Definition: (1) Autism Spectrum Disorder (ASD) per the DSM-5 encompasses four previously separate disorders that are actually a single condition with different levels of symptom severity in two core domains. These four disorders are the DSM-IV Autistic Disorder (autism), Asperger’s Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). ASD is characterized in early childhood by 1) deficits in social communication and social interaction and 2) restricted repetitive behaviors, interests, and activities (RRBs).

Etiology: (2) Although ASDs are heritable neurodevelopmental conditions with strong genetic underpinnings, their exact etiology is unknown. The etiology is multifactorial with a variety of genetic and, to a lesser extent, environmental factors playing a role. ASDs can be either idiopathic or associated with other diagnoses; most are idiopathic.

Inclusion Criteria
- All patients with suspected or diagnosed autism

Exclusion Criteria
- None

Differential Diagnosis (3,4)
- Hearing impairment
- Environmental deprivation
- Attachment disorder
- Abuse, trauma, neglect
- Language disorder
- Social (pragmatic) communication disorder
- Apraxia of speech
- Intellectual disability
- Selective mutism
- ADHD
- Oppositional defiant disorder
- Anxiety disorder
- Conduct disorder in the older child
- Landau-Kleffner syndrome
- Schizophrenia
- OCD
- Depression
- Schizophrenia
- Developmental coordination disorder
- Epilepsy
- Catatonia
- Nutritional deficiencies secondary to restricted diet
- Disorders of impulse control
- Substance abuse

Associated with ASD (3,4)
- Neurological or metabolic condition (chromosomal microdeletions, chromosomal duplications, metabolic disorders)
- Down syndrome
- Fetal alcohol spectrum disorder
- Fragile X syndrome
- Rett syndrome
- Tuberous sclerosis

Early Signs (2,5,6)

Social Skills Deficits
Early years
- Do not appear to seek connectedness
- Content being alone
- Ignore parents’ bids for attention
- Seldom make eye contact or bid for others’ attention with gestures or vocalizations
- Deficits in joint attention
- Fail to follow a point and/or share expression
- Fail to point to "comment"
- Fail to respond to name
- Selective hearing
- Less imitation

Later years
- Difficulty sharing the emotional state of others in cooperative games/group settings
- Have few, if any, friends
- Difficulties with empathy, sharing, and comforting

Communication Deficits
Early years
- Lack of appropriate gaze
- Lack of warm, joyful expressions with gaze
- Lack of the alternating to-and-fro pattern of vocalizations between infant and parent that usually occurs at approximately 6 months of age
- Lack of recognition of mother’s/father’s voice
- Disregard for vocalizations (i.e., lack of response to name), yet keen awareness for environmental sounds
- Delayed onset of babbling past 9 months of age
- Decreased or absent use of prespeech gestures (waving, pointing, showing)
- Lack of expressions such as “oh oh” or “huh”
- Lack of interest or response of any kind to neutral statements (e.g., “Oh no, it’s raining again!”)

Later years
- Lack of speech, especially when associated with a lack of desire to communication and lack of nonverbal compensatory efforts (e.g., gestures)
- Persistent echolalia (i.e., “parroting”, both immediate and delayed)
- Inability to follow commands
- Inability to combine words in novel or original phrases/sentences that convey true meaning

Regression
- ~25-30% of children with ASDs begin to say words but then stop speaking, often at 15-24 months
- Loss of gestural communication (e.g., wave, point) and/or social skills (e.g., eye contact, response to praise)
- Can be gradual or sudden

Play Skills
- Lack of, or significantly delayed, pretend play skills coupled with persistent sensory-motor and/or ritualistic play
- Repetitive play that lacks creativity and imitation
- Preference for common objects (e.g., sticks, rocks) rather than store-bought toys with the exception of trains or characters from favorite shows
- Enjoy puzzles, especially shape-matching ones
- Content playing alone, requiring little attention or supervision
- Play is often constructive, ritualistic, or sensory-motor in nature
- Trouble interacting in groups and cooperating in the social rules of more sophisticated games

**Restricted, Repetitive, and Stereotyped Patterns of Behavior, Interests, and Activities**
- Peculiar mannerisms, such as unusual attachments to objects, circumscribed interests, self-injurious behaviors, and stereotypies (repetitive, nonfunctional, atypical behaviors)
- Persistent attachment to objects
- Perseveration, or continuation of speech or play to an exceptional degree or beyond a desired point

**Diagnostic Evaluation**

**History: Assess for**
- Family history (e.g., autism, other neurodevelopmental disorder)
- Birth history/Pregnancy complications
- Medical history (e.g., history of seizures)

**Physical Examination**
- Skin findings, birthmarks
- Neurologic exam
- Growth
- Head circumference
- Dysmorphic features

**Critical Points of Evidence**

**Evidence Supports**
- The M-CHAT-R/F and its follow up interview should be used as a screening tool for children 16-36 months at the 18- and 24-month well-child visits or more frequently if parental concern is expressed. Children 16-36 months with a score of 3-6 should receive a follow-up interview; children 16-36 months with a score of ≥7 should be referred immediately for diagnosis. The results for children over 30 months should be interpreted with caution. (2,7-21) – Strong recommendation, moderate quality evidence
- The SCQ - Current should be used as a screening tool for children ≥36 months and <48 months if parental/clinician concern is expressed. A cutoff score of ≥11. If the SCQ - Current is not readily available, refer to a subspecialist for further evaluation. (2,7-21) – Strong recommendation, very low quality evidence
- The SCQ - Lifetime should be used as a screening tool for children ≥48 months if parental/clinician concern is expressed. A cutoff score of ≥15. If the SCQ - Lifetime is not readily available, refer to a subspecialist for further evaluation. (2,7-21) – Strong recommendation, very low quality evidence
- Use the same screening tools for preterm children. A higher false positive rate may be seen in preterm children versus the general population. (49-51) – Strong recommendation, low quality evidence
- Administer a standardized autism-specific diagnostic tool (i.e., ADOS, CARS) as part of the clinical diagnosis to all children referred to an autism specialty clinic (e.g., TCH Autism Center) for an initial evaluation or a second opinion. The diagnostic tool should be used in conjunction with clinical judgment to diagnose autism. (2,21,25-63) – Strong recommendation, moderate quality evidence
- The diagnosing physician should order a chromosomal analysis (CMA) ± fragile X testing for all children formally diagnosed with ASD. All males with autism should be tested for fragile X syndrome. Fragile X testing should be seriously considered in females with ASDs when prompted by clinical parameters such as; a phenotype compatible with fragile X; a family history positive for X-linked neurodevelopmental disorders; or premature ovarian insufficiency, ataxia, or tremors in close relatives. (36,64-74) – Strong recommendation, low quality evidence
- All children formally diagnosed with autism should be referred to a clinical geneticist. – Consensus recommendation

**Evidence Against**
- MRIs, EEGs, and metabolic studies should NOT routinely be part of the diagnosis or management of children with ASD. (2,25,36,39,64-74) – Strong recommendation, very low quality evidence
- Karyotype analysis should NOT be performed on children formally diagnosed with ASD. (64-74) – Strong recommendation, very low quality evidence

**Evidence Lacking/Inconclusive**
- A formal assessment of developmental level should be part of the ASD diagnosis; however, no specific tool can be recommended. (75-78) – Consensus recommendation

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.*
**Condition-Specific Elements of Clinical Management**

**Screening (PCP)**
1. Administer an age-appropriate screening tool:
   - For children 16-36 months, administer the M-CHAT-R/F at the 18- and 24-month well-child visits or more frequently if parental/clinician concern is expressed.
   - For children >36 months and <48 months, administer the SCQ - Current.
   - For children ≥48 months, administer the SCQ - Lifetime.
2. Refer to the PCP algorithm (p. 5) for referral decisions based on the child’s score.

**Diagnosis (Autism Center)**
1. Perform comprehensive medical and developmental histories and physical and neurodevelopmental exams.
2. Administer an ADOS.
3. Perform a formal assessment of developmental level.
4. If an autism diagnosis is made:
   - Order a chromosome microarray analysis (CMA) ± fragile X testing.
   - Make appropriate referrals (see below).

**Referrals/Follow-Up Care**
- All children formally diagnosed with ASD should be referred to a clinical geneticist.
- Any child with suspicion of seizures or isolated language regression confirmed by a clinician should be referred to Neurology.
- Refer to Social Work for additional support and community resources.
- Refer to Speech Therapy if not already done.
- Refer to Audiology if not already done.

**Measures**

**Outcome**
- Percentage of patients receiving appropriate age-based screening tool at the PCP level.
- Percentage of Autism Center providers trained to administer the ADOS.
- Percentage of patients receiving an ADOS at the Autism Center.
- Wait time for an appointment at the Autism Center.
### 16-36 months
Administer the M-CHAT-R/F at the 18- and 24-month well-child visits or more frequently if parental/clinician concern is expressed.

- **Score <3**
  - Unlikely concern for autism
  - If the child fails the follow-up interview, refer to a subspecialist for further evaluation and refer for a Full and Individual Evaluation through school.
  - OR
  - If the child clearly meets DSM-5 criteria for diagnosis, diagnose with ASD* and refer for a Full and Individual Evaluation through school.

- **Score ≥7**
  - Administer the follow-up interview.
  - If the child fails the follow-up interview, refer to a subspecialist for further evaluation and refer for a Full and Individual Evaluation through school.
  - OR
  - If the child clearly meets DSM-5 criteria for diagnosis, diagnose with ASD* and refer for a Full and Individual Evaluation through school.

### >36 months and <48 months
Administer the SCQ - Current if parental/clinician concern is expressed.

- **Score <11**
  - Unlikely concern for autism
  - Refer to a subspecialist for further evaluation and refer for a Full and Individual Evaluation through school.
  - OR
  - If the child clearly meets DSM-5 criteria for diagnosis, diagnose with ASD* and refer for a Full and Individual Evaluation through school.

- **Score ≥11**
  - Refer to a subspecialist for further evaluation and refer for a Full and Individual Evaluation through school.
  - OR
  - If the child clearly meets DSM-5 criteria for diagnosis, diagnose with ASD* and refer for a Full and Individual Evaluation through school.

### ≥48 months
Administer the SCQ - Lifetime if parental/clinician concern is expressed.

- **Score ≥15**
  - Refer to a subspecialist for further evaluation and refer for a Full and Individual Evaluation through school.
  - OR
  - If the child clearly meets DSM-5 criteria for diagnosis, diagnose with ASD* and refer for a Full and Individual Evaluation through school.

If the child passes the SCQ and/or the follow-up interview but clinician concern is still expressed, refer to a subspecialist for further evaluation. Refer also to ECI or for a Full and Individual Evaluation through school (depending on the child’s age).

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*If a diagnosis of ASD is made:
- Order a chromosome microarray analysis (CMA) ± fragile X testing
- Refer to a clinical geneticist
- Refer to Neurology if suspicion of seizures or isolated language regression confirmed by a clinician
- Refer to Social Work for additional support and community resources
- Refer to Speech Therapy if not already done
- Refer to Audiology if not already done

**Fragile X Testing**
- All males with autism should be tested for fragile X syndrome.
- Seriously consider fragile X testing in females with ASDs when prompted by clinical parameters such as: a phenotype compatible with fragile X; a family history positive for X-linked neurodevelopmental disorders; or premature ovarian insufficiency, ataxia, or tremors in close relatives.
Autism Center

- Perform comprehensive medical and developmental histories, physical and neurodevelopmental exams
- Administer an ADOS
- Perform a formal assessment of developmental level

Begin
Child has been referred to Autism Center

Diagnosis of ASD

No
Manage as appropriate to clinical findings

Yes

- Order a chromosome microarray analysis (CMA) ± fragile X testing
- Refer to a clinical geneticist
- Refer to Neurology if suspicion of seizures or isolated language regression confirmed by a clinician
- Refer to Social Work for additional support and community resources
- Refer to Speech Therapy if not already done
- Refer to Audiology if not already done

Fragile X Testing

- All males with autism should be tested for fragile X syndrome.
- Seriously consider fragile X testing in females with ASDs when prompted by clinical parameters such as: a phenotype compatible with fragile X; a family history positive for X-linked neurodevelopmental disorders; or premature ovarian insufficiency, ataxia, or tremors in close relatives.
References


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Texas Children’s Hospital
DATE: January 2018


Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children’s Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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Development Process
This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts

2. Review of Existing External Guidelines

3. Literature Review of Relevant Evidence
   - Search: PubMed, Cochrane, Google

4. Critically Analyze the Evidence
   - 2 systematic reviews, 1 randomized controlled trial (RCT), and 61 nonrandomized studies

5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Screening and Diagnosis of Autism Spectrum Disorder (ASD) evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence
Published clinical guidelines were evaluated for this review using the AGREE II criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence in support of or against specific interventions and identifies where evidence is lacking/inconclusive. The following categories describe how research findings provide support for treatment interventions.

“Evidence Supports” provides evidence to support an intervention.

“Evidence Against” provides evidence against an intervention.

“Evidence Lacking/Inconclusive” indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn from the evidence.

The GRADE criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

<table>
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<tr>
<th>Quality</th>
<th>Type of Evidence</th>
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<tr>
<td>High</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
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<tr>
<td>Moderate</td>
<td>Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Low</td>
<td>Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence</td>
</tr>
<tr>
<td>Very Low</td>
<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
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Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of Screening and Diagnosis of Autism Spectrum Disorder (ASD) in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process
Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.
Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

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