REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Evaluation and Management of the Child With Autism Spectrum Disorder

By Nicole Baumer, MD, MEd; Sarah J. Spence, MD, PhD

CITE AS:
CONTINUUM (MINNEAP MINN) 2018;24(1, CHILD NEUROLOGY): 248–275.

Address correspondence to Dr Sarah J. Spence, Boston Children's Hospital, Department of Neurology, Fegan 11, 300 Longwood Ave, Boston, MA 02115, *sarah.spence@childrens.harvard.edu*.

RELATIONSHIP DISCLOSURE:
Dr Baumer has received personal compensation for speaking engagements from the Massachusetts Down Syndrome Congress and St. Luke's Hospital, New Bedford, Massachusetts, and has provided expert legal testimony on cases regarding Down syndrome. Dr Spence has received personal compensation for speaking engagements from Cold Spring Harbor Laboratory, the Kennedy Krieger Institute, and Westwood Lodge psychiatric hospital and receives research/grant support from the National Institute of Mental Health (5R01MH100186-02).

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Baumer and Spence discuss the unlabeled/investigational use of several classes of psychoactive medications, including atypical neuroleptics, alpha agonists, selective serotonin reuptake inhibitors, stimulants, mood stabilizers, and melatonin, for the treatment of autism spectrum disorder.

ABSTRACT

PURPOSE OF REVIEW: Autism spectrum disorder is a neurodevelopmental disorder defined by deficits in social communication and the presence of restricted and repetitive behaviors and interests. This article provides the tools to diagnose and manage patients with autism spectrum disorder.

RECENT FINDINGS: Autism spectrum disorder is a heterogeneous condition with varying presentations, multiple etiologies, and a number of comorbidities that impact the course and management of the disorder. This article defines the core features of social communication deficits, including problems with social reciprocity, decreased nonverbal communication, and difficulties in developing and maintaining relationships. The second domain of repetitive behaviors and restricted interests, which includes the presence of stereotyped behaviors or speech, insistence on sameness and behavioral rigidity, intense or out of the ordinary interests, and unusual responses to sensory stimulation, is also delineated. Comorbidities commonly seen with autism spectrum disorder include medical, neurologic, and psychiatric conditions. Despite intense research efforts, the etiology of autism spectrum disorder remains unknown in most cases, but it is clear that a strong genetic component exists that interacts with various environmental risk factors. Current research is identifying overlapping neurobiological pathways that are involved in pathogenesis. Treatment involves intensive behavioral therapy and educational programming along with traditional ancillary services, such as speech/language, occupational, and physical therapies. Psychopharmacologic treatments are also used to target certain symptoms and comorbid conditions.

SUMMARY: Neurologists can play an important role in diagnosing autism spectrum disorder according to clinical criteria through a comprehensive evaluation that includes a thorough medical and developmental history, behavioral and play observations, and a review of standardized cognitive and language evaluations. Neurologists are also responsible for investigating etiologies, recommending and advocating for appropriate behavioral and educational interventions, and identifying and often managing comorbidities.

INTRODUCTION

Autism spectrum disorder is a complex heterogeneous neurodevelopmental disorder characterized by deficits in social communication and social reciprocity in addition to repetitive behaviors and restricted interests. Language and cognitive impairment may co-occur. Onset of symptoms is in early childhood, and the disorder is usually thought to be lifelong. First described in 1943 by Leo Kanner, autism was thought to be a rare disorder for many years. However, in the past 2 to 3 decades, the estimated prevalence has increased steadily and dramatically. This is thought to be due to a number of factors, including the broadening of the diagnostic criteria, some diagnostic substitution, and increased recognition and knowledge of the disorder. Additionally, there may be other reasons that are currently unknown and the target of much speculation. The most recent estimate from the Centers for Disease Control and Prevention (CDC) is that 1 in 68 children has a diagnosis of autism spectrum disorder.[1] Given the 4:1 male to female ratio, that represents an incidence of 1 in 42 boys and 1 in 189 girls.[1] The clear male preponderance has not yet been fully explained but likely reflects genetic and hormonal factors. Despite intense research efforts, the exact pathophysiology remains largely unknown but is believed to involve a complex interplay between genetics and environmental factors.

What is now termed autism spectrum disorder was historically made up of multiple distinct disorders (ie, autistic disorder, pervasive developmental disorder–not otherwise specified, and Asperger disorder).[2] In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, all of these disorders are combined into one, termed *autism spectrum disorder*.[3]

Neurologists are often called on to diagnose autism spectrum disorder. This article reviews the clinical features and diagnostic criteria of autism spectrum disorder according to the *DSM-5* and gives a framework for how to approach the diagnostic process, identify comorbidities, investigate etiologies, and manage the disorder.

KEY POINTS

- What is now termed autism spectrum disorder was historically made up of multiple distinct disorders (ie, autistic disorder, pervasive developmental disorder–not otherwise specified, and Asperger disorder). In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, all of these are combined into one, termed *autism spectrum disorder*.
- Current diagnostic criteria for autism spectrum disorder focus on two domains of function: deficits in social communication and the presence of restricted interests and repetitive behaviors.

DIAGNOSTIC CRITERIA

Current diagnostic criteria focus on two domains of function: deficits in social communication and the presence of restricted interests and repetitive behaviors (FIGURE 12-1).

Because behavioral profiles change with development and specific symptoms may come and go over time, *DSM-5* allows for a history of symptoms, even if not currently manifested, to meet criteria for diagnosis. The diagnosis can be made by showing these behaviors were present by history as long as the current profile is consistent with autism spectrum disorder and functional impairment that is considered clinically significant is ongoing.

Symptoms must be present in the early developmental period, and it is important to consider whether the impairing symptoms are best explained by autism spectrum disorder or another condition, such as global developmental delay or cognitive impairment/intellectual disability. In autism spectrum disorder, impairment in social and communication skills and behaviors must be out of proportion to what is expected for the individual's developmental functioning.

Deficits in Social Communication and Social Interaction

Social communication encompasses a number of skills. *DSM-5* requires that deficits be present in all three of the following areas: social-emotional reciprocity,

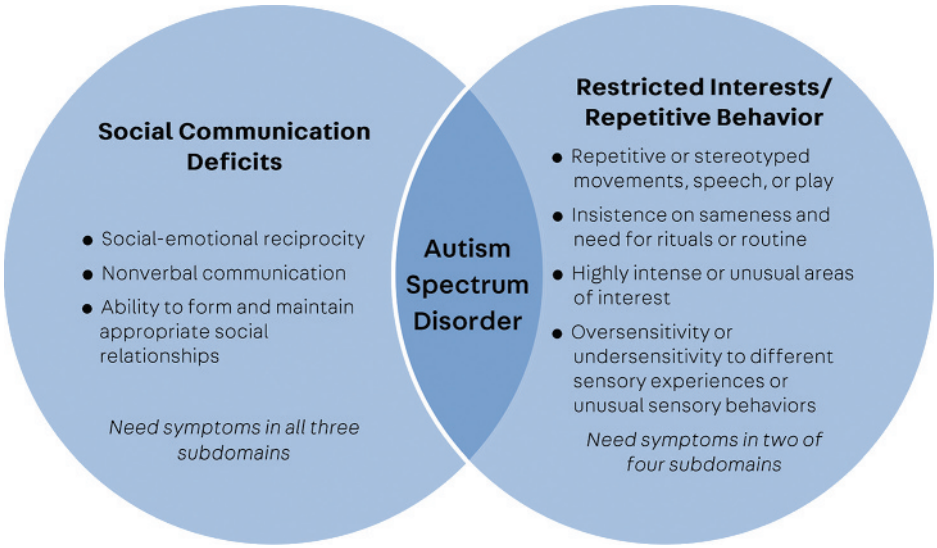

FIGURE 12-1
Autism spectrum disorder core symptom domains according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*.

nonverbal communication, and social relationships.[3] These are true deficits that represent a deviation from the expected developmental trajectory, irrespective of the level of developmental function.

SOCIAL-EMOTIONAL RECIPROCITY. Abnormalities in social reciprocity involve the quantity and quality of social interest and engagement, including social initiation, response and engagement in basic social exchange, reciprocal/back-and-forth communication, sharing of emotions, and appropriate response to environmental stimuli. This subdomain represents the very building blocks of social interaction (initiation, response, and turn taking).

The earliest symptoms can manifest as a lack of a reciprocal social smile, lack of response to the child's name being called, decreased engagement in interactive baby games like peekaboo or pat-a-cake, and problems imitating the actions of others. Children also struggle with social orienting, show little awareness or interest in others, have difficulty sharing interests and enjoyment with others, or have trouble with social overtures. Some children may demonstrate social interest but lack the social skills to initiate and join in play, take turns, follow rules, and play cooperatively. They may be socially immature and have difficulty respecting appropriate social boundaries or perceiving subtle social cues. They may also struggle with communicating their emotions or understanding the emotions of others. Children with good expressive speech often will not use it to functionally communicate in a social manner such as to express ideas, ask questions, engage in back-and-forth conversation, volunteer information, or comment on the environment.

NONVERBAL COMMUNICATION. Deficits in nonverbal communication encompass problems in expressing and understanding various behaviors (such as eye contact, tone of voice, body language, facial expressions, gestures, and bringing/sharing/showing of interests and activities) and the ability to integrate verbal and

nonverbal communication. Children with autism spectrum disorder do not typically compensate for difficulty in verbal communication with nonverbal strategies (as seen in those with developmental language disorder), demonstrating a more significant and specifically social communication deficit. They have difficulty initiating and responding to joint attention (ie, the shared focus on an object or an event, so that both parties are paying attention to the same thing).

SOCIAL RELATIONSHIPS. Children with autism spectrum disorder have deficits in a wide range of behaviors required for building and maintaining successful social relationships, especially with same-age peers. This subdomain can be conceptualized as difficulties with behaviors needed for higher-order social interaction. Young children with autism spectrum disorder may show little interest in other children or may be avoidant of any interaction, instead engaging in solitary or parallel play. Many children have difficulty varying or adapting their behavior to different social situations and have difficulty understanding different points of view or taking another's perspective, referred to as a deficit in theory of mind.[4] Verbal children often only converse about topics of personal interest and are not aware when someone is not interested (eg, lecturing like a "little professor"). Language can be overly literal, and children may not understand idioms or sarcasm, making it difficult to discern joking from teasing or real bullying. Many children with autism spectrum disorder do not have understanding or insight into friendships or other social relationships.

DEFICITS IN SOCIAL AND COMMUNICATIONS SKILLS IN OTHER CONDITIONS. Difficulties with social and communication skills can also be seen in children with other medical and neurodevelopmental disabilities, including hearing loss, specific language impairment, global developmental delay, attention deficit hyperactivity disorder (ADHD), social anxiety, and psychosocial deprivation (**TABLE 12-1**).

Repetitive Behavior and Restricted Interests

This domain includes a number of aberrant behaviors in four different areas, including repetitive behaviors or stereotypies, rigid or inflexible behavior, unusual or restricted interests, and differences in sensory reactivity (a new category in *DSM-5*).[3] *DSM-5* requires behaviors to be present in two of the four areas.

STEREOTYPIC MOVEMENTS, REPETITIVE OBJECT USE, OR VOCALIZATIONS/VERBALIZATIONS. Motor stereotypies include finger movements, body posturing, rocking, spinning, hand/arm flapping, full-body tensing, toe walking, or repetitive jumping. Unusual and repetitive use of objects can be seen in nonfunctional play, repetitive play (eg, flipping light switches, opening/closing doors), or unusual use of toys rather than playing with them as intended (eg, lining up toys, spinning the wheels on cars). Stereotypies can also be vocal, with repetitive sounds or verbal echolalia. Echolalia can be the immediate echoing of what was said around the child or delayed echoing, with scripting/reciting lines from books or videos.

INFLEXIBILITY, THE NEED FOR SAMENESS, ROUTINES, OR RITUALS. Resistance to change can be demonstrated by needing to take the same route to a given destination, eating the exact same foods or having food presented in the same way, or always having to finish what is started. Cognitive inflexibility is shown by black-and-white/rigid thinking, repetitive questioning, overly strict adherence to rules, and behavioral or verbal rituals. A hallmark of children with autism

spectrum disorder is that minor changes to routine, transitions, or unexpected events often elicit excessive tantrums or major changes in affect.

OVERLY INTENSE OR UNUSUAL INTERESTS. Interests can involve topics that are seemingly abnormal in focus (eg, a 5-year-old knowing everything about elevators, air conditioners, or the weather) or perseverative or excessive in intensity (eg, age-appropriate interest in cars/trains or letters/numbers but at an unusual level of detail and to the exclusion of other topics or activities). Children may show an unusual attachment to objects (eg, needing to carry something with them at all times) or show an atypical or intense interest in small parts of things or how things work.

OVERREACTIVITY OR UNDERREACTIVITY TO SENSORY STIMULATION OR UNUSUAL SENSORY BEHAVIORS. The sensory symptoms may involve any of the senses (eg, auditory, visual, tactile, or olfactory). They can be seen in unusual sensory interests (eg, overfascination with water play), adverse responses to seemingly innocuous sounds (eg, the vacuum cleaner) or things touching the skin (eg, clothing tags), a high pain tolerance, or excessive mouthing or smelling of objects. Individuals may show fascination with lights or spinning objects. Children may demonstrate unusual visual behaviors, such as peering out of the

TABLE 12-1 Differential Diagnostic Considerations in Autism Spectrum Disorder

Differential Diagnosis of Language Delay

- Developmental language disorder/specific language impairment
- Constitutional language delay ("late talker")
- Hearing loss
- Global developmental delay/intellectual disability
- Psychosocial deprivation

Differential Diagnosis of Social Impairment

- Social anxiety
- Generalized anxiety disorder
- Shy temperament
- Learning disabilities
- Attention deficit hyperactivity disorder
- Social communication disorder[a]

Differential Diagnosis of Stereotypic, Repetitive, or Rigid Behaviors

- Intellectual impairment
- Obsessive-compulsive disorder
- Stereotypic movement disorder
- Complex tics/Tourette syndrome

[a] A new diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [*DSM-5*] characterized by significant pragmatic language impairment without accompanying restricted interests and repetitive behaviors.

corners of their eyes, viewing objects from unusual angles, or holding objects very close to their eyes. Some children engage in behaviors such as crashing into things, pushing their bodies into small spaces, or being calmed by tight hugs, which may represent proprioceptive sensory seeking behaviors.

STEREOTYPIC AND REPETITIVE BEHAVIORS IN OTHER CONDITIONS. Stereotypic and repetitive behaviors can also be seen in children with intellectual impairment, obsessive-compulsive disorder, stereotypic movement disorder, and complex tics/Tourette syndrome.

Specifiers

Given the single diagnostic label in *DSM-5*, specifiers were added to better characterize the particular profile of any one patient. It is important for clinicians to indicate whether associated cognitive impairment or language disorder exists (CASE 12-1). These disorders not only impact the presentation of autism

KEY POINT

- Given the single diagnostic label in *DSM-5*, specifiers were added to better characterize the particular profile of any one patient with autism spectrum disorder. It is important for clinicians to indicate whether associated cognitive impairment or language disorder exists.

CASE 12-1

A 2-year-old boy was brought by his parents for evaluation of speech delay. He had no spoken language but did have some unusual and repetitive vocalizations, which were not directed to communicate with others. He did not use gestures or point to indicate what he wanted. He had no way of telling his parents what he wanted; he just cried and his parents had to "figure it out." He did not respond when his name was called, nor did he follow commands. His parents did not think he listened to them or understood them. On further questioning, his parents also reported that he seemed "in his own world" all the time. He did not approach them or other children, nor did he respond when others approached him. They also reported almost continuous repetitive behaviors, including hand flapping, toe walking, and flicking a string. He did not play with toys in a typical way; instead he just lined them up. He had major temper tantrums whenever his routine was disrupted. He would only drink out of one sippy cup and once required an emergency department visit for IV hydration when they lost the cup and he refused to drink. He would not allow anyone to touch his head or cut his fingernails. He would only wear sweatpants. He put his hands over his ears and became very distressed with loud noises, such as the flushing of a toilet or the hand dryer in a public bathroom. His hearing test was normal. The reports from early intervention suggested global developmental delay with a developmental quotient of 40 overall but relatively spared motor function.

COMMENT

This case illustrates a classic case of autism spectrum disorder with both language and cognitive impairment. Symptoms are present in both domains and all subdomains and are present in the early developmental period. This child is very young and presents with global developmental delay, but his social communication deficits are even greater than what would be expected for his cognitive level, with no response to social overtures, no social smiling, and no attempts to communicate.

spectrum disorder, they are also important for recommendations about therapy and management. Many co-occurring conditions are seen in individuals with autism spectrum disorder, so additional specifiers should be used when applicable. The specifier of whether a known medical, genetic, or environmental condition is present is used for medical comorbid conditions such as epilepsy, sleep disturbances, or metabolic disorders. It should also be used for known neurogenetic syndromes or for abnormal genetic findings from chromosomal microarray or gene panels that are thought to be pathogenic. Specifying a co-occurring neurodevelopmental or neurobehavioral disorder is important for acknowledgement of co-occurring psychiatric conditions such as anxiety or ADHD.

Severity Ratings

Historically (based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*]),[2] pervasive developmental disorder–not otherwise specified and Asperger disorder were used as a proxy for those with milder impairment, and autistic disorder was used for those with more severe impairment. The merging of these three diagnoses into a single diagnosis of autism spectrum disorder created the need to delineate severity. However, severity of different symptoms in the two domains is not always the same. Therefore, in the current diagnostic profile, severity should be assigned for each domain separately:

- **Level I: needs support**
- **Level II: needs substantial support**
- **Level III: needs very substantial support**

DSM-5 offers examples of behaviors that help assign the severity ratings.

COMORBID MEDICAL CONDITIONS

Several conditions that can co-occur with autism spectrum disorder are particularly relevant for neurologists. Defining these comorbidities guides proper management.

Intellectual Disability

Intellectual disability has always been defined as having an IQ score that is greater than two standard deviations below the mean (ie, less than 70) and showing functional impairment. Previous epidemiologic studies had reported that the majority of individuals with autism spectrum disorder had intellectual disability.[5] However, recent surveys now show that intellectual disability occurs in approximately 50% or less of individuals with autism spectrum disorder but is more common among females.[1]

Epilepsy

Large population-based studies suggest that approximately 20% of individuals with autism spectrum disorder will develop epilepsy in their lifetime and will likely need to see a neurologist for management. Therefore, neurology practices may see a higher percentage of individuals with autism spectrum disorder and epilepsy. Risk factors include syndromic autism,[6,7] intellectual disability, and female sex.[8] All seizure types can occur, and the age of onset appears to have a bimodal distribution, with peaks in early childhood and adolescence/early adulthood. It should be noted that children with very-early-onset seizures

(eg, infantile spasms) have an increased risk of autism spectrum disorder. Autism spectrum disorder is also more prevalent in individuals with epilepsy than in the general population[9,10]; although this sometimes goes unrecognized.[11] Treatment of epilepsy in a patient with autism spectrum disorder is similar to general treatment principles, but careful consideration should be taken to minimize behavioral side effects when choosing seizure medications.[12]

Sleep Disorders

Sleep disturbance, namely insomnia, is a very common symptom in individuals with autism spectrum disorder, and it greatly impacts quality of life for the child and family. Poor sleep has been associated with behavioral problems in autism spectrum disorder.[13] Sleep problems can involve difficulty with sleep onset, interrupted sleep, overnight and early morning awakenings, or overall decreased sleep time.[14] Some of the issues may be related to poor sleep hygiene, with a lack of consistent bedtime routine, behavioral dysregulation leading to conflict at night, inability to recognize or learn the environmental cues of it being time to settle down, or inability to sleep independently. Therefore, counseling on good behavioral techniques is important before treatment with medication.[15]

Abnormal Motor Profiles

In addition to motor stereotypies and tics, children with autism spectrum disorder may also have a history of delayed fine and gross motor milestones, poor coordination, motor planning difficulties, or even gait abnormalities.[16,17] Toe walking is a common stereotypy, but it is not usually related to lower extremity spasticity. Ancillary physical and occupational therapy is often needed.

Metabolic Disorders

In rare cases, individuals with metabolic disorders may present with an autism spectrum disorder phenotype. These are especially important to recognize, as they may represent treatable conditions. Disorders such as succinic semialdehyde dehydrogenase deficiency (SAADH), disorders of creatine transport, and mitochondrial disorders have been associated with autism spectrum disorder.[18]

Gastrointestinal Disorders

A variety of gastrointestinal disorders have been reported to be more prevalent in patients with autism spectrum disorder, including gastroesophageal reflux disease, constipation, and diarrhea. Initially this comorbidity was made (in)famous by the putative tie between "autistic enterocolitis" and the measles-mumps-rubella vaccine. While this theory was discredited with a number of studies in the past decade, the real gastrointestinal problems in patients should not be overlooked.[19] Often gastrointestinal symptoms can be tied to unusual feeding behavior with very restricted food intake. In some cases, the child may even present with failure to thrive or severe obesity secondary to the restricted intake pattern. In these situations, behavioral feeding therapy can be very beneficial.

COMORBID PSYCHIATRIC/BEHAVIORAL DISORDERS

Behavioral challenges are very common in individuals with autism spectrum disorder and may be reflective of a co-occurring neurodevelopmental or psychiatric disorder. Previously, behavioral issues were only attributed to the autism spectrum disorder itself; however, it is now recognized that comorbid

KEY POINTS

- **Large population-based studies suggest that approximately 20% of individuals with autism spectrum disorder will develop epilepsy in their lifetime. Risk factors include syndromic autism, intellectual disability, and female sex. All seizure types can occur, and the age of onset appears to have a bimodal distribution, with peaks in early childhood or adolescence/early adulthood.**

- **Previously, behavioral issues were only attributed to the autism spectrum disorder itself; however, it is now recognized that comorbid psychiatric conditions occur in children with autism spectrum disorder, and *DSM-5* explicitly allows the diagnosis of co-occurring psychiatric conditions as a specifier.**

psychiatric conditions occur in children with autism spectrum disorder, and *DSM-5* explicity allows the diagnosis of co-occurring psychiatric conditions as a specifier. Recent reports suggest that psychiatric conditions are more commonly reported in young children and adults with autism spectrum disorder compared to controls.[20] Unfortunately, the reported rates of different psychiatric disorders are quite variable. This is likely because of a number of factors, including changing definitions and diagnostic criteria for both autism spectrum disorder and other psychiatric disorders over time, overlap of certain symptoms (eg, obsessions seen in obsessive-compulsive disorder [OCD] and restricted/fixated interests seen in autism spectrum disorder), small and clinically referred samples, difficulty in determining psychiatric symptoms in individuals with intellectual disability and language disorders, and the previous prohibition in the *DSM* on making a diagnosis of certain psychiatric disorders in a patient with autism spectrum disorder. Co-occurring behavioral or psychiatric disorders can add significantly to functional impairment and therefore should represent treatment targets.

Attention Deficit Hyperactivity Disorder

A high degree of symptom overlap exists between ADHD and autism spectrum disorder. Reported rates of ADHD comorbidity range from 30% to 90%. Many young children with autism spectrum disorder present with symptoms of hyperactivity and impulsivity. Safety concerns such as bolting (suddenly running away from caregivers) or wandering are particularly problematic. Additionally, older children may appear to have inattention when in fact they may be hyperfocused on their own special interest. Learning problems, cognitive difficulty, and social challenges can also complicate the clinical picture. Careful, thorough evaluation is required to distinguish those with ADHD, autism spectrum disorder, or both autism spectrum disorder and ADHD and determine the most appropriate treatments.

Anxiety

Generalized anxiety disorder, social anxiety, separation anxiety, specific phobias, and OCD have all been reported at higher rates in autism spectrum disorder than in the general population. A meta-analysis showed that nearly 40% of those with autism spectrum disorder also had at least one type of anxiety disorder.[21] It may be difficult to distinguish the obsessive thoughts in OCD from preoccupations and fixations in autism spectrum disorder, and some overlap exists. However, it should be noted that in autism spectrum disorder, the thoughts do not usually lead to distress; in fact, they are thought to be pleasurable.[22]

Mood Disorders

Both depression and bipolar disorder can occur in individuals with autism spectrum disorder, although the reported rates of comorbidity are variable, ranging from 0% to 50%.[22] Depression is especially common in adolescents who have enough social awareness to realize that they are different and have difficulty establishing and maintaining friendships and romantic relationships.

Psychosis and Schizophrenia

Originally, childhood autism was thought to be a form of schizophrenia, but, over time, it was recognized that the two are separate disorders. Still, some

overlap exists with the negative symptoms of schizophrenia and the social communication impairments of autism spectrum disorder. Rates of diagnosis of psychosis and schizophrenia are reported to be quite low in those with autism spectrum disorder, ranging from 0% to 6%.[22] This may be, in part, because of the difficulty in determining the symptoms in an individual with autism spectrum disorder and comorbid language and intellectual disability. Clinically, hallucinations are uncommon, but the clinician must be careful when inquiring about symptoms, as overly literal interpretation of language may be misleading. For example, a patient with autism spectrum disorder may respond "yes" when asked "Do you ever hear voices when no one else is there?" but could be referring to someone talking on an electronic device or the telephone.

Catatonia

Catatonia is a relatively rare occurrence in individuals with autism spectrum disorder but is increasingly being recognized. It was included as a specifier in *DSM-5* and should be considered in individuals who experience a change in mental status and significant regression in skills with prominent motor symptoms, especially later in childhood or adolescence.

PROPOSED ETIOLOGIES

Despite years of inquiry and tremendous research efforts, the etiology of most cases of autism spectrum disorder remains unknown. As a heterogeneous, behaviorally defined disorder, it is clear that there will not be just one unifying cause. For this reason, some prominent researchers have referred to autism spectrum disorder as *the autisms*,[23] with the recognition that there are multiple etiologies. Clearly, a strong genetic component exists in autism spectrum disorder, but many other factors have been implicated, such as the role of the environment, immunologic dysregulation, metabolic disturbance, and various mechanisms of early brain injury (eg, teratogenicity, prematurity, developmental or acquired structural brain lesions). Given that social behavior and communication are some of the highest-order functions of the human brain, it is perhaps not surprising that many ways exist in which these aspects of development may get onto the wrong track. Recent research points to many different, yet often overlapping, neurobiological pathways involved in the pathogenesis of autism spectrum disorder.

Much of the research into etiology has focused on genetics, perhaps because autism spectrum disorder is one of the most heritable of all neuropsychiatric disorders. Twin and family studies suggest the heritability estimate to be about 50% (ranging from 26% to 93%). Monozygotic twins have a much higher concordance rate than dizygotic twins and siblings, and other relatives are at higher risk than the general population. Sibling recurrence risk is approximately 20%, and it increases as the number of affected children in the family rises.[24]

Various genetic mechanisms could be involved in the pathophysiology of autism spectrum disorder. The common variant hypothesis suggests that many different and commonly found inherited gene variants each contribute only a small amount to the phenotype but combine in such a way as to cause autism spectrum disorder. Many rare variants have also been identified. These pathologic mutations or variants are known to be causally related to the phenotype. These are often de novo in the individual with autism spectrum disorder. Autism spectrum disorder has long been associated with certain neurogenetic syndromes (eg, tuberous sclerosis complex and

fragile X syndrome); however, more and more monogenic forms of autism spectrum disorder are being discovered as detection methods for genetic variations have improved over time. Karyotyping was only able to detect large aberrations, such as the isodicentric chromosome 15q duplications. Chromosomal microarray detects far smaller copy number variations with microdeletion and duplication syndromes (eg, 16p11 deletion/duplication or 22q13 deletion/duplication), and now whole-exome and whole-genome sequencing allow for detection of changes at the individual gene level. Currently, over 800 genes have been associated with autism spectrum disorder, available on the Simons Foundation Autism Research Initiative (SFARI) gene list.[25] Large-scale sample collection and genotyping have been done, and more efforts are under way to try to untangle the exact genetic architecture of autism spectrum disorder. Recent efforts have focused on the overlapping neuronal pathways to which these genes contribute, including cellular signaling pathways that are responsible for synaptic function and synaptogenesis, cell adhesion molecules involved in circuit development (connectivity), and chromatin remodeling proteins involved in regulation of gene expression.[26–28]

Anatomically, theories have been proposed about aberrant circuitry or an overall disconnection syndrome, which have been supported by structural and functional imaging studies.[29,30] Physiologically, it is postulated that the mechanism could be an excitatory/inhibitory imbalance in the brain.[31] Interest in the immune system has also been ongoing, with one of the most robust animal models of autism spectrum disorder resulting from maternal inflammation during pregnancy.[32] Environmental factors present both prenatally and postnatally are also being actively investigated (eg, prematurity, teratogens, prenatal and postnatal toxicologic exposures).[33] Finally, recently research has been focused on the gene by environment interaction and epigenetic mechanisms.[34,35]

EXISTING PRACTICE GUIDELINES/PARAMETERS

Several sets of guidelines have been published by various professional organizations for screening, evaluation, and management of autism spectrum disorder.[36–42] Some are older and do not reflect the *DSM-5* diagnostic criteria. While some differences exist, all parameters recommend multidisciplinary evaluation, medical evaluation, and genetic testing. It should be noted that in 2016, a controversy arose over screening for autism spectrum disorder when the US Preventive Services Task Force stated that not enough data existed to endorse universal screening for children with autism.[43] In 2016, the American Association of Pediatrics reiterated recommendations for developmental surveillance and specific autism spectrum disorder screening at ages 18 and 24 months and for all children who fail routine developmental surveillance.[44]

CLINICAL OFFICE EVALUATION

To make a diagnosis of autism spectrum disorder, clinicians should obtain a detailed history, including specific queries about diagnostic criteria as well as a physical examination and targeted behavioral observations.

General History

The medical history should include birth history, age of parents at birth (older paternal age being a risk factor for autism spectrum disorder), perinatal risk factors, and pregnancy or delivery complications, such as maternal diabetes

mellitus or infection during pregnancy, prematurity, low birth weight, and potential prenatal exposures. Clinicians should assess for a history of frequent ear infections, hearing loss, and major illnesses or injuries (head injury). The general medical history should also include an assessment of medical issues, particularly those commonly seen in children with autism spectrum disorder (eg, feeding and gastrointestinal concerns, sleep disturbance, and seizures/epilepsy), and assessment for pica/lead exposure. Behavioral phenotypes or co-occurring medical conditions may also provide clues as to an underlying genetic or metabolic condition. A history of frequent illnesses, vomiting, growth problems, or regression may be suggestive of a metabolic disorder. Queries should be made about medications and use of vitamins, complementary and alternative therapies, dietary treatments or elimination of dietary items, and allergies/intolerances (food and medication).

A detailed family history should be obtained, including a history of disorders such as epilepsy and seizures, genetic/metabolic and autoimmune disorders, speech delay or language problems, intellectual disability or learning difficulties, or ADHD/attentional problems. A family history of psychiatric illness, such as schizophrenia, mood disorders, or anxiety, should be assessed, and the family should be asked about possible consanguinity.

Social history should include a history of trauma, neglect, or psychosocial deprivation. Developmental and educational services, including total number of hours and types of services and therapies and/or educational programming, should be noted.

KEY POINT

- The evaluation for autism spectrum disorder involves three primary components: a detailed developmental and behavioral history from primary caregivers, direct clinical observations, and review of data and impressions from other child care providers or teachers, especially with regard to peer interactions and behaviors. It is important to include a detailed and thorough assessment of early and previous developmental functioning to assess for past behaviors consistent with autism spectrum disorder.

General Developmental History

Because autism spectrum disorder often co-occurs with cognitive and language impairments and because *DSM-5* requires assessment of these specifiers, a detailed history of development and current functioning should be obtained. It should be noted that up to 30% of children with autism spectrum disorder experience a regression in skills in the early developmental period. Parental report of developmental history can be corroborated by review of developmental milestones in the medical record.

LANGUAGE. A history of the child's early expressive language and social communication skills should be obtained, including age of onset of babbling, single words, phrased speech, and sentences as well as a history of language regression. Current modes of communication should be documented, such as use of signs, picture systems, or technology systems. Evaluation should specifically assess skills in receptive language (understanding of yes/no, following of instructions/commands), expressive language (vocabulary, length of utterances), and pragmatic language (greetings, requests, commenting, conversations). Specific tools can be used to assess language skills (refer to TABLE 12-2[45–61]).

OVERALL DEVELOPMENTAL/COGNITIVE FUNCTIONING. Because the social and behavioral impairments must be more than what is expected of the child's developmental stage, the clinician must have information about the patient's cognitive skills. This can be done by reviewing previous cognitive testing and developmental assessments or by obtaining this as part of the comprehensive diagnostic evaluation. A review of the child's adaptive skills should include feeding, sleep, dressing, and toileting. In children with autism spectrum disorder, the adaptive skills may be lower than would be expected for the cognitive level.

Specific tools can be used to aid in the assessment of cognitive and adaptive skills (refer to the section that follows and TABLE 12-2).

Specific Autism Evaluation

The evaluation for autism spectrum disorder involves three primary components: a detailed developmental and behavioral history from primary caregivers, direct clinical observations, and review of data and impressions from other child care

TABLE 12-2 **Assessments for Evaluation of Development/Cognition, Adaptive Skills, Speech and Language, Behavior**

Developmental Testing: For very young children or those with significant cognitive impairment, these tests can be used and will yield a developmental quotient rather than a formal IQ score

- Bayley Scales of Infant and Toddler Development (BSID)[45]
- Mullen Scales of Early Learning (MSEL)[46]

Cognitive Testing (IQ): These assessments are often done in the school setting or by outside providers and should be reviewed by the neurologist

- Stanford-Binet Intelligence Scales (SB)[47]
- Wechsler Preschool and Primary Scales of Intelligence (WPPSI)[48]
- Wechsler Intelligence Scale for Children (WISC)[49]
- Differential Abilities Scale (DAS)[50,a]
- Leiter International Performance Scale-Revised (Leiter-R)[51,a]

Adaptive Skills

- The Vineland Adaptive Behavior Scales (VABS)[52]
- The Adaptive Behavior Assessment System (ABAS)[53]
- Scales of Independent Behavior-Revised (SIB-R)[54]

Speech and Language Tests

- Peabody Picture Vocabulary Test (PPVT)[55]
- Receptive-Expressive Emergent Language Test (REEL)[56]
- Clinical Evaluation of Language Fundamentals-preschool version, school-age version (CELF)[57]
- Test of Pragmatic Language (TOPL)[58]

Behavioral Scales: These scales are not autism spectrum disorder symptom specific, but they can be helpful in identifying comorbid behavioral or psychiatric symptoms and disorders, which can aid in treatment planning

- Achenbach Child Behavior Checklist (CBCL)[59]
- Aberrant Behavior Checklist (ABC) (for children with developmental delays)[60]
- Developmental Behavior Checklist (DBC)[61] (for children with intellectual disabilities; gives comparison score for children with same level of intellectual disability)

IQ = intelligence quotient.

[a] Especially helpful for minimally verbal/nonverbal children.

providers or teachers, especially with regard to peer interactions and behaviors. As the *DSM-5* diagnostic criteria allow for a history of symptoms, even if not currently manifested, it is important to include a detailed and thorough assessment of early and previous developmental functioning to assess for past behaviors consistent with autism spectrum disorder.

Autism spectrum disorder is a heterogeneous condition, and many symptoms and signs within each *DSM-5* diagnostic subdomain can be manifestations of relevant deficits. Detailed questions should be tailored to the child's developmental, cognitive, and language level. **TABLE 12-3** contains examples of questions to query specific impairments for each diagnostic subdomain in *DSM-5*, if a standardized tool is not being used. These questions were created by expert clinicians and are used by providers in the authors' clinic during an office assessment. These questions cover content similar to that assessed in standardized autism assessment tools. Standardized diagnostic tools (**TABLE 12-4**[62–68]) can be used to assess for autism spectrum disorder symptoms but are not required.

KEY POINT

- **The Centers for Disease Control and Prevention's Act Early Campaign website has resources on developmental milestones, including checklists for typical social and communication milestones from 2 months to 5 years of age, photo/video libraries of developmental milestones, and an autism case training curriculum for health care professionals.**

DEFICITS IN SOCIAL COMMUNICATION. Assessment of social communication deficits includes querying for delay or absence of typical developmental milestones as well for the presence of unusual behaviors. For example, typically, babies develop a social smile by 2 to 3 months of age; respond consistently to their name by 6 months; enjoy interactive baby games by 6 to 12 months; use and copy gestures, including pointing, by 12 months; demonstrate a range of emotions by 18 months; engage in simple pretend play by 18 months and more complex make-believe by 3 years; demonstrate verbal turn taking between 12 and 24 months; and play cooperatively at 4 years of age.[69] Atypical social communication behaviors may include social isolation and avoidance, using an adult's hand as a tool to get needs met, or atypical prosody.

The CDC Act Early Campaign website has resources on developmental milestones, including checklists for typical social and communication milestones from 2 months to 5 years of age, photo/video libraries of developmental milestones, and an autism case training curriculum for health care professionals.[69]

SOCIAL RECIPROCITY. Assess early social engagement and interactions as an infant or toddler, participation in reciprocal social interactions, social orienting, sharing of enjoyment and interests, social interest, and initiation. Older children may be socially immature and have difficulty perceiving social cues and conventions. When assessing social-emotional reciprocity, consider language level and whether language is used for social communication. Some children may be nonverbal, or they may use signs or pictures to communicate needs.

NONVERBAL COMMUNICATION. The clinician should determine how the child makes his or her needs known using nonverbal strategies as well as whether the child can accurately interpret or understand nonverbal cues. It is important to be aware that caregivers may be exquisitely able to anticipate the child's needs and wants, compensating for the deficits in verbal and nonverbal communication. Therefore, they may not always recognize and report these challenges.

SOCIAL RELATIONSHIPS. Difficulty with peer relationships is a core feature of children with autism spectrum disorder, but it can be difficult to assess, particularly in young children who may have limited exposure to same-aged peers. It is helpful to inquire about how the child behaves on the playground or

TABLE 12-3

Clinical Questions to Query *DSM-5* Diagnostic Criteria for Autism Spectrum Disorder

Social Reciprocity

- Age at which child developed social smile?
- Responds to name being called?
- Enjoyment of interactive baby games like peekaboo or pat-a-cake?
- Imitation of other's actions?
- Soothed by physical contact or cuddling?
- Awareness of or interest in others?
- During play, checks in with others, allows others to join in play, prefers to play alone, or actively resists when others attempt to join in play?
- Initiates social interaction or demonstrates social interest?
- Able to take turns during play, follow rules, play cooperatively?
- Engages only in physical or roughhouse play?
- In the more verbal child:
  - Use of language to make requests?
  - Offers information or comments?
  - Shares ideas, interests, emotions, or enjoyment?
  - Able to converse socially?
  - Use of turn-taking in conversation?
  - Able to discuss a variety of topics (not just preferred topics), stay on topic, or respond appropriately to questions?

Nonverbal Communication

- Responds to or initiates joint attention (eg, looks to a point or points to direct attention)?
- Abnormal reliance on physically directing others to communicate needs (eg, using an adult's hand as a tool, moving people's hands toward something or away from them, or leading or guiding others to gain access to items)?
- Accurately interprets facial expressions, gestures, and nonliteral language?
- A typical prosody (eg, singsong or robotic or announcer voice), imitation of original inflection of speaker, eg, like an announcement)?
- Uses common gestures, such as waving, clapping, nodding, or giving high fives?
- Integrates verbal and nonverbal strategies (eg, naturally combines eye gaze, natural gestures, spoken language)?

Social Relationships

- Atypical reaction to peers (eg, avoidant, running away when approached, watchful but not making overtures)?
- Engages in interactive/shared imaginative play?
- Preference for play with younger or older children or adults rather than same-aged peers?
- Has play dates?

CONTINUED ON PAGE 263

CONTINUED FROM PAGE 262

- Has a best friend?
- Is invited to birthday parties of classmates?
- Varies behavior in different social contexts, such as with familiar versus unfamiliar people or in outside versus inside settings?
- Understands friendships?
- Understands others' perspectives?
- Understands jokes or sarcasm?
- Distinguishes friendly teasing from meanness?
- Navigates social conflicts with friends or in romantic relationships?
- Makes inappropriate comments (eg, about another's appearance) and does not understand these may be hurtful?
- Perceives subtle social cues, such as someone not being interested in play or a hearing about a particular topic, lecturing like a "little professor"?

Stereotypic Movements, Repetitive Object Use, or Vocalizations/Verbalizations

- Motor stereotypies (eg, jumping up and down, rocking, hand flapping, finger wiggling or posturing, spinning objects or self, toe walking, pacing)?
- Unusual or repetitive play (eg, flipping lights on/off, flushing toilets, lining up toys, spinning or focusing on car wheels or spinning objects)?
- Vocal or verbal stereotypies (eg, repetitive sounds, immediate or delayed echolalia/scripted speech)?
- Use of rote or overlearned language, use of statements out of context or without social intent?
- Idiosyncratic language, pronoun reversal, or use of neologisms?

Inflexibility; the Need for Sameness, Routines, or Rituals

- Follows specific rituals (eg, needing to get dressed in exactly the same way every morning, needing the same sippy cup or place at the table, overly elaborate bedtime routines)?
- Insists on eating the same foods every day (eg, extreme food selectivity) or wearing same clothes every day (eg, only gray T-shirts)?
- Does not tolerate changes in routine?
- Difficulty with transitioning from one activity to another?
- Strict adherence to rules or black-and-white thinking?
- Needs to finish something once it is started?
- Compulsive fixing, arranging objects, or cleaning?

Overly Intense or Unusual Interests

- Extreme attachment to particular objects, excluding typical transitional object (eg, needing to hold a stick or a toy car in each hand)?
- Overly interested in letters and numbers at a very young age?
- Excessive interests in age-appropriate topics (eg, extensive knowledge about superheroes, dinosaurs, or certain video games but not being able to talk about or play with anything else)?

CONTINUED ON PAGE 264

CONTINUED FROM PAGE 263

- Unusual interests that would not be expected for age (eg, weather, maps, transportation schedules)?
- Excessively in-depth knowledge of topics such as history, science, trivia (to the exclusion of other interests)?

Overreactivity or Underreactivity to Auditory, Visual, or Tactile Stimulation or Unusual Sensory Behaviors

- Intolerance of certain sounds (eg, vacuum, blender, hand dryer in bathrooms), crowds, being touched?
- Refuses to wear certain clothing fabrics or is bothered by the tags in the back of the shirt, clothing seams?
- Extreme difficulty with things touching their heads (eg, wearing hats or getting haircuts) or with cutting fingernails and toenails?
- Restricted eating that is based on certain food textures or oral aversion?
- Looks at things from unusual angles or peers out of the corner of the eyes?
- Mouths, licks, or smells nonfood objects?
- Rubs objects against their skin?
- Proprioceptive sensory-seeking behavior (eg, craving deep pressure or being calmed by strong hugs or having body parts squeezed)?

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

TABLE 12-4 **Autism-Specific Assessments**[a]

Autism Spectrum Disorder Diagnostic Tools[b]

- **Autism Diagnostic Observation Schedule Second Edition (ADOS-2)**[62]
  - Semistructured standardized assessment of communication, social interaction, and play for children suspected to have social and communication challenges along the autism spectrum continuum
  - Several modules chosen based on language skills
  - During the assessment, the examiner pulls for social bids and makes note of specific repetitive or atypical behaviors; developed for research purposes, but may be used in clinical care as well
- **Autism Diagnostic Interview-Revised (ADI-R)**[63]
  - Companion tool to the ADOS; lengthy standardized interview querying all aspects of the child's development and current functioning

Screening Tools, Tools Used to Support Autism Spectrum Disorder Diagnosis

- **Social Communication Questionnaire (SCQ)**[64]
  - Parent questionnaire based on items from the ADI-R with 40 yes/no items; screening tool

CONTINUED ON PAGE 265

at the park. Children with autism spectrum disorder have particular difficulty with higher-order social or relational skills, such as empathy and the ability to appropriately adjust behaviors in different social contexts. Some children are highly reliant on others for direct communication or to provide the scaffolding for social interaction, and therefore they only succeed in highly supported social environments. Some children may show affection and social engagement with certain close family members and siblings, but they exhibit an overall atypical pattern of relating to people. Social skill deficits may become more prominent in late elementary school age or middle school, when social relationships become more complex and nuanced and children typically take more ownership of their social plans. Of note, excessive focus on unique interests and ideas and rigid behavior (CASE 12-2) may impair friendships for children with autism spectrum disorder, or they may be particularly drawn to others with similarly focused interests.

REPETITIVE BEHAVIOR AND RESTRICTED INTERESTS. Assessment of this domain requires querying the presence of abnormal or unusual behaviors that are atypical for age and developmental level. It is important to consider the severity and degree to which behaviors impair functioning when evaluating these symptoms.

STEREOTYPIC MOVEMENTS, REPETITIVE OBJECT USE, OR VOCALIZATIONS/VERBALIZATIONS. When assessing for the presence of repetitive motor patterns, note that many typically developing children flap their hands or jump up and down when excited; this should be distinguished from a persistent and repetitive pattern of hand flapping as seen in autism spectrum disorder. Children with intellectual disability can also have stereotypies. Fidgeting and tics can

CONTINUED FROM PAGE 264

- **Social Responsiveness Scale Second Edition (SRS-2)**[65]
  - Caregiver report measure (parent or teacher) that contains subscales in social awareness, social cognition, social communication, social motivation, and autistic mannerisms
- **Childhood Autism Rating Scale 2 (CARS-2)**[66]
  - Clinician-administered tool that scores observed and historical behavior; a parent-completed rating scale is also available to aid in the assessment
- **Gilliam Autism Rating Scale-3 (GARS-3)**[67]
  - Can be used by teachers, parents, and clinicians in individuals ages 3-22
  - Items are grouped into four subtests that examine stereotyped behaviors, communication, social interaction, and developmental disturbances
- **Developmental Play Scale**[68]
  - Qualitative measure of a child's play skills, including presymbolic play and symbolic play

[a] Note that many of these assessments are copyrighted and only available for purchase through testing companies.
[b] These tools can be used across ages. Specific training for administrator is required.

sometimes be seen in other neurodevelopmental disabilities and should be distinguished from stereotypies when coding symptoms. Echolalia can be normal in early language development but does not usually persist.

INFLEXIBILITY; THE NEED FOR SAMENESS, ROUTINES, OR RITUALS. Cognitive rigidity, inflexibility, and ritualistic behavior should be queried. Some children may be quite self-directed, following their own personal agenda. Attempts to guide the child's activities or conversation may be met with refusals or excessive distress. Often, families need to make extreme accommodations and adhere to strict routines to prevent meltdowns and tantrums.

CASE 12-2

A 16-year-old boy presented with school problems and anxiety. His parents reported that he was very bright, but he still had trouble completing his work at school. He got into frequent conflicts with teachers because he did not think he needed to show his work. He also interpreted language extremely literally. For example, he got into trouble at school for leaning on a desk. When the teacher told him sitting on the desk was not allowed, he explained that he was not sitting, he was leaning, which was "completely different." He was interested in friendships at school, but his peers did not want to spend time with him because play always had to be his way, and he was very inflexible. He even made up his own rules for his video games. He also had "no filter" and frequently made inappropriate overtures. He was bullied at school. He had fluent speech but had an unusual high-pitched prosodic tone. He was also described as a kid who "lectures at you" rather than having a conversation with you. He had intense and unique interests in maps and weather and had memorized the Paris Metro system, although he had never been to Paris. He talked about these a lot and did not realize when someone else was not interested. His early developmental history was notable for early speaking and reading and difficulty interacting with other kids his age but interacting well with adults and older children. He had some motor stereotypies but now only performed them in private. Previous cognitive testing showed strengths in verbal skills (verbal IQ of 140) and relative weakness in nonverbal skills (nonverbal IQ of 110.)

COMMENT

This case illustrates an adolescent with autism spectrum disorder and no language or cognitive impairment (in fact, note the discrepancy in verbal compared to nonverbal IQ, which is not uncommon in autism spectrum disorder). Despite fluent speech, he still has significant social communication deficits (difficulty with back-and-forth conversation, very literal language, social interest but poor skills). He also showed some stereotypies in the past but recognizes this is not typical behavior, so now only does them in private. He has rigid behavior and very intense interests. In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, he would have been diagnosed with Asperger disorder.

OVERLY INTENSE OR UNUSUAL INTERESTS. Assess for preoccupations or unusual attachments and for interests that seem overly intense (such that it is the only thing the child will talk about or play with, to the exclusion of new or different activities) or for interests in topics that would not otherwise be age appropriate.

OVERREACTIVITY OR UNDERREACTIVITY TO AUDITORY, VISUAL, OR TACTILE STIMULATION OR UNUSUAL SENSORY BEHAVIORS. Assess for both sensory aversions and sensory-seeking behavior in all sensory domains.

Behavioral/Play Observations/Direct Assessment

Behavioral observations must be made throughout the entirety of the visit. Observations begin in the waiting room with observation of the child with other children and assessment of greetings and transition to the examination room; passive observations continue throughout the visit while obtaining the developmental history with caregivers and through assessment during evaluator-directed play and interactions with the child. Specific behaviors the evaluator can directly observe include quality of the interaction with caregivers and medical staff (lack of response to name, lack of emotional reciprocity, difficulty initiating or responding to joint attention, poor social referencing, disengagement), quality of play (repetitive or stereotyped, or lack of imaginative interactive play), nonverbal communicative behaviors (poor eye contact, lack of pointing, paucity of gestures and facial expressions), quality and content of verbal language (repetitive or unusual vocalizations, echolalic or scripted speech, abnormal prosody, lack of back and forth conversation, engagement in monologues about preferred interests), presence of rigid or maladaptive behaviors (intolerance to transition, reduced frustration tolerance, aggression or self-injurious behavior), and sensory-seeking or avoidant behaviors (unusual inspection of toys, oversensitivity to tactile portions of the examination, licking/mouthing objects).

It is often helpful for the evaluator to point out to parents any pertinent observations during the evaluation. For example, "I'm noticing ___. Does this occur in other settings?" Again, as the direct observations and assessment only reflect a brief snapshot and do not occur in the child's natural environment, it is important to determine whether observations in the office setting are consistent with those reported in other settings. Observations must be considered in the context of the overall developmental history and corroborative information and within the context of the social and cultural convention for the child's age group and cultural/ethnic status.

A wide variety of presentations of the deficits and the presence of abnormal behaviors can be observed in the office setting in children with autism spectrum disorder. Many of these behaviors are listed in various autism spectrum disorder–specific questionnaires and observational scales (TABLE 12-4).

Physical Examination

Because of the association of autism spectrum disorder with neurogenetic syndromes, the general physical examination should include assessment for dysmorphic features (eg, large prominent ears as in fragile X syndrome or facial features indicative of genetic or metabolic syndromes), growth parameters (height, weight, and head circumference [macrocephaly greater than 98% is present in 20% of patients with autism spectrum disorder[70]]); and skin examination, including Wood's lamp, to assess for neurocutaneous stigmata such as hypopigmented spots or ash leaf spots as in tuberous sclerosis complex

KEY POINTS

- **Behavioral observations must be made throughout the entirety of the clinic visit. Observations begin in the waiting room with observation of the child with other children and assessment of greetings and transition to the examination room; passive observations continue throughout the visit while obtaining the developmental history with caregivers and through assessment during evaluator-directed play and interactions with the child.**
- **Observations must be considered in the context of the overall developmental history and corroborative information and within the context of the social and cultural convention for the child's age group and cultural/ethnic status.**

(CASE 12-3) or hyperpigmented spots as in neurofibromatosis.[36,37,41] Neurologic examination should focus on the patient's level of activity, attention, cranial nerves, muscle tone assessing for severe hypotonia, motor coordination/planning, reflexes, and gait (toe walking).

Standardized Tools, Rating Scales, and Assessments

By *DSM-5* diagnostic criteria, no standardized tools are required for diagnosing autism spectrum disorder. However, a number of tools, such as standardized questionnaires and rating scales, parent interviews, and direct assessments (including autism spectrum disorder–specific tools), can help clarify the diagnostic profile (TABLE 12-4).

An accurate diagnosis of autism spectrum disorder does require standardized assessments of cognition, adaptive function, and speech and language skills to help clinicians distinguish global delays from deficits limited or targeted to language and social communication skills.[36,37,41] Children with autism spectrum disorder may have global delays, but they will have more extreme deficits in socialization and communication. Formal cognitive and language assessments are also needed to determine specifiers required in the *DSM-5* and should be considered when assigning the diagnosis. In some cases, an occupational therapy assessment for sensory issues is helpful. An understanding of the child's specific

CASE 12-3

A 3-year-old girl with autism spectrum disorder with cognitive and language impairment was referred by her pediatrician for neurologic evaluation. Her past medical history revealed that she was born in a poorly resourced country and had early-onset seizures and developmental delay. Her mother had a hard time describing the seizure symptomatology the patient experienced as an infant, and, unfortunately, no records were available. She had been on medication but was taken off after 6 months, and the seizures did not return. However, she had recently developed some new spells with behavioral arrest and unresponsiveness. Physical examination revealed macrocephaly and hypopigmented lesions seen on the trunk on Wood's lamp examination. Given the diagnoses of autism spectrum disorder, global developmental delay, seizures, and the examination findings, tuberous sclerosis complex was suspected.

An EEG showed multifocal spikes and one electroclinical seizure, and a brain MRI revealed tubers and subependymal nodules. Therefore, the autism spectrum disorder diagnostic specifiers were amended to include an association with tuberous sclerosis complex and epilepsy. Recommendations included starting anticonvulsant treatment; medical surveillance for tuberous sclerosis complex–associated conditions; genetic counseling; and intensive speech, educational, and behavioral interventions for autism spectrum disorder.

COMMENT

This case exemplifies the importance of a careful physical examination, which, in this case, pointed to a distinct etiology. It also illustrates how to use the specifiers in the diagnosis.

areas of strengths and weaknesses in these developmental domains is also important for tailored treatment planning.

Evaluation of Etiology

Ruling out treatable conditions is important in all children. Formal audiologic evaluation should be completed in all children with language delay and diagnosis (or suspicion) of autism spectrum disorder.[36,37,41] Lead testing should be done for all children with developmental delays and those still in an oromotor stage of development or with pica.[36,37]

The neurologist has an important role in identifying possible neurogenetic or metabolic syndromes in individuals diagnosed with autism spectrum disorder and should be aware of phenotypes that may be suggestive of specific syndromes. Neurogenetic syndromes and disorders occur in about 10% to 20% of children with autism spectrum disorder.[24] For example, children with fragile X syndrome, tuberous sclerosis complex, 15q duplication syndrome, neurofibromatosis, Angelman syndrome, Prader-Willi syndrome, Down syndrome, and Williams syndrome have higher rates of autism than in the general population.[37]

Chromosomal microarray is recommended for all individuals with autism spectrum disorder.[37,40,42] Fragile X testing is commonly performed, although it is important to note that conflicting recommendations exist regarding whether fragile X analysis should be offered to all patients with autism spectrum disorder, only boys, or only those with autism spectrum disorder and cognitive impairment.

The yield of genetic testing is higher in those who have syndromic features, dysmorphology, or intellectual disability.[40] Additional etiologic testing, including gene mutation analyses, should be considered for children if concerns exist for a specific neurogenetic or metabolic syndrome or if the child has a history of developmental regression. The American College of Medical Genetics and Genomics guidelines include estimates of diagnostic yield that can be discussed with families. Genetic counseling should be offered to all families.[40]

Further etiologic testing, including metabolic testing, EEG, and neuroimaging/brain MRI, are not recommended as standard care but should be considered for some children based on individual phenotypic features.[36,37,40,41] EEG should be considered if concern exists for clinical or subclinical seizures or in the setting of regression to assess for possible Landau-Kleffner syndrome/acquired epileptic aphasia. For more information on Landau-Kleffner syndrome, refer to the article "Epileptic Encephalopathies" by Shaun A. Hussain, MD, MS,[71] in this issue of *Continuum*.

Neuroimaging is indicated in the setting of microcephaly, hypertonia, focal examination, or concern for tuberous sclerosis complex or a neurodegenerative condition. Toe walking in the absence of evidence of spasticity/upper motor neuron signs is likely behavioral and does not require neuroimaging.

Metabolic/mitochondrial testing; general screening for immunologic deficiencies; evaluation for toxins, heavy metals, food allergies, and celiac antibodies; and thyroid tests can be considered in those with appropriate phenotypes but are not recommended routinely.[36]

Differential Diagnosis

Social and communication difficulties and repetitive behaviors are seen in other medical and neurodevelopmental disorders. The evaluator must determine whether impairing symptoms are best explained by autism spectrum disorder or

KEY POINTS

- By *DSM-5* diagnostic criteria, no standardized tools are required for diagnosing autism spectrum disorder. However, a number of tools, such as standardized questionnaires and rating scales, parent interviews, and direct assessments (including autism spectrum disorder–specific tools), can help clarify the diagnostic profile.
- An accurate diagnosis of autism spectrum disorder requires standardized assessments of cognition, adaptive skills, and speech and language skills to help clinicians distinguish global delays from deficits limited or targeted to language and social communication skills.
- Formal audiologic evaluation should be completed in all children with language delay and diagnosis (or suspicion) of autism spectrum disorder.
- Lead testing should be done for all children with developmental delays and those still in an oromotor stage of development or with pica.
- The neurologist has an important role in identifying possible neurogenetic or metabolic syndromes in individuals diagnosed with autism spectrum disorder and should be aware of phenotypes that may be suggestive of specific syndromes.

another condition (TABLE 12-1). It should be noted that multiple conditions can co-occur in the same child.

Applying Specifiers

The medical history, formalized assessments, ancillary testing, record review, and direct observation can be used to determine if a child has cognitive and language impairment and any comorbid medical or neurodevelopmental disorders that should be assigned as specifiers. While some of these symptoms may not be specific to autism spectrum disorder, they are important to document because they can represent significant morbidity in the patient and can be targets for specific interventions.

GENERAL MANAGEMENT OF AUTISM SPECTRUM DISORDER

When a child is diagnosed with autism spectrum disorder, adequate time should be made available to answer questions, guide the family toward treatment and service options, and make appropriate referrals. All families should be offered information and support and should be provided with accessible materials. Multiple resources are available, including those available online from various government resources (eg, the CDC and the National Institutes of Health [NIH]) and private foundations and groups (eg, Autism Speaks, Autism Society of America, American Academy of Pediatrics). Families should also be referred and given information about local autism support centers, which are available in most states.

The written evaluation report is often used by families to advocate for services, therapies, and educational programs. Therefore, it should provide specific documentation of the diagnostic evaluation findings and evidence-based recommendations for treatment. Recommendations should be detailed and tailored to the child's individual developmental needs.

Behavioral and educational therapies are the mainstay of treatment for autism spectrum disorder.[38,41,72] Children younger than 3 years of age should be assessed by the early intervention team, and an individualized family service plan (IFSP) should be developed. They should be referred for both general developmental and autism-intensive services. Children older than age 3 years should be referred to their local public school for a school evaluation to determine special education eligibility (often referred to as a team or core evaluation). Most children with autism spectrum disorder will be deemed eligible for services through an individualized education program (IEP) through Individuals With Disabilities Education Act (IDEA). Some children may receive accommodations under a 504 plan through the Rehabilitation Act of 1973. Home-based services may also be accessed through the IFSP, IEP, or private or public health insurance. Many states now have laws mandating private insurance to pay for autism spectrum disorder–related behavioral therapies. Recently, the Centers for Medicare & Medicaid Services mandated public insurance coverage for autism spectrum disorder services as well.

The National Research Council Recommendations for Educating Children With Autism include at least 25 hours of total service time, maximal individualized instruction with a low student to teacher ratio, and parent/family involvement. These recommendations are available for free download from the National Academies Press (*nap.edu/catalog/10017/educating-children-with-autism*) and can be referenced when advocating for appropriate services.[72]

Behavioral Therapy

Research has consistently shown that early intensive behavioral interventions can help young children with autism spectrum disorder gain skills and improve long-term outcomes.[72–74] Applied behavior analysis (ABA) is currently considered the gold-standard treatment for autism spectrum disorder. ABA is a methodology based on learning theory principles that teaches skills and decreases maladaptive behaviors through repetition and reinforcement. It can be used to improve communication, socialization, adaptive behaviors, and cognition.[72,75] ABA can be delivered in an outpatient clinical setting, in the home, or in school. Several kinds of behavioral therapies are available, including discrete trial training (traditional ABA) and ABA-based hybrids such as the Early Start Denver Model (ESDM)[73] and pivotal response treatment (PRT).[76] Naturalistic approaches are also available, such as Floortime.[77] Some of these models incorporate parents as interventionists. Play-based and social-pragmatic behavioral interventions are also used to target core autism deficits of social engagement, emotional thinking, and social skills. Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) is a structured teaching method that is especially useful for visual learners.[78]

Allied Services and Therapies

Speech and language therapy and a total communication approach involving the use of gestures and signs (American Sign Language), picture exchange communication systems (PECS), communication boards, visual supports, and assistive technology and devices may be used to support functional communication. Occupational therapy can be helpful for addressing adaptive skill needs, sensory needs, and fine motor/visuomotor support. While not a lot of research-based evidence exists to support most sensory integration techniques, some techniques and tools may be helpful for some children, such as the use of brushing, weighted vests, and sensory toys. The development of social skills can also be facilitated by using social skills groups. Some school programs have "lunch bunch" groups, and social skills groups are also available in the community.

Counseling

In those with average intelligence and typical language skills, counseling methodologies can be successfully employed for core symptoms of rigidity and inflexibility as well as comorbid psychiatric disorders (eg, depression, anxiety) and behavioral dysregulation. While the use of psychotherapy is obviously limited for individuals with language and cognitive impairment, cognitive-behavioral therapy (CBT) techniques have been modified for use with the autism spectrum disorder population with good outcomes.[79]

Pharmacologic Therapies

Currently, no medications are US Food and Drug Administration (FDA) approved for the treatment of the core symptoms of autism spectrum disorder; this is an area of unmet need and active research. However, up to two-thirds of children with autism spectrum disorder use psychoactive medications to treat impairing symptoms associated with autism spectrum disorder,[80,81] and medication use increases with age.[82]

Co-occurring behavioral or psychiatric disorders are common in autism spectrum disorder, such as ADHD (with lack of safety awareness), anxiety, aggression/irritability, and self-injurious behavior. Medications used in other

KEY POINTS

- The yield of genetic testing for autism spectrum disorder is higher in those who have syndromic features, dysmorphology, or presence of intellectual disability. Additional etiologic testing, including gene mutation analyses, should be considered for children if concerns exist for a specific neurogenetic or metabolic syndrome or if the child has a history of developmental regression.
- The evaluator must determine whether social and communication difficulties and repetitive behaviors are best explained by autism spectrum disorder or another medical or neurodevelopmental disorder.
- Behavioral and educational therapies are the mainstay of treatment for autism spectrum disorder.
- The National Research Council Recommendations for Educating Children With Autism include at least 25 hours of total service time, maximal individualized instruction with a low teacher to student ratio, and parent/family involvement.
- Applied behavior analysis, a methodology based on learning theory principles that teaches skills and decreases maladaptive behaviors through repetition and reinforcement, is currently considered the gold-standard treatment for autism spectrum disorder.

KEY POINTS

- Currently, no medications are US Food and Drug Administration approved for the treatment of the core symptoms of autism spectrum disorder; however, risperidone and aripiprazole are approved specifically for treating the symptoms of irritability and aggression in children.
- Co-occurring behavioral or psychiatric disorders are common in autism spectrum disorder. Medications used in other psychiatric disorders can be effective in individuals with autism spectrum disorder as well.
- Children with autism spectrum disorder tend to experience more side effects from medications; therefore, medication dosing trials should "start low and go slow."

psychiatric disorders can be effective in individuals with autism spectrum disorder as well. The only two medications that are FDA approved for use in this population are risperidone and aripiprazole, both atypical antipsychotics and approved specifically for treating irritability and aggression in children with autism spectrum disorder. Other medications are used to treat commonly occurring symptoms, such as anxiety or OCD (selective serotonin reuptake inhibitors [SSRIs]); ADHD symptoms of impulsivity, hyperactivity, and inattention (alpha agonists, stimulants); sleep dysfunction (melatonin or sedatives); and mood disorders (SSRIs, atypical neuroleptics, and mood stabilizers). Children with autism spectrum disorder tend to experience more side effects from medications; therefore, medication dosing trials should "start low and go slow." For medications commonly used, published doses may be used, although the starting dose is often lower than published dosing recommendations.

Complementary and Alternative Medicine

Treatments such as dietary modifications, vitamins and supplements, acupuncture, chiropractic, chelation, hyperbaric oxygen, and immunologic agents are widely used by families in children with autism spectrum disorder. To date, inadequate scientific peer-reviewed research exists to support these treatments.[83] Treating clinicians should inquire about the use of these treatments and provide guidance regarding potential side effects or harm. Even if not thought to be harmful, many complementary and alternative medicine treatments can be costly. Families should be provided with information about the lack of controlled data available, but this should be done in a nonjudgmental manner, and resources and information should be provided to families about how to evaluate and monitor alternative treatments. Families should be advised that complementary and alternative medicine treatments should not replace proven behavioral treatments.

CONCLUSION

Autism spectrum disorder is a complex heterogeneous disorder, with symptoms of social communication deficits and restricted/repetitive behaviors that are present early in development and are usually lifelong. The impairments significantly impact the child's ability to function both at home and in the community. Because of the neurodevelopmental nature of the disorder, neurologists are often called upon to make the diagnosis and perform an etiologic evaluation. Neurologists may also primarily manage neurologic comorbidities and may serve as a medical home for overall care of the patient with autism spectrum disorder. To aid in this task, this article has reviewed core symptoms, comorbidities, and proposed etiologies and provided an approach to the office visit with questions for the diagnostic evaluation, recommendations for workup, and a summary of treatment approaches.

REFERENCES

1 Christensen DL, Baio J, Van Naarden Braun K, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveill Summ 2016;65(3):1–23. doi: 10.15585/mmwr.ss6503a1.

2 American Psychiatric Association Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders, 4th ed, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.

3 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed (DSM-5). Washington, DC: American Psychiatric Association, 2013.

4 Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind"? Cognition 1985;21(1):37–46. doi:10.1016/0010-0277(85)90022-8.

5 Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disord 2003;33(4):365–382. doi:10.1023/A:1025054610557.

6 Pavone P, Incorpora G, Fiumara A, et al. Epilepsy is not a prominent feature of primary autism. Neuropediatrics 2004;35(4):207–210. doi:10.1055/s-2004-821079.

7 Miles JH, Takahashi TN, Bagby S, et al. Essential versus complex autism: definition of fundamental prognostic subtypes. Am J Med Genet A 2005;135(2):171–180. doi:10.1002/ajmg.a.30590.

8 Amiet C, Gourfinkel-An I, Bouzamondo A, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychiatry 2008;64(7):577–582. doi:10.1016/j.biopsych.2008.04.030.

9 Rai D, Kerr MP, McManus S, et al. Epilepsy and psychiatric comorbidity: a nationally representative population-based study. Epilepsia 2012;53(6):1095–1103. doi:10.1111/j.1528–1167.2012.03500.x.

10 Surén P, Bakken IJ, Aase H, et al. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. Pediatrics 2012;130(1):e152–e158. doi:10.1542/peds.2011–3217.

11 Clarke DF, Roberts W, Daraksan M, et al. The prevalence of autistic spectrum disorder in children surveyed in a tertiary care epilepsy clinic. Epilepsia 2005;46(12):1970–1977. doi:10.1111/j.1528–1167.2005.00343.x.

12 El Achkar CM, Spence SJ. Clinical characteristics of children and young adults with co-occurring autism spectrum disorder and epilepsy. Epilepsy Behav 2015;47:183–190. doi:10.1016/j.yebeh.2014.12.022.

13 Mazurek MO, Engelhardt CR, Hilgard J, Sohl K. Bedtime electronic media use and sleep in children with autism spectrum disorder. J Dev Behav Pediatr 2016;37(7):525–531. doi:10.1097/DBP.0000000000000314.

14 Elrod MG, Hood BS. Sleep differences among children with autism spectrum disorders and typically developing peers: a meta-analysis. J Dev Behav Pediatr 2015;36(3):166–177. doi:10.1097/DBP.0000000000000140.

15 Malow BA, Byars K, Johnson K, et al. A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. Pediatrics 2012:S106–S124. doi:10.1542/peds.2012–0900I.

16 Ming X, Brimacombe M, Wagner GC. Prevalence of motor impairment in autism spectrum disorders. Brain Dev 2007;29(9):565–570. doi:10.1016/j.braindev.2007.03.002.

17 Maski KP, Jeste SS, Spence SJ. Common neurological co-morbidities in autism spectrum disorders. Curr Opin Pediatr 2011;23(6):609–615. doi:10.1097/MOP.0b013e32834c9282.

18 Zecavati N, Spence SJ. Neurometabolic disorders and dysfunction in autism spectrum disorders. Curr Neurol Neurosci Rep 2009;9(2):129–136. doi:10.1007/s11910–009–0021-x.

19 Buie T, Campbell DB, Fuchs GJ 3rd, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics 2010;125(suppl 1):S1–S18. doi:10.1542/peds.2009–1878C.

20 King BH. Psychiatric comorbidities in neurodevelopmental disorders. Curr Opin Neurol 2016;29(2):113–117. doi:10.1097/WCO.0000000000000299.

21 van Steensel FJA, Bögels SM, Perrin S. Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. Clin Child Fam Psychol Rev 2011;14(3):302–317. doi:10.1007/s10567–011–0097–0.

22 Skokauskas N, Gallagher L. Psychosis, affective disorders and anxiety in autistic spectrum disorder: prevalence and nosological considerations. Psychopathology 2010;43(1):8–16. doi:10.1159/000255958.

23 Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol 2007;17(1):103–111. doi:10.1016/j.conb.2007.01.009.

24 Bourgeron T. Current knowledge on the genetics of autism and propositions for future research. C R Biol 2016;339(7):300–307. doi:10.1016/j.crvi.2016.05.004.

25 Simons Foundation Autism Research Initiative Gene List. *sfari.org/resource/sfari-gene*. Accessed December 4, 2017.

26 de la Torre-Ubieta L, Won H, Stein JL, Geschwind DH. Advancing the understanding of autism disease mechanisms through genetics. Nat Med 2016;22(4):345–361. doi:10.1038/nm.4071.

27 Geschwind DH, State MW. Gene hunting in autism spectrum disorder: on the path to precision medicine. Lancet Neurol 2015;14(11):1109–1120. doi:10.1016/S1474–4422(15)00044–7.

28 Pinto D, Delaby E, Merico D, et al. Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. Am J Hum Genet 2014;94(5):677–694. doi:10.1016/j.ajhg.2014.03.018.

29 Hernandez LM, Rudie JD, Green SA, et al. Neural signatures of autism spectrum disorders: insights into brain network dynamics. Neuropsychopharmacology 2015;40(1):171–189. doi:10.1038/npp.2014.172.

30 Just MA, Keller TA, Malave VL, et al. Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity. Neurosci Biobehav Rev 2012;36(4):1292–1313. doi:10.1016/j.neubiorev.2012.02.007.

31 Rubenstein JLR, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav 2003;2(5):255–267. doi:10.1034/j.1601-183X.2003.00037.x.

32 Estes ML, McAllister AK. Maternal immune activation: implications for neuropsychiatric disorders. Science 2016;353(6301):772–777. doi:10.1126/science.aag3194.

33 Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Mol Autism 2017;8(1):13. doi:10.1186/s13229-017-0121-4.

34 Mandy W, Lai MC. Annual research review: the role of the environment in the developmental psychopathology of autism spectrum condition. J Child Psychol Psychiatry 2016;57(3):271–292. doi:10.1111/jcpp.12501.

35 Vogel Ciernia A, LaSalle J. The landscape of DNA methylation amid a perfect storm of autism aetiologies. Nat Rev Neurosci 2016;17(7):411–423. doi:10.1038/nrn.2016.41.

36 Filipek PA, Accardo PJ, Ashwal S, et al. Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. Neurology 2000;55(4):468–479. doi:10.1212/WNL.55.4.468.

37 Johnson CP, Myers SM. American Academy of Pediatrics Council on Children With Disabilities. Identification and evaluation of children with autism spectrum disorders. Pediatrics 2007;120(5):1183–1215. doi:10.1542/peds.2007-2361.

38 Myers SM, Johnson CP. Management of children with autism spectrum disorders. Pediatrics 2007;120(5):1120–1182. doi:10.1542/peds.2007-2362.

39 American Academy of Pediatrics. Autism: caring for children with autism spectrum disorders, a resource toolkit for clinicians. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics, 2012.

40 Schaefer GB, Mendelsohn NJ. Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2013;15(5):399–407. doi:10.1038/gim.2013.32.

41 Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2014;53(2):237–257.

42 Satya-Murti S, Cohen BH, Michelson D. Chromosomal microarray analysis for intellectual disabilities: template coverage policy. American Academy Neurology. *aan.com/uploadedFiles/Website_Library_Assets/Documents/3.Practice_Management/1.Reimbursement/1.Billing_and_Coding/5.Coverage_Policies/13%20ChromoMicroIntelDisabil.pdf*. Published 2013. Accessed December 7, 2017. doi:10.1016/j.jaac.2013.10.013.

43 Siu AL, Bibbins-Domingo K, Grossman DC, et al. Screening for autism spectrum disorder in young children: US Preventive Services Task Force Recommendation Statement. JAMA 2016;315(7):691–696. doi:10.1001/jama.2016.0018.

44 Dreyer B. AAP statement on US Preventive Services Task Force final recommendation statement on autism screening. *aap.org/en-us/about-the-aap/aap-press-room/Pages/AAP-Statement-on-US-Preventive-Services-Task-Force-Final-Recommendation-Statement-on-Autism-Screening.aspx*. Published February 16, 2016. Accessed December 7, 2017.

45 Bayley N. Bayley scales of infant and toddler development. 3rd ed, San Antonio, TX: Pearson, 2006.

46 Mullen E. Mullen scales of early learning. Circle Pines, MN: AGS Edition, 1995.

47 Roid GH. Stanford Binet intelligence scales. 5th ed, Itasca, IL: Riverside Publishing, 2003.

48 Wechsler D. Wechsler preschool and primary scale of intelligence. 4th ed, San Antonio, TX: Pearson, 2012.

49 Wechsler D. Wechsler intelligence scale for children–4th ed (WISC-IV). San Antonio, TX: Pearson, 2003.

50 Elliott CD. Differentialability scales-II. San Antonio, TX: Pearson, 2007.

51 Roid GH, Miller L, Pomplun M, Koch C. Leiter International Performance Scale 3rd ed, Los Angeles, CA: Western Psychological Services, 2013.

52 Sparrow S, Cicchetti D. The Vineland adaptive behavior scales. Boston, MA: Allyn & Bacon, 1989.

53 Harrison P, Oakland T. Adaptive behavior assessment system 2nd ed, San Antonio, TX: Pearson, 2003.

54 Bruininks RH, Bradley HK, Weatherman RF, Woodcock RW. SIB-R: Scales of independent behavior–revised. St. Charles, IL: Riverside Publishing Company, 1996.

55 Dunn DM, Dunn LM. Peabody picture vocabulary test: manual. San Antonio, TX: Pearson, 2007.

56 Bzoch K, League R, Brown V. Receptive-expressive emergent language test: examiner's manual Austin, TX: PRO-ED, Inc, 2003.

57 Wiig EH, Semel E, Secord WA. Clinicalevaluation of language fundamentals 5th ed, San Antonio, TX: Pearson, 2013.

58 Phelps-Terasaki D, Phelps-Gunn T. Test of pragmatic language. 2nd ed, Los Angeles, CA: Western Psychological Services, 2007.

59 Achenbach TM, Rescorla LA. Manual for the ASEBA preschool forms & profiles: an integrated system of multi-informant assessment. Burlington, VT: Vermont Center for Children, Youth, and Families, 2000.

60 Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. Am J Ment Defic 1985;89(5):485–491.

61 Einfeld SL, Tonge BJ. The Developmental Behavior Checklist: The development and validation of an instrument to assess behavioral and emotional disturbance in children and adolescents with mental retardation. J Autism Dev Disord 1995;25(2): 81–104. doi:10.1007/BF02178498.

62 Lord C, Rutter M, DiLavore P, Risi S. Autism diagnostic observation schedule. 2nd ed, Los Angeles, CA: Western Psychological Servives, 2012.

63 Rutter M, Couteur ALe, Lord C. ADI-R: autism diagnostic interview–revised: manual. Los Angeles, CA: Western Psychological Services, 2003.

64 Rutter M. The social communication questionnaire: manual. Los Angeles, CA: Western Psychological Services, 2003.

65 Constantino JN. Social responsiveness scale 2nd ed, Los Angeles, CA: Western Psychological Services, 2012.

66 Schopler E, Van Bourgondien ME. Childhood autism rating scale. 2nd ed, Los Angeles, CA: Western Psychological Servcies, 2010.

67 Gilliam JE. Gilliam Autism Rating Scale-third edition (GARS-3). Austin, TX: PRO-ED, Inc, 2014.

68 Westby C. Assessment of cognitive and language abilities through play. Lang Speech Hear Serv Sch 1980:154–168. doi:10.1044/0161–1461.1103.154.

69 Centers for Disease Control and Prevention. Learn the signs. Act early. Milestones. *cdc.gov/ncbddd/actearly/milestones/index.html*. Updated August 18, 2016. Accessed December 7, 2017.

70 Fombonne E, Rogé B, Claverie J, et al. Microcephaly and macrocephaly in autism. J Autism Dev Disord 1999;29(2):113–119. doi: 10.1023/A:1023036509476.

71 Hussain SA. Epileptic encephalopathies. Continuum (Minneap Minn) 2018;24(1 Child Neurology):171–185.

72 National Research Council, Division of Behavioral and Social Sciences and Education. Educating children with autism. Washington, DC: National Academies Press, 2001.

73 Dawson G, Rogers S, Munson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. Pediatrics 2010;125(1):e17–e23. doi:10.1542/peds.2009–0958.

74 Reichow B. Overview of meta-analyses on early intensive behavioral intervention for young children with autism spectrum disorders. J Autism Dev Disord 2012;42(4):512–520. doi:10.1007/s10803–011–1218–9.

75 Schreibman L, Dawson G, Stahmer AC, et al. Naturalistic developmental behavioral interventions: empirically validated treatments for autism spectrum disorder. J Autism Dev Disord 2015; 45(8):2411–2428. doi:10.1007/s10803–015–2407–8.

76 Koegel RL, Kern Koegel L. Pivotal response treatments for autism: communication, social, and academic development. Baltimore, MD: Brookes Publishing Company, 2006.

77 Greenspan SI, Weider S. Engaging autism: using the floortime approach to help children relate, communicate, and think. Cambridge, MA: Da Capo Press, 2009.

78 Mesibov GB, Shea V, Schopler E. The TEACCH approach to autism spectrum disorders. New York, NY: Springer Science+Business Media, Inc, 2005.

79 Danial JT, Wood JJ. Cognitive behavioral therapy for children with autism. J Dev Behav Pediatr 2013;34(9):702–715. doi:10.1097/DBP.0b013e31829f676c.

80 Schubart JR, Camacho F, Leslie D. Psychotropic medication trends among children and adolescents with autism spectrum disorder in the Medicaid program. Autism 2014;18(6):631–637. doi: 10.1177/1362361313497537.

81 Spencer D, Marshall J, Post B, et al. Psychotropic medication use and polypharmacy in children with autism spectrum disorders. Pediatrics 2013;132(5):833–840. doi:10.1542/peds.2012–3774.

82 Rosenberg RE, Mandell DS, Farmer JE, et al. Psychotropic medication use among children with autism spectrum disorders enrolled in a national registry, 2007–2008. J Autism Dev Disord 2010;40(3):342–351. doi:10.1007/s10803–009–0878–1.

83 Levy SE, Hyman SL. Complementary and alternative medicine treatments for children with autism spectrum disorders. Child Adolesc Psychiatr Clin N Am 2015;24(1):117–143. doi:10.1016/j.chc.2014.09.004.