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


## abstract

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



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**ABBREVIATIONS**

ASD—autism spectrum disorder
IJA—initiating joint attention
MSEL—Mullen Scales of Early Learning
RJA—responding to joint attention

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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 Mandell[2]), 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 attention[14,15]) 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 designs[17] 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 after a period of relatively typical development into the second year of life.[22–24] There is also heterogeneity at an etiologic level, with hundreds of susceptibility genes[25] and potentially a wide range of environmental and/or epigenetic factors[26–28] implicated in ASD causation. The variability in behavioral profiles, developmental course, and underlying etiologic factors must be taken into account when synthesizing findings across studies. There are also methodologic differences that may affect comparability across studies (eg, prospective versus retrospective designs, measurement strategies, 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.[29] 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.[32,38,42,45] 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]

**TABLE 1** Selected Studies of Potential Markers Identifying ASD in Children Aged 12 to 24 Months

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Social/emotional behavioral markers (from studies with outcome assessments) | | | | | | |
| Bryson et al,[32] 2007 | At ages 12–24 mo, 2 broadly defined ASD subgroups:<br>• Decrease in IQ from average/near average to severe cognitive impairment, with ASD signs emerging earlier or more striking earlier<br>• Continued average or near average IQ<br>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 | 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<br>Clinical diagnosis of ASD for 4 children at 24 mo and for 3 children at 30 mo | Assessments every 6 mo from age 6 to 24 mo, including:<br>• AOSI and/or ADOS to assess for ASD symptoms<br>• BSID-II to assess cognition<br>• CDI-WG to assess gestural and early language development<br>• Infant Temperament Scale or Toddler Behavior Assessment Questionnaire to assess temperament<br>• Semi-structured interviews regarding parental concerns |
| Fodstad et al,[33] 2009 | At ages 17–37 mo:<br>• Deficits in communications and social skills more obvious and pronounced in AD versus other groups<br>• Greater deficits in PPD-NOS versus controls<br>• 5 of 20 items on socialization/nonverbal communication subscale discriminated between groups[a]<br>• 5 of 7 items on communication subscale were most predictive of diagnostic group[b] | Prospective | • 161 children with AD<br>• 140 children with PDD-NOS<br>• 585 controls: children at risk for other developmental delays or to have disorder such as Down syndrome and cerebral palsy<br>Aged 17–37 mo | 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 | • 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 |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Garon et al,[34] 2009 | At 24 mo, children with later diagnosis of ASD were distinguished from non-ASD siblings and controls by:<br>• Temperament profile ("effortful emotion regulation") of lower positive affect, higher negative affect, and difficulty controlling attention and behavior<br>• Lower sensitivity to social reward cues (low "behavioral approach")<br>Two ASD subgroups distinguished by number of ASD symptoms, IQ, age at diagnosis, Behavioral Approach profile | Prospective<br>Ongoing ($N$ = 211 with data collected at age 24 mo) | • 138 high-risk infants (SIBS-A)<br>• 73 low-risk infants (no family history of ASD)<br>84% and 80%, respectively, enrolled in study at age 6 mo; rest by age 12 mo | Enrolled in larger study; recruited through autism diagnostic and treatment centers | Gold standard diagnostic assessment for ASD at 36 mo based on ADI-R, ADOS, DSM-IV-TR criteria<br>34 of 138 SIBS-A (24.6%) diagnosed with ASD | • TBAQ-R to assess temperament (parent report) at 24 mo<br>• MSEL at 24 and 36 mo |
| Goldberg et al,[35] 2005 | 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:<br>• Responses to social interaction bids: less frequent eye contact, gestures, and turn-taking ($P < .05$)<br>• Initiation of joint attention: fewer nonverbal behaviors to initiate shared experiences of objects or events ($P < .001$)<br>• Differences in frequency of requesting behaviors ($P < .05$)<br>• No significant differences in responses to JA | Prospective | • 8 children diagnosed with AD or PPD-NOS aged 21.0–33.0 mo<br>• 8 SIBS-A aged 14.0–19.0 mo<br>• 9 children with TD from families without ASD aged 10.0–19.0 mo | From larger sample of families participating in autism study at university medical center; controls from community volunteer sample | 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 |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Mosconi et al,[36] 2009 | In 2-y-olds with AD: | Longitudinal MRI study | • 50 children with AD | Children with AD recruited after receiving clinical diagnosis or while awaiting clinical evaluation | Diagnosis of AD confirmed at 2 y and reassessed at 4 y by using ADI-R, ADOS, DSM-IV criteria; controls screened with CARS | • 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 |
| | • Amygdala enlargement that persisted through age 4 y (16% larger volumes than in controls) | Ongoing | • 33 controls (11 with developmental delay and 22 with TD)<br>Aged 2 y (18–35 mo) | Details of subject ascertainment described in Hazlett et al,[37] 2005 | | • Repetitive Behavior Scale–Revised to assess specificity of hypothesized relationship between amygdala and JA, investigated only in children with AD |
| Nadig et al,[38] 2007 | At age 12 mo, failure to respond to name is highly suggestive of developmental abnormality | Prospective longitudinal study | • 101 at-risk infants (SIBS-A) | Enrollees in university-based study | Clinical best diagnosis of AD or PDD-NOS at 24 mo based on clinical observation, ADOS, and DSM-IV criteria | • Subjects followed up to age 36 mo |
| | • 86% of at-risk infants responded to first or second name call vs 100% of controls | Ongoing | • 46 infants at no known risk (SIBS-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 | • MSEL to assess development |
| | • Failure to respond to name at age 12 mo highly specific for 24-mo outcome of developmental delay, including ASD | | Aged 12 mo | | | • ADOS to measure social and communicative behaviors<br>• 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 |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Osterling et al,[39] 2002 | At 1 y, infants with ASD:<br>• Look at others less frequently<br>• Orient to their names less frequently than infants with mental retardation:<br>At 1 y, infants with ASD or MR:<br>• Use gestures less frequently<br>• Look to objects held by others less frequently<br>• Engage in repetitive motor actions more frequently than infants with TD | Retrospective video study | • 20 infants with later diagnosis of AD (35% of sample) or PPD-NOS<br>• 14 infants later diagnosed with MR (without ASD and without distinguishing physical anomalies)<br>• 20 infants with TD<br>Aged 2.5–10 y at time of study | Recruited from university subject pools, state autism society, Division of Developmental Disabilities, local newspaper and local radio advertisements, local schools | AD or PPD-NOS diagnosis confirmed at study entry on basis of DSM-III-R plus score of ≥30 on CARS | Home videos of first birthday parties coded by blind raters on frequencies of specific social and communicative behaviors and repetitive motor actions |
| Ozonoff et al,[22] 2010 | 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)<br>By 18 mo, significant group differences on all social communication variables (see Comments)<br>Between 6 and 18 mo:<br>• Declining trajectories of social communication behavior and loss of skills in most infants with later ASD diagnosis<br>• Increase in cognitive and language skills (MSEL raw scores) over time in both groups, with significantly slower growth in ASD starting at 12 mo | Prospective longitudinal study | • 25 high-risk infants with later diagnosis of AD or PDD-NOS (22 were SIBS-A)<br>• 25 gender-matched SIBS-TD determined later to have TD | Sample drawn from larger longitudinal study | 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) | Assessments at ages 6, 12, 18, 24, and 36 mo of:<br>• 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<br>• Frequency of infant social engagement rated by blind examiners<br>• MSEL to assess cognitive functioning<br>• Symptom onset by parent reports |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| | • Discrepancy in autism symptom onset with parent reports | | | | | |
| Pierce et al,[40] 2011 | • Toddlers with an ASD as young as 14 mo spent significantly more time fixating on geometric images than on social images | Prospective longitudinal study | • 37 with ASD | Sample recruited from general population screening approach starting at 12 mo and community referral | Clinical best diagnosis of AD or PDD-NOS at ≥24 mo based on clinical observation, ADOS, and DSM-IV criteria | • 1-min eye-tracking test used to measure visual attention |
| | • Individual visual fixation levels could be used to diagnostically classify a toddler as having ASD at 100% accuracy level | | • 22 with DD | | | • Diagnosis confirmed by experienced diagnostician blinded to eye-tracking test results |
| | • Toddlers with ASD who visually examined geometric images exhibited significantly fewer saccades when looking at geometric images than other toddlers | | • 51 with TD | | | • MSEL and VABS used to measure cognitive and adaptive behavior |
| Sullivan et al,[41] 2007 | By age 14 mo, children later diagnosed with ASD or broader autism phenotype had deficits in RJA | Prospective | 51 high-risk children (SIBS-A) who received outcome assessments: | Subsample of subjects of large study; recruited through ASD advocacy group, schools, word of mouth | 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 | RJA bids were coded from videotapes of 3 measures administered at ages 14 and 24 mo: |
| | Between 14 and 24 mo, children with ASD had minimal improvement in RJA, unlike with BAP and non-BAP | | • AD ($n$ = 13) or PDD-NOS ($n$ = 3) | | | • "Look only" trials adapted from Butterworth and Jarrett, 1991[97] |
| | Significant ($P < .01$) group differences in RJA at 24 mo | | • BAP ($n$ = 8) | | | • Look + point trials from CSBS DP |
| | RJA at 14 mo predicted ASD outcome | | • Non-BAP ($n$ = 27) | | | • RJA item from ADOS |
| Wetherby et al,[42] 2004 | During second year of life, 9 prelinguistic behaviors serve as red flags to distinguish ASD from DD and TD: | Prospective | • 18 children with later diagnosis of AD or PDD-NOS | Recruited to larger study | 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 | • Direct observation within standardized Behavior Sample, videotaped and scored by using standard CSBS DP procedures |
| | • 7 related to social and communication symptoms[c] | Ongoing | • 18 with DD without ASD | | | • Behavior Sample videotape recoded by using SORF scoring |
| | • 2 related to repetitive movements with objects and/or body parts | | • 18 with TD | | | |
| | | | Aged 13.0–26.9 mo at Behavior Sample | | | |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| | 4 additional "red flags" differentiated ASD from TD but not from DD[d] | | | | | |
| Yoder et al,[43] 2009 | Later social impairment and later ASD diagnosis predicted by: | Prospective longitudinal correlational design | • 43 SIBS-A | 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 | ASD diagnosis assessed ~1.5 y after study entry (ie, after age 30 mo) using ADOS, ADI-R, and DSM-IV-TR criteria | • Hierarchical linear modeling to assess growth in early social skills (ie, RJA and WTC) as predictors of social impairment in SIBS-A |
| | • Initial level of RJA (at age 15 mo) | | • 24 age-matched SIBS-TD who provided social outcome benchmarks | | ASD diagnosed in 6 (AD in 3 and PDD-NOS in 3) | • 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) |
| | • Growth rate of weighted triadic communication (from ages 15–34 mo) | | Aged 12–23 mo at study entry | | | • Weighted frequency of unprompted triadic communications derived from STAT |
| | At 30 mo, delay in RJA and more general social skills in SIBS-A but large variation in social outcome scores | | | | | • Experimental task described in Presmanes et al,[44] 2007, to assess RJA<br>• SBC to assess social behaviors by parent report |
| Zwaigenbaum et al,[45] 2005 | By age 12 mo, infants with later diagnosis of autism may be distinguished from other siblings and controls by: | Prospective longitudinal study | • 65 SIBS-A | Recruited mainly at age ≤6 mo from autism diagnostic and treatment programs; low-risk infants recruited from nurseries in same regions | Formal independent diagnostic assessment at 36 mo based on DSM-IV criteria, ADI-R, and ADOS | • AOSI at 6 and 12 mo to assess autism-specific behaviors |
| | • Behavior markers[e] | Ongoing ($N$ = 88 followed up to age 24 mo) | • 23 low-risk infants (no first- or second-degree relatives with ASD) | | 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) | • ADIS (24 mo) to assess autism-related social communication impairments |
| | • Prolonged latency to disengage visual attention (starting after 6 mo) | | "Roughly" matched by gender, birth order, and age; $N$ values varied by assessment | | | • Computerized visual orienting task (6 and 12 mo) to assess ability to disengage from 1 of 2 competing visual stimuli (attentional disengagement) |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| | • Temperament profile[f] | | Available 12-mo outcome data for 65 SIBS-A: | | | • IBQ (6 and 12 mo) and TBAQ (24 mo) to measure infant temperament |
| | • Delayed expressive and receptive language | | • 7 with AD<br>• 12 with ASD classification on ADOS<br>• 46 without ASD | | | • MSEL-ABS edition and CDI-WG (12 mo) to assess language and cognitive development |
| Social/emotional behavioral markers (from studies without outcome assessments) | | | | | | |
| Macari et al,[46] 2012 | At age 12 mo, lack of attention-sharing behaviors, including: | Prospective | • 53 SIBS-A | Recruited from university research programs, Web site, advertising, word of mouth | Provisional CBE diagnosis at age 24 mo | • ADOS-T administered at 12 and 24 mo and analyzed by using nonparametric decision-tree learning algorithms |
| | • Showing<br>• IJA | | • 31 low-risk infants (no ASD history in first- or second-degree relative)<br>64% male, enrolled by age 6 mo | | Diagnosis not done at 36 mo | • MSEL to assess developmental status |
| | Can predict ASD or other atypical development at age 24 mo<br>Various combinations of social communicative features associated with ASD presentation at 24 mo | | | | | |
| Presmanes et al,[44] 2007 | In second year of life, SIBS-A showed impaired RJA relative to SIBS-TD across range of prompt types | Prospective | • 46 SIBS-A | 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 | "Not yet available" | • 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 |
| | Attention disengagement similar for 2 groups | Ongoing | • 35 SIBS-TD<br><br>Aged 12–23 mo | | | • 20 RJA trials per subject were videotaped and coded<br>• MSEL cognitive scales administered<br>• STAT to assess social communicative behaviors |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Stone et al,[47] 2007 | At ages 12–23 mo, weaker performance by SIBS-A in:<br>• Nonverbal problem solving (ie, visual reception)<br>• Directing attention (ie, IJA)<br>• Understanding words and phrases<br>• Gesture use<br>• Social communicative interactions with parents<br>Increased autism symptoms in SIBS-A<br>Significant correlations between child-based measures and parent reports | Prospective | • 64 SIBS-A<br>• 42 SIBS-TD<br>Aged 12–23 mo (mean: 16 mo) | 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 | Not known | Child-based and parent report measures:<br>• MSEL to assess cognitive function<br>• CARS to assess autism symptoms<br>• STAT to assess play, requesting, directing attention, and motor imitation<br>• MCDI questionnaire to assess verbal and nonverbal understanding and expression<br>• DAISI to assess social engagement behaviors |
| Yirmiya et al,[48] 2006 | At age 14 mo, SIBS-A:<br>• Initiated fewer nonverbal requesting gestures<br>• Achieved lower language scores (accounted for by 5-mo language delay in 6 SIBS-A) than SIBS-TD<br>In general, most SIBS-A functioned well | Prospective ($N$ = 61 with 14-mo assessments) | • 30 SIBS-A<br>• 31 SIBS-TD<br>Matched on 1-to-1 basis according to chronologic age, gender, birth order, number of children in family, and Bayley mental and motor scales | Sibs-A recruited from treatment centers, special schools, and contacts with families of children with ASD<br>Comparison group recruited from hospital maternity wards | 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 | Measures at age 4 and 14 mo:<br>• BSID-II to assess general development and language<br>• ICQ to assess maternal perception of infant temperament<br>Communication and cognition measures at age 14 mo:<br>• ESCS to assess nonverbal communication skills<br>• CHAT to assess JA behavior |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Language/communication behavioral markers (from studies with outcome assessments) | | | | | | |
| Landa and Garrett-Mayer,[49] 2006 | By 14 mo of age, significantly worse performance in fine motor, gross motor, and receptive and expressive language (ASD versus unaffected) | Prospective longitudinal | • 24 children with later diagnosis of ASD | 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 | ASD classified at 24 mo based on PLS, ADOS, and MCDI | • 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 |
| | By 24 mo, significantly worse performance in all 5 domains (ASD versus unaffected) and significantly worse performance in gross motor, fine motor, and receptive language (ASD versus LD) | | • 11 with later diagnosis of language delay | | | • PLS-III or PLS-IV at 24 mo for receptive and expressive standard scores and age equivalences |
| | Slower developmental trajectory in ASD group versus other groups, with significant decline between first and second birthdays | | • 52 classified as unaffected (at 24 mo)<br>Enrollees entered study as SIBS-A and infants with no family history of idiopathic autism | | | • CDI at 14 and 24 mo to assess child's understanding and production of language |
| Oller et al,[50] 2010 | 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 | Prospective | • 77 children aged 16–48 mo with AD or PDD-NOS | Recruited through advertisements | 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 | • 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 |
| | | | • 49 children aged 10–44 mo with language delay without autism<br>• 106 children aged 10–48 mo with TD | | | • Analysis of 1486 all-day recordings |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Language/communication behavioral markers (from studies without outcome assessments) | | | | | | |
| Gamliel et al,[51] 2007 | At 14 and 24 mo, cognitive and/or language delays (≥2 SDs below average on measures) in SIBS-A subsets, compared with other SIBS-A and SIBS-TD | Prospective | • 39 SIBS-A | Recruited through treatment centers, special schools, national autism organization, families of children with autism; comparison group recruited from hospital maternity wards | Not known | • BSID-II at 4, 14, and 24 mo to assess development |
| | At ages 14–36 mo, cognitive and/or language difficulties in 11 of 39 SIBS-A vs 2 SIBS-TD | Ongoing ($N$ = 78 with developmental trajectories to age 54 mo) | • 39 SIBS-TD | | | • RDLS (24 mo) to assess expressive and verbal comprehension |
| | By 54 mo, cognitive differences gone, but some differences in language ability (receptive and expressive) remained | | 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 | | | • K-ABC (36 and 54 mo) to assess intelligence |
| | Most siblings with language impairments at age 14 mo functioning well at 54 mo without intervention | | | | | • Clinical Evaluation of Language Fundamentals–Preschool (36 and 54 mo) |
| | | | | | | • Parent questionnaire regarding clinical and educational services (24, 36, and 54 mo) |
| | | | | | | • This is a follow-up report to Yirmiya et al,[48] 2006 |
| Markers of motor dysfunction (from studies with outcome assessments) | | | | | | |
| Esposito and Venuti,[52] 2008 | At age ~20 mo, boys with AD had: | Retrospective video study | • 16 boys mean age 20.2 mo with AD | Recruited from referrals to university-based center for developmental disabilities | AD diagnosis before study confirmed by using DSM-IV criteria and ADOS | • Analysis of home videos taken after 6 mo of independent walking |
| | • Different distributions in WOS scores from other groups | | • 10 boys mean age 21 mo with mental retardation | | | • WOS used to code videos by assessing gait on 3 axes: foot, arm, and global movements |
| | • Different gait patterns: problems with heel-to-toe pattern, more asymmetric posture of arm while walking, higher frequency of general movement anomalies (eg, "waddling walk") | | • 16 boys mean age 20.5 mo with TD<br>AD and MR groups matched by chronological and developmental ages | | | |
| Esposito et al,[53] 2011 | Aged <2 y, significant ($P \leq .001$) differences in gait pattern in toddlers with AD versus TD and DD: | Retrospective video study | • 20 toddlers with AD | Recruited from 2 nationwide referral centers for developmental disabilities | Clinical diagnosis of AD based on DSM-IV-R and confirmed by using ADI-R, ADOS-G, and CARS | Analysis when toddlers were first walking without assistance |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| | • Higher levels of postural asymmetry during walking | | • 15 toddlers with nonautistic DD | | | • Home videos taken when child was aged <2 y (plus all footage within 2-h window) |
| | • Some atypical arm and foot movements during walking | | • 20 toddlers with TD | | | • WOS to code videos by assessing gait on 3 axes: foot, arm, and global movements |
| | | | Mean ages 12.9–14.2 mo when first walking without assistance | | | • PPSW to assess static and dynamical symmetry during gait |
| Matson et al,[54] 2009 | At ages 17–37 mo: | Prospective | • 140 infants with AD | Enrollees of state-funded early intervention program for DDs | AD and PDD-NOS diagnoses based on DSM-IV-TR criteria, M-CHAT, and Battelle Developmental Inventory–Second Edition developmental profile | • BISCUIT Part 1—specifically the repetitive behavior/restricted interests subscale—to assess for ASD symptoms |
| | • Stereotypies and repetitive/ritualistic behaviors were most common in AD, followed by PDD-NOS and then other DDS | | • 121 with PDD-NOS | | | • Child observation and 1-to-1 parent assessment; administered as part of battery of assessments of physical and social development |
| | • Striking differences across groups in limited number of interests, engages in repetitive motor movements for no reason, eye-to-eye gaze, maintains eye contact | | • 499 at risk for DD but no ASD diagnosis | | | |
| | • BISCUIT subset could accurately predict diagnostic group membership | | Aged 17–37 mo (mean: 26.63 mo) | | | |
| Ozonoff et al,[57] 2008 | At age 12 mo: | Prospective | • 35 SIBS-A | Recruited from SIBS-A and SIBS-TD | Diagnosis at 24 ($n$ = 29) or 36 ($n$ = 37) mo based on ADOS, SCQ, and DSM-IV criteria | Manner in which infants explore objects was examined in task that afforded range of repetitive uses |
| | • Atypical uses of objects (spinning, rotating, and, especially, unusual visual exploration of objects) significantly ($P \leq .005$) more frequent in infants with ASD compared with other groups | | • 31 in SIBS-TD | | For 37 with outcome data at 24 and 36 mo, 31 (83.8%) had the same classifications at both ages; the later classification was used in analyses | • Four objects presented to the infant, 1 at a time, for 30 s each |
| | • Repetitive behaviors significantly related to | | Aged 12 mo, with following outcomes:<br>• 9 with ASD diagnosis | | | • Behavior recorded on DVD |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| | cognitive and symptom status at 36 mo | | • 10 with later diagnosis of other delays[g]<br>• 47 with no concerns (did not meet criteria for other groups) | | | • 8 object uses coded by blinded raters as either frequency or duration; 4 hypothesized as typical and age-appropriate and 4 as atypical[h] |
| Ozonoff et al,[55] 2008 | During first 2 y of age: | Retrospective video study | • 26 children aged 26–61 mo with nonregression-type AD | 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 | 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 | • 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 |
| | • Neither regression nor nonregression types of AD differed from TD in rates of movement abnormalities or lack of protective responses | | • 28 children aged 26–61 mo with regression-type AD | | | • Videos coded for motor maturity, protective responses, and movement abnormalities by using Infant Motor Maturity and Atypicality Coding Scales |
| | • Toddlers with nonautistic DD displayed higher rates of movement abnormalities in sitting and prone and fewer protective responses in crawling than other groups | | • 25 with nonautistic DD matched for chronologic and developmental age<br>• 24 with TD | | | |
| Provost et al,[56] 2007 | At ages 21–41 mo: | Prospective | • 19 children aged 21–41 mo with ASD | Recruited from referrals to university-based early childhood evaluation program for developmental disabilities | ASD diagnosis made by study team evaluation | • BSID-II Motor Scale to assess motor skills |
| | • Motor dysfunction to some degree in all children with ASD (delay in gross and/or fine motor skills) | | • 19 with other DD including motor delay | | Diagnosis of AD in 18, PDD-NOS in 1 | • PDMS-2 also to assess presence and degree of delay in motor skills |
| | • Significant motor impairments versus those with developmental concerns without motor delay | | • 18 with developmental concerns (eg, speech and emotional issues) but no motor delay | | | |
| | • No significant difference in motor scores versus children with DD | | 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 | | | |

**TABLE 1** Continued

| Reference | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Watt et al,[58] 2008 | At ages 18–24 mo, children with ASD demonstrated significantly higher frequency and longer duration of:<br>• RSB with objects<br>• RSB with body<br>• Sensory behaviors than DD and TD groups<br><br>In children with ASD and those with other DDs, RSB with objects predicted developmental outcomes and severity of ASD symptoms at 3 y | Prospective | • 50 children with ASD (AD or PDD-NOS)<br>• 25 with developmental delay without ASD<br>• 50 with TD<br><br>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 | 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 | Best-estimate assessment of ASD or DD diagnosis at age ≥30 mo based on battery of tests including ADOS | In second year of life:<br>• CSBS Behavior Sample to assess communication behaviors; RSB coded from Behavior Sample videotapes<br>• Symbolic composite of Behavior Sample to measure developmental level<br>• Social composite of Behavior Sample to assess social competence<br>In fourth year:<br>• MSEL to measure developmental level<br>• VABS to assess adaptive behavior<br>• ADOS to measure autism symptoms |

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-T, Autism Diagnostic Observation Schedule–Toddler Module; AOSI, Autism Observation Scale for Infants; BAP, broader autism phenotype; BISCUIT, Baby and Infant Scale for Children with Autism Traits; BSID-II, Bayley Scales of Infant Development–2nd Edition; CARS, Childhood Autism Rating Scale; CBE, 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, Revised*; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; ESCS, Early Social Communication Scales; IBQ, Infant Behavior Questionnaire; JA, joint attention; K-ABC, Kaufman Assessment Battery for Children; LD, language delay; MR, mental retardation; PDD-NOS, pervasive developmental disorder not otherwise specified; PDMS-2, Peabody Development Motor Scales, Second Edition; PLS, Preschool Language Scale; PPSW, Positional Pattern for Symmetry during Walking; RDLS, 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; SOC-RS, 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; TBAQ, Toddler Behavior Assessment Questionnaire; TBAQ-R, 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 IJA but considered to have imperative as well as declarative functions).

[a] Fodstad et al 2009[33]: 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[33]: 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[42]: Red flags differentiating ASD from both DD and TD: lack of appropriate gaze; lack of warm, joyful expressions with gaze; lack of sharing enjoyment or interest; lack of response to name; lack of coordination of gaze, facial expression, gesture, and sound; lack of showing; and unusual prosody.

[d] Wetherby et al 2004[42]: 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[45]: 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[45]: Temperament 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] Ozonoff et al 2008[57]: Other delays were general developmental delay, speech/language delay, marked hyperactivity, and marked anxiety.

[h] Ozonoff et al 2008[57]: Behaviors hypothesized as typical: shaking, banging, mouthing, throwing; behaviors hypothesized as atypical: spinning, rolling, rotating, unusual visual exploration (eg, 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 studies[41,43] 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 non–broader 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 ASD[35] and younger siblings of children with ASD[47] 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 children[35,63] and from children with other developmental disorders.[33,39]

### *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 use[42,58,64] and prolonged visual fixation on objects[32] or repetitive geometric shapes[40] in infants who subsequently develop ASD. In 2 samples, such repetitive behaviors correlated with subsequent diagnostic outcomes and other ASD symptoms.[57,58,64]

### *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 movements[58,64] compared with typically developing or "unaffected" children, respectively. Similar findings have been reported in other prospective studies[32,42,54,65] as well as in retrospective studies.[39,52,53] In contrast, 1 retrospective video study of children with autistic disorder found no differences from typically developing children in rates of movement abnormalities.[55]

There is a growing interest as to whether atypicalities in developmental motor patterns may appear very early and possibly predate social and communication markers. General delays in 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 al[67] 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 al[69] 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.

### *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]

Clifford et al[70] 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[34]), 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.[22,32,38,45,46,48,49,71–78] Some researchers reported no behavioral differences at the age of 6 months in social communication behaviors[22] or in language or motor development[49,66] 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),[32,74] atypical sensory behaviors,[32] repetitive or otherwise atypical motor behaviors, and nonverbal communication (differences in gesture use).[77] Additional similar studies during the first 6 months of life have suggested differences in responding to social stimuli[72] and "at least some suggestion of" more difficult temperaments, characterized by marked irritability, intolerance to intrusions, and being prone to distress/negative affect.[32]

Jones and Klin[18] 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[48] or differences in visual fixation[73]; orienting to nonsocial versus social stimuli[76]; and prespeech vocalizations.[78] 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.[79]

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

The term "trajectory" encompasses the degree, rate, and direction of changes in the behaviors 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,[32] 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 2** Selected Studies of Potential Markers Identifying ASD in Infants Aged 12 Months

| First Author and Year of Publication | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Social/emotional behavioral markers (from studies with outcome assessment) | | | | | | |
| Bryson et al,[32] 2007 | 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 | 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 by using ADI-R, ADOS, and DSM-IV-TR criteria<br>Clinical diagnosis of ASD for 4 children at 24 mo and for 3 at 30 mo | Assessments every 6 mo from age 6–24 mo, including:<br>• AOSI and/or ADOS to assess for ASD symptoms<br>• BSID-II to assess cognition<br>• CDI-WG to assess gestural and early language development<br>• Infant Temperament Scale or Toddler Behavior Assessment Questionnaire to assess temperament<br>Semi-structured interviews regarding parental concerns |
| Maestro et al,[71] 2005 | • Between ages 0 and 6 mo, significant group differences in social attention (high scores in social versus nonsocial stimuli in "typical" infants) | Retrospective video study | • 15 children aged 3.5–5.2 y with AD diagnosis | Subjects with AD recruited from community sources referred to public academic hospital; controls were kindergarten attendees | Diagnosis made at study entry through symptom checklist based on DSM-IV plus ≥30 score on CARS | • 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 |
| | • Between ages 7 and 12 mo, no group differences in social or nonsocial attention; but behaviors regarding attention to nonsocial stimuli increased in both AD and typical groups but "more evident" in the former | | • 13 "typical" children with mean age of 4.7 y | | | • Social attention behaviors assessed: looking at people, orienting toward people, smiling at people, vocalizing to people<br>• Nonsocial attention behaviors assessed: looking at objects, orienting toward objects, smiling at objects, vocalizing to objects |

**TABLE 2** Continued

| First Author and Year of Publication | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Maestro et al,[72] 2002 | Between ages 0 and 6 mo, significant group differences in social attention and social behavior, including:<br>• Less frequent looking at people ($P < .001$)<br>• Less frequent vocalizing to people ($P < .001$)<br>• Less frequent orienting toward people ($P > .01$)<br>No group differences in items referring to interest and attention versus nonsocial stimuli | Retrospective video study | • 15 children aged 3.5–5.6 (mean: 4.1) y with diagnosis of AD ($n = 7$) or PPD-NOS ($n = 8$)<br>• 15 "typical" "normal" children with mean age of 4.7 y<br>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 (eg, looking at people), social behavior (eg, anticipating the other's aim), and nonsocial attention (eg, "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<br>• 11 of 13 children with ASD and 68 of 71 children without ASD correctly classified<br>These items included: level of engagement, amount of requesting, imitation, fussiness, showing, gestures, and intonation | Prospective longitudinal study<br>Ongoing | • 53 at-risk infants (SIBS-A); 13 diagnosed with ASD at 24 mo<br>• 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<br>• MSEL to assess development<br>• ADOS-T to measure social and communicative behaviors<br>• 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<br>• 82% of controls responded on first or second call of name vs. 66% of SIBS-A | Prospective longitudinal study<br>Ongoing | • 55 at-risk infants (SIBS-A)<br>• 43 infants at no known risk (SIBS-TD)<br>Aged 6 mo | 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<br>• MSEL to assess development<br>• ADOS to measure social and communicative behaviors<br>• 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<br>• Same sample as in Merin et al,[73] 2007 |

**TABLE 2** Continued

| First Author and Year of Publication | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Ozonoff et al,[22] 2010 | At 6 mo:<br>• No group differences in social communication behaviors (including frequency of gaze to faces, shared smiles, and vocalizations to others)<br>• Better (NS) social communication behaviors for ASD versus TD outcome group "on all variables" | Prospective longitudinal study | • 25 high-risk infants with later diagnosis of AD or PDD-NOS (22 were SIBS-A)<br>• 25 gender-matched SIBS-TD determined later to have TD | 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:<br>• 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<br>• Frequency of infant social engagement rated by blind examiners<br>• MSEL to assess cognitive functioning<br>• Symptom onset by parent reports |
| Werner et al,[74] 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<br>• 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 ($n = 7$)<br>• 15 children with TD | 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,[75] 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<br>• 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)<br>• 25 infant SIBS-TD | 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<br>Clinical outcome data available on 49 infants | • Longitudinal follow-up for sample in Merin et al,[73] 2007<br>• Assessment at 6 mo of eye-tracking data and behavioral data during live mother–infant interaction |

**TABLE 2** Continued

| First Author and Year of Publication | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| | | | | | | • MSEL to assess development at 6, 12, 18, and 24 mo<br>• VABS to assess social, communication, and motor skills at 12, 18, and 24 mo<br>• CDI to assess language development at 18 and 24 mo |
| Zwaigenbaum et al,[45] 2005 | At 6 mo, siblings with later diagnosis of ASD showed: | Prospective longitudinal study | • 44 SIBS-A | Recruited mainly at age ≤6 mo from autism diagnostic and treatment programs; low-risk infants recruited from nurseries in same regions | Formal independent diagnostic assessment at 36 mo based on DSM-IV criteria, ADI-R, and ADOS | • AOSI at 6 and 12 mo to assess autism-specific behaviors |
| | • No difference in number of risk markers measured by using AOSI | Ongoing ($N$ = 88 followed up to age 24 mo; 6-mo data available on 44 SIBS-A) | • 15 low-risk infants (no first- or second- degree relatives with ASD) | | 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) | • Computerized visual orienting task at 6 and 12 mo to assess ability to disengage from 1 of 2 competing visual stimuli (attentional disengagement) |
| | • No difference ($P$ = .12) in disengagement of visual attention | | "Roughly" matched according to gender, birth order, and age; N values varied by assessment | | | • IBQ at 6 and 12 mo to measure infant temperament |
| | • Temperament characterized by marked passivity and decreased activity level ($P$ = .019) | | Available 6-mo outcome data for 44 SIBS-A: | | | • MSEL and CDI-WG at 12 mo to assess language and cognitive development |
| | Compared with non-ASD siblings and controls | | • 4 with AD | | | |
| | Behavioral observations at 6 mo do not predict later diagnosis | | • 8 with ASD classification on ADOS<br>• 32 without ASD | | | |
| Social/emotional behavioral markers (from studies without outcome assessments) | | | | | | |
| Merin et al,[73] 2007 | At 6 mo, diminished gaze to mother's eyes relative to mouth (10 of 11 infants with this finding were in at-risk group) | Prospective | • 31 at-risk infants (SIBS-A) | Recruited by using research institute database and word of mouth | Not done | • Visual fixation assessment during reciprocal social interaction, conducted at age 6 mo via eye tracking during modified still-face paradigm |

**TABLE 2** Continued

| First Author and Year of Publication | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| | | | • 24 with an older sibling without autism | | | • Same sample as in Nadig et al,[38] 2007 |
| Noland et al,[76] 2010 | At 6.5–9 mo, higher working memory scores for SIBS-A versus SIBS-TD for nonsocial stimuli; no group difference for social stimuli | Prospective | • 25 SIBS-A | SIBS-A recruited primarily through university-based service and ASD outreach program; SIBS-TD recruited from telephone contacts by using state birth record database | Not done | • 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 |
| | | | • 30 SIBS-TD | | | • Trials videotaped, coded for correct first looks |
| Yirmiya et al,[48] 2006 | At 4 mo: | Prospective | • 21 dyads of mothers and infants who were SIBS-A | Comparison group recruited from hospital maternity wards | 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 | Measures at age 4 and 14 mo: |
| | • No significant group difference in mother–infant synchrony, although SIBS-A exhibited weaker synchrony during infant-led interactions | Ongoing ($N$ = 42 with 4-mo assessments) | • 21 dyads and infants who were SIBS-TD | | | • BSID-II to assess general development and language |
| | • No significant group difference in infant gaze behavior during still-face procedure but more neutral affect and less upset with SIBS-A | | Matched on 1-to-1 basis according to chronologic age, gender, birth order, number of children in family, and Bayley mental and motor scales | | | • ICQ to assess maternal perception of infant temperament |
| | • Significantly more SIBS-A responded to name being called by mother than SIBS-TD | | | | | Social engagement measures at 4 mo:<br>• Synchrony during mother–child free play interaction<br>• Infant gaze and affect during still-face paradigm<br>• Procedure to assess responsiveness to name being called |

**TABLE 2** Continued

| First Author and Year of Publication | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Language/communication behavioral markers (from studies with outcome assessment) | | | | | | |
| Colgan et al,[77] 2006 | At 9–12 mo, decreased variety in types of social interaction gestures used was significantly associated with autism status | Retrospective video study | • 21 children later diagnosed with AD | Recruited through mailings to child care centers and developmental evaluation centers; parent advocacy group meetings; hospital clinics; university-based autism subject registry | 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 >30 on CARS | 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 |
| | • Other measures were not associated with an AD diagnosis: total number of social interaction gestures, number of child-initiated social interaction gestures | | • 14 children with TD | | | • Only gestures defined as social interaction were used in this study ("gestural act used to attract or maintain attention of another for social purposes"; eg, waving hello or good-bye, shaking head yes or no) |
| Landa and Garrett-Mayer,[49] 2006 | At 6 mo, no significant group differences in domains of motor, visual reception, and language development | Prospective longitudinal | • 24 children with later diagnosis of ASD<br>• 11 with later diagnosis of language delay<br>• 52 classified as unaffected (at 24 mo)<br>58 SIBS-A and infants with no family history of autism evaluated at 6 mo | 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 | ASD classified at 24 mo based on PLS, ADOS, and CDI | 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 |

**TABLE 2** Continued

| First Author and Year of Publication | Findings | Type of Study | Sample | Ascertainment | Outcome Diagnosis | Comments |
|---|---|---|---|---|---|---|
| Paul et al,[78] 2011 | At age 6–12 mo, group differences for certain prelinguistic vocal behaviors | Prospective cross-sectional design | • 28–38 high-risk infants (SIB-A) | Recruited from university research pool; also referrals from local pediatric practices, local autism advocacy groups, word of mouth, advertising in parenting media | Provisional diagnoses at 24 mo based on clinical observations, ADOS-T, and MSEL | • Vocalization samples collected at age 6, 9, and 12 mo during play with mother and standard set of toys |
| | • Significantly fewer speech-like vocalizations and more nonspeech vocalization | Ongoing ($N = 43$ who have participated in 24-mo follow-up) | • 20–31 low-risk infants (no sibling with ASD diagnosis) | | Of the 24 high-risk subjects who made a 24-mo visit: | • Detailed analysis of vocal production (eg, for consonant inventory, presence of canonical syllables) and development of prespeech vocalization |
| | • Significantly fewer consonant types<br>• Significantly fewer canonical syllable shapes<br>Differences in vocal production in first year of life associated with "outcomes in terms of autistic symptoms" in second year for children at high risk | | | | • 7 with ASD<br>• 6 with symptoms without meeting full BAP criteria<br>• 1 with nonautistic developmental delay<br>• 10 without a clinical diagnosis | • Discriminant function analyses included only children at high risk |

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-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; CARS, Childhood Autism Rating Scale; CDI-WG, MacArthur Communicative Development Inventories–Words and Gestures; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; DVD, digital video disc (high-capacity optical disk); IBQ, Infant Behavior Questionnaire; ICQ, Infant Characteristics Questionnaire; M-CHAT, Modified Checklist for Autism in Toddlers; PLS, Preschool Language Scale; PDD-NOS, pervasive developmental disorder not otherwise specified; SIBS-A, younger siblings of children with ASD; SIBS-TD, younger siblings of children with typical development; TD, typical development; VABS, Vineland Adaptive Behavior Scales.

24 months, 4 of these 7 subjects (all boys) exhibited dramatic declines in IQ into the severe impairment range. In a second study comparing 50 infants aged 6 to 36 months who received a later diagnosis of ASD or typical development,[22] MSEL scores increased over time for all, but starting at 12 months of age, the ASD group exhibited slower nonverbal cognitive/language growth. Similarly, Landa and Garrett-Mayer[49] reported that 24 children with ASD, ascertained from a group of 87 high-risk infants, demonstrated reduced language and motor skills by age 14 months and reduced skills in all areas at age 24 months on the MSEL, compared with high-risk siblings who were developing typically. More recently, Landa et al[66,80] have provided evidence that declining trajectories in language and nonverbal cognitive skills (as indexed by using the MSEL) in high-risk infants are strongly associated with a later diagnosis of ASD. Although there may be uncertainty with regard to what is being measured by "cognitive" assessments at young ages, the measurement equivalence of verbal and nonverbal indices over the first few years of life (ie, whether measures are tapping the same developmental constructs at different ages), and the extent to which social and attentional abilities may be contributing to children's performance, the findings of declining trajectories on standardized measures may nevertheless provide important predictive information.

### *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[22] 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.[45] Declining trajectories of social communicative behaviors associated with subsequent ASD diagnoses have also been reported in another cohort of 204 high-risk infants.[80] Yoder et al[43] also reported declining rates of joint attention behaviors in high-risk infants subsequently diagnosed with ASD. As previously noted, Jones and Klin[18] 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.[79]

### 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.[81] 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.[82,83] Variations in genetic mechanisms and the brain

networks to which they map might also correlate with variation in early behavior profiles,[83] 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 end points 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 ASDs 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[22] or the assessment of head lag at 6 months,[67] 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.[22] 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.[37,84–89] Enlargement has been noted in the frontal and temporal lobes[37,90] and in specific subcortical structures, such as the amygdala.[36,91] Enlargement has been observed in children as young as age 12 months and may be accompanied by an increase in extra-axial fluid.[87] Head circumference, which is a crude proxy for brain size, is generally consistent with brain enlargement in ASD,[84] 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.[92] 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[36] and with severity of social and communicative impairments measured at age 5 years.[91] In another recent study,[93] 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.[19] 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

ASD relative to typically developing peers while listening to a simple bedtime story. Notably, these toddlers with ASD were referred from the community rather than being identified from a high-risk sibling sample.[94] Another functional MRI study, also with ASD toddlers from the general population, found reduced correlation between the right and left hemispheres in brain regions key for language and social processing.[95] Moreover, the levels of abnormal interhemispheric correlation could be used to distinguish toddlers with ASD from control subjects at an individual level, with a sensitivity of 72% and a specificity of 84%. These reports encourage the search for neurologic biomarkers or others that may reflect underlying pathologic processes in ASD and possibly precede and/or predict behavioral changes.

### *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.[96] Moreover, such a risk-profiling approach could incorporate both behavioral and biological markers[24] 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.

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