores. The Ages and Stages

Questionnaire, M-CHAT-R/F and SCQ are parent questionnaires that are followed up by questioning of critical items. The efficient part of these questionnaire is that they can be completed by a caretaker and reviewed by a trained nurse or other paraprofessional and they provide quantitative scores, leaving limited subjective judgment to the evaluation. It is then recommended that the child undergo a secondary (Level 2) screener if they fail the primary (Level 1) screener.

Third, evaluation by a secondary (Level 2) screener is essential. Secondary screening tools need to be confrontational instruments where a trained professional interacts with the child and they need to provide a quantitative score in order to minimize subjective judgements. All other screening tools until this point are usually parent rated and may be administered by an individual who is not specifically trained in ASD. Thus, the secondary screening tool is the chance for the physician to *actually lay eyes* on the patient and get the chance to evaluate the identified problematic behaviors or delays for themselves. The 2 secondary screening tools with the most evidence are the STAT and RITA-T. In our program we have included training in both tools so the physician can use the instrument that they feel most comfortable. Since the RITA-T can be performed in about half of the time required for the STAT, physicians can perform a quick secondary screening assessment. If the RITA-T does not give the physician the information they want, the STAT can be used as an alternative. Physicians that are more comfortable with the STAT can use that instrument if they like. Unfortunately, the

RITA-T and the STAT are only valid for children aged 36 months or less. For children above this age there are several instruments. We recommend the Childhood Autism Rating Scale because of its long history of use in both the clinical and research settings and because it provides a quantitative score of severity. If an individual fails the secondary screener they should be immediately referred for evaluation for therapeutic services while the evaluation to confirm the ASD diagnosis is ongoing.

Fourth, those individuals that fail the secondary (Level 2) screener require a gold-standard instrument to confirm the diagnosis. Our recommendation is the ADOS since this is an interactive test which involves the child. Since this requires specialized training, we are developing a network of providers that PCPs can work with in order to have the test performed. PCPs with significant interest can have their qualified staff also be trained for the ADOS. Because of the length of the tests, many PCPs do not have time to perform the test themselves.

Fifth, if a diagnosis of ASD is confirmed then functional limitations need to be documented. Since PCPs did not feel completely comfortable with documenting functional limitations, we have added an instrument that measures adaptive behavior in order to quantitatively document the child's functional limitations. The Vineland Adaptive Behavior Scale is probably the most widely used instruments used in children with ASD to measure adaptive behavior and has been shown to have good psychometric properties in ASD,²³ although other scales such as the Adaptive Behavioral Assessment System is also used by some. The Vineland Adaptive Behavior Scale can be filled out by parents or, preferably, with the help of a trained interviewer. Using a quantitative scale provides the concrete proof of the child's functional limitations to backup the PCP's report.

Sixth, the PCP needs to review the testing and write a report documenting the child's symptoms and the need for treatment. With the quantitative nature of the instruments used in the workup pipeline, the report can easily be written using a template customized for the particular child. Such as report will provide support for obtaining services. Given that the wait for a workup for ASD at specialty clinics is not uncommonly 6-12 months, centralizing the workup and diagnosis at the front lines should improve efficiency of the diagnostic process and get services started earlier.

Admittedly, there are several potential limitations of this pipeline. One of the most important limitations is the procedures for children that are not diagnosed with ASD as many they have significant symptoms which may or may not point to an alternative diagnosis. Although we have included education in our program about the differential diagnosis of other disorders, the evaluation and treatment are not covered comprehensively in our program. However, a significant amount of information will be available if an outside referral to a specialty health provider is needed. Other important aspects are the management of children with ASD as they can be very complex medically and behaviorally. Our annual conference includes specific topics on many of the

comorbidities involved in ASD but the management of such comorbidities can be complex.

Future Methods for Efficient Diagnosis and Screening

This process of using a sequence of primary and secondary screening tools is very important to reduce unnecessary referral for ASD evaluations. Unnecessary evaluations result in undue stress on the family and, perhaps more importantly, result in a saturation of resources required to perform comprehensive gold-standard evaluations. This leads to a long delay in the evaluation of patients and long delays in the ability of children to start treatments. One overriding theme in the research of effective treatments for ASD is that the earlier the initiation of standard behavioral and educational therapies, the more effective the treatments.⁸ Thus, there is a priority for identifying children early to initiate treatment.

Developing biomarkers that could be used in conjunction with the screening methods proposed by the AAP is another method for improving the efficiency of the diagnostic process. Thus, biomarkers that could (1) stratify risk for determining which children should be screened, (2) be used as a secondary screen, and/or (3) confirm the behavioral observations of diagnostic tests, could greatly improve the efficiency of diagnosis and potentially improve the age at which children start therapeutic interventions. In our recent review of biomarkers we noted 5 types of biomarkers (see Table).²⁴ Biomarkers at prenatal and presymptomatic stages can be used to help stratify risk in order to focus behavioral screening tools while biomarkers at the diagnostic stage can be used to verify diagnosis once behavioral symptoms develop.

Additionally, biomarkers aimed at assisting with the diagnosis of ASD most likely cannot be used in isolation. As

Table Categories of Biomarkers Used to Stratify Risk, Diagnose, and Assist With Etiological Classification and Treatment

Prenatal	Starting from preconception through the gestation period, biomarkers can stratify pregnancies which are at high risk for the offspring developing ASD
Presymptomatic	During the presymptomatic stages, biomarkers can identify high-risk populations to determine who requires further diagnostic testing, early intervention or increased surveillance.
Diagnostic	Once symptoms are obvious, biomarkers can confirm diagnosis
Subgrouping	Biomarkers can be used to divide individuals with ASD into biological subgroups.
Treatment	Biomarkers can be used to select the most optimal therapy by predicting treatment response

discussed in the introduction, the diagnosis of ASD involves primary and secondary screening as well as confirmatory gold-standard testing. Developers of biomarkers for diagnosis must carefully consider the placement of diagnostic biomarkers in this evaluation pathway as even the best biomarkers will not provide an adequate PPV with the current ASD prevalence if used in isolation. In this way, we can see that the identification and diagnosis of ASD is not a single event but an ongoing process.

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