Autism spectrum disorder: advances in diagnosis and evaluation

Lonnie Zwaigenbaum,1 2 Melanie Penner3

ABSTRACT

Autism spectrum disorder (ASD) has a variety of causes, and its clinical expression is generally associated with substantial disability throughout the lifespan. Recent advances have led to earlier diagnosis, and deep phenotyping efforts focused on high risk infants have helped advance the characterization of early behavioral trajectories. Moreover, biomarkers that measure early structural and functional connectivity, visual orienting, and other biological processes have shown promise in detecting the risk of autism spectrum disorder even before the emergence of overt behavioral symptoms. Despite these advances, the mean age of diagnosis is still 4-5 years. Because of the broad consistency in published guidelines, parameters for high quality comprehensive assessments are available; however, such models are resource intensive and high demand can result in greatly increased waiting times. This review describes advances in detecting early behavioral and biological markers, current options and controversies in screening for the disorder, and best practice in its diagnostic evaluation including emerging data on innovative service models.

Introduction

Autism spectrum disorder (ASD) is characterized by impaired social communication and interaction, and by restricted, repetitive interests and behaviors.1 2 Lifetime societal costs related to services and lost productivity by patients and their parents average $1.4m (£1.0m; €1.1m) to $2.4m in the United States and £0.9-£1.5m per child in the United Kingdom, depending on comorbid intellectual disability. When the prevalence of ASD is factored in, the annual estimated societal costs of ASD are $236bn in the US and £47.5bn in the UK.3 Cost effectiveness studies have modeled the potential long term functional benefits4 and savings5 associated with earlier access to interventions. In a two to three year follow-up of a clinical trial,7 toddlers who had received early intensive treatment not only experienced functional gains but also needed fewer services than those who received “treatment as usual,” resulting in overall cost savings.8 Thus, early intervention—and by extension, early diagnosis—have the potential to improve function and reduce societal costs.

Advances over the past decade have set the stage for earlier diagnosis. Deep phenotyping efforts focused on high risk infants, including younger siblings of children with ASD, have expanded the evidence base that informs early detection.9 Moreover, measures of underlying biological mechanisms (biomarkers) could be used to assess risk concurrent with or before the emergence of overt behavioral symptoms.10 However, many factors influence the age of diagnosis, including the child’s cognitive and language levels, as well as ethnicity and socioeconomic status.11 Waiting lists can also influence timing. Despite advances in knowledge about early signs of the disorder, the mean age of clinical diagnosis has stayed at 4-5 years, with modest12 or no evidence12 of a decline. These estimates do not take account of underdiagnosis in older youths and adults (see expert review on adult ASD diagnosis).13 Although efforts toward earliest possible diagnosis are justified,4 timely and accurate diagnostic assessments are needed throughout the lifespan. Published guidelines are broadly consistent regarding benchmarks for high quality comprehensive assessments, but high demand has prompted consideration of the impact that the resource intensity of such models can have on waiting times. To increase capacity among many types of providers, models that balance the quality and accuracy of assessment with timeliness and family preferences are being tested.

This review will summarize key advances and major scientific and practice problems related to the evaluation of ASD. We will describe advances in characterizing early symptom development, as well as behavioral and biologic strategies that can support early detection. We will review current best practice and controversies in screening and diagnostic evaluation, including emerging data on innovative service models, and we will discuss the importance of ongoing assessment of co-occurring conditions across the lifespan. Our main goals are to highlight recent findings and emerging methodologies that could improve the timeliness of diagnosis for years to come.
Prevalence

ASD is one of the most common childhood onset neurodevelopmental disorders. Recent prevalence estimates are between 1% and 1.5%, with relative consistency across studies internationally. The interpretation of apparent increases over the past 20 years remains controversial (the relative contributions of a genuine increase versus greater awareness or improved ascertainment), but the current prevalence warrants consideration of assessment models that use community capacity rather than relying entirely on tertiary level centers.

Sources and selection criteria

To maximize sensitivity, we searched health, psychology, and education citation databases (including Medline, EMBASE, PsychINFO, CINAHL, and ERIC). Search terms included autism spectrum disorder (including Asperger’s syndrome, autism, autistic children, autistic psychopathy, early infantile autism, and pervasive developmental disorders). For sections on early identification of the disorder, we combined these terms with “early detection” or “early diagnosis” or “mass screening” or “screen [tw]” using the age filter “infant, birth-23 months.” Our search was limited to English language papers only. For the diagnosis section, autism spectrum disorder terms were combined with diagnosis terms including medical diagnosis, delayed diagnosis, early diagnosis, differential diagnosis, and psychiatric diagnosis. The systematic review extended from 2000, when the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR) was published, to 31 March 2017, when the search was conducted. We also searched bibliographies of identified articles for other relevant citations and included articles that were published after the search date to ensure that our review reflects the latest information.

This review could not capture all of the complexities of the assessment of ASD. We focused on early identification, elements of diagnostic assessment across childhood, family preferences, and ongoing assessment. Exhaustive reviews of ASD screening tools27-29 and diagnostic tools20,21 have been published and for this reason were not repeated. Some important topics related to the assessment of ASD are not covered in this review, including interventions and assessment of adults.

Early behavioral symptoms in ASD

From the earliest case descriptions by Kanner,22 parents’ recollections of their initial concerns have informed the search for early behavioral markers. The most commonly reported initial concerns include delayed language skills, atypical social emotional responses (such as orienting to name), repetitive interests and behaviors, difficulties with biological functions (such as feeding and sleeping), and extremes of behavioral reactivity.24-25 An extensive literature based on coding of home videos also indicated differences in social behavior and repetitive and sensory oriented behaviors between affected children and typically developing children that was detectable by age 12 months.26-29

The shift to prospective studies of high risk infants has enabled early features to be further delineated. Evaluations in the first year suggest the emergence of an ASD prodrome,30 which includes reduced motor control,11-14 attention, and emotional regulation before the development of overt social communication impairments and repetitive behaviors.30 In the second year, reduced orienting to name34-37 and deficits in joint attention behaviors (both responding38-39 and initiating40-41), as well as reduced shared positive affect,29-31 are among the most consistently identified features. Several independent longitudinal studies have implicated atypical developmental trajectories, with progressive reduction in age appropriate social behaviors,31 as well as evidence of “plateauing” of language and non-verbal cognitive skills.34-45

Atypical use of objects, such as spinning, lining up, and visual exploration, has also been consistently reported to start at 1 year.37-49 Several groups have investigated parent reported temperament in high risk infants, both as a theoretical framework for relevant domains50 as well as a potential early detection strategy. Reduced effortful control (self regulation) and surgency (positive effect and social approach), and increased negative affect have been associated with ASD among high risk infants, as reported in older children with the disorder.50-53 With the exception of a few studies, which have examined individual symptoms such as repetitive behaviors54 and response to name,55 and a preliminary analysis of a more comprehensive scale,56 most behavioral studies in high risk infants have focused on group comparisons rather than individual level classification.
Potential for presymptomatic detection: advances in biomarker research

Although behavioral features may not be fully manifest or sufficiently specific to support early detection, measures of underlying biological processes offer an alternative means to identify at risk infants. Biomarkers are defined as characteristics that are objectively measured as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic interventions. Biomarkers can be applied for many purposes in relation to ASD including risk assessment, diagnosis, and characterization of symptom severity. Longstanding interest in potential biomarkers for the diagnosis of ASD dates back to studies on blood serotonin reported in the 1970s. Several reviews have highlighted the potential benefits of earlier detection and targeted interventions by pursuing assessment measures that focus on underlying biology rather than downstream behavioral effects.

Cross sectional studies of potential biomarkers

Until recently, most published studies compared biomarkers of typically developing controls or reference norms with those of older children or adults with the disorder. This is also true for recent studies examining metabolomics, markers of inflammation and oxidative stress, and salivary proteomics. Such findings cannot be readily generalized to early detection because biomarkers generally reflect dynamic processes that change over the course of development. Cross sectional studies of blood based biomarkers in newborn and infant samples may be more informative—for example, in one case-control study mRNA expression profiles in community identified toddlers with ASD differed from those of typically developing controls, with optimal sensitivity and specificity of 73% and 68%, respectively, in a cross validated sample. Maternal and newborn immunoglobulin levels have also been examined in relation to the risk of ASD, although no data on individual level prediction have been reported.

Prospective studies of potential biomarkers in high risk infants: early brain development

The search for early brain based biomarkers is guided by extensive evidence of atypical cortical activation, brain growth trajectories, and functional and structural connectivity in children and adults with the ASD. Electroencephalography (EEG) provides a temporally precise measure of postsynaptic brain activity at rest and in response to specific stimuli (event related potentials; ERPs) and can be useful when studying early brain functioning in ASD. Several prospective studies have posited EEG metrics as potential early biomarkers of ASD. Tierney and colleagues reported that developmental trajectories of resting EEG power from 6 months to 12 months of age distinguished high risk from low risk infants but was not specifically associated with symptoms of ASD. Righi and colleagues reported on linear coherence, a global index of EEG signal synchronization, in response to auditory stimuli in a sample of 28 high risk and 26 low risk infants. Compared with the low risk group, at 12 months of age high risk infants displayed lower linear coherence, with marginal differences related to ASD outcome (n=5). Elsabbagh and colleagues, in an extension of a previous report, assessed ERPs in 40 high risk and 45 low risk infants who viewed faces that appeared to gaze toward rather than away from them. ERP responses at 6 months to 12 months of age differentiated the 13 high risk infants diagnosed with ASD at 36 months from non-diagnosed high risk infants and low risk infants. Sensitivity and specificity with respect to individual diagnostic outcomes were not reported in these studies.

A series of findings from the US Infant Brain Imaging Study (IBIS) Network indicate that magnetic resonance imaging (MRI) based biomarkers are remarkably accurate in predicting ASD at 6-12 months of age. Hyperextension of cortical surface area at 6 months and 12 months, which preceded brain volume overgrowth at 12 months and 24 months, informed a deep learning algorithm that correctly classified 30 of 34 high risk infants diagnosed with ASD at 24 months (sensitivity 88%) and 138 of 145 high risk infants not diagnosed with ASD (specificity 95%). Also in the IBIS high risk cohort (n=59), a functional connectivity MRI based machine learning algorithm applied at 6 months of age had a 81% sensitivity and 100% specificity for the diagnosis of ASD. Increased extra-axial cerebral spinal fluid volume at 6 months of age correlated with motor function at 6 months and was associated with a diagnosis of ASD at 24 months (80% sensitivity and 67% specificity). ASD related connectivity differences mapped to functional networks underlying joint attention skills at 12 months and 24 months. Such differences were associated with reduced local efficiency (reduced capacity to transmit information across a network) in several brain regions. Functionally relevant developmental progression with reduced efficiency in the right primary auditory cortex was seen at 6 months, which extended to regions underlying higher order cognitive functions by 24 months. High risk infants were also differentiated by white matter tract development starting at 6 months of age, as assessed by diffusion tensor imaging, which was related to atypical visual orienting at 7 months and repetitive behavior and sensory responsiveness at 24 months.

These findings are complemented by a smaller study of community identified 1 year to 4 year old children with ASD who had atypical development of white matter ultrastructure relative to typically developing controls, particularly in the frontal tracts and within the corpus callosum in those younger than 30 months.

Prospective studies of potential biomarkers in high risk infants: early visual orienting

Gaze metrics might be considered at the boundary between behavioral and biologic markers of ASD. Although visual orienting is directly observable, it may index a more basic neuropsychological process than other behavioral symptoms and can be objectively measured using eye tracking. A review of 122 studies indicated atypical gaze patterns across the lifespan in people with ASD, consistent with fundamental deficits in selecting and attending to information needed to perceive social interactions accurately. Numerous studies

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3 of 16
have examined early correlates of these findings in high risk infants. Several of these have focused on cross sectional group differences in visual orienting between high risk and low risk infants in relation to face processing, gaze following, and language processing. These studies do not directly inform early detection because diagnostic outcomes were not reported. Other studies have examined whether orienting patterns in the first year predict subsequent diagnosis of ASD. In a prospective study, 6 month olds diagnosed as having ASD at 24-36 months (n=15) showed reduced spontaneous social orienting while watching a video of a socially engaging actress when compared with non-diagnosed high risk and low risk infants (n=63 and n=49, respectively). Effect sizes were moderate (0.32-0.47) but classification accuracy (sensitivity and specificity of reduced social orienting) was not reported. No ASD related differences were seen in attention to the eyes versus mouth, consistent with an earlier prospective study. In a more intensive longitudinal study, with prospective data collected at several time points between 2 months and 24 months of age, the location and duration of visual orienting of 39 high risk and 26 low risk male infants was analyzed as they watched a similarly engaging video. Girls were assessed but not included in the main analysis. The 11 infants with ASD at 36 months (n=11; 10 from the high risk group) showed a decline in gaze duration over the first two years relative to 25 typically developing infants from the low risk cohort. Cross sectional group differences reached statistical significance at 12 months, but differences in trajectories were detectable earlier. Change in eye gaze duration between 2 months and 6 months differentiated the ASD and typically developing groups with near 100% accuracy; however, other high risk infants (particularly those with subthreshold “broader phenotype” symptoms) had intermediate fixation times. In a recent cross sectional study, eye versus mouth fixation times showed greater concordance in monzygotic versus dizygotic twins, which suggests that this attentional bias has a genetic basis. An overview of Klin, Jones, and colleagues’ work argues that eye versus mouth fixation is a strong translational candidate as a universal screener for ASD, but that large scale clinical trials would be needed to assess its potential utility in the general community.

Eye tracking has also been used to assess impairments in visual disengagement—the ability to withdraw attention from one stimulus in order to shift to another while the first is still present—reported in older children and adults with ASD. In three prospective studies, high risk infants who were subsequently diagnosed as having ASD had prolonged disengage latencies. In one of these prospective studies, Bryson and colleagues found that prolonged latencies at 12 months not only predicted an ASD diagnosis at 36 months but were also associated with emotional dysregulation. None of these studies reported whether prolonged latency could be used to predict individual outcomes. Finally, a preference for moving geometric patterns over social images is predictive of ASD risk and symptom severity in a community toddler sample.

Potential clinical utility of predictive biomarkers for ASD
As summarized in table 1, some of these candidate biomarkers are associated with sensitivity and specificity estimates that compare favorably with those of previously reported behavioral signs and they have the advantage of potentially being detectable earlier. Presymptomatic detection of ASD within a high risk family is an important advance and the potential for broader application in the community could transform clinical practice. However, the generalizability of findings to non-familial low risk (and other high risk) samples must first be established. Moreover, screening algorithms derived from machine learning (thus, sample dependent) analyses need replication using hypotheses driven designs. The feasibility of implementation in the general community must also be established, with consideration of necessary training, acceptability to parents, and costs, although potential long term savings related to improved outcomes resulting from earlier diagnosis and treatment should be taken into account. Finally, because of the etiologic heterogeneity of the disorder some biomarkers may be specific to certain subtypes of ASD and informative for only a subset of cases. Such biomarkers might be used to individualize treatment in the future, but are less likely to be useful for early detection and screening in the absence of clinical correlates that could be used to pre-stratify the target sample.

Although there is reason for excitement at the promise of biomarker based screening, from a public health perspective, behavioral markers such as parental concerns can be just as informative. “Pencil and paper” tasks are not inherently inferior to technologically sophisticated measurement strategies. All potential markers can be considered with respect to classification accuracy, feasibility, acceptability to parents, and cost effectiveness.

Screening and surveillance
Whereas biomarkers have mainly been assessed in relatively small high risk cohorts, several behaviorally based screening tools have been evaluated in large community samples. An exhaustive review of ASD screening tools is beyond the scope of this article (see recent reviews). However, as an illustration we will discuss a few that meet important criteria (replication in multiple primary care settings and accuracy of classification) and thus warrant consideration for clinical application.

Modified Checklist for Autism in Toddlers
The Modified Checklist for Autism in Toddlers (M-CHAT) was adapted from the Checklist for Autism in Toddlers (CHAT), which, although it was groundbreaking in demonstrating the feasibility of ascertaining toddlers with ASD in the general population, was too insensitive for clinical application. The 23 item M-CHAT includes content from the CHAT (joint attention and pretend play) but covers a broader range of developmental domains. M-CHAT includes a follow-up interview, which clarifies parent questionnaire responses to reduce false positives. M-CHAT has been assessed in multiple independent primary care samples and internationally in multiple languages using validated translations. It is also available as an electronic tablet based version; this product improves utilization by primary care pediatricians and can be completed by parents
Table 1 | Sensitivity and specificity of early detection strategies for autism spectrum disorder

<table>
<thead>
<tr>
<th>First author</th>
<th>Sample</th>
<th>Predictor</th>
<th>Outcome</th>
<th>Sensitivity (Se)</th>
<th>Specificity (Sp)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Select behavioral markers</strong></td>
<td></td>
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<tr>
<td>Miller94</td>
<td>96 HR (19 ASD)/60 LR (1 ASD)</td>
<td>Did not respond to name (per ADOS) at least once at 12, 15, 18, and/or 24 months</td>
<td>ASD at 36 months (CBE by DSM-IV, ADOS positive)</td>
<td>0.70</td>
<td>0.70</td>
<td>Se and Sp also assessed at each time point between 6 and 24 months and by 1+ failure at 6-24 months (Se=0.30, Sp=0.52)</td>
</tr>
<tr>
<td>Ozonoff95</td>
<td>35 HR (8 ASD)/31 LR (1 ASD)</td>
<td>Atypical behavior (2 SD above mean of “no concerns” group) on Object Exploration Task at 12 months</td>
<td>ASD at 24 or 36 months (CBE by DSM-IV, ADOS positive)</td>
<td>0.78</td>
<td>0.72</td>
<td>Sp calculated from data reported on two non-ADOS groups (“other delays” and “no concerns”)</td>
</tr>
<tr>
<td>Chawarska90</td>
<td>719 HR (157 ASD)</td>
<td>CART analysis using ADOS items at 18 months</td>
<td>ASD at 36 months (CBE by DSM-IV, ADOS positive)</td>
<td>0.46</td>
<td>0.87</td>
<td>CART predictors included poor eye contact, lack of giving, repetitive stereotyped behaviors, atypical imitation, and lack of imaginative play</td>
</tr>
<tr>
<td>Zwaigenbaum96</td>
<td>65 HR (19 ASD)/23 LR (0 ASD)</td>
<td>AOSI: 7 or more risk markers (non-zero coded items) at 12 months</td>
<td>24 month ADOS: ASD classification</td>
<td>0.84</td>
<td>0.98</td>
<td>Updated data using 36 month CBE under review</td>
</tr>
<tr>
<td><strong>Select biomarkers</strong></td>
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<tr>
<td>Hazlett78</td>
<td>179 HR (34 ASD)</td>
<td>MLA based on cortical surface area, cortical thickness, and brain volume at 6 and 12 months</td>
<td>CBE at 24 months, by DSM-IV, informed by ADOS, ADI-R</td>
<td>0.88</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Emerson79</td>
<td>59 HR (11 ASD)</td>
<td>MLA based on tMRI at 6 months</td>
<td>CBE at 24 months, by DSM-IV, informed by ADOS, ADI-R</td>
<td>0.81</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Shen80</td>
<td>Increased extra-axial cerebral spinal fluid volume at 6 months</td>
<td>CBE at 24 months, by DSM-IV, informed by ADOS, ADI-R</td>
<td>0.80</td>
<td>0.67</td>
<td></td>
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</tr>
<tr>
<td>Jones81</td>
<td>59 HRS1 LR</td>
<td>Declining gaze towards eyes (of actress in video)</td>
<td>CBE at 24 months by DSM-IV (confirmed at 36 months), informed by ADOS, ADI-R</td>
<td>N/A</td>
<td>NA</td>
<td>Analyses limited to 11 ASD (10 from HR, 1 LR) and 25 TD (all from LR); ROC curves reported but not specificity and specificity estimates</td>
</tr>
<tr>
<td>Pierce82</td>
<td>444 toddlers, ITC</td>
<td>Preference for dynamic dyadic social images at 10-49 months; assessed by eye tracking</td>
<td>CBE at 24 months, by DSM-IV, informed by ADOS</td>
<td>0.21</td>
<td>0.98</td>
<td>High-risk cohort ascertained by community screening (ITC). Examination of age effects suggests this test is not informative &gt;4 years</td>
</tr>
<tr>
<td><strong>Behavioral screening</strong></td>
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<tr>
<td>M-CHAT-R/F</td>
<td>16 071 LR</td>
<td>Screened at 16-30 months, 3 of 20 items endorsed (plus positive follow-up interview if 3-7 items)</td>
<td>CBE by DSM-IV (=6 months after screen; informed by ADOS, CARS-2)</td>
<td>N/A</td>
<td>NA</td>
<td>56 and Sp cannot be directly estimated owing to limited follow-up of screen negative children; PPV for ASD=0.475; for any DD=0.946</td>
</tr>
<tr>
<td>CSBS-ITC</td>
<td>5385 LR</td>
<td>Screened at 24-36 months, any screen positive (cut-off point 10th centile, based on standardization sample)</td>
<td>CBE at 3 years or older, by DSM-IV, informed by ADOS, SCQ</td>
<td>0.93</td>
<td>0.83</td>
<td>Potential ASD cases identified by population surveillance, independent of ITC</td>
</tr>
<tr>
<td>FYI</td>
<td>698 LR</td>
<td>Screened at 12 months; cut-off point based on risk algorithm derived from standardization sample</td>
<td>CBE at age 3, by DSM-IV, informed by ADOS</td>
<td>N/A</td>
<td>NA</td>
<td>Potential ASD cases flagged for assessment based on secondary screening at age 3 years using SRS-P and DCQ</td>
</tr>
<tr>
<td>STAT</td>
<td>26 ASD/26 DD/LU</td>
<td>Screened at 24-35 months; cut-off point identified then validated in independent sample</td>
<td>Concurrent CBE</td>
<td>0.92</td>
<td>0.85</td>
<td>2nd level interactive screen applied to children referred for diagnostic assessment</td>
</tr>
</tbody>
</table>

*Abbreviations: ASD=autism spectrum disorder; ADOS=Autism Diagnostic Observation Schedule; ADI-R=Autism Diagnostic Interview-Revised; ADOS=Autism Observation Scale for Infants; CARS-2=Childhood Autism Rating Scale, 2nd edition; CART=classification and regression tree analysis; CBCL=cclinical best estimate; CSBS=Communication and Symbolic Behavior Scales; DD=Developmental delay; DSM-IV=Diagnostic and Statistical Manual, fourth edition; HR=high risk; ITC=interactive screening test; M-CHAT-R/F=Autism Diagnostic Screening Check; PPV=positive predictive value; ROC=receiver operating curve; SCQ=Social Communication Questionnaire; SD=standard deviation; Se=sensitivity; Sp=specificity; SRS-P=Social Responsiveness Scale-Preschool version; STAT=Screening Tool for Autism in Toddlers and Young Children.

online, potentially increasing access by underserved populations.124 The most recent version, the M-CHAT-Revised with Follow-Up (M-CHAT-R/F), consists of 20 items and only those in a medium risk category require the follow-up interview.109 When assessed in a community sample of 16 115 toddlers, the revised M-CHAT-R/F algorithm reduced the initial screen positive rate, increasing the ASD detection rate compared with the original M-CHAT (67/10 000 vs 45/10 000), without compromising positive predictive value (PPV; 47.5% for ASD).109 The sensitivity and specificity of the M-CHAT-R/F (and earlier versions) has not been directly assessed in community samples because ascertainment of ASD was limited to screen positive children, and this is a serious limitation.

Communication and Symbolic Behavior Scales Developmental Profile Infant/Toddler Checklist

The Communication and Symbolic Behavior Scales Developmental Profile (CSBS DP) Infant/Toddler Checklist (ITC) was originally designed as a broadband screener for communication delays but has shown high sensitivity for ASD.110 Within a community sample of 5385 6-24 month olds, the ITC identified 56 of 60 (93%) children with ASD ascertained independently at age 3 years. The ITC also identified problems sooner and more consistently than an open ended question about parents’ developmental concerns.110 With a cut-off at the 10th centile relative to population norms, follow-up assessment is needed to distinguish toddlers at risk of ASD from those with other communication delays. The Systematic Observation of Red Flags (SORF), coded from videos of the interactive component of the CSBS DP, is recommended for that purpose.123 In a prospective screening study, Pierce and colleagues reported the clinical utility of the ITC in early detection of ASD as part of routine 1 year check-ups in pediatric primary care practices.112 However, only, 26.3% of screen positive children were referred, of whom 53.2% completed diagnostic assessment. Among these children the PPV for ASD was 17.4%, but this increased to 75% if other atypical developmental features were classified as screen positive. The low PPV for ASD is probably a reflection of moving directly from screen positive ITC to diagnostic assessment, although the feasibility of imple-
menting the video coded SORF as an intermediate step within the community remains to be evaluated.

Other screening tools
The Early Screening of Autistic Traits (ESAT) was evaluated in a population sample (N=31 724) of 14-15 month olds but had a low case detection rate (<1/10000) and a PPV of 0.25. The Brief Infant-Toddler Social Emotional Assessment was evaluated in a combined community low risk sample of 2 year old children (n=3127) and a clinical sample of preschool children with ASD; receiver operating curve analyses identified a subset of items (“autism score”) showed good discrimination of children with and without ASD. Clinical cut-off points were recently proposed on the basis of a case-control study but have yet to be evaluated in a prospective screening study. Other ASD screening tools have shown some promise, but initial data are limited to case-control comparisons (for example, Baby and Infant Screen for Children with autism Traits (BISCUIT), Quantitative Checklist for Autism in Toddlers (Q-CHAT), high risk cohorts (for example, Autism Parent Screen for Infants (APSI)), or modest community samples with small numbers of true positives requiring further study (for example, First Year Inventory (FYI)), Interactive screens have shown utility in secondary (targeted rather than universal) screening contexts, particularly the Screening Tool for Autism in Two-Year-Olds (STAT) and the Rapid Interactive Screening Test for Autism in Toddlers (RITA-T), for which data are only preliminary.

Current best practice in ASD screening
Currently consensus is poor regarding what would constitute sufficient evidence to recommend universal or secondary screening for ASD as part of standard practice. This has created confusion and concern in the clinical community and raises important questions about how to achieve acceptable translational pathways for the next generation of screening measures, including those incorporating biomarkers. The question is whether screening, particularly of children whose parents do not spontaneously raise concerns, is only warranted if it results in long term improvements in health outcomes as assessed in community based cluster randomized clinical trials with multi-year follow-up. For example, the US Preventative Services Task Force (USPSTF) concluded that there was “insufficient evidence to recommend screening for ASD in children aged 18 months to 30 months for whom no concerns of ASD have been raised,” defining critically needed evidence as “large, high-quality cluster randomized clinical trials of treatment that enroll young children with ASD identified through screening.” However, screening (for example, using M-CHAT) has been shown to have predictive validity (as acknowledged by the USPSTF), identifies ASD symptoms earlier and more consistently than general inquiry about parent concerns (an alternative strategy recommended by the USPSTF), may reduce disparities in access to diagnostic services, and accelerates the pathway to accessing specialized interventions that improve outcomes. Thus, some have argued that screening is warranted on the basis of the balance between potential risks and benefits, even in the absence of evidence from randomized controlled trials (RCTs). Ultimately, estimates of sensitivity and specificity as well as changes in age of diagnosis and access to intervention are needed to fully evaluate the systems impact of ASD screening. Notably, one published RCT showed reduced age of diagnosis with the implementation of ASD screening (using the ESAT), although the differences may have reflected collateral effects of the trial (such as engagement of community physicians, clarification of referral pathways) rather than the screen itself.

ASD assessment guidelines
Many diagnostic guidelines for ASD have been published and the key contents have been described in several recent publications (table 2). A recent systematic review of ASD diagnostic guidelines showed that these guidelines contained variable recommendations and were of variable quality, with relatively higher Appraisal of Guidelines for Research and Evaluation (AGREE) quality ratings in scope and purpose and clarity of presentation and lower ratings in applicability and rigor of development. The highest rated guidelines from this review were the UK’s National Institute for Health and Care Excellence guideline and the New Zealand autism spectrum disorder guideline. All guidelines reviewed supported the use of multidisciplinary team assessment for ASD, although with little supporting empirical evidence, and had varying recommendations for the use of diagnostic tools.

Table 2 | Comparison of autism spectrum disorder practice parameters for autism spectrum disorder

<table>
<thead>
<tr>
<th>Document</th>
<th>Year</th>
<th>Clinicians who can diagnose</th>
<th>MDT needed</th>
<th>Recommended assessments</th>
<th>Specific tools recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN142</td>
<td>2000</td>
<td>NS</td>
<td>Yes</td>
<td>Cognitive</td>
<td>SLP if child fails language screening</td>
</tr>
<tr>
<td>AAP143</td>
<td>2007</td>
<td>Physician psychologist</td>
<td>Ideally</td>
<td>Medical1</td>
<td>Developmental and psychometric evaluation</td>
</tr>
<tr>
<td>AACAP144</td>
<td>2014</td>
<td>NS</td>
<td>Yes</td>
<td>Medical Cognitive</td>
<td>SLP</td>
</tr>
<tr>
<td>National guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UK (NICE)145</td>
<td>2011</td>
<td>Care members of MDT</td>
<td>Yes</td>
<td>Assessment by core team members/Physician (pediatrician or psychiatrist)</td>
<td>Psychologist SLP</td>
</tr>
<tr>
<td>New Zealand146</td>
<td>2016</td>
<td>NS</td>
<td>Ideally</td>
<td>Hearing</td>
<td>Medical Speech-language Cognitive** Mental health and behavior Family needs and strengths</td>
</tr>
<tr>
<td>Scotland (SIGN)147</td>
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<td>Yes</td>
<td>History Clinical observation and assessment Contextual and functional information Speech and language Cognitive and adaptive skills</td>
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</table>

*Abbreviations: AAN=American Academy of Child and Adolescent Psychiatrists; AAP=American Academy of Pediatrics; MDT=multidisciplinary team; NICE=National Institute for Health and Care Excellence; NS=not specified; SIGN=Scottish Intercollegiate Guidelines Network; SLP=speech language pathology.

1With reference to the American Speech-Language-Hearing guideline statement (rescinded 2015), which stated that an SLP with experience in ASD could make the diagnosis.

2Excluding health, developmental, and behavioral histories, as well as physical examination.

3Guidelines note that tools can be used to supplement clinical opinion.

4Guideline notes that cognitive assessment should be undertaken “if possible.”
Personnel involved in the diagnostic assessment of ASD

Clinical guidance documents generally recommend that multidisciplinary teams are involved in the diagnosis of ASD.\textsuperscript{20,142-146,150-152} There is some dissent to this opinion, including from a group of Canadian ASD experts who propose a clinical pathway in which a diagnosis of ASD can be conferred by an experienced pediatrician, developmental pediatrician, child psychiatrist, or clinical psychologist, provided the child meets the diagnostic criteria.\textsuperscript{153} The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) does not specify necessary personnel, but does outline that the diagnosis should be accompanied by a comment on the presence of cognitive or language impairment (or both).\textsuperscript{1}

The diagnostic accuracy of individual clinicians and multidisciplinary teams has rarely been compared, and the extant literature is difficult to apply owing to the legacy of pre-DSM-5 ASD subtypes. Some groups that advocate for multidisciplinary team assessment have highlighted the need to assess for co-occurring or alternative diagnoses,\textsuperscript{144,152} while others endorse the idea that this information will inform treatment strategies.\textsuperscript{150} However, the process by which intervention providers would incorporate such information is poorly understood and further challenged by changes in the child’s profile that can occur during extended wait times for publicly funded interventions.\textsuperscript{155} In addition, although team diagnostic assessment may be recommended, actual clinical practice varies greatly. A survey of Australian ASD clinicians found that 39% (n=52) worked as part of a team for all diagnostic assessments, 37% (n=49) performed solo assessments, and the remaining 23% (n=31) performed both types of assessment.\textsuperscript{156} Among 284 US based ASD diagnostic assessments completed by 56 developmental behavioral pediatricians, only 17.3% of assessments were completed by a multidisciplinary team.\textsuperscript{156}

There have been recent efforts to train community based clinicians who have less ASD experience to expand diagnostic capacity. A group in Scotland trained teams consisting of a pediatrician, psychiatrist, and a speech language pathologist to perform ASD diagnostic assessments.\textsuperscript{157} There was agreement between the newly trained pediatricians and an expert MD in 71% of diagnostic assessments, which increased to 86% in a follow-up evaluation. After the training, ASD diagnostic assessments completed by 56 developmental behavioral pediatricians, only 17.3% of assessments were completed by a multidisciplinary team.\textsuperscript{156}

In summary, few studies have evaluated the personnel involved in the diagnostic assessment of ASD. Clinical guidance documents generally recommend that multidisciplinary teams are involved in the diagnosis of ASD.\textsuperscript{20,142-146,150-152} There is some dissent to this opinion, including from a group of Canadian ASD experts who propose a clinical pathway in which a diagnosis of ASD can be conferred by an experienced pediatrician, developmental pediatrician, child psychiatrist, or clinical psychologist, provided the child meets the diagnostic criteria.\textsuperscript{153} The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) does not specify necessary personnel, but does outline that the diagnosis should be accompanied by a comment on the presence of cognitive or language impairment (or both).\textsuperscript{1}

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The evaluation of the pilot trial of this program showed agreement between the pediatricians and an expert MD in 71% of diagnostic assessments, which increased to 86% in a follow-up evaluation. After the training, ASD diagnostic assessments performed by participating pediatricians increased by 85%.\textsuperscript{159}

In summary, few studies have evaluated the personnel needed for diagnostic assessment. All studies have been observational or retrospective and most had small samples. Until further data are available, practice will continue to be guided by clinical/expert consensus and pressures on service delivery systems. Few data are available on how diagnostic assessment models affect waiting times, which makes the trade-offs of various models difficult to determine. Given the heterogeneity inherent to ASD, it is possible that the optimal assessment structure needed for one child may differ from that of another child. Future clinical guidance and practice should consider needs across this continuum so that the breadth and depth of assessment ensure high quality and well integrated diagnoses while also efficiently managing available resources.

Diagnosis assessment tools

Table 3 provides a summary of selected tools. Two broad categories of assessments exist: those that are used when interviewing caregivers for ASD related signs and symptoms and those that code observations and interactions with the child. Such tools can inform the diagnosis, but assessors should not rely solely on the score to make the diagnosis. In studies evaluating ASD diagnostic tools, the reference test is always compared with the clinical best estimate, generally determined by a team of experts.

Of the diagnostic interview tools, the Autism Diagnostic Interview-Revised (ADI-R) is the most thoroughly studied.\textsuperscript{182} The ADI-R requires extensive training and takes at least 90 minutes to administer. There are two cut-off points for the ADI-R: a research one, which has generally been shown to have lower sensitivity (0.44-0.84)\textsuperscript{159,170} and higher specificity (0.82-0.96)\textsuperscript{159,170} and a clinical one, which has higher sensitivity (0.60-0.90)\textsuperscript{169,171} and lower specificity (0.70-0.81)\textsuperscript{170}; these estimates vary considerably (see table 3). In all identified studies evaluating the ADI-R, the clinical best estimate included review of the ADI-R. This study design may be more feasible than independent evaluation of the ADI-R but introduces a degree of circularity. In addition, given the resource intensive nature of the ADI-R, further work is needed to determine whether a more streamlined interview can generate acceptable accuracy.

The Developmental, Dimensional and Diagnostic Interview (3di) is a computer based ASD interview consisting of mandatory modules related to core ASD features, and optional modules covering co-occurring conditions.\textsuperscript{179} Initial results for the 3di were promising, with a reported sensitivity of 1.0 and specificity of 0.98 in differentiating 27 children with ASD from 93 children without ASD.\textsuperscript{179} Two additional studies have evaluated the 3di: one from China,\textsuperscript{180} which showed a sensitivity of 0.95 and specificity of 0.77, and one from the Netherlands,\textsuperscript{181} which used a short version and showed lower sensitivity (0.84) and specificity (0.54).

Alternatively, information can be obtained from caregivers about the child’s ASD symptoms using questionnaires. The two most commonly studied are the Social Responsiveness Scale (SRS, SRS-2)\textsuperscript{182,184} and the Social Communication Questionnaire (SCQ).\textsuperscript{188} Relatively few studies have evaluated the SRS, with many advising caution when using the SRS to distinguish between ASD and related conditions, such as intellectual disability,\textsuperscript{186} oppositional defiant disorder or conduct disorder,\textsuperscript{188} social phobia,\textsuperscript{188} and selective mutism.\textsuperscript{188} Only two studies evaluated the SCQ,\textsuperscript{188,189} both focused on distinguishing ASD from attention-deficit/hyperactivity...
Table 3 | Summary of selected ASD diagnostic tools

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>N</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
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<td></td>
<td></td>
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<tr>
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</tr>
<tr>
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</tbody>
</table>

*A abbreviations: ADQ=autism spectrum disorder; ADOS=Autism Diagnostic Observation Schedule; ADI=R=Autism Diagnostic Interview-Revised; BCE=best clinical estimate; CARS/CARS-2=Childhood Autism Rating Scale/Childhood Autism Rating Scale; 2nd edition; 3di=Developmental, Dimensional and Diagnostic Interview; NPV=negative predictive value; PPV=positive predictive value; Se=sensitivity; Sp=specificity.
†Where accuracy statistics for multiple groups were reported, these were combined into a single statistic. Reported values for the ADOS are for the ASD cut-off. Reported values for the ADI-R are for the clinical cut-off.
‡Two of the three sites in this study had BCE independent of test administration.

To rate the presence and severity of ASD symptoms, although the authors in both studies caution against using it alone as a definitive diagnostic test. Of the observational and interactive tools for ASD assessment, the Autism Diagnostic Observation Schedule (ADOS), now in its second edition, is the best studied. Its validation was limited by similar design problems as the ADI-R—namely, its performance was evaluated against the clinical best estimate, which included information from the ADOS. The ADOS takes 40-60 minutes to administer and requires extensive training to achieve reliability in administration and coding. The ADOS has two cut-off points, one for “autism” (lower sensitivity, higher specificity) and one for “autism spectrum” (higher sensitivity, lower specificity). Studies have varied in their use of these cut-off points depending on which ADOS module was used, which complicates comparisons.

The Childhood Autism Rating Scale (CARS, CARS-2) is a clinician completed tool that incorporates information from caregiver reports and direct observation to rate the presence and severity of ASD symptoms. Although it takes only 5-10 minutes to complete the tool, this does not account for the time taken to collect the information. In addition, many of the studies that have evaluated CARS have not been blinded to the CARS result when assigning the clinical best estimate diagnosis. Reported sensitivities (in English speaking countries) range from 0.89 to 0.94, and reported specificities range from 0.61 to 1, depending on the algorithm and CARS version used.

Synthesizing the classification properties of even one diagnostic tool for ASD is complicated by the release of new versions of the tools, as well as the use of different scoring algorithms for different purposes or to detect different clinical conditions (such as classic autism versus ASD). As noted, psychometric studies for most of the described tools have been limited by lack of an independent and blinded clinical best estimate. Disparities exist in how these data are interpreted in clinical guidelines, with some calling the ADI-R and ADOS the gold standard.
STATE OF THE ART REVIEW

others encouraging the use of interview and observation—interaction tools but falling short of recommending specific tools, and yet others highlighting that tools do not replace clinical judgment. Until further evidence is available on the clinical utility of these tools, clinicians are left to follow regional requirements or to select the tools that provide the most valuable information in a given case.

Family preferences for ASD diagnostic assessment
Quantitative and qualitative methods have been used to investigate family perspectives on the diagnostic process. The most consistent theme in these studies is a negative view on the prolonged wait time to receive an ASD diagnostic assessment. A survey of nearly 500 parents of children with ASD reported that 60% were dissatisfied with the diagnostic process, with inverse associations between satisfaction and diagnostic age and the number of professionals seen before diagnosis. No association was seen between satisfaction and the type of professional who made the diagnosis. A survey from Singapore found that parental stress correlated with both the number of professionals consulted in the course of diagnostic assessment and decreased perceived collaboration with professionals. A survey of 55 families of children with ASD reported that it was common for them to wish for an earlier diagnosis. A qualitative study that included 15 focus groups of parents also identified a faster and easier diagnostic process as desirable.

The quantity and quality of information provided during the diagnostic assessment is a common focus. A perception of more helpful information being provided was associated with parental satisfaction in the survey from Singapore. Most parents in the survey by Mansell and Morris felt that sources of information and treatment were discussed either “slightly well” or “not at all well.” Similarly, a high proportion of families in a qualitative study thought they had been given no helpful information, support, or advice about ASD. Most parents of young children in this study felt that information should be provided immediately after the diagnosis, including information on organizations and services and on what to expect with ASD. In a more recent Australian survey of 404 parents and 53 pediatricians, parents rated the following as most important information to receive at diagnosis: how to find allied health professionals with ASD experience, what the diagnosis meant, how it was made, and what the prognosis was. Crucially, pediatricians reported giving more information on allied health professionals, prognosis, and funding than parents perceived receiving. The authors suggested that it might be helpful to provide lists of resources tailored to the child’s presentation and needs as part of diagnostic feedback.

Communication of information affects family perceptions of the diagnostic assessment. The survey by Mansell and Morris found that preparing the family for the diagnosis is an important aspect of assessment. Families in the Osborne and Reed qualitative study identified the need for better training of clinicians, particularly in interpersonal skills. A mixed methods French study reported that satisfied families described professionals who made them feel respected, gave them time, and were open minded, direct, and sympathetic, whereas harmful practices included not checking to ensure that parents understood the explanation or to see if further time or discussion would be helpful. One qualitative study of how the diagnosis was communicated found that tensions between “realism” and “hopefulness” were negotiated by using a parent friendly frame, complemented by a hopeful formulation or by a defocusing of a “bad news” approach. The tension of how optimistic to be when communicating the diagnosis and prognosis was also highlighted in a qualitative study in which parents described feeling more positive than professionals about the prognosis; in turn the professionals described parents as being too optimistic. This paper generated suggestions for disclosure of an ASD diagnosis (box).

Although many areas of the world are represented in the studies reviewed in this section, there is relatively little research on how culture or ethnicity influence family preferences and experiences in relation to the diagnosis of ASD. Some authors have suggested that some families, by virtue of their ethnicity, are less familiar with the early manifestations of ASD or ascribe a different meaning to atypical behaviors or late milestones within their cultural context, and that this may contribute to delays in diagnosis. However, other studies have examined the broader context by which ethnicity and cultural matters may contribute to variations in care and lived experience in relation to the diagnosis of ASD. For example, in an ethnographic study of 24 relatives of African-American children with ASD, which also integrated the perspectives of professionals from diverse ethnic backgrounds, participants described experiences related to unequal and in some cases discriminatory treatment that contributed to distrust, as well as biases among care providers that contributed to delays in the diagnosis. Specific family priorities were also identified (such as the promotion of self-sufficiency) that could have contributed to under-recognition of functional impairments and a higher threshold for diagnosis. These findings emphasize the importance of a respectful and family centered approach to optimizing the care experience in relation to diagnosing ASD. Clinicians should ask (rather than make assumptions) about parents’ beliefs (for example, how observed behaviors are interpreted) and priorities in relation to clinical information sharing. They should also take account of cultural background as well as the broader social context, including past experiences with providers.

<table>
<thead>
<tr>
<th>Suggestion for diagnostic disclosure of autism spectrum disorder (ASD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Become knowledgeable about ASD</td>
</tr>
<tr>
<td>Establish a family friendly setting</td>
</tr>
<tr>
<td>Understand the family’s needs</td>
</tr>
<tr>
<td>Use good communication skills</td>
</tr>
<tr>
<td>Provide a list of resources and interventions</td>
</tr>
<tr>
<td>Provide follow-up</td>
</tr>
<tr>
<td>Discuss prognosis</td>
</tr>
<tr>
<td>Provide hope</td>
</tr>
<tr>
<td>Recognize that it is not unusual for professionals to react to giving the diagnosis of ASD</td>
</tr>
</tbody>
</table>
Additional elements of ASD assessment

In accordance with DSM-5, some features related to ASD require additional assessment, including the presence of cognitive or language impairment (or both). Abilities in these areas can range from severely impaired to advanced. The presence of developmental delays or co-occurring diagnoses, such as ADHD, in addition to ASD symptoms may add complexity to the diagnostic assessment process. Another important consideration is exposure to trauma and attachment disorder; a history suggestive of these problems should prompt the assessor to consider the overlap in presentation between attachment disorders and ASD and seek out expertise as needed.203-205 Given these complexities, cognitive and language assessments and consideration of comorbid emotional behavioral disorders are recommended for all patients with ASD.

For complex presentations, cognitive and language assessments provide vital information needed to establish the diagnosis. However, for children who clearly meet diagnostic criteria, it may be reasonable to establish the diagnosis first so that the family can access diagnosis specific resources, which often have substantial wait times in publicly funded systems.204 and to link these additional assessments more closely with treatment planning at the time of intervention.207-209

Further service planning and program evaluation are needed for service provision to be based on a child’s functional needs (as recommended in the International Classification of Functioning, Disability and Health; ICF207), as opposed to a categorical diagnosis, thereby enabling a greater focus on the bio-psycho-social effects of ASD.208-209

Such shifts in service eligibility will influence the diagnostic assessment process and deserve thoughtful planning, implementation, and evaluation. Indeed, as part of an ongoing initiative to develop an ICF “Core Sets” measurement framework for ASD, a recent qualitative study was conducted with 19 stakeholder groups (n=90) from Canada, India, Saudi Arabia, South Africa, and Sweden. Findings highlighted key functional challenges as well as positive attributes (such as memory skills, attention to detail) on a continuum.210

Assessment does not end at diagnosis: ASD symptom trajectories

Because of the many complexities within and accompanying ASD, assessment must be an ongoing process that extends past the categorical diagnostic determination. Longitudinal studies of ASD symptoms have shown considerable heterogeneity in symptom trajectories. Two ASD symptom trajectory groups were reported in a prospective sample of 421 children followed from diagnosis to age 6 years: a small subset (11.4%) had less severe symptoms and an improving trajectory, whereas most children (88.6%) had more severe symptoms at baseline with little change over time.210 A prospective study of 129 children evaluated with the ADOS calibrated severity score from ages 2.5 to 5.5 years identified four trajectory groups: persistent high symptoms (36%), persistent moderate symptoms (42%), worsening symptoms (8%), and improving symptoms (14%).211 These trajectories were identical to four identified in an earlier longitudinal cohort.212 A large retrospective study in California that analyzed ASD symptoms found six trajectories, including communication and social “bloomers” (comprising 10% of the sample), who showed rapid improvement, particularly before age 6 years.213 Georgiades, Bishop, and Frazier introduced the concept of “chronogeneity” in relation to the heterogeneity of ASD over time.214 Chronogeneity refers to variability in change over time at the group and individual level, and the potential for individuals to deviate from group trajectories, further emphasizing the value of longitudinal assessment.

Beyond longitudinal changes in ASD symptoms, the assessment of co-occurring physical and mental health conditions and behavioral disorders is essential to providing quality care. Several physical health problems occur at higher rates in patients with ASD, including gastrointestinal disorders,215 feeding difficulties,216 seizures,217 and sleep problems,218 all of which have been shown to be negatively associated with health related quality of life.219 Clinicians must actively ask about signs and symptoms of these conditions, although management is generally similar to that for children without ASD. Co-occurring mental health conditions, such as anxiety and depression,220-223 and behavioral disorders such as ADHD,224-225 also have important effects on health related quality of life.226 Here again, clinicians should specifically ask about symptoms of co-occurring mental health conditions and behavioral disorders, recognizing that specialized assessment, which takes into account communication challenges and symptom overlap, may be needed.

Conclusions

The assessment of ASD constitutes more than a one-off assignment of a categorical diagnosis; instead, assessment should begin early in life when the first signs emerge and continue throughout the lifespan. ASD biomarkers research has grown exponentially and the integration of such technology into the future assessment of ASD risk is almost certain. Although the assessment of ASD may evolve towards a more extended process of early risk determination and prediagnostic intervention, receipt of a clinical diagnosis of ASD is still a landmark moment for families. Future developments in ASD diagnostic frameworks must foster timely and coherent assessment processes that are respectful of the family’s values. Diagnostic assessments that require multiple specialized clinicians are in limited supply and prone to long wait times when demand outpaces supply. Movement toward an assessment process that achieves both a holistic profile and also optimizes access for the large and diverse population in need is an important future goal. Whether it be a screening tool, clinical diagnostic tool, or biomarker, any tool to aid ASD assessment must be rigorously evaluated for its effectiveness, with related trade-offs identified for all stakeholders before widespread adoption. The complexity, heterogeneity, and chronogeneity of ASD demand attention from a multitude of disciplines across time and circumstance. As such, the most important future development for the assessment of ASD will be the integration of multiple
HOW PATIENTS WERE INVOLVED IN THE MAKING OF THIS ARTICLE

The section on family preferences for the diagnostic assessment of autism spectrum disorder was reviewed by Susan Cosgrove, a family leader from Holland Bloorview Kids Rehabilitation Hospital.

RESEARCH QUESTIONS

• How accurately can biomarkers classify autism spectrum disorder (ASD) when used in clinically heterogeneous community based samples?
• Does the addition of biomarker approaches to existing behavioral screens improve the classification accuracy of early ASD screening? What is the optimal combination of approaches for different age groups?
• Does the use of these novel early detection strategies (biomarkers and combined behavioral and biomarker approaches) lead to earlier diagnosis of ASD?
• What are parents’ and other stakeholders’ preferences in relation to the application of these novel early detection strategies and related care processes, such as communication of findings?
• What is the diagnostic accuracy of streamlined assessment models, such as community based teams and solo clinicians, as well as the cost effectiveness and systemic outcome measures such as wait times?

data sources, both concurrent and over time, to tailor therapeutic strategies. Finally, the future of ASD assessment must prioritize the preferences of the most important stakeholders in the assessment process: people with ASD and their families.

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STATE OF THE ART REVIEW

Page 46


STATE OF THE ART REVIEW

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