



Identification, Evaluation, and Management of Children With Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a common neurodevelopmental disorder with reported prevalence in the United States of 1 in 59 children (approximately 1.7%). Core deficits are identified in 2 domains: social communication/interaction and restrictive, repetitive patterns of behavior. Children and youth with ASD have service needs in behavioral, educational, health, leisure, family support, and other areas. Standardized screening for ASD at 18 and 24 months of age with ongoing developmental surveillance continues to be recommended in primary care (although it may be performed in other settings), because ASD is common, can be diagnosed as young as 18 months of age, and has evidenced-based interventions that may improve function. More accurate and culturally sensitive screening approaches are needed. Primary care providers should be familiar with the diagnostic criteria for ASD, appropriate etiologic evaluation, and co-occurring medical and behavioral conditions (such as disorders of sleep and feeding, gastrointestinal tract symptoms, obesity, seizures, attention-deficit/hyperactivity disorder, anxiety, and wandering) that affect the child's function and quality of life. There is an increasing evidence base to support behavioral and other interventions to address specific skills and symptoms. Shared decision making calls for collaboration with families in evaluation and choice of interventions. This single clinical report updates the 2007 American Academy of Pediatrics clinical reports on the evaluation and treatment of ASD in one publication with an online table of contents and section view available through the American Academy of Pediatrics Gateway to help the reader identify topic areas within the report.

INTRODUCTION

Autism spectrum disorder (ASD) is a category of neurodevelopmental disorders characterized by social and communication impairment and

abstract



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Drs Hyman, Levy, and Myers all participated in development of the outline of material to be covered, generation of content, and editing of the document; and all authors approved the final manuscript as submitted.

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DOI: <https://doi.org/10.1542/peds.2019-3447>

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To cite: Hyman SL, Levy SE, Myers SM, AAP COUNCIL ON CHILDREN WITH DISABILITIES, SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics*. 2020;145(1):e20193447

restricted or repetitive behaviors.¹ ASD affects more than 5 million Americans, with an estimated prevalence of approximately 1.7% in children.² The care needs of children with ASD are significant, affect parents and siblings as well, and require substantial community resources. Direct and indirect costs of caring for children and adults with ASD in the United States in 2015 were estimated to be \$268 billion, more than the cost of stroke and hypertension combined.³ The lifetime cost of education, health, and other service needs for an individual with ASD ranges from \$1.4 to \$2.4 million dollars, depending on whether he or she has any co-occurring intellectual disabilities.⁴ To deliver timely and effective medical, behavioral, educational, and social services across the lifespan means that primary care providers must understand the needs of individuals with ASD and their families. ASD is more commonly diagnosed now than in the past, and the significant health, educational, and social needs of individuals with ASD and their families constitute an area of critical need for resources, research, and professional education.

In the 12 years since the American Academy of Pediatrics (AAP) published the clinical report "Identification and Evaluation of Children With Autism Spectrum Disorders"⁵ and its companion, "Management of Children With Autism Spectrum Disorders,"⁶ reported prevalence rates of ASD in children have increased, understanding of potential risk factors has expanded, awareness of co-occurring medical conditions and genetic contribution to etiology has improved, and the body of research supporting evidence-based interventions has grown substantially. This updated clinical report builds on previous reports and guidance for care of children and youth with ASD. It also reflects changes in diagnostic

criteria after publication of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*¹ in 2013. The DSM-5 established a single category of ASD to replace the subtypes of autistic disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. With the current reported prevalence rate of 1:59 children (approximately 1.7%), all primary care providers can expect to have children and youth with ASD in their practices.² As noted in earlier clinical reports, the primary care provider has critical access to the child in the context of the medical home to identify symptoms of ASD early in childhood, support the family through the process of diagnosis and intervention, address etiologic evaluations, help the family understand how to interpret the evidence supporting different interventions so they can effectively engage in shared decision-making, and manage co-occurring medical conditions that may influence outcome and affect daily function. The primary care provider can help minimize disparities in age of diagnosis of African American and Hispanic children and be alert to the potential for gender bias in symptom recognition.⁷ This updated document aims to provide primary care providers with a summary of current information in a single report that will help guide them in providing a medical home for the patient with ASD.

SECTION 1: PREVALENCE

Incidence is the onset of new diagnoses over time in a selected cohort. Without consistent longitudinal data in a specified cohort, incidence cannot be determined. Because of the heterogeneity of symptoms and severity in ASD, it may be diagnosed

in children at different ages. What is reported is age at recognition of symptoms, not the actual onset. As a result, prevalence is more typically reported than incidence, reflecting rates of ASD in the population at a point in time.

The reported prevalence of children with ASD has increased over time, and primary care providers are often asked about the reasons for this increase. This increase may be attributable to several factors, including broadening in the diagnostic criteria with ongoing revisions of the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, the more inclusive definition of pervasive developmental disorder with the adoption of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* in 1994,⁸ increased public awareness of the disorder and its symptoms, recommendations for universal screening for ASD,^{5,9} and increased availability of early intervention and school-based services for children with ASD. In part, the increasing numbers of children with a diagnosis of ASD may reflect diagnostic substitution, the recognition of ASD in children previously primarily diagnosed with intellectual disability or a co-occurring genetic syndrome.¹⁰ A true increase in the prevalence of ASD associated with other biological risk factors is also possible.

Prevalence rates in US populations are similar to those of other industrialized countries,¹¹ and lower rates are reported in resource-limited countries, where epidemiological data are more difficult to collect.¹² Data on national samples suggest that the prevalence of ASD is stabilizing.^{2,13} Ongoing epidemiological studies help to understand changes in the reported prevalence over time. Epidemiological data help to predict the need for services and identify potential risk factors. Surveillance methods include regional, state, and/or national registry systems;

records- or services-based analyses; surveys; and other methods, including population-based case findings.

In 2000, the US Centers for Disease Control and Prevention (CDC) established the Autism and Developmental Disabilities Monitoring (ADDM) Network as a population-based public health surveillance system to estimate the prevalence of ASD in children 8 years of age. ADDM reports published in 2014 and 2016 revealed comparable prevalence rates (approximately 1 in 68),^{14,15} but the report published in 2018² revealed a slightly increased rate (1 in 59). Additional data over time will help determine if rates have stabilized. The data also revealed some variation in prevalence rates across the participating states, with the highest rates in the locations where both educational and health records were available for chart abstraction and standardized application of diagnostic criteria. Regional variation in prevalence may also reflect availability of services, local provider practices for ASD screening, educational policies, school and/or community resources, and insurance mandates, among other factors. The CDC also published data on the prevalence of ASD in children who were 4 years of age in 2010. A lower prevalence rate for diagnosis (1.34%) was reported in these children (approximately 30% less than that of children 8 years of age). The lower identified prevalence and higher proportional rate of children 4 years of age with ASD and intellectual disabilities may be attributable, in part, to later diagnosis of children with ASD and average-range cognitive abilities.¹⁶ The National Survey of Children's Health (2011–2012) and the National Survey of Children with Special Health Care Needs (2009–2010) were analyzed for the age the parents reported diagnosis as well as for parent-reported subjective severity. The minority of children were identified

as having ASD before 3 years of age. Diagnosis later than 6 years of age was reported in one-third to half of children. Later age at diagnosis was associated with reported mild presentation.¹⁶

CDC surveillance data published in 2014 revealed that white, non-Hispanic children were approximately 20% more likely to be identified with ASD before the case review than were non-Hispanic African American children and were about 50% more likely to be identified with ASD than were Hispanic children.¹⁴ Recent prevalence data reveal increasing rates of ASD in Hispanic and African American children. This may reflect more widespread awareness of the symptoms among parents, schools, and health care providers and improved rates of screening in health supervision care.² Studies examining the effects of race and ethnicity on age at diagnosis are conflicting,⁷ but earlier diagnosis of ASD is associated with higher socioeconomic status and access to services. African American and Hispanic children diagnosed with ASD by age 4 years were more likely to have coexisting intellectual disability than were white, non-Hispanic children, suggesting that some African American and Hispanic children with ASD and average to above-average intelligence may not have been identified.¹⁷

SECTION 2: CLINICAL SYMPTOMS

Despite advances in understanding the neurobiology and genetics of ASD, the diagnosis of ASD continues to be based on identifying and reporting behaviorally defined clinical symptoms. The challenges in determining accurate prevalence rates, in part, relate to the need for consistency in clinical diagnosis of a very heterogeneous disorder. In 2013, the DSM-5 consolidated the diagnosis of ASD into a single category and emphasized the importance of identifying coexisting

developmental and behavioral disorders and symptoms. In the years since the 2007 AAP clinical reports on ASD, both professional education and public awareness have promoted recognition of symptoms that might lead to early identification of ASD, use of standardized screening approaches, and management of associated medical and behavioral features of ASD from infancy through adolescence.

Core Symptoms

Although symptoms of ASD are neurologically based, they manifest as behavioral characteristics that present differently depending on age, language level, and cognitive abilities. Core symptoms cluster in 2 domains (social communication/interaction and restricted, repetitive patterns of behavior), as described in the DSM-5.¹ Atypical development in several functional areas contribute to symptoms of ASD. Abnormalities in understanding the intent of others, diminished interactive eye contact, and atypical use and understanding of gesture presage atypical development of social communication and pretend play as well as interest in other children. Symptoms of ASD are further shaped by deficits in imitation and of processing information across sensory modalities, such as vision (gesture) and hearing (language). Repetitive behaviors and perseveration may be primary compulsions but may also be related to atypical processing of sensory information or may reflect a desire to instill predictability when an individual does not understand the intent of others. The CDC "Learn the Signs. Act Early" Web site provides free resources to help families recognize developmental concerns, including autism (<https://www.cdc.gov/ncbddd/actearly/>), and Autism Navigator (www.autismnavigator.com) has a video glossary of early symptoms in toddlers.

Approximately one-quarter of children with ASD will be reported to have a regression in language or social skills, most typically between 18 and 24 months of age.^{18,19} The reason for this loss of previously acquired milestones is not yet known. Although medical evaluation of loss of milestones is indicated, a history of regression in language and social interaction in children with ASD within the expected age range is not likely to be attributable to seizures or neurodegenerative disorders. Note that the processes underlying regression are not yet well understood. Current theories include synaptic “over pruning” in response to genetic factors.²⁰

Diagnostic Criteria: DSM-5

The DSM has been central in establishing criteria for diagnosing mental and behavioral disorders. The diagnosis of infantile autism was introduced in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* nearly 30 years after the first edition of the DSM was published in 1952. The initial descriptions were narrow and referred to individuals with profound impairment. Publication of the DSM-IV in 1994 expanded the diagnosis to a spectrum of symptoms called pervasive developmental disorders (PDDs), which included the diagnoses of autistic disorder, Asperger disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), childhood disintegrative disorder, and Rett disorder. The PDDs included individuals with lower- and higher-functioning cognitive skills. PDD-NOS was a diagnostic category requiring some, but not all, of the core symptoms necessary for other diagnoses in this category. Subsequent research has demonstrated that the subgroupings within PDD were not reproducible across research sites by using the same diagnostic data^{21,22} and were not stable over time. The overlap between DSM-IV–defined subgroupings

paired with inconsistency in their application across research sites supports the decision to consolidate the subgroupings into 1 diagnostic category, ASD, in the DSM-5. The DSM-IV divided the symptoms of ASD into 3 areas: qualitative impairment of social reciprocity, qualitative impairment of communication, and restricted and repetitive behaviors. In the DSM-5, core symptoms were divided into 2 domains (social communication and social interaction and restrictive, repetitive patterns of behaviors).²³ To fulfill diagnostic criteria for ASD by using the DSM-5, all 3 symptoms of social affective difference need to be present in addition to 2 of 4 symptoms related to restrictive and repetitive behaviors. Examples in Table 1 are illustrative but not exhaustive. The recognition of symptoms of ASD related to sensory processing led to the inclusion of sensory symptoms, such as hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment. Examples include apparent indifference to pain or temperature; sensitivity to sound, taste, or textures; and intense visual interest in objects or movement. The DSM-5 notes that a diagnosis may be made at older ages, when the demands of the social or school environment may result in functional impairment.

Almost all individuals with a diagnosis of autistic disorder or Asperger syndrome by using DSM-IV criteria would be diagnosed with ASD by using DSM-5 criteria.²⁴ To determine if the same patients would be identified by the DSM-IV and DSM-5 criteria, the CDC ADDM Network looked at its chart abstraction data on 8-year-old children.²⁵ This analysis revealed that more than 80% of children diagnosed with PDD-NOS would also be diagnosed with ASD.²⁵ It is possible that the narrative in the charts that were abstracted was influenced by knowledge of the DSM-IV criteria.²⁶ There is a high level of

agreement of surveillance data by using DSM-IV-TR and DSM-5 criteria.

The DSM-5 criteria have been shown to appropriately identify younger children and those with mild symptoms.^{25,27} These children with milder cognitive and adaptive symptoms may be the ones most likely to have significant change with early intervention services.

The DSM-5 also introduced an approach to severity rating, which is summarized in Table 2. Severity rating reflects the impairment of the ASD symptoms and the resultant service needs of the individual. Severity rating is not a quantifiable score that can be used to monitor progress at this time; in clinical use, it often reflects the impact of cognitive limitations.²⁸ Measures have been published that attempt to capture severity of core symptoms^{29,30} and allow for measurement of improvement with intervention.³¹ To date, no single measure adequately reflects the combination of medical, behavioral, and educational severity in a fashion that will help clinicians and families determine progress with intervention across multiple functional domains. Coexisting medical disorders also affect the perception of severity and the prognosis for children with a diagnosis of ASD. The DSM-5 includes course specifiers that help describe the variation in symptoms of individuals with ASD. Course specifiers include the presence or absence of intellectual impairment, language impairment, catatonia, medical conditions, and known genetic or environmental etiologic factors. Patients with Rett syndrome are no longer automatically considered to have a diagnosis of ASD according the DSM-5, although individuals with this neurogenetic disorder may also meet diagnostic criteria for ASD. Specific genetic causes of ASD should be recorded as specifiers for individuals with ASD when identified. The DSM-5 promotes

TABLE 1 DSM-5 Criteria for Autism Spectrum Disorder

Domains	Criteria: Deficits	Examples
A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history; must have all 3 symptoms in this domain	1. Social-emotional reciprocity	Abnormal social approach and failure of normal back-and-forth conversation; reduced sharing of interests, emotions, or affect; failure to initiate or respond to social interactions
	2. Nonverbal communicative behaviors used for social interaction	Poorly integrated verbal and nonverbal communication; abnormalities in eye contact and body language or deficits in understanding and use of gestures; total lack of facial expressions and nonverbal communication
	3. Developing, maintaining, and understanding relationships	Difficulties adjusting behavior to suit various social contexts; difficulties in sharing imaginative play or in making friends; absence of interest in peers
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least 2 of the following, currently or by history; must have 2 of the 4 symptoms	1. Stereotyped or repetitive motor movements, use of objects, or speech	Simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases
	2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior	Extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day
	3. Highly restricted, fixated interests that are abnormal in intensity or focus	Strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest
	4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment	Apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement

Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life). Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and ASD frequently co-occur; to make comorbid diagnoses of ASD and intellectual disability, social communication should be below that expected for the general developmental level. Specify whether: with or without accompanying intellectual impairment, language impairment or associated with a known medical or genetic condition or environmental factor. Add code 293.89 if catatonia is also present. Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (copyright 2013). American Psychiatric Association. All Rights Reserved.

notation of all coexisting diagnoses as specifiers.

Social pragmatic communication disorder is a new diagnosis described within the DSM-5 that describes individuals who exhibit functionally impairing symptoms in social language use but do not have habitual or repetitive behaviors.¹ Individuals who are affected must have deficits in using language for social purposes, impaired ability to match their communication style with the context for communication, difficulty following the conventional rules for conversation, and difficulty with idioms and unstated meanings in language (Table 3). As with ASD, the symptoms cannot be better explained by another DSM-5 diagnosis. Research and experience with DSM-5 diagnoses over time will give clinicians a better sense of how ASD

and social communication disorder are similar and different in terms of etiology, prognosis, and treatment. Evaluation of pragmatic (social) language use by a speech-language pathologist provides additional information to consider this diagnosis.³² The characteristics of social pragmatic communication disorder and how best to address symptoms require additional study.

Although the DSM-5 provides the criteria and definitions to accurately assign mental health and behavioral diagnoses, the *International Classification of Diseases, 10th Revision, Clinical Modification* is the standardized code set used for payment as well as for statistical tracking through electronic medical records. The *International Classification of Diseases, 10th Revision, Clinical Modification*

continues to include the subtypes of diagnoses as defined by the DSM-IV.³³ The DSM-5 provides the clinician with criteria and definitions for diagnosis of ASD and should guide the clinician in the diagnosis and management of ASD.

Co-occurring Symptoms and Conditions

Co-occurring conditions are common in children with ASD and may have great effects on child and family functioning and clinical management (see also Section 5: Interventions). Examples include medical conditions such as sleep disorders and seizures; other developmental or behavioral diagnoses, such as attention-deficit/hyperactivity disorder (ADHD), anxiety, and mood disorders; and behavioral disorders, such as food refusal, self-injury, and aggression.³⁴ Approximately 30% of children with

TABLE 2 ASD Symptoms by Level of Severity

Severity Level	Social Affective	Restricted and Repetitive Behaviors
Level 1. "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful response to social overtures of others. May appear to have decreased interest in social interactions.	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.
Level 2. "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills. Social impairments apparent even with supports in place. Limited initiation of social interactions and reduced or abnormal responses to social overtures from others.	Inflexibility of behavior; difficulty coping with change, or other restricted and repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 3. "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others.	Inflexibility of behavior, extreme difficulty coping with change, or other restricted and repetitive behaviors markedly interfere with functioning in all spheres. Great distress at or difficulty with changing focus or action.

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a diagnosis of ASD will also have intellectual disability,² and 30% are minimally verbal.³⁵ Increasingly, researchers and clinicians recognize how co-occurring disorders help identify phenotypic differences within populations affected by ASD, which can influence prognosis and choice of interventions.

Prognosis

The prognosis and trajectory of development for a young child diagnosed with ASD typically cannot be predicted at the time of diagnosis. However, most children ($\geq 80\%$) who are diagnosed with ASD after a comprehensive evaluation at less than 3 years have retained their diagnosis.^{36,37} It may be more difficult to recognize mild symptoms of ASD in children younger than

3 years of age, especially if they have average or above-average cognitive abilities.³⁸ Across early childhood development, communication skills and social affective symptoms may improve, whereas repetitive behaviors may change, possibly reflecting maturation and/or intervention.³⁹ In general, young children with ASD with language impairment appear to have more social difficulty than do children with ASD without language impairment. Children with ASD and intellectual disability have the most difficulty developing social competence.⁴⁰ The prognosis for children with ASD in phenotypic and demographic subgroups (eg, girls, racial and ethnic subgroups, children with macrocephaly) needs additional study.

Approximately 9% of children who are diagnosed with ASD in early childhood may not meet diagnostic criteria for ASD by young adulthood. Youth who no longer meet criteria for ASD are more likely to have a history of higher cognitive skills at 2 years of age, to have participated in earlier intervention services, and to have demonstrated a decrease in their repetitive behaviors over time.⁴¹ A change in clinical diagnosis (eg, to ADHD or obsessive-compulsive disorder [OCD]) is more likely in children who were diagnosed with ASD before 30 months of age or had a diagnosis of PDD-NOS per the DSM-IV.^{42,43} Severity scores are most likely to improve in youth who have had the greatest increase in tested verbal IQ.⁴⁴ Executive function difficulties

TABLE 3 DSM-5 Social (Pragmatic) Communication Disorder (DSM-5 315.39)

- A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following:
 1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context.
 2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on the playground, talking differently to a child than to an adult, and avoiding use of overly formal language.
 3. Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction.
 4. Difficulties understanding what is not explicitly stated (eg, making inferences) and nonliteral or ambiguous meanings of language (eg, idioms, humor, metaphors, multiple meanings that depend on the context for interpretation).
- B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination.
- C. The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities).
- D. The symptoms are not attributable to another medical or neurologic condition or to low abilities in the domains of word structure and grammar and are not better explained by ASD, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder.

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are associated with poorer adaptive outcomes, independent of IQ.⁴⁵

Measured intelligence (eg, IQ) and language ability in childhood tend to predict outcome in adulthood.⁴⁶

However, reported quality of life in high-functioning adults with ASD was associated more with the presence of family and community supports than their symptoms related to ASD.⁴⁷

SECTION 3: SCREENING AND DIAGNOSIS

The AAP recommends screening all children for symptoms of ASD through a combination of developmental surveillance at all visits and standardized autism-specific screening tests at 18 and 24 months of age in their primary care visits⁵ because children with ASD can be identified as toddlers, and early intervention can and does influence outcomes.⁴⁸ This autism-specific screening complements the recommended general developmental screening at 9, 18, and 30 months of age.⁹ Efficient screening of all children would be aided by inclusion of valid screening tools in the electronic health record with appropriate compensation for the staff and professional time necessary to complete the administration, scoring, and counseling related to screening.⁴⁹

Screening tools are designed to help caregivers identify and report symptoms observed in children at high risk for ASD. The screens are based on early manifestations of symptoms of core deficits related to social communication. Some of these early symptoms that may alert the provider to the risk for ASD have been called “red flags” (Table 4).

Developmental surveillance for ASD includes asking caregivers about concerns they have about their child’s development or behavior; informal observation, and monitoring of symptoms in the context of routine health supervision. The “Learn the Signs. Act Early” parent resources

TABLE 4 Red Flags: Early Symptoms of ASD

	Symptom
By 12 months	• Does not respond to name
By 14 months	• Does not point at objects to show interest
By 18 months	• Does not pretend play
General	<ul style="list-style-type: none"> • Avoids eye contact and may want to be alone • Has trouble understanding other people’s feelings or talking about their own feelings • Has delayed speech and language skills • Repeats words or phrases over and over (echolalia) • Gives unrelated answers to questions • Gets upset by minor changes • Has obsessive interests • Makes repetitive movements like flapping hands, rocking, or spinning in circles • Has unusual reactions to the way things sound, smell, taste, look, or feel

Information from this table is adapted from <http://www.cdc.gov/ncbddd/autism/signs.html>.

developed by the CDC may help educate families about developmental and behavioral milestones (<https://www.cdc.gov/ncbddd/actearly/index.html>). Developmental surveillance alone is not sufficient to identify children who need further evaluation because children with ASD may not demonstrate characteristic symptoms in brief office visits,⁵⁰ and caregivers may not volunteer social and emotional concerns unless specifically asked. Use of a standardized screening tool for ASD can help families identify potential symptoms. In a large study evaluating universal screening with the Modified Checklist for Autism in Toddlers (M-CHAT), researchers asked physicians to note whether they were concerned about ASD. Sensitivity of physician clinical concern was low (0.244; 30 of 123 cases; 95% confidence interval 0.17–0.32). The sensitivity of the M-CHAT when used as directed in this low-risk population was 0.91.⁵¹ Accurate early identification has been a goal of the AAP since the publication of the 2 previous autism clinical reports in 2007, with focused continuing medical education and a tool kit (AAP Autism Toolkit: <https://toolkits.solutions.aap.org/toolkits.aspx>). The goal of universal screening, including screening for ASD, has been supported by public health agencies⁵² and family support organizations.⁵³ Rates of screening for both developmental delays and ASD in

primary pediatric care have increased steadily. In the 2015 AAP survey of screening practices, almost three-quarters of pediatricians who responded reported routine ASD screening.⁵⁴ Pediatricians increasingly report including office staff for efficient workflow, including administration and scoring of screening tests. Although time and remuneration remain as concerns, fewer pediatricians rate these as barriers. Referral for and tracking of evaluation and services remain a challenge associated with lack of office-based systems for making referrals and after screen-positive outcomes.⁴³

The authors of the 2019 AAP developmental surveillance and screening clinical report discuss strategies for billing for screening and counseling in primary care.⁴⁹ The following sections describe tools commonly used to screen and diagnose ASD and emphasize the importance of ongoing surveillance, especially in children at high risk.

Screening

Results of a screening test are not diagnostic; they help the primary care provider identify children who are at risk for a diagnosis of ASD and require additional evaluation. General developmental screening tools used for screening at ages 9, 18, and 30 months identify language,

cognitive, and motor delays but may not be sensitive to social symptoms associated with identification of ASD.^{43,55} This limitation associated with general developmental screening is why ASD-specific tools⁵⁶ are needed to capture differences in social interaction, play, and repetitive behaviors. See the AAP clinical report “Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening,”⁴⁹ Table 1 (developmental screening tests; a description of general developmental and behavioral screening tests), and Table 5 in this report for resources and guidance on developmental screening.

Parent-completed questionnaires are the most common screening tests used in primary care. Commonly used autism-specific screening tools that are based on questionnaires and observation are summarized in Table 6. Many clinician-administered screening tests require specific training (eg, the Screening Tool for Autism in Toddlers and Young Children [STAT]).^{5,57} A clinician-administered test like the STAT increases the likelihood of an ASD diagnosis on further testing and may be used to support a preliminary diagnosis of ASD to obtain services.⁵⁸ Identification of infants and toddlers at risk for ASD based on neurophysiologic makers or other biomarkers is discussed in the subsection The Biology of ASD in Section 4: Etiologic Evaluation.

Screening by Age Group

Children Younger Than Age 18 Months

Earlier diagnosis of ASD may lead to earlier treatment. The M-CHAT is the most studied and widely used tool for screening toddlers for ASD. Additional tools are under investigation and are listed in Table 6 as promising autism screening tests. Language delay can be identified by using the Infant and Toddler Checklist (parent questionnaire) in low-risk infants and toddlers between 12 and 18 months of age.^{43,59} This questionnaire might be useful in identifying infant siblings of children with ASD who are at increased risk for ASD. Additional research may allow for screening of toddlers as young as 12 months by using parent-administered questionnaires such the Communication and Symbolic Behavior Scales Development Profile and the Infant and Toddler Checklist.⁵⁸

Primary care providers are tasked with identifying all children who would benefit from early intervention, not just children at risk for ASD (see the AAP clinical report “Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening”⁴⁹ for further information). It is important to identify all clinically significant delays in children with referral for appropriate diagnostic evaluation and intervention. Problems with sleep, eating, constipation, and state regulation are common in the general population but may be particularly challenging in young children with

ASD. Pediatricians can help families with management of these symptoms.

Children Ages 18 to 30 Months

The most commonly used questionnaire-based screening tool is the M-CHAT. It has been further validated, and the scoring has been modified for ease of administration in primary care settings for children ages 16 to 30 months.⁵¹ The Modified Checklist for Autism in Toddlers, Revised with Follow-Up (Questions) (M-CHAT-R/F) eliminates 3 questions from the previous version. Children who score ≥ 8 are at high risk for ASD or another developmental disorder and should be referred immediately for diagnostic assessment. For children with scores of 3 to 7, publicly available scripted follow-up interview questions are required for the items scored as positive. Children who continue to have 3 to 7 items positive for ASD diagnosis after clarifying follow-up questions have a 47% risk of having ASD diagnosed and a 95% chance of being identified with some other developmental delay that would benefit from intervention. Children screened with the M-CHAT-R/F are identified with ASD at younger ages than predicted by national statistics.⁴⁹ Children who do not pass ASD screening tests or who score as at risk for a diagnosis should be referred for both diagnostic assessment and intervention services. A definitive diagnosis is not necessary to institute services for documented delays that would be served through early intervention or school services. Although the M-CHAT-R/F appears to be useful for general screening of diverse populations,⁶⁰ decreasing the disparity in early diagnosis will require adapting and validating measures and addressing cultural and linguistic barriers to screening.⁶¹

Measures under development may provide rapid screening while addressing clinician concerns for compatibility with an electronic record system and open access.⁶²

TABLE 5 Resources and Guidance for Developmental Screening

- AAP *Bright Futures: Guidelines for the Health Supervision of Infants, Children, and Adolescents*
- AAP early childhood screening
- AAP clinical report: “Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening”⁴⁹
- Additional guidance for developmental and behavioral screening can be found in “Birth to 5: Watch Me Thrive!” which contains helpful information for the primary care provider about how to present the results of developmental screening (available at: https://www.acf.hhs.gov/sites/default/files/ecd/pcp_screening_guide_march2014.pdf).

TABLE 6 Commonly Used ASD Screening Tests

Autism Screening Tests	Description	Age Range	Average No. Items	Administration Time	Forms Available EHR compatible	Psychometric Properties	Scoring Method	Cultural Considerations	Source	Key References
M-CHAT-R/F	Parent-completed questionnaire designed to identify children at risk for autism from the general population; follow-up clinician-administered questions and repeat questionnaire required for specificity	16–30 mo	20	5–10 min	Yes	Standardization sample included 16 071 children screened; 115 had positive screen results, 348 needed evaluation, 221 were evaluated, and 105 diagnosed with an ASD, validated by using the ADI-R, ADOS-G, CARS, and DSM-IV-TR; sensitivity: 0.91; specificity: 0.95 for low-risk 18- and 24-mo-old children with follow-up questionnaire and interview; 45% of children with a score ≥ 3 on the initial screen and ≥ 2 on follow-up had ASD; 95% had clinically significant developmental delay	Risk categorization for questionnaire (pass/need interview/ fail); after interview (pass/fail)	Available in multiple languages; see test information for details	http://mchat.screen.com/	Ref 51
SCQ	Parent-completed questionnaire; designed to identify children at risk for ASD from the general population; based on items in the ADI-R	4+ y	40	5–10 min	No	Validated by using the ADI-R and DSM-IV on 200 subjects (160 with pervasive developmental disorder; 40 without pervasive developmental disorder); for use in children with mental age of at	Risk categorization (pass/fail)	Available in multiple languages; see test information for details.	Western Psychological Corporation: www.wpspublish.com	Refs 77 and 572

TABLE 6 Continued

Autism Screening Tests	Description	Age Range	Average No. Items	Administration Time	Forms Available EHR compatible	Psychometric Properties	Scoring Method	Cultural Considerations	Source	Key References
STAT	Clinician-directed, interactive, and observation measure; requires training of clinician for standardized administration; not for population screening	24–35 mo; <24 mo (exploratory)	12	20–30 min	No	Validated by comparison with ADOS-G results in 52 children 24–35 mo (26 with autism, 26 with developmental delay); sensitivity: 0.83, specificity: 0.86, PPV: 0.77, NPV: 0.90, for <24 mo: sensitivity: 0.95, specificity: 0.73, PPV: 0.56, NPV: 0.97; screening properties improved for children >14 mo	12 activities to observe early social-communicative behavior; risk categorization (high risk/low risk)	English	http://stat.vueinnovations.com/	Refs 573 and 574
Promising autism screening tests The Infant/Toddler Checklist (Communication and Symbolic Behavior Scales	Parent questionnaire: screens for language delay	6–24 mo	24	15 min	No	PPV DD: 0.43 (6–8 mo); PPV DD: 0.79 (21–24 mo)	Identifies language delays (alone/with ASD); risk for ASD; risk status for social, children >14 mo	Available in multiple languages; see test	Paul H. Brookes Publishing Co Inc: 800-638-3775 or www.brookespublishing.com	Ref 59

TABLE 6 Continued

Autism Screening Tests	Description	Age Range	Average No. Items	Administration Time	Forms Available EHR compatible	Psychometric Properties	Scoring Method	Cultural Considerations	Source	Key References
Developmental Profile)							speech, symbolic composites, and total score	information for details	brookespublishing.com	
Early Screening for Autism and Communication Disorders	Parent questionnaire; research edition, 47 items	12–36 mo	47	10–15 min	No	Sensitivity: 0.85–0.91; specificity: 0.82–0.84; PPV: 0.55–0.81; NPV: 0.88–0.98	Investigation ongoing of subset (24 items)	English	https://firstwordproject.com/screen-my-child/	Not in peer-reviewed literature
First-Year Inventory	Parent questionnaire; promising in high-risk population to identify risk in 12-mo-old infants	12 mo	63	10 min	No	Sensitivity, specificity, PPV not reported	Scores at risk; promising in high-risk (infant sibling) cohort (Rowberry et al ⁵⁷⁵)	English	https://www.med.unc.edu/ahs/pearls/research/first-year-inventory-fyi-development/	Ref 575
Parent's Observations of Social Interactions	Parent questionnaire used to assess autism risk; ASD screening included on 18-, 24-, and 30-mo The Survey of Well-Being of Young Children: forms	16–35 mo	7	~5 min	Available through patient tools, epic, and CHADIS; available for free download as pdfs from www.theswyc.org	Sensitivity: 83%–93%, average 88.5%; specificity: 42%–75%, average 56.9%	3 of 7 symptoms in at-risk range	Available in multiple languages; see test information for details	Free download from www.theswyc.org	Publications and Users' Manual available at www.theswyc.org; Refs 576 and 577
Rapid Interactive Screening Test for Autism in Toddlers 13	Clinician observation; administered by trained examiner	12–36 mo	9 interactive items	20–30 min	No	Cutoff > 15; sensitivity: 1; specificity: 0.84; PPV: 0.88; NPV: 0.94; needs further study in larger samples	9 interactive activities; total score summed, cutoff score of 15 (for that sample)	English	https://umassmed.edu/AutismRITA-T/about-the-test/	Ref 578

The AAP does not approve/endorse any specific tool for screening purposes. This table is not exhaustive, and other tests may be available. ADOS-G, Autism Diagnostic Observation Schedule – Generic; CARS, Childhood Autism Rating Scale; CHADIS, Comprehensive Health and Decision Information System; EHR, electronic health record; ICD-10, *International Classification of Diseases, 10th revision*; IMFAR, International Meeting for Autism Research; NPV, negative predictive value; PPV, positive predictive value.

Further adaptations of the Communication Symbolic Behavior Scale for use in screening for language delays in addition to ASD have the potential to identify children at risk for both disorders (functional communication; ages 6–24 months).^{49,59} Use of this or other screening tools may be coupled with the online support of a video glossary of symptoms of ASD, such as that in the Autism Navigator (<http://www.autismnavigator.com/>). These and other online approaches to support screening strategies may be integrated into efficient patterns of practice. Results of screening conducted online, in community settings, and in preschools should be communicated to the primary care provider to ensure appropriate evaluation of etiology, co-occurring conditions, referral for diagnosis, and follow-up to ensure that intervention is accessed.⁴⁹

A systematic review by the US Preventive Services Task Force (USPSTF) concluded that the literature on existing screening tools did not demonstrate sufficient specificity to justify universal screening.⁶³ The USPSTF noted that no study has directly examined whether children with ASD detected by early screening have better outcomes than those detected by other means. However, such a study would require random assignment of large representative samples from across the country to either a screening or nonscreening condition, with follow-up of long-term outcomes and societal costs. Given that early treatment of children younger than 36 months has been shown to result in positive outcomes,^{43,64} such a study would be challenging to support. The USPSTF concluded that further research is indicated to evaluate the appropriate ages and populations of children who should be screened for ASD and that more accurate and culturally sensitive measures should be developed. The

AAP continues to recommend screening using the most valid of current measures at 18 and 24 months of age. Pediatricians cannot assume that early intervention systems will screen participants being served for language or global delays for ASD at the recommended ages. Universal screening is recommended because symptoms of ASD can be identified in early childhood, and a diagnosis of ASD by skilled professionals is accurate in children as young as 18 months of age.⁶⁵ Diagnostic stability is high for children who are diagnosed with ASD at 18 to 36 months of age.⁴³ Early screening does not identify many children with milder symptoms and typical cognitive ability as at risk for ASD; therefore, ongoing surveillance remains necessary.¹⁶ Participation in early intervention in general is greatest among children who had screening and surveillance.⁶⁶

Children Older Than 30 Months

At present, for children older than 30 months, there are no validated screening tools available for use in pediatric practice, nor are there current recommendations by the AAP for universal screening for ASD in that age group. The Social Communication Questionnaire (SCQ) (see Table 6) has been studied in different populations (eg, clinical sample, population reference sample, community sample, and convenience sample), with best results in population samples⁶⁷ when using the lifetime version, and appears to have reasonable psychometric properties. However, questionnaires like the SCQ may identify symptoms that overlap with other conditions, such as ADHD, that affect function at school age.^{68,69} Further validation of population-based screening tools for children older than 30 months is needed before recommendations for universal screening of school-aged children can be made. At this time, ongoing surveillance in the context of primary care is recommended.

Barriers to Identifying Risk for ASD

Children with milder symptoms and/or average or above-average intelligence may not be identified with symptoms until school age, when differences in social language or personal rigidities affect function. Some children who are later diagnosed with ASD are initially believed to have precocious language, reading, or math skills, and it is not until the social demands of school that the social language symptoms become problematic. It has also been suggested that girls may have lesser intensity of symptoms and fewer externalizing behaviors. These differences may, in part, result in underdiagnosis in girls.⁷⁰ Specific coexisting conditions may prevent clinicians from recognizing symptoms of ASD in early childhood. For example, 1 study revealed that children who were initially identified with ADHD in primary care were diagnosed with ASD 3 years later compared with children who did not have earlier symptoms of ADHD.⁶⁹ Recognition and referral for older children with social-skill deficits would be facilitated by the development of accurate and brief screening tests for use in primary care and school settings.

Population surveillance data reveal later age at diagnosis for African American and Hispanic children, suggesting that there are barriers to screening and surveillance and referral for diagnosis in groups with other unmet health needs.² Race, ethnicity, and socioeconomic status did not affect the accuracy of routine screening tests for ASD in low-risk toddlers, suggesting that screening with appropriate supports for follow-up care can lower the age at diagnosis in diverse populations.⁶⁰ Language barriers, inaccurate translations, and low parental literacy may compromise use of parent-completed questionnaires.⁷¹ Limited understanding of cultural differences experienced by the patient's family

and lack of trust in the health care provider may further limit identification and reporting of symptoms of autism.⁷² Screening tools need to be developed for populations of individuals whose primary language is not English and who are also sensitive to cultural barriers that may limit reporting of symptoms of ASD.⁷³

Diagnostic Evaluation

Once a child is determined to be at risk for a diagnosis of ASD, either by screening or surveillance, a timely referral for clinical diagnostic evaluation and early intervention or school services, depending on his or her age, is indicated.⁷⁴ Children with developmental delay with or without an ASD diagnosis should be referred to early intervention or school services, in which cognitive and language testing may be completed. The primary care provider should discuss with the family the importance of both the assessment of developmental status and evaluation for an ASD diagnosis and assist the family in navigating through the process, including connecting them with community resources. Families with low income or language barriers may need additional attention to take the next steps.

Although most children will need to see a specialist, such as a developmental-behavioral or neurodevelopmental pediatrician, psychologist, neurologist, or psychiatrist, for a diagnostic evaluation, general pediatricians and child psychologists comfortable with application of the DSM-5 criteria can make an initial clinical diagnosis. Having a clinical diagnosis may facilitate initiation of services. At this time, there are no laboratory tests that can be used to make a diagnosis of ASD, so careful review of the child's behavioral history and direct observation of symptoms are necessary.^{75,76} To meet diagnostic criteria, the symptoms must impair

function. Formal assessment of language, cognitive, and adaptive abilities and sensory status is an important component of the diagnostic process.

Short clinical visits may not allow even a skilled clinician the opportunity to accurately recognize symptoms of ASD.⁵⁰ An accurate history needs to reflect a longitudinal experience with the individual and reflect the effects of symptoms on the patient's ability to function in family, peer, and school settings. This history is obtained by interview with the patient and caregivers, reports of behavior in other environments (such as school), and descriptions of behavior during formal testing. The history of symptoms of ASD can be supported by questionnaires such as the SCQ⁷⁷ or Social Responsiveness Scale (SRS).⁷⁸ None of these questionnaires is sufficient alone to make a diagnosis of ASD, but all provide a structured approach to elicit symptoms of ASD. Measures such as the Behavior Assessment System for Children,⁷⁹ Diagnostic Interview for Social and Communication Disorders (DISCO),^{80,81} and the Child Behavior Checklist⁸² are used to assess children and youth for other behavioral health conditions but may also identify behavioral profiles consistent with ASD.

In some clinical and research settings, the behaviors associated with ASD are reported through the Autism Diagnostic Inventory-Revised (ADI-R), a lengthy, semistructured parent interview.^{83,84} It supports a knowledgeable clinician in applying diagnostic criteria of ASD. The SCQ was designed to elicit similar information to the ADI-R in an abbreviated questionnaire format. The SRS is a 65-item questionnaire that may be used to measure autistic traits on a continuum as part of a more complete evaluation of ASD.^{78,85}

Elevated scores may be seen with greater severity of symptoms of ASD as well as with intellectual disability, communication difficulties, and behavioral challenges.

Structured observation of symptoms of ASD during clinical evaluation is helpful to inform the diagnostic application of the DSM-5 criteria. Validated observation tools used to provide structured data to confirm the diagnosis include the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and the Childhood Autism Rating Scale, Second Edition (CARS-2).⁸⁶ No single observation tool is appropriate for all clinical settings. The observation tool is meant to support application of the DSM-5 criteria informed by history and other data.

The ADOS-2 was developed to elicit atypical social language and behaviors. With the ADOS-2, modules are specific for use across the age span of toddlers to adults.^{87,88} The ADOS-2 requires intensive training to accurately administer and score and takes 30 to 45 minutes to administer. It is often a component of both research and clinical evaluations. The information obtained from the ADOS-2 is used by the clinician in conjunction with the history of peer interactions, social relationships, and functional impairment from symptoms to determine if the DSM-5 criteria are met. The CARS-2 is another structured approach a clinician might use to support a clinical diagnosis of ASD.⁸⁹ The clinician completes a 15-point scale that is based on history and observation. The ADOS-2, CARS-2, and SRS (Parent and Teacher) all rate children similarly in approximately half of identified cases.⁹⁰ The integration of historical information and objective observation by a clinician trained to diagnose autism and related conditions to inform the DSM-5 diagnostic criteria is the

critical element to diagnostic evaluation.

Evaluation of Co-occurring Developmental Conditions

Patients with ASD may have intellectual disabilities, learning disabilities, ADHD, anxiety disorders, or speech and language disorders, among others. These conditions may influence the presentation of the symptoms of ASD. These conditions may influence the presentation of symptoms of ASD and may influence the social and functional impairment of the individual in different ways at different ages. Valid assessment of cognitive and language ability is an important component of the diagnostic evaluation. In the United States, early intervention services and school systems will evaluate children in these domains to assess educational needs. In some areas, initial evaluations are performed in clinical settings and paid for by insurance.

Cognitive Testing

A range of standardized measures are used to determine developmental levels of younger children and IQ in children older than 3 years. The intelligence test selected by the psychologist will depend on the age and language level of the child. Administration of a valid cognitive test is important in ascribing symptoms to ASD as part of the initial diagnosis but also helps to establish co-occurring diagnoses with ASD, such as intellectual disability. There are valid tests that can be used in children who are nonverbal. Although the prevalence of a diagnosis of ASD is increased in children with an intellectual disability,⁹¹ other children diagnosed with intellectual disability may have some symptoms of ASD without meeting diagnostic criteria for the disorder.

Language Testing

Inherent in the core symptoms of ASD are differences in the use of verbal

and nonverbal communication for social interaction. Formal assessment of communication by a speech or language pathologist at the time of diagnosis should include the documentation of expressive and receptive language skills as well as the pragmatic or conversational use of language.⁹²

Adaptive Function Testing

A caregiver report and/or teacher report of adaptive functioning complements objective cognitive testing. Determining the extent that ASD affects daily function is necessary to establish eligibility for some publicly funded programs as well as to identify and monitor developmental goals for treatment. Adaptive behaviors are typically delayed in people who have intellectual disability with ASD but can be impaired in people with ASD and an average-range IQ.^{93,94} Commonly used adaptive measures include the Vineland Adaptive Behavior Scales and the Adaptive Behavior Assessment System.⁹⁵

Motor Assessment

Children with ASD are more likely to have mild delays in gross motor skills and coordination compared with children in the general population and may meet DSM-5 criteria for developmental coordination disorder in addition to ASD.⁹⁶ General screening tests or adaptive measures may suggest motor delays that would benefit from formal evaluation by an occupational or physical therapist. A relationship of early motor delays and subsequent language and adaptive development in children with ASD has been proposed.^{97,98}

Sensory Assessment: Hearing

Children with language delay or inattention to language should have an evaluation of their hearing as part of their initial evaluation.⁹⁹ Hearing loss may co-occur with ASD and needs to be considered in children with language delays, behavior

problems, or inattention. Appropriate amplification should be offered, if indicated. The clinical utility of auditory processing evaluations available in current practice remain an area of study.^{100,101}

Sensory Assessment: Vision

Visual function should be considered in the initial evaluation of children who are visually inattentive, have stereotypical behaviors (such as eye poking or close visual scrutiny), or do not make eye contact. Decreased visual acuity may affect interactive gaze and require accommodations in the educational setting.¹⁰² Children with visual impairment may also demonstrate stereotyped motor behaviors.

Sensory Assessment: Sensory Processing

The DSM-5 includes sensory symptoms in the diagnostic criteria for ASD. The DSM-5 does not include sensory processing disorder as a discrete diagnosis. Commonly used evaluation tools (such as the Short Sensory Profile and others) quantify parent perception of sensory differences relative to smell, taste, vision, hearing, and touch.^{103,104} In addition to capturing what is conventionally considered as a sensory disturbance, questionnaires that are used to assess sensory symptoms also capture motor hyperactivity and hypoactivity as sensory-seeking or sensory-avoiding behaviors. These latter symptoms may reflect co-occurring ADHD. Sensory symptoms may be more evident at younger ages and may define subtypes of the disorder.^{105,106}

SECTION 4: ETIOLOGIC EVALUATION

Children with a diagnosis of ASD should be assessed for potential etiology and common coexisting medical conditions. At the time of the 2007 AAP clinical reports on autism, karyotype and DNA testing for fragile X syndrome were the state-of-the-art

etiologic investigations. Soon thereafter, chromosomal microarray (CMA) was endorsed by the American College of Medical Genetics and Genomics and the American Academy of Child and Adolescent Psychiatry as the most appropriate initial test for etiologic evaluation of children with ASD.^{76,107–110} Despite rapid technological advances in neuroimaging and other areas, many of the recommendations for clinical evaluation published in 2007 are unchanged. This section summarizes recent advances in understanding the etiologies of ASD and how they translate into recommendations for clinical practice.

Medical Workup of the Child With ASD

Genetic Testing

Advances such as the development of CMA and next-generation sequencing technologies and the application of these technologies to well-characterized patient cohorts have led to progress in the understanding of the complex genetics of ASD and other neurodevelopmental disorders in the last decade. Identifying a genetic etiology provides clinicians with more information for families about prognosis and recurrence risk and may help to identify and treat or prevent co-occurring medical conditions, guide patients and families to condition-specific resources and supports, and avoid ordering unnecessary tests (Table 7).^{111–117} Most parents find this information to be useful.¹¹⁸ As research progresses, genetic testing may contribute to identifying effective interventions related to specific etiologies.

Etiologic investigation begins with a careful medical, developmental-behavioral, and family history and a thorough physical and neurologic examination.¹⁰⁹ The history should include potential prenatal exposure to teratogens (such as medications, alcohol, drugs) and other factors that increase risk for ASD.^{109,119} The

TABLE 7 Potential Benefits of Establishing a Genetic Etiologic Diagnosis

- Improving accuracy of counseling provided to patients and families:
 - o Prognosis or expected clinical course
 - o Recurrence risk for the family and the individual affected
- Providing condition-specific family support, such as:
 - o Improving psychosocial outcomes for patients and their families (eg, knowledge and sense of empowerment, parental quality of life)
- Preventing morbidity and treating medical conditions associated with the genotype, such as:
 - o Conditions or anomalies likely to be present at diagnosis
 - o Conditions that may develop later
- Refining treatment options, including:
 - o Avoiding therapeutic interventions that may be based on unfounded etiologic theories
 - o Avoiding ineffective or potentially harmful treatments
 - o Providing access to emerging etiology-specific treatments
- Facilitating acquisition of needed services and access to research treatment protocols
- Avoiding additional diagnostic tests, which may be unnecessary, expensive, and/or uncomfortable

Adapted from Sun F, Oristaglio J, Levy SE, et al. *Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2015; Amiet C, Couchon E, Carr K, Carayol J, Cohen D. Are there cultural differences in parental interest in early diagnosis and genetic risk assessment for autism spectrum disorder? *Front Pediatr*. 2014;2:32; Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. *Ann Neurol*. 2014;76(4):473–483; Iglesias A, Anyane-Yeboah K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med*. 2014;16(12):922–931; Linggen M, Albers L, Borchers M, et al. Obtaining a genetic diagnosis in a child with disability: impact on parental quality of life. *Clin Genet*. 2016;89(2):258–266; Riggs ER, Wain KE, Riethmaier D, et al. Chromosomal microarray impacts clinical management. *Clin Genet*. 2014;85(2):147–153; and ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2015;17(6):505–507.

physical examination should include assessment of growth relative to typical curves (including head circumference), dysmorphic features, organomegaly, skin manifestations of neurocutaneous disorders (eg, tuberous sclerosis and neurofibromatosis), and neurologic

abnormalities.¹⁰⁹ Genetic evaluation should be recommended and offered to all families as part of the etiologic workup. A stepwise general approach is provided in Table 8 as a practical guideline.^{110,120} The presence of dysmorphic features or intellectual disability is generally associated with

TABLE 8 Genetic Etiologic Investigations in Patients With ASD

Step	Genetic Etiologic Investigations
1	Consider referral for pediatric genetics evaluation
2	Comprehensive history (including 3-generation family history with emphasis on individuals with ASD and other developmental, behavioral and/or psychiatric, and neurologic diagnoses) Physical examination (including dysmorphology, growth parameters [including head circumference], and skin examination) <ul style="list-style-type: none"> • If syndrome diagnosis or metabolic disorder is suspected, go back to step 1 (genetics and/or metabolism referral) and/or order the appropriate targeted testing • Otherwise, proceed to step 3
3	Laboratory studies <ul style="list-style-type: none"> • Discuss and offer CMA analysis • Discuss and offer fragile X analysis; if family history is suggestive of sex-linked intellectual disabilities, refer to genetics for additional testing • If patient is a girl, consider evaluation for Rett syndrome, <i>MECP2</i> testing • If these studies do not reveal the etiology, proceed to step 4
4	Consider referral to genetics, workup might include WES

Adapted from 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; Srivastava S, Love-Nichols JA, Dies KA, et al; NDD Exome Scoping Review Work Group. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders [published online ahead of print June 11, 2019]. *Genet Med*. and Shevell M, Ashwal S, Donley D, et al; Quality Standards Subcommittee of the American Academy of Neurology; Practice Committee of the Child Neurology Society. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2003;60(3):367–380.

increased likelihood of finding a genetic abnormality.¹²¹ However, authors of some clinical studies have identified similar yield for genetic testing in children without these risk factors.^{122,123}

In some cases, individuals with clinical genetic syndromes, such as fragile X syndrome, tuberous sclerosis complex, and others (such as those described in Supplemental Table 13), also meet criteria for ASD.^{124,125}

When a specific syndrome or metabolic disorder is suspected, the clinician should proceed with the appropriate targeted testing or referral to a pediatric geneticist or neurologist. For example, a girl with significant developmental delays, deceleration in head growth velocity, and characteristic midline hand movements should prompt genetic testing for a mutation or deletion or duplication of *MECP2*, the gene implicated in Rett syndrome.^{109,126} Another specific example would be a boy with ASD with marked macrocephaly and pigmented macules on the penis, findings that would warrant sequencing and deletion or duplication analysis of the *PTEN* gene.¹²⁷ Descriptions of these and other clinical syndromes associated with ASD are provided in Supplemental Table 13.

CMA is recommended if the etiology for developmental disability is not known. CMA identifies copy number variants (CNVs) at this time, which are DNA duplications or deletions that alter the function of genes (Table 8, step 2). CMA reveals a definitively pathogenic CNV in 5.4% to 14% (median 9%) of individuals with ASD in clinical samples.^{121,128-135} When CNVs of uncertain significance are included, approximately 17% to 42% of patients with ASD have findings on the CMA. Some of the variants of uncertain significance may be determined as pathogenic in the future. The most commonly identified recurrent pathogenic CNVs among

individuals with ASD are provided in Supplemental Table 14.

Because fragile X syndrome increases risk for ASD, DNA testing for fragile X syndrome should be recommended for all children with ASD, but especially for boys and children with a suggestive family history of male members with intellectual disability. Physical examination might reveal the common features of a large head size, prominent jaw, large ears, ligamentous laxity, and, in male patients, large testes after puberty. The cytosine-guanine-guanine trinucleotide repeat expansion that is responsible for fragile X syndrome is not detected on CMA and must be ordered as a separate test. The current estimate is that approximately 0.45% of individuals with ASD have the full mutation for fragile X syndrome, and many of them are female.^{130,132,135-137} Because fragile X syndrome testing is relatively inexpensive and the condition has important genetic counseling implications, it is reasonable to consider testing both male and female patients with ASD, at least until more data become available to clarify the issue.

When the history and physical examination, CMA, and fragile X analysis do not identify an etiology, the next step at this time in the etiologic evaluation for ASD is whole-exome sequencing (WES). WES technology allows for the identification of single-nucleotide variants, including pathogenic loss-of-function mutations and missense mutations, which have been found to be associated with ASD.¹³⁸⁻¹⁴² Examples of ASD risk genes identified or confirmed in WES studies are provided in Supplemental Table 15. As with other tests, clinicians ordering this test should be familiar with both pretest counseling and interpretation of the results. A genetic counselor is helpful in explaining the reason for testing as well as the results. Large clinical WES studies

have consistently been used to identify a molecular diagnosis in 26% to 29% of individuals for whom neurodevelopmental disorders were the primary indication for testing.¹⁴³⁻¹⁴⁵ Authors of studies of clinical populations with ASD have reported diagnostic yields of 8% to 20%.^{121,144} The yield of WES is higher when both the parents and the child who is affected are evaluated¹⁴⁴ to allow for comparison of the child with parents who are unaffected.

Some geographic areas may have limited availability of pediatric subspecialists (eg, in genetics or metabolism) who can guide the genetic workup, so primary care providers may be in the position to consider and direct etiologic evaluation. The complexity of genetic testing is such that most primary care providers may want to consult with a specialist to plan testing and interpret results. The clinical etiologic evaluation should be tailored to the individual patient, taking into consideration information from the history and physical examination^{109,110} and the values and wishes of the family. The stepwise general approach summarized in Table 8 can be used to guide this process.

It is important for families to understand that genetic tests may explain the cause of their child's ASD or provide information about the statistical risk of ASD, but they are not diagnostic of ASD; the diagnosis of ASD is made on the basis of clinical symptoms. Unlike CMA and WES, commercially marketed tests may not have the potential to provide a molecular etiologic diagnosis. Genomic testing technology is evolving rapidly, as is our understanding of the genetic architecture of ASD, and these recommendations for testing will need to be updated as new studies are published.¹⁴⁶ For example, it is anticipated that CMA and WES will soon be combined because of

improvements in accurate identification of CNVs using sequence data and that sequencing of the exome will be replaced by sequencing of the entire genome as issues with interpretation and cost become more manageable.^{121,130,147-150}

Parents of a child with ASD should be counseled regarding recurrence risk in subsequent offspring, and the nature of the counseling depends greatly on whether a specific genetic cause of the child's ASD has been identified. When a specific genetic etiology has been determined, the family can be provided with information about the risk of recurrence in subsequent offspring. However, when genetic testing has not been completed or has not revealed the etiology of the child's ASD, recurrence risk counseling is based on group averages derived from the existing literature. For a couple with 1 child with ASD of unknown cause, the current best estimate of recurrence in a subsequent child is approximately 10% (range 4%–14%¹⁵¹⁻¹⁵³). If a couple already has ≥ 2 children with ASD of unknown etiology (idiopathic), the chance of a subsequent child having ASD may be as high as 32% to 36%.^{151,154} However, the risk is not limited to ASD. Siblings of children with ASD who do not have ASD themselves may have a 20% to 25% risk for language disorders and other neurodevelopmental and psychiatric disorders.^{152,155,156}

Neuroimaging

Specific clinical neuroimaging findings are not more prevalent in ASD compared with other neurodevelopmental disorders, nor do specific abnormalities correlate with clinical, etiologic, or pathophysiological aspects of ASD.^{120,157,158} Incidental findings are common in neuroimaging studies obtained in the workup of children diagnosed with ASD but rarely provide etiologic information or

require intervention.^{159,160} The need for clinical MRI should be directed by a history and physical examination. MRI may be indicated in the evaluation of atypical regression, microcephaly, macrocephaly, seizures, intracranial manifestations of genetic disorders, abnormal neurologic examination, or other clinical indications.^{76,109,161,162} Imaging technology used to examine brain structure and function provides valuable insight into the neurobiology of ASD in research settings and may lead to useful clinical applications in the future.

Metabolic Testing

The yield of routine metabolic testing for children with ASD is low and not recommended for regular use.¹⁶³⁻¹⁶⁷ However, large population-based studies are lacking, so accurate prevalence and diagnostic yield estimates are not available. Metabolic workup should be informed by history, family history, symptoms, and examination and might include measurement of fasting plasma amino acid levels, urine organic acid levels, and acylcarnitine metabolite levels and other testing for specific metabolic disorders. History of atypical regressions (later than 2 years of age, motor regression, or multiple regressions), family history of early childhood death or diagnosed metabolic disorders, and physical features, such as significant hypotonia or weakness, visual and hearing impairment, and dysmorphic features, would suggest consultation with a specialist to guide evaluation for metabolic or mitochondrial disorders.^{109,168} Children who present with motor delay should be evaluated with creatine kinase and thyroid-stimulating hormone testing, according to AAP recommendations.^{9,49} Although metabolic disorders are uncommon causes of ASD, the potential impact is high because treatment may be available and the inheritance pattern may be known.^{109,124} Examples of

metabolic conditions that may be associated with an ASD phenotype are provided in Supplemental Table 16. There is no evidence at this time for routine testing of hair, blood, or urine for environmental toxins or heavy metals outside of laboratory screening for lead exposure.¹⁶⁹

EEG

Children with ASD have an increased risk for seizures, and EEG abnormalities are common in the absence of clinical seizures (see Seizures section for more information).¹⁷⁰⁻¹⁷⁵ However, EEG is not recommended as a routine baseline evaluation in the absence of clinical concern about seizures, atypical regression, or other neurologic symptoms on history or examination that would suggest an EEG is indicated.^{161,170,172,176} Late or atypical loss of language, as might be observed in electrical status epilepticus of sleep with loss of language, should be evaluated with an overnight EEG.^{161,170,172,176} Primary care clinicians should discuss the increased risk and the signs and symptoms of seizures with the families of children diagnosed with ASD, maintain a high index of clinical suspicion for seizures, and consult with a pediatric neurologist when concerned about atypical regression or the possibility of seizures.^{170,172,176}

The Biology of ASD

Genetics and ASD

ASD is clinically and etiologically heterogeneous yet highly heritable. The rate of ASD in siblings is much higher than the rate in the general population. Twin studies demonstrate substantially higher concordance rates for symptoms of ASD in monozygotic twins than in dizygotic twins.¹⁷⁷ A meta-analysis involving 6413 twin pairs revealed a 98% concordance in monozygotic twins, a 53% to 67% concordance in dizygotic twins, and heritability estimates from 64% to 91%.^{177,178}

Siblings may also be at risk for symptoms related to ASD that do not meet the threshold for a diagnosis of ASD and have been described as the broader autism phenotype.^{141,179} These data provide strong evidence for a genetic contribution to ASD risk.¹⁸⁰⁻¹⁸⁴

Risk for ASD also is increased in the children of both older fathers and older mothers.¹⁸⁵⁻¹⁸⁷ The increased risk with parental age may be related to germline mutations in older fathers.^{143,188} Mechanisms mediating the effect of advancing maternal age on ASD risk are less clear.¹⁴³ Increased maternal and paternal age are independently associated with ASD risk, and a joint effect seems to occur as well.¹⁸⁵⁻¹⁸⁷

Important aspects of the genetics of ASD are still poorly understood, including the role of common variants, epistasis (gene-gene interactions), and environmental modification of genotype effects. In contrast, advances such as CMA and next-generation sequencing technologies have resulted in identification of large-effect (pathogenic) rare variants that appear to be causally associated with ASD, including CNVs, which are deletions or duplications ≥ 1000 bp in size that alter the dosage of genes, and sequence-nucleotide variants.¹⁸⁹⁻¹⁹² Pathogenic rare variants may arise de novo or be inherited as autosomal dominant, autosomal recessive, or X-linked mutations. Researchers of CMA and WES studies have established that although de novo and inherited rare variants of large effect size are collectively common, no individual pathogenic variant accounts for more than 1% of cases of ASD.* Genes that contribute to ASD are involved in a variety of biological functions, with convergence on aspects of brain development and function, including synaptic structure and function,

intracellular signaling, transcription regulation, and chromatin remodeling.^{139,190,191,196} It is important to note that no specific mutation has been identified that is unique to ASD; there is substantial genetic overlap between ASD and other neurodevelopmental disorders, including intellectual disability, epilepsy, and schizophrenia.¹⁹⁷⁻²⁰⁴

Genes, Environmental Exposures, and ASD

The potential environmental factors that may be related to increased reported prevalence of ASD is an area of active study that, as yet, is without firm conclusions.¹¹⁹ Environmental factors associated with ASD include in utero exposure to medications such as valproate and thalidomide. Other prenatal influences, such as short interpregnancy interval, multiple gestation, maternal obesity, gestational bleeding, gestational diabetes, advanced parental age, and infections (eg, rubella and cytomegalovirus), may be associated with increased risk for ASD.²⁰⁵⁻²⁰⁹ Perinatal factors, such as preterm birth, low birth weight, fetal growth restriction (ie, small for gestational age), intrapartum hypoxia, and neonatal encephalopathy, are associated with increased ASD risk.^{205,210-212} Environmental factors may present independent risk to prenatal brain development or may affect gene function in individuals with genetic predisposition.²¹³ Population-level associations with ASD have been examined for organophosphates and certain other pesticides, metals, volatile organic compounds, and air pollution, particularly particulate matter and nitrogen dioxide.²¹⁴⁻²¹⁶ Research on environmental exposures may be of great importance in identifying modifiable risk factors related to ASD and other developmental disorders. It is prudent to limit exposure of children and pregnant women to known neurotoxicants.

Genes, Immunologic Exposures, and ASD

It has been proposed that children with ASD-associated CNVs may be more susceptible to environmental insult in the form of maternal immune activation. Report of maternal infection or fever during pregnancy may be associated with increased severity of ASD-related symptoms in offspring who are affected.²¹⁷ The pathogenic role of circulating maternal antibodies directed to fetal brain tissue and the potential value of maternal antibody panels as biomarkers of ASD are currently being studied.²¹⁸⁻²²² Unless otherwise indicated (eg, history suggestive of autoimmune or immunologic disorder), no immune testing is recommended in the etiologic workup of a child with ASD.

Epigenetics

Epigenetic modifications, such as DNA methylation and posttranslational histone modification, produce heritable changes in gene expression that do not involve a change in the DNA sequence. Some genetic disorders associated with ASD (eg, Rett syndrome; CHARGE syndrome; 15q duplication; Angelman syndrome; and fragile X syndrome), involve genes that either encode epigenetic regulators or are sensitive to alterations in their epigenetic regulation.^{223,224} Because epigenetic modifications can be influenced by environmental factors, such as prenatal maternal exposures and postnatal experience, they represent 1 interface between genes and environment. However, epigenetic modifications are not the only mechanisms by which gene expression is regulated, and epigenetics should not be conflated with the broader category of environmental effects.^{223,225} Currently, the evidence that alteration of gene expression by environmental factors plays a causal role in ASD is very limited.²²³⁻²²⁸ Investigation of

* Refs 121, 144, 189-195.

the role of epigenetic and other nongenetic modifications that alter gene activity without changing the DNA sequence is an active area of etiologic research in ASD.

Vaccines

The scientific literature does not support an association of vaccination as an environmental factor that increases the risk for ASD. Children with ASD should be vaccinated according to the recommended schedule. Epidemiological studies do not demonstrate any association of the measles-mumps-rubella vaccine, mercury exposure by thimerosal-containing vaccines, aluminum in vaccines, or increased level of immunologic exposure attributable to a larger number of vaccines (either given at 1 time or cumulatively) with ASD.^{214,229–246} Vaccines used for children in the United States have not contained thimerosal since 2001. The authors of a 2012 Cochrane review²³⁴ and a 2014 quantitative meta-analysis of pooled data from cohort studies involving 1 256 407 children and case-control studies involving 9920 children reviewed the scientific literature and came to this conclusion.²³¹ Evidence implicating immunizations as a “second hit” conferring ASD risk in genetically susceptible subgroups is lacking. It has been shown that the measles-mumps-rubella vaccine is not associated with increased risk for ASD, even among children who are already at higher risk because of having an older sibling with ASD.²²⁹ Media coverage of vaccine issues may inflate the perception of uncertainty by equal coverage of vaccine proponents and opponents. The overwhelming weight of evidence supports vaccine safety.²⁴⁷ Communicating information about vaccine safety is a critical component of pediatric practice.²⁴⁸

Brain Structure and ASD: Neuropathology

Neuropathological research has been limited by the small number of postmortem brains available for study. Developmental brain abnormalities in people with ASD are reported in the cerebral neocortex; limbic system structures, including the hippocampal formation and amygdala; basal ganglia; thalamus; brainstem; and cerebellum. These brain abnormalities include dysplasia, altered neurogenesis, and abnormal neuronal migration.^{249–251} The vast majority of abnormalities described originate during prenatal brain development.^{249,251,252} Findings in the cerebral cortex may include focal disruption of neuronal migration, minicolumnar abnormalities, and variations in neuronal density.^{249,251,252} A decreased number of Purkinje cells in the cerebellum is 1 of the most consistently reported neuropathologic findings associated with ASD. Although it was initially thought to be of prenatal onset, evidence now indicates that this phenomenon is more likely to be an acquired process that occurs postnatally, potentially related to seizures, medications, and/or ischemia near the time of death or factors other than ASD.²⁴⁹ No uniform neuropathology has been identified in people with ASD.

Biomarkers

Objectively measured biological characteristics, or biomarkers, of ASD could potentially be used to predict ASD risk, enhance screening, and permit presymptomatic detection. Their use could improve the reliability and validity of clinical diagnosis (identifying clinically meaningful subgroups that would allow for prediction of prognosis or treatment response), identify mechanisms for developing treatment, and confirm the need for a specific intervention.^{221,253–255}

Early Brain Overgrowth

Cross-sectional and longitudinal studies suggest that as a group, children later diagnosed with ASD may have an average or below-average head circumference at birth, with an acceleration in brain growth before 2 years of age.²⁵⁶ This rapid brain growth leads to significantly above-average head circumferences and MRI brain volumes in toddlers, followed by a plateau in brain growth, with brain volumes in adolescence and adulthood similar to those of controls.^{257,258} Almost 16% of young children with ASD have a head circumference greater than the 97th percentile.²⁵⁸ A preliminary study suggested that infant siblings of children with ASD who exhibited a larger head circumference at 12 months and showed more slowing of head circumference growth from 12 to 24 months had an increased chance of demonstrating symptoms of ASD.^{259,260} Although this finding raises the possibility that patterns of brain growth might be used for early identification, the rate of head growth did not predict which infants developed ASD in the first 3 years of life in a large prospective study of high-risk infants.²⁶¹ It is possible that a large head size is unrelated to ASD and/or may be part of general somatic overgrowth.^{262–265}

Neuroimaging Patterns Associated With ASD in Research Studies

Although there are conflicting findings, structural MRI volumetric studies suggest that young children with ASD differ from controls in total brain volume, cortical gray and white matter volume (particularly frontal, temporal, and cingulate cortices), extraaxial cerebral spinal fluid volume, and amygdala volume.^{266–271} A research-level analysis also has identified asymmetries in multiple brain structures in people with ASD.²⁷² Diffusion tensor imaging has been used to identify altered patterns in white matter by 6 months of age in

infants later diagnosed with ASD.^{270,273} Functional MRI has demonstrated differences in people with ASD relative to controls in efficiency of visual processing, executive function, language, and basic and complex social processing skills.^{274,275} Functional MRI in research settings demonstrate differences in the mechanisms of attention to social stimuli, modulation in response to task demands or intensity of stimuli, and executive function in people with ASD.²⁷⁴ Functional underconnectivity has also been demonstrated across a wide variety of the brain regions that support language, executive function, social cognition, emotion processing, and motor tasks, especially for long-range, frontal-posterior networks.^{274,276,277}

Electrophysiologic Testing and Measurement of Eye Tracking

Electrophysiologic research studies demonstrate differences in auditory processing (including language processing), visual processing (including face processing), somatosensory response, multisensory integration, attentional shifting, selective attention, recognition memory, and neural connectivity in people with ASD.^{278–281} Continuous measures of resting-state and task-related quantitative EEG are used to calculate and describe spectral power, complexity, and coherence. Although promising, the clinical utility of these measures as biomarkers requires additional study.²⁷⁹ Eye tracking has been used to determine if infants who are younger siblings of children with ASD and, therefore, at increased risk for ASD exhibit differences in fixation on faces.^{282–284} Preliminary evidence suggests that infants later diagnosed with ASD exhibit a decline in gaze fixation from age 2 to age 6 months.²⁸⁵

Other Potential Biomarkers

Although some studies have attempted to differentiate people with and without ASD on the basis of differences in laboratory profiles of platelet serotonin, plasma melatonin, urine melatonin sulfate, redox status, placental trophoblast inclusions, and immune function, currently no diagnostic laboratory tests have been approved for ASD.^{286,287} To date, none of these potential biomarkers under study has sufficient evidence to be recommended.

Biomarkers: Future Directions

Proposed biomarkers for ASD risk include genetic and biochemical findings in blood, urine, or brain tissue; placental pathology; maternal autoantibody profiles; structural and functional MRI patterns; electrophysiological test results on EEG, including event-related potentials; responses in eye tracking; and physical parameters such as head circumference growth trajectory. Although none of these proposed biomarkers has demonstrated sufficient predictive validity for clinical use at this time,^{221,253–255,288} the search for biomarkers is a major research focus. Biomarker research has important ethical issues,²⁵³ and concerns have appropriately been raised regarding premature translation of research data into commercially available tests marketed to patients and families.^{221,253,289,290} However, the capabilities to screen large numbers of bioactive compounds, examine the entire genome, and simultaneously analyze large data sets have accelerated research into the neurobiology of ASD and may result in the identification of valid biomarkers.^{221,255,291}

SECTION 5: INTERVENTIONS

The goals of treatment of children with ASD are to (1) minimize core deficits (social communication and interaction and restricted or

repetitive behaviors and interests)¹ and co-occurring associated impairments^{292–294}; (2) maximize functional independence by facilitating learning and acquisition of adaptive skills; and (3) eliminate, minimize, or prevent problem behaviors that may interfere with functional skills.^{6,295,296} Treatments should be individualized, developmentally appropriate, and intensive, with performance data relevant to treatment goals to evaluate and adjust intervention.^{6,297} All interventions should be based on sound theoretical constructs, rigorous methodologies, and objective scientific evidence of effectiveness. Since the publication of the 2007 AAP clinical reports on autism, a substantial published literature has examined the effectiveness of interventions.^{48,295,297,298} Legal mandates in education law in the United States, which include the Individuals with Disabilities Education Improvement Act of 2004 (IDEA) (Public Law 108–446) and the No Child Left Behind Act of 2001 (Public Law 107–110) and its successor, the Every Student Succeeds Act of 2015 (Public Law 114–95), require the use of practices supported by scientifically based research (IDEA and the No Child Left Behind Act of 2001) or evidence-based practices (Every Student Succeeds Act of 2015) (<https://www.ed.gov/>). Early intervention services under part C of IDEA provide for assessment and intervention for children younger than 3 years with developmental delays, including ASD.

Interventions for children with ASD are provided through educational practices, developmental therapies, and behavioral interventions. Treatment strategies may vary by the age and strengths and weaknesses of the child. For example, intervention for a toddler with a recent diagnosis of ASD may include behavioral and developmental approaches (individually or in the context of

comprehensive approach) and, as he or she progresses, involvement in a specialized or typical preschool program. For older children, intervention is more likely to occur in educational settings, with integration of behavioral and developmental therapies to promote skill development. In addition to variation by age of the child, interventions differ in theoretical approach and scope (eg, focused and targeted or comprehensive), settings and/or modality of delivery (eg, individual versus group or classroom, delivered by a professional versus a trained parent, and school versus home setting), and targets of intervention.^{48,297} Interventions may be provided through public and/or not-for-profit agencies, schools, and early intervention services, and some may be paid for through insurance.²⁹⁹ Families should be involved in the selection of intervention approaches and remain an involved participant in subsequent educational and therapeutic decisions. There is regional variation in the availability of various types of therapy and providers that sometimes results in long waits for service, less-than-desired intensity, or inability to obtain a desired intervention altogether. By law, students with ASD should receive an appropriate educational program, although it may not include all of the components desired by the family. Advocacy is often necessary to obtain desired services through schools or through mechanisms paid for by insurance. It is noted that many of the interventions in common use do not have a strong evidence base. Some types of intervention may not be paid for by insurance.

Systematic reviews of the evidence base for treatment have been completed on early intensive intervention,^{44,300} medical treatments,³⁰¹ behavioral interventions,^{294,298} and evidence-based practice guidelines.^{292,302}

Wong et al²⁹⁵ described 2 categories of evidence-based interventions, the comprehensive treatment model (CTM) and focused interventions. These interventions may be provided in different settings (eg, the home, classroom, naturalistic environment, or community), by different providers (eg, developmental specialist, behavioral therapist, educator, or trained parent), individually or in group settings, and by using a set curriculum or guide.

The CTM uses a central conceptual framework to address a broad array of symptoms and is designed to address specific skill(s) or symptom(s). A CTM should be replicable, intense, and designed to address multiple therapeutic goals over a period of time. Provision of services may occur in individual instruction or class settings (specialized or inclusive), should include parents, and may involve technology-assisted intervention.³⁰³

Applied behavior analysis (ABA), developmental approaches, and/or naturalistic approaches may be used in CTMs.³⁰³ Examples of CTMs include early intensive behavioral intervention, Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH), and the Early Start Denver Model (ESDM).^{295,303}

Focused intervention practices are designed to address a single or limited range of skills, such as increasing social communication or learning a specific task, and may be delivered over a short period of time.^{295,297,303} Focused intervention practices may be behavioral, developmental, and/or educational. Focused interventions may be grounded in principles of ABA, in which specific skills are taught in a stepwise progression by using principles of reinforcement or developmental theory, in which the emerging skills inherent in neurobehavioral maturation are

promoted. These interventions are provided in a structured setting by an adult, in naturalistic environments with peers, or as a component of a more comprehensive approach.²⁹⁵ Focused interventions may be effective for promoting skill development and communication.^{295,297,304,305}

Pediatricians may be asked to advise families on therapy choices or write prescriptions for therapies.³⁰⁶ It is helpful for clinicians to have an understanding of intervention terminology and of the evidence base so they can effectively communicate the rationale for medically indicated treatment recommendations with families, educators, therapists, and other service providers as well as with insurance companies, health care administrators, funding agencies, and policy makers.²⁹⁵

This report describes various types of interventions provided for children and youth with ASD. Additional research is needed to evaluate the effectiveness of current approaches and develop interventions that address core deficits of ASD. At the time of diagnosis, parents of young preschool children may ask their provider to help them decide what type of intervention they should elect. Two common theoretical approaches to intervention for symptoms of ASD are ABA and developmental models.^{296–298,307} Although these approaches have important distinctions, they also have significant overlap, and interventions increasingly are incorporating aspects of both. There is considerable regional variation in the availability of various interventions. Table 9 describes common characteristics of empirically supported interventions.^{296,297,308,309}

Approaches to Intervention

ABA

Most evidence-based treatment models are based on principles of ABA. ABA has been defined as “the

TABLE 9 Characteristics of Effective Interventions

Features of Practice	Common Characteristics of Empirically Supported Interventions
Assessment and goals	Systematically assess skills Include input of family (shared decision-making) Select individualized measurable goals and instructional procedures on the basis of objective assessment of each child Use assessment-based, empirically supported instructional methods to build, generalize, and maintain skills and reduce problem behaviors
Instructional methods	Address core symptoms in social communication and restricted and repetitive behaviors as well as skill deficits Provide a student/teacher ratio low enough to address the child's individualized goals Interventions should be by providers who are properly trained and should maintain fidelity with the treatment approach selected Ensure that multiple providers work collaboratively
Services and supports	Individualize services and support Make use of the child's interests and preferences in determining reinforcement systems Incorporate preferred activities to increase engagement in activities
Environment	Provide a structured learning environment that helps children anticipate transition between activities, including a predictable routine and visual activity schedules Organize workspaces to minimize distraction and promote task completion Limit access to things that may distract a student The environment should promote opportunities for the student to initiate communication and interact with peers
Behavioral management	Implement a functional behavioral analysis to identify the reasons why challenging behaviors occur and develop a behavior improvement plan based on this assessment (IDEA-mandated approach) Teach children more appropriate responses using the behavior improvement plan
Progress	Systematically measure and document the individual child's progress Adjust instructional strategies as necessary to enable acquisition of target skills
Family support	Involve and educate families so they can use the behavioral strategies at home and in the community
Transition planning	Plan for transitions in school settings and to adulthood (eg, from home-based early intervention to preschool services, preschool to elementary school, elementary school to middle school, middle school to high school, high school to work or postsecondary education, and home to community living)

Adapted from Smith T, Iadarola S. Evidence base update for autism spectrum disorder. *J Clin Child Adolesc Psychol.* 2015;44(6):897–922; Myers SA, Pipinos II, Johanning JM, Stergiou N. Gait variability of patients with intermittent claudication is similar before and after the onset of claudication pain. *Clin Biomech (Bristol, Avon).* 2011;26(7):729–734; and Myers SM. Management of autism spectrum disorders in primary care. *Pediatr Ann.* 2009;38(1):42–49.

process of systematically applying interventions based upon the principles of learning theory to improve socially significant behaviors to a meaningful degree, and to demonstrate that the interventions employed are responsible for the improvement in behavior.³¹⁰ The use of ABA methods to treat symptoms of ASD suggests that behaviors exhibited can be altered by programmatically reinforcing skills related to communication and other skill acquisition.^{311,312} Thus, ABA treatments may target development of new skills (eg, social engagement) and/or minimize behaviors (eg, aggression) that may interfere with a child's progress.

ABA interventions vary from highly structured adult-directed approaches (eg, discrete trial training or instruction, verbal behavior applications, and others) to interventions in natural

environments that may be child led and implemented in the context of play activities or daily routines and activities and are altered on the basis of the child's skill development (eg, pivotal response training, reciprocal imitation training, and others).^{297,309,312,313} To determine what intervention is most appropriate, the behavioral clinician works with the family and child to determine which skills to target for development and maintenance and what goals are appropriate.

ABA programs are typically designed and supervised by professionals certified in behavior analysis. The majority of states at this time have licensure for board-certified behavior analysts with provisions for payment by insurance. ABA may be prescribed or recommended by a physician or licensed psychologist.

A comprehensive ABA approach for younger children, also known as early

intensive behavioral intervention, is supported by a few randomized controlled trials (RCTs) and a substantial single-subject literature.²⁹⁷ When only RCTs are considered, few interventions have sufficient evidence to be endorsed either for children younger than 12 years²⁹⁸ or for adolescents.³¹⁴

Children younger than 12 years receiving more hours per week of ABA were found to be more likely to achieve the individualized goals identified in their programs.³¹⁵ In retrospective studies, more intense ABA therapy was associated with achieving optimal developmental outcomes.³¹⁶ Given the heterogeneity of the ASD phenotype, the service needs of children, youth, and adults need to be individualized by using available clinical data.

In some instances, a behavioral intervention is needed to address acute serious problem behaviors that

must be given priority, for example, because of safety issues.²⁹⁵ Whether a student is getting formal ABA under IDEA or not, a family can request that challenging behaviors be evaluated in the school setting by using behavioral principles through a functional behavioral assessment. The target symptoms to treat may then be divided into component parts that are addressed in a stepwise fashion (task analysis).^{313,317} Once the reasons for the behavior are understood, a behavior improvement plan may be implemented.

Developmental Relationship-Focused Interventions

Intervention for young children also may be derived from developmental theory, which is focused on the relationship between the caregiver's level of responsiveness and the child's development of social communication.^{296,318-320} Through interaction with others, children learn to communicate and regulate emotions and establish a foundation for increasingly complex thinking and social interaction. Therefore, developmental models designed to promote social development in children with ASD are focused on the relationship between the child with ASD and his or her caregiver through coaching to help increase responsiveness to the adult (ie, the interventionist or parent or caregiver) through imitating, expanding on, or joining into child-initiated play activities. This approach may address core symptoms of ASD, such as joint attention, imitation, and affective social engagement.^{296,297,321,322}

Developmental models for intervention are focused on teaching adults to engage in nondirective interactive strategies to foster interaction and development of communication in the context of play. One such approach is known as DIRFloortime (The Developmental, Individual Differences, and

Relationship-Based model). In 1 RCT comparing parent coaching using this approach to community intervention alone ($N = 112$) in children ages 2 to 5 years, parents who were taught this approach were less directive, and their children were rated as more socially responsive, although IQ and language scores were no different between groups, and half of the children in the control group improved in their affective ratings.³²³ A similar approach is relationship development intervention,³²⁴ and more research is needed to evaluate efficacy and community use.

Naturalistic Developmental Behavioral Intervention

Naturalistic developmental behavioral interventions (NDBIs) incorporate elements of ABA and developmental principles, such as emphasis on developmentally based learning targets and foundational social learning skills, with delivery of interventions in the context of naturally occurring social activities within natural environments. They use child-initiated teaching episodes, naturally occurring opportunities for learning, and turn-taking interactions within play routines and implement ABA-based approaches to address measurable goals.²⁹⁶

The most extensively studied NDBI approach is the ESDM, which prepares children to learn in naturalistic environments.³²⁵ In a multisite trial of ESDM, early age at entry to therapy and more hours of total therapy were associated with improved outcome.³²⁶ Of note, the 48 children randomly assigned to ESDM or community treatment in the original trial were studied by using event-related potentials and spectral power on EEG while viewing faces as opposed to objects and were compared with typical controls on these tasks. This is an early demonstration of improvement on a neurophysiologic measure associated with improvement on

a clinical measure of social behavior through an early intervention program.³²⁷

Combined Approaches

Common factors in combined developmental and behavioral approaches include use of principles of ABA to reinforce skill building; a systematic approach with a manual for training practitioners who would use the intervention in a standard fashion; individualized treatment goals for the child and means of measuring progress; child-initiated teaching, imitation, and modeling; and adult prompting that fades over time to promote independence.²⁹⁶ It may be difficult to advise parents on specific programs in community settings because the way the program is conducted may differ from the research settings.³²⁸ However, it is always accurate to describe the common characteristics of empirically supported interventions and recommend that families seek interventions that incorporate these features (Table 9).

Parent-Mediated Treatment or Parent Management Training

Increasing evidence reveals that focused interventions delivered by trained parents or other caregivers can be an important part of a therapeutic program.^{297,329-332} More RCTs have been published on parent-mediated therapies than on other nonpharmacologic interventions. What is sometimes called parent management training is divided into 2 categories: parent support and parent-mediated interventions. Parent support interventions, which are knowledge-focused and provide indirect benefit to the child, include care coordination and psychoeducation. Parent-mediated interventions, which are technique-focused and provide direct benefit to the child, may target core symptoms of ASD or other behaviors or skills and may be built on ABA approaches in natural settings.³³¹

Training sessions for caregivers may be delivered in the home, clinic, school, or other community settings or remotely by telehealth.^{297,329–331,333–337} An RCT involving 86 toddlers and their primary caregivers demonstrated that 10 weeks of hands-on parent training in joint attention, symbolic play, engagement and regulation (an NDBI) was superior to a parent-only psychoeducational intervention for increasing joint engagement.³³⁸ A parent training approach may be used to promote compliance with instruction, social communication, and other identified goals of the caregiver, such as reducing maladaptive behaviors.^{331,339–342} Including parents in the intervention process is critically important.^{43,326,343}

Educational Interventions

Classroom-Based Models

It is the expectation that school-aged children will be educated in classroom settings with supports for a broad effect on the symptoms of ASD and associated deficits. Educating students with ASD in the least restrictive environment typically requires an individualized program that is modified to meet the Individualized Education Program (IEP) goals set by the family, student, and school team. Some students who do not qualify for an IEP by educational criteria may be supported with accommodations through a Section 504 plan or with classroom-level accommodations. Many students with ASD are educated in inclusive classrooms with supports. Other school-aged children and youth benefit from disorder-specific approaches. Examples of classroom-based models include Learning Experiences and Alternative Programs for Preschoolers and their Parents (LEAP) and TEACCH.³⁴⁴

LEAP blends principles of ABA with special and general education teaching techniques for elementary-

aged pupils in inclusive settings for teaching social interaction.^{344–346} An RCT of 294 preschool-aged children revealed that LEAP was associated with improvement in socialization, cognition, language, and challenging behavior and that LEAP was superior to a treatment-as-usual method.³⁴⁵

TEACCH class settings are visually organized to promote engagement and learning.³⁴⁴ The TEACCH approach to skill acquisition includes assessment-based curriculum development and an emphasis on structure, including predictable organization of activities and use of visual schedules, organization of the physical environment to optimize learning and avoid frustration (eg, by minimizing distractions and/or sensory dysregulation), and adaptation and organization of materials and tasks to promote independence from adult directions or prompts.^{344,347} Instruction is organized in a predictable fashion and uses visual schedules with promotion of independence in activities planned into the instruction.³⁴⁷ This approach is associated with a small, but measurable, benefit in perceptual, motor, verbal, and cognitive skills in students with ASD, with less measured effect on adaptive and motor function³⁴⁷ and challenging behaviors. Rigorous studies of educational interventions for students with ASD at school age and beyond are necessary to understand the effectiveness of different models.²⁹⁸

A comparison of the effects of LEAP and TEACCH classrooms with those of standard special education classes taught by teachers familiar with ASD revealed that the common features of these interventions may be responsible for improvements seen in all students. TEACCH was associated with more reported improvement in ASD severity for students who had greater cognitive delays. This finding may speak to the benefit of the

environmental and behavioral supports.³⁴⁴ Research interventions may not be comparable with community-provided school programs. Future research is needed to address how best to provide evidence-based intervention in classroom settings.

Education in the Least Restrictive Educational Environment

Pediatricians have an important role in advocating for children and youth with special health care needs, including ASD, in the educational setting. Students have a right to a free and appropriate public education. Educational programs for school-aged children with ASD should promote language, academic, adaptive, and social skills development and prepare them for postsecondary education or employment.³⁴⁸ Most, but not all, students with ASD will have some individualization of their education under the guidance of an IEP determined by the school multidisciplinary team in conjunction with the family. Others may receive accommodation and/or environmental modifications under Section 504 of the Rehabilitation Act of 1973.³⁴⁹ A medical diagnosis of ASD alone does not automatically translate into eligibility for school-based services. Functional impairment that affects participation in the typical curriculum is required to qualify for supports in the educational setting and may lead to an IEP for the educational handicap of autism. Most youth with ASD and average-range intelligence will likely require academic intervention because of coexisting learning disabilities, executive function challenges, ADHD, motor processing deficits, the effects of their pragmatic language differences on reading and writing, and/or challenges in comprehension of spoken or written language.³⁵⁰ Attention to the needs of the individual student must be central to the IEP process. Social skills of students with ASD may benefit

from students being in class and on the playground with peers with typical development.^{351,352} However, spending more than 75% of their time in an inclusive educational setting alone was not sufficient in transition-aged youth to increase rates of college attendance, high school graduation, or functional ratings.³⁵³ How to best support students with ASD in the least restricted environment requires further study.

Social Skills Instruction

Social skills deficits may present differently depending on language abilities, developmental level, and age. Examples of social skills deficits include the following:

- challenges with entering, sustaining, and exiting interactions;
- difficulty attending to, understanding, and using nonverbal and verbal social cues, such as eye contact, facial expressions, and gestures;
- difficulty in understanding “unwritten” social rules of the environment;
- not understanding the perspective of others;
- struggling with negotiation, compromise, and conflict resolution; and
- problems with interactive play or participation in leisure activities.

The importance of caregiver involvement in teaching social skills to preschool-aged children needs to be emphasized for families of young children with ASD. Reinforcing social interaction is central to the success of evidence-based ABA, developmental, and NDBI approaches.^{296,354} Teaching and coaching social interaction involves both behavioral therapy and speech and language therapy approaches.

School-aged children and adolescents with ASD, including those with typical academic skills, should have social

skills support considered in their school and perhaps in other therapeutic settings if indicated.^{351,354–356} Although families identify the need to address social skill developments in settings outside of school, the success of these types of interventions is variable. Interventions may be divided into adult-mediated (skill building with the individual child), peer-mediated (skill building with the child and typically developing classmates), and mixed approaches. Child-directed social skills interventions are often delivered individually or in small groups with other children with similar needs. Therapy may be provided in behavioral health settings to complement the social skills interventions at school.

Interventions addressing social skills may increase the child’s knowledge of the cues for social behavior and teach strategies for social problem-solving. A popular method uses the social narrative to help a child define the social context of an anticipated or experienced situation, put it in perspective, and then develop statements on how it makes the child feel and on what to do in response to the event and feelings.³⁵⁷ This coached rehearsal strategy may be included within other programmatic approaches. Implementation may use a cognitive behavioral intervention strategy in which the child identifies feelings and thoughts and learns to substitute more socially appropriate alternatives.³⁵⁴ Video- and computer-based social skill interventions may extend access to intervention once an evidence base is established. A systematic review of RCTs of social skills training for children aged 6 to 21 years revealed that interventions improved social competence and friendship quality but did not result in differences in emotional recognition and social communication. Transfer of skills to other settings was inconsistent.³⁵⁶

Because child-mediated interventions taught separately from social settings have not had consistently beneficial effects, interventions have been developed for implementation in the social settings that include peers, such as the classroom and playground. These interventions demonstrate improved playground interaction between children with and without ASD and improved identification as friends by typical peers.³⁵¹ Peer-mediated intervention for students with ASD have revealed improved social connectedness and reduced social isolation and provide evidence to support the use of these interventions in the classroom and playground. An evidence-based approach designed for group administration, the Program for the Education and Enrichment of Relational Skills, may improve both teacher-reported social functioning and adolescent-reported social cognition.³⁵⁸ Fewer studies are available to guide programs to promote social skills development for adults with ASD. However, the Program for the Education and Enrichment of Relational Skills group model has been demonstrated to improve social skills in young adults with ASD.³⁵⁹

Families should be counseled to include development of social skills with discrete goals and interventions in the IEP or educational plan as well as to be cognizant of potential opportunities to promote social interaction in the natural environment and in the context of other therapies.³⁶⁰ Implementing IEP goals across the day and generalizing specific skills to promote conversation and nonverbal communication, such as providing eye contact, directing facial expressions, and using appropriate gestures, is important, independent of age, and should involve both the caregivers and professionals. More information about IEPs in

general can be found at <http://www.wrightslaw.com/info/iep.index.htm>.

Other Therapeutic Interventions

Speech and Language Interventions

Delayed language is an early concern for many children who are later diagnosed with ASD. The communication symptoms included in the DSM-5 criteria for ASD reflect core deficits in social communication and interaction, such as failure of back-and-forth communication, deficits in nonverbal communication (such as eye gaze and use of gesture), difficulty adjusting behavior to suit the social context, and restricted and repetitive behaviors leading to perseverative vocalization, echolalia, and preoccupation with restricted topics of interest. All children with ASD should have documentation of specific coexisting speech and language diagnoses so that appropriate intervention might be provided.

Speech-language therapy is the most commonly identified intervention provided for children with ASD.³⁶¹

The strategies used by speech-language pathologists to reinforce sound repetition and word use in children with typical development are often initially used with young children with ASD. Such strategies include reinforcement of speech sounds and communicative acts, imitation of the sounds the child makes, and exaggerated imitation and slowed tempo.³⁶² The literature offers the most support for approaches with preverbal children with ASD in which adult prompts are used for communication, prompt fading, and reinforcement of their own attempts at communication. Intervention in naturalistic settings and involvement of caregivers may help reinforce the initiation of communication and functional use of sounds, gestures, and words.

A significant minority (up to 30%) of individuals with ASD ultimately do not acquire verbal speech.³⁶³ Delayed

onset of speech may be complicated by general delays in development (intellectual disabilities) or coexisting speech disorders, such as childhood apraxia of speech. Although using communicative spoken phrases before age 4 years is considered a good prognostic sign for language development in youth with ASD, emergence of phrase speech may occur to at least age 10 years, especially in children with preserved nonverbal skills and evidence of social engagement.³⁶⁴

When children do not spontaneously speak, augmentative and alternative communication (AAC) may be introduced. Examples of AAC strategies include sign language, the Picture Exchange Communication System, and speech-generating devices.^{365,366} The use of AAC may help promote social interaction and understanding of the purpose of communication and does not delay onset of speech. Indeed, it may enhance emergence of spoken words by pairing nonverbal and verbal communication.

The Picture Exchange Communication System is used to build communication through picture identification and exchange as communication. With training, pictures can be sequenced to build on communication.³⁶⁷ Picture strips that sequentially explain medical procedures, for example, take advantage of this approach. Use of speech-generating devices and programs that use AAC on digital tablets also are increasing. These devices provide acoustic feedback to the child, and touch-screen tablets are relatively inexpensive and portable. Medical providers are often asked to justify the purchase of touch-screen tablets or AAC devices. It cannot be assumed that the use of AAC alone will lead to functional oral communication without a therapeutic plan.³⁶⁸ Current scientific evidence does not support the use of facilitated communication in which a nonverbal

individual is guided to communicate.^{369,370} This differs from AAC, in which the individual is taught to communicate independently. Future strategies to promote communication are expected to incorporate evolving knowledge about sensory processing and connectivity of brain functions in people with ASD.

Children and youth with ASD often have deficits in pragmatic language that can affect social interaction with adults and peers and academic performance as more complex language becomes required for reading comprehension and analysis of information. In addition, literal interpretation of language and difficulty in understanding the intent of other people leads to behavioral challenges in some people with ASD and affects success in school, leisure activities, and employment. School-aged students with spoken language should have their pragmatic language assessed as part of their school-related reevaluations, with consideration of pragmatic language testing if academic problems and inattention are noted in the classroom. Interventions may include individual and group approaches that include teaching and practicing conversation. The pediatrician may refer the child for private speech-language therapy if he or she is not eligible for services in school or if increased intensity of intervention is desired. Although the impact of speech-language therapy on structural language improvement has not been adequately studied, improvement in ratings of conversational competence by parents and of classroom learning skills by teachers supports the recommendation for social skills and social language interventions for students with ASD.³⁷¹

Motor Therapies

Children with ASD may have low muscle tone or a developmental

coordination disorder. Although the ages for sitting and walking do not differ between children with ASD and children with typical development, both fine and gross motor skills may be delayed in preschool-aged children with ASD.³⁷² Attention to position in space in children with a coexisting diagnosis of ADHD may further complicate delays in coordination.³⁷³ Occupational therapy services may be indicated to promote fine motor and adaptive skills, including self-care, toy use, and handwriting. Almost two-thirds of preschool-aged children with ASD are reported to receive occupational therapy services.³⁷⁴

Similarly, some children with ASD may have gross motor impairment on formal testing that may benefit from therapeutic intervention focused on building strength, coordination, motor planning, or skill acquisition to promote safer mobility or play. Toe walking is common among children with ASD as well as in other developmental disorders in early childhood. The etiology of toe walking in ASD is unclear, although sensory aversion and habit or perseveration have been proposed. Common interventions for toe walking may include passive stretching, orthotics, and casting. Impairment in gross motor function may affect the capacity of a child with ASD to participate in leisure activities with the family or with peers and may impair participation in sports or interactive play beyond the effect of their social skills alone. Impaired motor skills may further decrease opportunities for social skills development and active learning and may be a risk factor for overweight and obesity.³⁷⁵ For motor therapies to be provided in the educational setting, a significant delay for age that affects function in school must be identified on a valid assessment measure.

Sensory Therapies

In 2012, the AAP published a clinical report, "Sensory Integration Therapies for Children With Developmental and Behavioral Disorders," providing important background information and recommendations for pediatricians.³⁷⁶ Since that publication, the DSM-5 criteria now includes sensory symptoms in the diagnostic criteria for ASD in recognition of the fact that individuals with ASD have sensory challenges that may be related to repetitive and other challenging behaviors.³⁷⁷ Indeed, sensory symptoms exhibited by young children, such as food selectivity, covering their ears for certain sounds, and visual scrutiny of aspects of objects, may be among the earliest differences families identify in their children's development. Sensory goals may be included in treatment objectives for students with ASD. Adult-directed approaches provided through sensory-based interventions may be included in the context of motor and behavioral therapies and in educational settings. Despite the increasing scientific understanding of the neurobiological basis for sensory symptoms in individuals with ASD, empirical interventions in common practice have modest evidence to support their general use at this time.³⁷⁸ Commonly used sensory-based interventions, including brushing of the skin, proprioceptive stimulation by using weighted vests, or kinesthetic stimulation (such as swinging or use of specialized seating, such as a therapy ball, to modulate level of arousal), are not yet supported in the peer-reviewed literature.

Proponents of sensory integration therapies distinguish them from interventions with sensory modalities because of the active engagement with the child in skill building or desensitization. This type of therapy requires a trained clinician, often an

occupational therapist, to work with a child by using play and sensory activities to reinforce adaptive responses. The therapist explains the child's behaviors and responses to caregivers in sensory terms and provides them with strategies to help the caregivers accommodate the child's sensory needs to decrease functional impairment and tolerate environmental triggers. Advocates of these interventions claim that dysfunction in integration of sensory input contributes to inefficiencies in learning and to behavioral challenges and that therapeutic approaches to sensory integration need to be considered separately from focal sensory-based treatments.³⁷⁹ Although sensory-based therapies are among the most commonly requested therapies by caregivers,³⁶¹ the evidence supporting their general use remains currently limited.^{378,379} As with any other intervention, specific goals for sensory-based therapies should be identified, and outcomes should be monitored so that the utility for any given child can be documented.³⁷⁶

Medical Management of Co-occurring Conditions

Co-occurring medical and other conditions, such as seizures, sleep disorders, gastrointestinal (GI) disorders, feeding disorders, obesity, catatonia, and others, have a significant effect on the health and quality of life for children and youth with ASD and their families.^{380,381} In this section, the co-existing conditions commonly observed in children and youth with ASD are described, and anticipatory guidance and management strategies that primary care providers may consider are provided.³⁸⁰

Seizures

There is both an increased risk for ASD among children and youth with epilepsy and an increased risk for seizures in those with ASD. The pooled risk for ASD among children

with epilepsy is 6.3%, with almost 5 times as many in samples with the highest rates of co-occurring intellectual disabilities.^{173,382,383} The rate of seizures among people with ASD in community-based populations has been reported to range from 7% to 23%, with rates as high as 46% reported in clinically ascertained samples.¹⁷⁰ It has been suggested that the risk for seizures is not increased in individuals with ASD without intellectual disability. Risk factors for the increased likelihood of seizures in people with ASD include intellectual disability (as noted), female sex, and lower gestational age.¹⁷⁴ Specific genetic disorders associated with ASD, such as tuberous sclerosis, also may contribute to seizure risk in early childhood. Onset is bimodally distributed, with most first seizures occurring in early childhood and in adolescence; 20% of first seizures occur in adults with ASD.¹⁷⁰ Children with ASD and seizures tend to have more behavioral challenges, independent of cognitive skills.³⁸² Screening EEGs are not recommended for patients who are asymptomatic. An overnight EEG should be considered when the clinical history suggests seizures and atypical regression. Response to conventional antiepileptic drug therapy varies greatly, with some reports suggesting an increased risk for treatment-resistant epilepsy in individuals with early onset of seizures and delayed global development.³⁸⁴

GI Symptoms

GI symptoms, such as abdominal pain, constipation, diarrhea, gastroesophageal reflux, and feeding problems, are more commonly reported in children and adolescents with ASD than in those with developmental delay or typical development.^{385–387} A large prospective cohort study revealed differences as early as 6 to 18 months of age in stooling patterns and feeding behaviors in children who

were later diagnosed with ASD.³⁸⁸ Because of language delays and atypical sensory perception or report of pain, individuals with ASD may be less likely to report specific GI discomfort and may present with agitation, sleep disruption, or other behavioral symptoms rather than GI discomfort.³⁸⁷ Characteristics of ASD that might affect GI symptoms include resistance to change (feeding and constipation), comorbid anxiety (pain, feeding, and motility disorders),³⁸⁹ and altered sensory perception (pain, feeding, and constipation). At present, there is no evidence of an association of ASD with celiac disease, specific immune dysfunction, or motility disorders (eg, gastroesophageal reflux) in children with ASD.

It would be expected that these disorders would occur at least as frequently among individuals with ASD as among individuals in the general population, and they should be considered when the child has a history of GI symptoms or a change in behavior.^{390,391} Ongoing research is focused on whether differences are present in immunologic function, motility, or the microbiome in individuals with ASD.^{392–394}

Selective eating is common in children with ASD.³⁸⁶ A limited diet may influence GI symptoms, such as constipation,³⁹⁵ and alter the intestinal microbiota. GI disorders should be considered in patients with ASD if they present with typical GI symptoms or with agitation, food refusal, or sleep disturbance.^{387,396} The indicated GI workup will depend on the specific symptoms. Children with ASD should be offered the same approaches to treatment of GI disorders as other children. Modifications of conventional interventions to accommodate for symptoms of ASD might include consistent behaviorally informed approaches for constipation and encopresis.

Feeding Disorders

Up to three-quarters of children with ASD have problems related to eating, including food selectivity based on texture, color, or temperature; rituals around food presentation; and compulsive eating of certain foods.^{397–399} Behavioral refusal may also present as the child holding food in the mouth, volitional gagging, and emesis. Common related problems include pica (eating of nonfood items) and rumination (self-stimulatory emesis and reswallowing of stomach contents). By age 16 months, children who are later diagnosed with ASD are observed to be more selective in their eating patterns than are other toddlers.⁴⁰⁰ Problems around mealtime behavior and food choice often persist into adolescence. The frequency of feeding challenges in children and youth with ASD may relate to the core symptoms of restrictive and repetitive behavior and differences in sensory perception related to smell, taste, and texture.⁴⁰¹

Children with developmental delays may also have delayed oral motor skill development and may demonstrate food refusal of textures that they cannot physically chew or swallow. Discomfort can lead to food refusal, so initial evaluation should include consideration of gastroesophageal reflux, dental pain, food allergies, lactose intolerance, and significant constipation.³⁸⁷ If oral-motor concerns are observed, speech or occupational therapy assessment is indicated.

Because feeding problems are so common among children with ASD, a dietary history should be obtained at health supervision visits. Physiologic needs for macronutrients and micronutrients are the same for children with ASD as for other children. As with other children in the United States, insufficient intake of fiber, vitamin D, and calcium are common.⁴⁰² Rare cases of severe nutritional deficiencies, such as

rickets (vitamin D),⁴⁰³ scurvy (vitamin C),⁴⁰⁴ and keratoconus (vitamin A),⁴⁰⁵ have been reported in children with ASD with severe food aversions. If supplements are used to correct for poor vitamin D or calcium intake, it is important to confirm that the dose is sufficient for the age and sex of the child.⁴⁰⁶ Food fortification in the United States may supply adequate amounts of vitamins and minerals for some children with selective diets, so additional multivitamins may not be necessary.⁴⁰⁷ Consultation with a registered dietitian may be helpful to be able to guide families regarding the nutritional sufficiency of their child's diet.

The clinician can counsel families about offering children routine meals and snacks, discouraging snacking through the day, promoting self-feeding, and using basic behavioral approaches to encourage mealtime structure and predictability with minimal distraction. Children with ASD need to be offered new foods multiple times to become familiar with them. Feeding problems that affect nutrition or family function or that are specialized, such as mouth packing, rumination, severe pica, and intense aversions, are likely to need the support of professionals with expertise in behavior management and/or oral-motor therapies (speech or occupational therapy).^{408,409} Food refusal may stem from discomfort, so consultation with a gastroenterologist may be helpful. Gastrostomy-tube placement and nonoral feeding should only be considered after appropriate behavioral intervention has failed.

Obesity

Children and youth with ASD have greater risk for overweight and obesity than those in the general population.⁴¹⁰⁻⁴¹³ People with ASD have fewer opportunities and perhaps less interest for active leisure or organized sports, have repetitive

eating patterns that may include energy-dense foods, and are more likely to be prescribed medications, such as atypical neuroleptics (or antipsychotic medication) and anticonvulsants, that often contribute to excessive weight gain. Sleep disorders may further predispose them for obesity. Primary care providers should monitor a child's age-specific BMI percentile in the context of health supervision care and address modifiable risk factors through anticipatory guidance for their patients with ASD. Programs that address healthy weight for children and youth with typical development may need to be modified for successful use for patients with ASD.⁴¹⁴

Dental Health

Children with ASD commonly have unmet dental needs. Difficulty cooperating with hygiene and professional care are reported barriers for dental care. Even when insurance coverage is available, children with ASD have fewer visits for routine care.⁴¹⁵ There are limited data about the prevalence of caries or gingival disease in children with ASD. As with other children, anticipatory guidance should include attention to dental hygiene and fluoride use, if appropriate, from a young age. Behavioral strategies may be helpful to prevent the need for dental care under sedation.

Pica

Children and youth with ASD may put nonfood items in their mouths long after the developmental period of early childhood, when pica is expected. Pica is reported in up to one-quarter of preschool-aged children with ASD and is documented to persist in individuals with intellectual disability.^{416,417} The persistence of pica may be attributable to sensory differences, perseveration or obsession, and oral exploration of the environment. Clinicians need to be aware of

persistence of pica in children and youth with ASD because of the risk for toxic ingestions, risk for lead intoxication, potential for infection, and the risk for mechanical ingestions ranging from batteries to bezoars.⁴¹⁸ Obstruction and perforation need to be considered in children with pica who have acute abdominal symptoms. Iron deficiency is associated with pica in the general population.⁴¹⁹ Laboratory monitoring of blood lead and iron deficiency in children with pica is suggested in the context of primary care. Behavioral intervention includes reinforcing appropriate behaviors, ensuring adult supervision, and putting into place environmental safeguards for prevention.

Sleep Problems

Sleep disturbance is common in individuals with ASD and may be associated with exacerbation of problematic daytime behavior.⁴²⁰⁻⁴²⁷ Problems with initiating and maintaining sleep are reported for 50% to 80% of children with ASD.⁴²⁸ Children who are later diagnosed with ASD are reported to have had sleep problems by 30 months of age.⁴²⁹ Sleep problems in individuals with ASD persist; almost half of adolescents with ASD continue to have sleep symptoms.⁴³⁰ Adolescents are more likely to have shorter sleep duration, daytime sleepiness, and delayed sleep onset compared with younger children with ASD, who are more likely to have bedtime resistance, parasomnias, and night-waking. Reasons for the increased frequency of sleep disturbances in children and youth with ASD may include differences in melatonin metabolism,⁴³¹ developmental disruption of other neurotransmitter systems critical to sleep, and lack of social expectations, among other explanations. Genetic disorders, such as Smith-Magenis syndrome, are associated with both ASD and sleep disruption.⁴³² Biological reasons for disrupted sleep that are not unique to

children with ASD may include restless leg syndrome, which may be associated with low iron stores,⁴³³ and coexisting neurologic or behavioral diagnoses, such as epilepsy, anxiety, ADHD, or mood disorders. The most common cause of both delayed sleep onset and night wakings are learned behaviors. As with other children, the evaluation of the child with ASD with delayed sleep onset, night wakings, and/or early-morning wakings should include a history of comorbid medical conditions that might disrupt sleep, such as gastroesophageal reflux, seizures, asthma, allergies, eczema, or enuresis. Snoring might suggest obstructive sleep apnea and would prompt referral for additional assessment. Children who play video games or engage in other screen time close to bedtime have later bedtimes and may have more difficulty falling asleep.^{434,435} Restless sleep and night wakings would suggest a need for laboratory evaluation for ferritin and other indicators of iron sufficiency to determine if low iron stores might be present.⁴²⁸ An environmental history of the household may help to determine if household noise, parental work hours, or other factors may affect sleep. The bedtime routine and response to night-waking should be reviewed to determine the behavioral approaches to consider.

Empirical support exists for the effectiveness of parent education and behavioral interventions for children with ASD and sleep disturbances.^{425,436–440} Behavioral intervention includes parents establishing bedtime routines and making clear their expectation that the child sleeps in his or her own bed. This may be difficult to establish for children with ASD, who may not appreciate the social conventions around sleep time and may have repetitive rituals and comorbid anxiety or ADHD. Despite these

challenges, behavioral strategies are successful when consistently implemented.⁴⁴⁰

No medication is currently approved by the US Food and Drug Administration for the treatment of insomnia in children with or without ASD. Any medication elected should be started at a low dose and monitored for adverse effects.⁴²⁷ Sleep onset may be aided by treatment with melatonin^{441,442} at doses from 1 to 6 mg⁴⁴³ and may be maintained with long-acting melatonin.⁴⁴² Adverse effects are uncommon but may include nightmares. α -adrenergic agents (eg, clonidine) and antihistamines (eg, diphenhydramine) are often prescribed to help with sleep onset or to address night-waking in children, but the literature provides little support for their use.^{444,445} Disordered sleep is associated with challenging daytime behaviors in children with ASD⁴⁴⁶; addressing one may help with the other.

Wandering

Accidents, including drowning, are a major cause of morbidity and mortality in children and youth with developmental disabilities, including ASD.^{447,448} Children and youth with ASD may have decreased awareness of social convention and community rules as well as impulsivity and perseverative interests that draw them to potential dangers, such as bodies of water and busy roads. Wandering off (also called elopement) places them at risk for injury. Wandering, if present, should be included in the problem list as a coexisting diagnosis in patients with ASD. In an online study, 1218 families of children with ASD were questioned about elopement.⁴⁴⁷ Nearly half of children with ASD between the ages of 4 and 10 years had tried to elope. Almost half of those children were missing long enough for their parents to contact the police. Of those children, approximately two-thirds

were at risk for traffic-related injury and almost one-third were reported to have had near-drowning episodes. Data from a national survey revealed that elopement attempts in the past year were reported by approximately one-third of parents whose children had ASD with or without intellectual disability.⁴⁴⁹ Wandering may persist into adulthood.

In the survey by Anderson et al,⁴⁴⁷ parents reported that the most common perceived reasons for elopement were enjoyment of running, attempts to get to a desired location (such as a park), pursuit of an intense interest (eg, water), and escape from situations or sensory events that made them anxious. Because the risk for elopement increases with the severity of ASD and with co-occurring intellectual disabilities, many of the individuals at greatest risk have limited language and cannot tell first responders their names, addresses, or phone numbers if they get lost. Police may interpret aggression caused by fear as combative behavior.

Prevention is the most important intervention for elopement. Parents participating in a large national survey of children with special health care needs reported primarily using physical and electronic barriers to try to prevent elopement, especially in children who also had intellectual disabilities.^{447,449} Information on prevention and management of wandering is available for parents and clinicians (<http://nationalautismassociation.org/big-red-safety-box/>). Consistent, adequate adult supervision is important in all environments: school, home, and community settings. Families note that increased supervision needs result in increased family stress. Families may need to consider deadbolts, fencing, and alarm systems for safety as well as personal GPS devices and identification bracelets or other identification. Local law enforcement

agencies may support GPS tracking. Alerting neighbors and local law enforcement officials as well as securing pools in the neighborhood and creating a family emergency plan are suggested. If impulsivity and motor hyperactivity contribute to elopement, examining the utility of medication as part of an overall plan may be considered. Similarly, addressing sleep issues becomes important if the child is at risk for wandering at night. Teaching safety skills and appropriate community behaviors is critical to prevention. All children with ASD, no matter their level of cognitive skills, are at risk for wandering.⁴⁴⁹

Motor Disorders

There is increasing appreciation that individuals with ASD may have developmental coordination disorder and other neurologic problems. Tic disorders occur with an increased frequency in children with ASD.⁴⁵⁰ Distinguishing complex tics from stereotyped movements may be challenging.

Catatonia was added as a possible coexisting condition to ASD in the DSM-5. Slow initiation of movement and reported deterioration in motor performance have been treated with lorazepam, electroconvulsive therapy, and behavioral interventions, but the therapies do not have a strong

literature base.⁴⁵¹ Later loss of motor skills in adolescence should prompt evaluation by a neurologist for underlying reasons. Regression in language or social interest is reported in approximately one-quarter of children later diagnosed with ASD. It is recognized most commonly between 18 and 24 months of age. Regression later in childhood requires evaluation.

Co-occurring Behavioral Health Conditions

Co-occurring behavioral symptoms include hyperactivity or inattention, aggression, outbursts, and self-injurious behaviors. Although these behaviors are not core features of ASD, they commonly interfere with functioning in school, at home, and in the community and contribute substantially to the challenges faced by families.^{293,294,381,452–457}

Psychiatric conditions (such as ADHD, anxiety, OCD, mood disorders, conduct disorders, or others) are identified in 70% to 90% of children and youth with ASD.^{458,459} Behavioral challenges have a significant effect on health and quality of life for children and adolescents with ASD and their families.⁴⁶⁰ Patients with ASD, like other children and adolescents, should be regularly screened for behavioral and/or emotional conditions, as recommended by the AAP.⁴⁶¹ The effect of behavior on

home and school functioning is often assessed as part of school testing by using parent and teacher questionnaires, such as the Behavior Assessment System for Children, Third Edition, Parent Rating Scales,^{79,462} or the Child Behavior Checklist.^{82,463,464}

With change in behavioral symptoms, physical sources of discomfort and behavioral intervention should be considered.⁴⁶⁵ If behavioral interventions are insufficient to address the challenges or are unavailable at the time, medication might be considered (see Table 10 for guidance on prescribing medication).

ADHD

Changes in DSM-5 criteria have provided flexibility to diagnose other DSM-5 disorders in addition to ASD, which can help guide treatment. Approximately half of children and youth with ASD also may fulfill diagnostic criteria for ADHD.⁴⁵⁹ Pediatricians should keep in mind that some children who are later diagnosed with ASD may have been initially identified as having ADHD.⁶⁹ Symptoms of ADHD may further compromise social skills function in children with ASD because of inattention to social cues and impulsivity. Standard rating scales used to assess symptoms of ADHD have not yet been validated for

TABLE 10 Considerations Surrounding Medication Use

No current medication corrects core social and communication symptoms of ASD

Accurate diagnosis of coexisting psychiatric conditions guide therapy

Medication is used to help manage

- Coexisting behavioral health disorders (eg, ADHD, mood disorders, or anxiety disorders)
- Associated problem behaviors or symptoms causing significant impairment and distress
 - Examples include the following: aggression, self-injurious behavior, sleep disturbance, mood lability, anxiety, hyperactivity, impulsivity, inattention

Medication should only be considered after

- Careful accounting of when the behavior started and what seems to exacerbate it
- A functional behavioral assessment should guide development of a treatment plan in the school setting
 - Consider whether the behavior serves as communication of distress or refusal
- Consider referral to a behavior therapist outside of school to assess the reasons for the behavior; provide the family with strategies, and collaborate in care
- Careful history and physical to look for medical factors that may cause or exacerbate challenging behaviors (eg, gastroesophageal reflux and acute sources of pain, such as otitis media, dental injury, fracture, and others)^{34,380,391,485,579}

Consider medication after treatable medical conditions and behavioral factors assessed and intervention does not address the symptoms of concern

Include the family and patient in shared decision making that considers their goals and values⁵⁴³

individuals with ASD. However, they are useful in determining the clinical impact of symptoms for an individual patient and in monitoring treatment. It is important, however, to consider the differential diagnosis of inattention and hyperactivity in the context of the language impairment and perseverative focus that often accompanies ASD. Children with delayed language may appear more inattentive. If they are expected to perform activities (including schoolwork) that they are not able to understand or accomplish, a child with ASD may engage in behaviors to escape, which can be interpreted as inattention and hyperactivity. Patients with ASD may be focused on their perseverative interests and may be internally distracted, as opposed to distracted by the environment. Evaluation of the symptom of inattention or impulsivity includes assessing language and educational abilities. Appropriate educational modifications and use of language for instruction that the student can understand are critical for successful intervention. Behavioral strategies should address reinforcement of on-task behaviors, breaking down tasks into units that can be completed successfully, breaks for activity (often included in sensory activities), and adult supervision appropriate for the demands. The same medications that are used for symptoms of ADHD in children without ASD are used in similar doses for children with ASD.⁴⁶⁶ Routine monitoring is important because children with ASD may be at greater risk for adverse effects⁴⁶⁷ (Table 11). The evaluation of a child for a possible co-occurring diagnosis of ADHD also should include consideration of a co-occurring diagnosis of anxiety.^{464,466}

Anxiety Disorders

The DSM-5 classification system separates anxiety disorders into separation anxiety disorder, selective mutism, specific phobia, social phobia, panic disorder, agoraphobia,

and generalized anxiety disorder as well as unspecified anxiety disorder. As many as 40% to 66% of school-aged children and adults with ASD are reported to also have anxiety disorders.^{458,459} Anxiety disorders are most commonly identified in children with ASD and typical cognitive and language abilities.^{468,469} Symptoms may be present in early childhood and manifest as behavioral challenges, such as overreactivity. Biological predisposition to both ASD and anxiety may be attributable to common genetic factors and/or altered neurophysiologic responses to stress.⁴⁷⁰

Core symptoms of ASD decrease the ability of individuals with ASD to predict the actions or interpret the beliefs of others, which may lead to a constant state of heightened worry. Repetitive behaviors may, in part, serve to instill predictability, so anxiety may lead to increased stereotyped behaviors or perseverative thoughts. Evaluation of anxiety requires consideration of the language demands of the environment, academic expectations, social demands, and underlying fears or phobias. Youth with ASD may lack sufficient language or insight to describe their symptoms. Getting information from multiple sources and looking at the behavioral manifestations related to context will help to correctly identify anxiety in patients with ASD.⁴⁷¹

Strong evidence from RCTs supports the use of cognitive behavioral therapy for anxiety symptoms in school-aged children with ASD, especially those with typical-range intelligence.^{295,298,472-475} Anxiety may be associated with reported GI and sensory symptoms.³⁸⁹ Some individuals find that sensory redirection or sensory activities used in the context of a behavioral program are helpful to diminish feelings of anxiety. Other individuals may find symptom relief with the introduction of routine and structure

if anxiety is exacerbated by uncertainty or associated with sensory under- and overreactivity.³⁷⁷ Nonpharmacologic approaches, such as neurofeedback and digitally delivered approaches to self-regulation, are being evaluated for their therapeutic potential. Medications used for anxiety in the general population may be considered as part of an overall treatment plan for children and youth with ASD (see Table 11 for psychopharmacotherapy of children with ASD and anxiety).

Mood Disorders

Depressive disorders are more common among children and adults with ASD than in the general population. Reported rates of coexisting depression in adults and children are highly variable, ranging from 12% to 33%.^{458,476,477}

Symptoms of depression are more likely to lead to dual mental health and developmental disability diagnoses in adolescents and adults with ASD than in children. The coexistence of mood disorders and ASD may be associated with genetic and neurobiological factors as well as environmental factors related to chronic stress and difficulty with understanding social situations. Both elevated and depressed mood may present as behavioral symptoms in youth with ASD. Changes in affect, participation, sleep habits, and eating may be symptoms of an underlying mood disorder. Attempted suicide is reported to occur more frequently in people with ASD than in the general population. Risk factors include peer victimization, behavioral problems, minority race or ethnicity, male sex, lower socioeconomic status, and lower level of education.⁴⁷⁸ The AAP recommends screening for depression in patients older than 12 years. Until ASD-specific measures are developed, the same approaches used for all other adolescents at increased risk for depression should be considered.⁴⁷⁹

TABLE 11 Continued

Target Symptoms	Medication Class (Examples)	Comments
Repetitive behavior <ul style="list-style-type: none"> • Stereotyped motor mannerisms • Compulsions • Behavioral rigidity, insistence on sameness 	Anticonvulsant mood stabilizers (valproic acid and divalproex sodium) ^{613–618}	Small studies suggestive of improvement in irritability; need larger studies; a limited number of placebo-controlled studies either do not support or are inconclusive regarding anticonvulsant medication as a treatment of irritability in patients with ASD
	Serotonin-norepinephrine reuptake inhibitor (venlafaxine) ⁶¹⁹	Effect size of improvement associated with venlafaxine was small, and irritability was not the primary outcome measured
	Atypical (second generation) antipsychotics (aripiprazole, risperidone) ^{595–598,620}	Multiple DB/PCs documenting improvement in repetitive behavior; short-term treatment Common adverse effects include increased appetite, fatigue, drowsiness, dizziness, and drooling More effective for targets of tantrums, aggression, and SIB
	Anticonvulsants (valproic acid and divalproex sodium) ^{613,621,622}	Modest improvement has been reported with divalproex sodium treatment May have improvement with topiramate as a second agent with risperidone Most antiseizure drugs have potential for sedation, cognitive adverse events
Anxiety, depression	SSRI (fluoxetine, fluvoxamine) ^{480,509,611,612,623–627}	Studies to date have not revealed effectiveness of SSRI medications for repetitive behaviors related to ASD, although they may diminish anxiety SSRIs may be effective for reducing symptoms of OCD and of anxiety when included in a comprehensive approach to treatment Need comprehensive behavioral approaches to minimize repetitive behaviors
	SSRIs ^{469,628}	Anxiety relief has been reported in trials of citalopram and buspirone, with fluvoxamine revealing some effect in female patients with ASD; documented utility in children and youth without ASD
	α-adrenergic (clonidine, guanfacine)	Hyperactivation is an adverse effect of SSRIs in children and youth with ASD that may result in stopping the medication The anxiety disorders most amenable to treatment are generalized anxiety disorder, separation anxiety disorder, and social phobias
	Atypical (second generation) antipsychotics ^{469,620}	If a mood dysregulation disorder is identified, treatment with a mood stabilizer and/or a second-generation antipsychotic is recommended, although an SSRI may be used to treat comorbid anxiety, OCD, or depression; behavioral activation with hypomanic or manic switches has been reported First-line treatment is a program of cognitive behavioral therapy to reduce symptoms ^{472–475} Few studies have examined the specific effects for these symptoms; clinicians may consider use of these agents; although SSRIs, SNRIs, and/or buspirone may be effective for the treatment of anxiety in children with ASD, they have not been rigorously evaluated for this purpose ^{507,626,627,629,630} Medications to consider include sertraline, fluoxetine, citalopram, or escitalopram for symptoms of anxiety and α-2 agonists (eg, guanfacine and clonidine and β-blockers such as propranolol), which may be useful for anxiety-related physiologic symptoms and behavioral dysregulation, and a short-acting benzodiazepine, such as lorazepam, could be considered for event related anxiety

DB/PC, double-blind placebo-controlled trial; FDA, US Food and Drug Administration; SIB, self-injurious behavior; SNRI, selective norepinephrine reuptake inhibitor. Adapted from Riddle MA. *Pediatric Psychopharmacology for Primary Care*. 1st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

As in children and youth with typical development, assessment of depression and other mood disorders must include family history, history of environmental stressors, the potential for toxic ingestions, and evaluation for comorbid conditions.

Interventions for depression include supportive therapy, cognitive behavioral therapy, and medication, if indicated, as coordinated interventions (see Table 11 for medication use). Antidepressant use in people with ASD has not been demonstrated to address aggression and has inconsistent effect on anxiety.⁴⁸⁰ Medication recommendations are based on data from the general pediatric population and expert consensus.⁴⁶⁹

The DSM-5 criteria for bipolar illness include changes in activity, energy, and mood. It may be difficult to make a diagnosis in people with ASD with limited language. The co-occurrence of bipolar illness and ASD in individuals with typical intelligence ranges from 6% to 21%.⁴⁸¹ Lifetime diagnosis of bipolar illness in adults with ASD is reported to be 9%.⁴⁵⁸

OCD-Related Disorders

Although restricted and repetitive behaviors are symptoms of ASD, some individuals with ASD may also have coexisting OCD. Obsessions are recurrent, unwanted, and persistent thoughts, images, or urges that cause distress. Compulsions are repetitive behaviors or thoughts with rigid rules

performed to reduce anxiety. Unlike the stereotypic behaviors of ASD, compulsions usually follow an obsession, diminish anxiety, and are not desired by the individual or perceived as pleasurable.⁴⁸² Under the DSM-5, OCD-related disorders include hoarding disorder, excoriation (skin-picking) disorder, trichotillomania, substance- or medication-induced obsessive-compulsive and related disorder, and obsessive-compulsive and related disorder due to another medical condition. The perseverations associated with ASD may be qualitatively different and less sophisticated than the repetitive and intrusive thoughts and actions associated with OCD.⁴⁸³ Repetitive behaviors in general may help an individual with ASD regain a sense of predictability. Anxiety, phobias, and/or depression may coexist with OCD in youth with ASD.

Behavioral approaches are recommended as the first line of treatment of symptoms of OCD, depending on the language and cognitive level of the patient. Cognitive behavioral therapy, including exposure and response prevention with or without a selective serotonin reuptake inhibitor, has been demonstrated to be the most effective treatment for youth with OCD who do not have ASD. Cognitive behavioral therapy may be less effective, with fewer remissions, in youth who also have ASD⁴⁸⁴ (see

Table 11 for medication management).

Disruptive Behavior Disorders: Aggression, Self-Injurious Behavior, and Tantrums

Disruptive behaviors, such as aggression, self-injury, and tantrums, may complicate home and community management of individuals with ASD. Behavioral outbursts may occur in response to stressful events in the environment, in reaction to a medical condition, as functional communication, or as a symptom supporting diagnosis of a co-occurring mental health disorder.⁴⁸⁵ Functional behavioral analysis and implementation of behavioral strategies can be an important initial step in management.⁴⁸⁶ A proposed pathway for the primary care setting for management of irritability that leads to disruptive behaviors in youth with ASD is proposed by McGuire et al.⁴⁸⁵ Disruptive behaviors may serve as communication to escape from a demand or an undesired situation. If successful, they may become part of a behavioral pattern. New onset of severe behaviors requires consideration of potential medical reasons (see Table 12). Pharmacologic treatment should be considered if no medical etiology is identified and if the behavior is associated with irritability, is not responsive to available behavioral interventions, or is related to a co-occurring diagnosable behavioral health disorder, such as anxiety, mood

TABLE 12 Common Presentations of Self-Injurious Behavior and the Medical Conditions to Consider If New Onset

Type of Self-Injury	Potential Associated Conditions	Potential Associated Injury
Head banging	Headache, toothache, sinus infection, ear infection	Detached retina, abrasions, contusions
Head hitting or slapping	Headache, toothache, sinus infection, ear infection	Fracture of bones in hand, detached retina, abrasions, contusions
Eye poking	Vision loss, eye pain	Eye abrasion
Gum or tooth digging or banging	Dental pain, gingivitis	Gum injury, tooth autoextraction, tooth fracture
Scratching and skin picking	Allergy, eczema, drug reaction, skin infection or infestation (eg, fleas, scabies)	Infection, scarring
Finger and toenail biting or picking	Pain	Infection, nail removal, ingrown nails, paronychia
Kicking or stomping	Restless leg syndrome, leg pain	Bruises, fractures
Rumination	Gastroesophageal reflux, eosinophilic esophagitis	Esophageal ulceration and bleeding, dental damage, nutritional compromise, precancerous lesions of esophagus

disorders, thought disorders, and/or ADHD.

It has been reported that between 8% and 68% of children with ASD demonstrate aggressive behavior, depending on how stringent the definition is.⁴⁵⁴ Aggressive behaviors were reported on the Child Behavior Checklist for one-quarter of children attending an ASD clinic, with similar rates from 2 to 16 years of age. Aggression was associated with hyperactivity, lower cognitive skills, sleep problems, and internalizing behaviors such as anxiety. There was no association with sex. Researchers of other studies have observed increased rates of physical aggression in children with ASD who have lower adaptive skills and frequent repetitive behavior.⁴⁸⁷ Management of co-occurring sleep problems and hyperactivity may be helpful in a treatment plan⁴⁸⁸ that includes behavioral intervention to address aggression and targeted pharmacotherapy.⁴⁸⁷

Self-injurious behaviors are reported in 40% to 50% of individuals with ASD at some point across the lifespan⁴⁸⁹ and may occur more frequently in people with ASD who also have aggressive behaviors and sleep problems.⁴⁹⁰ Self-injurious behaviors in individuals with ASD may be repetitive and self-stimulatory (such as scratching, pica, or rumination). Head banging and self-hitting may occur as part of a tantrum. Like aggression and other disruptive behaviors, self-injurious behaviors may serve as communication to escape from demands or situations that the individual does not want to be in. The type of self-injurious behavior may change if the intervention of prevention or blocking is not associated with addressing the underlying reason for the behavior. Persistence of self-injurious behaviors in individuals with ASD is associated with more limited cognitive and language abilities,

hyperactivity, impulsivity, repetitive behavior, and more challenges with social interaction.⁴⁹¹ There is an association of self-injury with specific genetic disorders that are not associated with ASD, such as the severe self-biting of Lesch-Nyhan syndrome. Self-injurious behavior is associated with genetic disorders that are also associated with ASD, such as Cornelia de Lange syndrome, fragile X syndrome, and Smith-Magenis syndrome.⁴⁹² In the case of aggressive, self-injurious, and disruptive behaviors, the primary care provider needs to assess the safety of the child and family in an ongoing fashion. Referral to community services and for behavioral intervention should take place if behaviors are unsafe or if the patient is not responding to the treatment plan.

Psychopharmacologic Approaches to Management

The use of medications to treat behavioral and psychiatric symptoms in children and youth with ASD has increased significantly since the publication of the 2007 AAP clinical reports.^{493,494} With a shortage of specialists, more medication management, including prescription of atypical antipsychotic medications, is taking place in the primary care setting.^{495,496} Large national studies of insurance claim data from Medicaid and commercial insurers reveal rates of psychopharmacology prescription for patients with ASD to be 56% to 65%.^{476,493,497} One or more psychotropic medications are prescribed for 1% of children with ASD younger than 3 years, for 10% to 11% of children aged 3 to 5 years, for 38% to 46% of children aged 6 to 11 years, and for 64% to 67% of adolescents aged 12 to 17 years.^{498,499} Psychotropic medication use increases with increased age, lower range of cognitive skills and/or presence of intellectual disability, and higher prevalence levels of challenging

behavior or coexisting psychiatric diagnoses.^{476,497-501} Prescription of medication also appears to be affected by demographic factors, such as race, ethnicity, and geography.^{497,498,502} Reported polypharmacy rates range from 12% in a registry cohort recruited from diagnostic clinics⁴⁹⁹ to 29% to 35% in large studies of Medicaid claims data.^{476,493}

Medication may be helpful to address co-occurring symptoms or disorders. Clinicians should carefully weigh potential risks and benefits before prescribing medication for behavior and use psychotropic medications as part of a comprehensive treatment approach. The prescribing clinician should understand the indications and contraindications, dosing, potential adverse effects, drug-drug interactions, and monitoring requirements of the medications they prescribe.⁶ Table 10 provides guidance for principles of prescribing medication, and Table 11 lists pharmaceutical options for common behavioral-symptom clusters. Psychopharmacogenomic testing for genetic variants that increase the likelihood of adverse effects is an emerging area for precision medicine. Prescribers should consider CYP2D6 and CYP2C19 metabolizer status in making medication decisions for selective serotonin reuptake inhibitors (SSRIs), for example, despite limited data at present to guide practice.^{503,504} The limited data on the utility of psychopharmacogenomic testing at the time of this publication limits insurance coverage for many patients. Recommendations for testing are expected to rapidly change with ongoing research.⁵⁰³⁻⁵⁰⁵

Areas of Psychopharmacologic Research

As the neurobiology of ASDs are better understood, novel psychopharmacologic agents might be developed that will better manage

co-occurring symptoms and/or address core deficits. Some potentially important lines of research involve medications that modulate metabolism of excitatory neurotransmitters (such as glutamate and γ -aminobutyric acid), block acetylcholinesterase and/or nicotinic acid receptors, and act as hormones that naturally promote social affiliation (such as oxytocin and vasopressin). Drug trials involve newly formulated agents as well as repurposing existing medications used for other purposes.⁵⁰⁶⁻⁵⁰⁹

Better understanding of the neurobiology responsible for the symptoms of ASD will allow for the identification of targeted psychopharmacologic interventions. The use of psychopharmacogenomics to identify which patients might genetically be at greater likelihood of benefit or at increased risk for adverse effects from specific medications is an important area of research.⁵¹⁰

Integrative, Complementary, and Alternative Therapies

Despite the advances in understanding the neurobiology of ASD, many unanswered questions remain about why ASD occurs and how best to treat it. Families often consider nutritional interventions and nonmedical therapies without a scientific evidence base to address the symptoms that conventional interventions cannot rapidly address, or there is limited access to conventional services in their community. Primary care providers are often asked about nonstandard interventions that are used in integrative practice or are promoted on the Internet, in the popular press, by other families, and by celebrities.⁵¹¹⁻⁵¹⁶ The National Center for Complementary and Integrative Health maintains a Web site in which current information on novel therapies in popular use for people with ASD is reviewed.⁵¹⁷ In

the past decade, an increasing number of interventions based on theories of causation of ASD that are, as yet, unproven have been examined in clinical trials. Appropriately designed trials have provided evidence to support some interventions, such as the dietary supplement melatonin, and have disproven others, such as secretin.⁵¹⁸ Many interventions, although still widely used, remain unproven.

Complementary therapies are often attractive to families because they are purported to correct putative biological causes of behavioral symptoms and may be discussed with an optimism about outcome that is often not conveyed with the recommendation for conventional therapies. Between 28% and 74% of children with ASD are given at least 1, and usually more than 1, complementary therapy.⁵¹⁹⁻⁵²¹ Although use of novel therapies is common among children with a range of developmental disabilities, children with ASD who are irritable or overactive or who are reported to have food allergies may be more likely to be given additional therapies.⁵²²

Complementary, alternative, and integrative therapies used for ASD can be grouped into 3 general areas: (1) natural products (including herbs, vitamins and minerals, and probiotics), (2) mind and body practices (including yoga, chiropractic, massage, acupuncture, progressive relaxation, and guided imagery), and (3) other therapies (including traditional medicine and naturopathy).⁵¹⁷

Dietary interventions used to treat symptoms of ASD are perceived by many families as beneficial because they are natural and without adverse effects. Dietary elimination of gluten- and casein-containing foods is often implemented in an attempt to ameliorate core symptoms of ASD, not on the basis of allergy or celiac

disease.^{523,524} The double-blind clinical trials to date have not demonstrated a treatment effect with diet.^{524,525} Whether a subgroup of children with GI symptoms might benefit from these or other dietary interventions requires additional study. Children may be adequately nourished on a casein-free diet with calcium and vitamin D supplementation. Nutritional counseling is recommended if a trial of this diet is elected.⁴⁰⁶ It may be that improvement in unrelated conditions may influence behavioral symptoms (eg, removal of dairy products may decrease irritability attributable to lactose intolerance).

Dietary supplements are often given to children who are selective eaters by their families to compensate for a limited diet.⁴⁰⁶ However, many children with ASD are given vitamins and minerals to treat proposed biochemical abnormalities that have been proposed to be unique to ASD. Popular dietary supplements include vitamin D,^{526,527} vitamin B₁₂,⁵²⁸ vitamin B₆ with magnesium,⁵²⁹ omega-3 fatty acids,⁵³⁰ and multivitamin preparations. The literature to date is controversial with respect to vitamin supplementation as a treatment of symptoms of ASD, and at this time, no conclusive evidence exists that people with ASD require different nutrient intake than that recommended in the Dietary Reference Intakes (<https://www.ncbi.nlm.nih.gov/books/NBK225472/>). The long-term risks of high-dose supplementation have not been studied.⁵³¹ Although maternal folic acid status may provide biologically plausible risk for ASD, there is no evidence that supplementing with B vitamins has therapeutic benefit at this time, whether a child carries common variants in the *MTHFR* gene.^{532,533} Of dietary supplements in common use, melatonin has been demonstrated to be a safe and effective intervention for sleep in children with ASD.⁴²⁸

Nonbiological interventions used for symptoms of ASD are popular and have also been increasingly studied. There has been conflicting evidence regarding the effect of music therapy,⁵³⁴ yoga,^{535,536} massage,⁵³⁷ and equine-assisted therapy^{538,539} on the symptoms of ASD in children, but evidence does not support these therapies for treatment of the core deficits of ASD at this time. Evidence to date does not support the use of auditory integration training, in which an individual listens to altered sounds through headphones in an effort to change auditory or other processing.⁵⁴⁰ Existing studies are insufficient at this time to support dance therapy, drama therapy, and chiropractic therapy.⁵⁴¹

Medical interventions used for nonstandard purposes also are sometimes prescribed for symptoms of ASD. Clinical trials do not support the use of antifungal agents, immunotherapy, or hyperbaric oxygen treatment, and concern for safety, in addition to lack of supporting data, cautions against chelation therapy for children with ASD.⁵¹⁶

As with any intervention, families electing a novel therapy should work with their therapeutic team to identify target symptoms they hope to address and develop a monitoring system to track change. Interventions should be implemented in a stepwise fashion so that proper attribution of effect is possible and confounding factors can be identified. It is important that the medical home provider and family collaborate to select and monitor safe and effective interventions.⁵⁴²

SECTION 6: WORKING WITH FAMILIES

Families play a key role in effective treatment for children with ASD. Recognition that individuals who are affected and their families are partners with the professionals in all aspects of planning a personal, local,

and national agenda for ASD has emerged and has shaped approaches to community services as well as research planning.⁵⁴³ Provision of patient- and family-centered care requires the clinician to educate the family about the child's health and engage in respectful dialogue. Resources to support the clinician in talking to families about the diagnosis include a toolkit developed by the Autism Speaks Autism Treatment Network (<https://www.autismspeaks.org/tool-kit/atnair-p-guide-providing-feedback-families-affected-autism>).

Impact of ASD on the Family

The impact of having a child with ASD on other family members and on society is considerable. Parents of children with ASD report more stress^{544,545} and increased costs⁵⁴⁶ than do parents who do not have a child with ASD. More than half of families report that a parent needs to cut back on work or stop working because of the care needs of the child.⁵⁴⁷ The largest societal costs associated with ASD are special education, residential care, and lost days of caregiver work.⁴ Peer support for families of children with ASD is associated with less parental stress, less negative mood, and more positive perceptions.⁵⁴⁸ Parents who understand more about their child's ASD can advocate for more intensive and appropriate services.⁵⁴⁹ Best practice includes giving families contact information for a family support group at the time of diagnosis. This support may be a local group that provides face-to-face interaction and community activities or an online community.⁵⁵⁰ Many families may not have the time or inclination at the time of diagnosis to communicate with other families affected by ASD but may find the support useful later when they are facing the transitions of preschool, adolescence, or adulthood. National support groups that address a wider community of children and youth

with special health care needs (such as Family Voices and Parent2Parent), autism-specific national support organizations (such as Autism Speaks and the Autism Society), and local organizations are effective in helping families obtain information and feel supported. Clinicians should familiarize themselves with national and local sources of support and information so that families can be given Web sites or phone numbers at the time of diagnosis and again as indicated. State-specific information on services and Maternal and Child Health Bureau-supported programs are found online (<https://mchb.hrsa.gov/maternal-child-health-initiatives/autism>). It is important for providers to advocate for instructional material in other languages as well as be knowledgeable of other resources in their communities that can provide services or support to the culturally diverse groups they serve.

Comorbid conditions, such as intellectual disability and/or psychiatric disorders, add to the impact of ASD on family functioning and access to care.⁵⁵¹ Although families of older children and youth typically report fewer interactions with professionals, the stress on the parent related to the ASD diagnosis persists.⁵⁵² Primary care providers should speak with families about the stresses associated with ASD and the health of other family members and make appropriate referrals, either for supportive counseling for the caregivers or agencies that can address behavioral and respite needs of the child or to address unmet health needs in family members.

The effect on siblings also needs to be considered in the context of both anticipatory guidance and primary care. Most siblings of children with ASD do not report having a sibling with a disability to be a negative experience; however, they, too, are at risk for increased stress and subsequent emotional problems.⁵⁵³

Siblings may have precocious involvement in the care of the child with ASD, and some resent the amount of attention and resources the child with ASD requires or the family's inability to participate in activities in which they see their peers engaging. Proactively teaching siblings about ASD and providing them with peer support may be helpful (Autism Speaks Sibling tool kit: http://www.autismspeaks.org/sites/default/files/a_siblings_guide_to_autism.pdf). Many areas have groups to provide education and support to siblings. It appears that positive parental attitudes and a supportive family setting are associated with better sibling adjustment as well. The pediatrician should monitor the well-being and need for behavioral health supports of siblings as well as parents.

Medical Home

In the AAP's medical home model, primary care is envisioned as accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally sensitive for all children and youth, including those with special health care needs. Children with ASD represent a population that has had difficulty accessing comprehensive coordinated services. The chronic care model provides the structure for clinicians to collaborate with patients and their families.⁵⁵⁴ Parents of children with ASD perceive care to be less comprehensive, less well coordinated, and less family centered than they desire and report that they are less satisfied with their care compared with parents of children with other special health care needs.⁵⁵⁵ Parents also perceive their providers as less well informed regarding treatments for ASD, especially complementary, alternative, and integrative therapies, than they would like them to be. Pediatricians report that they lack the knowledge to provide this support to patients with ASD⁵⁵⁶ as well as the

time and resources for specialized care.^{555,557} Parents of children and youth with ASD would like better access to specialty care and report greater unmet medical and behavioral health care needs⁵⁵⁸ and a higher financial burden for care compared with parents of children without ASD.⁵⁵⁹

Increasing family awareness and understanding of the medical home can promote partnership of the parents and primary care provider in planning and coordinating the child's care and advocating for their needs. National survey data reveal that family-centered and coordinated care through a medical home results in fewer unmet needs,⁵⁵⁸ including dental needs.⁵⁶⁰ Organizations, such as Family Voices and Family-to-Family Health Information Centers, can provide information and support as well as resources for guiding families in developing care notebooks for their child. Through their ongoing relationship, providers can help children understand their own diagnosis at their developmental level. Clinicians can remind their patients with ASD of their strengths, such as focus, memory, visual-spatial problem-solving, and others, as well as their personal accomplishments in building skills and mastering barriers to achieve goals. Recognition of achievement of milestones, whether it is toilet training or college graduation, should be acknowledged.

Shared decision-making promotes a collaborative process for planning care through dialogue among the individual who is affected, caregivers, and clinicians. It can be particularly useful when the evidence for an intervention is either controversial or if there is not a uniformly accepted approach.⁵⁶¹ Shared decision-making requires clarity of the question to be answered, the options to be understood, and the family context and beliefs to be respected. It is often a process rather than a single conversation. Helping children and

youth with ASD understand their diagnosis within the context of their developmental level can help them understand their symptoms and participate in decision-making.⁵⁶²

Transition to Adulthood

Planning for children with ASD to understand and participate in their own health care should begin early in adolescence, with adaptation for developmental abilities. The AAP clinical report "Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home" provides guidance on the steps necessary to address health care transitions for all patients with chronic conditions.⁵⁶³ Got Transition recommends 6 core elements that need to be addressed for health care transition without disruption in care, including (1) a transition policy for the practice, (2) tracking and monitoring transition, (3) assessing transition readiness for youth and/or family, (4) actively planning the details of transition, (5) transfer of care, and (6) transition completion.⁵⁶⁴ The pediatric health care provider is also in a position to advise the family about teaching their adolescent with ASD about sexuality.⁵⁶⁵ Planning for wellness requires considering young adult opportunities for exercise and leisure activities. Planning for medical transition for all aspects of health care should start around ages 12 to 14 years. Educational transition starts at the school level at age 14 years and should involve the student as much as possible.

As a child approaches legal adulthood, the family may need to consider guardianship, either full guardianship in cases in which an adult child cannot make health, financial, or other decisions because of cognitive impairment; limited guardianship in cases in which an individual can participate in decision-making; or conservatorship in cases in which the oversight extends only to

financial decision-making. Many young adults with ASD will be capable of independent decision-making and should be prepared for transition to adulthood like other teenagers. The young adult with ASD may be eligible for Supplemental Security Income (SSI) benefits. SSI is a federal program that provides funds for the care of individuals with developmental disabilities who will not be able to support themselves independently. Because of the strict guidelines regarding cognitive and adaptive delays, some adults with ASD may not be eligible for SSI even if their disability is a barrier to employment. Families may wish to meet with a counselor who can advise them on financial planning, with attention to the needs of an adult child with developmental disability.

Students with disabilities who plan to continue their education need to be advised of the transitioning process into postsecondary education. Students with disabilities are protected under IDEA (1990; amended 1997 and 2004); Section 504 of the Rehabilitation Act of 1973; the Americans with Disabilities Act (1990); and the ADA Amendments Act of 2008. Some colleges may provide accommodations to students with developmental disabilities with proper documentation of their needs, including recent academic testing. College students with ASD may benefit from continued supports around social skills development, medication monitoring, and mentoring on living independently.⁵⁶⁶

Although resources are still insufficient, attention is growing for the need to provide social skills training for youth with ASD with and without intellectual disabilities to enter the workforce in competitive employment as well as job skill development. There are insufficient group-home and supported community-living arrangements for adults with ASD to meet the demands in most communities. The clinician

should initiate discussions with parents regarding their plans for where their child with ASD will progress to postsecondary school education and/or employment and their plans for where their child will live in adulthood early in adolescence so the family can plan appropriately with community agencies.

Families should work with their child's school throughout adolescence to target the skills their child will need to master to be successful in young adult programs, the workforce, or postsecondary education. Goals for increasing skills may include academic, social, communication, leisure, and self-care goals. Families need information to be as proactive as possible in planning for health, academic, job, and residential needs in young adulthood. Additional research is needed to develop and evaluate evidence-based and effective interventions for this age group.³¹⁴ The pediatric health care provider should provide anticipatory guidance to the family in the context of ongoing health supervision and communicate with identified adult providers for smooth health care transition.⁵⁶⁷

State Programs, Supports, and Laws

State laws related to education, social service, and insurance for individuals with ASD vary significantly. Although the federal government mandates early intervention for children at risk for developmental delay and a free and appropriate education for students aged 3 to 21 years who have specific educationally handicapping conditions, the implementation of educational services varies by state and locality. The law states that services need to be appropriate, not necessarily optimal. No legal mandate for adult services exists, although the agencies that provide residential services, service coordination, job training, and adult day services typically are funded through the states.

The social services and home- and community-based waiver services available to families whose children have developmental disabilities, including ASD, differ from state to state.⁵⁶⁸ The clinician should be familiar with the requirements for programs in their state that might lead to a Medicaid waiver (medical assistance as a secondary insurance for children with special health care needs), service coordination, respite care, and other financial or behavioral supports afforded a family when a child has special health care needs. The clinician may need to complete a form to verify the diagnosis and needs for eligibility. Of note, some children with ASD who have typical cognitive abilities may not qualify for many special education and social service supports. However, later on, at the time of transition to adulthood, if they experience difficulty with employment and daily-living skills, they may qualify for support services.

SECTION 7: RESEARCH AND SERVICE NEEDS

More than \$1.5 billion of private and public research funding was devoted to ASD between 2008 and 2010.⁵⁶⁹ The passage of the Combating Autism Act of 2006 (Public Law 109-416) and its reauthorization in 2014 as the Autism Collaboration, Accountability, Research, Education and Support Act (CARES) Act (Public Law 113-157) continued a trend in funding to address the intervention needs of individuals diagnosed with ASD. Before this time, research funding was largely focused on the genetics and neurobiology of the disorder. However, this changed with the convening of the National Institutes of Health Interagency Autism Coordinating Committee in 2006. The committee was assembled to provide guidance to the agencies funding autism services, and the research agenda was expanded on the basis of the contributions of stakeholders, including families, individuals

affected, and federal agencies. The committee's 2009 strategic plan, updated in 2017,⁵⁷⁰ identified 7 areas for research funding: (1) early detection, (2) underlying biology, (3) genetic and environmental risk factors, (4) treatments and interventions, (5) services and implementation science, (6) lifespan services and supports, and (7) epidemiological surveillance and infrastructure.⁵⁷¹ The committee recommended that multiple levels of inquiry be pursued simultaneously to inform evidence-based clinical care. These levels include the following:

- basic and translational science in the areas of genetics and epigenetics, neurobiology, and psychopharmacology to understand typical and atypical brain development and function to develop ASD-specific behavioral and pharmacologic therapies; additional research is needed to identify and understand ASD risk factors that might be mitigated to reduce ASD-related disability;
- research into the underlying neurobiology of sensory symptoms and restricted interests and repetitive behaviors to inform development of targeted interventions;
- clinical trials to test focused interventions based on the underlying biological processes involved with ASD to determine if they are appropriate for community application;
- epidemiological surveillance to gather data important for planning for current and future needs, including screening, diagnosis, and lifespan health and mental health services; and
- health services research to provide guidance for comprehensive, accessible, and culturally appropriate medical, educational, and behavioral care for children, youth, adults, and families affected by ASD.

Research in all of these areas is critical to move forward with early diagnosis, effective treatment, and evidence-based interventions at each age.

PEDIATRIC RECOMMENDATIONS

To provide appropriate care to all children and families affected by ASD, health, education, and public health systems need to collaborate and build integrated and adequately funded and staffed systems.

- Early identification and treatment: Pediatric providers should use screening and surveillance to provide accurate and early identification, cost-effective and timely diagnosis, prompt implementation of evidence-based interventions, and elimination of disparities to access to care for children with ASD. Clinicians should respond appropriately to family or clinical concerns and results of screening to avoid delays in diagnosis and treatment.
- Collaboration of systems of care: Children with ASD should be provided evidence-based services to address social, academic, and behavioral needs at home and school; access to appropriate pediatric and mental health care; respite services; and leisure activities.
- Planning for adolescence and transition to adult systems of care: Communities should build services to promote social skills appropriate for work and postsecondary education, access to appropriate medical and behavioral health services, job skills development, and community leisure opportunities. Pediatricians need to engage with families and youth to plan a transition to adult medical and behavioral health care. The medical home provider should support the family and youth in advocating for appropriate

postsecondary work or schooling, residential supports, and activities to maintain a healthy lifestyle.

- Informed individuals and families: The pediatrician can educate youth with ASD and their families about the evidence for interventions, refer families for possible participation in clinical research when appropriate, refer families to support organizations, and prepare families to navigate transitions.
- Informed pediatric providers: To best serve patients and families affected by ASD, the clinician caring for children and youth with ASD should be familiar with issues related to diagnosis, coexisting medical and behavioral conditions, and the impact of ASD on the family to provide a medical home for these patients. Actively addressing capacity building to care for children and youth with ASD requires initiatives directed at provider education and practice quality improvement and public health, educational, and social programs to support families in their journey from diagnosis to service provision to transition to adult care.

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ABBREVIATIONS

AAC: augmentative and alternative communication
 AAP: American Academy of Pediatrics
 ABA: applied behavior analysis
 ADDM: Autism and Developmental Disabilities Monitoring
 ADHD: attention-deficit/hyperactivity disorder
 ADI-R: Autism Diagnostic Inventory-Revised
 ADOS-2: Autism Diagnostic Observation Schedule, Second Edition
 ASD: autism spectrum disorder
 CARS-2: Childhood Autism Rating Scale, Second Edition
 CDC: Centers for Disease Control and Prevention
 CMA: chromosomal microarray
 CNV: copy number variant
 CTM: comprehensive treatment model
 DSM: *Diagnostic and Statistical Manual of Mental Disorders*

DSM-5: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
 DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
 DSM-IV-TR: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*
 ESDM: Early Start Denver Model
 GI: gastrointestinal
 IDEA: Individuals with Disabilities Education Improvement Act of 2004
 IEP: Individualized Education Program
 LEAP: Learning Experiences and Alternative Programs for Preschoolers and their Parents
 M-CHAT: Modified Checklist for Autism in Toddlers
 M-CHAT-R/F: Modified Checklist for Autism in Toddlers, Revised with Follow-Up (Questions)

NDBI: naturalistic developmental behavioral intervention
 OCD: obsessive-compulsive disorder
 PDD: pervasive developmental disorder
 PDD-NOS: pervasive developmental disorder not otherwise specified
 RCT: randomized controlled trial
 SCQ: Social Communication Questionnaire
 SRS: Social Responsiveness Scale
 SSI: Supplemental Security Income
 SSRI: selective serotonin reuptake inhibitor
 STAT: Screening Tool for Autism in Toddlers and Young Children
 TEACCH: Treatment and Education of Autistic and Related Communication-Handicapped Children
 USPSTF: US Preventive Services Task Force
 WES: whole-exome sequencing

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: MeMix LLC is a company that makes an application (for phones). Dr Levy is on the advisory board for the application's development. This application is being developed to assist in nutritional and dietary management of children with autism. Dr Levy has not received any money yet from this company. This application is the focus of a National Institutes of Health R21 grant, for which Dr Levy is funded for ~2% of her salary. Once it is studied and marketed (if appropriate), Dr Levy will (possibly in the future) earn some money. Her years of relationship with the company are 2015 to the present. Dr Hyman has a relationship with Roche. Dr Hyman is the site principal investigator of a clinical trial of a novel agent being tested to promote social function in patients with autism. The University of Rochester (Dr Hyman's institution) was 1 of >40 sites and had 2 study participants in 2018. University of Rochester will be leaving the trial in 2019 (withdrawal submitted) because of staffing, and that reimbursement for staff time does not cover the cost of participation. Funding was for the staff to complete the assessments required for the clinical trial. Dr Hyman got no personal reimbursement from the company; the funding was for staff time for recruitment and assessment and clinical research center support for the trial.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2019-3448.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, 5th ed. Washington, DC: American Psychiatric Association; 2013
2. Baio J, Wiggins L, Christensen DL, et al. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR Surveill Summ*. 2018;67(6):1–23
3. Leigh JP, Du J. Brief report: forecasting the economic burden of autism in 2015 and 2025 in the United States. *J Autism Dev Disord*. 2015;45(12):4135–4139
4. Buescher AV, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatr*. 2014;168(8):721–728
5. 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
6. Myers SM, Johnson CP; American Academy of Pediatrics Council on Children With Disabilities. Management of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1162–1182
7. Daniels AM, Mandell DS. Explaining differences in age at autism spectrum disorder diagnosis: a critical review. *Autism*. 2014;18(5):583–597
8. Kim YS, Fombonne E, Koh YJ, Kim SJ, Cheon KA, Leventhal BL. A comparison of DSM-IV pervasive developmental disorder and DSM-5 autism spectrum disorder prevalence in an epidemiologic sample. *J Am Acad Child Adolesc Psychiatry*. 2014;53(5):500–508
9. Council on Children With Disabilities; Section on Developmental Behavioral Pediatrics; Bright Futures Steering Committee; Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening [published correction appears in *Pediatrics*. 2006;118(4):1808–1809]. *Pediatrics*. 2006;118(1):405–420
10. King M, Bearman P. Diagnostic change and the increased prevalence of autism. *Int J Epidemiol*. 2009;38(5):1224–1234
11. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. *Psychol Med*. 2015;45(3):601–613
12. Tomlinson M, Yasamy MT, Emerson E, Officer A, Richler D, Saxena S. Setting global research priorities for developmental disabilities, including intellectual disabilities and autism. *J Intellect Disabil Res*. 2014;58(12):1121–1130
13. Xu G, Strathearn L, Liu B, Bao W. Prevalence of autism spectrum disorder among US children and adolescents, 2014-2016 [published correction appears in *JAMA*. 2018;319(5):505]. *JAMA*. 2018;319(1):81–82
14. Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators; Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill Summ*. 2014;63(2):1–21
15. Christensen DL, Baio J, Van Naarden Braun K, et al; Centers for Disease Control and Prevention (CDC). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2012 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2016;65(15):404]. *MMWR Surveill Summ*. 2016;65(3):1–23
16. Sheldrick RC, Maye MP, Carter AS. Age at first identification of autism spectrum disorder: an analysis of two US surveys. *J Am Acad Child Adolesc Psychiatry*. 2017;56(4):313–320
17. Christensen DL, Bilder DA, Zahorodny W, et al. Prevalence and characteristics of autism spectrum disorder among 4-

- year-old children in the Autism and Developmental Disabilities Monitoring Network. *J Dev Behav Pediatr*. 2016; 37(1):1–8
18. Barbaresi WJ. The meaning of “regression” in children with autism spectrum disorder: why does it matter? *J Dev Behav Pediatr*. 2016;37(6):506–507
 19. Bradley CC, Boan AD, Cohen AP, Charles JM, Carpenter LA. Reported history of developmental regression and restricted, repetitive behaviors in children with autism spectrum disorders. *J Dev Behav Pediatr*. 2016; 37(6):451–456
 20. Tammimies K. Genetic mechanisms of regression in autism spectrum disorder. *Neurosci Biobehav Rev*. 2019; 102:208–220
 21. Huerta M, Bishop SL, Duncan A, Hus V, Lord C. Application of DSM-5 criteria for autism spectrum disorder to three samples of children with DSM-IV diagnoses of pervasive developmental disorders. *Am J Psychiatry*. 2012; 169(10):1056–1064
 22. Lord C, Petkova E, Hus V, et al. A multisite study of the clinical diagnosis of different autism spectrum disorders. *Arch Gen Psychiatry*. 2012;69(3): 306–313
 23. Mandy WP, Charman T, Skuse DH. Testing the construct validity of proposed criteria for DSM-5 autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51(1):41–50
 24. Mazurek MO, Lu F, Symecko H, et al. A prospective study of the concordance of DSM-IV and DSM-5 diagnostic criteria for autism spectrum disorder. *J Autism Dev Disord*. 2017;47(9):2783–2794
 25. Maenner MJ, Rice CE, Arneson CL, et al. Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. *JAMA Psychiatry*. 2014;71(3): 292–300
 26. Wiggins L, Christensen D, Van Naarden Braun K, Martin L, Baio J. Comparison of autism spectrum disorder surveillance status based on two different diagnostic schemes: findings from the Metropolitan Atlanta Developmental Disabilities Surveillance Program, 2012. *PLoS One*. 2018;13(11): e0208079
 27. Wiggins LD, Rice CE, Barger B, et al. DSM-5 criteria for autism spectrum disorder maximizes diagnostic sensitivity and specificity in preschool children. *Soc Psychiatry Psychiatr Epidemiol*. 2019;54(6):693–701
 28. Mazurek MO, Lu F, Macklin EA, Handen BL. Factors associated with DSM-5 severity level ratings for autism spectrum disorder. *Autism*. 2019;23(2): 468–476
 29. Hus V, Lord C. The autism diagnostic observation schedule, module 4: revised algorithm and standardized severity scores. *J Autism Dev Disord*. 2014;44(8):1996–2012
 30. Shumway S, Farmer C, Thurm A, Joseph L, Black D, Golden C. The ADOS calibrated severity score: relationship to phenotypic variables and stability over time. *Autism Res*. 2012;5(4): 267–276
 31. Kanne SM, Mazurek MO, Sikora D, et al. The Autism Impact Measure (AIM): initial development of a new tool for treatment outcome measurement. *J Autism Dev Disord*. 2014;44(1): 168–179
 32. Mandy W, Wang A, Lee I, Skuse D. Evaluating social (pragmatic) communication disorder. *J Child Psychol Psychiatry*. 2017;58(10): 1166–1175
 33. World Health Organization. International classification of diseases for mortality and morbidity statistics (11th Revision). Geneva, Switzerland: World Health Organization; 2018. Available at: <https://icd.who.int/browse11/l-m/en>. Accessed December 1, 2019
 34. Coury D. Medical treatment of autism spectrum disorders. *Curr Opin Neurol*. 2010;23(2):131–136
 35. Tager-Flusberg H, Kasari C. Minimally verbal school-aged children with autism spectrum disorder: the neglected end of the spectrum. *Autism Res*. 2013;6(6):468–478
 36. Kim SH, Macari SL, Koller J, Chawarska K. Examining the phenotypic heterogeneity of early autism spectrum disorder: subtypes and short-term outcomes. *J Child Psychol Psychiatry*. 2016;57(1):93–102
 37. Ozonoff S, Young GS, Landa R, et al. Diagnostic stability in young children at risk for autism spectrum disorder: a baby siblings research consortium study. *J Child Psychol Psychiatry*. 2015; 56(9):988–998
 38. Jashar DT, Brennan LA, Barton ML, Fein D. Cognitive and adaptive skills in toddlers who meet criteria for autism in DSM-IV but not DSM-5. *J Autism Dev Disord*. 2016;46(12):3667–3677
 39. Guthrie W, Swineford LB, Nottke C, Wetherby AM. Early diagnosis of autism spectrum disorder: stability and change in clinical diagnosis and symptom presentation. *J Child Psychol Psychiatry*. 2013;54(5):582–590
 40. Bennett TA, Szatmari P, Georgiades K, et al; Pathways in ASD Study Team. Language impairment and early social competence in preschoolers with autism spectrum disorders: a comparison of DSM-5 profiles. *J Autism Dev Disord*. 2014;44(11): 2797–2808
 41. Anderson DK, Liang JW, Lord C. Predicting young adult outcome among more and less cognitively able individuals with autism spectrum disorders. *J Child Psychol Psychiatry*. 2014;55(5):485–494
 42. Wiggins LD, Baio J, Schieve L, Lee LC, Nicholas J, Rice CE. Retention of autism spectrum diagnoses by community professionals: findings from the autism and developmental disabilities monitoring network, 2000 and 2006. *J Dev Behav Pediatr*. 2012;33(5):387–395
 43. Zwaigenbaum L, Bauman ML, Fein D, et al. Early screening of autism spectrum disorder: recommendations for practice and research. *Pediatrics*. 2015;136(suppl 1):S41–S59
 44. Gotham K, Pickles A, Lord C. Trajectories of autism severity in children using standardized ADOS scores. *Pediatrics*. 2012;130(5). Available at: www.pediatrics.org/cgi/content/full/130/5/e1278
 45. Pugliese CE, Anthony L, Strang JF, Dudley K, Wallace GL, Kenworthy L. Increasing adaptive behavior skill deficits from childhood to adolescence in autism spectrum disorder: role of executive function. *J Autism Dev Disord*. 2015;45(6):1579–1587

46. Magiati I, Tay XW, Howlin P. Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: a systematic review of longitudinal follow-up studies in adulthood. *Clin Psychol Rev*. 2014; 34(1):73–86
47. Renty JO, Roeyers H. Quality of life in high-functioning adults with autism spectrum disorder: the predictive value of disability and support characteristics. *Autism*. 2006;10(5): 511–524
48. Zwaigenbaum L, Bauman ML, Choueiri R, et al. Early intervention for children with autism spectrum disorder under 3 years of age: recommendations for practice and research. *Pediatrics*. 2015; 136(suppl 1):S60–S81
49. Lipkin PH, Macias MM; American Academy of Pediatrics, Council on Children With Disabilities, Section on Developmental and Behavioral Pediatrics. Promoting optimal development: identifying infants and young children with developmental disorders through developmental surveillance and screening. *Pediatrics*. 2020;145(1):e20193449
50. Gabrielsen TP, Farley M, Speer L, Villalobos M, Baker CN, Miller J. Identifying autism in a brief observation. *Pediatrics*. 2015;135(2). Available at: www.pediatrics.org/cgi/content/full/135/2/e330
51. Robins DL, Casagrande K, Barton M, Chen CM, Dumont-Mathieu T, Fein D. Validation of the modified checklist for autism in toddlers, revised with follow-up (M-CHAT-R/F). *Pediatrics*. 2014; 133(1):37–45
52. Centers for Disease Control and Prevention. Screening and diagnosis of autism spectrum disorder. Available at: <https://www.cdc.gov/ncbddd/autism/screening.html>. Accessed December 1, 2019
53. Autism Speaks. Learn the signs. Available at: <https://www.autismspeaks.org/what-autism/from-first-concern-to-action/get-child-screened>. Accessed December 1, 2019
54. American Academy of Pediatrics. Periodic survey: cross-survey results and findings. 2018. Available at: <https://www.aap.org/en-us/professional-resources/Research/pediatrician-surveys/Pages/Periodic-Survey-List-of-Surveys-and-Summary-of-Findings.aspx>. Accessed December 16, 2018
55. Pinto-Martin JA, Young LM, Mandell DS, Poghosyan L, Giarelli E, Levy SE. Screening strategies for autism spectrum disorders in pediatric primary care. *J Dev Behav Pediatr*. 2008;29(5):345–350
56. Norris M, Lecavalier L. Screening accuracy of level 2 autism spectrum disorder rating scales. A review of selected instruments. *Autism*. 2010; 14(4):263–284
57. Zwaigenbaum L, Bauman ML, Stone WL, et al. Early identification of autism spectrum disorder: recommendations for practice and research. *Pediatrics*. 2015;136(suppl 1):S10–S40
58. Rotholz DA, Kinsman AM, Lacy KK, Charles J. Improving early identification and intervention for children at risk for autism spectrum disorder. *Pediatrics*. 2017;139(2):e20161061
59. Wetherby AM, Brosnan-Maddox S, Peace V, Newton L. Validation of the Infant-Toddler Checklist as a broadband screener for autism spectrum disorders from 9 to 24 months of age. *Autism*. 2008;12(5):487–511
60. Herlihy LE, Brooks B, Dumont-Mathieu T, et al. Standardized screening facilitates timely diagnosis of autism spectrum disorders in a diverse sample of low-risk toddlers. *J Dev Behav Pediatr*. 2014; 35(2):85–92
61. Zuckerman KE, Mattox K, Donelan K, Batbayar O, Baghaee A, Bethell C. Pediatrician identification of Latino children at risk for autism spectrum disorder. *Pediatrics*. 2013;132(3): 445–453
62. Sheldrick RC, Perrin EC. Evidence-based milestones for surveillance of cognitive, language, and motor development. *Acad Pediatr*. 2013;13(6):577–586
63. Siu AL, Bibbins-Domingo K, Grossman DC, et al; US Preventive Services Task Force (USPSTF). Screening for autism spectrum disorder in young children: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;315(7):691–696
64. Rogers SJ, Vismara LA. Evidence-based comprehensive treatments for early autism. *J Clin Child Adolesc Psychol*. 2008;37(1):8–38
65. Zwaigenbaum L, Bryson SE, Brian J, et al. Stability of diagnostic assessment for autism spectrum disorder between 18 and 36 months in a high-risk cohort. *Autism Res*. 2016;9(7):790–800
66. Barger B, Rice C, Wolf R, Roach A. Better together: developmental screening and monitoring best identify children who need early intervention. *Disabil Health J*. 2018;11(3):420–426
67. Chesnut SR, Wei T, Barnard-Brak L, Richman DM. A meta-analysis of the social communication questionnaire: screening for autism spectrum disorder. *Autism*. 2017;21(8):920–928
68. Schwenck C, Freitag CM. Differentiation between attention-deficit/hyperactivity disorder and autism spectrum disorder by the social communication questionnaire. *Atten Defic Hyperact Disord*. 2014;6(3):221–229
69. Miodovnik A, Harstad E, Sideridis G, Huntington N. Timing of the diagnosis of attention-deficit/hyperactivity disorder and autism spectrum disorder. *Pediatrics*. 2015;136(4). Available at: www.pediatrics.org/cgi/content/full/136/4/e830
70. Ratto AB, Kenworthy L, Yerys BE, et al. What about the girls? Sex-based differences in autistic traits and adaptive skills. *J Autism Dev Disord*. 2018;48(5):1698–1711
71. Scarpa A, Reyes NM, Patriquin MA, et al. The modified checklist for autism in toddlers: reliability in a diverse rural American sample. *J Autism Dev Disord*. 2013;43(10):2269–2279
72. Burkett K, Morris E, Manning-Courtney P, Anthony J, Shambley-Ebron D. African American families on autism diagnosis and treatment: the influence of culture. *J Autism Dev Disord*. 2015;45(10): 3244–3254
73. Zuckerman KE, Lindly OJ, Reyes NM, et al. Disparities in diagnosis and treatment of autism in Latino and non-Latino white families. *Pediatrics*. 2017; 139(5):e20163010
74. Daniels AM, Halladay AK, Shih A, Elder LM, Dawson G. Approaches to enhancing the early detection of autism spectrum disorders: a systematic review of the literature. *J Am Acad*

- Child Adolesc Psychiatry*. 2014;53(2): 141–152
75. Jones RM, Lord C. Diagnosing autism in neurobiological research studies. *Behav Brain Res*. 2013;251:113–124
 76. Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). 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
 77. Corsello C, Hus V, Pickles A, et al. Between a ROC and a hard place: decision making and making decisions about using the SCQ. *J Child Psychol Psychiatry*. 2007;48(9):932–940
 78. Constantino JN, Davis SA, Todd RD, et al. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. *J Autism Dev Disord*. 2003;33(4): 427–433
 79. Bradstreet LE, Juechter JI, Kamphaus RW, Kerns CM, Robins DL. Using the BASC-2 parent rating scales to screen for autism spectrum disorder in toddlers and preschool-aged children. *J Abnorm Child Psychol*. 2017;45(2): 359–370
 80. Leekam SR, Libby SJ, Wing L, Gould J, Taylor C. The Diagnostic Interview for Social and Communication Disorders: algorithms for ICD-10 childhood autism and Wing and Gould autistic spectrum disorder. *J Child Psychol Psychiatry*. 2002;43(3):327–342
 81. Wing L, Leekam SR, Libby SJ, Gould J, Larcombe M. The Diagnostic Interview for Social and Communication Disorders: background, inter-rater reliability and clinical use. *J Child Psychol Psychiatry*. 2002;43(3):307–325
 82. Havdahl KA, von Tetzchner S, Huerta M, Lord C, Bishop SL. Utility of the Child Behavior Checklist as a screener for autism spectrum disorder. *Autism Res*. 2016;9(1):33–42
 83. Kim SH, Lord C. New autism diagnostic interview-revised algorithms for toddlers and young preschoolers from 12 to 47 months of age. *J Autism Dev Disord*. 2012;42(1):82–93
 84. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994;24(5): 659–685
 85. Aldridge FJ, Gibbs VM, Schmidhofer K, Williams M. Investigating the clinical usefulness of the Social Responsiveness Scale (SRS) in a tertiary level, autism spectrum disorder specific assessment clinic. *J Autism Dev Disord*. 2012;42(2): 294–300
 86. Dawkins T, Meyer AT, Van Bourgondien ME. The relationship between the Childhood Autism Rating Scale: Second Edition and clinical diagnosis utilizing the DSM-IV-TR and the DSM-5. *J Autism Dev Disord*. 2016;46(10):3361–3368
 87. Lord C, Luyster R, Gotham K, Guthrie W. *Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) Manual (Part II): Toddler Module*. Torrance, CA: Western Psychological Services; 2012
 88. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop SL. *Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) Manual (Part 1): Modules 1-4*. Torrance, CA: Western Psychological Services; 2012
 89. Chlebowski C, Green JA, Barton ML, Fein D. Using the childhood autism rating scale to diagnose autism spectrum disorders. *J Autism Dev Disord*. 2010; 40(7):787–799
 90. Reszka SS, Boyd BA, McBee M, Hume KA, Odom SL. Brief report: concurrent validity of autism symptom severity measures. *J Autism Dev Disord*. 2014; 44(2):466–470
 91. Bryson SE, Bradley EA, Thompson A, Wainwright A. Prevalence of autism among adolescents with intellectual disabilities. *Can J Psychiatry*. 2008; 53(7):449–459
 92. O'Hare A, Bremner L. Management of developmental speech and language disorders: part 1. *Arch Dis Child*. 2016; 101(3):272–277
 93. Kanne SM, Gerber AJ, Quirnbach LM, Sparrow SS, Cicchetti DV, Saulnier CA. The role of adaptive behavior in autism spectrum disorders: implications for functional outcome. *J Autism Dev Disord*. 2011;41(8):1007–1018
 94. Liss M, Harel B, Fein D, et al. Predictors and correlates of adaptive functioning in children with developmental disorders. *J Autism Dev Disord*. 2001; 31(2):219–230
 95. Kenworthy L, Case L, Harms MB, Martin A, Wallace GL. Adaptive behavior ratings correlate with symptomatology and IQ among individuals with high-functioning autism spectrum disorders. *J Autism Dev Disord*. 2010;40(4): 416–423
 96. Dewey D, Cantell M, Crawford SG. Motor and gestural performance in children with autism spectrum disorders, developmental coordination disorder, and/or attention deficit hyperactivity disorder. *J Int Neuropsychol Soc*. 2007; 13(2):246–256
 97. Bhat AN, Galloway JC, Landa RJ. Relationship between early motor delay and later communication delay in infants at risk for autism. *Infant Behav Dev*. 2012;35(4):838–846
 98. Provost B, Lopez BR, Heimerl S. A comparison of motor delays in young children: autism spectrum disorder, developmental delay, and developmental concerns. *J Autism Dev Disord*. 2007;37(2):321–328
 99. Beers AN, McBoyle M, Kakande E, Dar Santos RC, Kozak FK. Autism and peripheral hearing loss: a systematic review. *Int J Pediatr Otorhinolaryngol*. 2014;78(1):96–101
 100. Bennetto L, Keith JM, Allen PD, Luebke AE. Children with autism spectrum disorder have reduced otoacoustic emissions at the 1 kHz mid-frequency region. *Autism Res*. 2017;10(2):337–345
 101. Dawes P, Bishop D. Auditory processing disorder in relation to developmental disorders of language, communication and attention: a review and critique. *Int J Lang Commun Disord*. 2009;44(4): 440–465
 102. Anketell PM, Saunders KJ, Gallagher SM, Bailey C, Little JA. Brief report: vision in children with autism spectrum disorder: what should clinicians expect? *J Autism Dev Disord*. 2015;45(9): 3041–3047
 103. Rogers SJ, Hepburn S, Wehner E. Parent reports of sensory symptoms in

- toddlers with autism and those with other developmental disorders. *J Autism Dev Disord.* 2003;33(6): 631–642
104. McCormick C, Hepburn S, Young GS, Rogers SJ. Sensory symptoms in children with autism spectrum disorder, other developmental disorders and typical development: a longitudinal study. *Autism.* 2016;20(5): 572–579
 105. Lane AEAE, Molloy CA, Bishop SL. Classification of children with autism spectrum disorder by sensory subtype: a case for sensory-based phenotypes. *Autism Res.* 2014;7(3):322–333
 106. Ausderau KK, Furlong M, Sideris J, et al. Sensory subtypes in children with autism spectrum disorder: latent profile transition analysis using a national survey of sensory features. *J Child Psychol Psychiatry.* 2014;55(8): 935–944
 107. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010;86(5): 749–764
 108. Manning M, Hudgins L; Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* 2010;12(11):742–745
 109. 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
 110. Muhle RA, Reed HE, Vo LC, et al. Clinical diagnostic genetic testing for individuals with developmental disorders. *J Am Acad Child Adolesc Psychiatry.* 2017;56(11):910–913
 111. Sun F, Oristaglio J, Levy SE, et al. *Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder.* Rockville, MD: Agency for Healthcare Research and Quality (US); 2015
 112. Amiet C, Couchon E, Carr K, Carayol J, Cohen D. Are there cultural differences in parental interest in early diagnosis and genetic risk assessment for autism spectrum disorder? *Front Pediatr.* 2014; 2:32
 113. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. *Ann Neurol.* 2014;76(4):473–483
 114. Iglesias A, Anyane-Yeboha K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med.* 2014;16(12):922–931
 115. Linggen M, Albers L, Borchers M, et al. Obtaining a genetic diagnosis in a child with disability: impact on parental quality of life. *Clin Genet.* 2016;89(2): 258–266
 116. Riggs ER, Wain KE, Riethmaier D, et al. Chromosomal microarray impacts clinical management. *Clin Genet.* 2014; 85(2):147–153
 117. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2015;17(6): 505–507
 118. Reiff M, Giarelli E, Bernhardt BA, et al. Parents' perceptions of the usefulness of chromosomal microarray analysis for children with autism spectrum disorders. *J Autism Dev Disord.* 2015; 45(10):3262–3275
 119. 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
 120. Myers S, Challman C; American Academy of Pediatrics. Autism Spectrum Disorders. In: *Developmental and Behavioral Pediatrics.* Itasca, IL: American Academy of Pediatrics; 2018: 407–475
 121. Tammimies K, Marshall CR, Walker S, et al. Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. *JAMA.* 2015;314(9):895–903
 122. Alvarez-Mora MI, Calvo Escalona R, Puig Navarro O, et al. Comprehensive molecular testing in patients with high functioning autism spectrum disorder. *Mutat Res.* 2016;784–785:46–52
 123. Fernandez BA, Scherer SW. Syndromic autism spectrum disorders: moving from a clinically defined to a molecularly defined approach. *Dialogues Clin Neurosci.* 2017;19(4): 353–371
 124. Carter MT, Scherer SW. Autism spectrum disorder in the genetics clinic: a review. *Clin Genet.* 2013;83(5): 399–407
 125. Persico AM, Napolioni V. Autism genetics. *Behav Brain Res.* 2013;251: 95–112
 126. Schönewolf-Greulich B, Bisgaard AM, Møller RS, et al. Clinician's guide to genes associated with Rett-like phenotypes—investigation of a Danish cohort and review of the literature. *Clin Genet.* 2019;95(2):221–230
 127. McBride KL, Varga EA, Pastore MT, et al. Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. *Autism Res.* 2010;3(3):137–141
 128. Battaglia A, Doccini V, Bernardini L, et al. Confirmation of chromosomal microarray as a first-tier clinical diagnostic test for individuals with developmental delay, intellectual disability, autism spectrum disorders and dysmorphic features. *Eur J Paediatr Neurol.* 2013;17(6):589–599
 129. Bremer A, Giacobini M, Nordenskjöld M, et al. Screening for copy number alterations in loci associated with autism spectrum disorders by two-color multiplex ligation-dependent probe amplification. *Am J Med Genet B Neuropsychiatr Genet.* 2010;153B(1): 280–285
 130. Eriksson MA, Liedén A, Westerlund J, et al. Rare copy number variants are common in young children with autism spectrum disorder. *Acta Paediatr.* 2015; 104(6):610–618
 131. Ho KS, Wassman ER, Baxter AL, et al. Chromosomal microarray analysis of consecutive individuals with autism spectrum disorders using an ultra-high resolution chromosomal microarray optimized for neurodevelopmental disorders. *Int J Mol Sci.* 2016;17(12): E2070

132. McGrew SG, Peters BR, Crittendon JA, Veenstra-Vanderweele J. Diagnostic yield of chromosomal microarray analysis in an autism primary care practice: which guidelines to implement? *J Autism Dev Disord*. 2012; 42(8):1582–1591
133. Rosenfeld JA, Ballif BC, Torchia BS, et al. Copy number variations associated with autism spectrum disorders contribute to a spectrum of neurodevelopmental disorders. *Genet Med*. 2010;12(11):694–702
134. Schaefer GB, Starr L, Pickering D, Skar G, Dehaai K, Sanger WG. Array comparative genomic hybridization findings in a cohort referred for an autism evaluation. *J Child Neurol*. 2010; 25(12):1498–1503
135. Shen Y, Dies KA, Holm IA, et al; Autism Consortium Clinical Genetics/DNA Diagnostics Collaboration. Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics*. 2010; 125(4). Available at: www.pediatrics.org/cgi/content/full/125/4/e727
136. Roesser J. Diagnostic yield of genetic testing in children diagnosed with autism spectrum disorders at a regional referral center. *Clin Pediatr (Phila)*. 2011;50(9):834–843
137. Tassone F, Choudhary NS, Tassone F, et al. Identification of expanded alleles of the FMR1 gene in the CHildhood Autism Risks from Genes and Environment (CHARGE) study. *J Autism Dev Disord*. 2013;43(3):530–539
138. Iossifov I, Ronemus M, Levy D, et al. De novo gene disruptions in children on the autistic spectrum. *Neuron*. 2012; 74(2):285–299
139. Krumm N, O’Roak BJ, Shendure J, Eichler EE. A de novo convergence of autism genetics and molecular neuroscience. *Trends Neurosci*. 2014; 37(2):95–105
140. Krumm N, Turner TN, Baker C, et al. Excess of rare, inherited truncating mutations in autism. *Nat Genet*. 2015; 47(6):582–588
141. Pisula E, Ziegart-Sadowska K, et al. Broader autism phenotype in siblings of children with ASD—a review. *Int J Mol Sci*. 2015;16(6):13217–13258
142. O’Roak BJ, Vives L, Fu W, et al. Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. *Science*. 2012; 338(6114):1619–1622
143. Lee BK, McGrath JJ. Advancing parental age and autism: multifactorial pathways. *Trends Mol Med*. 2015;21(2): 118–125
144. Retterer K, Juusola J, Cho MT, et al. Clinical application of whole-exome sequencing across clinical indications. *Genet Med*. 2016;18(7):696–704
145. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA*. 2014;312(18):1870–1879
146. Srivastava S, Love-Nichols JA, Dies KA, et al; NDD Exome Scoping Review Work Group. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders [published online ahead of print June 11, 2019]. *Genet Med*. 2019;21(11): 2413–2421
147. Glusman G, Severson A, Dhankani V, et al. Identification of copy number variants in whole-genome data using reference coverage profiles. *Front Genet*. 2015;6:45
148. Jiang YH, Wang Y, Xiu X, Choy KW, Pursley AN, Cheung SW. Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the genomics era. *Crit Rev Clin Lab Sci*. 2014;51(5):249–262
149. Jiang YH, Yuen RK, Jin X, et al. Detection of clinically relevant genetic variants in autism spectrum disorder by whole-genome sequencing. *Am J Hum Genet*. 2013;93(2):249–263
150. Retterer K, Scuffins J, Schmidt D, et al. Assessing copy number from exome sequencing and exome array CGH based on CNV spectrum in a large clinical cohort. *Genet Med*. 2015;17(8): 623–629
151. Ozonoff S, Young GS, Carter A, et al. Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics*. 2011; 128(3). Available at: www.pediatrics.org/cgi/content/full/128/3/e488
152. Jokiranta-Olkoniemi E, Cheslack-Postava K, Sucksdorff D, et al. Risk of psychiatric and neurodevelopmental disorders among siblings of probands with autism spectrum disorders. *JAMA Psychiatry*. 2016;73(6):622–629
153. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. *JAMA*. 2014; 311(17):1770–1777
154. Werling DM, Geschwind DH. Recurrence rates provide evidence for sex-differential, familial genetic liability for autism spectrum disorders in multiplex families and twins. *Mol Autism*. 2015;6: 27
155. Constantino JN, Zhang Y, Frazier T, Abbacchi AM, Law P. Sibling recurrence and the genetic epidemiology of autism. *Am J Psychiatry*. 2010;167(11): 1349–1356
156. Lindgren KA, Folstein SE, Tomblin JB, Tager-Flusberg H. Language and reading abilities of children with autism spectrum disorders and specific language impairment and their first-degree relatives. *Autism Res*. 2009; 2(1):22–38
157. Erbetta A, Bulgheroni S, Contarino VE, et al. Low-functioning autism and nonsyndromic intellectual disability: magnetic resonance imaging (MRI) findings. *J Child Neurol*. 2015;30(12): 1658–1663
158. Vasa RA, Ranta M, Huisman TA, Pinto PS, Tillman RM, Mostofsky SH. Normal rates of neuroradiological findings in children with high functioning autism. *J Autism Dev Disord*. 2012;42(8): 1662–1670
159. Cooper AS, Friedlaender E, Levy SE, et al. The implications of brain MRI in autism spectrum disorder. *J Child Neurol*. 2016;31(14):1611–1616
160. Monterrey JC, Philips J, Cleveland S, et al. Incidental brain MRI findings in an autism twin study. *Autism Res*. 2017; 10(1):113–120
161. 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
162. Moeschler JB, Shevell M; Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays.

- Pediatrics*. 2014;134(3). Available at: www.pediatrics.org/cgi/content/full/134/3/e903
163. Campistol J, Díez-Juan M, Callejón L, et al. Inborn error metabolic screening in individuals with nonsyndromic autism spectrum disorders. *Dev Med Child Neurol*. 2016;58(8):842–847
 164. Hadjixenofontos A, Schmidt MA, Whitehead PL, et al. Evaluating mitochondrial DNA variation in autism spectrum disorders. *Ann Hum Genet*. 2013;77(1):9–21
 165. Herman GE, Henninger N, Ratliff-Schaub K, Pastore M, Fitzgerald S, McBride KL. Genetic testing in autism: how much is enough? *Genet Med*. 2007;9(5):268–274
 166. Schiff M, Benoist JF, Aïssaoui S, et al. Should metabolic diseases be systematically screened in nonsyndromic autism spectrum disorders? [published correction appears in *PLoS One*. 2011;6(8)]. *PLoS One*. 2011;6(7):e21932
 167. Shevell M, Ashwal S, Donley D, et al; Quality Standards Subcommittee of the American Academy of Neurology; Practice Committee of the Child Neurology Society. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2003; 60(3):367–380
 168. Zecavati N, Spence SJ. Neurometabolic disorders and dysfunction in autism spectrum disorders. *Curr Neurol Neurosci Rep*. 2009;9(2):129–136
 169. Council on Environmental Health. Prevention of childhood lead toxicity [published correction appears in *Pediatrics*. 2017;140(2):e20171490]. *Pediatrics*. 2016;138(1):e20161493
 170. 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
 171. Ghacibeh GA, Fields C. Interictal epileptiform activity and autism. *Epilepsy Behav*. 2015;47:158–162
 172. Jeste SS, Tuchman R. Autism spectrum disorder and epilepsy: two sides of the same coin? *J Child Neurol*. 2015;30(14): 1963–1971
 173. Jokiranta E, Sourander A, Suominen A, Timonen-Soivio L, Brown AS, Sillanpää M. Epilepsy among children and adolescents with autism spectrum disorders: a population-based study. *J Autism Dev Disord*. 2014;44(10): 2547–2557
 174. Woolfenden S, Sarkozy V, Ridley G, Coory M, Williams K. A systematic review of two outcomes in autism spectrum disorder - epilepsy and mortality. *Dev Med Child Neurol*. 2012;54(4):306–312
 175. Yasuhara A. Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). *Brain Dev*. 2010;32(10):791–798
 176. Kagan-Kushnir T, Roberts SW, Snead OC III. Screening electroencephalograms in autism spectrum disorders: evidence-based guideline. *J Child Neurol*. 2005; 20(3):197–206
 177. Tick B, Bolton P, Happé F, Rutter M, Rijdsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *J Child Psychol Psychiatry*. 2016;57(5):585–595
 178. Nordenbæk C, Jørgensen M, Kyvik KO, Bilenberg N. A Danish population-based twin study on autism spectrum disorders. *Eur Child Adolesc Psychiatry*. 2014;23(1):35–43
 179. Charman T, Young GS, Brian J, et al. Non-ASD outcomes at 36 months in siblings at familial risk for autism spectrum disorder (ASD): a baby siblings research consortium (BSRC) study. *Autism Res*. 2017;10(1):169–178
 180. Bailey A, Le Couteur A, Gottesman I, et al. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med*. 1995;25(1):63–77
 181. Robinson EB, Neale BM, Hyman SE. Genetic research in autism spectrum disorders. *Curr Opin Pediatr*. 2015; 27(6):685–691
 182. Bourgeron T. Current knowledge on the genetics of autism and propositions for future research. *C R Biol*. 2016;339(7–8): 300–307
 183. Tick B, Bolton P, Happé F, Rutter M, Rijdsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *J Child Psychol Psychiatry*. 2016;57(5):585–595
 184. Colvert E, Tick B, McEwen F, et al. Heritability of autism spectrum disorder in a UK population-based twin sample. *JAMA Psychiatry*. 2015;72(5): 415–423
 185. Sandin S, Hultman CM, Kolevzon A, Gross R, MacCabe JH, Reichenberg A. Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis [published correction appears in *J Am Acad Child Adolesc Psychiatry*. 2012;51(6):660]. *J Am Acad Child Adolesc Psychiatry*. 2012;51(5):477–486.e1
 186. Sandin S, Schendel D, Magnusson P, et al. Autism risk associated with parental age and with increasing difference in age between the parents. *Mol Psychiatry*. 2016;21(5):693–700
 187. Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. *Mol Psychiatry*. 2011;16(12):1203–1212
 188. Kong A, Frigge ML, Masson G, et al. Rate of de novo mutations and the importance of father's age to disease risk. *Nature*. 2012;488(7412):471–475
 189. Bourgeron T. From the genetic architecture to synaptic plasticity in autism spectrum disorder. *Nat Rev Neurosci*. 2015;16(9):551–563
 190. 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
 191. De Rubeis S, Buxbaum JD. Genetics and genomics of autism spectrum disorder: embracing complexity. *Hum Mol Genet*. 2015;24(R1):R24–R31
 192. Sanders SJ, He X, Willsey AJ, et al; Autism Sequencing Consortium. Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. *Neuron*. 2015;87(6): 1215–1233
 193. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014;312(18): 1880–1887

194. Liu X, Takumi T. Genomic and genetic aspects of autism spectrum disorder. *Biochem Biophys Res Commun*. 2014; 452(2):244–253
195. Rossi M, El-Khechen D, Black MH, Farwell Hagman KD, Tang S, Powis Z. Outcomes of diagnostic exome sequencing in patients with diagnosed or suspected autism spectrum disorders. *Pediatr Neurol*. 2017;70: 34–43.e2
196. Brandler WM, Sebat J. From de novo mutations to personalized therapeutic interventions in autism. *Annu Rev Med*. 2015;66:487–507
197. Coe BP, Girirajan S, Eichler EE. The genetic variability and commonality of neurodevelopmental disease. *Am J Med Genet C Semin Med Genet*. 2012;160C(2): 118–129
198. Gonzalez-Mantilla AJ, Moreno-De-Luca A, Ledbetter DH, Martin CL. A cross-disorder method to identify novel candidate genes for developmental brain disorders. *JAMA Psychiatry*. 2016; 73(3):275–283
199. Li J, Cai T, Jiang Y, et al. Genes with de novo mutations are shared by four neuropsychiatric disorders discovered from NPdenovo database [published correction appears in *Mol Psychiatry*. 2016;21(2):298]. *Mol Psychiatry*. 2016; 21(2):290–297
200. Moreno-De-Luca A, Myers SM, Challman TD, Moreno-De-Luca D, Evans DW, Ledbetter DH. Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence [published correction appears in *Lancet Neurol*. 2013;12(5):423]. *Lancet Neurol*. 2013;12(4):406–414
201. Mullin AP, Gokhale A, Moreno-De-Luca A, Sanyal S, Waddington JL, Faundez V. Neurodevelopmental disorders: mechanisms and boundary definitions from genomes, interactomes and proteomes. *Transl Psychiatry*. 2013;3: e329
202. Pescosolido MF, Gamsiz ED, Nagpal S, Morrow EM. Distribution of disease-associated copy number variants across distinct disorders of cognitive development. *J Am Acad Child Adolesc Psychiatry*. 2013;52(4):414–430.e14
203. Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJL, Nurnberger Jr Jr, Hallmayer JF. Autism genetics: opportunities and challenges for clinical translation. *Nat Rev Genet*. 2017; 18(6):362–376
204. Waltereit R, Banaschewski T, Meyer-Lindenberg A, Poustka L. Interaction of neurodevelopmental pathways and synaptic plasticity in mental retardation, autism spectrum disorder and schizophrenia: implications for psychiatry. *World J Biol Psychiatry*. 2014;15(7):507–516
205. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. *Pediatrics*. 2011;128(2):344–355
206. Christensen J, Grønberg TK, Sørensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA*. 2013; 309(16):1696–1703
207. Bromley RL, Mawer G, Clayton-Smith J, Baker GA; Liverpool and Manchester Neurodevelopment Group. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology*. 2008;71(23):1923–1924
208. Dodds L, Fell DB, Shea S, Armson BA, Allen AC, Bryson S. The role of prenatal, obstetric and neonatal factors in the development of autism. *J Autism Dev Disord*. 2011;41(7):891–902
209. Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Advanced parental age and autism risk in children: a systematic review and meta-analysis. *Acta Psychiatr Scand*. 2017;135(1):29–41
210. Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. *Pediatrics*. 2011;128(5): 883–891
211. Lampi KM, Lehtonen L, Tran PL, et al. Risk of autism spectrum disorders in low birth weight and small for gestational age infants. *J Pediatr*. 2012; 161(5):830–836
212. Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. *Acta Obstet Gynecol Scand*. 2012;91(3): 287–300
213. Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry*. 2011; 168(10):1041–1049
214. Kalkbrenner AE, Schmidt RJ, Penlesky AC. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. *Curr Probl Pediatr Adolesc Health Care*. 2014;44(10):277–318
215. Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient air pollution and autism in Los Angeles county, California. *Environ Health Perspect*. 2013;121(3):380–386
216. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry*. 2013;70(1): 71–77
217. Mazina V, Gerds J, Trinh S, et al. Epigenetics of autism-related impairment: copy number variation and maternal infection. *J Dev Behav Pediatr*. 2015;36(2):61–67
218. Braunschweig D, Van de Water J. Maternal autoantibodies in autism. *Arch Neurol*. 2012;69(6):693–699
219. Brimberg L, Sadiq A, Gregersen PK, Diamond B. Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. *Mol Psychiatry*. 2013;18(11):1171–1177
220. Bauman MD, Iosif AM, Ashwood P, et al. Maternal antibodies from mothers of children with autism alter brain growth and social behavior development in the rhesus monkey. *Transl Psychiatry*. 2013; 3:e278
221. Anderson GM. Autism biomarkers: challenges, pitfalls and possibilities. *J Autism Dev Disord*. 2015;45(4): 1103–1113
222. McDougle CJ, Landino SM, Vahabzadeh A, et al. Toward an immune-mediated subtype of autism spectrum disorder. *Brain Res*. 2015;1617:72–92
223. Isles AR. Neural and behavioral epigenetics; what it is, and what is hype. *Genes Brain Behav*. 2015;14(1): 64–72
224. Tordjman S, Somogyi E, Coulon N, et al. Gene × Environment interactions in autism spectrum disorders: role of epigenetic mechanisms. *Front Psychiatry*. 2014;5:53

225. Bohacek J, Mansuy IM. Molecular insights into transgenerational non-genetic inheritance of acquired behaviours. *Nat Rev Genet.* 2015;16(11):641–652
226. Ladd-Acosta C, Hansen KD, Briem E, Fallin MD, Kaufmann WE, Feinberg AP. Common DNA methylation alterations in multiple brain regions in autism. *Mol Psychiatry.* 2014;19(8):862–871
227. Loke YJ, Hannan AJ, Craig JM. The role of epigenetic change in autism spectrum disorders. *Front Neurol.* 2015;6:107
228. Wong CC, Meaburn EL, Ronald A, et al. Methyloomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits. *Mol Psychiatry.* 2014;19(4):495–503
229. Jain A, Marshall J, Buikema A, Bancroft T, Kelly JP, Newschaffer CJ. Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *JAMA.* 2015;313(15):1534–1540
230. Uno Y, Uchiyama T, Kurosawa M, Aleksic B, Ozaki N. Early exposure to the combined measles-mumps-rubella vaccine and thimerosal-containing vaccines and risk of autism spectrum disorder. *Vaccine.* 2015;33(21):2511–2516
231. Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine.* 2014;32(29):3623–3629
232. Maglione MA, Das L, Raaen L, et al. Safety of vaccines used for routine immunization of U.S. children: a systematic review. *Pediatrics.* 2014;134(2):325–337
233. DeStefano F, Price CS, Weintraub ES. Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. *J Pediatr.* 2013;163(2):561–567
234. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. *Cochrane Database Syst Rev.* 2012;(2):CD004407
235. Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis.* 2009;48(4):456–461
236. Schechter R, Grether JK. Continuing increases in autism reported to California's developmental services system: mercury in retrograde. *Arch Gen Psychiatry.* 2008;65(1):19–24
237. Baird G, Pickles A, Simonoff E, et al. Measles vaccination and antibody response in autism spectrum disorders. *Arch Dis Child.* 2008;93(10):832–837
238. Fombonne E, Zakarian R, Bennett A, Meng L, McLean-Heywood D. Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations. *Pediatrics.* 2006;118(1). Available at: www.pediatrics.org/cgi/content/full/118/1/e139
239. Institute of Medicine Immunization Safety Review Committee. *Immunization Safety Review: Vaccines and Autism.* Washington, DC: National Academies Press; 2004
240. Jefferson T, Price D, Demicheli V, Bianco E; European Research Program for Improved Vaccine Safety Surveillance (EUSAFEVAC) Project. Unintended events following immunization with MMR: a systematic review. *Vaccine.* 2003;21(25–26):3954–3960
241. Klein KC, Diehl EB. Relationship between MMR vaccine and autism. *Ann Pharmacother.* 2004;38(7–8):1297–1300
242. Mutter J, Naumann J, Schneider R, Walach H, Haley B. Mercury and autism: accelerating evidence? *Neuro Endocrinol Lett.* 2005;26(5):439–446
243. Kimmel SR, Burns IT, Wolfe RM, Zimmerman RK. Addressing immunization barriers, benefits, and risks. *J Fam Pract.* 2007;56(suppl 2):S61–S69
244. Parker SK, Schwartz B, Todd J, Pickering LK. Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data [published correction appears in *Pediatrics.* 2005;115(1):200]. *Pediatrics.* 2004;114(3):793–804
245. Ortvist Å, Blennow M, Carlsson RM, et al. Vaccination of children—a systematic review. *Acta Paediatr.* 2010;99(461):1–192
246. Wilson K, Mills E, Ross C, McGowan J, Jadad A. Association of autistic spectrum disorder and the measles, mumps, and rubella vaccine: a systematic review of current epidemiological evidence. *Arch Pediatr Adolesc Med.* 2003;157(7):628–634
247. Clarke CE, Weberling McKeever B, Holton A, Dixon GN. The influence of weight-of-evidence messages on (vaccine) attitudes: a sequential mediation model. *J Health Commun.* 2015;20(11):1302–1309
248. Nyhan B, Reifler J, Richey S, Freed GL. Effective messages in vaccine promotion: a randomized trial. *Pediatrics.* 2014;133(4). Available at: www.pediatrics.org/cgi/content/full/133/4/e835
249. Casanova MF. The neuropathology of autism. In: Volkmar FR, Rogers SJ, Paul R, Pelphrey KA, eds. *Handbook of Autism and Pervasive Developmental Disorders, 4th ed, Vol 1.* Hoboken, NJ: Wiley & Sons; 2014:346–351
250. Chen JA, Peñagarikano O, Belgard TG, Swarup V, Geschwind DH. The emerging picture of autism spectrum disorder: genetics and pathology. *Annu Rev Pathol.* 2015;10:111–144
251. Wegiel J, Kuchna I, Nowicki K, et al. The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta Neuropathol.* 2010;119(6):755–770
252. Stoner R, Chow ML, Boyle MP, et al. Patches of disorganization in the neocortex of children with autism. *N Engl J Med.* 2014;370(13):1209–1219
253. Walsh P, Elsabbagh M, Bolton P, Singh I. In search of biomarkers for autism: scientific, social and ethical challenges. *Nat Rev Neurosci.* 2011;12(10):603–612
254. Goldani AAS, Downs SR, Widjaja F, Lawton B, Hendren RL. Biomarkers in autism. *Front Psychiatry.* 2014;5:100
255. Ruggeri B, Sarkans U, Schumann G, Persico AM. Biomarkers in autism spectrum disorder: the old and the new. *Psychopharmacology (Berl).* 2014;231(6):1201–1216
256. Hazlett HC, Gu H, Munsell BC, et al; IBIS Network. Early brain development in infants at high risk for autism spectrum disorder. *Nature.* 2017;542(7641):348–351
257. Courchesne E, Campbell K, Solso S. Brain growth across the life span in autism: age-specific changes in

- anatomical pathology. *Brain Res.* 2011; 1380:138–145
258. Sacco R, Gabriele S, Persico AM. Head circumference and brain size in autism spectrum disorder: a systematic review and meta-analysis. *Psychiatry Res.* 2015;234(2):239–251
259. Elder LM, Dawson G, Toth K, Fein D, Munson J. Head circumference as an early predictor of autism symptoms in younger siblings of children with autism spectrum disorder. *J Autism Dev Disord.* 2008;38(6):1104–1111
260. Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K. Rate of head growth decelerates and symptoms worsen in the second year of life in autism. *Biol Psychiatry.* 2007;61(4):458–464
261. Zwaigenbaum L, Young GS, Stone WL, et al. Early head growth in infants at risk of autism: a baby siblings research consortium study. *J Am Acad Child Adolesc Psychiatry.* 2014;53(10):1053–1062
262. Chaste P, Klei L, Sanders SJ, et al. Adjusting head circumference for covariates in autism: clinical correlates of a highly heritable continuous trait. *Biol Psychiatry.* 2013;74(8):576–584
263. Chawarska K, Campbell D, Chen L, Shic F, Klin A, Chang J. Early generalized overgrowth in boys with autism. *Arch Gen Psychiatry.* 2011;68(10):1021–1031
264. Gray KM, Taffe J, Sweeney DJ, Forster S, Tonge BJ. Could head circumference be used to screen for autism in young males with developmental delay? *J Paediatr Child Health.* 2012;48(4):329–334
265. Raznahan A, Wallace GL, Antezana L, et al. Compared to what? Early brain overgrowth in autism and the perils of population norms. *Biol Psychiatry.* 2013; 74(8):563–575
266. Schumann CM, Bloss CS, Barnes CC, et al. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J Neurosci.* 2010;30(12):4419–4427
267. Shen MD, Nordahl CW, Young GS, et al. Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder. *Brain.* 2013; 136(pt 9):2825–2835
268. Schultz RT, Grelotti DJ, Klin A, et al. The role of the fusiform face area in social cognition: implications for the pathobiology of autism. *Philos Trans R Soc Lond B Biol Sci.* 2003;358(1430): 415–427
269. Nordahl CW, Scholz R, Yang X, et al. Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: a longitudinal study. *Arch Gen Psychiatry.* 2012;69(1): 53–61
270. Blackmon K. Structural MRI biomarkers of shared pathogenesis in autism spectrum disorder and epilepsy. *Epilepsy Behav.* 2015;47:172–182
271. Chen R, Jiao Y, Herskovits EH. Structural MRI in autism spectrum disorder. *Pediatr Res.* 2011;69(5, pt 2):63R–68R
272. Nickl-Jockschat T, Habel U, Michel TM, et al. Brain structure anomalies in autism spectrum disorder—a meta-analysis of VBM studies using anatomic likelihood estimation. *Hum Brain Mapp.* 2012;33(6):1470–1489
273. Wolff JJ, Gu H, Gerig G, et al; IBIS Network. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatry.* 2012;169(6):589–600
274. Philip RC, Dauvermann MR, Whalley HC, Baynham K, Lawrie SM, Stanfield AC. A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. *Neurosci Biobehav Rev.* 2012;36(2):901–942
275. Mahajan R, Mostofsky SH. Neuroimaging endophenotypes in autism spectrum disorder. *CNS Spectr.* 2015;20(4):412–426
276. Cerliani L, Mennes M, Thomas RM, Di Martino A, Thioux M, Keysers C. Increased functional connectivity between subcortical and cortical resting-state networks in autism spectrum disorder. *JAMA Psychiatry.* 2015;72(8):767–777
277. Doyle-Thomas KA, Lee W, Foster NE, et al; NeuroDevNet ASD Imaging Group. Atypical functional brain connectivity during rest in autism spectrum disorders. *Ann Neurol.* 2015;77(5): 866–876
278. Jeste SS, Nelson CA III. Event related potentials in the understanding of autism spectrum disorders: an analytical review. *J Autism Dev Disord.* 2009;39(3):495–510
279. Jeste SS, Frohlich J, Loo SK. Electrophysiological biomarkers of diagnosis and outcome in neurodevelopmental disorders. *Curr Opin Neurol.* 2015;28(2):110–116
280. Marco EJ, Hinkley LB, Hill SS, Nagarajan SS. Sensory processing in autism: a review of neurophysiologic findings. *Pediatr Res.* 2011;69(5, pt 2):48R–54R
281. Massand E, Bowler DM, Mottron L, Hosen A, Jemel B. ERP correlates of recognition memory in autism spectrum disorder. *J Autism Dev Disord.* 2013;43(9):2038–2047
282. Di Giorgio E, Frasnelli E, Salva OR, et al. Difference in visual social predispositions between newborns at low- and high-risk for autism. *Sci Rep.* 2016;6:29860
283. Constantino J, Kennon-McGill S, Weichselbaum C, et al. Infant viewing of social scenes is under genetic control and atypical in autism. *Nature.* 2017; 547(7663):340–344
284. Simion F, Di Giorgio E. Face perception and processing in early infancy: inborn predispositions and developmental changes. *Front Psychol.* 2015;6:969
285. Jones W, Klin A. Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. *Nature.* 2013;504(7480):427–431
286. Walker CK, Anderson KW, Milano KM, et al. Trophoblast inclusions are significantly increased in the placentas of children in families at risk for autism. *Biol Psychiatry.* 2013;74(3): 204–211
287. Anderson GM, Jacobs-Stannard A, Chawarska K, Volkmar FR, Kliman HJ. Placental trophoblast inclusions in autism spectrum disorder. *Biol Psychiatry.* 2007;61(4):487–491
288. Voineagu I, Yoo HJ. Current progress and challenges in the search for autism biomarkers. *Dis Markers.* 2013;35(1): 55–65
289. Anderson GM, Stahl SS. Two proposed early biomarker tests of ASD: more harm than good. *J Autism Dev Disord.* 2014;44(4):988–989
290. Jordan BR, Tsai DF. Whole-genome association studies for multigenic

- diseases: ethical dilemmas arising from commercialization—the case of genetic testing for autism. *J Med Ethics*. 2010;36(7):440–444
291. Hernandez LM, Rudie JD, Green SA, Bookheimer S, Dapretto M. Neural signatures of autism spectrum disorders: insights into brain network dynamics. *Neuropsychopharmacology*. 2015;40(1):171–189
 292. Ameis SH, Kasseh C, Corbett-Dick P, et al. Systemic review and guide to management of core and psychiatric symptoms in youth with autism. *Acta Psychiatr Scand*. 2018;138(5):379–400
 293. Mannion A, Leader G. Comorbidity in autism spectrum disorder: a literature review. *Res Autism Spectr Disord*. 2013;7(12):1595–1616
 294. Lyra L, Rizzo LE, Sunahara CS, et al. What do Cochrane systematic reviews say about interventions for autism spectrum disorders? *Sao Paulo Med J*. 2017;135(2):192–201
 295. Wong C, Odom SL, Hume KA, et al. Evidence-based practices for children, youth, and young adults with autism spectrum disorder: a comprehensive review. *J Autism Dev Disord*. 2015;45(7):1951–1966
 296. 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
 297. Smith T, Iadarola S. Evidence base update for autism spectrum disorder. *J Clin Child Adolesc Psychol*. 2015;44(6):897–922
 298. Weitlauf AS, McPheeters ML, Peters B, et al. *Therapies for Children With Autism Spectrum Disorder: Behavioral Interventions Update*. Rockville, MD: Agency for Healthcare Research and Quality; 2014
 299. Wang L, Mandell DS, Lawer L, Cidav Z, Leslie DL. Healthcare service use and costs for autism spectrum disorder: a comparison between Medicaid and private insurance. *J Autism Dev Disord*. 2013;43(5):1057–1064
 300. Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-Vanderweele J. A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics*. 2011;127(5). Available at: www.pediatrics.org/cgi/content/full/127/5/e1303
 301. McPheeters ML, Warren Z, Sathe N, et al. A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics*. 2011;127(5). Available at: www.pediatrics.org/cgi/content/full/127/5/e1312
 302. National Autism Center. *Findings and Conclusions: National Standards Project, Phase 2*. Randolph, MA: National Autism Center at May Institute; 2015
 303. Odom SL, Boyd BA, Hall LJ, Hume K. Evaluation of comprehensive treatment models for individuals with autism spectrum disorders. *J Autism Dev Disord*. 2010;40(4):425–436
 304. Schreibman L, Stahmer AC. A randomized trial comparison of the effects of verbal and pictorial naturalistic communication strategies on spoken language for young children with autism. *J Autism Dev Disord*. 2014;44(5):1244–1251
 305. Murza KA, Schwartz JB, Hahs-Vaughn DL, Nye C. Joint attention interventions for children with autism spectrum disorder: a systematic review and meta-analysis. *Int J Lang Commun Disord*. 2016;51(3):236–251
 306. Houtrow A, Murphy N; Council on Children With Disabilities. Prescribing physical, occupational, and speech therapy services for children with disabilities. *Pediatrics*. 2019;143(4):e20190285
 307. Maglione MA, Gans D, Das L, Timbie J, Kasari C; Technical Expert Panel; HRSA Autism Intervention Research – Behavioral (AIR-B) Network. Nonmedical interventions for children with ASD: recommended guidelines and further research needs. *Pediatrics*. 2012;130(suppl 2):S169–S178
 308. Stahmer AC. Effective strategies by any other name. *Autism*. 2014;18(3):211–212
 309. Roane HS, Fisher WW, Carr JE. Applied behavior analysis as treatment for autism spectrum disorder. *J Pediatr*. 2016;175:27–32
 310. Baer DM, Wolf MM, Risley TR. Some current dimensions of applied behavior analysis. *J Appl Behav Anal*. 1968;1(1):91–97
 311. Lovaas OI, Smith T. A comprehensive behavioral theory of autistic children: paradigm for research and treatment. *J Behav Ther Exp Psychiatry*. 1989;20(1):17–29
 312. Smith T, Eikeseth S. O. Ivar Lovaas: pioneer of applied behavior analysis and intervention for children with autism. *J Autism Dev Disord*. 2011;41(3):375–378
 313. Leaf JB, Leaf JA, Milne C, et al. An evaluation of a behaviorally based social skills group for individuals diagnosed with autism spectrum disorder. *J Autism Dev Disord*. 2017;47(2):243–259
 314. Lounds Taylor J, Dove D, Veenstra-Vanderweele J, et al. *Interventions for Adolescents and Young Adults With Autism Spectrum Disorders*. Rockville, MD: Agency for Healthcare Research and Quality; 2012
 315. Linstead E, Dixon DR, French R, et al. Intensity and learning outcomes in the treatment of children with autism spectrum disorder. *Behav Modif*. 2017;41(2):229–252
 316. Orinstein AJ, Helt M, Troyb E, et al. Intervention for optimal outcome in children and adolescents with a history of autism. *J Dev Behav Pediatr*. 2014;35(4):247–256
 317. Granpeesheh D, Tarbox J, Dixon DR. Applied behavior analytic interventions for children with autism: a description and review of treatment research. *Ann Clin Psychiatry*. 2009;21(3):162–173
 318. Landry SH, Smith KE, Swank PR, Miller-Loncar CL. Early maternal and child influences on children's later independent cognitive and social functioning. *Child Dev*. 2000;71(2):358–375
 319. Tamis-LeMonda CS, Bornstein MH, Baumwell L. Maternal responsiveness and children's achievement of language milestones. *Child Dev*. 2001;72(3):748–767
 320. Siller M, Sigman M. The behaviors of parents of children with autism predict the subsequent development of their children's communication. *J Autism Dev Disord*. 2002;32(2):77–89
 321. Green J, Charman T, McConachie H, et al; PACT Consortium. Parent-mediated communication-focused treatment in

- children with autism (PACT): a randomised controlled trial. *Lancet*. 2010;375(9732):2152–2160
322. Kasari C, Gulsrud AC, Wong C, Kwon S, Locke J. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. *J Autism Dev Disord*. 2010;40(9):1045–1056
323. Solomon R, Van Egeren LA, Mahoney G, Quon Huber MS, Zimmerman P. PLAY Project Home Consultation intervention program for young children with autism spectrum disorders: a randomized controlled trial. *J Dev Behav Pediatr*. 2014;35(8):475–485
324. Gutstein SE. Empowering families through relationship development intervention: an important part of the biopsychosocial management of autism spectrum disorders. *Ann Clin Psychiatry*. 2009;21(3):174–182
325. Estes A, Munson J, Rogers SJ, Greenson J, Winter J, Dawson G. Long-term outcomes of early intervention in 6-year-old children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(7):580–587
326. Rogers SJ, Estes A, Lord C, et al. Effects of a brief Early Start Denver model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2012;51(10):1052–1065
327. Dawson G, Jones EJ, Merkle K, et al. Early behavioral intervention is associated with normalized brain activity in young children with autism. *J Am Acad Child Adolesc Psychiatry*. 2012;51(11):1150–1159
328. Ingersoll BR, Wainer AL. Pilot study of a school-based parent training program for preschoolers with ASD. *Autism*. 2013;17(4):434–448
329. Oono IP, Honey EJ, McConachie H. Parent-mediated early intervention for young children with autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2013;(4):CD009774
330. Beaudoin AJ, Sébire G, Couture M. Parent training interventions for toddlers with autism spectrum disorder. *Autism Res Treat*. 2014;2014:839890
331. Bearss K, Johnson C, Smith T, et al. Effect of parent training vs parent education on behavioral problems in children with autism spectrum disorder: a randomized clinical trial. *JAMA*. 2015;313(15):1524–1533
332. Bearss K, Burrell TL, Stewart L, Scahill L. Parent training in autism spectrum disorder: what's in a name? [published correction appears in *Clin Child Fam Psychol Rev*. 2015;18(2):183]. *Clin Child Fam Psychol Rev*. 2015;18(2):170–182
333. Wainer AL, Ingersoll BR. Increasing access to an ASD imitation intervention via a telehealth parent training program. *J Autism Dev Disord*. 2015;45(12):3877–3890
334. Ingersoll B, Berger NI. Parent engagement with a telehealth-based parent-mediated intervention program for children with autism spectrum disorders: predictors of program use and parent outcomes [published correction appears in *J Med Internet Res*. 2015;17(11):e239]. *J Med Internet Res*. 2015;17(10):e227
335. Ingersoll B, Wainer AL, Berger NI, Pickard KE, Bonter N. Comparison of a self-directed and therapist-assisted telehealth parent-mediated intervention for children with ASD: a pilot RCT. *J Autism Dev Disord*. 2016;46(7):2275–2284
336. Turner-Brown L, Hume K, Boyd BA, Kainz K. Preliminary efficacy of family implemented TEACCH for toddlers: effects on parents and their toddlers with autism spectrum disorder. *J Autism Dev Disord*. 2019;49(7):2685–2698
337. Lindgren S, Wacker D, Suess A, et al. Telehealth and autism: treating challenging behavior at lower cost. *Pediatrics*. 2016;137(suppl 2):S167–S175
338. Kasari C, Gulsrud A, Paparella T, Hellemann G, Berry K. Randomized comparative efficacy study of parent-mediated interventions for toddlers with autism. *J Consult Clin Psychol*. 2015;83(3):554–563
339. Harrop C. Evidence-based, parent-mediated interventions for young children with autism spectrum disorder: the case of restricted and repetitive behaviors. *Autism*. 2015;19(6):662–672
340. Scahill L, Bearss K, Lecavalier L, et al. Effect of parent training on adaptive behavior in children with autism spectrum disorder and disruptive behavior: results of a randomized trial. *J Am Acad Child Adolesc Psychiatry*. 2016;55(7):602–609.e3
341. Bearss K, Lecavalier L, Minshawi N, et al. Toward an exportable parent training program for disruptive behaviors in autism spectrum disorders. *Neuropsychiatry (London)*. 2013;3(2):169–180
342. Grahame V, Brett D, Dixon L, et al. Managing repetitive behaviours in young children with autism spectrum disorder (ASD): pilot randomised controlled trial of a new parent group intervention. *J Autism Dev Disord*. 2015;45(10):3168–3182
343. Wetherby AM, Guthrie W, Woods J, et al. Parent-implemented social intervention for toddlers with autism: an RCT. *Pediatrics*. 2014;134(6):1084–1093
344. Boyd BA, Hume K, McBee MT, et al. Comparative efficacy of LEAP, TEACCH and non-model-specific special education programs for preschoolers with autism spectrum disorders. *J Autism Dev Disord*. 2014;44(2):366–380
345. Strain PS, Bovey EH II. Randomized, controlled trial of the LEAP model of early intervention for young children with autism spectrum disorders. *Topics Early Child Spec Educ*. 2011;31(3):133–154
346. Strain PS, Hoyson M. The need for longitudinal, intensive social skill intervention: LEAP follow-up outcomes for children with autism. *Topics Early Child Spec Educ*. 2000;20(2):116–122
347. Virues-Ortega J, Julio FM, Pastor-Barriuso R. The TEACCH program for children and adults with autism: a meta-analysis of intervention studies. *Clin Psychol Rev*. 2013;33(8):940–953
348. Lipkin PH, Okamoto J; Council on Children with Disabilities; Council on School Health. The Individuals With Disabilities Education Act (IDEA) for children with special educational needs. *Pediatrics*. 2015;136(6). Available at: www.pediatrics.org/cgi/content/full/136/6/e1650

349. US Department of Education. Protecting students with disabilities. Available at: <https://www2.ed.gov/about/offices/list/ocr/504faq.html>. Accessed December 1, 2019
350. Ricketts J. Research review: reading comprehension in developmental disorders of language and communication. *J Child Psychol Psychiatry*. 2011;52(11):1111–1123
351. Kasari C, Rotheram-Fuller E, Locke J, Gulsrud A. Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders. *J Child Psychol Psychiatry*. 2012;53(4):431–439
352. Kretzmann M, Shih W, Kasari C. Improving peer engagement of children with autism on the school playground: a randomized controlled trial. *Behav Ther*. 2015;46(1):20–28
353. Foster EM, Pearson E. Is inclusivity an indicator of quality of care for children with autism in special education? *Pediatrics*. 2012;130(suppl 2):S179–S185
354. Otero TL, Schatz RB, Merrill AC, Bellini S. Social skills training for youth with autism spectrum disorders: a follow-up. *Child Adolesc Psychiatr Clin N Am*. 2015; 24(1):99–115
355. Whalon KJ, Conroy MA, Martinez JR, Werch BL. School-based peer-related social competence interventions for children with autism spectrum disorder: a meta-analysis and descriptive review of single case research design studies. *J Autism Dev Disord*. 2015;45(6):1513–1531
356. Reichow B, Steiner AM, Volkmar F. Cochrane review: social skills groups for people aged 6 to 21 with autism spectrum disorders (ASD). *Evid Based Child Health*. 2013;8(2):266–315
357. Reichow B, Volkmar FR. Social skills interventions for individuals with autism: evaluation for evidence-based practices within a best evidence synthesis framework. *J Autism Dev Disord*. 2010;40(2):149–166
358. Laugeson EA, Ellingsen R, Sanderson J, Tucci L, Bates S. The ABC's of teaching social skills to adolescents with autism spectrum disorder in the classroom: the UCLA PEERS (®) Program. *J Autism Dev Disord*. 2014;44(9):2244–2256
359. Laugeson EA, Gantman A, Kapp SK, Orenski K, Ellingsen R. A randomized controlled trial to improve social skills in young adults with autism spectrum disorder: The UCLA PEERS (®) program. *J Autism Dev Disord*. 2015;45(12):3978–3989
360. Krasny L, Williams BJ, Provencal S, Ozonoff S. Social skills interventions for the autism spectrum: essential ingredients and a model curriculum. *Child Adolesc Clin North Am*. 2003;12(1):107–122
361. Green VA, Pituch KA, Itchon J, Choi A, O'Reilly M, Sigafoos J. Internet survey of treatments used by parents of children with autism. *Res Dev Disabil*. 2006; 27(1):70–84
362. DeThorne LS, Johnson CJ, Walder L, Mahurin-Smith J. When “Simon says” doesn't work: alternatives to imitation for facilitating early speech development. *Am J Speech Lang Pathol*. 2009;18(2):133–145
363. Anderson DK, Lord C, Risi S, et al. Patterns of growth in verbal abilities among children with autism spectrum disorder. *J Consult Clin Psychol*. 2007; 75(4):594–604
364. Wodka EL, Mathy P, Kalb L. Predictors of phrase and fluent speech in children with autism and severe language delay. *Pediatrics*. 2013;131(4). Available at: www.pediatrics.org/cgi/content/full/131/4/e1128
365. Schlosser RW, Wendt O. Effects of augmentative and alternative communication intervention on speech production in children with autism: a systematic review. *Am J Speech Lang Pathol*. 2008;17(3):212–230
366. Ganz JB, Mason RA, Goodwyn FD, Boles MB, Heath AK, Davis JL. Interaction of participant characteristics and type of AAC with individuals with ASD: a meta-analysis. *Am J Intellect Dev Disabil*. 2014;119(6):516–535
367. Knight V, Sartini E, Spriggs AD. Evaluating visual activity schedules as evidence-based practice for individuals with autism spectrum disorders. *J Autism Dev Disord*. 2015;45(1):157–178
368. Ganz JB. AAC interventions for individuals with autism spectrum disorders: state of the science and future research directions. *Augment Altern Commun*. 2015;31(3):203–214
369. American Academy of Pediatrics Committee on Children with Disabilities. Auditory integration training and facilitated communication for autism. *Pediatrics*. 1998;102(2, pt 1):431–433
370. Schlosser RW, Balandin S, Hemsley B, Iacono T, Probst P, von Tetzchner S. Facilitated communication and authorship: a systematic review. *Augment Altern Commun*. 2014;30(4):359–368
371. Adams C, Lockton E, Freed J, et al. The Social Communication Intervention Project: a randomized controlled trial of the effectiveness of speech and language therapy for school-age children who have pragmatic and social communication problems with or without autism spectrum disorder. *Int J Lang Commun Disord*. 2012;47(3):233–244
372. Lloyd M, MacDonald M, Lord C. Motor skills of toddlers with autism spectrum disorders. *Autism*. 2013;17(2):133–146
373. Ament K, Mejia A, Buhlman R, et al. Evidence for specificity of motor impairments in catching and balance in children with autism. *J Autism Dev Disord*. 2015;45(3):742–751
374. Bilaver LA, Cushing LS, Cutler AT. Prevalence and correlates of educational intervention utilization among children with autism spectrum disorder. *J Autism Dev Disord*. 2016; 46(2):561–571
375. Srinivasan SM, Pescatello LS, Bhat AN. Current perspectives on physical activity and exercise recommendations for children and adolescents with autism spectrum disorders. *Phys Ther*. 2014;94(6):875–889
376. Zimmer M, Desch L; Section on Complementary and Integrative Medicine; Council on Children with Disabilities; American Academy of Pediatrics. Sensory integration therapies for children with developmental and behavioral disorders. *Pediatrics*. 2012;129(6):1186–1189
377. Wigham S, Rodgers J, South M, McConachie H, Freeston M. The interplay between sensory processing abnormalities, intolerance of

- uncertainty, anxiety and restricted and repetitive behaviours in autism spectrum disorder. *J Autism Dev Disord*. 2015;45(4):943–952
378. Barton EE, Reichow B, Schnitz A, Smith IC, Sherlock D. A systematic review of sensory-based treatments for children with disabilities. *Res Dev Disabil*. 2015; 37:64–80
379. Case-Smith J, Weaver LL, Fristad MA. A systematic review of sensory processing interventions for children with autism spectrum disorders. *Autism*. 2015;19(2):133–148
380. Bauman ML. Medical comorbidities in autism: challenges to diagnosis and treatment. *Neurotherapeutics*. 2010; 7(3):320–327
381. Joshi G, Petty C, Wozniak J, et al. The heavy burden of psychiatric comorbidity in youth with autism spectrum disorders: a large comparative study of a psychiatrically referred population. *J Autism Dev Disord*. 2010;40(11):1361–1370
382. Viscidi EW, Triche EW, Pescosolido MF, et al. Clinical characteristics of children with autism spectrum disorder and co-occurring epilepsy. *PLoS One*. 2013;8(7): e67797
383. van Eeghen AM, Pulsifer MB, Merker VL, et al. Understanding relationships between autism, intelligence, and epilepsy: a cross-disorder approach. *Dev Med Child Neurol*. 2013;55(2): 146–153
384. Sansa G, Carlson C, Doyle W, et al. Medically refractory epilepsy in autism. *Epilepsia*. 2011;52(6):1071–1075
385. Ibrahim SH, Voigt RG, Katusic SK, Weaver AL, Barbaresi WJ. Incidence of gastrointestinal symptoms in children with autism: a population-based study. *Pediatrics*. 2009;124(2):680–686
386. Chaidez V, Hansen RL, Hertz-Picciotto I. Gastrointestinal problems in children with autism, developmental delays or typical development. *J Autism Dev Disord*. 2014;44(5):1117–1127
387. Buie T, Campbell DB, Fuchs GJ III, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics*. 2010;125(suppl 1): S1–S18
388. Bresnahan M, Hornig M, Schultz AF, et al. Association of maternal report of infant and toddler gastrointestinal symptoms with autism: evidence from a prospective birth cohort. *JAMA Psychiatry*. 2015;72(5):466–474
389. Mazurek MO, Vasa RA, Kalb LG, et al. Anxiety, sensory over-responsivity, and gastrointestinal problems in children with autism spectrum disorders. *J Abnorm Child Psychol*. 2013;41(1): 165–176
390. Buie T, Fuchs GJ III, Furuta GT, et al. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. *Pediatrics*. 2010;125(suppl 1):S19–S29
391. Maenner MJ, Arneson CL, Levy SE, Kirby RS, Nicholas JS, Durkin MS. Brief report: association between behavioral features and gastrointestinal problems among children with autism spectrum disorder. *J Autism Dev Disord*. 2012; 42(7):1520–1525
392. McElhanon BO, McCracken C, Karpen S, Sharp WG. Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. *Pediatrics*. 2014;133(5): 872–883
393. Santocchi E, Guiducci L, Fulceri F, et al. Gut to brain interaction in autism spectrum disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters. *BMC Psychiatry*. 2016;16:183
394. Son JS, Zheng LJ, Rowehl LM, et al. Comparison of fecal microbiota in children with autism spectrum disorders and neurotypical siblings in the Simons simplex collection. *PLoS One*. 2015;10(10):e0137725
395. Levy SE, Souders MC, Ittenbach RF, Giarelli E, Mulberg AE, Pinto-Martin JA. Relationship of dietary intake to gastrointestinal symptoms in children with autistic spectrum disorders. *Biol Psychiatry*. 2007;61(4):492–497
396. Hollway JA, Aman MG, Butter E. Correlates and risk markers for sleep disturbance in participants of the Autism Treatment Network. *J Autism Dev Disord*. 2013;43(12):2830–2843
397. Sharp WG, Berry RC, McCracken C, et al. Feeding problems and nutrient intake in children with autism spectrum disorders: a meta-analysis and comprehensive review of the literature. *J Autism Dev Disord*. 2013;43(9): 2159–2173
398. Bandini LG, Anderson SE, Curtin C, et al. Food selectivity in children with autism spectrum disorders and typically developing children. *J Pediatr*. 2010; 157(2):259–264
399. Hubbard KL, Anderson SE, Curtin C, Must A, Bandini LG. A comparison of food refusal related to characteristics of food in children with autism spectrum disorder and typically developing children. *J Acad Nutr Diet*. 2014;114(12):1981–1987
400. Emond A, Emmett P, Steer C, Golding J. Feeding symptoms, dietary patterns, and growth in young children with autism spectrum disorders. *Pediatrics*. 2010;126(2). Available at: www.pediatrics.org/cgi/content/full/126/2/e337
401. Johnson CR, Turner K, Stewart PA, et al. Relationships between feeding problems, behavioral characteristics and nutritional quality in children with ASD. *J Autism Dev Disord*. 2014;44(9): 2175–2184
402. Hyman SL, Stewart PA, Schmidt B, et al. Nutrient intake from food in children with autism. *Pediatrics*. 2012;130(suppl 2):S145–S153
403. Keown K, Bothwell J, Jain S. Nutritional implications of selective eating in a child with autism spectrum disorder. *BMJ Case Rep*. 2014;2014: bcr2013202581
404. Ma NS, Thompson C, Weston S. Brief report: scurvy as a manifestation of food selectivity in children with autism. *J Autism Dev Disord*. 2016;46(4): 1464–1470
405. Chiu M, Watson S. Xerophthalmia and vitamin A deficiency in an autistic child with a restricted diet. *BMJ Case Rep*. 2015;2015:bcr2015209413
406. Stewart PA, Hyman SL, Schmidt BL, et al. Dietary supplementation in children with autism spectrum disorders: common, insufficient, and excessive. *J Acad Nutr Diet*. 2015;115(8):1237–1248
407. Bailey RL, Fulgoni VL III, Keast DR, Lentino CV, Dwyer JT. Do dietary supplements improve micronutrient

- sufficiency in children and adolescents? *J Pediatr.* 2012;161(5):837–842
408. Marshall J, Ware R, Ziviani J, Hill RJ, Dodrill P. Efficacy of interventions to improve feeding difficulties in children with autism spectrum disorders: a systematic review and meta-analysis. *Child Care Health Dev.* 2015;41(2): 278–302
 409. Sharp WG, Jaquess DL, Morton JF, Herzinger CV. Pediatric feeding disorders: a quantitative synthesis of treatment outcomes. *Clin Child Fam Psychol Rev.* 2010;13(4):348–365
 410. de Vinck-Baroody O, Shui A, Macklin EA, Hyman SL, Leventhal JM, Weitzman C. Overweight and obesity in a sample of children with autism spectrum disorder. *Acad Pediatr.* 2015;15(4): 396–404
 411. Broder-Fingert S, Brazauskas K, Lindgren K, Iannuzzi D, Van Cleave J. Prevalence of overweight and obesity in a large clinical sample of children with autism. *Acad Pediatr.* 2014;14(4): 408–414
 412. Zuckerman KE, Hill AP, Guion K, Voltolina L, Fombonne E. Overweight and obesity: prevalence and correlates in a large clinical sample of children with autism spectrum disorder. *J Autism Dev Disord.* 2014;44(7):1708–1719
 413. Phillips KL, Schieve LA, Visser S, et al. Prevalence and impact of unhealthy weight in a national sample of US adolescents with autism and other learning and behavioral disabilities. *Matern Child Health J.* 2014;18(8): 1964–1975
 414. Hinckson EA, Dickinson A, Water T, Sands M, Penman L. Physical activity, dietary habits and overall health in overweight and obese children and youth with intellectual disability or autism. *Res Dev Disabil.* 2013;34(4): 1170–1178
 415. Du RY, Yiu CKY, King NM. Oral health behaviours of preschool children with autism spectrum disorders and their barriers to dental care. *J Autism Dev Disord.* 2019;49(2):453–459
 416. Call NA, Simmons CA, Mevers JE, Alvarez JP. Clinical outcomes of behavioral treatments for pica in children with developmental disabilities. *J Autism Dev Disord.* 2015;45(7):2105–2114
 417. Fields V. Prevalence of pica in preschool children with and without autism spectrum disorder, study to explore early development — United States 2008–2016. In: Proceedings from the Epidemic Intelligence Service Conference; April 29–May 2, 2019; Atlanta, GA
 418. Mohanty PH, Gabel M. Agitation and decreased oral intake in an adolescent with autism. *Pediatr Ann.* 2012;41(6): 1–3
 419. Barton JC, Barton JC, Bertoli LF. Pica associated with iron deficiency or depletion: clinical and laboratory correlates in 262 non-pregnant adult outpatients. *BMC Blood Disord.* 2010;10: 9
 420. Miano S, Ferri R. Epidemiology and management of insomnia in children with autistic spectrum disorders. *Paediatr Drugs.* 2010;12(2):75–84
 421. Cortesi F, Giannotti F, Ivanenko A, Johnson K. Sleep in children with autistic spectrum disorder. *Sleep Med.* 2010;11(7):659–664
 422. Cohen S, Conduit R, Lockley SW, Rajaratnam SM, Cornish KM. The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. *J Neurodev Disord.* 2014;6(1):44
 423. Fadini CC, Lamônica DA, Fett-Conte AC, et al. Influence of sleep disorders on the behavior of individuals with autism spectrum disorder. *Front Hum Neurosci.* 2015;9:347
 424. Veatch OJ, Maxwell-Horn AC, Malow BA. Sleep in autism spectrum disorders. *Curr Sleep Med Rep.* 2015;1(2):131–140
 425. Blackmer AB, Feinstein JA. Management of sleep disorders in children with neurodevelopmental disorders: a review. *Pharmacotherapy.* 2016;36(1): 84–98
 426. Mazurek MO, Sohl K. Sleep and behavioral problems in children with autism spectrum disorder. *J Autism Dev Disord.* 2016;46(6):1906–1915
 427. Malow BA, Katz T, Reynolds AM, et al. Sleep difficulties and medications in children with autism spectrum disorders: a registry study. *Pediatrics.* 2016;137(suppl 2):S98–S104
 428. Malow BA, Byars K, Johnson K, et al; Sleep Committee of the Autism Treatment Network. A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. *Pediatrics.* 2012;130(suppl 2):S106–S124
 429. Humphreys JS, Gringras P, Blair PS, et al. Sleep patterns in children with autistic spectrum disorders: a prospective cohort study. *Arch Dis Child.* 2014;99(2):114–118
 430. Goldman SE, Richdale AL, Clemons T, Malow BA. Parental sleep concerns in autism spectrum disorders: variations from childhood to adolescence. *J Autism Dev Disord.* 2012;42(4): 531–538
 431. Veatch OJ, Pendergast JS, Allen MJ, et al. Genetic variation in melatonin pathway enzymes in children with autism spectrum disorder and comorbid sleep onset delay. *J Autism Dev Disord.* 2015;45(1):100–110
 432. Williams SR, Zies D, Mullegama SV, Grotewiel MS, Elsea SH. Smith-Magenis syndrome results in disruption of CLOCK gene transcription and reveals an integral role for RAL1 in the maintenance of circadian rhythmicity. *Am J Hum Genet.* 2012;90(6):941–949
 433. Dosman C, Witmans M, Zwaigenbaum L. Iron's role in paediatric restless legs syndrome - a review. *Paediatr Child Health.* 2012;17(4):193–197
 434. Engelhardt CR, Mazurek MO, Sohl K. Media use and sleep among boys with autism spectrum disorder, ADHD, or typical development. *Pediatrics.* 2013; 132(6):1081–1089
 435. Foley LS, Maddison R, Jiang Y, Marsh S, Olds T, Ridley K. Presleep activities and time of sleep onset in children. *Pediatrics.* 2013;131(2):276–282
 436. Weiskop S, Richdale A, Matthews J. Behavioural treatment to reduce sleep problems in children with autism or fragile X syndrome. *Dev Med Child Neurol.* 2005;47(2):94–104
 437. Reed HE, McGrew SG, Artibeo K, et al. Parent-based sleep education workshops in autism. *J Child Neurol.* 2009;24(8):936–945
 438. Johnson CR, Turner KS, Foldes E, Brooks MM, Kronk R, Wiggs L. Behavioral

- parent training to address sleep disturbances in young children with autism spectrum disorder: a pilot trial. *Sleep Med*. 2013;14(10):995–1004
439. Vriend JL, Corkum PV, Moon EC, Smith IM. Behavioral interventions for sleep problems in children with autism spectrum disorders: current findings and future directions. *J Pediatr Psychol*. 2011;36(9):1017–1029
440. Malow BA, Adkins KW, Reynolds A, et al. Parent-based sleep education for children with autism spectrum disorders. *J Autism Dev Disord*. 2014; 44(1):216–228
441. Tordjman S, Najjar I, Bellissant E, et al. Advances in the research of melatonin in autism spectrum disorders: literature review and new perspectives. *Int J Mol Sci*. 2013;14(10):20508–20542
442. Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. *J Sleep Res*. 2012;21(6):700–709
443. Malow B, Adkins KW, McGrew SG, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. *J Autism Dev Disord*. 2012;42(8): 1729–1737; author reply 1738
444. Merenstein D, Diener-West M, Halbower AC, Krist A, Rubin HR. The trial of infant response to diphenhydramine: the TIRED study—a randomized, controlled, patient-oriented trial. *Arch Pediatr Adolesc Med*. 2006;160(7):707–712
445. Fiks AG, Mayne SL, Song L, et al. Changing patterns of alpha agonist medication use in children and adolescents 2009–2011. *J Child Adolesc Psychopharmacol*. 2015;25(4):362–367
446. Sikora DM, Johnson K, Clemons T, Katz T. The relationship between sleep problems and daytime behavior in children of different ages with autism spectrum disorders. *Pediatrics*. 2012; 130(suppl 2):S83–S90
447. Anderson C, Law JK, Daniels A, et al. Occurrence and family impact of elopement in children with autism spectrum disorders. *Pediatrics*. 2012; 130(5):870–877
448. Guan J, Li G. Injury mortality in individuals with autism. *Am J Public Health*. 2017;107(5):791–793
449. Rice CE, Zablotsky B, Avila RM, et al. Reported wandering behavior among children with autism spectrum disorder and/or intellectual disability. *J Pediatr*. 2016;174:232–239.e2
450. Canitano R, Vivanti G. Tics and Tourette syndrome in autism spectrum disorders. *Autism*. 2007;11(1):19–28
451. DeJong H, Bunton P, Hare DJ. A systematic review of interventions used to treat catatonic symptoms in people with autistic spectrum disorders. *J Autism Dev Disord*. 2014;44(9): 2127–2136
452. Gurney JG, McPheeters ML, Davis MM. Parental report of health conditions and health care use among children with and without autism: National Survey of Children's Health. *Arch Pediatr Adolesc Med*. 2006;160(8): 825–830
453. Simonoff E, Jones CR, Baird G, Pickles A, Happé F, Charman T. The persistence and stability of psychiatric problems in adolescents with autism spectrum disorders. *J Child Psychol Psychiatry*. 2013;54(2):186–194
454. Hill AP, Zuckerman KE, Hagen AD, et al. Aggressive behavior problems in children with autism spectrum disorders: prevalence and correlates in a large clinical sample. *Res Autism Spectr Disord*. 2014;8(9):1121–1133
455. Orinstein A, Tyson KE, Suh J, et al. Psychiatric symptoms in youth with a history of autism and optimal outcome. *J Autism Dev Disord*. 2015; 45(11):3703–3714
456. Gotham K, Brunwasser SM, Lord C. Depressive and anxiety symptom trajectories from school age through young adulthood in samples with autism spectrum disorder and developmental delay. *J Am Acad Child Adolesc Psychiatry*. 2015;54(5): 369–376.e3
457. Verheij C, Louwse A, van der Ende J, et al. The stability of comorbid psychiatric disorders: a 7 year follow up of children with pervasive developmental disorder-not otherwise specified. *J Autism Dev Disord*. 2015; 45(12):3939–3948
458. Buck TR, Viskochil J, Farley M, et al. Psychiatric comorbidity and medication use in adults with autism spectrum disorder. *J Autism Dev Disord*. 2014; 44(12):3063–3071
459. Salazar F, Baird G, Chandler S, et al. Co-occurring psychiatric disorders in preschool and elementary school-aged children with autism spectrum disorder. *J Autism Dev Disord*. 2015; 45(8):2283–2294
460. Kuhlthau KA, McDonnell E, Coury DL, Payakachat N, Macklin E. Associations of quality of life with health-related characteristics among children with autism. *Autism*. 2018;22(7):804–813
461. Weitzman C, Wegner L; Section on Developmental and Behavioral Pediatrics; Committee on Psychosocial Aspects of Child and Family Health; Council on Early Childhood; Society for Developmental and Behavioral Pediatrics; American Academy of Pediatrics. Promoting optimal development: screening for behavioral and emotional problems. *Pediatrics*. 2015;135(2):384–395
462. Volker MA, Lopata C, Smerbeck AM, et al. BASC-2 PRS profiles for students with high-functioning autism spectrum disorders. *J Autism Dev Disord*. 2010; 40(2):188–199
463. Ooi YP, Rescorla L, Ang RP, Woo B, Fung DS. Identification of autism spectrum disorders using the Child Behavior Checklist in Singapore. *J Autism Dev Disord*. 2011;41(9):1147–1156
464. Rosen TE, Mazefsky CA, Vasa RA, Lerner MD, et al. Co-occurring psychiatric conditions in autism spectrum disorder. *Int Rev Psychiatry*. 2018;30(1): 40–61
465. American Academy of Pediatrics. Caring for Children With Autism Spectrum Disorder: A Practical Resource Toolkit for Clinicians, 3rd edition. Available at: <https://toolkits.solutions.aap.org/autism/home>. Accessed December 1, 2019
466. Mahajan R, Bernal MP, Panzer R, et al; Autism Speaks Autism Treatment Network Psychopharmacology Committee. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum

- disorders. *Pediatrics*. 2012;130(suppl 2):S125–S138
467. Doyle CA, McDougle CJ. Pharmacologic treatments for the behavioral symptoms associated with autism spectrum disorders across the lifespan. *Dialogues Clin Neurosci*. 2012; 14(3):263–279
468. Sukhodolsky DG, Scahill L, Gadow KD, et al. Parent-rated anxiety symptoms in children with pervasive developmental disorders: frequency and association with core autism symptoms and cognitive functioning. *J Abnorm Child Psychol*. 2008;36(1):117–128
469. Vasa RA, Mazurek MO, Mahajan R, et al. Assessment and treatment of anxiety in youth with autism spectrum disorders. *Pediatrics*. 2016;137(suppl 2): S115–S123
470. Bitsika V, Sharpley CF, Andronicos NM, Agnew LL. Hypothalamus-pituitary-adrenal axis daily fluctuation, anxiety and age interact to predict cortisol concentrations in boys with an autism spectrum disorder. *Physiol Behav*. 2015; 138:200–207
471. Kerns CM, Maddox BB, Kendall PC, et al. Brief measures of anxiety in non-treatment-seeking youth with autism spectrum disorder. *Autism*. 2015;19(8): 969–979
472. Kreslins A, Robertson AE, Melville C. The effectiveness of psychosocial interventions for anxiety in children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. *Child Adolesc Psychiatry Ment Health*. 2015;9:22
473. Lickel A, MacLean WE Jr, Blakeley-Smith A, Hepburn S. Assessment of the prerequisite skills for cognitive behavioral therapy in children with and without autism spectrum disorders. *J Autism Dev Disord*. 2012;42(6): 992–1000
474. Sukhodolsky DG, Bloch MH, Panza KE, Reichow B. Cognitive-behavioral therapy for anxiety in children with high-functioning autism: a meta-analysis. *Pediatrics*. 2013;132(5). Available at: www.pediatrics.org/cgi/content/full/132/5/e1341
475. Ung D, Selles R, Small BJ, Storch EA. A systematic review and meta-analysis of cognitive-behavioral therapy for anxiety in youth with high-functioning autism spectrum disorders. *Child Psychiatry Hum Dev*. 2015;46(4):533–547
476. 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
477. De-la-Iglesia M, Olivar JS. Risk factors for depression in children and adolescents with high functioning autism spectrum disorders. *ScientificWorldJournal*. 2015;2015: 127853
478. Segers M, Rawana J. What do we know about suicidality in autism spectrum disorders? A systematic review. *Autism Res*. 2014;7(4):507–521
479. Zuckerbrot RA, Cheung A, Jensen PS, Stein REK, Laraque D; GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): part I. Practice preparation, identification, assessment, and initial management. *Pediatrics*. 2018;141(3): e20174081
480. Williams K, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2013;(8):CD004677
481. Vannucchi G, Masi G, Toni C, Dell’Osso L, Erfurth A, Perugi G. Bipolar disorder in adults with Asperger’s syndrome: a systematic review. *J Affect Disord*. 2014;168:151–160
482. Krebs G, Heyman I. Obsessive-compulsive disorder in children and adolescents. *Arch Dis Child*. 2015; 100(5):495–499
483. Zandt F, Prior M, Kyrios M. Repetitive behaviour in children with high functioning autism and obsessive compulsive disorder. *J Autism Dev Disord*. 2007;37(2):251–259
484. Murray K, Jassi A, Mataix-Cols D, Barrow F, Krebs G. Outcomes of cognitive behaviour therapy for obsessive-compulsive disorder in young people with and without autism spectrum disorders: A case controlled study. *Psychiatry Res*. 2015;228(1):8–13
485. McGuire K, Fung LK, Hagopian L, et al. Irritability and problem behavior in autism spectrum disorder: a practice pathway for pediatric primary care. *Pediatrics*. 2016;137(suppl 2): S136–S148
486. Doehring P, Reichow B, Palka T, Phillips C, Hagopian L. Behavioral approaches to managing severe problem behaviors in children with autism spectrum and related developmental disorders: a descriptive analysis. *Child Adolesc Psychiatr Clin N Am*. 2014;23(1):25–40
487. Fitzpatrick SE, Srivorakiat L, Wink LK, Pedapati EV, Erickson CA. Aggression in autism spectrum disorder: presentation and treatment options. *Neuropsychiatr Dis Treat*. 2016;12: 1525–1538
488. Chen C, Shen YD, Xun GL, et al. Aggressive behaviors and treatable risk factors of preschool children with autism spectrum disorder. *Autism Res*. 2017;10(6):1155–1162
489. Richards C, Davies L, Oliver C. Predictors of self-injurious behavior and self-restraint in autism spectrum disorder: towards a hypothesis of impaired behavioral control. *J Autism Dev Disord*. 2017;47(3):701–713
490. Soke GN, Rosenberg SA, Rosenberg GR, Vasa RA, Lee LC, DiGuseppi C. Self-injurious behaviors in children with autism spectrum disorder enrolled in the Study to Explore Early Development. *Autism*. 2018;22(5):625–635
491. Richards C, Moss J, Nelson L, Oliver C. Persistence of self-injurious behaviour in autism spectrum disorder over 3 years: a prospective cohort study of risk markers. *J Neurodev Disord*. 2016; 8:21
492. Powis L, Oliver C. The prevalence of aggression in genetic syndromes: a review. *Res Dev Disabil*. 2014;35(5): 1051–1071
493. 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
494. Jobski K, Höfer J, Hoffmann F, Bachmann C. Use of psychotropic drugs in patients with autism spectrum disorders: a systematic review. *Acta Psychiatr Scand*. 2017;135(1):8–28
495. Rettew DC, Greenblatt J, Kamon J, et al. Antipsychotic medication prescribing in children enrolled in Medicaid. *Pediatrics*. 2015;135(4):658–665

496. Riddle MA. *Pediatric Psychopharmacology for Primary Care*, 1st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016
497. Mandell DS, Morales KH, Marcus SC, Stahmer AC, Doshi J, Polsky DE. Psychotropic medication use among Medicaid-enrolled children with autism spectrum disorders. *Pediatrics*. 2008; 121(3). Available at: www.pediatrics.org/cgi/content/full/121/3/e441
498. Rosenberg RE, Mandell DS, Farmer JE, Law JK, Marvin AR, Law PA. 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
499. Coury DL, Anagnostou E, Manning-Courtney P, et al. Use of psychotropic medication in children and adolescents with autism spectrum disorders. *Pediatrics*. 2012;130(suppl 2):S69-S76
500. Mire SS, Nowell KP, Kubiszyn T, Goin-Kochel RP. Psychotropic medication use among children with autism spectrum disorders within the Simons Simplex Collection: are core features of autism spectrum disorder related? *Autism*. 2014;18(8):933-942
501. Witwer A, Lecavalier L. Treatment incidence and patterns in children and adolescents with autism spectrum disorders. *J Child Adolesc Psychopharmacol*. 2005;15(4):671-681
502. Frazier TW, Shattuck PT, Narendorf SC, Cooper BP, Wagner M, Spitznagel EL. Prevalence and correlates of psychotropic medication use in adolescents with an autism spectrum disorder with and without caregiver-reported attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2011;21(6):571-579
503. Bousman CA, Hopwood M. Commercial pharmacogenetic-based decision-support tools in psychiatry. *Lancet Psychiatry*. 2016;3(6):585-590
504. Hicks JK, Bishop JR, Sangkuhl K, et al; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther*. 2015;98(2): 127-134
505. Hess GP, Fonseca E, Scott R, Fagerness J. Pharmacogenomic and pharmacogenetic-guided therapy as a tool in precision medicine: current state and factors impacting acceptance by stakeholders. *Genet Res*. 2015;97:e13
506. Farmer C, Thurm A, Grant P. Pharmacotherapy for the core symptoms in autistic disorder: current status of the research. *Drugs*. 2013; 73(4):303-314
507. Politte LC, Henry CA, McDougle CJ. Psychopharmacological interventions in autism spectrum disorder. *Harv Rev Psychiatry*. 2014;22(2):76-92
508. Baribeau DA, Anagnostou E. An update on medication management of behavioral disorders in autism. *Curr Psychiatry Rep*. 2014;16(3):437
509. Accordino RE, Kidd C, Politte LC, Henry CA, McDougle CJ. Psychopharmacological interventions in autism spectrum disorder. *Expert Opin Pharmacother*. 2016;17(7):937-952
510. Brown JT, Eum S, Cook EH, Bishop JR. Pharmacogenomics of autism spectrum disorder. *Pharmacogenomics*. 2017;18(4): 403-414
511. Nath D. Complementary and alternative medicine in the school-age child with autism. *J Pediatr Health Care*. 2017; 31(3):393-397
512. Lindly OJ, Thorburn S, Heisler K, Reyes NM, Zuckerman KE. Parents' use of complementary health approaches for young children with autism spectrum disorder. *J Autism Dev Disord*. 2018; 48(5):1803-1818
513. Höfer J, Hoffmann F, Bachmann C. Use of complementary and alternative medicine in children and adolescents with autism spectrum disorder: a systematic review. *Autism*. 2017;21(4): 387-402
514. Green RR, Santoro N, Allshouse AA, Neal-Perry G, Derby C. Prevalence of complementary and alternative medicine and herbal remedy use in Hispanic and non-Hispanic white women: results from the study of women's health across the nation. *J Altern Complement Med*. 2017;23(10): 805-811
515. Hopf KP, Madren E, Santianni KA. Use and perceived effectiveness of complementary and alternative medicine to treat and manage the symptoms of autism in children: a survey of parents in a community population. *J Altern Complement Med*. 2016;22(1):25-32
516. 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
517. National Center for Complementary and Integrative Health. Autism. 2017. Available at: <https://nccih.nih.gov/health/autism>. Accessed November 12, 2017
518. Levy SE. Repeated doses of porcine secretin did not improve symptoms, language, or cognitive functioning in children with autism or autism spectrum disorder. *Evid Based Ment Health*. 2002;5(1):22
519. Perrin JM, Coury DL, Hyman SL, Cole L, Reynolds AM, Clemons T. Complementary and alternative medicine use in a large pediatric autism sample. *Pediatrics*. 2012; 130(suppl 2):S77-S82
520. Akins RS, Krakowiak P, Angkustsiri K, Hertz-Picciotto I, Hansen RL. Utilization patterns of conventional and complementary/alternative treatments in children with autism spectrum disorders and developmental disabilities in a population-based study. *J Dev Behav Pediatr*. 2014;35(1):1-10
521. Hanson E, Kalish LA, Bunce E, et al. Use of complementary and alternative medicine among children diagnosed with autism spectrum disorder. *J Autism Dev Disord*. 2007;37(4): 628-636
522. Valicenti-McDermott M, Burrows B, Bernstein L, et al. Use of complementary and alternative medicine in children with autism and other developmental disabilities: associations with ethnicity, child comorbid symptoms, and parental stress. *J Child Neurol*. 2014;29(3): 360-367
523. Mari-Bauset S, Zazpe I, Mari-Sanchis A, Llopis-González A, Morales-Suárez-Varela M. Evidence of the gluten-free and casein-free diet in autism spectrum disorders: a systematic

- review. *J Child Neurol*. 2014;29(12): 1718–1727
524. Dosman C, Adams D, Wudel B, Vogels L, Turner J, Vohra S. Complementary, holistic, and integrative medicine: autism spectrum disorder and gluten- and casein-free diet. *Pediatr Rev*. 2013; 34(10):e36–e41
525. Hyman SL, Stewart PA, Foley J, et al. The gluten-free/casein-free diet: a double-blind challenge trial in children with autism. *J Autism Dev Disord*. 2016;46(1): 205–220
526. Jia F, Wang B, Shan L, Xu Z, Staal WG, Du L. Core symptoms of autism improved after vitamin D supplementation. *Pediatrics*. 2015;135(1). Available at: www.pediatrics.org/cgi/content/full/135/1/e196
527. Saad K, Abdel-Rahman AA, Elserogy YM, et al. Vitamin D status in autism spectrum disorders and the efficacy of vitamin D supplementation in autistic children. *Nutr Neurosci*. 2016;19(8): 346–351
528. Bertoglio K, Jill James S, Deprey L, Brule N, Hendren RL. Pilot study of the effect of methyl B12 treatment on behavioral and biomarker measures in children with autism. *J Altern Complement Med*. 2010;16(5):555–560
529. Nye C, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database Syst Rev*. 2005;(4):CD003497
530. Mankad D, Dupuis A, Smile S, et al. A randomized, placebo controlled trial of omega-3 fatty acids in the treatment of young children with autism. *Mol Autism*. 2015;6:18
531. Valerie T. Discretionary fortification—a public health perspective. *Nutrients*. 2014;6(10):4421–4433
532. DeVilbiss EA, Gardner RM, Newschaffer CJ, Lee BK. Maternal folate status as a risk factor for autism spectrum disorders: a review of existing evidence. *Br J Nutr*. 2015;114(5): 663–672
533. Hickey SE, Curry CJ, Toriello HV. ACGM practice guideline: lack of evidence for MTHFR polymorphism testing. *Genet Med*. 2013;15(2):153–156
534. Geretsegger M, Elefant C, Mössler K, Gold C, et al. Music therapy for people with autism spectrum disorder. *Cochrane Database Syst Rev*. 2014;6: CD004381
535. Koenig KP, Buckley-Reen A, Garg S. Efficacy of the Get Ready to Learn yoga program among children with autism spectrum disorders: a pretest-posttest control group design. *Am J Occup Ther*. 2012;66(5):538–546
536. Hourston S, Atchley R. Autism and mind-body therapies: a systematic review. *J Altern Complement Med*. 2017;23(5): 331–339
537. Wan Yunus F, Liu KP, Bissett M, Penkala S. Sensory-based intervention for children with behavioral problems: a systematic review. *J Autism Dev Disord*. 2015;45(11):3565–3579
538. Borgi M, Loliva D, Cerino S, et al. Effectiveness of a standardized equine-assisted therapy program for children with autism spectrum disorder. *J Autism Dev Disord*. 2016;46(1):1–9
539. Hoagwood KE, Acri M, Morrissey M, Peth-Pierce R. Animal-assisted therapies for youth with or at risk for mental health problems: a systematic review. *Appl Dev Sci*. 2017;21(1):1–13
540. Sinha Y, Silove N, Hayen A, Williams K. Auditory integration training and other sound therapies for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2011;(12):CD003681
541. Brondino N, Fusar-Poli L, Rocchetti M, Provenzani U, Barale F, Politi P. Complementary and alternative therapies for autism spectrum disorder. *Evid Based Complement Alternat Med*. 2015;2015:258589
542. Committee on Children With Disabilities. Counseling families who choose complementary and alternative medicine for their child with chronic illness or disability [published correction appears in *Pediatrics*. 2001; 108(2):507]. *Pediatrics*. 2001;107(3): 598–601
543. Levy SE, Frasso R, Colantonio S, et al. Shared decision making and treatment decisions for young children with autism spectrum disorder. *Acad Pediatr*. 2016;16(6):571–578
544. Estes A, Olson E, Sullivan K, et al. Parenting-related stress and psychological distress in mothers of toddlers with autism spectrum disorders. *Brain Dev*. 2013;35(2): 133–138
545. Hayes SA, Watson SL. The impact of parenting stress: a meta-analysis of studies comparing the experience of parenting stress in parents of children with and without autism spectrum disorder. *J Autism Dev Disord*. 2013; 43(3):629–642
546. Horlin C, Falkmer M, Parsons R, Albrecht MA, Falkmer T. The cost of autism spectrum disorders. *PLoS One*. 2014;9(9):e106552
547. Child and Adolescent Health Measurement Initiative. National profile of children with special health care needs and autism spectrum disorders: key findings from the 2009/10 NS-CSHCN & 2011/12 NSCH. 2013. Available at: https://www.childhealthdata.org/docs/drc/asd-data-brief_7-30-13.pdf. Accessed December 1, 2019
548. Clifford T, Minnes P. Who participates in support groups for parents of children with autism spectrum disorders? The role of beliefs and coping style. *J Autism Dev Disord*. 2013;43(1): 179–187
549. Siller M, Reyes N, Hotez E, Hutman T, Sigman M. Longitudinal change in the use of services in autism spectrum disorder: understanding the role of child characteristics, family demographics, and parent cognitions. *Autism*. 2014;18(4):433–446
550. Mohd Roffeei SH, Abdullah N, Basar SK. Seeking social support on Facebook for children with autism spectrum disorders (ASDs). *Int J Med Inform*. 2015;84(5):375–385
551. Zablotsky B, Kalb LG, Freedman B, Vasa R, Stuart EA. Health care experiences and perceived financial impact among families of children with an autism spectrum disorder. *Psychiatr Serv*. 2014;65(3):395–398
552. McStay RL, Trembath D, Dissanayake C. Maternal stress and family quality of life in response to raising a child with autism: from preschool to adolescence. *Res Dev Disabil*. 2014;35(11):3119–3130
553. Green L. The well-being of siblings of individuals with autism. *ISRN Neuro*. 2013;2013:417194
554. Kuo DZ, Houtrow AJ; Council on Children With Disabilities. Recognition and

- management of medical complexity. *Pediatrics*. 2016;138(6):e20163021
555. Carbone PS, Behl DD, Azor V, Murphy NA. The medical home for children with autism spectrum disorders: parent and pediatrician perspectives. *J Autism Dev Disord*. 2010;40(3):317–324
556. Golnik A, Ireland M, Borowsky IW. Medical homes for children with autism: a physician survey. *Pediatrics*. 2009;123(3):966–971
557. Liptak GS, Orlando M, Yingling JT, et al. Satisfaction with primary health care received by families of children with developmental disabilities. *J Pediatr Health Care*. 2006;20(4):245–252
558. Cheak-Zamora NC, Farmer JE. The impact of the medical home on access to care for children with autism spectrum disorders. *J Autism Dev Disord*. 2015;45(3):636–644
559. Kogan MD, Strickland BB, Blumberg SJ, Singh GK, Perrin JM, van Dyck PC. A national profile of the health care experiences and family impact of autism spectrum disorder among children in the United States, 2005–2006. *Pediatrics*. 2008;122(6). Available at: www.pediatrics.org/cgi/content/full/122/6/e1149
560. McKinney CM, Nelson T, Scott JM, Heaton LJ, Vaughn MG, Lewis CW. Predictors of unmet dental need in children with autism spectrum disorder: results from a national sample. *Acad Pediatr*. 2014;14(6):624–631
561. Adams RC, Levy SE; Council on Children with Disabilities. Shared decision-making and children with disabilities: pathways to consensus. *Pediatrics*. 2017;139(6):e20170956
562. Huws JC, Jones RS. Diagnosis, disclosure, and having autism: an interpretative phenomenological analysis of the perceptions of young people with autism. *J Intellect Dev Disabil*. 2008;33(2):99–107
563. White PH, Cooley WC; Transitions Clinical Report Authoring Group; American Academy of Pediatrics; American Academy of Family Physicians; American College of Physicians. Supporting the health care transition from adolescence to adulthood in the medical home [published correction appears in *Pediatrics*. 2019;143(2):e20183610]. *Pediatrics*. 2018;142(5):e20182587
564. Got Transition. Health care providers. Available at: <http://www.gottransition.org/providers/index.cfm>. Accessed December 1, 2019
565. Autism Speaks. Puberty and adolescence resource: a guide for parents of adolescents with autism spectrum disorder. Available at: https://www.autismspeaks.org/sites/default/files/documents/atn/puberty_tool_kit.pdf. Accessed December 1, 2019
566. Kuder SJ, Accardo A. What works for college students with autism spectrum disorder. *J Autism Dev Disord*. 2018;48(3):722–731
567. Nicolaidis C, Kripke CC, Raymaker D. Primary care for adults on the autism spectrum. *Med Clin North Am*. 2014;98(5):1169–1191
568. Velott DL, Agbese E, Mandell D, et al. Medicaid 1915(c) Home- and Community-Based Services waivers for children with autism spectrum disorder. *Autism*. 2016;20(4):473–482
569. Interagency Autism Coordinating Committee. IACC strategic plan for autism spectrum disorder research: 2013 update. 2013. Available at: <https://iacc.hhs.gov/publications/strategic-plan/2013/>. Accessed March 25, 2017
570. Interagency Autism Coordinating Committee. IACC strategic plan for autism spectrum disorder: 2017 update. Available at: <https://iacc.hhs.gov/publications/strategic-plan/2017/>. Accessed December 1, 2019
571. Interagency Autism Coordinating Committee. IACC strategic plan for autism spectrum disorder research: 2011 update. 2011. Available at: <https://iacc.hhs.gov/publications/strategic-plan/2011/>. Accessed March 25, 2017
572. Rutter M, Bailey A, Lord C. *The Social Communication Questionnaire (SCQ) Manual*. Los Angeles, CA: Western Psychological Services; 2003
573. Stone WL, Coonrod EE, Ousley O. Brief report: screening tool for autism in two-year-olds (STAT): development and preliminary data. *J Autism Dev Disord*. 2000;30(6):607–612
574. Stone WL, Coonrod EE, Turner LM, Pozdol SL. Psychometric properties of the STAT for early autism screening. *J Autism Dev Disord*. 2004;34(6):691–701
575. Rowberry JJ, Macari S, Chen G, et al. Screening for autism spectrum disorders in 12-mo-old high-risk siblings by parental report. *J Autism Dev Disord*. 2015;45:221–229
576. Smith NJ, Sheldrick RC, Perrin EC. An Abbreviated Screening Instrument for Autism Spectrum Disorders. *Infant Ment Health J*. 2012;34(2):149–155
577. Salisbury LA, Nyce JD, Hannum CD, Sheldrick RC, Perrin EC. Sensitivity and specificity of 2 autism screeners among referred children between 16 and 48 mo of age. *J Dev Behav Pediatr*. 2018;39(3):254–258
578. Choueiri R, Wagner S. A new interactive screening test for autism spectrum disorders in toddlers. *J Pediatr*. 2015;167(2):460–466
579. Myers SM. Management of autism spectrum disorders in primary care. *Pediatr Ann*. 2009;38(1):42–49
580. Quintana H, Birmaher B, Stedje D, et al. Use of methylphenidate in the treatment of children with autistic disorder. *J Autism Dev Disord*. 1995;25(3):283–294
581. Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *J Autism Dev Disord*. 2000;30(3):245–255
582. Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Arch Gen Psychiatry*. 2005;62(11):1266–1274
583. Pearson DA, Santos CW, Aman MG, et al. Effects of extended release methylphenidate treatment on ratings of attention-deficit/hyperactivity disorder (ADHD) and associated behavior in children with autism spectrum disorders and ADHD symptoms. *J Child Adolesc Psychopharmacol*. 2013;23(5):337–351
584. Posey DJ, Aman MG, McCracken JT, et al. Positive effects of

- methylphenidate on inattention and hyperactivity in pervasive developmental disorders: an analysis of secondary measures. *Biol Psychiatry*. 2007;61(4):538–544
585. Reichow B, Volkmar FR, Bloch MH. Systematic review and meta-analysis of pharmacological treatment of the symptoms of attention-deficit/hyperactivity disorder in children with pervasive developmental disorders. *J Autism Dev Disord*. 2013;43(10):2435–2441
586. Jahromi LB, Kasari CL, McCracken JT, et al. Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. *J Autism Dev Disord*. 2009;39(3):395–404
587. Santosh PJ, Baird G, Pityaratstian N, Tavare E, Gringras P. Impact of comorbid autism spectrum disorders on stimulant response in children with attention deficit hyperactivity disorder: a retrospective and prospective effectiveness study. *Child Care Health Dev*. 2006;32(5):575–583
588. Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *J Am Acad Child Adolesc Psychiatry*. 2006;45(10):1196–1205
589. Harfterkamp M, Buitelaar JK, Minderaa RB, van de Loo-Neus G, van der Gaag RJ, Hoekstra PJ. Long-term treatment with atomoxetine for attention-deficit/hyperactivity disorder symptoms in children and adolescents with autism spectrum disorder: an open-label extension study. *J Child Adolesc Psychopharmacol*. 2013;23(3):194–199
590. Handen BL, Aman MG, Arnold LE, et al. Atomoxetine, parent training, and their combination in children with autism spectrum disorder and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(11):905–915
591. Jaselskis CA, Cook EH Jr., Fletcher KE, Leventhal BL. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol*. 1992;12(5):322–327
592. Fankhauser MP, Karumanchi VC, German ML, Yates A, Karumanchi SD. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. *J Clin Psychiatry*. 1992;53(3):77–82
593. Handen BL, Sahl R, Hardan AY. Guanfacine in children with autism and/or intellectual disabilities. *J Dev Behav Pediatr*. 2008;29(4):303–308
594. Scahill L, McCracken JT, King BH, et al; Research Units on Pediatric Psychopharmacology Autism Network. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. *Am J Psychiatry*. 2015;172(12):1197–1206
595. McCracken JT, McGough J, Shah B, et al; Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002;347(5):314–321
596. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114(5). Available at: www.pediatrics.org/cgi/content/full/114/5/e634
597. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110–1119
598. Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124(6):1533–1540
599. Arnold LE, Vitiello B, McDougle C, et al. Parent-defined target symptoms respond to risperidone in RUPP autism study: customer approach to clinical trials. *J Am Acad Child Adolesc Psychiatry*. 2003;42(12):1443–1450
600. Aman MG, McDougle CJ, Scahill L, et al; Research Units on Pediatric Psychopharmacology Autism Network. Medication and parent training in children with pervasive developmental disorders and serious behavior problems: results from a randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48(12):1143–1154
601. Aman MG, Lam KS, Van Bourgondien ME. Medication patterns in patients with autism: temporal, regional, and demographic influences. *J Child Adolesc Psychopharmacol*. 2005;15(1):116–126
602. Aman M, Rettiganti M, Nagaraja HN, et al. Tolerability, safety, and benefits of risperidone in children and adolescents with autism: 21-month follow-up after 8-week placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2015;25(6):482–493
603. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry*. 2005;162(7):1361–1369
604. Pandina GJ, Bossie CA, Youssef E, Zhu Y, Dunbar F. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. *J Autism Dev Disord*. 2007;37(2):367–373
605. Marcus RN, Owen R, Manos G, et al. Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: a 52-week, open-label, multicenter study. *J Clin Psychiatry*. 2011;72(9):1270–1276
606. Kent JM, Kushner S, Ning X, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *J Autism Dev Disord*. 2013;43(8):1773–1783
607. Findling RL, Mankoski R, Timko K, et al. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry*. 2014;75(1):22–30
608. Troost PW, Lahuis BE, Steenhuis MP, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J Am Acad Child Adolesc Psychiatry*. 2005;44(11):1137–1144
609. Anagnostou E, Aman MG, Handen BL, et al. Metformin for treatment of overweight induced by atypical antipsychotic medication in young people with autism spectrum disorder:

- a randomized clinical trial. *JAMA Psychiatry*. 2016;73(9):928–937
610. Fung LK, Mahajan R, Nozzolillo A, et al. Pharmacologic treatment of severe irritability and problem behaviors in autism: a systematic review and meta-analysis. *Pediatrics*. 2016;137(suppl 2):S124–S135
 611. King BH, Hollander E, Sikich L, et al; STAART Psychopharmacology Network. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. *Arch Gen Psychiatry*. 2009;66(6):583–590
 612. McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch Gen Psychiatry*. 1996; 53(11):1001–1008
 613. Hollander E, Chaplin W, Soorya L, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology*. 2010;35(4):990–998
 614. Belsito KM, Law PA, Kirk KS, Landa RJ, Zimmerman AW. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. *J Autism Dev Disord*. 2001;31(2): 175–181
 615. Hellings JA, Nickel EJ, Weckbaugh M, McCarter K, Mosier M, Schroeder SR. The overt aggression scale for rating aggression in outpatient youth with autistic disorder: preliminary findings. *J Neuropsychiatry Clin Neurosci*. 2005; 17(1):29–35
 616. Wasserman S, Iyengar R, Chaplin WF, et al. Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study. *Int Clin Psychopharmacol*. 2006;21(6): 363–367
 617. Hirota T, Veenstra-Vanderweele J, Hollander E, Kishi T. Antiepileptic medications in autism spectrum disorder: a systematic review and meta-analysis. *J Autism Dev Disord*. 2014;44(4):948–957
 618. Canitano R. Mood stabilizers in children and adolescents with autism spectrum disorders. *Clin Neuropharmacol*. 2015; 38(5):177–182
 619. Niederhofer H. Venlafaxine has modest effects in autistic children. *Therapy*. 2004;1(1):87–90
 620. McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Arch Gen Psychiatry*. 1998;55(7):633–641
 621. Hollander E, Soorya L, Wasserman S, Esposito K, Chaplin W, Anagnostou E. Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder. *Int J Neuropsychopharmacol*. 2006;9(2): 209–213
 622. Rezaei V, Mohammadi MR, Ghanizadeh A, et al. Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(7):1269–1272
 623. Hollander E, Soorya L, Chaplin W, et al. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders. *Am J Psychiatry*. 2012;169(3):292–299
 624. Hollander E, Phillips A, Chaplin W, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology*. 2005;30(3): 582–589
 625. Ji N, Findling RL. An update on pharmacotherapy for autism spectrum disorder in children and adolescents. *Curr Opin Psychiatry*. 2015;28(2):91–101
 626. Couturier JL, Nicolson R. A retrospective assessment of citalopram in children and adolescents with pervasive developmental disorders. *J Child Adolesc Psychopharmacol*. 2002; 12(3):243–248
 627. Namerow L, Thomas P, Bostic JQ, Prince J, Monuteaux MC. Use of citalopram in pervasive developmental disorders. *J Dev Behav Pediatr*. 2003;24(2):104–108
 628. Strawn JR, Welge JA, Wehry AM, Keeshin B, Rynn MA. Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. *Depress Anxiety*. 2015; 32(3):149–157
 629. Buitelaar JK, van der Gaag RJ, van der Hoeven J. Buspirone in the management of anxiety and irritability in children with pervasive developmental disorders: results of an open-label study. *J Clin Psychiatry*. 1998; 59(2):56–59
 630. Vasa RA, Carroll LM, Nozzolillo AA, et al. A systematic review of treatments for anxiety in youth with autism spectrum disorders. *J Autism Dev Disord*. 2014; 44(12):3215–3229

Supplemental Information

SUPPLEMENTAL TABLE 14 Recurrent CNVs Most Commonly Identified in Cohorts With ASD by Using CMA Analysis

CNV Region	Frequency ^a	Common Clinical Features
16p11.2 deletion	1 in 304	ASD, DD or ID, expressive language impairment, relative or absolute macrocephaly, overweight
16p11.2 duplication	1 in 396	ASD, schizophrenia, bipolar disorder, ADHD, relative or absolute microcephaly, underweight
15q11.2-q13 (BP2–BP3) duplication	1 in 494	ASD, DD or ID, epilepsy, hypotonia, ataxia, behavior problems
15q13.2-q13.3 (BP4–BP5) deletion	1 in 659	ASD, DD or ID, epilepsy, schizophrenia, cardiac defects
1q21.1 duplication	1 in 659	ASD, DD or ID, schizophrenia, ADHD, relative macrocephaly, hypertelorism
22q11.2 duplication	1 in 659	ASD, DD or ID, hypotonia, motor delay
16p13.11 deletion	1 in 791	ASD, DD or ID, epilepsy, schizophrenia, congenital anomalies
7q11.23 duplication	1 in 989	ASD, DD or ID, growth retardation, hypotonia
16p12.2 deletion	1 in 989	ASD, DD or ID, schizophrenia, epilepsy, growth retardation, cardiac defects, microcephaly, hypotonia
17q12 deletion	1 in 1978	ASD, DD or ID, schizophrenia, renal cysts, mature-onset diabetes of the young type 5
15q13.2–13.3 (BP4–BP5) duplication	1 in 1978	ASD, DD or ID, obesity

BP2 breakpoint 2; BP3 breakpoint 3; BP4 breakpoint 4; BP5 breakpoint 5; DD developmental delay; ID intellectual disability.

^a Moreno-De-Luca D et al⁶⁵¹; the frequency of each CNV among 3955 probands with ASD from the Autism Genetic Resource Exchange, Autism Genome Project, and Simons Foundation Autism Research Initiative Simplex Collection cohorts.

SUPPLEMENTAL TABLE 13 Selected Genetic Syndromes Associated With ASD

Condition	Physical Findings	Gene	Confirmatory Testing	Importance
Fragile X syndrome	Long face, prominent forehead and jaw, large ears, joint laxity, macroorchidism after puberty in boys	<i>FMR1</i> (CGG repeat expansion, abnormal methylation)	Targeted mutation analysis (PCR and Southern blot)	Genetic counseling (X-linked dominant inheritance); all mothers of individuals with an <i>FMR1</i> full mutation are carriers of an <i>FMR1</i> premutation or full mutation; extended family counseling is necessary; premutation carriers are at risk for fragile X–associated tremor/ataxia syndrome and <i>FMR1</i> -related primary ovarian insufficiency in female patients; several targeted pharmacologic therapies are under investigation
Neurofibromatosis 1	Multiple café-au-lait macules, axillary and inguinal freckling, iris Lisch nodules, cutaneous neurofibromas	<i>NF1</i>	Clinical criteria; optimized protein truncation testing, sequence analysis, and deletion or duplication analysis are available but infrequently required	Genetic counseling (autosomal dominant inheritance); 50% de novo, 50% inherited; associated problems requiring investigation or monitoring (optic gliomas, other CNS tumors, peripheral nerve sheath tumors, vasculopathy, hypertension, orthopedic issues, osteopenia)
<i>PTEN</i> hamartoma tumor syndrome (includes Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome)	Marked macrocephaly, skin hamartomas, pigmented macules of the glans penis	<i>PTEN</i>	<i>PTEN</i> sequence analysis, deletion or duplication analysis	Genetic counseling (autosomal dominant inheritance with highly variable expression); associated problems requiring investigation or monitoring (significant risk of benign and malignant tumors of the thyroid, breast, and endometrium as well as intestinal polyps, colorectal cancer, renal cell carcinoma, cutaneous melanoma, and cerebellar dysplastic gangliocytoma)
Rett syndrome	Deceleration of head growth velocity, acquired microcephaly, loss of purposeful hand use, prominent hand stereotypies (especially hand wringing or clasping), apraxia, hyperventilation or breath-holding, seizures	<i>MECP2</i>	<i>MECP2</i> sequence analysis, deletion or duplication analysis	Genetic counseling (>99% de novo, <1% germline mosaicism); associated problems requiring investigation or monitoring and anticipatory guidance (failure to thrive, gastroesophageal reflux, respiratory problems, osteopenia, sudden death); targeted pharmacologic therapy under investigation
Smith-Lemli-Opitz syndrome	Characteristic facial features (narrow forehead, low-set ears, ptosis, epicanthal folds, short nose, anteverted nares), microcephaly, cleft palate, 2- to 3-toe syndactyly, postaxial polydactyly, hypospadias in male	<i>DHCR7</i>	7-dehydrocholesterol level (elevated); <i>DHCR7</i> sequence analysis available	Genetic counseling (autosomal recessive inheritance); potential role for treatment with cholesterol

SUPPLEMENTAL TABLE 13 Continued

Condition	Physical Findings	Gene	Confirmatory Testing	Importance
Timothy syndrome	<p>patients, prenatal and postnatal growth retardation</p> <p>Long QT interval, other ECG abnormalities (atrioventricular block, macroscopic T-wave alternans), congenital heart defects, cutaneous syndactyly, low-set ears, flat nasal bridge, thin upper lip, round facies, baldness for the first 2 y of life followed by thin scalp hair, dental abnormalities, frequent infections because of altered immune response, intermittent hypoglycemia</p>	<i>CACNA1C</i>	Targeted mutation analysis, sequence analysis, deletion or duplication analysis	Genetic counseling, autosomal dominant, usually de novo, but parental germline mosaicism has been observed; treatment related to long QTc (β -blocker, pacemaker; implantable defibrillator) and avoidance of hypoglycemia
Tuberous sclerosis	<p>Hypopigmented macules, angiofibromas, shagreen patches (connective tissue nevi), ungual fibromas, retinal hamartomas</p>	<i>TSC1, TSC2</i>	Clinical criteria; <i>TSC1</i> and <i>TSC2</i> sequencing available	Genetic counseling (autosomal dominant inheritance); associated problems requiring investigation or monitoring (CNS tumors, seizures, renal angiomyolipomas or cysts, cardiac rhabdomyomas and arrhythmias); potential role for targeted pharmacologic therapy (mTOR inhibitors)

CACNA1C, calcium channel, voltage-dependent, L-type, α -1c subunit; C6G, cytosine-guanine-guanine; CNS, central nervous system; *DHCR7*, 7-dehydrocholesterol reductase; ECG, electrocardiogram; *FMR1*, fragile X mental retardation 1; *MECP2*, methyl CpG binding protein 2; mTOR, mammalian target of rapamycin; PCR, polymerase chain reaction; *PTEN*, phosphatase and tensin homolog; QTc, corrected QT interval; *TSC1*, tuberous sclerosis 1; *TSC2*, tuberous sclerosis 2. Adapted with permission from Myers SM, Challman TD. Autism Spectrum Disorders. In: Voigt RG, Macias MM, Myers SM, eds. *Developmental and Behavioral Pediatrics*. Elk Grove Village, IL: American Academy of Pediatrics; 2011:249–291.

SUPPLEMENTAL TABLE 15 Selected ASD Risk Genes Identified or Confirmed in Whole-Exome Studies

Gene	Gene Name	Broad Functional Categorization	
<i>SCN2A</i>	sodium channel, voltage-gated, type II, α subunit	Synaptic functions (eg, ion channels, neurotransmitter receptors, cell adhesion molecules, microtubule assembly, scaffolding proteins, actin cytoskeleton)	
<i>GRIN2B</i>	glutamate receptor, ionotropic, N-methyl-D-aspartate 2B		
<i>KATNAL2</i>	katanin p60 subunit A-like 2		
<i>ANK2</i>	ankyrin 2, neuronal		
<i>DSCAM</i>	Down syndrome cell adhesion molecule		
<i>NRXN1</i>	neurexin 1		
<i>SHANK2</i>	SH3 and multiple ankyrin repeat domains 2		
<i>SHANK3</i>	SH3 and multiple ankyrin repeat domains 3		
<i>PTEN</i>	phosphatase and tensin homolog		Intracellular signaling, activity-dependent synaptic protein synthesis and degradation
<i>SYNGAP1</i>	synaptic Ras GTPase activating protein 1		
<i>DYRK1A</i>	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A		
<i>POGZ</i>	pogo transposable element with ZNF domain		
<i>CUL3</i>	cullin 3		
<i>CHD2</i>	chromodomain helicase DNA binding protein 2	Transcription regulation, chromatin remodeling	
<i>CHD8</i>	chromodomain helicase DNA binding protein 8		
<i>ADNP^a</i>	activity-dependent neuroprotector homeobox		
<i>ARID1B</i>	AT rich interactive domain 1B (SWI1-like)		
<i>ASH1L</i>	ASH1 (absent, small, or homeotic)-like		
<i>KDM5B</i>	lysine-specific demethylase 5B		
<i>KMT2C</i>	lysine-specific methyltransferase 2C		
<i>SETD5</i>	SET domain containing 5		
<i>TBR1</i>	T-box, brain, 1		

Based on de novo loss of function variants and small de novo deletions (false discovery rate < 0.01). Adapted from Sanders SJ, He X, Willsey AJ, et al; Autism Sequencing Consortium. Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. *Neuron*. 2015;87(6):1215–1233; Krumm N, O’Roak BJ, Shendure J, Eichler EE. A de novo convergence of autism genetics and molecular neuroscience. *Trends Neurosci*. 2014;37(2):95–105; Brandler WM, Sebat J. From de novo mutations to personalized therapeutic interventions in autism. *Annu Rev Med*. 2015;66:487–507; De Rubeis S, He X, Goldberg AP, et al; DDD Study; Homozygosity Mapping Collaborative for Autism; UK10K Consortium. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*. 2014;515(7526):209–215; Bourgeron T. From the genetic architecture to synaptic plasticity in autism spectrum disorder. *Nat Rev Neurosci*. 2015;16(9):551–563; and Sanders SJ, Murtha MT, Gupta AR, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature*. 2012; 485(7397):237–241.

^a Also involved in microtubule dynamics at the synapse.

SUPPLEMENTAL TABLE 16 Selected Metabolic Conditions That May (Rarely) Be Associated With an ASD Phenotype

Disorders of amino acid metabolism
Phenylketonuria (untreated)
Homocystinuria
Branched-chain ketoacid dehydrogenase kinase deficiency
Disorders of γ -aminobutyric acid metabolism
Succinic semialdehyde dehydrogenase deficiency
Disorders of cholesterol metabolism
Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency)
Disorders associated with cerebral folate deficiency
Folate receptor 1 gene mutations
Dihydrofolate reductase deficiency
Disorders of creatine transport or metabolism
Arginine-glycine amidinotransferase deficiency
Guanidinoacetate methyltransferase deficiency
X-linked creatine transporter deficits
Disorders of carnitine biosynthesis
6-N-trimethyllysine dioxygenase deficiency
Disorders of purine and pyrimidine metabolism
Adenylosuccinate lyase deficiency
Adenosine deaminase deficiency
Cytosolic 5'-nucleotidase superactivity
Dihydropyrimidine dehydrogenase deficiency
Phosphoribosyl pyrophosphate synthetase superactivity
Lysosomal storage disorders
Sanfilippo syndrome (mucopolysaccharidosis type III)
Mitochondrial disorders
Mitochondrial DNA mutations
Nuclear DNA mutations
Others
Biotinidase deficiency
Urea cycle defects

Adapted from 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; Legido A, Jethva R, Goldenthal MJ. Mitochondrial dysfunction in autism. *Semin Pediatr Neurol*. 2013;20(3):163–175; Jiang YH, Wang Y, Xiu X, Choy KW, Pursley AN, Cheung SW. Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the genomics era. *Crit Rev Clin Lab Sci*. 2014;51(5):249–262; and Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. *Epilepsy Behav*. 2015; 47:147–157.

SUPPLEMENTAL REFERENCES

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| 631. Moreno-De-Luca D, Sanders SJ, Willsey AJ, et al. Using large clinical | data sets to infer pathogenicity for rare copy number variants in autism | cohorts. <i>Mol Psychiatry</i> . 2013;18(10):1090–1095 |
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