Early Identification and Interventions for Autism Spectrum Disorder: Executive Summary

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Early Identification and Interventions for Autism Spectrum Disorder: Executive Summary

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by impaired social communication skills and isolated areas of interest. The current prevalence of these disorders is estimated to be 1 in 68, and recent estimates of the risk of recurrence in families with at least 1 child diagnosed with ASD are 10% to 19%. Advances have been made in identifying genetic variants that can account for biological vulnerability to ASD, although recent studies examining patterns of heredity implicate environmental factors and potential gene-by-environment interactions. Although the exact etiology remains unknown in most families, some researchers suggest that the pathogenesis of the disorder begins during prenatal life. It is likely that ASD is heterogeneous in its etiology as well as in its clinical presentation.

The American Academy of Pediatrics has recommended screening for ASDs at 18 and 24 months of age, but recent research suggests that atypical behaviors may be detectable in some children at even younger ages. However, we are still learning how the timing and developmental course of early ASD symptoms vary across children and how best to detect such symptoms across the continuum of children seen in community practice. In addition, reports that early intervention can improve developmental and behavioral outcomes in infants and toddlers have lent urgency to identifying children across the autism spectrum at an earlier age. Advances in genetic, neuroimaging, and other neurobiological research have also raised the potential of biomarker screening. Given the progress in these areas, a review of the current state of the science on early identification, screening, and intervention of ASD was warranted.

These issues were the focus of an international, multidisciplinary panel of clinical practitioners and researchers with expertise in ASD and developmental disabilities. A meeting of the panel was convened in Marina del Rey, California in October, 2010, to develop best practice standards for early identification, screening, and early intervention for ASD in very young children and to identify priorities for future research.

To complement previously published reports, our literature review on early identification and screening for ASD focused on children aged ≤24 months, whereas our review of intervention studies focused on children aged ≤36 months. The panel reached consensus in 3 areas:

- What are the earliest signs and symptoms of ASD in children aged ≤24 months that can be used for early identification?
- How can we optimize developmental course and outcomes through ASD screening programs for children aged ≤24 months?
- What interventions have shown efficacy in children with ASD aged <36 months?

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ABBREVIATIONS
ASD—autism spectrum disorder
DSM—Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
M-CHAT—Modified Checklist for Autism in Toddlers

(Continued on last page)
METHODS

Before the conference, participants were assigned to 1 of 3 working groups, each comprising 7 to 10 experts and focusing on the early identification of ASD, early screening, and early interventions and outcomes. The Early Identification group comprised Drs Stone, Yirmiya (co-chairs), Chawarska, Estes, Hansen, McPartland, and Natowicz. The Early Screening group comprised Drs Fein, Pierce (co-chairs), Baranek, Davis, Newschaffer, Robins, and Wetherby. The Early Intervention and Treatment Outcome group comprised Drs Choueiri, Kasari (co-chairs), Buie, Carter, Charman, Granpeesheh, Mailloux, Mesibov, Smith, Roley, and Wagner.

To inform the work of each group, literature searches were conducted on Medline to identify relevant articles for each topic (the specific search terms are provided in the other articles in this supplement to *Pediatrics*16–19). Search results were complemented by additional publications identified by working group members. Although the search strategy was comprehensive, selection of articles was not systematic, which is an important limitation. A scoping approach, with some discretion by consensus of the multidisciplinary expert working group, was used instead to select articles of highest relevance and methodologic quality. Articles were assigned to working group members for review.

During the conference, each group presented a synthesis of the current literature and 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. A total of 18 to 21 participants voted on 28 statements, and 16 statements received solely agree or strongly agree votes. The number of statements was condensed to 25 during the writing process. The first statement pertains to the literature review as a whole, with subsequent statements specific to each of the 3 sections. Some of the statements summarize the state of the literature, whereas others are in the form of recommendations for research needed to deal with outstanding questions or aimed at addressing important clinical practice issues.

More recent peer-reviewed research was subsequently incorporated to ensure that the final article reflected the most recent literature. The search for each topic (ie, early identification, screening, intervention) was updated by using the same strategy to add articles published to December 31, 2013. Evidence tables and text references were updated, and the working group reviewed and approved the final wording of the summary and recommendations. We recognize that transition to recently published criteria for ASD as delineated by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM–5),1 may recast diagnostic boundaries, at least to some degree.19,20 At this point, it is probably too soon to tell how the revised diagnostic criteria will affect the identification and management of the ASDs, but it is likely that key principles regarding best practice and the “state of the science” from previous research will apply to DSM–5–defined ASD.

RESULTS

Consensus statements are summarized in Tables 1, 2, and 3 and are discussed in detail in the other articles of this supplement to *Pediatrics*.16–18 These other articles include tables summarizing the original research articles that support the recommendations.

DISCUSSION

Early diagnosis and intervention can have a significant positive impact on the developmental outcomes of children with ASD21,22 and can also improve parental well-being by addressing concerns and reducing the stress associated with untreated ASD and co-morbid behavioral challenges.23 Moreover, the human brain undergoes a profound period of establishing and refining connections between neurons during the first years of life. For example, synaptic density in the human prefrontal cortex (ie, the brain region centrally involved in higher order social behavior) peaks between 1 and 2 years of age.24 Synaptic density in language areas, such as Wernicke’s and Broca’s areas, peaks shortly thereafter by age 3 years. A period of refinement occurs after peaks in synapse number, during which effective connections are strengthened and weak ones die away. This important developmental step, namely the construction of specific neural circuits and the pruning of excess (unused) synapses, is believed to depend largely on input from the environment.25 Thus, early identification and intervention either before or while brain connections are being established may enable optimal prognosis.

The present review highlights the constellation of ASD-related symptoms emerging by the second year of life, the potential utility of clinical screening to facilitate early identification, and the growing number of empirically supported interventions for very young children. Considerable progress has been made over the past decade in delineating the ASD phenotype during the first 2 years of life, providing a solid foundation for early diagnosis. Moreover, there have been parallel advances in intervention research, ensuring that early diagnosis can lead to substantially improved outcomes. However, much work remains to be done to ensure that children across the ASD spectrum can benefit from clinical and therapeutic advances and that promising model programs can retain their effectiveness when implemented.
Evidence indicates substantial heterogeneity in the presentation and natural history of clinical features associated with ASDs. This heterogeneity has ramifications for the interpretation of research literature as well as for clinical practice.

There is evidence that reduced levels of social attention and social communication, as well as increased repetitive behavior with objects, are early markers of ASD between 12 and 24 mo of age. Additional potential markers include abnormal body movements and temperament dysregulation.

Reliable behavioral markers for ASD in children aged <12 mo have not yet been consistently identified.

Developmental trajectories may also serve as risk indicators of ASD.

Caution should be exercised in drawing conclusions about early risk markers of ASD from studies that do not include individual-level outcome data.

Caution should be exercised in generalizing findings from studies of HR infants.

Research about early markers of ASD should include diverse HR and LR samples.

Future research should aim to identify: (1) early markers that can be measured in routine clinical practice; (2) early biological processes; and (3) combined approaches.

Table 1: Consensus Statements on Early Identification of ASD

<table>
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<tr>
<th>No.</th>
<th>Statement</th>
<th>Key Messages</th>
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<tbody>
<tr>
<td>1.</td>
<td>Evidence indicates substantial heterogeneity in the presentation and natural history of clinical features associated with ASDs. This heterogeneity has ramifications for the interpretation of research literature as well as for clinical practice.</td>
<td>Given the marked clinical and etiologic diversity among individuals with ASD, it is not surprising that early manifestations and developmental course vary as well.</td>
</tr>
<tr>
<td>2.</td>
<td>There is evidence that reduced levels of social attention and social communication, as well as increased repetitive behavior with objects, are early markers of ASD between 12 and 24 mo of age. Additional potential markers include abnormal body movements and temperament dysregulation.</td>
<td>Methodologic differences (eg, prospective versus retrospective designs, measurement strategies) may affect comparability across published studies.</td>
</tr>
<tr>
<td>3.</td>
<td>Reliable behavioral markers for ASD in children aged &lt;12 mo have not yet been consistently identified.</td>
<td>Evidence supporting this statement is summarized in Table 1 of the article on early identification by Zwaigenbaum et al.</td>
</tr>
<tr>
<td>4.</td>
<td>Developmental trajectories may also serve as risk indicators of ASD.</td>
<td>Some studies report group differences between HR and LR infants.</td>
</tr>
<tr>
<td>5.</td>
<td>Caution should be exercised in drawing conclusions about early risk markers of ASD from studies that do not include individual-level outcome data.</td>
<td>If diagnostic outcomes are not reported at an individual level (ie, if it is not known which HR infants were later diagnosed), group differences are not necessarily related to ASD.</td>
</tr>
<tr>
<td>6.</td>
<td>Caution should be exercised in generalizing findings from studies of HR infants.</td>
<td>Findings from HR samples might not generalize to the general population due to differences in research design (eg, ascertainment) and biology.</td>
</tr>
<tr>
<td>7.</td>
<td>Research about early markers of ASD should include diverse HR and LR samples.</td>
<td>Although most current prospective studies involve younger siblings of children with ASD, studies of other HR infants (eg, premature infants) might also inform the field.</td>
</tr>
<tr>
<td>8.</td>
<td>Future research should aim to identify: (1) early markers that can be measured in routine clinical practice; (2) early biological processes; and (3) combined approaches.</td>
<td>In addition, it is essential that findings from HR samples be validated in LR (ie, community) samples.</td>
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HR, high-risk; LR, low-risk.

There is now robust evidence across a diversity of study designs that behavioral signs of ASD can be detected in the second year of life. Highly replicated findings point to impairments in social attention (eg, reduced response to name) and social communication (eg, reduced joint attention behaviors), as well as atypical object use (eg, repetitive actions such as tapping and spinning) and abnormal visual attention, emerging by 12 to 18 months of age in children subsequently diagnosed with ASD. Other potential early markers which have been less extensively studied but that may also contribute to identifying at-risk toddlers include unusual body movements, atypical emotional regulation, and reduced motor control. Although research to date has not yet identified clear behavioral markers of ASD in infants aged <12 months, evidence is growing that developmental trajectories (ie, change over time) in early social orienting and language and cognitive skills beginning as early as 6 months can be predictive of ASD. Thus, longitudinal studies of at-risk infants (eg, those with an older sibling with ASD), as well as those detected early in the general population, may be particularly informative. Such studies have the added advantage of including the potential to evaluate both biological and behavioral markers, the combination of which may further aid in early identification. Future longitudinal studies...
TABLE 2 Consensus Statements on Early Screening of ASD

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<th>No.</th>
<th>Statement</th>
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<tr>
<td>1</td>
<td>Evidence supports the usefulness of ASD-specific screening at age 18 and 24 mo</td>
<td>• Evidence supporting this statement is summarized in Table 1 of the article by Zwaigenbaum et al.17 on early screening.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ASD screening before age 24 mo may be associated with higher false-positive rates than screening at age 12-24 mo.</td>
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<td></td>
<td></td>
<td>• Broadband screening in children aged &lt;24 mo can also assist in early detection of ASD.</td>
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<tr>
<td>2</td>
<td>Siblings of children with ASD are at elevated risk for ASD and other developmental disorders and thus should receive intensified surveillance</td>
<td>• With risk of ASD as high as 11%,6 and of milder symptoms and/or developmental delays at ≥15%,16 siblings of children with ASD are high-risk group.</td>
</tr>
<tr>
<td>3</td>
<td>Children identified through ASD-specific screening should be immediately referred for diagnostic evaluation and appropriate intervention</td>
<td>• The potential benefits of a positive screen will be realized only if followed by consistent referral and timely access to specialized assessment and intervention services.</td>
</tr>
<tr>
<td>4</td>
<td>The long-term stability of ASD diagnosis in children &lt;24 mo of age is well established</td>
<td>• Evidence supporting this statement is summarized in Table 2 of the article by Zwaigenbaum et al.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Emerging data suggest that ASD diagnoses before 24 mo of age are stable, although further research is needed, particularly involving children identified via early screening.</td>
</tr>
<tr>
<td>5</td>
<td>Barriers to ASD-specific screening in the health care system need to be identified and removed to facilitate rapid diagnosis and early intervention</td>
<td>• Reported barriers include insufficient time and/or reimbursement and other logistic challenges (eg, disruption of work flow, lack of office-based systems for making referrals).</td>
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<td></td>
<td></td>
<td>• Health care provider beliefs regarding the potential benefits and risks can also influence participation in screening programs.</td>
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<td></td>
<td></td>
<td>• Recommendations for future research include applying current screens in large diverse community samples to maximize generalizability, assessing clinically relevant outcomes (eg, age of diagnosis), follow-up of both screen-positive and screen-negative children, and more detailed sample characterization to better understand what factors may influence accuracy of screening.</td>
</tr>
<tr>
<td>6</td>
<td>Methodologically rigorous research in ASD-specific screening should be a high priority</td>
<td>• Considerations for future research also include incorporating combined broadband and ASD-specific screening, randomized designs, repeat screening, use of technology, biomarkers, and examining factors that may influence screening uptake and outcomes.</td>
</tr>
<tr>
<td>7</td>
<td>There are several additional priorities for future ASD screening research</td>
<td>• Evidence supporting this statement is summarized in Table 1 of the article by Zwaigenbaum et al.17 on early screening.</td>
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</table>

Our review of published research evaluating ASD screening tools (Table 3) supports current American Academy of Pediatrics’ recommendations of ASD screening in the second year.28 These tools include both those targeted at ASD-specific behaviors (eg, the Modified Checklist for Autism in Toddlers [M-CHAT]) as well as measures targeting a broader range of delays (eg, the Communication and Symbolic Behavior Scales Infant/Toddler Checklist). Data from large community-based samples suggest that ASD screening by using the M-CHAT (specifically, its current version [revised, with follow-up])29 or the Infant/Toddler Checklist30 can identify children with ASD earlier and with greater sensitivity compared with open-ended questions regarding parental concerns and thus offers advantages over general developmental surveillance. There is some support for the potential utility of ASD screening before 18 months of age. For example, a positive screen on the Infant/Toddler Checklist at 12 months (as part of the First Year Check-Up model)31 was associated with a positive predictive value of 0.75 for ASD or other developmental delays but with considerable loss to follow-up (based on the ~1 in 7 screen-positive children who were ultimately seen for diagnostic assessment).

Other ASD screens targeting this younger age group have shown some promise. For example, the Early Screening of Autistic Traits questionnaire can identify ASD as early as 14 months but with a low case detection rate and presumably low sensitivity,32 and the First Year Inventory may detect some children with ASD at 12 months but also with only modest sensitivity.33 Further research on ASD screening for this age group is needed. It is also recognized that younger siblings of children with ASD are at substantial risk for the disorder (with estimated recurrence as high as 18.7%),4 as well as other developmental challenges,34 and thus warrant additional monitoring. It is also important to take into consideration what populations have been investigated for currently available screens (Table 3) and the degree to which this analysis may influence generalizability to other contexts. For example, community pediatric practices can be a highly informative setting to assess the screening properties of particular measures in children without specific risk factors but may not fully reflect the diversity (eg, socioeconomic, ethnic) of a true population sample. Screening must be linked to timely referral for additional evaluation.
TABLE 3  Consensus Statements on Early Intervention and Outcomes of ASD

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<th>No.</th>
<th>Statement</th>
<th>Key Messages</th>
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<tbody>
<tr>
<td>1.</td>
<td>Current best practice interventions for children aged &lt;3 y with suspected or confirmed ASD should include a combination of developmental and behavioral approaches and begin as early as possible</td>
<td>• Evidence supporting this statement is summarized in Table 1 of the article by Zwaigenbaum et al18 on early intervention.</td>
</tr>
<tr>
<td>2.</td>
<td>Current best practice interventions for children aged &lt;3 y with suspected or confirmed ASD should have active involvement of families and/or caregivers</td>
<td>• Behavioral interventions (i.e., based on applied behavioral analysis) use evidence-based principles to systematically change behavior.</td>
</tr>
<tr>
<td>3.</td>
<td>Interventions should enhance developmental progress and improve functioning related to both the core and associated features of ASD, including social communication, emotional/behavioral regulation, and adaptive behaviors</td>
<td>• Developmental models of intervention use developmental theory to design approaches to target ASD-related deficits.</td>
</tr>
<tr>
<td>4.</td>
<td>Intervention services should consider sociocultural beliefs of the family and family dynamics and supports, as well as economic capability, in terms of both the delivery and assessment of factors that moderate outcomes</td>
<td>• In practice, many empirically supported interventions for children aged &lt;3 y blend features of both approaches.</td>
</tr>
<tr>
<td>5.</td>
<td>Intervention research should include socially and culturally diverse populations and evaluate familial factors that may affect participation, acceptability, and outcomes of therapeutic approaches as well as willingness to participate</td>
<td>• Active family involvement is consistent with best practices of interventions for children aged &lt;3 y.</td>
</tr>
<tr>
<td>6.</td>
<td>Future research should prioritize well-defined sampling strategies, rigorous investigative design, fidelity of implementation, and meaningful outcome measurements</td>
<td>• Parents and caregivers can capitalize on teachable moments as they occur, provide learning opportunities during daily routines, and facilitate the generalization of learned skills across environments.</td>
</tr>
<tr>
<td>7.</td>
<td>Research is needed to sort the specific active components of effective interventions</td>
<td>• Targeted early interventions have been associated with improvements in early functional domains relevant to ASD, specifically in joint attention and other aspects of social communication, imitation, and functional and symbolic play.</td>
</tr>
<tr>
<td>8.</td>
<td>Adopting a common set of research-validated core measures of ASD symptoms that can be used across multiple sites will facilitate comparisons across studies of children with ASD aged &lt;3 y</td>
<td>• Comprehensive interventions for young children with ASD have also led to improvements in adaptive functioning.</td>
</tr>
<tr>
<td>9.</td>
<td>Future research should examine biological and behavioral heterogeneity as moderators of individual responses to interventions</td>
<td>• Respect for the perceptions, priorities, and preferences of family members is an important “family-centered” tenet to keep in mind when working with children with ASD.</td>
</tr>
<tr>
<td>10.</td>
<td>Intervention providers should monitor for medical disorders that may affect a child’s response to an intervention and refer to appropriate health care providers as indicated</td>
<td>• Service provider training should promote cultural competence, and families should be provided with culturally appropriate program materials.</td>
</tr>
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</table>

for risk-positive children as well as prompt access to interventions targeted to specific, identified functional concerns while diagnostic status is being clarified. Earlier research suggests only a modest increase in ASD screening in pediatric practice35; the routine implementation of diagnostic measures could be enhanced, however, by providing administrative support to assist with processing completed screens and facilitating subsequent...
Placing screening in the broader context of ASD assessment may also help engage community physicians. Additional barriers, including third-party reimbursement, lack of monitoring systems to track positive screening results, and challenges accessing early intervention services, need to be addressed to enhance incorporation of recommended screening practices into routine care for community practitioners.

Although some studies have reported that screening can identify children with ASD earlier and more consistently than routine inquiry about parental concerns, none has examined whether interventions offered to children with ASD identified solely according to screening yield improved outcomes. Indeed, screening effectiveness is generally assessed with respect to classification accuracy (ie, sensitivity and specificity) rather than clinically meaningful outcomes (ie, changes in developmental trajectories related to earlier initiation of intervention), an important focus for future ASD screening research.

Considerable progress has also been made in developing and evaluating ASD intervention models specific to the needs of children <3 years of age. Several groups have adapted treatments initially designed for older preschool-aged children with ASD by integrating best practice in behavioral teaching methods into a developmental framework based on current scientific understanding of how infants and toddlers learn. The central role of parents has been emphasized, and interventions are designed to incorporate learning opportunities into everyday activities, capitalize on “teachable moments,” and facilitate the generalization of skills beyond the familiar home setting. Although some trials were limited to 8- to 12-week outcome data, enhanced outcomes associated with some interventions (eg, the Early Start Denver Model) were evaluated over periods lasting as long as 2 years.

Although no studies to date have directly compared intervention models in children with ASD aged <3 years (even for older children, such studies are rare), there is clear evidence that interventions initiated at this early age can lead to marked improvements in targeted skills (eg, social communication, imitation) as well as more global improvements in cognitive and adaptive functions. Although additional research is needed to further optimize existing models (eg, to differentiate the specific active ingredients), accumulating evidence indicates that toddlers with ASD benefit from early, diagnosis-specific interventions, thus placing greater urgency on the need to ensure broader dissemination and uptake of evidence-based practices beyond initial research settings. Recent data indicate that such interventions not only improve adaptive and social behaviors but also lead to normalized patterns of brain activity in response to viewing faces further emphasize the potential to improve long-term neurodevelopmental trajectories. Efforts to implement effective research programs in formats that can reach larger numbers of children through innovative training approaches (eg, an Internet-based distance learning model for Early Start Denver Model therapists) have also been encouraging.

**STUDY LIMITATIONS**

The recommendations outlined in the present article (and discussed in greater detail in the other articles comprising this supplement) were informed by a review of the published literature as well as consensus of our expert group. However, it is important to acknowledge that the selection of articles for review by the working groups was not systematic. A scoping approach was instead used to select articles of highest relevance and methodologic quality; it is possible that this process excluded key references that might have further informed the recommendations.

**FUTURE DIRECTIONS**

Whereas better and earlier characterization of behavioral symptoms should continue to be a significant focus of research (especially those early characteristics that can be more easily applied in clinical practice), the active search for underlying biological markers should remain a high priority. Promising findings from neuroimaging and neuroelectrophysiology studies may also guide future biomarker-based strategies. For example, the observation of enlarged brain volume early in life could be useful in some cases. In addition, the pursuit of biologic examination of cord blood, placenta, maternal blood, and amniotic fluid, when available, may provide useful and more feasible resources for defining very early indicators of atypical neurologic development and might ultimately lead to more specific treatment modalities.

Although disturbances in sensory processing have not always been considered a core feature of ASD, atypical sensory processing is frequently reported by parents, therapists, teachers, and patients themselves. With the publication of the DSM-5 in May 2013, unusual sensory responses were included in the restricted and repetitive interests/behaviors domain, thus acknowledging that these symptoms play a role in ASD. More recently, imaging and neurophysiologic studies have reported abnormalities in the white matter microstructure of the brain in children with sensory-processing disorders. How disorders of sensory processing (including modulation and integration of sensory information) influence many of the behaviors, and potentially some of the core features of ASD,
remains poorly understood and will be an important area for future research; understanding these mechanisms could have important implications for early diagnosis and treatment.

There is a growing appreciation that ASD is heterogeneous in its causes, underlying neurobiology, and clinical presentation and that the “autisms” comprise a continuum of signs and symptoms, many of which may change over time, either as the result of age or therapeutic interventions or both. Currently, we have little understanding of the natural life history of ASD and how the clinical changes in any individual patient may be reflective of underlying neurobiological mechanism(s) not yet defined. Large-scale longitudinal studies designed to follow up cohorts of well-characterized individuals over time and examine the interplay between biological processes and subsequent experiences could generate new insights to help better individualize treatment strategies.

When considering research related to intervention outcomes, a more concerted focus should be placed on the investigation of those children with ASD who make dramatic progress, some of whom eventually “lose” their diagnosis (ie, the optimal outcome), and those who, despite well-designed, high-quality programs and strong family support, fail to make any significant improvement. Defining the differences between these 2 groups could potentially provide important information relative to the underlying causes of these subsets of children and, furthermore, what specific interventions should be tailored to which type of child. Other indices of heterogeneity (eg, symptom severity, variation in cognitive and language levels, comorbid behavioral and medical conditions) should be more explicitly considered in future studies to help better understand variation in intervention outcomes. It will also be essential that we learn more about how such diversity can affect the effectiveness of early detection and screening, and how this information can help us to develop multipronged strategies that lead to earlier diagnosis across the autism spectrum.

The potential effects of co-morbid medical conditions on the behavior, developmental progress, and general well-being of children with ASD are becoming increasingly apparent and warrant careful consideration, even in the context of early intervention. The autism community has begun to appreciate that a variety of medical conditions (including gastrointestinal disorders, sleep, airway obstruction related to enlarged tonsils and adenoids, and obesity) can—and do—occur among children with ASD and, when present, can negatively affect developmental progress and quality of life. Furthermore, some of the behaviors frequently associated with ASD (eg, stereotypies, aggression, self-injury) are often related to the pain and discomfort associated with these underlying medical conditions. It will be important to determine the prevalence of these co-morbid conditions; to identify their presenting symptoms, which may differ from those seen in typically developing children; and to effectively treat these conditions in concert with other interventions.

Future research related to early identification, screening, and intervention should address the impact of social and cultural beliefs and values, family expectations, stresses and involvement, and outcome goals. Belief systems among service providers may influence utilization of early detection and screening and referral to specialized assessment and interventions.53 Belief systems among families regarding social behavior and development, in addition to earlier experiences with health care providers, can influence communication regarding early risk markers and participation in screening programs. Cultural beliefs, as well as family dynamics and socioeconomic circumstances, can also influence a family’s effective engagement in intervention programs and thus may ultimately affect outcomes.54 Future research should take into account the diversity of beliefs and world views among families and consider how to adapt early detection, screening, and intervention strategies to minimize health disparities or systemic practices that marginalize historically underserved groups to ensure that barriers and health care disparities are overcome. The goal of treatment is early detection, diagnosis, and access to effective interventions for all children across the autism spectrum.

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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.
REFERENCES


(Continued from first page)

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 Choueiri, Fein, Kasari, Pierce, Stone, and Yirmiya co-chaired the working groups that conducted the literature review, generated initial recommendations that were discussed at the consensus meeting, and provided critical input to subsequent drafts of the manuscript; Drs Estes, Hansen, McPartland, Natowicz, Buie, Carter, Davis, Granpeesheh, Mailoux, Newschaffer, Robins, Smith, Rolye, Wagner, and Wetherby were members of the working groups that reviewed selected publications, contributed to recommendations, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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<td>References</td>
<td>This article cites 48 articles, 11 of which can be accessed free at: <a href="http://pediatrics.aappublications.org/content/136/Supplement_1/S1.full.html#ref-list-1">http://pediatrics.aappublications.org/content/136/Supplement_1/S1.full.html#ref-list-1</a></td>
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Early Identification of Autism Spectrum Disorder: Recommendations for Practice and Research

Pediatrics 2015;136:S10
DOI: 10.1542/peds.2014-3667C

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/136/Supplement_1/S10.full.html
Early identification of autism spectrum disorder (ASD) is essential to ensure that children can access specialized evidence-based interventions that can help to optimize long-term outcomes. Early identification also helps shorten the stressful “diagnostic odyssey” that many families experience before diagnosis. There have been important advances in research into the early development of ASDs, incorporating prospective designs and new technologies aimed at more precisely delineating the early emergence of ASD. Thus, an updated review of the state of the science of early identification of ASD was needed to inform best practice. These issues were the focus of a multidisciplinary panel of clinical practitioners and researchers who completed a literature review and reached consensus on current evidence addressing the question “What are the earliest signs and symptoms of ASD in children aged ≤24 months that can be used for early identification?” Summary statements address current knowledge on early signs of ASD, potential contributions and limitations of prospective research with high-risk infants, and priorities for promoting the incorporation of this knowledge into clinical practice and future research. 

Pediatrics 2015;136:S10–S40
Despite efforts to increase awareness of early signs of autism spectrum disorder (ASD) and promote early screening,1 as well as some evidence of recent trends toward diagnosing younger children (as reviewed by Daniels and Mandell2), several large-scale epidemiologic studies suggest that the mean age of diagnosis in the United States remains at ~4 to 5 years.3–5 Given that parents of children with ASD generally report initial concerns before the child is aged 18 to 24 months, considerable opportunity exists to shorten the stressful “diagnostic odyssey” that many families experience,6 maximize opportunities for children with ASD to benefit from early intensive interventions, and further develop evidence-based interventions for this age group.7

For many years, much of what was known about the early signs of ASD was informed by parents’ descriptions of their initial concerns.8–10 as well as analyses of early home videos.11–13 Rich insights from these data (complemented by experimental work that helped delineate key foundational processes impaired in ASD, such as affect sharing and joint attention14–15) helped to inform the development of ASD-screening tools and surveillance efforts by community health professionals.16 Over the past decade, important advances in research have been made into the early development of ASD, incorporating prospective research designs17 and new technologies aimed at more precisely delineating the early emergence of ASD.18,19 Advances have also been made in identifying potential biomarkers (eg, genetic, neuroimaging), although there are important clinical and ethical considerations regarding their potential application.20

These issues were the focus of an international, multidisciplinary panel of clinical practitioners and researchers with expertise in ASD and developmental disabilities that was convened in Marina del Rey, California, in October 2010. A working group (detailed in the Methods section) completed a literature review that informed the recommendations by the panel at the meeting; these recommendations were further refined by an updated review that was completed in December 2013. The panel reached consensus on the following key question: “What are the earliest signs and symptoms of ASD in children aged ≤24 months that can be used for early identification?”

METHODS

The Early Identification working group comprised Drs Stone, Yirmiya (co-chairs), Chawarska, Estes, Hansen, McPartland, and Natowicz. The working group co-chairs and panel co-chairs (Drs Zwaigenbaum and Bauman) conducted a literature search on PubMed to identify relevant articles on early features of ASD. The PubMed search was conducted on June 30, 2010, and used the search terms (“child developmental disorders, pervasive” or “autistic disorder”/ or autism [tw] or autistic [tw]) and (“early detection” or “early diagnosis”), with the age filter “infant, birth–23 months” and limited to English-language papers. This search yielded 341 references, which were reviewed by Drs Zwaigenbaum and Bauman, who selected articles that focused on studies examining the relationship between early behavioral or biological markers in the first 24 months of life and ASD diagnosis. The search results were complemented by additional publications identified by working group members. Hence, although the search strategy was comprehensive, selection of articles was not systematic, which is an important limitation. A scoping approach, with some discretion by the multidisciplinary expert working group, was used instead to select articles of highest relevance and methodologic quality.

Members of the working group reviewed the articles and evaluated their methodologic quality. In the absence of a standard evaluative tool for such research (eg, Grading of Recommendations Assessment, Development and Evaluation,21 which was used to evaluate the quality of evidence of clinical intervention trials), assessment of evidence quality focused on study design (retrospective versus prospective), measurement (eg, use of validated measures for both risk factors and diagnostic outcomes), and whether diagnostic outcomes were measured blinded to risk factor status. The working group also took into consideration whether findings were replicated across independent laboratories. Panel recommendations were based on this evaluative framework. 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. Some of the statements provided here are intended to summarize the state of the literature, whereas others are in the form of recommendations for research needed to fill important gaps or aimed at addressing issues critical for clinical practice.

To ensure that the final article reflected recent literature, the search was updated by using the same strategy to add articles published to December 31, 2013; this search yielded an additional 202 references. Evidence tables and text
references were updated with findings from prospective studies on early behavioral or biological markers. The working group reviewed and approved the final wording of the summary and recommendations.

SUMMARY STATEMENTS

Statement 1: Evidence indicates substantial heterogeneity in the presentation and natural history of clinical features associated with ASDs. This heterogeneity has ramifications for the interpretation of research literature as well as for clinical practice.

There is heterogeneity not only in the etiology, neurobiology, onset, and course of core clinical ASD symptoms but also in the rates and levels of cognitive and language development, adaptive functioning, and co-morbidity with other disorders. Given the tremendous clinical diversity evident among subjects with ASD across the life span, it is not surprising to find that early manifestations and developmental course vary as well. Some children with ASDs are described as having behavioral differences (eg, in reactivity and social orienting) from the earliest months of life, whereas others present with speech delay in the second year, and still others are described as becoming withdrawn and losing skills ages at which early signs and outcomes are examined).

Statement 2: There is evidence that reduced levels of social attention and social communication, as well as increased repetitive behavior with objects, are early markers of ASD between 12 and 24 months of age. Additional potential markers include abnormal body movements and temperament dysregulation.

ASD is not commonly diagnosed until 3 to 4 years of age.20 However, many parents express concerns to their pediatrician by the time their child is aged 18 months.30,31 In addition to parent reports, potential early markers have been identified according to retrospective analyses of home videos and prospective longitudinal studies of infants in the general population, as well as assessment of high-risk infants and toddlers who have an older sibling with ASD.

Studies directed toward the identification of early clinical diagnostic markers of ASD have examined atypicalities in the core domains of social communication and social interaction, as well as the presence of repetitive behaviors. There is strong evidence (ie, replication in multiple samples by independent groups) to support impairments in social attention and social communication as potential markers of ASD between the ages of 12 and 24 months (Table 1).32–56 as well as evidence for atypical object use during this same age period.57,58

When concern about any of these behaviors is conveyed by parents or observed by other care professionals (eg, a health care provider such as community physician or nurse, developmental service provider, or early childhood educator), it is recommended that the child be referred for further autism screening and, as appropriate, for a more comprehensive developmental and diagnostic evaluation.

Early marker: reduced levels of social attention and social communication

Social attention and social communication behaviors indicative of ASD include decreased response to one’s name being called (ie, “orienting to name”), reduced visual attention to socially meaningful stimuli, and less frequent use of joint attention and communicative gestures.

Reduced orienting to name is frequently identified by parents of children with ASD as 1 of their earliest concerns,8,59 and it has been identified in several prospective studies of at-risk infants as a robust early marker of the diagnosis.52,58,42,45 There is some evidence to suggest that decreased orienting to name can differentiate children with a later ASD diagnosis not only from typically developing children but also from children with other developmental delays/disabilities.42,60

Toddlers with ASD also exhibit a reduced tendency to visually examine socially meaningful stimuli. Eye-tracking technology provides a unique opportunity to understand visual attention in ASD and can accurately measure point of gaze with <1 degree of error. Studies of toddlers with ASD report reduced monitoring of social scenes even with an explicit dyadic cue (ages 13–25 months).61 and a preference for visually examining geometric shapes rather than images of children (ages 14–42 months).40

Attention in ASD is often abnormal not just in terms of what toddlers with ASD prefer to look at but also how they attend to their world. “Joint attention” refers to the development of specific skills that enable sharing attention with others through pointing, showing, and coordinating looks between objects and people; joint attention skills are associated with language acquisition.47
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<th>Reference</th>
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<th>Sample</th>
<th>Ascertainment</th>
<th>Outcome Diagnosis</th>
<th>Comments</th>
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| Bryson et al.32 2007 | At ages 12–24 mo, 2 broadly defined ASD subgroups:                        | Prospective case series | 9 SIBS-A later diagnosed with ASD                                      | Recruited from multidisciplinary autism diagnostic and treatment centers                             | Gold standard diagnostic assessment for ASD at age 36 mo using ADI-R, ADOS, and DSM-IV-TR criteria     | • Decrease in IQ from average/near average to severe cognitive impairment, with ASD signs emerging earlier or more striking earlier  
• Continued average or near average IQ  
In all 9 subjects, social-communicative impairments coexisted with atypical sensory or motor behaviors and temperament profile of irritability/distress and difficulties with self- or other-regulation of state |
| Fodstad et al.33 2009 | At ages 17–37 mo:                                                         | Prospective         | • 161 children with AD                                                | Enrollees in state-funded early intervention program for children with development delay or medical condition likely to result in a developmental delay                  | Diagnosis of AD or PDD-NOS based on DSM-IV-TR criteria, M-CHAT, and Battelle Developmental Inventory–2nd edition | • Deficits in communications and social skills more obvious and pronounced in AD versus other groups  
• Greater deficits in PDD-NOS versus controls  
• 5 of 20 items on socialization/nonverbal communication subscale discriminated between groups  
• 5 of 7 items on communication subscale were most predictive of diagnostic group  
• 140 children with PDD-NOS  
• 585 controls: children at risk for other developmental delays or to have disorder such as Down syndrome and cerebral palsy  
• Aged 17–37 mo  
• 5 of 7 items on communication subscale were most predictive of diagnostic group  
• BISCUIT–Part 1 20-item social/nonverbal communication subscale and 7-item communication subscale to assess autism symptoms in one-to-one parent interviews along with child observation |
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<tr>
<td>Garon et al.34 2009</td>
<td>At 24 mo, children with later diagnosis of ASD were distinguished from non-ASD siblings and controls by:</td>
<td>Prospective</td>
<td>• 138 high-risk infants (SIBS-A)</td>
<td>Enrolled in larger study; recruited through autism diagnostic and treatment centers</td>
<td>Gold standard diagnostic assessment for ASD at 36 mo based on ADI-R, ADOS, DSM-IV-TR criteria</td>
<td>• TBAQ-R to assess temperament (parent report) at 24 mo</td>
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<td>• Temperament profile ('effortful emotion regulation') of lower positive affect, higher negative affect, and difficulty controlling attention and behavior</td>
<td>Ongoing (N = 211 with data collected at age 24 mo)</td>
<td>• 73 low-risk infants (no family history of ASD)</td>
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<td>34 of 138 SIBS-A (24.8%) diagnosed with ASD</td>
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<td></td>
<td>• lower sensitivity to social reward cues (low “behavioral approach”)</td>
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<td>84% and 80%, respectively, enrolled in study at age 6 mo; rest by age 12 mo</td>
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<td>Two ASD subgroups distinguished by number of ASD symptoms, IQ, age at diagnosis, Behavioral Approach profile</td>
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<td>Goldberg et al.35 2005</td>
<td>At ages 14–19 mo, significant group differences in 3 of 4 social and communication behaviors between ASD and TD children but not between ASD and SIBS-A children:</td>
<td>Prospective</td>
<td>• 8 children diagnosed with AD or PPD-NOS aged 21.0–33.0 mo</td>
<td>From larger sample of families participating in autism study at university medical center; controls from community volunteer sample</td>
<td>For subjects recruited as part of larger study, ADI-R and ADOS-G were administered; controls were screened by using CARS ESCS (abridged version) structured interactions videotaped and coded to assess social interaction, joint attention, and behavioral regulation</td>
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<td>• Responses to social interaction bids: less frequent eye contact, gestures, and turn-taking (P &lt; .05)</td>
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<td>• 8 SIBS-A aged 14.0–19.0 mo</td>
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<td>• Initiation of joint attention: fewer nonverbal behaviors to initiate shared experiences of objects or events (P &lt; .001)</td>
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<td>• 9 children with TD from families without ASD aged 10.0–19.0 mo</td>
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<td>• Differences in frequency of requesting behaviors (P &lt; .05)</td>
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<td>• No significant differences in responses to JA</td>
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<td>Reference</td>
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<td>Mosconi et al,36 2009</td>
<td>In 2-y-olds with AD: Longitudinal MRI study</td>
<td>• 50 children with AD</td>
<td>Children with AD recruited after receiving clinical diagnosis or while awaiting clinical evaluation</td>
<td>Diagnosis of AD confirmed at 2 y and reassessed at 4 y by using ADI-R, ADOS, DSM-IV criteria; controls screened with CARS</td>
<td>• ADOS sessions videotaped and coded by using a new scale (SOC-RS) to rate social orienting and communications behaviors, including IJA, RJA, and nonverbal gestures</td>
<td>• Amgydala enlargement that persisted through age 4 y (18% larger volumes than in controls)</td>
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<tr>
<td>Nadig et al,38 2007</td>
<td>At age 12 mo, failure to respond to name is highly suggestive of developmental abnormality</td>
<td>Prospective longitudinal study</td>
<td>• 101 at-risk infants (SIBS-A)</td>
<td>Enrollees in university-based study</td>
<td>Clinical best diagnosis of AD or PDD-NOS at 24 mo based on clinical observation, ADOS, and DSM-IV criteria</td>
<td>• Subjects followed up to age 36 mo</td>
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<td>• 85% of at-risk infants responded to first or second name call vs 100% of controls</td>
<td>• 46 infants at no known risk (SIBS-TD)</td>
<td>12 children who failed to respond to name at 12 mo have outcome data: AD and PDD-NOS in 5, other delays in 4, TD in 3</td>
<td>12 children who failed to respond to name at 12 mo have outcome data: AD and PDD-NOS in 5, other delays in 4, TD in 3</td>
<td>• MSEL to assess development</td>
<td>• ADOS to measure social and communicative behaviors</td>
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<td>• Failure to respond to name at age 12 mo highly specific for 24-mo outcome of developmental delay, including ASD</td>
<td>Aged 12 mo</td>
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<td>• Response-to-name experimental task videotaped at 6 and 12 mo and coded for number of calls it took for response to child's name</td>
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<tr>
<td>Osterling et al.</td>
<td>At 1 y, infants with ASD:</td>
<td>Retrospective video study</td>
<td>• 20 infants with later diagnosis of AD (35% of sample) or PPD-NOS</td>
<td>Recruited from university subject pools, state autism society, Division of Developmental Disabilities, local newspaper and local radio advertisements, local schools</td>
<td>AD or PPD-NOS diagnosis confirmed at study entry on basis of DSM-III plus score of ≥30 on CARS</td>
<td>Home videos of first birthday parties coded by blind raters on frequencies of specific social and communicative behaviors and repetitive motor actions</td>
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<td>• Look at others less frequently</td>
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<td>• 14 infants later diagnosed with MR (without ASD and without distinguishing physical anomalies)</td>
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<td>• Orient to their names less frequently than infants with mental retardation:</td>
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<td>• 20 infants with TD</td>
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<td>At 1 y, infants with ASD or MR:</td>
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<td>• Use gestures less frequently</td>
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<td>• Look to objects held by others less frequently</td>
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<td>• Engage in repetitive motor actions more frequently than infants with TD</td>
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<td>Ozonoff et al.</td>
<td>By age 12 mo, significant differences between ASD and TD groups in frequency of gaze to faces and directed vocalizations (although not at 6 mo)</td>
<td>Prospective longitudinal study</td>
<td>• 25 high-risk infants with later diagnosis of AD or PDD-NOS (22 were SIBS-A)</td>
<td>Sample drawn from larger longitudinal study</td>
<td>Classification as ASD or TD at 36 mo by using Baby Siblings Research Consortium definitions (ADOS and DSM-IV-TR criteria for AD or PDD-NOS)</td>
<td>Assessments at ages 6, 12, 18, 24, and 36 mo of:</td>
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<td>By 18 mo, significant group differences on all social communication variables (see Comments)</td>
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<td>• Frequencies of 6 social communication behaviors (gaze to faces, gaze to objects, smiles, nonverbal vocalizations, single-word verbalizations, phrase vocalizations), recorded onto DVDs and coded during MSEL visual reception subtest</td>
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<td>Between 6 and 18 mo:</td>
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<td>• Frequency of infant social engagement rated by blind examiners</td>
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<td>• Declining trajectories of social communication behavior and loss of skills in most infants with later ASD diagnosis</td>
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<td>• MSEL to assess cognitive functioning</td>
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<td>• Increase in cognitive and language skills (MSEL raw scores) over time in both groups, with significantly slower growth in ASD starting at 12 mo</td>
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<td>• Symptom onset by parent reports</td>
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<td>Pierce et al.(^{40}), 2011</td>
<td>Toddlers with an ASD as young as 14 mo spent significantly more time fixating on geometric images than on social images</td>
<td>Prospective longitudinal study</td>
<td>37 with ASD</td>
<td>Sample recruited from general population screening approach starting at 12 mo and community referral</td>
<td>Clinical best diagnosis of AD or PDD-NOS at ≥24 mo based on clinical observation, ADOS, and DSM-IV criteria</td>
<td>1-min eye-tracking test used to measure visual attention</td>
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<td>Sullivan et al.(^{41}), 2007</td>
<td>By age 14 mo, children later diagnosed with ASD or broader autism phenotype had deficits in RJA</td>
<td>Prospective</td>
<td>51 high-risk children (SIBS-A) who received outcome assessments:</td>
<td>Subsample of subjects of large study; recruited through ASD advocacy group, schools, word of mouth</td>
<td>Outcome assessment at 30 (n = 7) or 36 (n = 44) mo; diagnosis of AD or PDD-NOS based on ADOS, DSM-IV criteria; BAP = language and/or social delays without ASD diagnosis</td>
<td>RJA bids were coded from videotapes of 3 measures administered at ages 14 and 24 mo: “look only” trials adapted from Butterworth and Jarrett, 1991; look + point trials from CSBS DP; RJA item from ADOS</td>
</tr>
<tr>
<td>Wetherby et al.(^{42}), 2004</td>
<td>During second year of life, 9 prelinguistic behaviors serve as red flags to distinguish ASD from DD and TD:</td>
<td>Prospective</td>
<td>18 children with later diagnosis of AD or PDD-NOS</td>
<td>Recruited to larger study</td>
<td>Best-estimate diagnosis of AD or PDD-NOS made between ages 30 mo and 5 y based on MSEL; VABS, Interview Edition, Survey Form; and ADOS</td>
<td>Direct observation within standardized Behavior Sample, videotaped and scored by using standard CSBS DP procedures; Behavior Sample videotape recorded by using SORF scoring</td>
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<td>Reference</td>
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<td>Yoder et al.43 2009</td>
<td>Later social impairment and later ASD diagnosis predicted by:</td>
<td>Prospective longitudinal correlational design</td>
<td>43 SIBS-A</td>
<td>Participants of another study, SIBS-A recruited from university-based autism and speech-language programs and community agencies; SIBS-TD through birth record database and word of mouth</td>
<td>ASD diagnosis assessed ~1.5 y after study entry (ie, after age 30 mo) using ADOS, ADI-R, and DSM-IV-TR criteria</td>
<td>• Hierarchical linear modeling to assess growth in early social skills (ie, RJA and WTC) as predictors of social impairment in SIBS-A</td>
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<td>• Initial level of RJA (at age 15 mo)</td>
<td></td>
<td>24 age-matched SIBS-TD who provided social outcome benchmarks</td>
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<td>ASD diagnosed in 6 (AD in 3 and PDD-NOS in 3)</td>
<td>• RJA and WTC assessed at 4 time points 4 mo apart; RJA, WTC, and SBC assessed at time 5, 6 mo after fourth measurement (ie, after age 30 mo)</td>
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<td>• Growth rate of weighted triadic communication (from ages 15–34 mo)</td>
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<td>Aged 12–23 mo at study entry</td>
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<td>• Weighted frequency of unprompted triadic communications derived from STAT</td>
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<td>At 30 mo, delay in RJA and more general social skills in SIBS-A but large variation in social outcome scores</td>
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<td>• Experimental task described in Presmanes et al.44 2007, to assess RJA</td>
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<td>• SBC to assess social behaviors by parent report</td>
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<td>Zwaigenbaum et al.43 2005</td>
<td>By age 12 mo, infants with later diagnosis of autism may be distinguished from other siblings and controls by:</td>
<td>Prospective longitudinal study</td>
<td>65 SIBS-A</td>
<td>Recruited mainly at age ≥6 mo from autism diagnostic and treatment programs; low-risk infants recruited from nurseries in same regions</td>
<td>Formal independent diagnostic assessment at 36 mo based on DSM-IV criteria, ADI-R, and ADOS</td>
<td>• AOSI at 6 and 12 mo to assess autism-specific behaviors</td>
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<td></td>
<td>• Behavior markers*</td>
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<td>23 low-risk infants (no first- or second-degree relatives with ASD)</td>
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<td>Clinical diagnosis of ASD made at 24 mo in up to 7 SIBS-A who met DSM-IV criteria (confirmed by using ADI-R and ADOS)</td>
<td>• ADS (24 mo) to assess autism-related social communication impairments</td>
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<td>• Prolonged latency to disengage visual attention (starting after 6 mo)</td>
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<td>“Roughly” matched by gender, birth order, and age; N values varied by assessment</td>
<td></td>
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<td>• Computerized visual orienting task (6 and 12 mo) to assess ability to disengage from 1 of 2 competing visual stimuli (attentional disengagement)</td>
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<tr>
<td>Reference</td>
<td>Findings</td>
<td>Type of Study</td>
<td>Sample</td>
<td>Ascertainment</td>
<td>Outcome Diagnosis</td>
<td>Comments</td>
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<tr>
<td>Macari et al, 2012</td>
<td>At age 12 mo, lack of attention-sharing behaviors, including:</td>
<td>Prospective</td>
<td>53 SIBS-A</td>
<td>Recruited from university research programs, Web site, advertising, word of mouth</td>
<td>Provisional CBE diagnosis at age 24 mo</td>
<td>• 31 low-risk infants (no ASD history in first- or second-degree relative) 64% male, enrolled by age 8 mo</td>
</tr>
<tr>
<td>Presmanes et al, 2007</td>
<td>In second year of life, SIBS-A showed impaired RJA relative to SIBS-TD across range of prompt types</td>
<td>Prospective</td>
<td>46 SIBS-A</td>
<td>SIBS-A recruited from regional multidisciplinary evaluation and speech language centers, state birth-to-3 service network, autism parent groups, and university-based autism service and outreach program; SIBS-TD recruited from birth records</td>
<td>“Not yet available”</td>
<td>• RJA task administered with different combinations of verbal and nonverbal cues; when number of attentional cues was increased, and where multiple objects or events competed for child’s attention</td>
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<td>Attention disengagement similar for 2 groups</td>
<td>Ongoing</td>
<td>55 SIBS-TD</td>
<td>Aged 12–23 mo</td>
<td></td>
<td>• 20 RJA trials per subject were videotaped and coded</td>
</tr>
<tr>
<td>Reference</td>
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<tr>
<td>Stone et al,47 2007</td>
<td>64 SIBS-A, 42 SIBS-TD</td>
<td>Prospective</td>
<td>SIBS-A recruited from university-based autism and speech-language programs and community agencies; SIBS-TD recruited from birth record database, university-based research programs, and community agencies</td>
<td>Not known</td>
<td>Child-based and parent report measures; MSEL to assess cognitive function; CARS to assess autism symptoms; STAT to assess play requesting, directing attention, and motor imitation; MCDI questionnaire to assess verbal and nonverbal understanding and expression; DAISI to assess social engagement behaviors</td>
<td></td>
</tr>
<tr>
<td>Yirmiya et al,48 2006</td>
<td>30 SIBS-A, 31 SIBS-TD</td>
<td>Prospective (N = 61 with 14-mo assessments)</td>
<td>Sibs-A recruited from treatment centers, special schools, and contacts with families of children with ASD; Comparison group recruited from hospital maternity wards</td>
<td>At age 14 mo, 1 subject was suspected of having autism, a diagnosis confirmed at ages 24 and 36 mo by using ADI-R and ADOS-G</td>
<td>Measures at age 4 and 14 mo: BSID-II to assess general development and language; ICQ to assess maternal perception of infant temperament; Communication and cognition measures at age 14 mo; ESCS to assess nonverbal communication skills; CHAT to assess JA behavior</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1 Continued**

- **Reference**
  - Stone et al,47 2007
  - Yirmiya et al,48 2006

- **Findings**
  - At ages 12–23 mo, weaker performance by SIBS-A in:
    - Nonverbal problem solving (ie, visual reception)
    - Directing attention (ie, JIA)
    - Understanding words and phrases
    - Gesture use
    - Social communicative interactions with parents
    - Increased autism symptoms in SIBS-A
    - Significant correlations between child-based measures and parent reports

- **Type of Study**
  - Prospective

- **Sample**
  - SIBS-A: 64
  - SIBS-TD: 42

- **Ascertainment**
  - SIBS-A recruited from university-based autism and speech-language programs and community agencies; SIBS-TD recruited from birth record database, university-based research programs, and community agencies

- **Outcome Diagnosis**
  - At age 14 mo, 1 subject was suspected of having autism, a diagnosis confirmed at ages 24 and 36 mo by using ADI-R and ADOS-G

- **Comments**
  - Measures at age 4 and 14 mo:
    - BSID-II to assess general development and language
    - ICQ to assess maternal perception of infant temperament
    - Communication and cognition measures at age 14 mo
    - ESCS to assess nonverbal communication skills
    - CHAT to assess JA behavior

- **Outcome Measures**
  - Measures at age 4 and 14 mo:
    - Nonverbal problem solving (ie, visual reception)
    - Directing attention (ie, JIA)

- **Sample**
  - SIBS-A: 64
  - SIBS-TD: 42

- **Ascertainment**
  - SIBS-A recruited from university-based autism and speech-language programs and community agencies; SIBS-TD recruited from birth record database, university-based research programs, and community agencies

- **Outcome Diagnosis**
  - At age 14 mo, 1 subject was suspected of having autism, a diagnosis confirmed at ages 24 and 36 mo by using ADI-R and ADOS-G

- **Comments**
  - Measures at age 4 and 14 mo:
    - BSID-II to assess general development and language
    - ICQ to assess maternal perception of infant temperament
    - Communication and cognition measures at age 14 mo
    - ESCS to assess nonverbal communication skills
    - CHAT to assess JA behavior
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</tr>
</thead>
<tbody>
<tr>
<td>Landa and Garrett-Mayer, 2006</td>
<td>By 14 mo of age, significantly worse performance in fine motor, gross motor, and receptive and expressive language (ASD versus unaffected)</td>
<td>Prospective Longitudinal</td>
<td>• 24 children with later diagnosis of ASD</td>
<td>SIBS-A recruited through Autism Society of America local chapters and university-based center for autism; children at low autism risk recruited through local physician offices and caregiver/child play groups</td>
<td>ASD classified at 24 mo based on PLS, ADOS, and MCDI</td>
<td>• MSEL to assess general and language development across 5 domains of nonsocial development (gross motor, fine motor, visual reception, receptive and expressive language); administered as close as possible to ages 6, 14, and 24 mo</td>
</tr>
<tr>
<td>Oller et al, 2010</td>
<td>From ~1 y of age, vocalizations from children with autism or language delay can be differentiated from children with TD by automated analysis of selected acoustic features</td>
<td>Prospective</td>
<td>• 11 with later diagnosis of language delay</td>
<td>• 52 classified as unaffected (at 24 mo) Enrollees entered study as SIBS-A and infants with no family history of idiopathic autism</td>
<td>• Phase I: children with reported diagnosis of language delay evaluated by speech-language clinician. Phase II: documentation of diagnosis from outside clinician, plus failure on M-CHAT</td>
<td>• CDI at 14 and 24 mo to assess child's understanding and production of language</td>
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<td>• 77 children aged 16–48 mo with AD or PDD/NOS</td>
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<td>• Phase I (2006–2008) and Phase II (2009) studies to assess automated method to determine presence or absence of 12 acoustic parameters on child vocalizations; parameters reflect rhythmic/syllabic articulation and voice</td>
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<td>• Analysis of 1486 all-day recordings</td>
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<td><strong>Language/communication behavioral markers (from studies without outcome assessments)</strong></td>
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<tr>
<td>Gamliel et al.51, 2007</td>
<td>At 14 and 24 mo, cognitive and/or language delays ($\geq 2$ SDs below average on measures) in SIBS-A subsets, compared with other SIBS-A and SIBS-TD.</td>
<td>Prospective</td>
<td>39 SIBS-A</td>
<td>Recruited through treatment centers, special schools, national autism organization, families of children with autism; comparison group recruited from hospital maternity wards.</td>
<td>BSID-II at 4, 14, and 24 mo to assess development.</td>
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<td>At ages 14–36 mo, cognitive and/or language difficulties in 11 of 39 SIBS-A vs 2 SIBS-TD.</td>
<td>Ongoing (N = 78 with developmental trajectories to age 54 mo)</td>
<td>39 SIBS-TD</td>
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<td>RDLS (24 mo) to assess expressive and verbal comprehension.</td>
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<td>By 54 mo, cognitive differences gone, but some differences in language ability (receptive and expressive) remained.</td>
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<td>Matched at age 4 mo on 1-to-1 basis according to chronologic age, gender, birth order, number of children in family, temperament profile, and mental and motor scales.</td>
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<td>Most siblings with language impairments at age 14 mo functioning well at 54 mo without intervention.</td>
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<td><strong>Markers of motor dysfunction (from studies with outcome assessments)</strong></td>
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<td>Esposito and Venuti,52, 2008</td>
<td>At age $\sim 20$ mo, boys with AD had:</td>
<td>Retrospective video study</td>
<td>16 boys mean age 20.2 mo with AD</td>
<td>Recruited from referrals to university-based center for developmental disabilities.</td>
<td>AD diagnosis before study confirmed by using DSM-IV criteria and ADOS.</td>
<td>Analysis of home videos taken after 8 mo of independent walking.</td>
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<td></td>
<td>• Different distributions in WOS scores from other groups.</td>
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<td>WOS used to code videos by assessing gait on 3 axes: foot, arm, and global movements.</td>
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<td>• Different gait patterns: problems with heel-to-toe pattern, more asymmetric posture of arm while walking, higher frequency of general movement anomalies (eg, &quot;waddling walk&quot;).</td>
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<td>Esposito et al,53, 2011</td>
<td>Aged $&lt;2$ y, significant ($P \leq 0.001$) differences in gait pattern in toddlers with AD versus TD and DD.</td>
<td>Retrospective video study</td>
<td>20 toddlers with AD</td>
<td>Recruited from 2 nationwide referral centers for developmental disabilities.</td>
<td>Clinical diagnosis of AD based on DSM-IV-R and confirmed by using ADI-R, ADOS-G, and CARS.</td>
<td>Analysis when toddlers were first walking without assistance.</td>
</tr>
<tr>
<td>Reference</td>
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<tr>
<td>Matson et al.54</td>
<td>Higher levels of postural asymmetry during walking</td>
<td>Prospective</td>
<td>15 toddlers with nonautistic DD</td>
<td>Home videos taken when child was aged &lt;2 y (plus all footage within 2 h window)</td>
<td>AD and PDD-NOS diagnoses based on DSM-IV-TR criteria, M-CHAT, and Battelle Developmental Inventory—Second Edition developmental profile</td>
<td>WOS to code videos by assessing gait on 3 axes: foot, arm, and global movements; PPSW to assess static and dynamical symmetry during gait</td>
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<td>Some atypical arm and foot movements during walking</td>
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<td>20 toddlers with TD</td>
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<td>BISCUIT Part 1—specifically the repetitive behavior/ restricted interests subscale—to assess for ASD symptoms</td>
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<td>Mean ages 129–142 mo when first walking without assistance</td>
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<td>Child observation and 1-to-1 parent assessment; administered as part of battery of assessments of physical and social development</td>
</tr>
<tr>
<td>Matson et al.54</td>
<td>Stereotypes and repetitive/ritualistic behaviors were most common in AD, followed by PDD-NOS and then other DDS</td>
<td></td>
<td>140 infants with AD</td>
<td>Enrollees of state-funded early intervention program for DDs</td>
<td>AD and PDD-NOS diagnoses based on DSM-IV-TR criteria, M-CHAT, and Battelle Developmental Inventory—Second Edition developmental profile</td>
<td>BISCUIT subset could accurately predict diagnostic group membership</td>
</tr>
<tr>
<td></td>
<td>Striking differences across groups in limited number of interests, engages in repetitive motor movements for no reason, eye-to-eye gaze, maintains eye contact</td>
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<td>121 with PDD-NOS</td>
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<td>Atypical uses of objects (spinning, rotating, and, especially unusual visual exploration of objects) significantly ( P \leq 0.05 ) more frequent in infants with ASD compared with other groups</td>
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<td>499 at risk for DD but no ASD diagnosis</td>
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<td>Repetitive behaviors significantly related to</td>
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<td>Aged 17–37 mo (mean: 26.63 mo)</td>
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<tr>
<td>Ozonoff et al.57</td>
<td>Atypical uses of objects (spinning, rotating, and, especially unusual visual exploration of objects) significantly ( P \leq 0.05 ) more frequent in infants with ASD compared with other groups</td>
<td>Prospective</td>
<td>35 SIBS-TD</td>
<td>Recruited from SIBS-A and SIBS-TD</td>
<td>Diagnosis at 24 (( n = 29)) or 36 (( n = 37)) mo based on ADOS, SCQ, and DSM-IV criteria</td>
<td>Manner in which infants explore objects was examined in task that afforded range of repetitive uses</td>
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<td>Repetitive behaviors significantly related to</td>
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<td>51 in SIBS-TD</td>
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<td>Four objects presented to the infant, 1 at a time, for 30 s each</td>
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<td>Aged 12 mo, with following outcomes:</td>
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<td>Behavior recorded on DVD</td>
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<td>• 9 with ASD diagnosis</td>
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<td>Reference</td>
<td>During first 2 y of age:</td>
<td>Sample</td>
<td>Ascertainment</td>
<td>Outcome Diagnosis</td>
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<tr>
<td>Ozonoff et al., 2008</td>
<td>Retrospective video study</td>
<td>28 children aged 26–61 mo with nonregression-type AD</td>
<td>82 recruited from university-based recruitment core and local agencies serving individuals with developmental disabilities; 21 recruited in another city from ongoing studies and university subject pool</td>
<td>Diagnosis of AD or PDD-NOS in the community confirmed at study entry; AD diagnosis based on ADI-R plus ADOS; regression versus no regression subgroups based on ADI-R</td>
<td>Participants seen at initial enrollment (when all home videos of child from birth to age 2 y were collected) and 1–2 y later for assessment battery that was part of another study</td>
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<tr>
<td>Provost et al., 2007</td>
<td>At ages 21–41 mo:</td>
<td>Prospective</td>
<td>Recruited from referrals to university-based early childhood evaluation program for developmental disabilities</td>
<td>ASD diagnosis made by study team evaluation</td>
<td>ASD and DD groups matched on gender, cognitive abilities within 3 mo; ASD matched to DD and no motor delay groups on chronologic age within 3 mo</td>
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</table>

- Cognitive and symptom status at 36 mo
- 10 with later diagnosis of other delays
- 47 with no concerns (did not meet criteria for other groups)

- Neither regression nor nonregression types of AD differed from TD in rates of movement abnormalities or lack of protective responses
- Toddlers with nonautistic DD displayed higher rates of movement abnormalities in sitting and prone and fewer protective responses in crawling than other groups
- Participants seen at initial enrollment (when all home videos of child from birth to age 2 y were collected) and 1–2 y later for assessment battery that was part of another study
- Videos coded for motor maturity, protective responses, and movement abnormalities by using Infant Motor Maturity and Atypicality Coding Scales

- Motor dysfunction to some degree in all children with ASD (delay in gross and/or fine motor skills)
- Significant motor impairments versus those with developmental concerns without motor delay
- No significant difference in motor scores versus children with DD

- Motor dysfunction to some degree in all children with ASD (delay in gross and/or fine motor skills)
- Significant motor impairments versus those with developmental concerns without motor delay
- No significant difference in motor scores versus children with DD

- 18 children aged 21–41 mo with ASD
- 19 with other DD including motor delay
- 18 with developmental concerns (eg, speech and emotional issues) but no motor delay
- ASD and DD groups matched on gender, cognitive abilities within 3 mo; ASD matched to DD and no motor delay groups on chronologic age within 3 mo

- 19 with other DD including motor delay
- 18 with developmental concerns (eg, speech and emotional issues) but no motor delay
- ASD and DD groups matched on gender, cognitive abilities within 3 mo; ASD matched to DD and no motor delay groups on chronologic age within 3 mo

- Motor dysfunction to some degree in all children with ASD (delay in gross and/or fine motor skills)
- Significant motor impairments versus those with developmental concerns without motor delay
- No significant difference in motor scores versus children with DD

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- Significant motor impairments versus those with developmental concerns without motor delay
- No significant difference in motor scores versus children with DD

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- Motor dysfunction to some degree in all children with ASD (delay in gross and/or fine motor skills)
- Significant motor impairments versus those with developmental concerns without motor delay
- No significant difference in motor scores versus children with DD

- Motor dysfunction to some degree in all children with ASD (delay in gross and/or fine motor skills)
- Significant motor impairments versus those with developmental concerns without motor delay
- No significant difference in motor scores versus children with DD
TABLE 1 Continued

<table>
<thead>
<tr>
<th>Reference</th>
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<tbody>
<tr>
<td>Watt et al.28,30</td>
<td>At ages 18–24 mo, children with ASD demonstrated significantly higher frequency and longer duration of: RSB with objects</td>
<td>Prospective</td>
<td>50 children with ASD (AD or PDD-NOS)</td>
<td>Recruited through screening project involving general population sample; ASD and DD participants were in bottom 10th percentile on ≥1 composite of CSBS Behavior Sample during second year of life</td>
<td>Best estimate assessment of ASD or DD diagnosis at age ≥30 mo based on battery of tests including ADOS</td>
<td>In second year of life: CSBS Behavior Sample to assess communication behaviors; RSB coded from Behavior Sample videotapes</td>
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<td>RSB with body</td>
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<td>50 with TD</td>
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<td>Symbolic composite of Behavior Sample to measure developmental level</td>
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<td>Sensory behaviors different than DD and TD groups</td>
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<td>Aged 18–24 mo; DD group matched groupwise to ASD group on age and developmental level; TD group matched individually to ASD group on gender and chronologic age</td>
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<td>Social composite of Behavior Sample to assess social competence In fourth year: MSEL to measure developmental level</td>
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<td>In children with ASD and those with other DDs, RSB with objects predicted developmental outcomes and severity of ASD symptoms at 3 y</td>
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<td>VABS to assess adaptive behavior</td>
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Studies may evaluate markers in >1 category (see “Comments”). AD, autistic disorder; ADI-R, Autism Diagnostic Interview—Revised; ADOS, Autism Diagnostic Observation Schedule; ADOS-G, Autism Diagnostic Observation Schedule—Generic; ADOS-G-T, Autism Diagnostic Observation Schedule—Toddler Module; AOSI, Autism Observation Scale for Infants; BAP, broader autism phenotype; BSID-II, Bayley Scales of Infant Development–2nd Edition (DD); Childhood Autism Rating Scale–CBR, clinical best estimate; CDI-WG, MacArthur Communicative Development Inventories–Words and Gestures; CSBS DP, Communication and Behavior Scales Developmental Profile; CHAT, Checklist for Autism in Toddlers; DAISI, Detection of Autism by Infant Sociability Interview; DD, developmental delay; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR, Fourth Edition; Text Revision; ESCS, Early Social Communication Scales; IBQ, Infant Behavior Questionnaire; IA, joint attention; K-ABC, Kaufman Assessment Battery for Children; LD, language delay; MR, mental retardation; PDD-NOS, pervasive developmental disorder not otherwise specified; POMS-2, Peabody Development Motor Scales, Second Edition; PLS, Preschool Language Scale; PPSW, Positional Pattern for Symmetry during Walking; RASI, Reynell Developmental Language Scales; RSB, repetitive and stereotyped behavior; SBC, Social Behavior Checklist; SCQ, Social Communication Questionnaire; SIBS-A, siblings of children with ASD; SIBS-TD, siblings of children with typical development; SOCD; Social Orienting Continuum and Response Scale; SORF, Systematic Observation of Red Flags for ASD in Young Children; STAT, Screening Tool for Autism in Two-Year-Olds; TBM, Toddler Behavior Assessment Questionnaire (Revised); TD, typical development; VABS, Vineland Adaptive Behavior Scales; WOS, Walking Observation Scale; WTC, weighted triadic communications (child-initiated communication of message about an object or event to another person, also called JUAT considered to have imperative as well as declarative functions).

a Fodstad et al.2009. Socialization/nonverbal communication subscale items that discriminated: intellectual abilities; shares enjoyment, interests, or achievement with others; interest in participating in social games, sports, and activities; use of too few or too many social gestures; and development of social relationships.

b Fodstad et al.2009. Communication subscale items that were predictive: age-appropriate self-help and adaptive skills; use of language to communicate, use of language in conversations with others, communicates effectively, and language development.

c Wetherby et al.2004. Red flags differentiating ASD from DD and TD: lack of appropriate gaze; lack of warm, joyful expressions with gaze; lack of sharing enjoyment or interest; lack of coordination of gaze; facial expression, gestural, and sound; lack of showing; and unusual prosody.

d Wetherby et al.2004. Red flags differentiating ASD from TD but not DD were lack of response to contextual cues, lack of pointing, lack of vocalizations with consonants, and lack of playing with a variety of toys conventionally.

e Zwaigenbaum et al.2005. Behavioral markers distinguishing autism by age 12 months were atypical eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest and affect, and sensory-oriented behaviors.

f Zwaigenbaum et al.2005. Temperamental marked by marked passivity and decreased activity level at 6 mo, followed by extreme stress reactions, tendency to fixate on particular objects in environment, and decreased expression of positive affect by 12 mo.

g Ozerooff et al.2008. Other delays were general developmental delay, speech/language delay, marked hyperactivity, and marked anxiety.

h Ozerooff et al.2008. Behaviors hypothesized as typical: shaking, banging, mouthing, throwing; behaviors hypothesized as atypical: spinning, rolling, rotating, unusual visual exploration (e.g., engages in prolonged visual inspection, examines object from odd angles or peripheral vision).
Some studies have reported group differences in both responding to joint attention (RJA) and initiating joint attention (IJA) between infants who receive a later diagnosis of ASD and children who are not diagnosed. RJA, also called attention following, is indicated by the child's shifting of attention in response to a cue, such as someone's gaze, head turn, point, or attention-directing utterance. Lower levels of RJA have been reported in children with ASD as early as 14 months in 2 prospective studies41,43 but not in a third.35 In 1 study,41 group differences in RJA between high-risk siblings with a later ASD diagnosis and high-risk siblings with later outcomes of broader autism phenotype or nonbroader autism phenotype became apparent at 24 months of age.

IJA behaviors, or directing attention, refer to a child's integration of gestures, gaze shifts, utterances, and other cues to initiate a shared experience of objects or events with others. As early as age 14 months, IJA behaviors have been found to be impaired in children with ASD35 and younger siblings of children with ASD47 compared with typically developing children. Reduced IJA (at 18 months) also distinguishes younger siblings who subsequently develop ASD from those who do not,62 as does a slower growth trajectory of IJA-related communication from age 15 months.43 Other studies have assessed the use of gestures more generally. During the second year of life, a lower frequency of gesture use differentiated children with ASD from typically developing children35,63 and from children with other developmental disorders.33,39

**Potential early marker: atypical body movements and motor development**

Evidence in this domain is less well established, but research suggests that atypicalities in body movements, which can encompass repetitive actions or posturing of the body, arms, hands, or fingers (including hand flapping, finger flicking, and atypical arm and foot movements during walking), may emerge as important early markers. Whether these atypical behaviors are noted to emerge early or late during the second year of life seems to vary depending on the design of the study.

Prospective studies in children with a later diagnosis of ASD have shown a higher frequency and longer duration of repetitive stereotyped movements58,64 compared with typically developing or “unaffected” children, respectively. Similar findings have been reported in other prospective studies52,42,54,65 as well as in retrospective studies39,52,53. In contrast, 1 retrospective video study of children with autistic disorder found no differences from typically developing children in rates of movement abnormalities.45

**Potential early marker: temperamental profile**

It has been reported that by 24 months of age, temperament profiles can distinguish high-risk siblings with a later diagnosis of ASD from high-risk siblings who do not receive an ASD diagnosis and siblings without a family history of ASD.34 One profile is characterized by lower sensitivity to social reward cues. A second profile, marked by negative affect and difficulty in controlling attention and behavior, can differentiate siblings diagnosed later with ASD from infants with no family history of ASD (low-risk infants). Two smaller case series by the same group identified temperamental differences in children with ASD as early as age 6 months.32,45

**Early marker: repetitive behavior with objects**

As early as 12 months of age, infants with a later diagnosis of ASD were found to exhibit atypical use of objects, such as the spinning, lining up, rotating, and especially visual exploration of objects, compared with infants with a later diagnosis of other developmental or language delays or no developmental concerns.57 These findings are consistent with other reports of repetitive behaviors associated with object use62,58,64 and prolonged visual fixation on objects52 or repetitive geometric shapes40 in infants who subsequently develop ASD. In 2 samples, such repetitive behaviors correlated with subsequent diagnostic outcomes and other ASD symptoms.57,58,64

gross and/or fine motor skills have been reported in high-risk infants,49,66 and more recent research has suggested very early emerging abnormalities in motor control. For example, in a preliminary study of 40 high-risk infant siblings, Flanagan et al67 reported that head lag at 6 months was predictive of a subsequent diagnosis of ASD at 30 to 36 months. In a related study,68 motor delays at 6 months were predictive of social communication delays across the high-risk cohort.

Bolton et al69 reported that fine motor behaviors were among a larger set of parent-report items on a general developmental screening tool that was informative for risk of ASD at 6 months of age. Although these studies suggest that, in some cases, delayed or atypical motor patterns may be predictive of ASD, definitive markers are not yet available. Certainly, children with atypical motor development should be closely monitored and followed up, not only for ASD but also for other developmental disorders. Further studies of the association between infant motor development and ASD risk are warranted.

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Clifford et al. reported on the presence of reduced positive affect and increased perceptual sensitivity at 7 months of age, as well as a pervasive pattern of emotional dysregulation and reduced attentional flexibility (consistent with findings from Garon et al), features that were predictive of ASD within a cohort of 54 high-risk infants. Measures of temperament have not yet been reported by other groups investigating infants at risk for autism, suggesting that these observations need further study. In addition, temperamental features in low-risk populations have not been investigated as a potential risk marker for ASD.

Statement 3: Reliable behavioral markers for ASD in children aged <12 months have not yet been consistently identified.

Many factors limit investigations into the earliest age at which markers for ASD can be identified, including: (1) the presence of considerable individual differences and variability in cognitive and social development in young infants; (2) the use of study designs that limit conclusions about whether differences are predictive of an ASD diagnosis and/or are specific to ASD; (3) the possibility that behavioral symptoms used in diagnosis are associated with neuronal circuitry that develops after 12 months of age; and (4) the possibility that early, prodromal symptoms at the time of ASD diagnosis may differ from behaviors observed and measured later in development.

Table 2 summarizes studies in which emerging markers over the first 12 months of life were assessed. Some researchers reported no behavioral differences at the age of 6 months in social communication behaviors or in language or motor development between infants who were later diagnosed with ASD and those with a later diagnosis of typical development. Other studies, which have also included outcome measures, suggest that there may be differences during the age range of 6 to 12 months in social attention (social gaze or orienting to name being called), atypical sensory behaviors, repetitive or otherwise atypical motor behaviors, and nonverbal communication (differences in gesture use). Additional similar studies during the first 6 months of life have suggested differences in responding to social stimuli and at least some suggestion of more difficult temperaments, characterized by marked irritability, intolerance to intrusions, and being prone to distress/negative affect.

Jones and Klin recently completed a landmark study that incorporated eye-tracking technology to assess a high-risk sibling sample. They reported that infants later diagnosed with ASD exhibited diminished orienting to the eye region of the face over time, specifically from 2 to 6 months of age. Cross-sectional group differences emerged later in the first year. However, these differences in orienting of visual attention, as measured by using the eye tracker, did not have straightforward behavioral correlates that were detected by either clinicians or parents.

Studies of younger siblings of children with ASD without a known diagnostic outcome have reported either no differences in specific social behaviors or differences in visual fixation; orienting to nonsocial versus social stimuli; and prespeech vocalizations. However, the predictive validity of these differences cannot be interpreted in the absence of outcome data.

To summarize, no definitive behavioral or diagnostic markers for ASD have yet been identified in infants aged <12 months. Replication of findings across research groups is needed. Nevertheless, caregivers are encouraged to be mindful of early developmental milestones (in social and emotional development, as well as motor, language, and problem-solving skills) and to raise questions if they have concerns that developmental goals are not being met.

Statement 4: Developmental trajectories may also serve as risk indicators of ASD.

The term “trajectory” encompasses the degree, rate, and direction of changes in behavior and/or developmental milestones being studied. An assessment of the time course of specific behaviors and patterns of development may be more sensitive than single-point, or “snapshot,” measures. Specifically, there is evidence that both early development (eg, language, nonverbal cognition) and social communication behaviors may follow atypical trajectories in children with ASD ascertained from high-risk infant sibling cohorts.

Atypical trajectory of early language and nonverbal development in ASD

Scores on standardized measures of early development reflect the slowing in acquisition of new skills over the first 2 years of life. Prospective studies have reported atypical trajectories of early verbal and nonverbal skills, with relatively typical development during the first year followed by declining standard scores corresponding with slowing of the acquisition of new skills during the second year of life. In a consecutive case series, 7 of 9 high-risk infants with a later diagnosis of ASD had average cognitive scores at the age of 12 months based on either the Bayley Scales of Infant Development or the Mullen Scales of Early Learning (MSEL). However, over the next 12 to
<table>
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<tr>
<th>First Author and Year of Publication</th>
<th>Findings</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Ascertainment</th>
<th>Outcome Diagnosis</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Social/emotional behavioral markers (from studies with outcome assessment)</strong></td>
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<td>Bryson et al, 2007</td>
<td>Between ages 6 and 12 mo, in subset of siblings with change in cognitive development between 12 and 24 mo; 5 of 6 infants were “more difficult to engage socially” (“less... eye contact, no or very little social smiling, and little interest or pleasure in interacting with others”); minimal exploration of toys; atypical sensory behavior (striking visual fixation); repetitive/atypical motor behaviors</td>
<td>Prospective case series</td>
<td>9 SIBS-A later diagnosed with ASD</td>
<td>Recruited from multidisciplinary autism diagnostic and treatment centers</td>
<td>Gold standard diagnostic assessment for ASD at age 36 mo by using ADI-R, ADOS, and DSM-IV-TR criteria</td>
<td>Assessments every 6 mo from age 6–24 mo, including: • AOSI and/or ADOS to assess for ASD symptoms • BSID-II to assess cognition • CDI-WG to assess gestural and early language development • Infant Temperament Scale or Toddler Behavior Assessment Questionnaire to assess temperament Semi-structured interviews regarding parental concerns</td>
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<td>Maestro et al, 2005</td>
<td>Between ages 0 and 6 mo, significant group differences in social attention (high scores in social versus nonsocial stimuli in “typical” infants)</td>
<td>Retrospective video study</td>
<td>15 children aged 3.5–5.2 y with AD diagnosis</td>
<td>Subjects with AD recruited from community sources referred to public academic hospital; controls were kindergarten attendees</td>
<td>Diagnosis made at study entry through symptom checklist based on DSM-IV plus ≥30 score on CARS</td>
<td>From each group, home movies lasting at least 10 min coded by blinded observers for frequency of behaviors via an 8-item “grid” for assessment of social and nonsocial attention • Social attention behaviors assessed: looking at people, orienting toward people, smiling at people, vocalizing to people • Nonsocial attention behaviors assessed: looking at objects, orienting toward objects, smiling at objects, vocalizing to objects</td>
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| Maestro et al, 72 2002               | Between ages 0 and 6 mo, significant group differences in social attention and social behavior, including:  
- Less frequent looking at people (P < .001)  
- Less frequent vocalizing to people (P < .001)  
- Less frequent orienting toward people (P > .01)  
No group differences in items referring to interest and attention versus nonsocial stimuli | • 15 children aged 3.5–5.6 (mean: 4.1) y with diagnosis of AD (n = 7) or PDD-NOS (n = 8)  
• 15 “typical” “normal” children with mean age of 4.7 y  
Matched for gender and age in home videos | Controls were kindergarten attendees | Diagnosis made at study entry through symptom checklist based on DSM-IV plus score of ≥30 on CARS | - Home movies lasting at least 10 min for each subject during age 0–6 mo were rated by blinded observers for frequency of behaviors by using 13-item “grid” covering 3 developmental areas of social attention (e.g., looking at people), social behavior (e.g., anticipating the other’s aim), and nonsocial attention (e.g., “explorative activity with object”) |
| Macari et al, 46 2012               | At 12 mo, 7 ADOS-T items optimized classification of children with and without ASD at 24 mo  
• 11 of 13 children with ASD and 68 of 71 children without ASD correctly classified  
These items included: level of engagement, amount of requesting, imitation, fussiness, showing, gestures, and intonation | • 53 at-risk infants (SIBS-A); 13 diagnosed with ASD at 24 mo  
• 31 infants at no known risk (SIBS-TD) | Recruited from multiple sources (existing research programs, Web site, advertising, and word of mouth) | Clinical best diagnosis of ASD at 24 mo based on developmental and medical history, developmental and language assessments and ADOS, and DSM-IV criteria | - Subjects assessed at 12 mo and followed up to 24 mo  
- MSEL to assess development  
- ADOS-T to measure social and communicative behaviors  
- Item-level analysis of ADOS-T, “decision tree” procedures to optimize prediction of ASD |
| Nadig et al, 38 2007               | At 6 mo, nonsignificant trend for controls to require fewer number of calls to respond to name  
• 82% of controls responded on first or second call of name vs. 96% of SIBS-A | • 55 at-risk infants (SIBS-A) | Enrolled in university-based study | Clinical best diagnosis of AD or PDD-NOS at 24 mo based on clinical observation, ADOS, DSM-IV criteria | - Subjects followed up to age 36 mo  
- MSEL to assess development  
- ADOS to measure social and communicative behaviors  
- Response-to-name experimental task videotaped at 6 and 12 mo and coded for number of calls it took for response to child’s name  
- Same sample as in Merin et al, 73 2007 |
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| Ozonoff et al.,22 2010              | At 6 mo:  
- No group differences in social communication behaviors (including frequency of gaze to faces, shared smiles, and vocalizations to others)  
- 25 high-risk infants with later diagnosis of AD or PDD-NOS (22 were SIBS-A)  
- 25 gender-matched SIBS-TD determined later to have TD | Prospective longitudinal study | Sample drawn from larger longitudinal study | Classification as ASD or TD at 36 mo using Baby Siblings Research Consortium definitions (ADOS and DSM-IV-TR criteria for AD or PDD-NOS) | Assessments at ages 6, 12, 18, 24, and 36 mo of:  
- Frequencies of 6 social communication behaviors (gaze to faces, gaze to objects, smiles, nonverbal vocalizations, single-word verbalizations, phrase vocalizations), recorded onto DVDs and coded during MSEL Visual Reception subtest  
- Frequency of infant social engagement rated by blind examiners  
- MSEL to assess cognitive functioning  
- Symptom onset by parent reports | |
| Werner et al.,24 2000               | At 8–10 mo, significant (P < .05) main effect of diagnostic group for social behaviors, after children with late-onset ASD (n = 3) were removed from analysis  
- Infants with ASD “much less likely” (P < .005) than infants with TD to orient when their name was called | Retrospective video study | 15 infants later diagnosed with AD (n = 8) or PPD-NOS (n = 7)  
Participants of earlier study plus additional recruits from university infant research pool | Confirmation of AD or PPD-NOS based on DSM-III-R plus ≥30 score on CARS | Home videos between ages 8–10 mo coded for presence or absence of behaviors categorized as social (e.g., looking at others, orienting to name being called), communication (vocalizations), and repetitive |
| Young et al.,25 2009                | No infant in Merin et al.,73 2007, who showed abnormal gaze behavior (decreased eye contact) at 6 mo had any signs of autism at outcome  
- The 3 infants in sample who were diagnosed with autism by 24 mo did not exhibit abnormal gaze patterns at 6 mo and had typical affective responses at 6 mo | Prospective | 33 high-risk infants (SIBS-A)  
Refer to Merin et al.,73 2007 (below) | Clinical diagnosis of autism at 18 and/or 24 mo based on ADOS-G supplemented by M-CHAT and MSEL | Longitudinal follow-up for sample in Merin et al.,73 2007 |
<p>|                                     |          |               | 25 infant SIBS-TD | Clinical outcome data available on 49 infants | Assessment at 6 mo of eye-tracking data and behavioral data during live mother–infant interaction |</p>
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<tbody>
<tr>
<td>Zwaigenbaum et al.45 2005</td>
<td>At 6 mo, siblings with later diagnosis of ASD showed:</td>
<td>Prospective longitudinal study</td>
<td>44 SIBS-A</td>
<td>Recruited mainly at age ≤6 mo from autism diagnostic and treatment programs; low-risk infants recruited from nurseries in same regions</td>
<td>Formal independent diagnostic assessment at 36 mo based on DSM-IV criteria, ADI-R, and ADOS</td>
<td>AOSI at 6 and 12 mo to assess autism-specific behaviors</td>
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<td>No difference in number of risk markers measured by using AOSI</td>
<td>Ongoing (N = 88 followed up to age 24 mo; 6-mo data available on 44 SIBS-A)</td>
<td>15 low-risk infants (no first- or second-degree relatives with ASD)</td>
<td>“Roughly” matched according to gender, birth order, and age; N values varied by assessment</td>
<td>Clinical diagnosis of ASD made at 24 mo in up to 7 SIBS-A who met DSM-IV criteria (confirmed by using ADI-R and ADOS)</td>
<td>Computerized visual orienting task at 6 and 12 mo to assess ability to disengage from 1 of 2 competing visual stimuli (attentional disengagement)</td>
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<td>No difference (P = .12) in disengagement of visual attention</td>
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<td>Available 6-mo outcome data for 44 SIBS-A:</td>
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<td>IBQ at 6 and 12 mo to measure infant temperament</td>
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<td>Marin et al.75 2007</td>
<td>At 6 mo, diminished gaze to mother’s eyes relative to mouth (10 of 11 infants with this finding were in at-risk group)</td>
<td>Prospective</td>
<td>31 at-risk infants (SIBS-A)</td>
<td>Recruited by using research institute database and word of mouth</td>
<td>Not done</td>
<td>MSEL and CDI-WG at 12 mo to assess language and cognitive development</td>
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Social/emotional behavioral markers (from studies without outcome assessments)
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<tr>
<th>First Author and Year of Publication</th>
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<tr>
<td>Noland et al., 2010</td>
<td>At 6.5–9 mo, higher working memory scores for SIBS-A versus SIBS-TD for nonsocial stimuli; no group difference for social stimuli</td>
<td>Prospective</td>
<td>• 24 with an older sibling without autism</td>
<td>SIBS-A recruited primarily through university-based service and ASD outreach program; SIBS-TD recruited from telephone contacts by using state birth record database</td>
<td>Not done</td>
<td>• Same sample as in Nadig et al., 2007 • Trials at age 6.5 mo and/or 9 mo involving tasks relating to orienting toward social and nonsocial targets (stimuli); correct response was infant gaze toward location where target most recently appeared • Trials videotaped, coded for correct first looks</td>
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<td></td>
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<td>• 25 SIBS-A</td>
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<td>• 30 SIBS-TD</td>
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<td>Yirmiya et al., 2006</td>
<td>At 4 mo:</td>
<td>Prospective</td>
<td>• 21 dyads of mothers and infants who were SIBS-A</td>
<td>Comparison group recruited from hospital maternity wards</td>
<td>At age 14 mo, 1 subject was suspected of having autism, a diagnosis confirmed at ages 24 and 36 mo by using ADI-R and ADOS-G</td>
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<td>Ongoing (N = 42 with 4-mo assessments)</td>
<td>• 21 dyads and infants who were SIBS-TD</td>
<td>Matched on 1-to-1 basis according to chronologic age, gender, birth order, number of children in family, and Bayley mental and motor scales</td>
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<td>• BSID-II to assess general development and language</td>
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<td></td>
<td>• No significant group difference in mother–infant synchrony although SIBS-A exhibited weaker synchrony during infant-led interactions</td>
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<td>• No significant group difference in infant gaze behavior during still-face procedure but more neutral affect and less upset with SIBS-A</td>
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<td></td>
<td>• Significantly more SIBS-A responded to name being called by mother than SIBS-TD</td>
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<td>Colgan et al.,77 2006</td>
<td>At 9–12 mo, decreased variety in types of social interaction gestures used was significantly associated with autism status</td>
<td>Retrospective video study</td>
<td>21 children later diagnosed with AD</td>
<td>Recruited through mailings to child care centers and developmental evaluation centers, parent advocacy group meetings, hospital clinics, university-based autism subject registry</td>
<td>Clinical diagnosis of AD made according to time of study recruitment (preschool age), by using DSM-III-R or DSM-IV criteria and, for 11 subjects, score &gt;30 on CARS</td>
<td>Home videotapes from ages 9–12 mo collected, edited footage totaling 5 min and including social scenes, comparable across groups, were coded for use of gestures. Only gestures defined as social interaction were used in this study (“gestural act used to attract or maintain attention of another for social purposes”; e.g., waving hello or good-bye, shaking head yes or no).</td>
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<tr>
<td>Landa and Garrett-Mayer,49 2006</td>
<td>At 6 mo, no significant group differences in domains of motor, visual reception, and language development</td>
<td>Prospective longitudinal</td>
<td>24 children with later diagnosis of ASD; 11 with later diagnosis of language delay; 52 classified as unaffected (at 24 mo); 58 SIBS-A and infants with no family history of autism evaluated at 6 mo</td>
<td>SIBS-A recruited through Autism Society of America local chapters and university-based center for autism; children at low autism risk recruited through local physician offices and caregiver-child play groups</td>
<td>ASD classified at 24 mo based on PLS, ADOS, and CDI</td>
<td>MSEL to assess general and language development across 5 domains of nonsocial development (gross motor, fine motor, visual reception, receptive and expressive language); administered as close as possible to ages 6, 14, and 24 mo</td>
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<tr>
<td>Paul et al, 2011</td>
<td>At age 6–12 mo, group differences for certain prelinguistic vocal behaviors</td>
<td>Prospective cross-sectional design</td>
<td>28–38 high-risk infants (SIB-A)</td>
<td>Recruited from university research pool; also referrals from local pediatric practices, local autism advocacy groups, word of mouth, advertising in parenting media</td>
<td>Provisional diagnoses at 24 mo based on clinical observations, ADOS-T, and MSEL</td>
<td>• Vocalization samples collected at age 6, 9, and 12 mo during play with mother and standard set of toys. • Detailed analysis of vocal production (eg, for consonant inventory, presence of canonical syllables) and development of prespeech vocalization. • Discriminant function analyses included only children at high risk.</td>
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<td>• Significantly fewer speech-like vocalizations and more nonspeech vocalization</td>
<td>Ongoing (N = 43 who have participated in 24-mo follow-up)</td>
<td>20–31 low-risk infants (no sibling with ASD diagnosis)</td>
<td>Of the 24 high-risk subjects who made a 24-mo visit</td>
<td>• 7 with ASD</td>
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<td>• Significantly fewer consonant types</td>
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<td>• 6 with symptoms without meeting full BAP criteria</td>
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<td>• Significantly fewer canonical syllable shapes</td>
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<td>• 1 with nonautistic developmental delay</td>
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<td>Differences in vocal production in first year of life associated with &quot;outcomes in terms of autistic symptoms&quot; in second year for children at high risk</td>
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<td>• 10 without a clinical diagnosis</td>
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Atypical trajectory of early social communication skills in ASD

The atypical trajectory of early social communication skills in ASD include decreased social gaze, social smiles, and vocalizations between 6 and 12 to 18 months of age. Ozonoff et al. reported on the emergence of social behavioral signs in 25 high-risk siblings with a later diagnosis of ASD and 25 low-risk children matched according to gender and later determined to have typical development. There were no group differences at age 6 months, but a declining trajectory of specific behaviors over the next 12 months was noted in the high-risk group. Group differences in gaze to faces and directed vocalizations were significant by age 12 months and in social smiling by 18 months; these findings persisted through to 36 months. Similarly, in a cohort of 125 high-risk infants, reduced social smiling, eye contact, social interest, affect, and response to name at 12 months (but not at 6 months) were predictive of diagnostic outcomes at 24 months. Declining trajectories of social communicative behaviors associated with subsequent ASD diagnoses have also been reported in another cohort of 204 high-risk infants. Yoder et al. also reported declining rates of joint attention behaviors in high-risk infants subsequently diagnosed with ASD. As previously noted, Jones and Klin reported that a decline in the relative amount of time that high-risk infants aged 2 to 6 months spent orienting to the eyes versus mouth of a highly engaging adult shown on video was predictive of ASD.

Thus, the monitoring of development over time may prove important in assessing ASD risk, consistent with the American Academy of Pediatrics’ recommendations for systematic surveillance during well-child visits.

Statement 5: Caution should be exercised in drawing conclusions about early risk markers of ASD from studies that do not include individual-level outcome data.

Studies comparing behavior profiles across high- and low-risk groups can contribute to our understanding of early emerging features as well as the extent of the broader ASD phenotype (milder constellation of behavioral, cognitive, and other developmental characteristics that present in some relatives of individuals with ASD). However, group-level correlations do not always reflect individual-level correlations. Although some high-risk siblings will go on to receive a diagnosis of ASD, others will be diagnosed with other disorders, and most will not. Therefore, prevalence of an early behavioral marker in a group known to have elevated ASD risk should not be taken as evidence that the marker predicts risk at the individual level without knowing the outcome status of individuals.

Statement 6: Caution should be exercised in generalizing findings from studies of high-risk infants.

Even when individual-level data on risk markers and ASD outcomes are available in high-risk samples and markers predictive of ASD are reported, such findings might not generalize to the general population. High-risk sibling cohorts are unique in that their outcome risk is many times greater than other populations. In light of this finding and the accepted substantive involvement of genetic susceptibility factors in ASD etiology, it is plausible to suspect that unique risk mechanisms could be operating in this group. For example, initial reports suggested that abnormalities in DNA copy number variation in children with ASD were more common in simplex families than in multiplex families. More recent array- and exome-based studies resulting from more advanced sequencing methods have not confirmed a higher overall burden of genetic variants in simplex families, although these studies continue to highlight the tremendous genetic diversity among and within families. Variations in genetic mechanisms and the brain...
networks to which they map might also correlate with variation in early behavior profiles, thus potentially limiting the extent to which risk markers seen in high-risk cohorts apply to other samples. Although it is premature to assume that findings from high-risk groups do not generalize more broadly, until more is known about underlying causal mechanisms and their relationship to phenotypic profiles, ample caution should be exercised.

Statement 7: Research about early markers of ASD should include diverse high- and low-risk samples.
Studies that examine cohorts at higher risk for ASD extending beyond infant sibling cohorts may offer some additional advantages in ASD research. First, these groups (eg, infants born prematurely or infants born to older parents) might be easier to assemble in large sample sizes. Moreover, such cohorts will also prove useful for assessing the generalizability of early risk marker profiles because they will have a mix of genetic susceptibility factors different from high-risk sibling cohorts yet still have elevated outcome rates compared with general population samples. Follow-up studies involving these cohorts may also create opportunities to study whether early behavioral markers for ASD are ASD-specific or also predict other developmental endpoints that occur (eg, intellectual disabilities). This point is particularly critical because in the absence of such comparison groups, we cannot conclude that behavioral markers associated with later diagnosis in high-risk infant sibling samples would be specific to ASDDs in community samples that include the full spectrum of developmental and mental health disorders of early onset.

Statement 8: Future efforts should aim to identify: (1) early markers that can be measured in routine clinical practice, involving direct observation and parental report; (2) early biological processes measurable concurrently with, or before, overt behavioral markers; and (3) combined approaches.

Markers measurable in routine clinical practice
Many measures currently used in early identification research involve video coding of discrete behaviors, eye tracking, and/or the development of study-specific cutoffs that are of limited utility for present-day clinical practice. Efforts should be directed toward the development and validation of easy-to-administer, reliable tools for measuring potential behavioral markers within the context of routine clinical assessments; examples include coding smiling during cognitive assessment or the assessment of head lag at 6 months, especially in high-risk infants. Methods should be developed for gathering information from caregivers and from direct observation and interaction with the child, and for integrating these sources of information to inform clinical judgment. In a recent study, 2 prospective measures of emerging symptoms of ASD were found to correlate highly: (1) frequency of specific social behaviors as coded from videotape; and (2) independent examiner ratings of the frequency of social engagement behaviors in a different setting. This type of study design may accelerate the development of measures that would be valid as well as more easily integrated into everyday practice.

Early neurobiological processes
Progress has also been made in studying and integrating biological data, such as brain volume and functional imaging (eg, from electrophysiological measurements) indices, with behavioral measures of ASD. For example, enlarged brain volumes including both gray and white matter have been reported in MRI studies of toddlers with ASD. Enlargement has been noted in the frontal and temporal lobes and in specific subcortical structures, such as the amygdala. Enlargement has been observed in children as young as age 12 months and may be accompanied by an increase in extra-axial fluid. Head circumference, which is a crude proxy for brain size, is generally consistent with brain enlargement in ASD, although a recent review has raised questions as to whether ASD-related increases in head circumference have been largely driven by comparison with outdated population-based norms. As such, MRI is the gold standard for indexing structural brain development in ASD.

In some MRI studies, brain overgrowth was found to correlate with behavioral markers at later ages. For example, amygdala size was correlated with joint attention ability measured at age 4 years and with severity of social and communicative impairments measured at age 5 years. In another recent study, aberrant development of white matter pathways was found between 6 and 24 months of age in high-risk infants symptomatic for ASD at 24 months. Atypical neural responses, as indexed by event-related potentials, at age 6 to 10 months to viewing faces (specifically, the contrast between viewing faces whose eye gaze was directed toward, versus away from, the infant) have also been reported to relate to risk of ASD among high-risk infants. Using functional MRI during natural sleep, a new study showed that the superior temporal gyrus (known to be involved in language processing) was less activated in toddlers with
Cumulative risk indices

Researchers have not found a single behavioral sign or a single developmental trajectory that is predictive of all diagnoses of ASD. Given the heterogeneity of ASD expression, it is unlikely that a single behavior will be found universally across all children or will serve as the defining marker for a later emerging ASD. Future research may improve ASD risk prediction by examining combinations of symptomatic abnormalities (both in a cross-sectional manner and over time) that constitute cumulative risk indices. Moreover, such a risk-profiling approach could incorporate both behavioral and biological markers and thus offer the possibility of more reliable identification of infants at very high risk who could benefit from early intervention and/or preventive approaches to mitigate symptom development. It is also essential that future studies report individual-level data and adopt more consistent measures of relevant constructs to allow for accurate estimates of sensitivity and specificity of precise risk markers, as well as meta-analysis across studies.

ACKNOWLEDGMENTS

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REFERENCES


(Continued from first page)

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 Stone and Yirmiya 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 Estes, Hansen, McPartland, and Natowicz 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; Drs Choueiri, Fein, Kasari, Pierce, Buie, Carter, Davis, Granpeesheh, Mailloux, Newschaffer, Robins, Smith Roley, and Wetherby contributed to the consensus meeting that formed the basis for the manuscript and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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### Early Identification of Autism Spectrum Disorder: Recommendations for Practice and Research


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

abstract

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
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 number of screen-negative cases. The 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 $\leq 24$ 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 $\geq 1$ 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 screeners 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),32 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),46 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 $\geq 24$ 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
<table>
<thead>
<tr>
<th>Screening Tool</th>
<th>Reference</th>
<th>Population (N, Age, Diagnosis, Level)</th>
<th>Sensitivity and Specificity</th>
<th>PPV and NPV</th>
<th>Comments/Recommendation</th>
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<tbody>
<tr>
<td>ASD-specific screeners: parent report</td>
<td>FYI</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,22 2006; Swinkels et al,23 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,24 2001</td>
<td>N = 1283, 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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<tr>
<td></td>
<td>Robins,25 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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<tr>
<td></td>
<td>Kleinman et al,26 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, 0.80 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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<tr>
<td></td>
<td>Pandey et al,27 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 = 0.48 for low-risk samples (younger and older combined for this study) and 0.76 for high-risk samples; PPV calculated based on M-CHAT + follow-up interview</td>
<td>Note: Sample overlaps with Kleinman et al,26 2008, but does not include samples from Robins et al,24 2001, or Robins,25 2008</td>
</tr>
<tr>
<td></td>
<td>Inada et al,28 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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<tr>
<td>Screening Tool</td>
<td>Reference</td>
<td>Population (N, Age, Diagnosis, Level)</td>
<td>Sensitivity and Specificity</td>
<td>PPV and NPV</td>
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<tr>
<td>Canal-Bedia et al.</td>
<td>2011</td>
<td>Validity study: 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>Validity study: PPV not reported separately for low-risk and high-risk samples</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>
</tr>
<tr>
<td>Canal-Bedia et al.</td>
<td>2011</td>
<td>Reliability study: 2055 low risk, 18–36 mo</td>
<td></td>
<td>Reliability study: PPV = 0.19</td>
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</tr>
<tr>
<td>Pinto-Martin et al.</td>
<td>2008</td>
<td>N = 152, 18–30 mo</td>
<td>No diagnostic follow-up, cannot assess psychometrics; comparison of M-CHAT and PEDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlebowski et al.</td>
<td>2013</td>
<td>N = 18 989, 18–30 mo</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study Note: some potential false-negative findings ascertained by concurrent screening using other instruments</td>
<td>Among screen-positive children who were evaluated (171 of 278 [60.7%]) 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). 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>M-CHAT-R/F</td>
<td>2014</td>
<td>N = 18 115 low-risk toddlers</td>
<td>Estimates of sensitivity and specificity cannot be determined from this study Note: some potential false-negative findings ascertained by concurrent screening using other instruments</td>
<td>Among screen-positive children who were evaluated (221 of 348 [63.9%]) 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>
</tr>
<tr>
<td>Q-CHAT</td>
<td>Allison et al.</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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<tr>
<td>Screening Tool</td>
<td>Reference</td>
<td>Population (N, Age, Diagnosis, Level)</td>
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<tr>
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<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>
</tr>
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<td></td>
<td>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></td>
<td>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>
</tr>
<tr>
<td></td>
<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 Autistic disorder, cutoff 90: Sensitivity = 0.84 and specificity = 0.58 PDD, cutoff 85: Sensitivity = 0.88 and specificity = 0.68 PDD, cutoff 90: Sensitivity = 0.78 and specificity = 0.77</td>
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<tr>
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<td>Stone et al 38, 2000</td>
<td>n = 40 (development sample), n = 33 (validation sample); 24–35 mo, level 2 (high risk)</td>
<td>Sensitivity = 0.85 and specificity = 0.86 for validation sample (sensitivity = 0.83 and specificity = 0.83 for development age-matched subsample)</td>
<td>Not reported</td>
<td>Strong evidence for use as level 2 tool, 24–35 mo; promising for 14–23 mo but additional data will be helpful</td>
</tr>
<tr>
<td></td>
<td>Stone et al 39, 2004</td>
<td>Study 1: N = 52, 24–35 mo, ASD and other developmental delay matched on chronological and mental age, level 2 Study 2: N = 104, 24–35 mo, level 2</td>
<td>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 = 0.95 Study 2: not reported, but based on table provided, sensitivity = 1.0 and specificity = 0.90 for autistic disorder (lower for PDD-NOS)</td>
<td>Study 1: PPV = 0.86 and NPV = 0.92 (validation subsample)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stone et al 40, 2008</td>
<td>N = 71, 12–23 mo, level 2 (follow-up assessment 24–42 mo)</td>
<td>Cutoff of 2: Sensitivity = 1.0 and specificity = 0.40 Cutoff of 2.75: Sensitivity = 0.95 and specificity = 0.73 Cutoff of 2.75 in subsample of children 14–23 mo (n = 50): Sensitivity = 0.93 and specificity = 0.83</td>
<td>Cutoff of 2: PPV = 0.38 and NPV = 1.0 Cutoff of 2.75: PPV = 0.56 and NPV = 0.97 Cutoff of 2.75 in subsample of children 14–23 mo (n = 50): PPV = 0.68 and NPV = 0.97</td>
<td></td>
</tr>
<tr>
<td>Screening Tool</td>
<td>Reference</td>
<td>Population (N, Age, Diagnosis, Level)</td>
<td>Sensitivity and Specificity</td>
<td>PPV and NPV</td>
<td>Comments/Recommendation</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>----------------------------</td>
<td>-------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>BISCUIT</td>
<td>Matson et al.41,42 2009</td>
<td>N = 1007 sample with ASD or DD aged 17–37 mo (mean: 26.4 mo)</td>
<td>Sensitivity = 84.7; Specificity = 86.4</td>
<td></td>
<td>Promising as diagnostic tool or level 2 screener; more data needed</td>
</tr>
<tr>
<td>SORF</td>
<td>Wetherby et al.43 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>Not reported</td>
</tr>
<tr>
<td>Broadband screener: parent report</td>
<td>CSBS ITC Wetherby et al. 2004; Wetherby et al.44 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>Mean: 16.4 mo (6–24 mo)</td>
<td></td>
<td>Need additional data, but promising tool for 9–&gt;24 mo; not recommended for age &lt;9 mo</td>
</tr>
<tr>
<td></td>
<td>Pierce et al.17 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 not provided</td>
<td>PPV = 0.75 (estimated) for developmental delays including ASD</td>
</tr>
<tr>
<td></td>
<td>Oosterling et al.45 2009</td>
<td>N = 238; 8–44 mo (mean: 29.6 mo)</td>
<td>See note (at right) Overall sensitivity reported at 0.71</td>
<td>Overall specificity reported at 0.59</td>
<td>See note (at right) Overall PPV reported at 0.78 Overall NPV reported at 0.50</td>
</tr>
</tbody>
</table>

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.46 1992; Baron-Cohen et al.47 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; AOS, 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.\textsuperscript{25,26,31} Pandey et al.\textsuperscript{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).\textsuperscript{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]),\textsuperscript{25–27} the PPV of the M-CHAT for ASD was 0.54, and for any developmental disorder, it was 0.98.\textsuperscript{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.\textsuperscript{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,\textsuperscript{50} although some items appeared less informative for ASD than in published reports on the original English-language version. Psychometric data on Japanese\textsuperscript{28} and Arabic\textsuperscript{51} translations have also been reported. (Additional information on available translations of the M-CHAT is available at \url{http://www2.gsu.edu/~psydr/Site/Official_M-CHAT_Website.html} [accessed October 17, 2014]).

Recently, Robins et al.\textsuperscript{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, \(\geq 8\) 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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).21 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.38 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.40 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.52

Systematic Observation for Red Flags

The Systematic Observation for Red Flags has shown promise in discriminating ASD from other communication delays.43 Additional data are needed in a screening context.

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

Delays and deviations 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,53 were shown to be effective at detecting autism before the onset of full-blown clinical symptoms. Wetherby et al44 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 al17 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)54,55 and the Ages & Stages Questionnaire,56 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%.57 More recently, several independent groups conducting prospective longitudinal research involving infant siblings of children with ASD reported a pooled estimated recurrence risk of 18%.58 In contrast, a recent population registry-based study from Denmark59 estimated recurrence risk at closer to the 7% to 8% level reported in older studies.60 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.61–64 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.2 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.65–74 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 (according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, or the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [median: 61%]). Four of these studies involved samples of children aged <24 months (Table 2),65–68 although only 1 study focused almost exclusively on this age group.67 These studies provide promising evidence of the stability of ASD diagnosed as early as 14 months; the samples were relatively small, however, and there is no direct comparison of stability in children diagnosed before versus after age 24 months. Of note, 2 studies focused on toddlers identified by using community-level ASD screening before age 24 months.65,66 Both studies indicated high diagnostic stability for children initially diagnosed with autistic disorder (85%–93%) but more modest stability for children diagnosed with 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 Pediatrics have a limited amount of time to complete an increasing number of tasks, including screening for non-ASD disorders, during a well-child visit.19 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 one 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 work flow, 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

### 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</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>Diagnosis at T2</th>
<th>N</th>
<th>% Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Daalen et al.65 2009</td>
<td>Population-based sample</td>
<td>23 (34–64)</td>
<td>45 (34–64)</td>
<td>Autism 40</td>
<td>ASD 38</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 2</td>
<td>Non-ASD 2</td>
<td>ASD 2</td>
<td>61.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 13</td>
<td>Non-ASD 13</td>
<td>ASD 8</td>
<td>57.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 78</td>
<td>Non-ASD 78</td>
<td>ASD 2</td>
<td>97.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kleinman et al.66 2008</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 46</td>
<td>ASD 39</td>
<td>84.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 76</td>
<td>Non-ASD 76</td>
<td>ASD 7</td>
<td>46.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 15</td>
<td>Non-ASD 15</td>
<td>ASD 7</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 16</td>
<td>Non-ASD 16</td>
<td>ASD 0</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chawarska et al.67 2007</td>
<td>Referrals to specialty clinic with suspected ASD</td>
<td>21.6 (14–25)</td>
<td>35.9</td>
<td>Autism 21</td>
<td>ASD 21</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 6</td>
<td>Non-ASD 6</td>
<td>ASD 6</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 4</td>
<td>Non-ASD 4</td>
<td>ASD 1</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 24</td>
<td>Non-ASD 24</td>
<td>ASD 3</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 4 ASD 0</td>
<td>Non-ASD 4 ASD 0</td>
<td>ASD 0</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gillberg et al.68 1980*</td>
<td>Referred sample</td>
<td>23.0 (8–35)</td>
<td>57.7 (38–140)</td>
<td>Autism 21</td>
<td>ASD 21</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 2</td>
<td>Non-ASD 2</td>
<td>ASD 2</td>
<td>50</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Non-ASD 2</td>
<td>Non-ASD 2</td>
<td>ASD 0</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-ASD 2</td>
<td>Non-ASD 2</td>
<td>ASD 2</td>
<td>50</td>
<td></td>
<td></td>
</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. 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 characterizations 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%) 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. 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.

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 al83; the second approach is currently recommended by the AAP.2 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.30 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 al34 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.17,84 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 al5) and in other public health screening interventions.85 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.86 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),87–89 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")  
  - Age-matched children with ASD having suboptimal outcome representative of the population giving rise to the case subjects ("control subjects") |
| Strengths                 | Random assignment to control for confounding by indication  
  - Temporality assured | Temporality assured | Less cost  
  - Less time to complete  
  - Potential for selection bias  
  - Need to control for confounding by indication (more challenging in retrospective designs)  
  - Need to be able to accurately identify true screening encounter |
| Weaknesses                | Ethnically feasible?  
  - Large sample needed | Potential for selection bias  
  - Need to control for confounding by indication | Substantial follow-up needed  
  - Expensive | Expensive |
|                          | Substantial follow-up needed  
  - Expensive  
  - Can raise generalizability issues | Large sample needed | 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 al17 to assemble a cohort of toddlers with ASD, Dinstein et al10 recorded functional MRI activity from 63 naturally sleeping toddlers with ASD, language disorder (ie, 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, Bosl et al,99 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 &gt; 80% accuracy into control groups and high-risk groups at age 9 months. More recently, Elsabbagh et al100 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 al101 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.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.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.105 Consideration of several biomarkers at once is consistent with the multitude of genetic and epigenetic factors (and potentially other biological factors [eg, immune, indices of atypical brain growth/connectivity]) that likely play a role in vulnerability to ASD in many children.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.107–110

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.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 (eg, cost, invasiveness), others, such as EEGs, are more readily available in pediatric settings (eg, 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.

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ABBRiEvAtiONS
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, Newschaffer, 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 Choureiris, 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.

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Early Intervention for Children With Autism Spectrum Disorder Under 3 Years of Age: Recommendations for Practice and Research

abstract

This article reviews current evidence for autism spectrum disorder (ASD) interventions for children aged <3 years, based on peer-reviewed articles published up to December 2013. Several groups have adapted treatments initially designed for older, preschool-aged children with ASD, integrating best practice in behavioral teaching methods into a developmental framework based on current scientific understanding of how infants and toddlers learn. The central role of parents has been emphasized, and interventions are designed to incorporate learning opportunities into everyday activities, capitalize on “teachable moments,” and facilitate the generalization of skills beyond the familiar home setting. Our review identified several comprehensive and targeted treatment models with evidence of clear benefits. Although some trials were limited to 8- to 12-week outcome data, enhanced outcomes associated with some interventions were evaluated over periods as long as 2 years. Based on this review, recommendations are proposed for clinical practice and future research. Pediatrics 2015;136:S60–S81

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ABBREVIATIONS

ABA—applied behavior analysis
ASD—autism spectrum disorder
ESDM—Early Start Denver Model
GRADE—Grading of Recommendations Assessment, Development, and Evaluation

(Continued on last page)
The ultimate goal of early detection and screening is to ensure that children with autism spectrum disorder (ASD) can access evidence-based interventions to provide the best opportunity for optimal development and outcomes. With the advances reviewed by Zwaigenbaum et al in this special issue of Pediatrics, and the growing evidence that ASD can be diagnosed accurately before 2 years of age, the need for ASD treatment programs specifically designed for this age group has never been greater. Some authors have also argued that the second year of life is a particularly critical developmental period for children with ASD, for various reasons. First, the second year is a dynamic period of brain growth, during which increases in brain volume and atypical connectivity associated with ASD first emerge but also a time of substantial neural plasticity providing greater potential to alter developmental course. Second, a proportion of children with ASD reportedly regress in the second year. Recent research has indicated only modest agreement between retroactively reported regression and analysis of behavioral change as observed on serial home videos and that acute skill loss may exist along a continuum of gradually declining trajectories of social and communicative behavior. However, interventions during this period may counter the developmental cascade that contributes to progressive symptom development and ultimately prevent ASD-related impairments before they fully manifest.

Intervention approaches for children aged <2 to 3 years need to be developmentally appropriate. We cannot assume that findings from treatment research involving older children with ASD will generalize to infants and toddlers, who differ with respect to the nature of their social relationships as well as their cognitive and communicative processes. Infants depend on experiential learning within their natural environments and on interactions rooted in social play that occur within the context of everyday caregiving activities. Fortunately, over the past several years, a growing number of studies have evaluated interventions specifically designed for children aged <2 to 3 years. An updated review of these interventions may provide needed direction and guidelines to clinicians and policy makers.

**METHODS**

The working group conducted a search of the literature published online between 2000 and 2012 related to intervention programs provided to children with ASD aged <3 years. The working group summarized published research on interventions developed for use in children aged ≈36 months, even if the age range of samples of children being evaluated extended beyond age 3 years (Table 1). A PubMed search was conducted on June 30, 2010, for articles published since January 1, 2000, by using the search terms (“child developmental disorders, pervasive” or “autistic disorder” or “autism [tw]” or “autistic [tw]”) and (“Early intervention”) or (“intervention [tw]”), with an age filter (“infant, birth-23 months” or “Pre-school child, 2-5 years”) and limited to English-language articles. This search provided 419 references, which were reviewed by Drs Zwaigenbaum and Bauman, who selected articles focusing on clinical trials of developmental/behavioral interventions (ie, not medications or trials of other biomedical therapies) that included children aged <36 months. Search results were complemented by additional publications identified by working group members. Hence, although the search strategy was comprehensive, selection of articles was not systematic, which is an important limitation. A scoping approach, with some discretion of the multidisciplinary expert working group, was used instead to select articles of highest relevance.

Each selected study was assessed, and working group members were asked to arrive at a consensus evaluation on each article after a detailed discussion. The search was updated by using the same strategy to add articles published to December 31, 2013, which yielded an additional 323 references; selection was again limited to clinical trials of developmental/behavioral interventions that included children aged <36 months. The working group reviewed and approved the final wording of the summary and recommendations.

We recognize that in addition to comprehensive early intervention programs, the management and treatment of young children with ASD often involves speech and language and occupational and physical therapies, as well as management of comorbid conditions such as associated medical disorders (eg, sleep, gastrointestinal), anxiety, and challenging and maladaptive behaviors. However, a review of these targeted interventions was beyond the scope of the current initiative.

**LITERATURE REVIEW**

Table 1 summarizes the key features and outcomes of 24 randomized controlled, quasi-experimental, and open-label studies involving children with ASD aged <3 years reviewed by the working group. Because few studies focused exclusively on this age group, studies in which participants included some children aged >3 years were assessed as long as there was sufficient information to draw inferences about younger children. The group reviewed additional reports, which have not been listed in Table 1, including single-subject studies, other relevant studies, and reviews.
## TABLE 1 Selected Intervention Studies Involving Children Aged <3 Years (2000–2013)

<table>
<thead>
<tr>
<th>Reference</th>
<th>N, Chronological Age, Gender</th>
<th>Design</th>
<th>Dose</th>
<th>Treatment Content</th>
<th>Approach</th>
<th>Outcomes</th>
<th>Degree of Parental Involvement</th>
<th>Comments</th>
<th>GRADE Quality of Evidence</th>
<th>GRADE Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers et al, 2012</td>
<td>N = 98 with ASD (screen-positive on the ITQ and ESAT and diagnosis by using ADOS-T and clinical judgment) Aged 12–24 mo (mean: 21.0 mo), 76 boys</td>
<td>RCT</td>
<td>1 h parent training per week × 12 wk, plus self-instruction manual for parent to review</td>
<td>Comprehensive ESDM (see Dawson et al, below), adapted as briefer parent training model</td>
<td>No main treatment effects on parent acquisition of ESDM intervention skills nor improvement in child development or ASD symptoms</td>
<td>Implemented by parents</td>
<td>Both groups showed improvement in child outcomes, related to hours of intervention and older child age at baseline</td>
<td>Moderate/high Weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carter et al, 2011</td>
<td>N = 62 with ASD symptoms or at risk (STAT) Aged 15–25 mo (mean: 20.3 mo), 51 boys</td>
<td>RCT</td>
<td>1 group session with parents per week × 8 wk, plus 5 at-home individualized sessions for parent and child</td>
<td>Targeted Hanen recommendations: parent training in small groups plus 1:1</td>
<td>No main treatment effects on parent responsivity or child communication outcomes immediately or 5 mo after treatment (although moderate to large effect sizes for parent responsivity gains)</td>
<td>Implemented by parents</td>
<td>Missing data precluded ITT analysis</td>
<td>Moderate/high Weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landa et al, 2011</td>
<td>N = 48 with ASD</td>
<td>RCT</td>
<td>10 h/week × 6 mo</td>
<td>Targeted Social curriculum (5.5, OII, routines-based interactions) added to comprehensive classroom-based intervention (AEPS)</td>
<td>Significant (P = .02) between-group difference for socially engaged imitation (moderate effect size at 6 mo, large effect size at 12 mo)</td>
<td>Implemented by interventionists</td>
<td>Control group without social curriculum nevertheless received some imitation and JA intervention</td>
<td>Moderate/high Weak</td>
<td></td>
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GRADE = Grading of Recommendations Assessment, Development and Evaluation.
<table>
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<tr>
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<tr>
<td>Dawson et al, 2010</td>
<td>N = 48 with ASD</td>
<td>RCT</td>
<td>20 h/week × 2 y (therapists) plus ≥5 h/wk × 2 y (parents)</td>
<td>Comprehensive</td>
<td>ESDM</td>
<td>Significant between-group differences in IQ and adaptive behavior after 2 y</td>
<td>Delivered by therapists and parents</td>
<td>Group differences larger than those in studies of comparable developmental behavioral approaches of shorter duration and fewer hours of delivery per week</td>
<td>Moderate/high</td>
<td>Strong</td>
</tr>
<tr>
<td>Green et al, 2010</td>
<td>N = 152 with AD</td>
<td>RCT</td>
<td>4 h/month × 6 mo, then 2 h/month × 6 mo</td>
<td>Targeted</td>
<td>PACT intervention to increase parent sensitivity and responsiveness; 1:1 with child present, plus treatment as usual</td>
<td>NS between-group difference in child autism symptom severity, language measures, or adaptive functioning in school at 15 mo</td>
<td>Parent mediated</td>
<td>ADOS-G, used as primary outcome, may not be sensitive measure of change</td>
<td>Moderate/high</td>
<td>Strong</td>
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<tr>
<td>Reference</td>
<td>N, Chronological Age, Gender</td>
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<tr>
<td>Ingersoll, 19</td>
<td>N = 21 with AD</td>
<td>RCT</td>
<td>3 h/week × 10 wk</td>
<td>Targeted Behavioral intervention (RIT): laboratory setting, naturalistic techniques</td>
<td>Significantly more gains in elicited (P &lt; .05) and spontaneous (P &lt; .02) imitation, in both object (P &lt; .05), and gesture (P &lt; .01) imitation compared with controls</td>
<td>Implemented by therapists</td>
<td>Groups not matched pretreatment (better imitation in RIT group)</td>
<td>Moderate/high</td>
<td>Strong</td>
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<tr>
<td>Kasari et al, 19</td>
<td>N = 38 with AD</td>
<td>RCT</td>
<td>2 h/wk (three 40-min sessions) × 8 wk</td>
<td>Targeted Immediate JA intervention: instructing caregiver–child dyad during play routines; combined developmental and ABA approach; laboratory setting</td>
<td>At 8 wk, significant (P &lt; .00) between-group differences in level of joint engagement, child responsiveness to JA, and diversity of functional play acts (generally large effect sizes)</td>
<td>Caregiver mediated</td>
<td>Concurrent early intervention (9–40 h/wk) received by both groups (no differences in dose or type)</td>
<td>Moderate/high</td>
<td>Strong</td>
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<td>S64</td>
<td>ZWAIGENBAUM et al</td>
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<tr>
<td>Oosterling et al, 2010</td>
<td>N = 75 with ASD</td>
<td>RCT</td>
<td>Year 1: Group sessions 2 h/wk × 4 wk, then home visits 5 h/wk every 6 wk</td>
<td>Targeted Parent training by psychologists or sociotherapists (nonintensive, home-based, called &quot;focus parent training&quot;) plus care as usual</td>
<td>After 12 mo Parents as everyday therapists</td>
<td>Flawed randomization of first 26 participants</td>
<td>Weak Moderate to low/very low</td>
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<tr>
<td>Zachor and Ben-Itzchak, 2010</td>
<td>N = 78 with ASD</td>
<td>Quasi-experimental</td>
<td>Year 2: Home visits every 3 mo plus plenary sessions every 6 mo</td>
<td>No between-group differences in language development, global clinical development, and mediating outcomes (ie, child engagement, early precursors of social communication, parental skills)</td>
<td>Stronger parent involvement in eclectic group</td>
<td>Groups not randomly assigned</td>
<td>Moderate Weak</td>
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<tr>
<td>Ben-Itzchak and Zachor, 2009</td>
<td>N = 68 with AD</td>
<td>Open</td>
<td>20 h/wk × 1 y</td>
<td>ABA-based intervention: 1:1, child-centered; part of community center–based ASD-specific preschool program (40 h/wk)</td>
<td>NS between-group differences in change in ASD diagnostic classification, cognitive abilities, or adaptive skills</td>
<td>Implemented by therapists and special education teachers</td>
<td>Moderate Strong</td>
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<td>Aged 12–24 mo (mean: 34.4 mo); 52 boys</td>
<td>Comprehensive</td>
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<td>Aged 15–35 mo (mean: 25.4); 71 boys</td>
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<td>ED: mix of developmental, DIR, and TEACCH; 7:5, part of same preschool program (40 h/wk)</td>
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<td>Treatment Content</td>
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<td>Outcomes</td>
<td>Degree of Parental Involvement</td>
<td>Comments</td>
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<tr>
<td>Eikeseth et al, 2009</td>
<td>N = 20 with AD</td>
<td>Open</td>
<td>Range of supervision intensity: 2.9–7.8 h/month (M: 5.2)</td>
<td>Comprehensive</td>
<td>EIBI (UCLA/Lovaas model): home-based, 1:1; mean: 34.2 h/wk × 50 wk, parent-managed service</td>
<td>Intensity of supervision significantly (P &lt; .05) correlated with changes in IQ and visual-spatial IQ after 14 mo</td>
<td>NS correlation with adaptive functioning</td>
<td>Implemented by tutors</td>
<td>3 children excluded from data analysis (2 withdrew from study; 1 required increased supervision)</td>
<td>Very low/low</td>
</tr>
<tr>
<td>Ben-Itzchak and Zacher, 2007</td>
<td>Of 23 who entered study, 17 boys</td>
<td>N = 25 with AD</td>
<td>≥35 h/wk × 1 y</td>
<td>Comprehensive</td>
<td>Intensive ABA intervention: center-based, 1:1, addressing developmental and behavioral areas</td>
<td>Significant (P &lt; .001) improvements after 1 y in imitation, receptive/expressive language, nonverbal communication, play skills, and stereotyped behaviors</td>
<td></td>
<td>Implemented by therapists</td>
<td>No control group</td>
<td>Low/moderate</td>
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</table>

Aged 18–35 mo (mean: 25.4 mo); 62 boys

Compared with children with unchanged status (n = 53), those with improved classification (n = 15) gained significantly more in cognitive abilities (P < .01), adaptive skills (P < .05 for communication scores), and stereotyped behaviors (P < .05).

But parent training is part of eclectic programs.

Aged 28–42 mo (mean: 34.9 mo)

Of 23 who entered study, 17 boys

Aged 20–32 mo (mean: 26.6 mo); 23 boys

Parent training on how to use behavioral methods at home.
<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Design</th>
<th>Dose</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Degree of Parental Involvement</th>
<th>Comments</th>
<th>GRADE Quality of Evidence</th>
<th>GRADE Recommendation</th>
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<tbody>
<tr>
<td>Goin-Kochel et al.</td>
<td>29</td>
<td>Open</td>
<td>≥30 h/wk × 12–18 mo</td>
<td>Comprehensive EIBI: ASD-specific preschool program in private school setting. ABA-based (ABLLS) curriculum; 1:1 plus small groups</td>
<td>Significant group progress over time across multiple skills (P &lt; .001 for all ABLLS domains)</td>
<td>Parents “required” to provide EIBI at home, 10 h/wk, to supplement school-based intervention</td>
<td>No control group</td>
<td>Low</td>
<td>Weak</td>
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<tr>
<td>Magiati et al.</td>
<td>44</td>
<td>Quasi-experimental</td>
<td>18–40 h/wk × 2 y</td>
<td>Comprehensive EIBI in community setting: home-based; 1:1; DTT and, in 2 families, verbal behavior</td>
<td>NS group differences in cognitive ability, language, play skills, or ASD severity at 2 y</td>
<td>Moderate to large effect sizes for adaptive behaviors; moderate effect size for ASD severity</td>
<td>Group differences in educational functioning</td>
<td>In 23 of 28 families, 1 parent trained as a therapist</td>
<td>Low/moderate</td>
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<td></td>
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<td>M, 33.2 at end of 2 y</td>
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<tr>
<td>Reed et al.</td>
<td>27</td>
<td>Quasi-experimental</td>
<td>20–40 h/wk (M, 50.4) × 9–10 mo</td>
<td>Comprehensive Home-based, high-intensity ABA programs, mostly 1:1 and in natural settings: UCLA/Lovaas model</td>
<td>Significant (P &lt; .01) between-group differences in educational functioning</td>
<td>Some involvement by family members</td>
<td>Group differences in intellectual functioning, adaptive behavior, and ASD severity</td>
<td>Within the high-intensity groups, ↑ temporal input (h/wk) was not associated with ↑ gains</td>
<td>Low/moderate</td>
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<td>M, 27.4 at end of 2 y</td>
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<td>Degree of Parental Involvement</td>
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<tr>
<td>Remington et al.</td>
<td>N = 44 with AD 30–42 mo (mean: 34.7, 34.4 mo)</td>
<td>Quasi-experimental</td>
<td>18.4–34.0 h/wk (mean: 25.6) × 2 y</td>
<td>Comprehensive</td>
<td>CABAS: emphasizing teacher–student interaction as unit of analysis</td>
<td>Large effect sizes for high-intensity group in intellectual and educational functioning; moderate effect sizes for low-intensity group</td>
<td>Moderate</td>
<td>Strong</td>
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<tr>
<td>Zachor et al.</td>
<td>N = 39 with ASD</td>
<td>Quasi-experimental</td>
<td>35 h/wk × 1 y</td>
<td>Comprehensive</td>
<td>ABA-based early intensive intervention: center-based, 1:1; DTT, naturalistic techniques</td>
<td>Implemented by therapists</td>
<td>Moderate</td>
<td>Weak</td>
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<td>Reference</td>
<td>N, Chronological Age, Gender</td>
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<tr>
<td>Cohen et al, 2006</td>
<td>N = 42 with ASD</td>
<td>Quasi-experimental</td>
<td>35–40 h/wk × 47 wk/y × 5 y^2</td>
<td>Comprehensive</td>
<td>EIBI (UCLA/Lovaas model): community based, 1:1 home instruction, DTT, plus classroom based regular education preschool</td>
<td>Significant differences in IQ (P &lt; .03) and adaptive behavior (P = .01) favoring EIBI</td>
<td>Implemented by tutors</td>
<td>Groups not randomly assigned</td>
<td>Very low/low</td>
</tr>
<tr>
<td>Kasari et al, 2006</td>
<td>N = 58 with AD</td>
<td>RCT</td>
<td>2.5 h/wk × 5–6 wk</td>
<td>Targeted</td>
<td>JA intervention: child centered ABA and milieu teaching strategies added to EIP; laboratory setting</td>
<td>After 6 wk: Children directly taught by trained interventionists</td>
<td>At year 3, 17 of 21 EIBI children in regular education (6 without support) vs 1 of 21 in comparison group</td>
<td>Treatment fidelity not assessable in comparison group</td>
<td>Moderate/high</td>
</tr>
<tr>
<td>Kasari et al, 2008</td>
<td>Aged 3–4 y (mean: 43.2, 42.7, 41.9 mo); 46 boys</td>
<td>2.5 h/wk × 5–6 wk</td>
<td>SP intervention using same strategies, added to same EIP; laboratory setting</td>
<td>↑ JA skills in JA group and ↑ diversity and sophistication of play in SP group compared with controls (large effect sizes)</td>
<td>Control group then received more hours of intervention services than former JA (P &lt; .05) and SP (P &lt; .01) groups</td>
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<td><strong>EIP: 30 h/wk × 5–6 wk</strong></td>
<td>Control group: Same EIP without JA or SP intervention: hospital day-treatment program for children with developmental disabilities and/or behavioral disorders; 1:1 or 1:2 ABA-based techniques; adult-centered, response-oriented approach to teaching</td>
<td>Acquired skills generalized to play with mothers (large effect sizes for JA and SP)</td>
<td>Some general effects of therapy (JA, functional play skills) in JA and SP groups</td>
<td>At 12-mo follow-up: Significantly (P &lt; .01) greater growth in expressive language for JA and SP (moderate effect sizes for JA and SP versus control)</td>
<td>Children with lowest language levels pretreatment had significantly (P &lt; .001) better language outcomes with JA than with SP or EIP (moderate to large effect sizes for JA)</td>
<td>JA and SP groups continued to show growth and generalization in skills and outperform control group</td>
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<td>Wetherby and Woods, 2006</td>
<td>N = 17 with ASD</td>
<td>Quasi-experimental</td>
<td>2 home visits/wk × 1 y</td>
<td>Targeted ESI: family training to follow child's focus of attention and build child's skills in daily routines (developmental approach, natural environment)</td>
<td>Significant improvements from baseline for ESI group in 11 of 13 social communication measures (large effect sizes for 12 OSBS DP behavioral sample measures, moderate effect size for 13th measure)</td>
<td>Implemented by parents</td>
<td>Not known whether groups were matched at baseline (age 2 y)</td>
<td>Very low/low</td>
<td>Weak</td>
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<td>Actual intervention intensity not documented</td>
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<td></td>
<td>N = 18 with ASD</td>
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<td>Plus 1 supervised parent–child play group (including TD children) per week × 9 wk × 1 y</td>
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<tr>
<td>Yoder and Stone, 2006</td>
<td>N = 36 with ASD</td>
<td>RCT</td>
<td>1 h/wk (three 20 min sessions) × 6 mo</td>
<td>Targeted University clinic–based PECS: 6 instructional phases conducted by speech-language pathologists</td>
<td>RPMT &gt; PEG in facilitating frequency of generalized IJA (in children with some pretreatment IJA) and generalized turn taking (large and moderately large effect sizes, respectively)</td>
<td>Parent training (up to 15 h) to support intervention use outside clinic</td>
<td>Examiners conducting pre/post assessments not blinded to treatment status</td>
<td>Moderate/high</td>
<td>Weak</td>
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<td>Howard et al, 2005</td>
<td>N = 61 with ASD</td>
<td>Quasi-experimental</td>
<td>25–40 h/wk × 14 mo</td>
<td>Comprehensive EIBI: 1:1, home, school, or community setting</td>
<td>EBI &gt; AP: significantly higher group mean scores for IQ, nonverbal, language, overall communication, and social skills</td>
<td>Delivered by trained tutors</td>
<td>Groups not randomly assigned</td>
<td>Very low/moderate</td>
<td>Weak</td>
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<td>Aged &lt;48 mo (mean: 30.9, 37.4, 34.6 mo), 54 boys</td>
<td>25–30 h/wk × 14 mo</td>
<td>Intensive, eclectic, autism-specific educational programming (AP): 1:1 or 2:1, public school classroom-based; including DTT, PECS, and TEACCH</td>
<td>NS differences in group mean scores between AP and GP</td>
<td>Parents to implement programs outside of scheduled intervention hours</td>
<td>No direct group comparison; statistical analysis of group mean scores</td>
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<td>15 h/wk × 14 mo</td>
<td>Nonintensive generic educational programming (GP): 6:1, community based, mix of methods</td>
<td>↑ Learning rates at 14 mo (P ≤ .05) for EIBI versus other 2 groups in all domains except motor skills (normal or above-normal rates, especially in acquisition of language skills)</td>
<td>Many techniques not operationally defined</td>
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<tr>
<td>Drew et al, 2002</td>
<td>N = 24 with AD RCT</td>
<td>3 h/wk every 6 wk × 12 mo</td>
<td>Targeted Parent training (home-based) that focused on joint attention skills; plus available community services</td>
<td>NS group differences in child language development after 12 mo</td>
<td>Parent mediated</td>
<td>Groups not matched on baseline nonverbal IQ</td>
<td>Very low/low/moderate</td>
<td>Weak/moderate</td>
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<tr>
<td>Aged &lt;24 mo (mean: 22.5 mo), 19 boys</td>
<td>3 h/wk</td>
<td>Parent to use learned techniques during daily routines and in set-aside joint play sessions (30–60 min/d)</td>
<td>No data on parent training implementation</td>
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<tr>
<td>Available community services only*</td>
<td>Language ability in both groups still severely compromised at 12 mo</td>
<td>Total intervention hours higher (P &lt; .07) in control group</td>
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<td>Reliance on parent report for language outcomes</td>
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<td>Smith et al, 2000</td>
<td>N = 28 with ASD</td>
<td>RCT</td>
<td>30 h/wk × 2–3 y (decreasing in later years with progress by child)</td>
<td>Comprehensive EIBI (UCLA/ Lovaas model): home-based 1:1, then shifting to classroom setting, ABA-based</td>
<td>Significant (P &lt; 0.05) between-group differences at age 7–8 y in IQ, visual spatial skills, and language development favoring EIBI</td>
<td>Intensive treatment implemented by therapists</td>
<td>Lacked standardized diagnostic instrument</td>
<td>Moderate/high</td>
<td>Strong</td>
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<tr>
<td>Aged 18–42 mo (mean: 35.8, 36.1 mo), 25 boys</td>
<td>5 h/wk parent training × 3–9 mo plus 10–15 h/wk of special education for children</td>
<td>Parent training in same treatment approaches; plus special education classes for children</td>
<td>Parent training in same treatment approaches; plus special education classes for children</td>
<td>No differences in adaptive functioning or behavior problems</td>
<td>In both groups, parents asked to provide 5 h/wk of intervention</td>
<td>Skewed distribution of scores precluded some statistical analyses</td>
<td>Improved school placement in intensive treatment group</td>
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**ABLLS, Assessment of Basic Language and Learning Skills; AD, autistic disorder; ADOS, Autism Diagnostic Observation Schedule; ADOS-G, Autism Diagnostic Observation Schedule–Generic; ADOS-T, Autism Diagnostic Observation Schedule–Toddler Module; AEPS, Assessment, Evaluation, and Programming System for Infants and Children; AP, intensive eclectic autism-specific educational programming; CABAS, Complete Application of Behavior Analysis to Schools approach; CSBS DP, Communication and Symbolic Behavior Scales Developmental Profile; DIR, Developmental, Individual Difference, Relationship; DTT, discrete trial training; EIBI, early intensive behavioral intervention; EIP, Early Intervention Program; ESAT, Early Screening of Autistic Traits questionnaire; ESI, Early Social Interaction Project; GP, non-intensive generic educational programming; ITT, intention-to-treat; ITT, intention-to-treat; JA, joint attention; PACT, Preschool Autism Communication Trial; PECS, Picture Exchange Communication System; RCT, randomized controlled trial; RIT, reciprocal imitation training; RJA, responding to joint attention; RPMT, Responsive Education and Prelinguistic Mileu Teaching; SP, symbolic play; SPELL, Structure, Positive (approaches and expectations), Empathy, Low (arousal), and Links framework; STAT, Screening Tool for Autism in Two-Year-Olds; TD, typically developing; TEACCH, Treatment and Education of Autistic and Related Communication Handicapped Children; UCLA, University of California, Los Angeles.**

*Child-to-teacher ratio.*

3. Green et al, 2010: Treatment as usual included group-based autism psychoeducation, communication-focused intervention, Portage therapy, speech and language therapy, and (for 1 child each in PACT group) home-based EIBI and Son-Rise therapy.
4. Kasari et al, 2010: Concurrent early interventions involved mostly ABA/educational services and speech and occupational therapy; study investigators did not coordinate with providers of these services.
5. Osterling et al, 2010: Care as usual, including speech and language therapy, motor therapy, music therapy, play therapy, and parental counseling.
7. Remington et al, 2007: Treatment-as-usual interventions in both groups included PECS, TEACCH, speech therapy, dietary intervention, and prescription medication.
8. Zachor et al, 2007: ED approach included speech and language, occupational, and music therapies, plus structured cognitive teaching (DIR, TEACCH, and ABA techniques).
9. Cohen et al, 2006: SS to 40 hours per week for children aged >3 years; 20 to 30 hours per week for children aged <3 years.
10. Drew et al, 2002: Children in control group received mix of speech and language therapy, occupational therapy, and preschool services. Within 5 mo of initial assessment, 3 children in control group started on intensive, home-based ABA interventions (UCLA/Lovaas, mean of 32 h/week for 12 months).
Compared with early intervention models evaluated for preschool-aged children (aged 3–5 years), programs for children aged <3 years were more likely to use developmental approaches, more intensively involve parents, and target social communication. These studies varied in sample size and severity of diagnosis, dose (level of intensity/frequency of service delivery), duration, agent (parent, therapist, or a combination), and format of delivery (parent-managed/home-based and/or center-based in a clinic or school) of the intervention. Some interventions were comprehensive, defined as addressing multiple core ASD deficits, while others targeted specific areas of functioning. A word of caution is warranted when interpreting any 1 interventional study or model. In some cases, elements of a particular programmatic approach varied from study to study (eg, the addition of training in advanced social skills in 1 early intensive behavioral intervention program). Furthermore, reported group differences may not reflect the range of individual responses in any 1 study, and participants who demonstrated gains in some end points may have continued to show impairment in others.

Six randomized controlled trials were considered to produce strong recommendations and an assessment that the desirable effects of an intervention clearly outweighed the undesirable effects. Only 2 studies focused solely on children aged <3 years; 1 was related to a comprehensive treatment approach, and 1 was a targeted intervention program. The remaining 4 studies included preschool-aged children as well as some children aged <3 years or focused on developmental tasks of infancy. Two of these studies evaluated the same sample of children aged 3 or 4 years at the beginning of treatment.

To briefly summarize these 6 studies, both of the comprehensive intervention programs (Early Start Denver Model [ESDM] and the UCLA/Lovaas model) and the 4 targeted interventions (focusing on social communication or imitation skills) exhibited significantly improved outcomes relative to comparison groups after therapeutic durations of 8 weeks to 2 to 3 years. Several of the 6 studies reported effect sizes: large effect sizes after 6 and 8 weeks of therapy for increases in joint attention skills, a moderate effect size after 12 months for expressive language growth, and small effect sizes after 13 months for parent–child interaction measures. It is notable that targeted interventions generally focused on outcomes related to ASD-specific characteristics, whereas the comprehensive models included teaching to the core deficits but often did not measure changes in these core deficits (or obtained nonsignificant findings); they instead focused on gains in general functioning (eg, cognitive and/or adaptive skills). Two nonrandomized controlled studies were rated as producing strong recommendations: comprehensive applied behavior analysis (ABA)-type interventions were associated with significantly improved outcomes relative to the comparison group after 2 years (compared with publicly funded educational services) and with significantly improved outcomes in a subset of participants after 1 year (compared with an eclectic mix of treatments).

Although other studies included in the present review exhibited less than moderate quality of evidence and/or produced weak recommendations, it was agreed that the findings in these studies might nevertheless inform treatment options as well as future research. Specifically, there were studies rated as having a strong quality of evidence but equivocal findings. For example, a recent trial evaluated the ESDM in a brief format: 1 hour per week of parent training for 12 weeks, as opposed to the original ESDM, which involved 20 hours per week of therapist involvement plus additional parent-mediated intervention for 2 years. The study failed to detect improvements in parental intervention skill acquisition and child-related outcomes relative to community intervention controls.

Based on expert opinion that arose from the review and discussion of the existing evidence, members of the working group agreed on several summary statements intended to guide clinical practice and future research. Practice recommendations are highlighted in statements 1 through 4, consensus regarding future research directions is highlighted in statements 5 through 9. Statement 10 focuses on the importance of considering the potential impact of medical comorbidities on treatment and developmental outcomes.

**SUMMARY STATEMENTS**

**Statement 1:** Current best practices for interventions for children aged <3 years with suspected or confirmed ASD should include a combination of developmental and behavioral approaches and begin as early as possible.

Based on current outcome data, the working group supported the provision of interventions targeted to the specific deficits of ASD (eg, language skills, joint attention, emotional reciprocity) for children aged <3 years that integrate both behavioral and developmental approaches. Behavioral interventions are techniques based on behavioral analysis of antecedents and consequences of specific behaviors, and they use principles derived from experimental psychology research to systematically change behavior. Developmental models of intervention use developmental theory to design approaches to target ASD deficits. Developmental approaches often
underlie community services, such as public school programs implemented by special education specialists and speech and language pathologists.\textsuperscript{56} However, the distinction between behavioral and developmental strategies may not be very helpful, as many intervention programs blend features of both approaches. The curricula of a behavioral intervention may be developmentally informed and based on developmental sequences, whereas a developmental program could use behavioral techniques to teach a curriculum.

Our analysis supports the effectiveness of integrated developmental and behavioral interventions, outside of the laboratory setting, in improving developmental quotients, adaptive functioning, and language skills.\textsuperscript{17,29}

In line with the American Academy of Pediatrics, the working group recommended initiating interventions as soon as a diagnosis of ASD is seriously considered or determined.\textsuperscript{57} Data available since 2001 support the fact that early intensive education and therapies can yield significantly improved developmental outcomes. In addition, it has been suggested that interventions initiated before 3 years of age may have a greater positive impact than those begun after the age of 5 years.\textsuperscript{58–60}

**Statement 2: Current best practices for children aged <3 years with suspected or confirmed ASD should have active involvement of families and/or caregivers as part of the intervention.**

There is a consensus that effective early intervention includes a family and/or caregiver component.\textsuperscript{57} For many intervention programs, this approach would mean parental involvement as a co-therapist, with appropriate supervision, training, and monitoring as part of the intervention. Specifically, parents should help set goals and priorities for their child’s treatment, identify and locate needed support for themselves, and teach or reinforce their child’s new skills at home and in the community.\textsuperscript{60}

Active family involvement can have a positive impact on developmental outcomes. Parental or caregiver involvement increases the amount of intervention time delivered to the child inasmuch as children in this age range are likely to spend more time with their parents in their home and neighborhoods than in other settings. Furthermore, parents and caregivers can capitalize on teachable moments as they occur, provide learning opportunities during daily routines, and facilitate the generalization of learned skills across environments.\textsuperscript{15} Family involvement is also likely to be cost-effective and increases the sense of empowerment on the part of parents and caregivers. In the 2 comprehensive developmental/behavioral programs for which we have moderate or high evidence of effectiveness,\textsuperscript{17,29} parents were supported in complementing educators and therapists in the delivery of the interventions because of the importance of, and challenges inherent in, carrying over services and generalizing skills across multiple settings. Importantly, the concept of parental involvement is consistent with the recommended broader best practices that support working with young children in natural environments. Several parent-mediated interventions have shown positive parent and/or child outcomes. However, the extent to which these interventions are as effective as therapist-mediated interventions or are more effective when added into comprehensive child services, or with the combination of therapist plus parent-mediated interventions, requires further study.\textsuperscript{18,20}

**Statement 3: Interventions should enhance developmental progress and improve functioning related to both the core and associated features of ASD, including social communication, emotional/behavioral regulation, and adaptive behaviors.**

Many behavioral interventions for ASD focus on cognitive, behavioral, and language outcomes, but interventions also need to address social communication challenges central to the diagnosis. Sensory dysregulation, challenging behaviors, and motor skills are also common in children with ASD and should be targeted by interventions when needed.

Despite an apparent lack of change on standardized measures of social communication symptoms in 2 randomized controlled trials,\textsuperscript{17,20,32,33} a growing body of research describes the beneficial effects early intervention has on the development of communication and social functioning. (This lack of change may reflect the utilization of symptom measures such as the Autism Diagnostic Observation Schedule, which, as a diagnostic tool, was designed to be relatively stable; measures specifically designed and validated as being sensitive to change are needed.) Specifically, targeted interventions have been associated with gains in imitation,\textsuperscript{16,19} joint attention,\textsuperscript{16,20,32,34} social engagement,\textsuperscript{20,32,33} other social communication measures,\textsuperscript{34} and functional and symbolic play.\textsuperscript{20,32}

Impaired effortful control (ie, a reduced ability to regulate attention, emotions, and behavior to achieve goals) has been reported in children with ASD as early as at 24 months of age.\textsuperscript{61} Interventions dealing with attention regulation in young children with ASD have not yet been reported, but in typically developing children, short-term training has improved attention control measures associated with effortful
control. Comprehensive interventions that blend developmental and behavioral approaches have successfully improved adaptive functioning in many studies. Thus, future intervention studies should address and assess various developmental domains as intervention and outcome targets.

Statement 4: Intervention services should consider the sociocultural beliefs of the family and family dynamics and supports, as well as economic capability, in terms of both the delivery and assessment of factors that moderate outcomes.

Socioeconomic status, family characteristics, and cultural factors may present barriers to service provision. Families with lower socioeconomic status are likely to have less access to services. Because cultural values and differences can affect the goals and priorities of the family and may in some cases lead to misunderstandings, clinicians and other service providers should aim to understand the values, beliefs, and accompanying practices of families of differing cultures and assimilate that knowledge into their practice parameters as it relates to autism occurring in ethnically diverse populations. Culturally competent care extends beyond fluency in a non-English language. As a minimum, culturally appropriate program materials should be developed for families. In addition, training programs should be created that can help service providers learn how to promote culturally responsive assessment and intervention services.

Management of a child with ASD should focus on the family as well as on the child. Important considerations for the clinician include the well-being of each person in the family, the comfort and support of each family member, the lifestyle that has evolved around the child with ASD, and the unmet needs among family members or problem areas that might otherwise go unaddressed. Service providers can be of assistance by monitoring the physical and mental health of the family as well as that of the child with ASD. Finally, respect for the perceptions, priorities, and preferences of family members is an important "family-centered" tenet to bear in mind when working with children on the autism spectrum and their complex needs.

Statement 5: Intervention research should include socially and culturally diverse populations of participants and evaluate familial factors that may affect participation, acceptability, and outcomes of therapeutic approaches as well as willingness to participate in investigative studies.

Parents are expected to play a prominent role in supporting optimal development and thus intervention program delivery for their children, particularly at a very young age. An important focus of intervention research should therefore include factors such as cultural background and other family characteristics that may influence participation in treatment programs and interventional results. Due to attitudes concerning childhood rearing and independence, shame regarding developmental delays and ASD, or other societal and cultural beliefs, parents may be reluctant to enroll a child in a research study. Cumulatively, such decisions can diminish the generalizability and clinical applicability of reported interventions. In addition, when there is participation, cultural differences and language barriers might influence and moderate treatment effects.

In addition to any cultural issues, when parents are expected to be the therapeutic provider, assessment should focus on more than just fidelity of implementation and adherence to intervention goals. The quality of a parent's involvement, consideration of a parent's other responsibilities and roles, and potential family stressors arising from fulfilling their role in an intervention or from coping with care for a child with ASD warrant examination to determine whether moderators of treatment are present or are needed. Apart from any possible reluctance by families to participate in research, there is also a need for investigators to make a particular effort to recruit as culturally diverse a research sample as possible.

Statement 6: Future research should prioritize well-defined sampling strategies, rigorous investigative design, fidelity of implementation, and meaningful outcome measurements.

The methodologic rigor of intervention trials in ASD is improving, but continued attention to key aspects of research design is needed to further develop the evidence base for toddlers.

Future directions include identifying characteristics of children and families who would benefit most from particular interventions to support a more individualized approach, as well as systematically varying components of multifaceted intervention programs to identify critical ingredients. Thorough characterization of research participants would help to define the subset of children and families who most strongly benefit from particular intervention approaches. In addition, to avoid systematic bias from confounding factors, research participants should be randomly allocated to the treatment approaches that are being compared, and each treatment (including
community-based “as-usual” treatment) should be thoroughly described. Although the optimal study design to minimize bias in treatment research is a randomized controlled trial, it is acknowledged that contexts occur in which other methods may be appropriate. For example, to determine whether an intervention holds promise, it is important that intervention procedures are carefully tested for feasibility and acceptability. Moreover, single case designs, carefully implemented and with attention to appropriate measurement, may also be informative. Attention to and systematic evaluation of fidelity of implementation and selection of well-validated measures of key constructs (e.g., joint attention, imitation, other indicators of age-appropriate social and communication skills and function) that are responsive to change are also essential.

Statement 7: Research is needed to determine the specific active components of effective interventions, including but not limited to the type of treatment provided, the agent implementing the intervention(s) (parent, therapist, teacher, or combination), consistency of service provision across environments and between providers, and duration of treatment and hours per week.

Information is lacking regarding the features of an intervention that drive its effectiveness, but progress is being made on identifying these active ingredients or mechanisms of change. Without appropriate study designs to carefully examine the effect of specific intervention strategies such as treatment type, dose, and agent, we may be unable to determine which of the potentially significant elements in an intervention model are responsible for change and for which subgroups. With such information, future intervention programs can be refined.

Intensity of intervention

The National Research Council has recommended a minimum intensity of 5 hours a day, 5 days a week, for interventions. However, some recent studies have suggested the possibility of positive outcomes with fewer hours of direct therapist involvement for young toddlers with ASD, particularly when parents are actively engaged in the treatment process. For example, gains in some social communication skills (e.g., play, joint attention, imitation) were demonstrated in some studies when directly targeted in interventions of relatively low intensity (based on hours per week or length of treatment). Notably, the “real-life” intensity of the intervention may be influenced by the degree to which parents are implementing the strategies in natural routines throughout the day. The effectiveness of interventions is also likely to be influenced by whether training and ongoing supports allow parents to correctly implement the treatment strategies (i.e., with fidelity to the treatment procedures as originally designed), as has been reported in the treatment of preschool-aged children with ASDs. In addition, other factors can affect the extent to which such interventions are effective, including age, degree of impairment, and the extent to which the child receives other services.

Treatment content

A recent study in toddlers with ASD has attempted to determine the additive value of joint attention, imitation, and affect on an intervention when applied within 2 developmental/behavioral toddler classroom environments. The investigators evaluated impact in 1 study group, and another group received the same overall comprehensive intervention but without the ingredient of interest. Few differences emerged in this study except for the apparent benefit of imitation in 1 group. Nonetheless, this research paradigm provides a possible model through which intervention research may be implemented. Similarly, other investigators have evaluated the additive effects of joint attention or play skills into an ABA program that did not include a focus on these developmental skills. Teaching these skills increased their spontaneous occurrence in generalized contexts and further predicted greater language outcomes compared with the children in the ABA program without a focus on play and joint attention.

Incorporating teaching targets of joint attention, play, and imitation are clearly indicated for early intervention programs for ASD. However, given the heterogeneity of the disorder, it will be critical to determine how treatment strategies can be most effectively tailored to the needs of subgroups of children with ASD who have particular clinical profiles.

Statement 8: Adopting a common set of research-validated core measures of ASD symptoms (including but not limited to cognitive function, communication, and adaptive behavior) that can be used across multiple sites will facilitate comparisons across studies of children with ASD aged <3 years.

The interpretation of study findings is often hampered when investigators use different variables, or measures, to report outcomes. A consistent set of core measures relevant to the specific intervention goal(s) of interest should be adopted for studies of toddlers with ASD as well as for older children. Outcome measures do not need to be identical across studies, but agreement on a subset of standardized instruments to use (which may assess
changes in cognitive function, core autism symptoms, and adaptive and language behavior) would facilitate future comparisons. Some early developmental skills could yield “early-read” measures that are important to later developmental outcomes. These early-read measures may include joint attention, shared affect, and imitation skills, with the expectation that these early developmental tasks may predict better functioning in later cognition, language, and adaptive behavior. Early-read measures may provide important information on the effectiveness of short-term interventions and may also offer information on active ingredients essential to include in comprehensive intervention programs. Additional measures related to the impact that having a child with ASD has on family life and parental stress would also be important.

Statement 9: Future research should examine biological and behavioral heterogeneity as moderators of individual responses to interventions.

In any sample population, positive responses to an intervention can range from dramatic to extremely limited. Factors that underlie such heterogeneity—possible moderators of individual responses—can include age at onset of intervention, patient characteristics (eg, baseline stage of development of cognitive function, language and preverbal skills, adaptive behavior, sociocultural characteristics), and symptom severity. As important, however, is the increasing appreciation that ASD is a heterogeneous disorder—etiologically, biologically, and clinically. Given this heterogeneity, it is highly likely that specific subsets of individuals with ASD may respond to specific interventions more effectively than to others, perhaps based on etiology and underlying biological factors alone. Thus, there is a critical need to begin to identify subtypes of individuals with ASD, to understand the cause of their disorder as well as the associated neurobiological mechanisms at work in each case, and to be able to offer more directed interventions depending on the biological subtype when available and present.

A number of genetic and neurobiological subgroups are already known to be associated with ASD. The most well-known groups are children with fragile X syndrome, tuberous sclerosis, and duplication 15q. Other genetic disorders have been identified as being associated with ASD features, and a growing number of candidate genes are being explored. For example, Campbell et al66 reported that children with ASD and MET gene mutations were more likely to have gastrointestinal disorders, raising the possibility that medical comorbidities in children with ASD could index underlying genetic heterogeneity. It is thus important for future research to determine both biological and clinical subtypes within the autism spectrum that may ultimately affect the effectiveness of treatment and intervention.

To date, few studies have been designed or powered for analysis of heterogeneous effects.67 Treatment modifiers were recently identified in 2 studies based on appropriate study design and statistical analysis. In both studies, a measure developed to index the level of initial object exploration determined the extent to which a child would benefit more from 1 language-based intervention versus another65 or the extent to which children had better communication outcomes from a parent-mediated intervention.15 Object exploration can reflect a child’s flexibility in play and play level, both of which may influence later cognitive and language outcomes.59 Further studies like these are needed before we can make informed choices and personalize the treatment of each individual child.

Statement 10: Intervention providers should consider medical disorders that may affect a child’s clinical presentation (especially behavior) and response to an intervention and should refer to appropriate health care providers as indicated.

It has become increasingly evident in the ASD population that changes in behavior may be associated with an underlying medical condition.13 For example, clinical experience would suggest that a child with ASD exhibiting behavioral changes might be experiencing pain or discomfort owing to a medical problem such as otitis media, a dental abscess, or constipation. Frequently encountered medical factors in ASD include: seizures, particularly in children who also have severe intellectual disability, motor deficits, or a positive family history of epilepsy68,69; other gastrointestinal symptoms57,70; and sleep disturbances affecting daytime functioning. The full effect of medical factors on the clinical presentation of children aged <3 years with ASD is not known, nor has the association between medical factors and maladaptive behaviors such as aggression and self-injury been well studied in general in ASD. Nevertheless, best practices would indicate that a patient with a potential medical comorbidity be referred to a medical specialist for appropriate evaluation, diagnosis, and management. It is important that future research address these and other potential medical factors, how they may be more reliably identified (especially in nonverbal or hypo-verbal ASD individuals), and what effect treatment of these conditions may have on behavior, developmental trajectory, and learning.

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REFERENCES


(Continued from first page)

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 Choueiri and Kasari 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 Carter, Granpeesheh, Mailloux, Smith Roley, and Wagner 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; Drs Fein, Pierce, Buie, Davis, Newschaffer, Robins, Wetherby, Stone, Yirmiya, Estes, Hansen, McPartland, and Natowicz contributed to the consensus meeting that formed the basis for the manuscript and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.


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