Texas Children's Hospital

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Screening and Diagnosis of Autism Spectrum Disorder (ASD)
Evidence-Based Guideline

Definition: [1] Autism Spectrum Disorder (ASD), per the DSM-5, encompasses four previously separate disorders that are 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 complex and multifactorial, with various genetic and, to a lesser extent, environmental factors playing a role.

Inclusion Criteria
- All patients with suspected or diagnosed ASD

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
Attention deficit hyperactivity disorder
Oppositional defiant disorder
Anxiety disorder
Conduct disorder in the older child
Landau-Kleffner syndrome
Obsessive-compulsive disorder
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 conditions (chromosomal microdeletions or microduplications, 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 an 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 clear facial 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 pre-speech 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 communicate 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, except for 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)
- Unusual sensory behaviors (hyposensitivity and/or hypersensitivity to sensory stimuli)
- 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 disorders)
- Birth history/Pregnancy complications
- Medical history (e.g., history of seizures)
- Developmental milestones
- School history
- Social history
- Treatment history
- ASD symptomatology

Physical Examination

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

Critical Points of Evidence*

Evidence Supports

- For children 16-36 months at the 18- and 24-month well-child visit, the M-CHAT-R/F and its follow-up interview should be used as a screening tool at well-child visits or more frequently if parental concern is expressed. Children 16-36 months with a score of 3-7 should receive a follow-up interview; children 16-36 months with a score of ≥8 should be referred immediately for diagnosis. The results for children over 30 months should be interpreted with caution. [2,7-21,79-84] – Strong recommendation, moderate quality evidence
- For children ≥36 months and <48 months, the SCQ - Current could be used as a screening tool 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. [2,7-21,79-84] – Strong recommendation, very low quality evidence
- For children ≥48 months, the SCQ - Lifetime should be used as a screening tool 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. [2,7-21,79-84] – Strong recommendation, very low quality evidence
- Use the same screening tools for preterm children. Preterm children may have a higher false positive rate than the general population. [49-51] – Strong recommendation, low quality evidence
- Administer a standardized ASD-specific diagnostic tool (e.g., ADOS-2, CARS2-ST/HF) 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 DSM-5-TR criteria and clinical judgment to diagnose ASD. [2,21,25-63,85] – Strong recommendation, moderate quality evidence
- All children diagnosed with ASD should have the following tests performed: [36,64-74,86-92] – Strong recommendation, low to moderate quality evidence
    - First-tier etiologic evaluation for ASD should include chromosomal microarray (CMA) and exome sequencing (ES). ES should ALWAYS be conducted as a trio (with both parental samples) or duo (with one parental sample) analysis when possible.
        - **Note:** *ES or CMA CANNOT detect Fragile X syndrome. All males with ASD should be tested for Fragile X syndrome. Fragile X FMR1 CGG repeat testing should be seriously considered in females with ASD when prompted by clinical parameters such as: a compatible phenotype; a family history suggestive of X-linked neurodevelopmental disorders; premature ovarian insufficiency, ataxia, or tremors in close maternal relatives*.
    - Refer to a clinical geneticist upon ordering first-tier genetic testing. If ordering genetic testing is challenging for logistical, insurance, or other reasons, referral to a clinical geneticist is an appropriate first step.
    - If insurance restrictions or laboratory offerings dictate a stepwise approach, CMA should be ordered first, followed by ES if CMA is non-diagnostic. ES should be pursued as the initial evaluation when possible.[88]
    - Chromosomal analysis, i.e., karyotype, should be reserved for patients with clinically suspected chromosomal aneuploidy (e.g., one or more congenital anomalies, developmental delay/intellectual disability, low birth weight, dysmorphic features, failure to thrive, recurrent first-trimester miscarriages, ambiguous genitalia, etc.).
    - Brain MRI with optional MR spectroscopy and testing for mitochondrial and metabolic disorders should be reserved for patients with developmental regression, significant neurological exam findings, or other clinical indicators of metabolic dysfunction, including:
        - Clinical decompensation or developmental regression with mild febrile illness, multiorgan system involvement, failure to thrive, hearing/vision impairment, unusual odors, specific food intolerance, inadequate or questionably adequate newborn screening, etc.

Evidence Against

- MRI scans or electroencephalography (EEG) 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
- Routine metabolic testing without clinical indicators (see above) is not recommended.

Evidence Lacking/Inconclusive

- A formal assessment of the developmental level utilizing clinical judgment and expertise should be completed as part of the ASD diagnosis; however, no specific tool can be recommended. [75-78] – Consensus recommendation
- ASD diagnosis must be re-evaluated every three years per Texas Medicaid requirements. A patient's diagnostic report should be valid for approximately 3 years. After that time, Texas Medicaid requires a re-evaluation for ASD for ASD-related services to continue to be covered by insurance. CHIP and commercial insurance companies may also require a re-evaluation for ASD for ASD-related services to continue to be covered by insurance, but this varies across insurance companies and specific plans. Families/caregivers should be reminded to schedule a diagnostic re-evaluation appointment at least 2-3 months before their child's current diagnostic report expires to avoid any gap in care from therapy service providers. – 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. 4) for referral decisions based on the child's score.
3. Application of the DSM-5-TR criteria and completion of the CARS2-ST/HF in the primary medical home for appropriate patients with clear clinical concerns for ASD

Diagnosis (Autism Center; or Primary Medical Home)

1. Perform comprehensive medical and developmental histories and physical and neurodevelopmental exams
2. Administer an ADOS-2 or CARS2-ST/HF
3. Perform a formal assessment of developmental level.
4. If an ASD diagnosis is made:
   - Order a chromosomal microarray analysis (CMA) and exome sequencing (ES) ± 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 (as necessary) if not already done
- Refer to Audiology if not already done

Measures

Outcome

- Percentage of patients receiving appropriate age-based screening tools at the PCP level
- Percentage of patients receiving first-tier genetic testing
- Percentage of Autism Center providers trained to administer the ADOS-2
- Percentage of Autism Center providers trained to administer the CARS2-ST/HF
- Percentage of patients receiving an ADOS-2 and/or CARS2-ST/HF at the Autism Center
- Wait time for an appointment with the Autism Center, Genetics, Neurology, Psychology, and Psychiatry

TCH Evidence-Based Outcomes Center
Clinical Algorithm for the Screening and Diagnosis of Autism Spectrum Disorder (ASD)
PCP

Screening Tools

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 ASD

Score 3-7
Administer the follow-up interview.

If the child fails the follow-up interview, refer to a subspecialist* for further evaluation
OR
If the child clearly meets DSM-5 TR criteria for diagnosis, diagnose with ASD*

Score ≥8
Refer immediately to a subspecialist* for further evaluation
OR
If the child clearly meets DSM criteria for diagnosis, diagnose with ASD*

If the child passes the M-CHAT-R/F and/or the follow-up interview but clinician concern is still expressed, refer to a subspecialist* for further evaluation. Also refer to Early Childhood Intervention.

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

Score <11
Unlikely concern for ASD

Score ≥11
Refer to a subspecialist* (TCH Autism Center for internal TCH referrals) for further evaluation and refer for a Full and Individual Evaluation through school.
OR
If the child clearly meets DSM-5 TR 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
Unlikely concern for ASD

Score ≥15
Refer to a subspecialist* (TCH Autism Center for internal TCH referrals) and refer for a Full and Individual Evaluation through school.
OR
If the child clearly meets DSM5-TR criteria for diagnosis, diagnose with ASD* and refer for a Full and Individual Evaluation through school.

If the child passes the SCQ but clinician concern is still expressed, the child needs referral to a subspecialist for further evaluation.

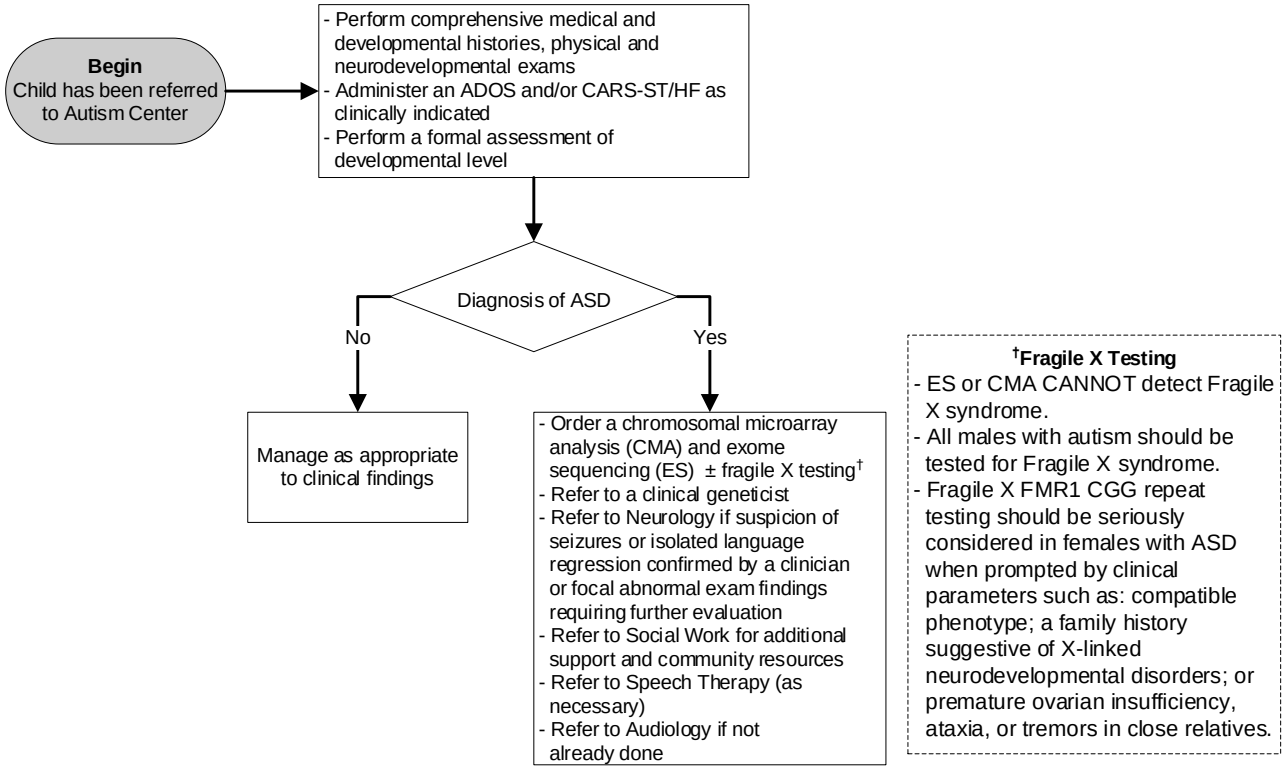
***Subspecialist providers**
- Developmental Pediatrician
- Neurologist
- Psychiatrist
- Psychologist
- Interdisciplinary Team
  - Includes a Medical Doctor (MD/DO), Physician Assistant (PA), or Nurse Practitioner (NP)
  - **+**
  - Licensed Clinical Social Worker (LCSW), Licensed Psychological Associate (LPA), Licensed Professional Counselor (LPC), Licensed Specialists in School Psychology (LSSP), Occupational Therapist (OT), or Speech Language Pathologist (SLP) with experience diagnosing and managing ASD

*If a diagnosis of ASD is made:
- Order a chromosomal microarray analysis (CMA) and exome sequencing (ES) ± 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 (as necessary)
- Refer to Audiology if not already done

†Fragile X Testing
- ES or CMA CANNOT detect Fragile X syndrome.
- All males with autism should be tested for Fragile X syndrome.
- Fragile X FMR1 CGG repeat testing should be seriously considered in females with ASD when prompted by clinical parameters such as: compatible phenotype; a family history suggestive of X-linked neurodevelopmental disorders; or premature ovarian insufficiency, ataxia, or tremors in close relatives.

Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.

TCH Evidence-Based Outcomes Center
Clinical Algorithm for the Screening and Diagnosis of Autism Spectrum Disorder (ASD)
Autism Center



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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
   - American Academy of Neurology and The Child Neurology Society Practice Parameter: Screening and Diagnosis of Autism (2000); American Academy of Pediatrics (AAP) Clinical Report (2007); ACMG Clinical Genetics Evaluation in Identifying the Etiology of Autism Spectrum Disorders: 2013 Guideline Revisions; National Initiative for Autism: Screening and Assessment (2003); New Zealand Autism Spectrum Disorder Guideline (2008); NICE Autism Diagnosis in Children and Young People (2011); SIGN Assessment, Diagnosis and Clinical Interventions for Children and Young People with Autism Spectrum Disorders (2007); U.S. Preventive Services Task Force Autism Spectrum Disorder in Young Children: Screening (2017); AAP Statement on U.S. Preventive Services Task Force Final Recommendation Statement on Autism Screening (2017); New York State Health Department of Health Clinical Practice Guideline on Assessment and Intervention Services for Young Children with Autism Spectrum Disorders (2017); Australia National Guideline on the Diagnostic Process for Children, Adolescents and Adults Referred for Assessment of Autism Spectrum Disorder (2017)

3. Literature Review of Relevant Evidence
   - Searched: 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 developing 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 is 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.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	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
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

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 should 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.

Permission of Use

Version History

Date	Action	Comments
Sep 2014	Originally completed	
Jan 2018	Revised and reaffirmed	
Mar 2024	Update	