Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research

This article reviews current evidence for autism spectrum disorder (ASD) screening based on peer-reviewed articles published to December 2013. Screening provides a standardized process to ensure that children are systematically monitored for early signs of ASD to promote earlier diagnosis. The current review indicates that screening in children aged 18 to 24 months can assist in early detection, consistent with current American Academy of Pediatrics’ recommendations. We identify ASD-specific and broadband screening tools that have been evaluated in large community samples which show particular promise in terms of accurate classification and clinical utility. We also suggest strategies to help overcome challenges to implementing ASD screening in community practice, as well as priorities for future research. Pediatrics 2015;136:S41–S59

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Although there have been considerable advances in characterizing early behavioral markers predictive of autism spectrum disorders (ASDs), as summarized in this special issue to *Pediatrics*, translation into clinical practice requires that the process of monitoring for such early risk markers be operationalized to facilitate broad implementation. To that end, universal screening for ASD has been recommended by the American Academy of Pediatrics (AAP) to ensure consistent practice and optimal detection of young children with early signs of ASD across a range of clinical and community contexts. The AAP has recommended that all children be screened with an ASD-specific instrument during well-child visits at ages 18 and 24 months in conjunction with ongoing developmental surveillance and broadband developmental screening. The rationale for this recommendation was based on the presence of ASD symptoms by age 18 months, promising data on early ASD-screening tools, and the availability of effective intervention strategies targeting this age group.

Recent randomized controlled trials have added new evidence that for many children aged <3 years, early intervention can improve outcomes, including core deficits of ASD (ie, social attention), IQ, language, and symptom severity, thus increasing the potential benefits of early diagnosis facilitated by early screening.

Some scientists and practitioners have questioned whether the evidence relative to general developmental surveillance warrants ASD screening, and others have argued that research needs to move beyond risk classification and evaluate longer term outcomes of ASD screening (eg, impact on age of diagnosis, related gains attributable to earlier enrollment in intervention). The uptake of ASD screening into pediatric practice has been modest. Although potential facilitators and barriers to ASD screening have been researched and debated, screening rates in many regions of the United States remain low. Community-based interventions aimed at implementing or increasing utilization of ASD screening have emphasized training primary care physicians and their front-line staff, providing ongoing technical assistance (eg, scoring, data management support), and clear referral pathways for specialized assessments. However, ongoing debate regarding whether there is sufficient evidence in support of ASD screening to warrant widespread practice change may undermine the degree to which community pediatricians are adopting the AAP policy.

Thus, an updated literature review and best practice recommendations regarding ASD screening are warranted, as well as further considerations of how to address potential barriers to uptake of screening into clinical practice. To that end, an international multidisciplinary panel of clinical practitioners and researchers with expertise in ASD and developmental disabilities was convened in Marina del Rey, California in October 2010. The panel reached consensus on “How can we optimize developmental course and outcomes through ASD screening programs for children aged ≤24 months?”

For further context, we briefly define terms used to describe the classification accuracy of specific screening measures. “Sensitivity” refers to the proportion of children with ASD who are correctly identified as “high risk” according to results of screening; a child with ASD who is not identified by the screen is considered to be a false-negative. Specificity refers to the proportion of children who do not have ASD who are correctly classified using the screening tool as not having risk for ASD; a child who does not have ASD yet screens positive is considered to be a false-positive. It has been suggested that to even receive consideration for population screening applications, the sensitivity and specificity of a screening tool should exceed 0.70. However, the relative “cost” associated with false-positive and false-negative findings, as well as the prevalence of the condition being screened, must also be taken into consideration. The positive predictive value (PPV) for ASD of a screening test is defined as the proportion of children screening positive who receive an ASD diagnosis divided by the total number of screen-positive cases. The negative predictive value (NPV) is the proportion of screen-negative children not receiving an ASD diagnosis divided by the total number of screen-negative cases. The positive predictive value (PPV) and NPV are influenced by the baseline prevalence of ASD in the population being screened as well as the sensitivity and specificity of the screening tool. Although sensitivity and specificity are intrinsic measures of test performance, PPV and NPV arguably have more inherent meaning for individual family-level and system-level evaluations of screening. It is also important to distinguish level 1 from level 2 screening. Level 1 screening applies to all children regardless of risk status (ie, “universal” screening). In contrast, level 2 screening is targeted at children already identified as being at increased risk (eg, due to a positive family history, concerns raised by parents or clinicians, identification by a level 1 screener).

**METHODS**

The working group co-chairs and panel co-chairs conducted a PubMed search to identify relevant articles on screening for ASD in children aged ≤24 months. Members of the working group reviewed the articles. We assessed whether tools were being evaluated in the population in which they were being considered for use and
whether these tools met the minimum criteria for specificity and sensitivity to support implementation in the general community. Panel recommendations were based on this evaluative framework.

The working group summarized published research on screening tools developed for use in children aged ≤24 months, even if the age range of these screens exceeded 2 years (Table 1). A PubMed search was conducted on June 30, 2010, by using the search terms (“child developmental disorders, pervasive” or “autistic disorder/” or “autism [tw]” or “autistic [tw]”) and (“mass screening” or “screen [tw]”), with the age filter (“infant, birth-23 months”) and limited to English-language articles. This search yielded 111 references, which were reviewed by Drs Zwaigenbaum and Bauman, who selected articles focusing on studies that involved prediagnostic screening for early behavioral or biological features (as opposed to postdiagnostic screening for etiologic factors or associated comorbidities). The search results were complemented by additional publications identified by working group members. Thus, although the search strategy was comprehensive, selection of articles was not systematic, which is an important limitation. A scoping approach was used instead, with some discretion of the multidisciplinary expert working group, to select articles of highest relevance.

Most of the instruments reviewed were designed to identify children at risk for ASD who warranted further evaluation. Also reviewed were general developmental, or broadband, screening instruments that had been evaluated for the purpose of early identification of ASD, even if not specifically designed to distinguish risk for ASD from risk for other developmental delays. We also distinguished between the instruments that had been evaluated as level 1 screens, level 2 screens, or both.

During the conference, the working group offered draft recommendations for discussion, modification, and ratification by all attendees. Electronic voting was used to express opinions and guide consensus building. A modified nominal group technique was used to review the recommendations, with consensus reached by ≥1 round of voting. The consensus statements and discussion were summarized as draft proceedings of the conference, which were subsequently edited by all participants. The search was updated by using the same strategy to add articles published to December 31, 2013, which yielded an additional 85 references; selection was limited to prediagnostic screening of early behavioral or biological markers. The working group reviewed and approved the final wording of the summary and recommendations.

The measurement properties that characterize the accuracy of screening instruments used to identify children at risk for ASDs are summarized in Table 1.17,20–47 ASD screening tools with published evaluation data include parent questionnaires such as the Modified Checklist for Autism in Toddlers (M-CHAT),24 the Quantitative Checklist for Autism in Toddlers (Q-CHAT),33 the Early Screening of Autistic Traits questionnaire (ESAT),22,23 and the First Year Inventory (FYI).20,48 Table 1 also summarizes ASD screening instruments with only preliminary data (eg, the Pervasive Developmental Disorders Rating Scale),56 which will not be included in the present discussion.

The results of the overall process are listed as summary statements. Some of the statements summarize the state of the literature, whereas others provide recommendations for research needed to fill important evidence gaps and/or address issues important for clinical practice.

SUMMARY STATEMENTS

Statement 1: Evidence supports the usefulness of ASD-specific screening at 18 and 24 months. ASD screening before 24 months may be associated with higher false-positive rates than screening at ≥24 months but may still be informative.

ASD-specific screening in children aged 18 to 24 months can assist in early detection

Table 1 summarizes the measurement properties of ASD-specific level 1 screening tools for children aged <36 months. These include the following tools.

CHAT

The CHAT was the first ASD screening tool to be assessed at a population level.46 It cannot be recommended, however, for current early detection efforts due to its low sensitivity (18%, based on 6-year follow-up of a screened cohort of 18-month-olds).49

Q-CHAT

The Q-CHAT extends the measurement model of the CHAT, covering a broader range of ASD symptoms, which are rated on a 5-point scale (rather than present/absent). Preliminary data suggest that the Q-CHAT distinguishes children with ASD from low-risk 18- to 24-month-olds.53 A recent secondary analysis using the 10 Q-CHAT items that best discriminated groups with and without ASD and that optimized a screening cut-point indicated sensitivity and specificity estimates as high as 91% and 89%, respectively, in a case-control sample.34 Further validation of this abbreviated screen is needed, however, in independent, community-based samples similar to where the screen would be used.

M-CHAT

The M-CHAT, also adapted from the CHAT, has been assessed in large community populations...
<table>
<thead>
<tr>
<th>Screening Tool</th>
<th>Reference</th>
<th>Population (N, Age, Diagnosis, Level)</th>
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<tbody>
<tr>
<td>ASD-specific screeners: parent report FYI</td>
<td>Reznick et al (Turner-Brown et al, 2007)</td>
<td>N = 698 infants aged 12 mo General population mailing at 12 mo, with follow-up at 42 mo</td>
<td>Preliminary findings: N = 699 with outcomes at 42 mo Diagnosis with ASD = 9. FYI 2-domain risk algorithm flagged 4/9 cases later diagnosed with ASD Sensitivity = 0.44; Specificity = 0.99</td>
<td>(PPV = 0.31 and NPV = 0.99)</td>
<td>Promising tool for infants aged 12 mo, but additional data needed</td>
</tr>
<tr>
<td>ESAT</td>
<td>Dietz et al, Swinkels et al, 2006</td>
<td>N = 31 724 from general population Stage 1, n = 370 screened positive; Stage 2, of n = 255 100 screened positive 14–15 mo (mean: 14.9 mo)</td>
<td>Sensitivity and specificity not reported Identified 18 ASD from 31 724 screened</td>
<td>PPV = 0.25</td>
<td>Not yet recommended as level 1 screener; additional data needed</td>
</tr>
<tr>
<td>M-CHAT</td>
<td>Robins et al, 2001</td>
<td>N = 1235, mix of low and high risk Mean: 14.9 mo (14–15 mo)</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study (screen-negative cases not systematically evaluated)</td>
<td></td>
<td>Strong evidence for use as both level 1 and level 2 tool, 16–30 mo; additional data will be helpful, especially in estimating sensitivity</td>
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<td></td>
<td>Robins, 2008</td>
<td>N = 4797; 362 screened positive (qualified for follow-up interview); 16–26 mo 15–18, and 24-mo well-child visit results</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study (screen-negative cases not systematically evaluated)</td>
<td>Without follow-up interview, PPV = 0.058</td>
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<td></td>
<td>Kleinman et al, 2008</td>
<td>n = 3309 low risk, n = 484 high risk 16–30 mo</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study (screen-negative cases not systematically evaluated)</td>
<td>PPV = 0.11 for low-risk sample, 0.60 for high-risk sample, without interview. This improved to 0.85 (low risk) and 0.76 (high risk) when follow-up interview was considered part of the screening procedure</td>
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<td></td>
<td>Pandey et al, 2008</td>
<td>n = 6050 low risk and n = 726 high risk 16–30 mo</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study (screen-negative cases not systematically evaluated)</td>
<td>PPV = 0.45 for low-risk samples (younger and older combined for this table) and 0.76 for high-risk samples; PPV calculated based on M-CHAT + follow-up interview</td>
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<tr>
<td></td>
<td>Inada et al, 2011</td>
<td>N = 659, 18 mo</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study (screen negative cases not systematically evaluated)</td>
<td>PPV = 0.733</td>
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TABLE 1 Continued

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<tr>
<td>Canal-Bedia et al,29 2011</td>
<td>2417 low risk and 63 high risk, 18–36 mo</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study (screen negative cases not systematically evaluated)</td>
<td>PPV not reported separately for low-risk and high-risk samples</td>
<td>PPV = 0.19</td>
<td>In validity study, 19 of 23 children diagnosed with ASD were from high-risk sample. In reliability study, rate of ASD in low-risk sample was 2.9 in 1000</td>
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<td>Reliability study: 2055 low risk, 18–36 mo</td>
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<td>Reliability study: PPV = 0.19</td>
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<tr>
<td>Pinto-Martin et al,30 2008</td>
<td>N = 152, 18–30 mo</td>
<td>No diagnostic follow-up, cannot assess psychometrics; comparison of M-CHAT and PEDS</td>
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<tr>
<td>Chlebowski et al,31 2013</td>
<td>N = 18 989, 18–30 mo</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study</td>
<td>Among screen-positive children who were evaluated (171 of 278 [60.7%])</td>
<td>PPV = 0.538 for ASD (if any DD is included, PPV increases to 0.977)</td>
<td>Emphasizes potential clinical utility of M-CHAT as level 1 screen (high PPV)</td>
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<tr>
<td></td>
<td></td>
<td>Note: some potential false-negative findings ascertained by concurrent screening using other instruments</td>
<td></td>
<td>Note: Sample overlaps with Kleinman et al,26 2008; Pandey et al,27 2008; Robins et al,24 2001; Robins et al,28 2008</td>
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<tr>
<td>M-CHAT-R/F</td>
<td>Robins et al,32 2014</td>
<td>N = 18 115 low-risk toddlers</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study</td>
<td>Among screen-positive children who were evaluated (221 of 348 [63.9%])</td>
<td>Authors suggested that if initial M-CHAT score is ≥7, the follow-up M-CHAT interview may not be needed due to high PPV for ASD (&gt;0.80). However, the follow-up M-CHAT interview is essential for children with initial scores of 3–6</td>
</tr>
<tr>
<td></td>
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<td>Note: some potential false-negative findings ascertained by concurrent screening using other instruments</td>
<td></td>
<td>PPV = 0.475 for ASD (if any DD is included, PPV increases to 0.948)</td>
<td>Children with &lt;3 items endorsed (93% of all cases) did not require the follow-up interview or any other evaluation. Children with 3–7 items endorsed (8% of all cases) required the follow-up interview, if at least 2 items remained positive, then referral for diagnostic evaluation was indicated. Children with ≥8 items endorsed (1% of all cases) were at sufficiently high risk to be referred directly for diagnostic assessment. Using this strategy reduced the case positive rate (from 9.2% to 7.2%) without significant change to PPV, relative to previous follow-up M-CHAT strategy</td>
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<tr>
<td>Q-CHAT</td>
<td>Allison et al,33 2008</td>
<td>779 low-risk toddlers with mean age of 21 mo; plus 160 toddlers and preschoolers with ASD with mean age of 44 mo</td>
<td>Sensitivity and specificity not provided</td>
<td>Not reported</td>
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Note: Sample overlaps with Kleinman et al,26 2008; Pandey et al,27 2008; Robins et al,24 2001; Robins et al,28 2008
### TABLE 1 Continued

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<tr>
<td>Allison et al,34 2012</td>
<td>754 controls; mean: 36 mo (drawn from low-risk sample in Allison et al,33 2008)</td>
<td>Sensitivity = 0.91; Specificity = 0.89</td>
<td>PPV = 0.58 (with pretest odds = 0.16 based on available sample)</td>
<td>Clinical diagnoses based on parent report, with recruitment through Web-based research registry Further evaluation in independent samples warranted</td>
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<tr>
<td>DBC-ES Gray et al,35 2008</td>
<td>N = 207; 20–51 mo; level 2</td>
<td>Sensitivity = 0.83 (estimated); Specificity = 0.48 (estimated)</td>
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<tr>
<td>PDDRS Eaves and Williams,36 2006</td>
<td>N = 199 with autistic disorder, rated by teachers, teaching interns, and family members; aged 1–6 y</td>
<td>Factor analysis, no psychometrics calculated</td>
<td></td>
<td>Insufficient data to evaluate utility as screening tool for young children</td>
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<tr>
<td>Eaves et al,37 2006</td>
<td>N = 134, rated by teachers, teaching interns, or parents; aged 3–26 y (mean: 9.7 y); diagnosis: autism (n = 86), Asperger disorder (n = 11), PDD-NOS (n = 15), non–ASD disorder (n = 23)</td>
<td>Autistic disorder, cutoff 85: Sensitivity = 0.93 and specificity = 0.48</td>
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<td>Autistic disorder, cutoff 90: Sensitivity = 0.84 and specificity = 0.58</td>
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<td>PDD, cutoff 85: Sensitivity = 0.88 and specificity = 0.68</td>
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<td>PDD, cutoff 90: Sensitivity = 0.78 and specificity = 0.77</td>
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**ASD-specific screeners: interactive observational measures**

<p>| STAT Stone et al,38 2000 | n = 40 (development sample), n = 33 (validation sample); 24–35 mo, level 2 (high risk) | Sensitivity = 0.85 and specificity = 0.86 for validation sample (sensitivity = 0.83 and specificity = 0.83 for development age-matched subsample) | Not reported | Strong evidence for use as level 2 tool, 24–35 mo but additional data will be helpful |
| Stone et al,39 2004 | Study 1: N = 52, 24–35 mo, ASD and other developmental delay matched on chronological and mental age, level 2 | Study 1: one-half of sample used to determine cutoff with optimal sensitivity/specificity and one-half used to validate cutoff of 2: Sensitivity = 0.92 and specificity = 0.85 | Study 1: PPV = 0.86 and NPV = 0.92 (validation subsample) | |
| | Study 2: N = 104, 24–35 mo, level 2 | Study 2: not reported, but based on table provided, sensitivity = 1.0 and specificity = 0.90 for autistic disorder (lower for PDD-NOS) | | |
| Stone et al,40 2008 | N = 71, 12–23 mo, level 2 (follow-up assessment 24–42 mo) | Cutoff of 2: Sensitivity = 1.0 and specificity = 0.40 | Cutoff of 2: PPV = 0.38 and NPV = 1.0 | |
| | | Cutoff of 2.75: Sensitivity = 0.95 and specificity = 0.73 | Cutoff of 2.75: PPV = 0.56 and NPV = 0.97 | |
| | | Cutoff of 2.75 in subsample of children 14–23 mo (n = 50): Sensitivity = 0.93 and specificity = 0.83 | Cutoff of 2.75 in subsample of children 14–23 mo (n = 50): PPV = 0.68 and NPV = 0.97 | |</p>
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<tbody>
<tr>
<td>BISCUIT</td>
<td>Matson et al, 2009</td>
<td>N = 1007 sample with ASD or DD aged 17–37 mo (mean: 26.4 mo)</td>
<td>330 confirmed ASD diagnosis</td>
<td>Sensitivity = 84.7; Specificity = 86.4</td>
<td>AUC = 0.55</td>
</tr>
<tr>
<td>SORF</td>
<td>Wetherby et al, 2004</td>
<td>N = 150, level 2 screen of low-risk sample of 6581 children aged 18–24 mo</td>
<td>20 Significant red flags; cutoff of 8 red flags</td>
<td>Sensitivity = 0.87 and Specificity = 0.84</td>
<td>AUC = 0.93</td>
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<tr>
<td>Broadband screener: parent report</td>
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<td>CSBS ITC</td>
<td>Wetherby et al, 2004; Wetherby et al, 2008</td>
<td>N = 5385 children aged 6–24 mo screened; follow-up evaluation of n = 813; general population (consecutive screens from 6 to 24 mo; diagnostic outcome/follow-up questionnaire at 4+ years)</td>
<td>60 ASD from 5385 screened</td>
<td>Mean: 16.4 mo (6–24 mo)</td>
<td>PPV and NPV for communication delay vary with age; sensitivity = 88.9–94.4; specificity = 88.9</td>
</tr>
<tr>
<td>Pierce et al, 2011</td>
<td>N = 10,479 infants whose parents completed checklist at 1 y well-child visit (mean age: 12.34 mo); level 1 screen</td>
<td>32 with ASD from 10,479 screened</td>
<td>Sensitivity and specificity not provided</td>
<td>PPV = 0.75 (estimated) for developmental delays including ASD</td>
<td></td>
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<tr>
<td>Oosterling et al, 2009</td>
<td>N = 238; 8–44 mo (mean: 29.6 mo)</td>
<td>See note (at right)</td>
<td>Overall sensitivity reported at 0.71; overall specificity reported at 0.59</td>
<td>See note (at right)</td>
<td>Note: True sensitivity, specificity, PPV, and NPV cannot be estimated because another tool (ESAT) was used as “prescreen” and only ESAT screen-positive cases were subsequently screened with ITC</td>
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Adapted from the table developed by the Autism Subcommittee for the National Children’s Study. Other instruments not listed in the table: CHAT (Baron-Cohen et al, 1992; Baron-Cohen et al, 1996; and other articles); longitudinal data indicated poor sensitivity; not recommended for use as level 1 screen; and Social Responsiveness Scale—Preschool (SRS-P), under development for screening preschool-aged children; ADI-R, Autism Diagnostic Interview—Revised; AOSI, Autism Observation Scale for Infants; BISCUIT, Baby and Infant Screen for Children with Autism Traits; CSBS ITC, Communication and Symbolic Behavior Scales Infant Toddler Checklist (or Infant Toddler Checklist, ITC); DBC-ES, Developmental Behavior Checklist—Early Screen; DD, developmental delay; ESAC, Early Screening for Autism and Communication Disorders; ESAT, Early Screening of Autistic Traits; M-CHAT-R/F, M-CHAT, Revised With Follow-Up; PDD-NOS, pervasive developmental disorder not otherwise specified; PDDRS, Pervasive Developmental Disorder Rating Scale; Q-CHAT, Quantitative Checklist for Autism in Toddlers; SORF, Systematic Observation of Red Flags of ASD; STAT, Screening Tool for Autism in Toddlers & Young Children.
samples as a level 1 screen. The 23-item M-CHAT questionnaire, combined with a follow-up interview to help clarify items endorsed by parents on the initial screen, is estimated to have a PPV as high as 0.57 to 0.65 in low-risk samples.\(^{25,26,31}\) Pandey et al\(^{27}\) reported that the PPV of the M-CHAT (as used for first-level screening in a low-risk community sample with follow-up interview) is lower in younger children, with a PPV of 0.28 in toddlers aged 16 to 23 months compared with a PPV of 0.61 in those aged 24 to 30 months. There are many reasons for false-positive findings, including developmental concerns that may resolve and behaviors in typically developing toddlers that overlap with ASD deficits, such as repetitive behaviors (eg, turning lights on and off) and restricted interests (eg, insistence on routines).\(^{19}\) However, despite lower specificity for autism at 18 months, PPV for any diagnosable developmental disorder was high for all groups. In the largest sample of toddlers (aged 18–30 months) reported to date (\(N = 18,989\) [including some children in previous reports]),\(^{25–27}\) the PPV of the M-CHAT for ASD was 0.54, and for any developmental disorder, it was 0.98.\(^{31}\) As in other community-based ASD-screening studies, estimates of PPV were based on those screen-positive children who attended and completed a diagnostic evaluation (39.3\% of screen-positive children were not assessed).

The M-CHAT has also been evaluated internationally and in multiple languages. Canal-Bedia et al\(^{29}\) assessed the reliability and predictive validity of a Spanish translation of the M-CHAT in a combined community and at-risk sample in Spain. The PPV in the community sample was 0.19, although this finding may have reflected a relatively low base rate of identified preschool-aged children with the disorder (2.9 in 1000) (Table 1). Another study that evaluated the psychometric properties of the Spanish version of the M-CHAT in a community sample of children in Mexico reported similar discriminative validity,\(^{50}\) although some items appeared less informative for ASD than in published reports on the original English-language version. Psychometric data on Japanese\(^{28}\) and Arabic\(^{51}\) translations have also been reported. (Additional information on available translations of the M-CHAT is available at http://www2.gsu.edu/~psydlr/Site/Official_M-CHAT_Website.html [accessed October 17, 2014]).

Recently, Robins et al\(^{32}\) reported validation data for a new version of this screening tool, the M-CHAT, Revised with Follow-Up, in 16,115 toddlers. The questionnaire was reduced to 20 items, removing 3 items that had performed poorly ("peek-a-boo," "playing with toys," and "wandering without purpose"); wording on other items was simplified and/or examples provided for further clarity. A scoring algorithm with 3 risk ranges was developed. Children in the low-risk range (ie, \(<3\) items endorsed) did not require the follow-up interview or any other additional evaluation (93\% of all cases). Children in the medium-risk range (ie, \(3–7\) items endorsed [6\% of all cases]) required the follow-up interview to clarify their risk for ASD; if at least 2 items remained positive, then referral for diagnostic evaluation was indicated. Children in the high-risk range (ie, \(\geq8\) items endorsed [1\% of all cases]) were at sufficiently high risk to be referred directly for diagnostic assessment without the follow-up interview. This revised scoring and referral algorithm reduced the initial screen-positive rate (from 9.2\% to 7.2\%) and increased the overall rate of ASD detection (67 vs 45 per 10,000) compared with the original follow-up M-CHAT.

### Early Screening for Autistic Traits

Population screening at an even earlier age has been associated with higher false-negative rates (lower sensitivity), which is somewhat expected given the slow onset of symptoms that emerges across the first 24 months of life. The ESAT was assessed in a large (\(N = 31,724\)) population sample of 14- to 15-month-olds, with a low case detection rate (\(<1\) in 1000).\(^{22,23}\) Moreover, PPV of the ESAT was only 0.25, which would potentially lead to the referral of a large number of toddlers without ASD based on a positive screen (PPV for other developmental delays was not reported). The authors recommended a second screening at 24 months of age to identify children who regress after age 18 months or those who are missed for other reasons.

### Baby and Infant Screen for Children With Autism Traits

Preliminary data on the Baby and Infant Screen for Children With Autism Traits tool indicate good discrimination between toddlers with known ASD diagnoses and those with other developmental delays as identified clinically.\(^{41}\) Additional data are needed, however, to confirm how this measure would perform in a screening context.

### FYI

The FYI is a parent questionnaire designed to screen for signs of autism in 12-month-olds. Initial data on the FYI suggest the potential for modest sensitivity.\(^{26}\) In a recent prospective follow-up study of a community sample of 699 children whose parents initially completed the FYI at approximately the child’s first birthday, 4 of 9 children subsequently diagnosed with ASD at 3 years of age were identified. A scoring algorithm that optimized prediction of ASD identified 13 (1.9\%) of 699 participants who met cutoffs on 2 domains (social communication and sensory
regulation). Assessment of PPV in an independent/validation sample is still needed.

The working group suggested that additional efforts are needed to develop and validate population-based ASD screening tools aimed at the 12- to 18-month age range, anticipating that modest sensitivity at this age may warrant follow-up with additional screening at a later age (eg, at 24 months). In addition, the working group recommended that standardized screening specifically for ASD should be performed when parents raise concerns between well-child visits or when concerns are raised upon general developmental surveillance or screening during scheduled visits. Parental concern effectively raises the prior probability that a child will have ASD, thereby increasing the PPV of a screening test regardless of its intrinsic sensitivity and specificity.

Level 2 Screening Tools

Two interactive observational assessments have been developed for use as level 2 screeners in young children identified as being at high risk of ASD.

Screening Tool for Autism in Two-Year-Olds

The Screening Tool for Autism in Two-Year-Olds (STAT) has been assessed in clinical samples of 2-year-olds referred for suspected ASD, with a sensitivity and specificity as high as 92% and 85%, respectively. Recent data indicate that the STAT may also have utility in younger toddlers aged 14 to 23 months, although additional data are needed for this age group. Although the STAT requires a higher level of expertise to administer than parent questionnaires such as the M-CHAT, a recent study provided evidence of the effectiveness of Web-based training of community services providers of various professional backgrounds; this training could enhance the feasibility of the STAT.

Systematic Observation for Red Flags

The Systematic Observation for Red Flags has shown promise in discriminating ASD from other communication delays. Additional data are needed in a screening context.

Broadband screening in children aged <24 months can assist in early detection of ASD

Delays and deviances in social communication are often subtly present around the first birthday but are often not strongly ASD-specific at that early age. Broadband developmental screening tools, such as the Communication and Symbolic Behavior Scales Developmental Profile (CSBS DP) Infant/Toddler Checklist developed by Wetherby and Prizant, were shown to be effective at detecting autism before the onset of full-blown clinical symptoms. Wetherby et al evaluated the CSBS DP Infant/Toddler Checklist in a community sample of 5385 children aged 6 to 24 months recruited from health and child care services. The Infant/Toddler Checklist identified 56 (83%) of 60 children with ASD classified independently at age 3 years in a concurrent prevalence study of the same region. Some Infant/Toddler Checklist findings were positive as early as 9 to 11 months, although in some cases, an initial screen was negative at 9 to 11 months and did not become positive until a later administration. The Infant/Toddler Checklist also identified concerns sooner and more consistently than an open-ended question about parents’ developmental concerns. Subsequently, Pierce et al assembled a network of 137 pediatricians who administered the CSBS DP Infant/Toddler Checklist at every routine 1-year check-up examination. Of ~10,000 screens administered, 1318 children failed the screen. The pediatricians referred 346 screen-positive children as “at-risk” children (the screening was thus embedded within a surveillance context, in which clinical judgment contributed to referral decisions); 184 ultimately received further evaluation. Of this group, 32 toddlers received an ASD diagnosis by age 3 years. This general population screening approach also detected 65 toddlers with a language delay or global developmental delay, and 36 children with other delays. Thus, the PPV for detecting toddlers with ASD or developmental delay in this study was estimated to be 0.75. Importantly, all toddlers identified with delays were referred for treatment, and the majority started intervention well before their second birthday.

This research illustrates that autism can sometimes be detected by the first birthday by using a broadband developmental screen in real-world pediatric practices as standard of care. The CSBS DP Infant/Toddler Checklist is not specific for ASD (ie, does not differentiate ASD from other communication disorders), but follow-up evaluation by a developmental specialist (eg, speech language pathologist, psychologist, developmental behavioral pediatrician) can help determine the need for ASD-specific diagnostic assessment as well as identify other developmental delays in need of support and intervention. Use of even broader, more general developmental screening tools, such as the Parents’ Evaluation of Developmental Status (Peds) and the Ages & Stages Questionnaire, to detect ASD are under investigation. Because these tools are commonly used in pediatric practice, it will be important to determine their utility in detecting ASD in the second year of life even though their sensitivity and specificity are not expected to be as high as those of ASD-specific screeners.

Statement 2: The evidence indicates that siblings of children with ASD are at elevated risk for ASD and other developmental disorders and thus should receive intensified surveillance.

Based on data from a US register of 2920 children aged 4 to 18 years in families...
affected by ASD, the frequency of ASD in a later-born sibling has been estimated at 14%. More recently, several independent groups conducting prospective longitudinal research involving infant siblings of children with ASD reported a pooled estimated recurrence risk of 18%. In contrast, a recent population registry-based study from Denmark estimated recurrence risk at closer to the 7% to 8% level reported in older studies. Regardless, rates of ASD in siblings greatly exceed population risk, emphasizing the need for intensified monitoring. Moreover, younger siblings of children with ASD demonstrate significant deficits on indices of social communicative development and cognitive functioning, as well as elevated ASD symptoms relative to younger siblings of typically developing children. Because these children are at elevated risk, they require intensified developmental surveillance. At a minimum, they should receive continuous surveillance for developmental issues and be screened for ASD at 18 and 24 months of age, as recommended by the AAP for all children.2

Statement 3: Children identified through ASD-specific screening should be immediately referred for diagnostic/developmental evaluation and appropriate intervention.

The AAP has recommended that children who screen positive on an ASD-specific screening tool be scheduled for a comprehensive evaluation and referred concurrently to early intervention services as appropriate. Available interventions are mandated in the United States but vary in availability and quality by locality, and they may consist of non–ASD-specific public early intervention programs, such as speech therapy, and early childhood education programs. It is hoped that early screening will lead to improved outcomes as a result of earlier referral and earlier initiation of intervention. However, recent studies suggest that such benefits of early screening frequently go unrealized. In a national study of 17 pediatric practices, implementation of general developmental screening did not always lead to referral of screen-positive children to a medical subspecialist or early intervention programs.12 These investigators noted that some families did not understand the reason for a follow-up evaluation. Additional research is needed to address how to better engage families in the screening process to facilitate rapid follow-up, as well as to identify and characterize other potential barriers to early diagnosis and treatment related to system capacity or provider attitudes and practices.

Statement 4: The long-term stability of ASD diagnosis in children aged ≥24 months is well established. Emerging data suggest that ASD diagnoses in substantial proportions of children diagnosed before age 24 months are also stable, although further research is needed, particularly in the context of early screening.

Ten articles were identified in which children received an initial diagnostic assessment for possible ASD before age 3 years and were then reassessed at least 1 year later. In general, the stability of ASD diagnoses established at ≥24 months (ie, the rate at which an ASD diagnosis was confirmed on reassessment) was very high, ranging from 68.4% to 100% when the initial diagnosis was autistic disorder (median: 92%), and from 40% to 100% when the initial diagnosis was pervasive developmental disorder not otherwise specified (47%–62%). Further research in larger samples is needed, but the evidence to date supports the stability of ASD diagnoses before age 2 years.

Statement 5: Further attention to potential barriers to ASD-specific screening in the health care system is needed.

Pediatricians have noted major barriers to screening, including the following: lack of time and inadequate reimbursement; logistic challenges, such as disruption of work flow, lack of familiarity with tools, and difficulty with scoring; and lack of office-based systems for making referrals and monitoring outcomes.

Lack of Time and Reimbursement

Insufficient time and inadequate reimbursement are often cited by providers as barriers to performing screening.12,13,19,75 Pediatricians have a limited amount of time to complete an increasing number of tasks, including screening for non-ASD disorders, during a well-child visit. Selection of a broad-band screening instrument would meet with greater acceptance if the tool could detect multiple developmental disorders of interest. Busy periods, such as the onset of the winter viral season, often impede the ability of a practice to consistently screen.12 To optimize
screening, some practices have instituted ongoing data collection and monitoring of their efforts. The lack of reimbursement for screening is commonly cited as a barrier. However, in a study, the practices that routinely screened at the 30-month well-child visit reported no difficulties in collecting payment. In another study, pediatric offices received no payment at all for screening but rather received training and data collection support, as well as streamlined follow-up diagnostic assessments for screen-positive children. Thus, reimbursement challenges may be mediated by infrastructure support (eg, staff training/mentoring) to make screening easier to implement, as well as timely access to appropriate follow-up. In this way, pediatricians may be reassured that there is capacity in the health system to support children who screen positive.

**Logistic Challenges**

Other challenges to screening implementation include concerns over a disruption of workflow, unfamiliarity with screening instruments, and difficulty with scoring. Providers often express concerns about how to distribute screening questionnaires without slowing the flow of patients through the office. Nevertheless, in a national sample of 17 pediatric practices, >85% of children presenting at recommended screening ages were screened, with practices dividing responsibilities among staff members and proactively monitoring implementation. Miller et al found that screening at sick visits was necessary to achieve coverage of the age-eligible children, especially for the small number of uninsured children. Training of office staff as well as professional education can remedy a lack of familiarity with the use and scoring of screening tools.

**Lack of Office-Based Systems for Making Referrals and Monitoring Outcomes**

In the sample of 17 pediatric practices, only 61% of children with failed screens were referred, and many practices struggled to track their referrals. Practice-specific referral rates varied widely, from 27% to 100%. It is important that each pediatric practice establish a specific implementation system to expedite referrals, communicate with specialists and early intervention programs, and track follow-through and outcomes. Clearly, early screening initiatives are only as effective as access to resources for follow-up evaluation and early intervention. Communication back to the referring office relative to the outcomes of follow-up actions is critical if only to reassure all concerned of the value of such referrals. For children with ASDs, early intervention services have become more accessible through Part C of the 2009 Individuals With Disabilities Education Act but access may not be equal in all parts of the country, and the quality of services can vary widely and affect outcomes. Indeed, although the National Research Council has recommended entry into an intervention program as

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**TABLE 2: Studies of Diagnostic Stability That Include Children Initially Assessed With ASD Before 2 Years of Age**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample Description</th>
<th>Mean Age, Age Range at T1, mo</th>
<th>Mean Age, Age Range at T2, mo</th>
<th>Diagnosis at T1</th>
<th>N</th>
<th>Diagnosis at T2</th>
<th>N</th>
<th>% Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Daalen et al.65</td>
<td>Population-based sample</td>
<td>23 (34–64)</td>
<td>45 (34–64)</td>
<td>Autism</td>
<td>40</td>
<td>ASD</td>
<td>38</td>
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<tr>
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<td>PDD-NOS</td>
<td>13</td>
<td>ASD</td>
<td>8</td>
<td>61.5</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Non-ASD</td>
<td>76</td>
<td>ASD</td>
<td>39</td>
<td>84.8</td>
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<td></td>
<td>46.7</td>
</tr>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Non-ASD</td>
<td>16</td>
<td>ASD</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Kleinman et al.66</td>
<td>Mixed level 1 (physician office) and level 2 (early intervention, sibling) sample</td>
<td>26.7 (16–35)</td>
<td>52.9 (41–82)</td>
<td>Autism</td>
<td>46</td>
<td>ASD</td>
<td>39</td>
<td>84.8</td>
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<td>Non-ASD</td>
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<td></td>
<td>PDD-NOS</td>
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<td>ASD</td>
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<td>46.7</td>
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<td>16</td>
<td>ASD</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Chawarska et al.67</td>
<td>Referrals to specialty clinic with suspected ASD</td>
<td>21.6 (14–25)</td>
<td>35.9</td>
<td>Autism</td>
<td>21</td>
<td>ASD</td>
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<td>100</td>
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<td>ASD</td>
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<td>ASD</td>
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<td>Non-ASD</td>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>Gillberg et al.68</td>
<td>Referred sample</td>
<td>23.0 (38–35)</td>
<td>57.7 (38–140)</td>
<td>Autism</td>
<td>21</td>
<td>ASD</td>
<td>21</td>
<td>100</td>
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<td></td>
<td>Non-ASD</td>
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<td>Non-ASD</td>
<td>2</td>
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</tr>
</tbody>
</table>

PDD-NOS, pervasive developmental disorder not otherwise specified; T1, initial diagnostic assessment of ASD; T2, reassessment of ASD diagnosis, at least 1 year later in these studies.

* One child, diagnosed at 8 months, was followed up only to age 26 months and thus was excluded from the table.
soon as an ASD is suspected, local factors, including funding, can affect access to services (wait-listing) or make certain early intervention programs unavailable to some children.75,77

Thus, barriers to screening can be overcome with specific strategies such as training and involvement of clinic staff and use of reminder systems, even in busy practices. However, better-coordinated efforts are needed to ensure access to specialized assessment and intervention for children at risk identified through the screening process, as well as communication back to community pediatricians. In addition, further consideration is needed regarding how physician beliefs related to ASD screening (eg, potential risks and benefits to children and families, system capacity to provide timely specialized assessment and treatment services) may influence practice behavior. Such beliefs can contribute to incongruence between physician knowledge and actions when managing ASD-related concerns and thus may also need to be addressed to facilitate uptake of ASD screening into community pediatric practices.

Statement 6: Methodologically rigorous research in ASD-specific screening should be a high priority.

Future research in ASD screening would be aided by attention to the following methodologic issues:

- use of large, representative high- and low-risk samples, to strengthen the generalizability of findings
- use of meaningful end points (eg, validated diagnostic measures to assess for ASD and other developmental disorders, as well as an increased focus on outcomes of greatest relevance to families and to the health system, such as age of diagnosis, age of entry into intervention, and long-term developmental gains resulting from screening)
- inclusion of systematic surveillance methods, as well as follow-up tracking of screen-negative cases, to improve estimates of sensitivity, specificity, and NPV
- evaluation of different scoring approaches (categorical versus continuous) and, potentially, different age-specific scoring algorithms for specific ages, to further optimize screening strategies that might be implemented longitudinally
- reporting of detailed characterization of study participants, including social factors, cognitive level, and medical history, to improve comparisons across studies and to better understand what factors might influence the accuracy of screening for individual children
- evaluation of potential differences between screen-positive children who are seen for a diagnostic assessment and those who do not complete follow-up (which is often in the range of 25%-40% and in some studies exceeds 50%17) to further evaluate potential barriers and facilitators, and provide information essential to evaluating the generalizability of study findings
- inclusion of underrepresented minority and historically underserved groups, to help ensure representative samples and the development of culturally appropriate adaptations of screening tools for such populations
- Lower socioeconomic status and non-white ethnicity (particularly Hispanic) have been associated with delayed age of diagnosis, potentially due to disparities in access to health services.79-81 However, there is evidence that application of standardized screening can help reduce such disparities and ensure timely diagnosis of children across a diversity of backgrounds.82

Statement 7: Additional priorities for future research include studies that:

- Examine how broadband and ASD-specific screening tools can be used in a complementary fashion to maximize both sensitivity and specificity of early screening, perhaps in the context of multistage screening, in which a wide net is cast initially and false-positives are winnowed out in successive assessments
- Evaluate screening strategies by using randomized experimental designs
- Consider additional outcome metrics for screening: potential financial savings to society, unintended effects (eg, family stress)
- Examine whether computer technology can improve screening accuracy
- Examine the effectiveness of repeated screening for ASD
- Evaluate how belief systems affect screening uptake and outcomes
- Examine potential screening strategies that include measurement of biomarkers

Examine how broadband and ASD-specific screening tools can be used in a complementary fashion to maximize both sensitivity and specificity of early screening

Can a general developmental tool be relied on to identify children who should be evaluated for ASD? If a broadband screening tool is indeed dependable, as suggested by Wetherby et al and Pierce et al, then a multistage screening strategy focusing on routine surveillance and use of a broadband screening tool, followed by an ASD-specific instrument for children who test positive on the initial screen, can help reduce the need for extra testing and the additional clinic time and effort. A notable value of this approach is the limiting of referrals for specialized assessment, without sacrificing case detection rate. If broadband screening cannot reliably detect ASD, then a screening strategy mandating ASD-specific screening for all children, alongside broadband screening to
detect other potential developmental concerns, would be more appropriate. The first approach was described by Filipek et al., the second approach is currently recommended by the AAP. Unfortunately, the effectiveness (and cost-effectiveness) of the 2 strategies has not been well studied. Data from a single pediatric practice showed that ~75% of children with positive results on the ASD-specific screening tool (the M-CHAT) were missed by the PEDS, a standardized general developmental screening questionnaire. It should be noted, however, that this study did not report actual ASD diagnoses but rather simply examined agreement in screening classification by the 2 tools. However, Wiggins et al. reported that the M-CHAT had higher sensitivity for ASD than the high-risk threshold for any area of general concern covered by the PEDS. Although the PEDS detected many children with other developmental concerns, sensitivity for ASD could not be achieved without lowering the screen-positive threshold to a level that would identify a substantial proportion of the general population (25%).

A study assessing the efficacy of such a multistage screening program would also assess/validate the effectiveness of: (1) training of health care professionals in recognizing early ASD signs and using a specific screening tool; (2) a specific referral protocol; and (3) feedback to the referring offices.

**Evaluate screening strategies by using randomized designs**

The evaluation of ASD screening is often limited to measurement of classification accuracy (estimates of sensitivity and specificity, and/or PPV and NPV) without sufficient attention to whether the ultimate goals of screening are achieved (eg, earlier diagnosis and access to treatment) or the possibility that, as with other interventions, screening might be associated with positive or adverse outcomes. Moreover, alternate approaches to screening (eg, broadband versus ASD-specific, level 1 versus level 2, or some combination) have never been directly compared. We would argue that screening is a public health intervention; that is, a comprehensive early detection strategy should not be solely based on the selection of a particular screening instrument but rather must include other changes to the overall system of care, such as enhanced training for health professionals and expanded capacity for early diagnosis and intervention by specialized teams. Thus, the outcomes of screening may not simply be related to the measurement properties of a tool but also to the successful implementation of other aspects to the overall care pathway for children with suspected ASD. As such, researchers should explicitly define their screening strategy (ie, the screening instrument plus collateral changes to the system of care) as well as the outcomes of interest, and evaluate the effectiveness of these strategies in real-life community settings by using randomized designs. Randomized designs have become the standard in other ASD intervention research (eg, Dawson et al.) and in other public health screening interventions. However, observational studies will also need to be continued because of the well-known challenges to constructing randomized designs that reflect real-world clinical practice. Table 3 presents a comparison of the relative strengths and limitations of randomized and observational designs with respect to screening research.

**Consider additional outcome metrics for ASD screening**

In the near term, evaluation of ASD screening strategies will likely continue to focus on process measures, such as rates of targeted children screened, referred, and diagnosed. However, ultimately, the idea of evaluating any screening program is to gauge its impact on distal health outcomes. For potentially fatal conditions, mortality is the ultimate distal outcome. For nonfatal conditions, developing approaches to measure impact on morbidity, disability, or impairment can be a challenge. With respect to ASD, although increases in referral and early diagnosis rates can serve as meaningful initial outcomes, screening should ultimately demonstrate a reduction in population impairment and the effect of that impairment on society. Studies of ASD screening will thus eventually need to consider the impact of this screening on long-term changes in symptoms and functional status. Determining how to best measure these distal health outcomes is one of the challenges of ASD research. In addition to distal health outcomes, assessing the cost impact of screening is often critical to its eventual broad dissemination.

Because ASDs impose a sizable financial burden, not only in direct medical expenditures but also in indirect costs (eg, special education services, lost productivity by family caregivers), a more in-depth understanding of these costs is needed to adequately compare different screening strategies and to identify potential cost savings to society for those that are effective. Finally, indirect costs associated with screening include an emotional dimension. Evaluations of screening effectiveness, in addition to including distal outcomes, need to consider these “costs” in addition to the financial costs associated with false-positive findings.

**Examine whether computer technology can improve screening accuracy**

The use of computer technology holds promise for improving screening accuracy. Parents can complete a screening questionnaire online and have access to video exemplars for more accurate reporting. The capability to upload videos can expedite specialist evaluations. A recent preliminary report suggested that the M-CHAT (including follow-up questions) could be feasibly completed...
TABLE 3  Designs for One-Step Evaluation Studies of ASD Screening Programs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Randomized Trial</th>
<th>Prospective Observational (Cohort)</th>
<th>Retrospective Observational (Case-Control)</th>
</tr>
</thead>
</table>
| Comparison groups               | Young children randomly assigned to different screening control groups            | Naturally occurring “screened” and “unscreened” groups in the community.  
Perhaps identified via different:  
- Health care providers  
- Geographic area                                                                 | Children with ASD having optimal outcomes (‘case subjects’)                                                                 |
|                                 | Hold the value and potential cost-benefit of repeat periodic screening for ASD,   | Temporality assured                                                                 | Age-matched children with ASD having suboptimal outcome representative of the population giving rise to the case subjects (“control subjects”) |
|                                 | as well as identify potential factors that can improve the efficiency and efficacy of specific approaches. |                                                                                                     |                                                                                                              |
| Strengths                       | • Random assignment to control for confounding by indication                     | • Potential for selection bias  
• Need to control for confounding by indication                                                                 | • Less cost                                                                                                     |
| Weaknesses                      | • Temporality assured                                                            |                                                                                                     | • Less time to complete                                                                                       |
|                                 | • Ethnically feasible?                                                           |                                                                                                     | • Potential for selection bias                                                                                   |
|                                 | • Large sample needed                                                            |                                                                                                     | • Need to control for confounding by indication (more challenging in retrospective designs)                        |
|                                 | • Substantial follow-up needed                                                   | • Large sample needed                                                                 | • Need to be able to accurately identify true screening encounter                                               |
|                                 | • Expensive                                                                     | • Substantial follow-up needed                                                                      |                                                                                                              |
|                                 | • Can raise generalizability issues                                              | • Expensive                                                                                         |                                                                                                              |

electronically, with fewer false-positive findings and good to excellent parent satisfaction. Further studies should be conducted to determine feasibility and accuracy in a larger sample of community practices.

Examine the effectiveness of repeat screening

ASD is heterogeneous in the presentation and time course of core deficits. It would therefore be important for a screening program to administer ASD-specific screening tools periodically at differing ages to detect children at risk who, for a number of reasons, may have been missed on an earlier occasion. Formal research can better define the value and potential cost-benefit of repeat periodic screening for ASD, as well as identify potential factors that can improve the efficiency and efficacy of specific approaches.

Examine how belief systems impact screening uptake and outcomes

Belief systems of both providers and parents may influence screening outcomes. The uptake, or implementation, of clinical recommendations for screening can be diminished if pediatricians and other health care professionals have misconceptions about ASDs (eg, a belief that children can “outgrow” ASD) or are unfamiliar with pertinent interventions. For example, cultural beliefs may influence the significance attached to differences in early social behavior or the reporting of such differences to health care providers. A child who does not make eye contact with adults or point may not be worrisome if such behaviors are considered disrespectful. Families may also be less likely to participate in follow-up assessments if they are not confident in the referring clinician’s skills and expertise. Studies examining the impact of belief systems would improve both provider and parental understanding of diverse perspectives and inform targeted supports and interventions.

Examine potential screening strategies that include measurement of biomarkers

Given that neuroanatomical abnormalities in ASD have been shown to occur consistently across development and biological mechanisms (including genetic) may provide a measurable “signature” even before symptom expression, there is hope that specific biomarkers may eventually be identified that could contribute to early diagnosis. Indeed, recent studies from developmental neuroscience and molecular biology have shown promise in identifying specific markers that can distinguish children with ASD from other high-risk and low-risk peers, even during infancy. However, most of these studies focused on group differences rather than predicting outcomes at an individual level (needed to determine sensitivity and specificity) and/or focused on distinguishing children with known diagnostic status rather than predicting diagnosis in children whose status is not yet known. This small, yet growing body of research includes studies with well-defined high-risk cohorts (notably, younger siblings) as well as general population cohorts that begin screening, tracking, and studying the biology of ASDs at 12 months. What both approaches have in common is that studies are conducted within highly controlled research contexts. Thus, although biomarker-based research holds considerable promise, the clinical utility of incorporating such markers into community-based early detection strategies remains to be demonstrated. At present, no specific biomarkers are recommended for ASD screening.

Several examples of studies using brain-based measures identifying candidate biomarkers are summarized here to illustrate the potential contribution of this emerging field of research. Using the general population–based screening
approach described by Pierce et al\textsuperscript{17} to assemble a cohort of toddlers with ASD, Dinstein et al\textsuperscript{100} recorded functional MRI activity from 63 naturally sleeping toddlers with ASD, language disorder (i.e., standardized score at least 1 SD below the mean), or typical development. Relative to the other groups, toddlers with an ASD exhibited significantly weaker interhemispheric correlations in the inferior frontal gyrus and superior temporal gyrus, 2 areas central to language production and comprehension. Levels of interhemispheric coordination enabled accurate identification of toddlers diagnosed with ASD, with high sensitivity (72\%) and specificity (84\%). As another example, Elsabbagh et al\textsuperscript{100}, using the modified multiscale entropy computed on the basis of a resting state EEG, showed that infants at high risk for autism exhibit a different developmental trajectory than typically developing control subjects and that these differences are most evident between 9 and 12 months of age. Infants were classified with \( > 80\% \) accuracy into control groups and high-risk groups at age 9 months. More recently, Elsabbagh et al\textsuperscript{101} reported that evoked responses to dynamic gaze at 8 months in high-risk infants were predictive of an ASD diagnosis at 36 months. In addition, Wolff et al\textsuperscript{102} described a pattern of blunted white matter trajectories based on serial brain MRI (using diffusion tensor imaging) between 6 and 24 months of age in high-risk infants with ASD symptoms at 24 months; differences in these imaging indices were detectable by 12 months. Blood-based biomarker studies of ASD have yet to reveal themselves as viable screening approaches, mainly due to the fact that discovered genetic mutations occur at relatively low rates in the ASD population. Until recently, it was reported that de novo genetic copy number variations are present only in 3\% to 10\% of the ASD population.\textsuperscript{102} However, recent data using exome and whole genome sequencing methods suggest the yield of such testing for clinically informative variants may be much higher.\textsuperscript{103,104} Moreover, although the contribution of specific biomarkers to risk prediction may be modest, combined results from a panel of predisposing biomarkers can produce information about an individual’s probability of developing ASD.\textsuperscript{105} Consideration of several biomarkers at once is consistent with the multitude of genetic and epigenetic factors (and potentially other biological factors [e.g., immune, indices of atypical brain growth/connectivity]) that likely play a role in vulnerability to ASD in many children.\textsuperscript{106} The sensitivity and specificity for the risk score could be used to indicate the predictive performance of the biomarker combination. The approach of combining multiple alleles/biomarkers to predict risk status has also been undertaken with other disorders of complex etiology, including breast and prostate cancer, coronary heart disease, and type 2 diabetes.\textsuperscript{107\textendash}110 Additional avenues of biomarker identification are actively being explored. There is growing interest in possible biologic measures that could be used before (or immediately after) birth to assess risk for ASD. Such markers include metabolites, amino acids, hormones, and immune factors, either individually or in combination with the goal of creating biomarker arrays to assess risk as well as severity, thus providing information that could lead to specific therapeutic interventions.\textsuperscript{111,112}

Thus, future biomarker research should consider how combinations of biomarkers could be used in prediction of ASD risk, and how incorporation of biomarker profiles together with behavioral markers might improve on screening methods based on the markers alone. Although some methods present logistical difficulties (e.g., cost, invasiveness), others, such as EEGs, are more readily available in pediatric settings (e.g., auditory brainstem response in newborns), noninvasive, and relatively inexpensive. With further laboratory and community-based research, such methods might ultimately exhibit the potential to improve the sensitivity and specificity of early detection, as well as enable detection earlier in development.

ACKNOWLEDGMENTS

The conference chairs and working groups acknowledge the preconference contribution of Grace Baranek, PhD, OTR/L, FAOTA, who was unable to attend the conference. We also acknowledge the efforts of Katherine F. Murray, BSN, RN, Massachusetts General Hospital for Children, in coordinating the forum and subsequent conference report process, and Sifor Ng in the conference report process. The meeting and consensus report were sponsored by the Autism Forum. An important goal of the forum is to identify early indicators of ASDs that may lead to effective health care services. Autism Forum programs are developed under the guidance of its parent organization, the Northwest Autism Foundation. For this project, the Autism Research Institute provided financial support.

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ABBREVIATIONS
AAP—American Academy of Pediatrics
ASD—autism spectrum disorder
CHAT—Checklist for Autism in Toddlers
CSBS DP—Communication and Symbolic Behavior Scales Developmental Profile
ESAT—Early Screening of Autistic Traits questionnaire
FYI—First Year Inventory
M-CHAT—Modified Checklist for Autism in Toddlers
NPV—negative predictive value
Peds—Parents’ Evaluation of Developmental Status
PPV—positive predictive value
Q-CHAT—Quantitative Checklist for Autism in Toddlers
STAT—Screening Tool for Autism in Two-Year-Olds

Drs Zwaigenbaum and Bauman initiated a literature review, co-chaired the meeting that generated the consensus recommendations outlined in this article, and drafted the initial manuscript; Drs Fein and Pierce co-chaired the working group that conducted the detailed literature review, generated initial recommendations that were discussed at the consensus meeting, and provided critical input to subsequent drafts of the manuscript; Drs Buie, Davis, Newshaffer, Robins, and Wetherby were members of the working group that reviewed selected publications, contributed to initial recommendations that were reviewed at the consensus meeting, and critically reviewed the manuscript; and Drs Choureir, Kasari, Stone, Yirmiya, Estes, Hansen, McPartland, Matowicz, Carter, Granpeesheh, Mailloux, Smith Roley, and Wagner contributed to the consensus meeting that formed the basis for the manuscript and critically reviewed the manuscript. All authors approved the final manuscript as submitted.


doi:10.1542/peds.2014-3667D

Accepted for publication Aug 3, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2015 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Zwaigenbaum was the site Principal Investigator of a study sponsored by SynapDx (he received operating funds but no honoraria). Drs Fein and Robins are co-owners of M-CHAT, LLC, which licenses use of the Modified Checklist for Autism in Toddlers in electronic products. Dr Stone is the author of the Screening Tool for Autism in Two-Year-Olds and receives a share of royalties from sales of this instrument. The authors received an honorarium as well as travel expenses from Autism Forum for contributing to the expert panels.

FUNDING: Sponsored by the Autism Forum under the guidance of the Northwest Autism Foundation and with the support of the Autism Research Institute.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research
Pediatrics 2015;136;S41
DOI: 10.1542/peds.2014-3667D

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Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research

Pediatrics 2015;136;S41
DOI: 10.1542/peds.2014-3667D

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