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CLINICAL REPORT

Identification and Evaluation of Children With Autism Spectrum Disorders

Chris Plauché Johnson, MD, MEd, Scott M. Myers, MD, and the Council on Children With Disabilities

Guidance for the Clinician in Rendering Pediatric Care

ABSTRACT

Autism spectrum disorders are not rare; many primary care pediatricians care for several children with autism spectrum disorders. Pediatricians play an important role in early recognition of autism spectrum disorders, because they usually are the first point of contact for parents. Parents are now much more aware of the early signs of autism spectrum disorders because of frequent coverage in the media; if their child demonstrates any of the published signs, they will most likely raise their concerns to their child's pediatrician. It is important that pediatricians be able to recognize the signs and symptoms of autism spectrum disorders and have a strategy for assessing them systematically. Pediatricians also must be aware of local resources that can assist in making a definitive diagnosis of, and in managing, autism spectrum disorders. The pediatrician must be familiar with developmental, educational, and community resources as well as medical subspecialty clinics. This clinical report is 1 of 2 documents that replace the original American Academy of Pediatrics policy statement and technical report published in 2001. This report addresses background information, including definition, history, epidemiology, diagnostic criteria, early signs, neuropathologic aspects, and etiologic possibilities in autism spectrum disorders. In addition, this report provides an algorithm to help the pediatrician develop a strategy for early identification of children with autism spectrum disorders. The accompanying clinical report addresses the management of children with autism spectrum disorders and follows this report on page 1162 [available at www.pediatrics.org/cgi/content/full/120/5/1162]. Both clinical reports are complemented by the toolkit titled "Autism: Caring for Children With Autism Spectrum Disorders: A Resource Toolkit for Clinicians," which contains screening and surveillance tools, practical forms, tables, and parent handouts to assist the pediatrician in the identification, evaluation, and management of autism spectrum disorders in children.

INTRODUCTION

Public and physician awareness of autism has increased markedly in the new millennium because of increased media coverage and a rapidly expanding body of knowledge published in professional journals. Professionals who specialize in autism have proliferated over the past 2 decades and have introduced the terminology "autism spectrum disorders" (ASDs) to reflect the broader spectrum of clinical characteristics that now define autism.^{1,2} ASDs represent 3 of the pervasive developmental disorders defined in the *Diagnostic and Statistical Manual of Mental*

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words

autism, autism spectrum disorders, Asperger syndrome, pervasive developmental disorders, fragile X syndrome, joint attention, self-injurious behaviors, theory of mind, neuropathologic abnormalities

Abbreviations

ASD—autism spectrum disorder
AD—autistic disorder
DSM—*Diagnostic and Statistical Manual of Mental Disorders*
AS—Asperger syndrome
PDD-NOS—pervasive developmental disorder—not otherwise specified
PCP—primary care pediatrician
AAP—American Academy of Pediatrics
IDEA—Individuals With Disabilities Education Act
MR—mental retardation
GDD—global developmental delay
ADHD—attention-deficit/hyperactivity disorder
FISH—fluorescence in situ hybridization
MMR—measles-mumps-rubella
JA—joint attention
ToM—theory of mind
SLP—speech-language pathologist
CHAT—Checklist for Autism in Toddlers
M-CHAT, Modified Checklist for Autism in Toddlers
CAST—Childhood Asperger Syndrome Test
EEG—electroencephalography
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Disorders, Fourth Edition (DSM-IV),³ and the newer *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*⁴: autistic disorder (AD), Asperger syndrome (AS [this terminology will be used in this report, although “Asperger’s disorder” is used in the aforementioned publications]), and pervasive developmental disorder—not otherwise specified (PDD-NOS). In addition to being a spectrum disorder, autism has wide variability with respect to the presence and intensity of symptoms, even within the DSM-IV-TR categories, which indicates that there may be additional subtypes.

ASDs are not rare; many primary care pediatricians (PCPs) care for several children with ASDs. In fact, a survey completed in 2004 revealed that 44% of PCPs reported that they care for at least 10 children with ASDs; however, only 8% stated that they routinely screened for ASDs.⁵ Another survey indicated that although PCPs were aware of the current DSM-IV-TR diagnostic criteria, they sometimes held beliefs about ASDs that were outdated.⁶ It is critical that PCPs recognize the early signs of ASDs and be aware of new data that support better outcomes in children whose conditions are diagnosed early and who participate in appropriate intervention programs.^{7–11} Because it is a chronic condition, the PCP also needs to feel comfortable with the ongoing care of children with ASDs within the context of the medical home. To support PCPs in the identification and care of children with ASD, the American Academy of Pediatrics (AAP) has developed and distributed several documents:

- The “*Autism A.L.A.R.M.*”¹²: a flyer that highlights the prevalence of autism, the importance of screening and listening to parents’ concerns, and the urgency of making simultaneous referrals to specialists in ASDs and early intervention programs to promote improved outcomes.
- “*Is Your One-Year-Old Communicating With You?*”¹³: a brochure that focuses on early identification of social communication deficits and behavior problems that may be associated with developmental disorders, primarily ASDs. This brochure is intended for distribution to all parents of infants at the 9- or 12-month well-child visit. It encourages parents to share any concerns they have about their infant’s language development and social skills with the pediatrician as early as possible.
- “*Understanding Autism Spectrum Disorders*”¹⁴: a 48-page introductory booklet for parents of children in whom an ASD has been diagnosed recently or is suspected strongly.

In addition, the AAP has developed an ASD toolkit and resource guide to assist the PCP with implementation of the principles discussed herein.

Although ASDs are neurodevelopmental conditions with strong genetic underpinnings, their exact etiology is unknown. In 1943, Leo Kanner, a psychiatrist at Johns Hopkins University, first described autism in a small group of children who demonstrated extreme aloofness and total indifference to other people.¹⁵ In 1944, Hans Asperger, an Austrian pediatrician who was unaware of Kanner’s work, published an article¹⁶ that described children who demonstrated symptoms similar to those of Kanner’s patients, with the exception that verbal and cognitive skills were higher. The term “infantile autism” first appeared as a diagnostic label in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)*.¹⁷ Since then, terminology has changed and diagnostic criteria have broadened.¹⁸ Diagnostic criteria for AS were not included in the DSM until the fourth edition (DSM-IV). The most recent criteria for AD and AS (Asperger’s disorder) are found in the DSM-IV-TR⁴ (Tables 1 and 2, respectively). PDD-NOS, the remaining ASD, is described in the DSM-IV-TR as a subthreshold diagnostic term used when a child demonstrates severe and pervasive impairments in reciprocal social skills associated with deficits in language skills or with the presence of stereotypic behaviors or restricted interests or activities but does not meet full criteria for AD or AS. Although Rett syndrome and childhood disintegrative disorder are included in the DSM-IV-TR listings, they are not considered ASDs but should be considered in the differential diagnosis of each child, depending on the presenting signs and symptoms.

EPIDEMIOLOGY

Authors of studies published early in the new millennium concluded that the best estimate of current prevalence of ASDs in Europe and North America is approximately 6 per 1000.^{19–27} In 2000, the Centers for Disease Control and Prevention organized the Autism and Developmental Disabilities Monitoring Network, a multi-site, records-based surveillance program, to study the prevalence of ASDs. The network uses systematic screening of developmental evaluation records for autistic behaviors rather than depending on a medical or educational diagnostic label of an ASD. In 2007, the network reported ASD rates for 8-year-old children ranging from 1 in 303 to 1 in 94 for 2 time periods (2000 and 2002) in a total of 14 sites in the United States; the average rate was 1 in 150 or 6.6 per 1000 8-year-olds.^{28–31} Although these studies reflect a 10-fold increase from studies published a half-century ago that chiefly targeted AD alone, most of the newer studies also included individuals with AS and PDD-NOS. One of the few studies that analyzed the prevalence in regard to type of ASD revealed that in Canada, where the overall rate was 6.5 per 1000, the individual rates were 2.2 per 1000 for AD, 1.0 per 1000 for AS, and 3.3 per 1000 for PDD-NOS.²⁷ Studies have varied in design, and

TABLE 1 Diagnostic Criteria for 299.00: AD

- A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):
- (1) **qualitative impairment in social interaction, as manifested by at least two of the following:**
 - (a) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
 - (b) failure to develop peer relationships appropriate to developmental level
 - (c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (eg, by a lack of showing, bringing, or pointing out objects of interest)
 - (d) lack of social or emotional reciprocity
 - (2) **qualitative impairments in communication as manifested by at least one of the following:**
 - (a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
 - (b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
 - (c) stereotyped and repetitive use of language or idiosyncratic language
 - (d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
 - (3) **restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:**
 - (a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
 - (b) apparently inflexible adherence to specific, nonfunctional routines or rituals
 - (c) stereotyped and repetitive motor mannerisms (eg, hand or finger flapping or twisting, or complex whole-body movements)
 - (d) persistent preoccupation with parts of objects
- B. Delays or abnormal functioning in at least one of the following areas, with onset before 3 years old: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.
- C. The disturbance is not better accounted for by Rett's Disorder or childhood disintegrative disorder.

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TABLE 2 Diagnostic Criteria for 299.80: Asperger's Disorder (Referred to as AS in This Report)

- A. Qualitative impairment in social interaction, as manifested by at least two of the following:
- (1) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
 - (2) failure to develop peer relationships appropriate to developmental level
 - (3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (eg, by a lack of showing, bringing, or pointing out objects of interest to other people)
 - (4) lack of social or emotional reciprocity
- B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least 1 of the following:
- (1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
 - (2) apparently inflexible adherence to specific, nonfunctional routines or rituals
 - (3) stereotyped and repetitive motor mannerisms (eg, hand or finger flapping or twisting, or complex whole-body movements)
 - (4) persistent preoccupation with parts of objects
- C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.
- D. There is no clinically significant general delay in language (eg, single words used by 2 years old, communicative phrases used by 3 years old).
- E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.
- F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

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case-ascertainment strategies make comparisons difficult.^{20-22,24,31-34}

With recent heightened public awareness, parents are more likely to raise a concern specifically about autism.³⁵⁻³⁷ In addition, as screening tools and more reliable evaluation instruments have been developed, professionals have become increasingly proficient in recognizing and diagnosing ASD. Apart from greater awareness and better ascertainment, additional reasons for the apparent increase have been debated hotly in the lay media; in fact, the publicized "autism epidemic" may be one of the most challenging public health issues today.

The prevalence of autism and, more recently, ASDs is closely linked to a history of changing criteria and diag-

nostic categories. Autism first appeared as a separate entity with specific criteria in the DSM-III in 1980.¹⁷ In 1987, the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)*³⁸ listed broadened AD criteria and the new subthreshold category of PDD-NOS, both of which promoted inclusion of milder cases. Later, these changes received criticism for being too inclusive and for promoting overdiagnosis.³⁹ The DSM-IV³ criteria published in 1994 reflected the result of years of analyses to reduce the overinclusiveness of the DSM-III-R criteria; however, it included AS for the first time, which, in effect, broadened the range of disorders. Studies have revealed that the DSM-IV criteria have better specificity (0.87) than DSM-III-R criteria.⁴⁰ The DSM-IV-

TR⁴ criteria for AD and AS are unchanged; however, the text description of PDD-NOS was edited slightly to increase specificity. Collaboration with European groups that worked on the revised *International Statistical Classification of Diseases and Related Health Problems* (10th edition)⁴¹ promoted better conformity between the 2 classification systems.

AD did not become a diagnosis for which children became eligible to receive special education services until passage of the Individuals With Disabilities Education Act (IDEA) in 1990.⁴² Before the IDEA was enacted, children were labeled as having conditions such as mental retardation (MR), learning disability, speech impairment, or emotional disturbance to obtain eligibility for services.⁴³ Hence, after passage of the IDEA, the resulting increase in the number of children served under the AD category reflected both newly diagnosed young children entering the school system and older children who were previously eligible for special services under a different educational label. This reflects the phenomenon of “diagnostic substitution,” whereby the number of children receiving special education under other categories (primarily MR, speech impairment, and learning disabilities) has decreased over the same time period. In addition, some increase in prevalence may be attributable to inaccuracies in diagnosis for a number of reasons, including labeling biases when schools used less rigorous criteria than those needed for a DSM diagnosis,^{44–48} when educational funding trends influenced diagnosis,⁴⁹ and/or when parents of children with marginal criteria advocated for the AD label to qualify for supplementary services (eg, year-round schooling) described in the IDEA amendments.^{50,51} The impact of these factors on current prevalence estimates has been controversial and illustrates the reason why educational administrative data reported in some studies that receive media attention should not be considered for epidemiologic studies.^{47,48,52–56}

Just at the time when school eligibility laws were changing, the Americans With Disabilities Act of 1990⁵⁷ was passed, obliging states to administer their programs in the most integrated settings appropriate to the needs of the person with disabilities. This was the culmination of a long series of state and federal legislation that promoted closure of institutions and encouraged governments to support families in their efforts to raise their children with disabilities at home. Thus, children with autism, especially those with comorbid MR and behavior problems who might have been institutionalized in the past, began to attend community schools and to be “counted” in educational prevalence data.

Other factors that may also be contributing to the perceived increase in prevalence include the recent identification of children with genetic disorders unrelated to ASDs who also sometimes can meet criteria for an ASD, such as Down syndrome^{58,59} and CHARGE (coloboma,

heart disease, choanal atresia, retarded growth and development and/or central nervous system anomalies, genital anomalies and/or hypogonadism, and ear anomalies and/or deafness) syndrome.⁶⁰ Finally, diagnosis of an ASD may be made in an older family member with milder symptoms that were previously unrecognized until after the diagnosis of a younger child.⁶¹

Regardless of the study, the year conducted, or the reported rate of prevalence, more boys than girls are consistently found to be affected with ASDs, with male-to-female ratios ranging from 2:1 to 6.5:1.^{24,28,29,34,62} The male-to-female ratio is even higher for high-functioning autism and AS, ranging from 6:1 to as high as 15:1.⁶³ (In recognition of these statistics and for the sake of brevity, this report uses masculine pronouns.)

ETIOLOGY

ASDs are biologically based neurodevelopmental disorders that are highly heritable.⁶⁴ Despite this fact, the exact cause still is unknown. Finding the cause has been daunting because of genetic complexity and phenotypic variation. ASDs are complex heritable disorders that involve multiple genes and demonstrate great phenotypic variation. Estimates of recurrence risks, based on family studies of idiopathic ASDs, are approximately 5% to 6% (range: 2%–8%) when there is an older sibling with an ASD and even higher when there are already 2 children with ASDs in the family.^{65–68}

In a minority of cases (<10%), ASDs may be associated with a medical condition or a known syndrome.^{20,21} Although ASDs are believed to be mainly genetic in origin, environmental factors may modulate phenotypic expression.^{64,69} Advanced paternal age^{70,71} and maternal age^{71,72} have been shown to be associated with an increased risk of having offspring with ASDs, possibly because of de novo spontaneous mutations and/or alterations in genetic imprinting. Environmental exposures may act as central nervous system teratogens in early gestational life.⁷³ Some researchers have suggested that an epigenetic mechanism (heritable changes in gene expression that occur without changes in DNA sequence) may be responsible.⁷⁴ Thus, it has become more and more apparent that the etiology is multifactorial with a variety of genetic and, to a lesser extent, environmental factors playing a role.⁷⁵

Two major strategies have been used in the search for the ASD genes: targeted cytogenetic/molecular studies and whole-genome screens of families of children with ASD.^{76–79} The first strategy depends on developing a hypothesis regarding the pathogenesis of ASDs, focusing on a potential candidate gene and testing it genetically for an association with ASDs. Candidate genes in ASDs include, among others, those that seem to play a role in brain development (eg, cerebellar Purkinje cell proliferation) or neurotransmitter function (eg, serotonin).⁸⁰ The second strategy uses an indirect method and does

not require investigators to make assumptions regarding the mechanism of inheritance. Instead, families with multiple members who demonstrate an ASD (multiplex families) are studied to identify recurring DNA markers (break points, translocations, duplications, and deletions) present in affected members but not in unaffected members. Unfortunately, progress in determining a genetic etiology using this method has been impaired, because the phenotypic end points of ASDs are not well defined. Changing DSM criteria and inconsistent ascertainment strategies, which results in a hazy delineation between affected versus unaffected family members, obscure outcomes and challenge interpretation of results.⁶⁷ This phenotypic heterogeneity has challenged molecular searches for the ASD gene(s) despite several genome-wide screens of the International Molecular Genetic Study of Autism Consortium and multicenter collaborative efforts over the past couple of decades.^{78,81–84} Although at least 1 autism-linked abnormality has been found on almost every chromosome, sites on a few chromosomes (X, 2, 3, 7, 15, 17, and 22) seem to be more promising than others.^{67,68,75,79,85–90} Maternally derived 15q duplications are common; depending on the investigator, yields vary from 1% to 10%,⁹¹ with most in the range of 1% to 3%.^{92,93} Patients with these duplications may not display dysmorphic features, but they often have hypotonia and/or global developmental delay (GDD) and may develop seizures later. The abnormality can often be identified on high-resolution karyotype analysis. Other less common abnormalities have also been reported.⁹⁴

Finally, the male predominance noted above also suggests a genetic role in the inheritance of autism. Several genetic processes can lead to male predominance, including causative genes located on the X chromosome (X-linked disorders) and imprinted genes, but the reason for male predominance in autism is not completely understood.⁹⁵

In a discussion of etiology, subtyping ASDs as either idiopathic or secondary is helpful.^{67,79,95} For the purposes of this discussion, the term “idiopathic” ASDs refers to cases in which children meet criteria for ASDs but do not have a comorbid associated medical condition known to cause ASDs. Most individuals with an ASD have the idiopathic type. Children with idiopathic ASDs demonstrate variable behavioral phenotypes, are somewhat less likely to have comorbid GDD/MR, and generally do not have dysmorphic features that herald a recognizable syndrome. Nevertheless, twin and family studies have revealed that idiopathic ASDs are heritable and have a recurrence rate of 5% to 6%.^{67,94,95} The term “secondary” ASDs refers to cases with an identifiable syndrome or medical disorder known to be associated with ASDs. Whereas earlier reviews reported that the proportion of individuals with ASDs who have a comorbid syndrome or medical condition was 10% to 20%,^{2,96–98} the propor-

tion has decreased to less than 10% when using more recent data sets.^{79,89,95,99–101} In a meta-analysis of 23 epidemiologic studies, Chakrabarti and Fombonne^{20,21} revealed that a recognizable condition was identified in only 6% of those with a confirmed ASD. The rate of coexisting MR (cognitive impairment associated with an IQ of <70) in children with ASDs seemed to decrease from 90% before the 1990s to less than 50% after 2000,^{28,29,34,35,102,103} possibly because of improved methods in testing intelligence in this population and to the increased awareness of children with ASD with milder features and higher functioning. This trend is important, because coexisting severe MR, especially in the presence of dysmorphic features, increases the likelihood of identifying a known disorder.^{89,104–108} Neurogenetic syndromes that seem to play a causative role or otherwise are associated with ASDs include, but are not limited to:

- **Fragile X syndrome^{109,110}:** Fragile X syndrome is the most common known genetic cause of AD and of MR in males. The phenotype includes MR, macrocephaly, large pinnae, large testicles (particularly after puberty), hypotonia, and joint hyperextensibility. Identifying a patient with fragile X syndrome is important for genetic counseling purposes, because the diagnosis has implications for other family members. Depending on the prevalence of comorbid MR in study subjects with ASD, the etiologic yield of fragile X syndrome–DNA testing has ranged from 0% to 8%, with a median of approximately 3% to 4%.^{99,109,111} On the other hand, as many as 30% to 50% of individuals with genetically confirmed fragile X syndrome will demonstrate some characteristics of ASDs.^{102,110}
- **Neurocutaneous disorders:** Tuberous sclerosis^{112–116} is characterized by hypopigmented macules (sometimes requiring a Wood’s lamp examination for visualization in young children), fibroangiomas, kidney lesions, central nervous system hamartomas, seizures, MR, and autistic and/or attention-deficit/hyperactivity disorder (ADHD)–like behaviors. Although tuberous sclerosis is a dominant disorder (with genes located at 9q and 16p), most cases represent new mutations. Although it is the most common neurocutaneous disorder, neurofibromatosis is less likely to be associated with ASDs. It also is autosomal-dominant, with half of cases representing new mutations of the neurofibromatosis 1 gene on 17q.¹¹⁷ It is characterized by café au lait macules and freckling in the axillary and inguinal regions, neurofibromas, and ocular Lisch nodules. Although most patients have a benign course and normal intelligence, a small subset of individuals have MR and behavioral features that are consistent with ASDs.
- **Phenylketonuria¹¹⁸:** phenylketonuria now is a rare cause of ASDs and MR in the United States, because it

is preventable as a result of newborn screening and dietary intervention.

- Fetal alcohol syndrome¹¹⁹: Children who are exposed to alcohol during gestation have an increased risk of ASDs in addition to other neurodevelopmental disorders.
- Angelman syndrome^{93,94,120–123}: Angelman syndrome is associated with loss of the maternally expressed ubiquitin-protein ligase gene (*UBE3A*) on 15q through deletion, paternal uniparental disomy, or imprinting errors. Children with Angelman syndrome present with GDD (and often are nonverbal), hypotonia in early childhood, wide-based ataxic gait, seizures, and progressive spasticity. Angelman syndrome associated with a deletion of 15q can be detected with fluorescence in situ hybridization (FISH) testing; however, when it results from uniparental disomy, methylation studies are necessary.
- Rett syndrome^{124–127}: Rett syndrome usually presents with a classic phenotype and should be considered in all females who demonstrate autistic-like regression, especially if they have microcephaly, seizures, and hand-wringing stereotypies. Retrospective videos have revealed early subtle motor symptoms during the first year of life.¹²⁸ Now that it is possible to confirm this diagnosis with DNA testing (methyl CpG-binding protein 2 [*MECP2*]) in approximately 80% of cases, it has become apparent that there is a spectrum of severity, and some patients may present with atypical features including those consistent with ASDs. Rett syndrome is much less common in males, and the presentation is more varied. Some males die in infancy as a result of neonatal encephalopathy; others with comorbid Klinefelter syndrome (as well as a few males [in isolated case reports] with a normal number of sex chromosomes) demonstrate more classic symptoms.^{129,130}
- Smith-Lemli-Opitz syndrome¹³¹: Smith-Lemli-Opitz syndrome is a rare (1 in 20 000) autosomal-recessive disorder caused by a metabolic error in cholesterol biosynthesis. Although most patients present with multiple congenital anomalies, failure to thrive, and MR, some may present with subtle physical features such as webbing (syndactyly) of the second and third toes, mild hypotonia, and autistic features. Recurrence risk is 25%; thus, appropriate genetic counseling is important.

Whether the aforementioned conditions play a direct or indirect etiologic role or simply are associated with ASDs, they still represent a small minority of patients with ASDs. Conversely, a few children with genetic syndromes that are characterized by features quite different from ASDs also may meet DSM-IV-TR criteria. For example, recent studies have reported that 6% to 7% of

children with Down syndrome (typically characterized by relatively good social skills compared with those in other domains)⁵⁹ and almost 50% of children with CHARGE syndrome (associated with mutations of the *CHD7* gene¹³²) meet criteria for one of the ASDs.⁶⁰ There have also been a few isolated reports of a mitochondrial and/or metabolic abnormality (eg, carnitine deficiency) being associated with an ASD, but the significance of these reports is not clear.¹³³

Increased and decreased levels of T lymphocytes, immunoglobulins, and antibrain autoantibodies in the systemic circulation have been reported.¹³⁴ These have been observed chiefly in retrospective case studies of patients with idiopathic ASDs, but systematic prospective studies have confirmed neither their existence nor their relevance.⁸⁷ Prospective studies have revealed that, except for a few individuals with recurrent infections, healthy children with ASDs generally have normal immune function.¹³⁵ Some studies have reported increased rates of autoimmune disorders in families of children with ASDs,¹³⁶ particularly in the mothers (eg, thyroid disorders¹³⁷ and psoriasis¹³⁸); however, the relevance of these common disorders to ASDs in children is unknown. Furthermore, studies have shown no increase in autoimmune disorders of the central nervous system, and patients with ASDs did not themselves exhibit autoimmune disorders.¹³⁹ The contribution of possible immunologic dysfunction remains to be further defined.

Environmental Issues

Regardless of the mechanism, a review of studies published in the past 50 years revealed convincing evidence that most cases of ASDs result from interacting genetic factors.^{67,95} However, the expression of the autism gene(s) may be influenced by environmental factors.^{66,67,69,140} Although currently under investigation, these factors may represent a “second-hit” phenomenon that primarily occurs during fetal brain development. That is, environmental factors may modulate already existing genetic factors responsible for the manifestation of ASDs in individual children.

Prenatal Period

Because many of the developmental brain abnormalities known to be associated with ASDs occur during the first and second trimesters of pregnancy,^{141,142} environmental factors (eg, teratogens, such as thalidomide and valproic acid)⁷³ are more likely to play a role in the fetus via maternal factors. It is possible that maternal illness (eg, rubella) during pregnancy plays a role.^{143,144} Recently, the possible association between fetal testosterone concentration and certain autistic behaviors such as abnormal social relationships and restricted interests at 4 years of age was investigated.¹⁴⁵

Perinatal Period

The effects of birth weight, duration of gestation, and events around the time of birth have been investigated also, but findings have not been consistent.^{72,146–152} A significant association between term newborn encephalopathy and children later diagnosed with ASD was reported recently.^{72,150} Badawi et al¹⁵⁰ reported that 5% of survivors of newborn encephalopathy were diagnosed with an ASD, which represented an almost sixfold increase compared with matched controls. This increase may represent a genetically derived predisposition (which makes the infants vulnerable to both encephalopathy and ASD) or an independent mechanism.

Postnatal Period

Etiologic possibilities occurring after birth have been proposed—in particular, measles-mumps-rubella (MMR) vaccine¹⁵³ and mercury-containing vaccines.^{154–156} In 2001, the Institute of Medicine¹⁵⁷ reviewed epidemiologic population-based studies and concluded that there was no evidence of a causal association between the MMR vaccine and autism. Studies that examined the association between MMR vaccine and autism since the publication of that review have supported this conclusion.^{27,95,103,158–161} Questions also have been raised about the effects of environmental mercury exposure (including mercury-containing vaccines) on brain development in ASDs and other developmental disabilities.^{154–156} Mercury, in its organic form, is a known neurotoxin with neurologic sequelae, including motor impairment and visual and intellectual deficits, depending on the age at exposure and the type of mercury. There is no evidence to date that children with neurodevelopmental disabilities, including autism, in the United States have increased mercury concentrations or environmental exposures.¹⁶² Using large data sets from the United States, Sweden, and Denmark, to date, no consistent association has been found between thimerosal-containing vaccines and neurodevelopmental outcomes or prevalence of ASDs.^{27,95,162–164} Despite evidence to the contrary, a recent survey of parents of children with ASDs revealed that 54% believed that their child's ASD was caused by immunizations; 53% thought it was caused by genetics.¹⁶⁵

Although the previous discussion reveals the wide variety of conditions known to be associated with ASDs, currently, an etiologic investigation of the individual child with an ASD infrequently identifies a known cause in the absence of GDD/MR, dysmorphic features, a positive family history, and/or a focal neurologic examination.^{2,20,21,89,101,106–108}

NEUROPATHOLOGY AND NEUROIMAGING

In recent years, intense research efforts have focused on elucidating the neurobiological basis of ASDs. A growing body of evidence from neuropathology and neuroimag-

ing studies indicates that there are fundamental differences in brain growth and organization in people with ASDs that have their origin in the prenatal period but extend through early childhood and into adulthood.

Neuropathologic studies of brain tissue from people with autism have revealed several abnormalities^{166–171} including:

- reduced numbers of Purkinje cells in the cerebellum;
- abnormal maturation of the forebrain limbic system, including reduced neuronal size, increased cell-packing density, and decreased complexity of the neuropil (ie, the complex net of axonal, dendritic, and glial branching in which the nerve cell is embedded);
- abnormalities in frontal and temporal lobe cortical minicolumns, which are more numerous, smaller, and less compact in their cellular configuration and demonstrate reduced neuropil space in the periphery¹⁶⁷;
- developmental changes in cell size and number in the nucleus of the diagonal band of Broca, deep cerebellar nuclei, and inferior olive; and
- brainstem abnormalities and neocortical malformations (eg, heterotopias).¹⁷¹

The most consistent neuropathologic findings suggest pathology that arises in utero. The association of increased risk of ASDs associated with prenatal exposure to teratogens, such as thalidomide and valproic acid, suggests that early insults during critical periods of brain development (as early as 20–24 days after conception in the case of thalidomide) may be sufficient to cause ASDs.¹⁷¹ However, all of these neuropathologic findings are based on detailed study of a relatively small number of brains, and further investigation is required. Limited availability of brain tissue from people with well-characterized ASDs and age-matched controls has impeded neuropathologic investigations. Efforts to remedy this are underway with the establishment of the Autism Tissue Project (1-800-272-4622 [for physicians] or 1-877-333-0999 [for families]; www.memoriesofhope.org).¹⁶⁸

Kanner, in his initial clinical description of autism, noted large head size in several of his patients.¹⁵ Increased head circumference has since been shown to be a common physical finding in children with ASDs, and 20% to 30% have macrocephaly, defined as a head circumference that measures more than 2 SDs above the mean.^{172,173} MRI studies have supported the finding of increased brain volume in children with ASDs, with 90% of toddlers with ASDs having larger-than-normal brain volumes in 1 study.^{174,175} Postmortem brain weights also are increased.¹⁶⁶ Children later diagnosed with an ASD have been shown, as a group, to have average or below-average head circumference at birth, with acceleration in brain growth during the first year of

life, leading to above-average head circumference or overt macrocephaly.^{176,177} Fewer adults with ASDs have been found to exhibit increased brain size compared with controls, indicating that there may be deceleration of brain growth at some point beyond early childhood.^{176,178,179} It is interesting to note that increased blood concentrations of brain-derived neurotrophic factor and several other neurotrophins have been detected in newborn infants who are later diagnosed with ASDs.¹⁸⁰ This finding, if replicated, may have implications regarding the mechanism of early brain overgrowth. Age-related differences in serotonin synthesis capacity also have been demonstrated between children with ASDs and children in control groups,¹⁸¹ which leads to speculation regarding the neurotrophic role of serotonin in abnormal brain growth and organization in children with ASDs.

In addition to whole-brain volume differences, specific regional gray- and white-matter volumetric differences have been described. The frontal, limbic, basal ganglia, and cerebellar regions have been implicated most consistently.^{172,182–184} Abnormalities in sulcal and gyral anatomy have been found by using surface-mapping techniques.^{185,186} The regional gray- and white-matter volume differences also seem to be age related, although larger cross-sectional studies and longitudinal studies are needed to clarify the meaning of these findings.

A variety of functional MRI studies during cognitive tasks or in response to visual or auditory stimuli suggest that individuals with ASDs use different cognitive strategies and, in some cases, different brain areas to process certain types of information.^{182,187} For example, functional neuroimaging techniques have indicated the presence of abnormalities in face recognition and executive functioning in adults with high-functioning ASDs.¹⁸⁸ Hypoactivation of the fusiform gyrus in face-recognition tasks has been one of the most consistent findings¹⁸⁷ and, in concert with abnormalities in amygdala activation, may relate to the abnormalities in gaze fixation that are seen in people with ASDs.¹⁸⁹ Functional MRI evidence has also been used to postulate impaired “connectivity” between various cortical regions in the brains of people with ASDs.^{190–192} Most recently, some investigators have attempted to explain deficits in empathy, imitation, and language as abnormalities in the functioning of mirror neuron systems.¹⁹³ These systems are a newly discovered subset of cells found in several areas of the brain that seem to fire when an individual simply observes another’s actions—that is, it seems they directly reflect actions performed by another in the observer’s brain. They also may play a role in the ability to recognize and empathize with or “mirror” the feelings of others. These functional brain differences provide intriguing links between the neuroanatomical substrate and the characteristic clinical features of people with ASDs.

Although neuroimaging research has identified volumetric and other abnormalities in groups of patients with ASDs compared with controls, a reliable marker has not been identified, and routine clinical neuroimaging for individuals with ASDs is not recommended.^{106,107,183,194}

CLINICAL SIGNS

Whereas severe social skills deficits and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities are core features of all ASDs, significant language delays are characteristic of only AD and PDD-NOS.^{3,4} One of the most challenging aspects in recognizing ASDs is the wide heterogeneity of features in individual children. There is no pathognomonic feature; however, a few of the early social deficits (eg, delayed or absent joint attention [JA]) seem to be fairly reliable red flags for ASDs. The autism spectrum encompasses an extremely heterogeneous phenotype with indistinct end points, especially at the mild end of the spectrum. The severity of each of the core deficits varies significantly among children with ASDs.

Although the social deficits occur earlier and may be more specific, they can be subtle and less often recognized or articulated by parents. Speech delays usually prompt parents to raise concerns to their child’s PCP. Most parents become concerned between 15 and 18 months of age but may delay discussing their concerns with their child’s physician for several months.^{35,195–198} Recently, the media and public agencies have raised public awareness about the importance of recognizing the early signs, including those present during the first years of life. This being the case, it is anticipated that parents may begin to voice concerns to their infant’s pediatrician earlier and that these concerns may now target the often earlier-appearing social deficits. Presentations can differ widely from one child to the next; some are perceived by parents as “different” during the first few months of life, others present with delayed speech development during the second year of life, and still others may appear to be normal only to regress and lose skills after the first year of life.^{199,200} AS in children may go unnoticed until they are of school age, when teachers notice difficulties with peer interactions. Expanded reviews regarding early signs are available.^{201–203}

Social Skills Deficits

Although more specific than language deficits, social deficits appearing in the first 2 years of life often have escaped parent recognition.^{204–206} Children with ASDs universally demonstrate deficits in social relatedness defined as the inherent drive to connect with others and share complementary feeling states.²⁰⁷ Children with ASDs often do not appear to seek connectedness; they are content being alone, ignore their parents’ bids for attention, and seldom make eye contact or bid for others’ attention with gestures or vocalizations. In later

years, they have difficulty sharing the emotional state of others in cooperative games and group settings and may have few, if any, friends.

Deficits in JA seem to be one of the most distinguishing characteristics of very young children with ASDs.^{198,208–216} JA is a normal, spontaneously occurring behavior whereby the infant shows enjoyment in sharing an object (or event) with another person by looking back and forth between the two. Later, gestures and/or speech also can be used to engage another's attention with regard to the objects and events simply for the enjoyment of sharing the experiences. Just like other developmental skills, development of JA skills is stepwise; it occurs in stages beginning in the first few months of life. Similar to language skills, receptive JA skills usually are mastered before expressive ones. JA begins with joyous smiling in recognition of and response to a parent or familiar caregiver's smiles and vocalizations. At approximately 8 months of age, an infant will follow the parent's gaze and look in the same direction when a parent looks away (ie, to check the time). Children begin to "follow a point" at approximately 10 to 12 months of age. If a parent points in the direction of an interesting object or event and says, "Look!" the typically developing child will look in the intended direction and then, after seeing the object/event, look back at the parent in acknowledgment and shared expression. Infants with ASD may not follow a point, even when one tries repeatedly in a loud voice calling their name or uses physical prompts, such as touching the child's shoulder before pointing.²⁰⁴ They may look in the indicated direction eventually, but this is not followed by shared looking and expression.

At approximately 12 to 14 months of age, the typically developing child will begin himself to initiate a point, at first to request a desired object that is out of reach and, a couple of months later, to draw the parent's attention to share an interesting object, person, or event. Depending on his speech skills, he may utter simple sounds ("uh") or actual words while pointing. Pointing to request an object is called "protoimperative pointing." Deficits vary, as some children with ASDs may make rudimentary pointing efforts by opening and closing their hand while it is raised in the direction of the desired item but without any back-and-forth looking between it and the caregiver. Another frequent strategy is to take the parent's hand to lead him or her to the object. At 14 to 16 months of age, the typically developing child will begin to point simply to "comment" about or "share" an interesting object/event (which is called "protodeclarative pointing"). As he points, he will look alternatively between the object/event of interest and the parent. It is the shared social experience, not the tangible object/event, that the child seeks. Children with ASDs consistently fail to point to "comment" at age-appropriate times, and when they do, they are less likely to show

positive affect and connectedness during the act. Some high-functioning children with ASDs may point to label objects, shapes, and colors that they have learned in a rote fashion, but this often is done without any intent of communicating in a social context and is not considered JA. Mastery of JA seems to be necessary for functional language development; in fact, mastery of protodeclarative pointing seems to be a reliable predictor of functional language development within 1 year.^{7,217–219} JA skills progress to involve ongoing back-and-forth bids for attention and social interactions with multiple emotional expressions, sounds, words, and other gestures.

Orienting to social stimuli—in particular, turning consistently to respond to one's own name—is an early skill (8–10 months of age) that often is deficient in children with ASDs.^{215,220} However, it is not specific to children with ASDs, because children with hearing impairments also may fail to orient to their name. In fact, parents of children later diagnosed with ASDs often raise a concern about hearing. Hearing seems "selective" in that children with ASDs may hear and attend well to environmental sounds but not to human voices.²²¹ Social referencing²²² is the ability to recognize the emotional states of others as they respond to various stimuli. When faced with a novel situation, a typically developing infant might look to his mother for an indication of delight, anger, or fear in her facial expression. His facial expression then usually will mimic hers, although he may not fully understand the situation. A child with an ASD engages in less imitation.²²³

Because children with ASDs lack fundamental social skill building blocks, they may be less likely to develop appropriate peer relationships according to age and language ability. They may have few or no friends, and when they do, the relationships may evolve around the child's own special interests. Another factor that impedes lasting friendships is impaired central coherence or the inability to interpret stimuli in a global way.^{224,225} Instead, they focus on the parts, make less use of context, and miss the "big picture," which makes social interactions challenging. They also have difficulties understanding the perspective of others or lack "theory-of-mind" (ToM) skills. ToM is the awareness that others have thoughts and emotions that are independent from one's own; it is the ability that allows one to infer states of mind on the basis of external behavior.^{226,227} Typically developing children begin to have some sense of mental states of others by 4 years of age.^{197,228,229} Because of ToM impairments, children with ASDs have difficulties with empathy, sharing, and comforting. Baron-Cohen²³⁰ coined the term "mindblindness" when referring to persons with ASDs who demonstrate severe ToM deficits.

Communication Deficits

Most children who are later diagnosed with AD and PPD-NOS present to their PCP with "speech delay," al-

though this may change as parents are becoming more aware of social milestones. As noted previously, most parents sense something is wrong by the time the child is 18 months old.¹⁹⁵⁻¹⁹⁸ Lack of speech has been considered a hallmark of AD, especially when it is associated with the lack of desire to communicate and lack of nonverbal compensatory efforts such as gestures. However, children with milder symptoms, especially those with normal cognitive skills, may have some speech. Their speech may not be functional or fluent and may lack communicative intent. It can be scripted (from favorite videos or television programs) and stereotypic. Echolalia, sometimes called “parroting,” is the repetition of another person’s speech. Echolalia is classified as “immediate” when the child repeats vocalizations promptly after hearing them or “delayed” when there is a time lapse (hours, days, weeks). Typically developing children pass through a “vocabulary-burst stage,” when brief periods of immediate echolalia are not unusual.¹⁹⁷ On the other hand, echolalia in children with ASDs may persist throughout the life span and consist of a mixture of immediate and delayed varieties. Utterances of children with ASDs may be more clearly articulated, have a more monotone quality, and/or consist of larger verbal “chunks” (ie, entire television advertisement jingles, video reenactments, or recitations of nursery rhymes) than those of typically developing children. Sometimes, echolalia may even give the impression of “advanced” speech because of sophisticated vocabulary, grammar, and syntax. The clinician should be careful to differentiate between typical and autistic echolalia; usually, a formal evaluation by a speech-language pathologist (SLP) is needed. Such an assessment also may reveal a dissociation between these “advanced” expressive skills and delayed receptive ones in that the child may be unable to follow simple 1-step commands, which is a 12- to 14-month-old skill. Some parents will note that their child seems overly “independent” because, rather than ask for desired objects, he uses advanced motor skills to obtain them himself (ie, moving a stool to a counter top to obtain an object at an age younger than typically expected). Some children with ASDs become quite skilled at rote labeling colors, shapes, numbers, and letters of the alphabet, yet they are unable to point to them when asked to do so by another or incorporate the labels into functional language. A few may later develop hyperlexia or advanced verbal reading without corresponding comprehension skills.

Some children with ASDs say “pop-up words” without any apparent stimulus or communicative intent. They are spontaneous and inconsistent, although sometimes they may occur during acutely stressful situations. These words are said out of context for a short period of time (days or weeks) and then, as suddenly as they might pop up for no apparent reason, they disappear.^{197,119} Children with ASDs also may develop “lan-

guage” in overlearned or gestalt phrases that are acquired and spoken almost as a single “giant-word” (ie, Whatisit? Idontknow). At the same time, they are unable to combine words in novel or original phrases or sentences that convey true meaning.

Although lack of speech, scripted speech, parroting without communicative intent, and pop-up and giant words are common classic presentations, earlier pre-speech deficits often exist that, if detected, could facilitate earlier diagnosis.* These deficits include:

- lack of appropriate gaze;
- lack of warm, joyful expressions with gaze;
- lack of the alternating to-and-fro pattern of vocalizations between infant and parent that usually occurs at approximately 6 months of age (ie, infants with ASDs usually continue vocalizing without regard for the parent’s speech);
- lack of recognition of mother’s (or father’s or consistent caregiver’s) voice;
- disregard for vocalizations (ie, lack of response to name), yet keen awareness for environmental sounds;
- delayed onset of babbling past 9 months of age;
- decreased or absent use of prespeech gestures (waving, pointing, showing);
- lack of expressions such as “oh oh” or “huh”;
- lack of interest or response of any kind to neutral statements (eg, “Oh no, it’s raining again!”)

The AAP brochure “*Is Your One-Year-Old Communicating With You?*”¹³ was developed to help raise parent and physician awareness of these earlier social communication milestones and to promote recognition of symptoms of ASDs before 18 months of age.

Regression

Approximately 25% to 30% of children with ASDs begin to say words but then stop speaking, often between the ages of 15 and 24 months.^{199,200,208} Regression of skills in children with ASDs may also include loss of gestural communication (wave, point, etc) and social skills (eg, eye contact and response to praise) or a combination of both. Regression can be gradual or sudden, and it may be superimposed on subtle preexisting developmental delays or atypical development, such as an unusually intense interest in objects or other nonsocial stimuli during the first year of life.²⁰⁵ Although it may be tempting to attribute regression to environmental stressors (eg, birth of a new sibling or a move to a new house), this results in a delay in diagnosis. Regression is a well-documented hallmark of ASDs and should always alert the PCP to consider ASDs.

*Refs 197, 204, 213, 214, 219, and 222.

Asperger Syndrome

Children with AS may have mild or limited speech delays (see the DSM-IV-TR⁴ criteria in Table 2) and escape recognition until preschool or early school age, when their inability to make friends becomes a concern. Although often unnoticed, language development usually is atypical. Children with AS often are quite verbal about a certain topic of interest, but they are unable to express simple feelings or recognize the feelings and viewpoints of others. Speech may be fluent but limited to only a few topics, typically those that hold a strong, all-consuming interest for the child. Speech also can be overly formal (pedantic), which is a reason why children with AS sometimes are described as “little professors.”²²⁷ Children with AS also have deficits in the social use of language (pragmatics): how to choose a topic of conversation; understanding and producing appropriate tempo, facial expression, and body language during conversation; turn taking; recognizing when the partner has lost interest in a topic; knowing when to start, sustain, and end a conversation on the basis of listener cues; knowing when and how to repair a communication breakdown; and using the appropriate degree of formality and politeness.^{197,227} Children with AS especially have difficulty sustaining a conversation on a topic that is initiated by another. Language may seem odd, self-centered, and not listener responsive and results in a monotone monologue. They may demonstrate unique delivery of speech (prosody) in regard to intonation, volume, rhythm, pitch, and personal space that also tends to disregard listener needs. Children with AS may have difficulty with abstract reasoning and discussion of thoughts and opinions of others. Inability to discern and judge the conversational intents of others, especially when their conversation includes words or phrases with ambiguous meanings, impairs their ability to understand metaphors, humor, teasing idioms, irony, lies, jokes, and faux pas.^{226,227,229} Older children with high-functioning AD or PDD-NOS and fluent speech also may demonstrate some of the above-mentioned language characteristics.

Play Skills

Lack of, or significantly delayed, pretend play skills coupled with persistent sensory-motor and/or ritualistic play are characteristic of ASDs. Some children with severe ASDs may never progress past the sensory-motor play stage. They mouth, twirl, bang, and manipulate objects in a stereotypic or ritualistic manner. The play of children with ASDs often is repetitive and lacks creativity and imitation.^{3,4} Typical examples include spinning the wheels or lining up cars instead of “driving” them, arranging crayons instead of coloring with them, or stacking blocks in the same sequence time after time. Often they prefer to play with common objects (string, sticks, rocks, or ballpoint pens) rather than store-bought toys with the exception of trains or characters from

favorite videos and television shows. Puzzles, especially shape-matching ones and computerized “puzzle games,” also are quite popular.²²² Children with ASDs often are content to play alone for hours, requiring little attention or supervision. Often this “play” is either constructive (puzzles, computer games, and blocks), ritualistic (lining objects up or sorting/matching shapes or colors) or sensory-motor (mouthing, banging, twirling) in nature. Children with ASDs may seem to enjoy chase games and roughhousing, but it is often the sensory-motor aspects of these activities, rather than their social aspects, that are enjoyable. They have trouble interacting in groups and cooperating in the social rules of more sophisticated games. Often they are left out, ignored, and at high risk of being victimized and bullied by peers.²³¹

Restricted, Repetitive, and Stereotyped Patterns of Behavior, Interests, and Activities

Children with ASDs can demonstrate atypical behaviors in a variety of areas including peculiar mannerisms, unusual attachments to objects, obsessions, compulsions, self-injurious behaviors, and stereotypes. Stereotypes are repetitive, nonfunctional, atypical behaviors such as hand flapping, finger movements, rocking, or twirling.^{3,4,203} Although most stereotypes are harmless, they are problematic in that they may prevent the child from accomplishing a task or learning new skills. Although stereotypes are distinctive and obvious, they are not specific to children with ASDs, because many children with profound MR and/or severe sensory deficits also demonstrate stereotypes. Even typically developing toddlers, especially before the onset of fluent language, may flap their arms briefly when they are excited or frustrated. Stereotypes associated with ASDs often do not appear until after 3 years of age²³² and commonly manifest as finger flicking, unusual eye gazing, habitual toe walking, and/or persistent sniffing and licking of nonfood items.

Although most children, at some time during their early development, form attachments with a stuffed animal, special pillow, or blanket, children with ASDs may prefer hard items (ballpoint pens, flashlight, keys, action figures, etc). Moreover, the attachment is more persistent, in that they may insist on holding the object at all times, although these are rarely, if at all, used in real “play.” Whereas younger children with ASDs may have restricted interests in regards to objects, the restricted interests in those with AS more often relate to topics and facts.²²⁷ For example, rather than carrying a toy train at all times, there is an obsession with train schedules. Sometimes the item/topic of interest may be typical for any child, but it is the degree of interest that is abnormal. For example, similar to typically developing children, a child with an ASD may be fascinated with dinosaurs, but he knows far more details about them and persists in playing or discussing them to the exclusion of all else.

Perseveration, or continuation of speech or play to an exceptional degree or beyond a desired point, is common in children with ASDs. Children with ASDs may protest vigorously when forced to transition from an activity or topic of interest or when a usual routine is changed. Without warning, these protests may quickly escalate to severe and prolonged temper tantrums characterized by aggression or self-injurious behaviors.

Self-injurious behaviors (head banging, skin picking, eye poking, hand biting) are stereotypies that may cause bodily harm and are more common in children with severe GDD/MR (intellectual disabilities) or ASDs with comorbid GDD/MR.²³³ Self-injurious behaviors may be precipitated by frustration during unsuccessful communication attempts, transitions, anxiety in new environments, boredom, depression, fatigue, sleep deprivation, or pain. The presence of self-injurious behaviors, aggression, and other extreme behaviors may prevent the child from participating in integrated activities in the community with typically developing peers and cause significant family stress.

Additional Coexisting Conditions That Are Not Core Features in the DSM-IV-TR

Cognitive Abnormalities (GDD/MR or Intellectual Disability, Learning Differences, and Splinter/Savant Skills)

The prevalence of comorbid GDD/MR or intellectual disability (the appropriate term depends on age and availability of both a standardized IQ score and a formal assessment of adaptive skills) with ASDs was estimated to be approximately 90% before 1990.⁶² On the basis of later studies published in the 1990s, consensus guidelines reported the prevalence as approximately 70% to 75%.^{1,2,106,107,234} Prevalence studies published in the new millennium have reported rates of ASDs with comorbid GDD/MR of just under 50%,^{28,29,34,103} whereas 2 English studies reported rates as low as 26% to 29%.^{20,21} Better ascertainment of children without cognitive deficits (in particular AS, which by definition is characterized by normal intelligence), improved professional training, and more effective strategies/tools for evaluating cognitive abilities in children with ASDs all may contribute to the decreasing prevalence of comorbid GDD/MR.

One unique characteristic of ASDs is the “unevenness” of skills. Abilities may be significantly delayed in some areas of development yet “advanced” in others, often because of exceptional focusing, memory, calculation, music, or art abilities.²³⁵ They may be labeled as “splinter skills” when they serve no purpose in day-to-day life and do not improve functional outcomes. Rarely, highly developed talents or savant skills may promote a vocation that provides financial independence and, occasionally, national recognition.^{236–238}

Sensory-Motor Symptoms

Although sensory symptoms (eg, hyperacusis) are more frequent and prominent in children with ASDs, there is no evidence that sensory symptoms differentiate children with ASDs from children with other developmental disabilities.²³⁹ Children with ASDs may demonstrate simultaneous hyposensitivities and hypersensitivities for stimuli within the same sensory modality.²⁴⁰ For example, they may seem overly sensitive to certain environmental noises but lack response to human voice, or they may visually inspect the details of an object but not notice the comings and goings of other people in the room. Others may have oral aversions and/or total-body “tactile defensiveness” to soft touch (fabric bumps on socks and sweatshirts) or hugs yet be insensitive to pain.²⁴¹ Sensory factors related to food, such as texture, color, and taste, may lead to highly restricted diets. More research is needed to operationalize the concept of sensory integration and possible interventions and define its role in ASDs.

In addition to unusual motor stereotypies that serve as defining characteristics of ASDs discussed previously, some children with ASDs also may demonstrate atypical motor development, poor coordination, or deficits in praxis (motor planning, execution, and sequencing).²⁴⁰ Some investigators believe that, although not a defining characteristic by DSM standards, motor clumsiness is a distinguishing characteristic of AS.^{86,242} Finally, some children may appear to be “hyperactive” and motor driven with an exterior focus of attention and actually meet criteria for comorbid ADHD (although current DSM-IV-TR criteria exclude making the diagnosis of ADHD in the presence of an ASD).^{8,240,243} Other children may be hypoactive and withdrawn and have an interior focus of attention.²⁴⁰

In summary, ASDs are characterized by a broad array of clinical features; some are more specific to ASDs than others (JA deficits versus stereotypies). Familiarity with the early social and preverbal communication deficits will help the PCP recognize ASDs earlier, which should, in turn, facilitate the prompt initiation of appropriate interventions.

SURVEILLANCE AND SCREENING

Because the prevalence of ASDs is approximately 6 to 7 per 1000 in the United States,^{28,29} PCPs are likely to provide care for children with ASDs. Early identification of ASDs is important, because it allows early intervention, etiologic investigation, and counseling regarding recurrence risk. The medical home is an important setting for surveillance and screening to detect ASDs and other developmental disorders. In the past, it was not unusual for parents’ initial concerns to be dismissed and for diagnosis and intervention to be delayed.^{195,196,244,245} In a recent study in metropolitan Atlanta, Georgia, the mean age of the first evaluation for 115 8-year-old chil-

dren with ASDs was 48 months, and the mean age of the first ASD diagnosis was 61 months.³⁵

The goal of this clinical report is to help pediatricians identify children at an earlier age who are at risk of an ASD. An ASD-specific surveillance and screening algorithm (Fig 1) has been developed to facilitate the identification process. It builds on the developmental surveillance and screening algorithm for pediatric preventive care visits that was published in the 2006 policy statement "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening."²⁴⁶

General Developmental Surveillance and Screening

According to the AAP policy statement "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening,"²⁴⁶ "surveillance" is the ongoing process of identifying children who may be at risk of developmental delays, and "screening" is the use of standardized tools at specific intervals to support and refine the risk. As an analogy, whereas surveillance represents a "moving picture" of the child's unfolding development, screening represents "snapshots" of the child's development at specific times. Developmental surveillance should occur at every preventive visit throughout childhood and includes the following components: eliciting and attending to the parents' concerns; maintaining a developmental history; making accurate and informed observations of the child; identifying the presence of risk and protective factors; and documenting the process and findings.²⁴⁶ Research has revealed that parents have valid concerns about their children's development, although careful interpretation of the concerns is needed.^{247,248} However, parental concerns may not be shared if the PCP does not ask about the child's development, and lack of parental concern about development does not imply typical development.²⁴⁷⁻²⁵⁰ Therefore, a systematic surveillance strategy must be used for all children.²⁴⁶ Screening with a standardized developmental tool should be performed whenever concerns are raised through the ongoing surveillance process. The AAP also recommends that all children be screened with a standardized developmental tool at specific intervals (ie, at the 9-, 18-, and 24- or 30-month visits) regardless of whether a concern has been raised or a risk has been identified during the surveillance process (see the AAP developmental screening and surveillance algorithm²⁴⁶).

Surveillance for ASD

Surveillance at the first preventive care visit (Fig 1, *Steps 1a* and 2) should begin with a family history to determine if there are any family members, especially a sibling, who have been diagnosed with ASDs. Because the risk of having symptoms of ASDs in younger siblings of children with ASDs is approximately 10 times higher,

the pediatrician needs to be extra vigilant in monitoring for early abnormal signs. Studies of infant siblings with ASDs have revealed that very subtle early signs do exist and can be perceived during the first year of life.^{204,205} Until recently, most knowledge regarding very early signs was obtained from retrospective systematic reviews of home videos, particularly first birthday party videos.²⁵¹ Studies of home videos at earlier ages have provided additional retrospective information that reveals subtle abnormalities in infants who were thought to be typically developing and later diagnosed as having regressive autism.²⁰⁵ Several groups of investigators are following younger siblings of children diagnosed with ASDs and providing prospective information as symptoms emerge in these infants at high risk.²⁰⁴ Preliminary results support the feasibility of recognizing subtle signs of ASDs in infants at high risk.^{204,206,213,214,252,253} Some of the very early signs reported by several investigators include extremes of temperament and behavior (ranging from marked irritability to alarming passivity); poor eye contact; poor response to other's voices, especially to one's name being called²⁵²; poor attempts at interactive play; more interest in looking at objects than people; delayed pointing to request or share; decreased to-and-fro babbling and jargonizing; and lack of warm, joyful, reciprocating expressions.

Surveillance should include asking parents open-ended questions about their concerns regarding the child's development and behavior (*Step 2*). Parental concerns about inconsistent hearing or unusual responsiveness also are important; for example, parents may notice that the child responds consistently to a quiet sound, such as the crinkle of a plastic snack bag, but not to a human voice calling his name. In addition, parent concerns may be stimulated by comments made by other care providers such as child care staff or preschool teachers. Recently, however, the public media have significantly increased awareness of ASDs and sometimes has stimulated unnecessary concerns. The AAP patient education brochure "*Is Your One-Year-Old Communicating With You?*"¹³ can be distributed to all parents at their child's 9- or 12-month preventive visit to educate them about early social communication milestones to help them identify valid areas of concern.

Surveillance also includes asking age-specific questions about whether certain developmental milestones have been attained. When this approach is used, it is important to include social and emotional milestones in addition to the traditional motor, language, and problem-solving milestones^{254,255} (see www.firstsigns.org). To recognize ASDs as early as possible, it is important to ask about the development of verbal and nonverbal communication, reciprocal social interaction (including eye contact, JA and social referencing, and sharing of interests or achievements), and representational or pretend play skills. The American Academy of Neurology and

Surveillance and Screening Algorithm: Autism Spectrum Disorders (ASDs)

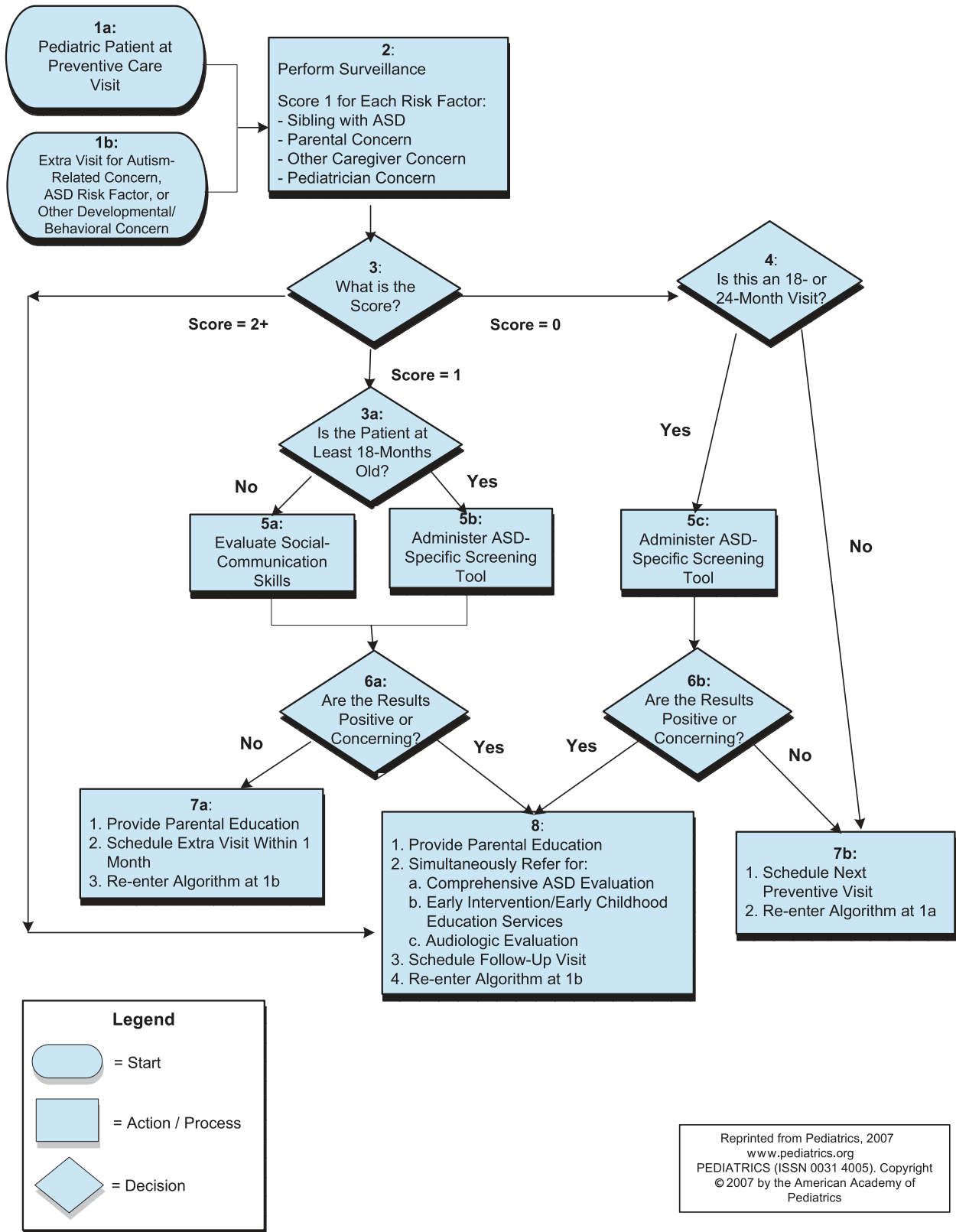
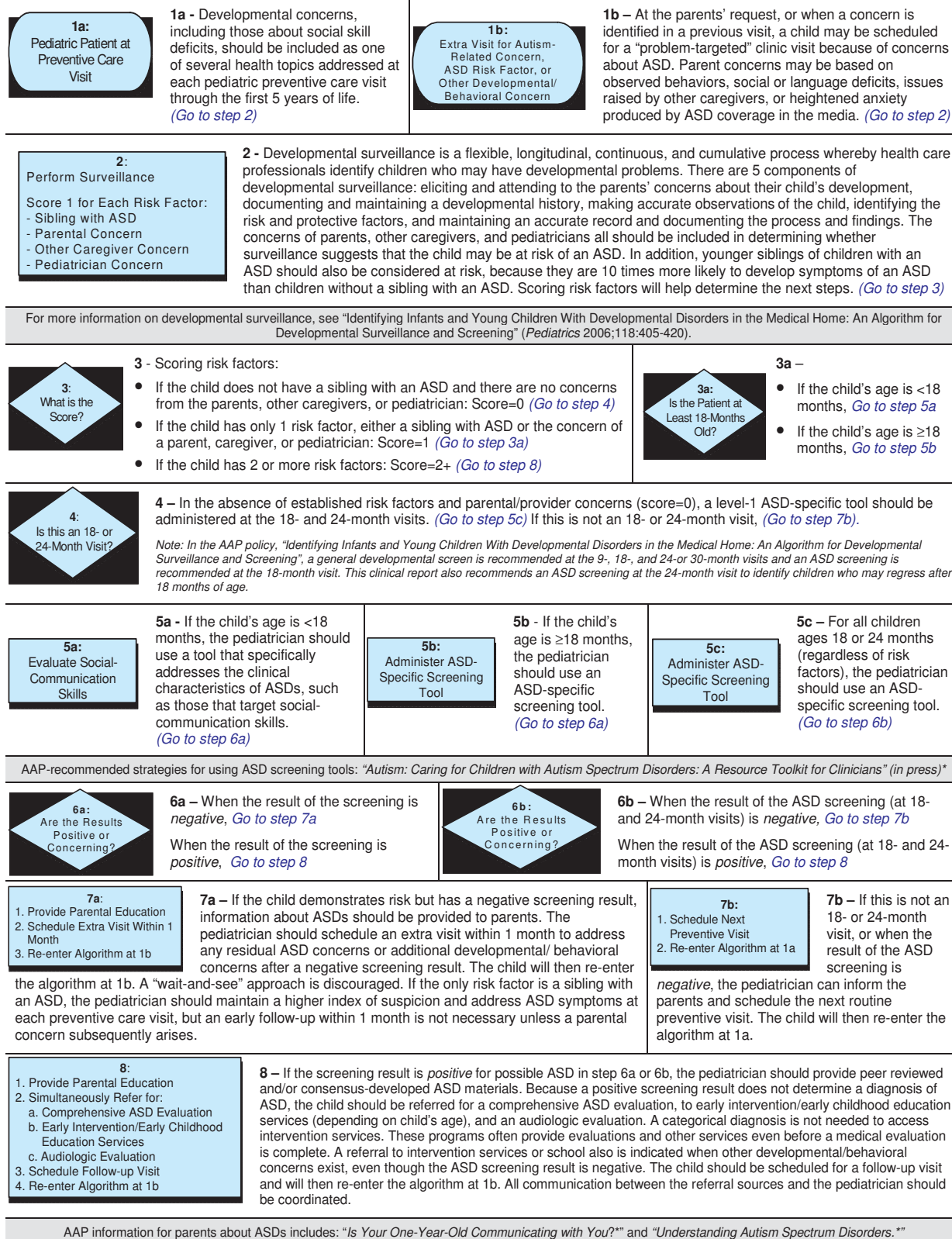


FIGURE 1
Surveillance and screening algorithm: ASDs.

Surveillance and Screening Algorithm: Autism Spectrum Disorders (ASDs)



*Available at www.aap.org

FIGURE 1
Continued

Child Neurology Society practice parameter on screening and diagnosis of autism¹⁰⁷ suggests that the following “red flags” are absolute indications for immediate evaluation:

- no babbling or pointing or other gesture by 12 months;
- no single words by 16 months;
- no 2-word spontaneous (not echolalic) phrases by 24 months; and
- loss of language or social skills at any age.

Pediatricians should become concerned (*Step 2*) if the answers to these questions reveal deficits or delays in milestones or if behaviors typical of ASD are observed during an office visit.

In older, more developmentally advanced children, including many with AS, surveillance questions (*Step 2*) may elicit concerns about social interaction difficulties related to more subtle communication problems, such as pragmatic language impairment and lack of understanding of nonliteral forms of communication (figures of speech, humor, sarcasm, metaphor, etc), difficulty taking the perspective of another (resulting in inappropriate or offensive behavior, gullibility, and lack of common sense), and obsession with facts, details, or collections. Pragmatic language refers to the use of language in social interaction and includes instinctive rules governing factors, such as topic maintenance and turn taking in conversation, how sentences are made to fit in with the flow of a conversation, how unspoken premises are inferred, how degrees of formality and politeness are signaled, and prosody (modulation of the intonation, rhythm, volume, timing, and stress of the voice). The parents may note that the child lacks true friendships and is viewed as odd, eccentric, or “weird” by his ‘peers.

In addition, during the well-child visit, the PCP may try to interact with the patient by using a few simple strategies depending on the child’s age. For example, the PCP can note the response when calling the child’s name at the 12-month well-child visit, and/or the JA milestone of “following a point” can be elicited at the 12-, 18-, and 24-month well-child visits as part of routine developmental surveillance. In the latter, the pediatrician points to an object at a distance, such as a picture on the wall or a mobile, while making a verbal request for the child to look. Whereas a typically developing child would look in the direction of the point and then afterward engage in eye contact with the physician or the parent, a child with an ASD may appear to be oblivious to the PCP’s gesture and verbal request. This is true even if the PCP increases the intensity of the stimulus by calling louder, adding the child’s name, or touching the child’s shoulder first and then pointing and exclaiming, “Look!” The child may still fail to respond even if the parent repeats the maneuvers. With an older, higher-functioning child, the PCP may enter into conversation

with the child to determine if he has difficulty interpreting a figure of speech, telling a joke, or explaining why a joke is funny. In addition, the PCP may ask a question or two about one of the child’s areas of interest to observe a response that is characteristic of AS, such as a long-winded, overly precise, or pedantic reply. Any of these responses should raise the concern of a PCP.

Each concern raised by a parent, other caregiver, or the pediatrician constitutes a separate risk factor, as does a positive family history of a sibling with an ASD (*Step 2*). To determine how to proceed, the pediatrician should assess the number of risk factors (*Step 3*). Possible scores include 0, 1, 2, 3, or 4.

1. If no concerns have been raised during the course of the preventive visit and the child is not the sibling of a child who has already been diagnosed with an ASD, then the PCP should proceed to *Step 4*. ASD-specific screening is indicated only if the visit is the 18- or 24-month preventive visit. See *Step 5c* below.
2. If the child’s only risk factor is having a sibling with an ASD, then the PCP should make sure the parents are aware of early signs of ASDs and continue to monitor carefully.²⁵³ If the parents call with a concern between scheduled routine preventive visits, the child should be seen within 1 or 2 weeks and reenter the algorithm at *Step 1b* for a “targeted visit” to address concerns about ASDs. If the score = 1 as a result of a single concern (parent, other caregiver, or PCP), the PCP should screen the child formally with a standardized tool; the choice of tool will depend on the child’s age (*Step 3a*) (see “Screening Tools for Implementation of *Step 5*”).
3. If 2 or more risk factors are identified, then the PCP should proceed directly to *Step 8*, which includes several activities that should be accomplished simultaneously and without delay.

Screening for ASDs (*Steps 5a–5c*)

Physician estimates of the developmental status of children are much less accurate when only clinical impressions, rather than formal screening tools, are used,^{256,257} yet a minority of PCPs use formal developmental screening instruments,^{258,259} and few pediatricians specifically screen for ASDs.⁵ A standardized screening tool should be administered at any point when concerns about ASDs are raised spontaneously by a parent or as a result of clinician observations or surveillance questions about social, communicative, and play behaviors (*Steps 5a* and *5b*).^{246,260} In the general developmental screening and surveillance policy statement discussed previously, the AAP also recommended administering a standardized autism-specific screening tool on all children at the 18-month preventive care visit (*Step 5c*).²⁴⁶ The AAP Autism Expert Panel responded to the statement with a com-

mentary²⁶⁰ that suggested a repeat screening be performed at 24 months of age (*Step 5c*) to identify those who may regress after 18 months of age.

Screening Tools for Implementation of Step 5

A variety of general developmental screening tools are available to practitioners.²⁴⁶ General developmental screening tools are appropriate for use with unselected primary care populations and are likely to detect ASDs in many young children because of associated language and cognitive delays, but they do not differentiate children with ASDs from those with other developmental disorders, and data are not available on sensitivity for detection of ASDs. Tools to screen specifically for ASDs also have been designed (Table 3), but they have not yet been validated on children younger than 18 months. The PCP should remember that screening tools are likely to be overinclusive, so children with developmental and behavioral disorders other than ASDs also might have positive screening results. Similar to other developmental screening measures, ASD-specific screening tools may rely entirely on parent report, or they may require direct observation and engagement by the clinician. Parent-report tools often have the advantage of being brief, inexpensive, and practical in the office setting. The people who know the child best are surveyed and can describe the child's behavior over time in a variety of settings rather than being constrained to sampling behavior in one setting at one point in time.

Step 5a: Tools for Use in "at-Risk" Children Younger Than 18 Months

Although several tools are in development for screening children younger than 18 months, none are available yet for routine clinical use. The Infant/Toddler Checklist from the Communication and Symbolic Behavior Scales Developmental Profile²⁶¹ (which can be downloaded at www.brookespublishing.com/store/books/wetherby-cs-bsd/CSBSDP_Checklist.pdf) may be particularly well suited for identifying 6- to 24-month-old children who are at risk of ASDs, because it focuses on social and communication skills. It is anticipated that this and other screening tools under investigation as possible ASD-specific tools for use in infants younger than 18 months may prove valuable in identifying children at high risk and will become available to clinicians in the near future.^{213,262,263}

Step 5b: Tools for at-Risk Children 18 Months and Older

ASD-specific screening tools are available for children 18 months and older, and many of them are age specific. Recently, such tools have been classified as "level 1" or "level 2" screening tools.²⁶⁴ Level 1 screening tools are administered to all children within the context of a primary care medical home and are designed to differentiate children who are at risk of ASDs from the general population, especially those with typical development.

Level 2 screening tools are used more often in early intervention programs or developmental clinics that serve children with a variety of developmental problems; they help to differentiate children who are at risk of ASDs from those at risk of other developmental disorders such as GDD or specific language impairment. Level 2 screening tools generally require more time and training to administer, score, and interpret than level 1 measures. There is considerable overlap between the concept of a level 2 screening tool and that of a diagnostic instrument.^{264,265} Level 2 screening measures may be used as part of a diagnostic evaluation, but they should not be used in isolation to make a diagnosis.

Properties of some level 1 and 2 ASD screening tools are reviewed in Table 3. Reported sensitivity and specificity values are included, but in most cases, sensitivity and specificity of the instruments have been determined only in clinical samples or in populations that included a mixture of clinical and population-based samples, and they must be interpreted with caution. Estimates of sensitivity and specificity of developmental screening tests may be unstable, and they are not the only criteria that should be used to assess validity.²⁶⁶ In low-prevalence conditions, such as ASDs, the positive predictive value of screening tools will be low even with good sensitivity and specificity, whereas the negative predictive value will be quite high. Many of the existing ASD-specific screening measures are being revised or further evaluated, and new tools are being developed to address some of their weaknesses.

Some measures, such as the Checklist for Autism in Toddlers (CHAT),²⁶⁷ Modified Checklist for Autism in Toddlers (M-CHAT),²⁶⁸ and Pervasive Developmental Disorders Screening Test-II Primary Care Screener,²⁶⁹ were designed specifically for early detection of ASDs in young children. The CHAT and M-CHAT are level 1 screening tools that are available at no cost to practitioners for use in primary care (Table 3).

For older children who are diagnosed later with AS, school personnel often raise concerns to the parents. Staff may then administer a published AS-specific tool. Although many level 2 screening tools have been marketed for use in older children who have been identified as being at risk of AS, further study is needed before any one of them can be recommended as superior to others.²⁷⁰ See Table 3 for characteristics of selected AS screening tools.

Step 5c: Tools for Screening Children Without Risk Factors at the 18- and 24-Month Preventive Visit

Level 1 ASD tools described in *Step 5b* also are appropriate for routine screening of young children without any identified risk.

Among the tools designed for screening the elementary school-aged population, only the Childhood Asperger Syndrome Test (CAST) has been assessed in a

TABLE 3 Selected Level 1 and 2 ASD Screening Measures

Screening Tool	Age	Format (No. of Items)	Time to Complete, min	Reported Sensitivity	Reported Specificity	Selected Key References	Availability
Level 1^a							
CHAT	18–24+ mo	Parent interview or questionnaire and interactive (parent: 9; clinician: 5)	5	0.18–0.38 ^b ; 0.65 ^c	0.98–1.0 ^b ; 1.0 ^c	Baron-Cohen et al, ²⁶⁷ Baron-Cohen et al, ²⁷² Baird et al, ¹⁹ Scambler et al ²⁷³	Download: www.autismresearchcentre.com/tests/chat_test.asp
CHAT, Denver Modifications	18–24+ mo	Parent interview or questionnaire and interactive (parent: 9; clinician: 5)	5	0.85 ^c	1.0 ^c	Scambler et al ²⁷³	CHAT scoring modifications; available in Scambler et al ²⁷³
Checklist for Autism in Toddlers-23 (CHAT-23)	16–86 mo (all had mental ages of 18–24 mo)	Parent interview or questionnaire and interactive (parent: 23; clinician: 5)	10	0.84–0.93 ^c (part A); 0.74 ^c (part B)	0.77–0.85 ^c (part A); 0.91 ^c (part B)	Wong et al ²⁷⁴	Combination of M-CHAT and CHAT items; protocol available in Wong et al ²⁷⁴
CAST	4–11 y	Questionnaire completed by parent (37)	10	0.88–1.0 ^d	0.97–0.98 ^d	Scott et al, ²⁷⁵ Williams et al, ²³⁵ Williams et al ²⁷⁶	Download: www.autismresearchcentre.com/tests/cast_test.asp
M-CHAT	16–48 mo	Questionnaire completed by parent (23)	5–10	0.85 ^d	0.93 ^d	Dumont-Matthieu and Fein, ²⁷⁷ Robins et al ²⁸⁸	Download: www.dbpediatrics.org/media/mchat.pdf or www.firstsigns.org/downloads/m-chat.pdf ; for scoring: www.firstsigns.org/downloads/m-chat_scoring.PDF Purchase: PsychCorp/Harcourt Assessment (www.harcourtassessment.com)
Level 2							
Asperger Syndrome Diagnostic Scale (ASDS)	5–18 y	Questionnaire completed by parent, teacher, or clinician (50)	10–15	0.85 ^c		Myles et al, ²⁷⁸ Campbell ²⁷⁰	Purchase: Pro-Ed (www.proedinc.com)
Autism Behavior Checklist (ABC)	≥18 mo	Behavioral checklist completed by interviewer (57)	10–20	0.38–0.58 ^c	0.76–0.97 ^c	Krug et al ²⁷⁹	Purchase: Pro-Ed (www.proedinc.com) as part of the Autism Screening Instrument for Educational Planning (ASIEP-2) Download: www.autismresearchcentre.com/tests/aq_adolescentL_test.asp Questions are included as an appendix in Ehlers et al ²⁸¹
Autism Quotient (AQ)–Adolescent Version	11–16 y	Questionnaire completed by parent (50)	15	0.89 ^c	1.0 ^c	Baron-Cohen et al ²⁸⁰	
Autism Spectrum Screening Questionnaire (ASSQ)	6–17 y	Questionnaire completed by parent (27)	10	0.62–0.82 ^c (parent); 0.65–0.70 ^c (teacher)		Ehlers et al ²⁸¹	
Childhood Autism Rating Scale (CARS)	>2 y	Behavioral checklist completed by trained interviewer/observer (15)	Variable	0.92–0.98 ^c ; 0.94 ^c	0.85 ^c	Eaves and Milner, ²⁸² Perry et al, ²⁸³ Schopler et al ²⁸⁴ , Sevin et al ²⁸⁵ Gilliam, ²⁸⁶ Campbell ²⁷⁰	Purchase: Western Psychological Services (www.wpspublish.com)
Gilliam Asperger's Disorder Scale (GADS)	3–22 y	Questionnaire completed by parent, teacher, or clinician (32)	10			Gilliam, ²⁸⁶ Campbell ²⁷⁰	Purchase: Pro-Ed (www.proedinc.com)
Gilliam Autism Rating Scale–2nd Edition (GARS-2)	3–22 y	Questionnaire completed by parent or teacher (42)	5–10			Gilliam ²⁸⁷	Purchase: Pro-Ed (www.proedinc.com)

TABLE 3 Continued

Screening Tool	Age	Format (No. of Items)	Time to Complete, min	Reported Sensitivity	Reported Specificity	Selected Key References	Availability
Krug Asperger's Disorder Index (KADI)	6–21 y	Questionnaire completed by parent or clinician (32)	15–20	0.78 ^c	0.94 ^c	Krug and Aitick, ²⁸⁸ Campbell ²⁷⁰	Purchase: Pro-Ed (www.proedinc.com)
Pervasive Developmental Disorders Screening Test-II, Developmental Clinic Screener (PDDST-II, DCS)	18–48 mo	Questionnaire completed by parent (14)	10–15	0.73 ^c	0.49 ^c	Siegel ²⁶⁹	Purchase: PsychCorp/Harcourt Assessment (www.harcourtassessment.com)
Pervasive Developmental Disorders Screening Test-II, Autism Clinic Severity Screener (PDDST-II, ACSC)	18–48 mo	Questionnaire completed by parent (12)	10–15	0.58 ^c	0.60 ^c	Siegel ²⁶⁹	Purchase: PsychCorp/Harcourt Assessment (www.harcourtassessment.com)
Screening Tool for Autism in Two-Year-Olds (STAT)	24–36 mo	Interactive, requires specific training (12)	20	0.92 ^d	0.85 ^d	Stone et al, ²⁸⁹ Stone et al ²⁹⁰	Author: Wendy Stone, PhD (triad@vanderbilt.edu)
Social Communication Questionnaire (SCQ) (formerly the Autism Screening Questionnaire [ASQ])	≥4 y	Questionnaire completed by parent (40)	5–10	0.85–0.96 ^c	0.67–0.80 ^c	Berument et al, ²⁹¹ Rutter et al ²⁹²	Purchase: Western Psychological Services (www.wpspublish.com)

The measures were selected on the basis of availability of some published psychometric properties (in English) with scoring instructions and pass/fail cutoffs or the equivalent.

^a Level 1 tools are most likely to be used in primary care settings.

^b Population-based sample.

^c Clinical sample.

^d Clinical and population-based samples.

Adapted from Coomb EE, Stone WL. Screening for autism in young children. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. Vol 2. Hoboken, NJ: John Wiley & Sons; 2005:707–729; Campbell JM. Diagnostic assessment of Asperger's disorder: a review of five third-party rating scales. *J Autism Dev Disord*. 2005;35:25–35; and Rutter M, Bailey A, Lord C, et al. *The Social Communication Questionnaire (SCQ) Manual*. Los Angeles, CA: Western Psychological Services; 2003.

large, unselected population as a level 1 screening tool.²⁷¹ The authors concluded that the CAST is useful as a screening test for ASDs in epidemiologic research but that there is not enough evidence to recommend it for routine screening in the general population as part of a public health program.²⁷¹ In addition, the AAP does not currently recommend universal screening of school-aged children with a level 1 AS-specific tool.

See Appendix 1 for reimbursement codes.

Results of Screening (Steps 6a and 6b)

If the screening result for an at-risk child is negative in *Step 6a*, the PCP should proceed to *Step 7a*, provide parent educational materials (such as the AAP brochure, “*Is Your One-Year-Old Communicating With You?*”¹³ or the AAP parent booklet, “*Understanding Autism Spectrum Disorders*”¹⁴) and schedule an extra visit (*Step 1b*) within 1 month to address residual concerns. If the only risk factor is having a sibling with an ASD, an extra visit is not necessary unless the parents become concerned after the visit. When the screening result is negative for children without risk at the 18- or 24-month preventive visit (*Step 6b*), the PCP should proceed to *Step 7b* and schedule the next routine preventive care visit (*Step 1a*). If the screening result is positive (*Steps 6a* or *6b*) or 2 or more risk factors are present at *Step 3*, the PCP should proceed to *Step 8*, at which simultaneous activities should take place in an expedient manner. The PCP should consider the possibility that the child with a negative ASD screening result may have another developmental disorder that would warrant further investigation and referral to resources similar to those listed in *Step 8*.

When surveillance does not identify any risk factors and the visit is not an 18- or 24-month visit (*Step 4*), no screening is recommended, and the PCP may proceed directly to *Step 7b*.

Step 8: Activities Needed When Multiple Risk Factors Are Present or When the ASD Screening Result Is Positive

Activities described herein will depend on certain community characteristics, especially in regard to obtaining a comprehensive evaluation. Depending on the number of ASD experts in a given community, the interval wait for an appointment may be long. Thus, it is important that the PCP simultaneously accomplish all of *Steps 8.1* through *8.4* while the family is waiting for a specialty appointment to confirm or rule out an ASD diagnosis.

Step 8.1: Provide Parental Education

If the PCP feels fairly certain that the child has a developmental disorder that falls somewhere in the autism spectrum, it will be helpful to give the parents reading materials. As discussed in the introduction to this report, the AAP has published “*Understanding Autism Spectrum Disorders*,” an educational booklet for parents with this

intent.¹⁴ The comprehensive evaluation will progress more efficiently if the parents are more knowledgeable about the characteristic clinical symptoms of ASDs and can report them more accurately. Some PCPs are reticent to share their concerns with parents, fearful that premature “labeling,” although it is tentative, might cause undo stress and anxiety on the part of the family. However, sincerity, honesty, and admitting uncertainty is appreciated by most parents. On the other hand, concealing a concern and taking a “wait-and-see” approach rarely is appreciated; in fact, this strategy often breeds parental discontent and, worse, resentment and anger. With the recent high visibility in the media, most parents (unlike before the 1990s) now are aware of ASDs and may suspect it and search the Internet for information. It is important that they receive peer-reviewed and consensus-driven information that is evidence based and that they understand how to interpret Web-site information that is not peer reviewed.

Step 8.2.a: ASD Comprehensive Evaluation

For some children, the diagnosis might be quite obvious to the PCP who is using the DSM-IV-TR criteria as a guide. In others, the diagnosis may be challenging, especially when externalizing behavioral symptoms are mild or variable and/or there are associated comorbid disorders. Ideally, the definitive diagnosis of an ASD should be made by a team of child specialists with expertise in ASDs. Unfortunately, teams are not available in every locale, and when they are, long waiting lists may exist. Most communities will have at least 1 pediatric subspecialist (eg, child neurologist, developmental pediatrician, psychiatrist) with at least some expertise in making an ASD diagnosis. Other professionals, such as child psychologists, SLPs, pediatric occupational therapists, and social workers with expertise in ASDs, can be helpful by performing independent evaluations, often using standardized tools that can assist in the diagnostic process, especially when no team or pediatric “expert” is available. Child psychologists with appropriate training and experience can make the diagnosis independently and often do so, especially in school systems. Recently, the American Speech-Language-Hearing Association published guidelines that stated that an SLP with expertise in ASDs can make the diagnosis independently when other resources are not available.^{294,295} Older children who first present with symptoms of AS after school entry often are first recognized and evaluated by the school district’s educational diagnostic team and subsequently, but unfortunately not always, referred to a health care professional.

If it seems fairly certain, on the basis of general developmental screening and/or available psychometric testing with standardized tools, that the child also has GDD or intellectual disability, then the PCP might order high-resolution karyotype and DNA testing for fragile X

syndrome. If the child has clinical features (history, family history, physical examination) that are characteristic of a specific genetic or neurologic disorder that can be easily confirmed by a specific laboratory test, then the PCP may want to proceed with that test. On the other hand, the PCP may opt to refer the child to pediatric subspecialists for assistance with an etiologic workup and/or a search for coexisting conditions. Depending on availability and the nature of the concern(s), the PCP should consider a referral to a developmental pediatrician, a geneticist, and/or a child neurologist.^{104,296} See the next section for a more extensive discussion of the components of a comprehensive evaluation.

Step 8.2.b: Early Intervention/Early Childhood Education Services

As soon as an infant or toddler is suspected of having a delay or being at risk of a delay or developmental disorder such as an ASD, he should be referred immediately to an early intervention program (a government-subsidized public program designed to serve children with special needs and/or developmental delays from the time the problem is identified until the third birthday). If the child has had his third birthday, the referral should be made to the special education department in the local school. Among other professionals, assessment teams will almost always include SLPs and occupational therapists who can develop appropriate intervention plans without a categorical diagnosis. Intervention is important and often can be effective, even if it begins as generic speech therapy (ie, therapy that addresses most forms of language delay) and general developmental strategies. This intervention plan can be revised later to a more specific ASD intervention protocol (such as teaching JA) once the diagnosis is made. Experienced therapists often recognize ASD symptomatology and use strategies tailored to the child's individual deficits, even without a definitive ASD diagnosis.

Step 8.2.c: Audiology Evaluation

All children with language delays, including those suspected of having ASDs, should undergo an audiologic evaluation, even if the neonatal screening result was normal. This testing may be challenging to accomplish, because children with ASDs often are uncooperative for behavioral audiometry, the test most frequently used with toddlers. If the attempt is unsuccessful, an auditory brainstem response or brainstem auditory evoked-response test can be ordered; it is likely that sedation will be required. Sedation may be challenging, because some children with ASDs may respond paradoxically to sedatives.

Steps 8.3 and 8.4: Schedule Follow-up Visit and Reenter Algorithm

The child should be scheduled for a targeted follow-up visit within 1 month and reenter the algorithm at *Step 1b* to determine the status of the aforementioned referrals and to discuss any additional parental concerns once they have had the opportunity to read and learn more about ASDs.

COMPREHENSIVE EVALUATION (SEE STEP 8.2.a)

There are 3 major diagnostic challenges in the comprehensive assessment of a child with a suspected ASD: determining the child's overall level of functioning; making the categorical diagnosis of an ASD; and determining the extent of the search for an associated etiology. To accomplish these 3 goals, a comprehensive evaluation should include the following components^{212,297,298}:

1. Health, developmental, and behavioral histories that include at least a 3-generation family pedigree and a review of systems.
2. Physical examination including a thorough search for dysmorphic features and neurologic abnormalities and a Wood's lamp examination of the skin.
3. Developmental and/or psychometric evaluation (depending on age/skill level) to determine the child's overall level of functioning and whether a discrepancy between motor-adaptive problem-solving and social communication skills is evident.^{299,300}
4. Determination of the presence of a categorical DSM-IV-TR diagnosis, preferably with standardized tools that operationalize the DSM criteria.
5. Assessment of the parents' knowledge of ASDs, coping skills, and available resources and supports.
6. A laboratory investigation to search for a known etiology or coexisting condition guided by information obtained in *Steps 1* through *5*.

When appropriate, the evaluation should include information from multiple sources, because the child's performance may vary among settings and caregivers. Depending on level of comfort, the PCP may opt to refer to an experienced pediatric subspecialist, such as a neurologist, geneticist, or developmental pediatrician, to further evaluate the child, especially when there is an abnormal neurologic finding, seizures, regression, dysmorphic features, and/or a complex family history.

Laboratory testing for children with ASDs (component 6 above) is controversial. Newer technology has been developed since publication of the 2001 AAP statement and technical report^{1,2}; however, some tests are not yet clinically available. Various specialists hold differing opinions about the definition of a "positive yield," defined herein as a positive test result that indicates a known autism-related etiology (eg, a positive result on

DNA testing for fragile X syndrome or a karyotype revealing a mutation at 9q or 16p indicating tuberous sclerosis). They also promote varying clinical indications for extensive molecular testing and neuroimaging when the clinical validity of a positive finding is yet unknown in many cases.³⁰¹ Some investigators have reported a positive yield when, in fact, the identified abnormality was nonspecific, did not relate to a known autism-related etiology, and did not affect counseling and/or management (eg, delayed myelination on MRI).³⁰² Medical symptoms should be evaluated on a case-by-case basis; rather than reflect an etiology, an abnormal test result may indicate that a child with an ASD has a coexisting condition (eg, a gastrointestinal disorder). Thus, an abnormal laboratory test result does not necessarily indicate a positive yield but may, indeed, indicate a condition that needs medical attention (see the AAP clinical report "Management of Children With Autism Spectrum Disorders"³⁰³). Reporting it as a positive yield makes it difficult to translate research methodology into recommendations that will help the clinician in the care of any given patient.

The yield of an etiologic investigation may be more highly correlated with the presence or absence of coexisting GDD/MR (intellectual disability) rather than with an isolated ASD. In fact, the presence of autism in a cohort of children with GDD/MR (intellectual disability) decreased the chance of a positive yield.³⁰⁴ Depending on the population characteristics, specific test(s) studied, and the decision-making process by which they were ordered (ie, as a screening technique for all study patients with ASDs versus a targeted test indicated by a specific clinical finding), positive yields range from as low as 0%^{101,305,306} to as high as 25% to 40%,^{307–309} but most yield rates fall between 2% and 10%.† It is difficult to compare studies because of variability in the workups, analysis in terms of GDD/MR or other phenotypic variables, and interpretation of positive test results (eg, delayed myelination on MRI) or symptoms (eg, gastrointestinal) that are not definitively associated with ASDs.³¹⁰

Although the original ASD-specific consensus guidelines published between 1999 and 2001^{1,2,106,107} have been helpful in guiding the etiology-search strategy in children with ASDs, the presence of coexisting GDD/MR (intellectual disability) in a cohort of children with ASD (especially severe GDD/MR or intellectual disability associated with dysmorphic features) is more highly correlated with a positive yield and a recognizable syndrome.¹⁰⁸ Thus, guidelines that address the etiologic workup of children with GDD/MR^{104,296,311,312} also should be considered when evaluating a child with both an ASD and GDD/MR but not necessarily a child with an isolated ASD.

Among laboratory tests, high-resolution chromosome analysis by G-banding and molecular testing for fragile X syndrome have the highest yield in determining etiology in patients with ASDs.‡ Some investigators have suggested a battery of additional screening cytogenetic and molecular studies for all patients with ASDs regardless of gender, presence or absence of coexisting GDD/MR, dysmorphic features, or family history.³⁰⁹ However, current data do not support extensive testing of all children with ASDs in clinical settings. Published studies have begun to address some of the newer molecular genetic techniques that have revolutionized genetic testing by detecting microdeletions, duplications, and rearrangements not visible with high-resolution chromosomal testing. Targeted FISH studies can be used to screen for deletions or duplications, such as those associated with chromosomes 15q and 22q.^{305,310} A relatively recent use of FISH technology is genome-wide subtelomere screening, which detects clinically significant abnormalities in 2.5% of individuals with unexplained GDD/MR.³¹³ This technology can detect a wide variety of abnormalities, including some such as 22q13.3 deletion, that have been reported in a subset of children with ASDs.^{314,315} Several studies that examined the yield of subtelomere FISH screening in ASD failed to detect a single abnormality, which suggests that it may not be helpful in the routine evaluation of these patients.^{89,305} However, additional studies are needed. Comparative genomic hybridization-microarray analysis is a promising tool that may become standard of care in the future, but this technique has not been evaluated systematically in children with ASDs.

Screening neurologic tests also have been suggested—for example, electroencephalography (EEG [routine and/or prolonged sleep studies]) for all children with ASDs.³¹⁶ Although nonspecific abnormalities have been found in most children, the significance of these abnormalities is not clear, and additional research is needed to determine if intervention is of any value. Thus, there is no evidence to support universal screening EEG without a clinical indication.^{317,318} An EEG should be considered for children who demonstrate clinical signs that might represent seizures and for children with clear language regression. However, EEGs in children that demonstrate "classic autistic regression" between 12 and 24 months are often nonspecific and not helpful in the diagnostic process. Previously published guidelines contain clear recommendations that screening MRIs on all children who present with ASDs, including those with isolated macrocephaly, are not necessary.^{106,107,194} Given the heterogeneity of ASDs, the likelihood of multiple etiologies, and the questionable clinical validity of an extensive battery of screening tests on all children with ASDs, more evidence is needed before a battery of genetic and neurologic testing becomes standard of care.

†Refs 20, 23, 33, 89, 97, 101, 105, 302, and 310.

‡Refs 20, 23, 33, 89, 101, 105, 302, and 310.

Although for the individual patient, it is important to differentiate an idiopathic ASD (with a recurrence rate of 5%–6% [range: 2%–8%]) from an ASD-associated syndrome that may have a higher or lower recurrence rate, there is no simple 1-size-fits-all search strategy.^{1,2,106,107,300} Instead, the search should be guided by clinical judgment based on history (eg, health, birth, developmental, behavioral, family) and clinical presentation (eg, comorbid MR, regression, seizures, neurodevelopmental findings, dysmorphic features, comorbid medical conditions). The importance of dysmorphic features and/or neurologic abnormalities in predicting a positive yield particularly has been emphasized.¹⁰⁸ Family characteristics (eg, insurance status, concern about the child's discomfort, or interest in pursuing a "no-stone-left-untuned" etiologic workup) also may affect parental decisions regarding the extent of the workup. Finally, the availability of technology, the need for and feasibility of sedation, managed care cost/benefit guidelines, and physician motivation each may play a role. There are certainly many advantages to having a diagnosis, including genetic counseling and provision of recurrence risks of known syndromes, the possibility of a specific treatment strategy, counseling regarding the natural history of a known disorder, anticipation of a later associated comorbid disorder, prevention of secondary disorders, availability of prenatal diagnosis, access to public support systems, access to syndrome-specific parent support groups, and, in some cases, the psychological benefits of knowing that empower parents to move on and focus on habilitative interventions.

A "search strategy" might be conceptualized as consisting of 3 levels.

1. Studies that should be considered for all young children with ASDs (ie, an audiology evaluation; however, school-based hearing screening may be adequate in the older child with AS and no significant language or learning deficits).

2. Studies that should be considered in all children with both an ASD and coexisting GDD/MR or intellectual disability (ie, high-resolution karyotype [650 bands] and DNA testing for fragile X syndrome). Although a high-resolution karyotype might reveal larger duplications, some clinicians believe that FISH testing for 15q duplications also might be indicated.^{92,93} In the future, a microarray analysis may replace high-resolution karyotyping. A methyl CpG-binding protein 2 (*MECP2*) analysis should be considered in females who present with regression and autistic features that are also consistent with Rett syndrome.³¹⁰

3. Targeted studies (eg, EEG, metabolic studies, MRI) should be considered when specific clinical findings are identified by history or physical examination (eg, seizures, cyclic vomiting and lethargy associated with mild illnesses and/or unusual odors, hypopigmented macules). Identification of more subtle indicators and their

corresponding appropriate laboratory tests might be facilitated by referral to a geneticist, pediatric neurologist, and/or developmental pediatrician.

Ongoing multisite studies are investigating specific test protocols. Such evaluations are not recommended as clinical standard of care at this time until analysis of the data indicates which of the extended tests, if any, are indicated and for which ASD populations. These research protocols include many tests that are investigational, have unknown medical validity, and currently are not available for clinical use. Some of these tests include functional neuroimaging, immunologic studies, metabolic testing, fibroblast karyotypes, neuroigin gene testing, mitochondrial gene sequencing, genomic microarrays, and identification of endophenotypes.^{90,319} Although these tests may not be relevant in clinical practice, they do have the potential to expand the fund of knowledge about ASDs, reveal more specific ASD subtypes, and provide a better understanding of coexisting disorders and future prognosis. As the fund of knowledge regarding genetic markers for ASDs expands and technology continues to become more sophisticated, the yield of these laboratory investigations may eventually prove to be useful in the routine clinical evaluation of children with idiopathic ASDs. For now, the existing dichotomy regarding the extent of testing in research versus clinical settings is challenging.³⁰¹ Existing data do not support routine application of any particular test battery, nor do they suggest that tests currently under investigation be routinely performed on all children with ASDs at this time.

Prognosis

Although prognosis is one of the parents' most pressing concerns at the time of diagnosis, it depends on many factors and usually cannot be predicted during early childhood, especially in children younger than 3 years.³²⁰ Important early predictors include JA skills, functional play skills,³²¹ cognitive abilities, and severity of ASD symptoms.^{322–334} Recent studies have revealed that although most children diagnosed with AD retain their diagnosis at 9 years of age,²⁰⁸ many, especially those with PDD-NOS, improve, and a minority have optimal outcomes; that is, they have normal intelligence and function reasonably well in mainstream classrooms without an aid but still exhibit residual clinical signs of social awkwardness, restrictive interests, or mild, infrequent stereotypies. Some may show signs of ADHD, language-based learning disabilities, or other learning challenges.^{8–11,217} Poorer outcomes are associated with lack of JA by 4 years of age and lack of functional speech by 5 years of age,^{7,217} MR, seizures (especially with onset during adolescence), comorbid medical (eg, tuberous sclerosis) or psychiatric (eg, schizophrenia) disorders, and severe autistic symptoms, especially when associated with extreme "aloofness." Factors associated with better out-

comes include early identification resulting in early enrollment in appropriate intervention programs^{7,332} and successful inclusion in regular educational and community settings with typically developing peers.

Adult outcomes seem to correlate better with level of cognitive-adaptive functioning than with the severity of autistic symptoms. People with normal intelligence/adaptive functioning and milder autistic symptoms generally have the best outcomes, those with MR or intellectual disability and severe autistic symptoms have the worst outcomes within the continuum, and those with normal cognitive-adaptive skills and severe autistic symptoms generally do better than those with MR or intellectual disability and mild autistic symptoms,^{328,333} which reaffirms the contribution of intelligence rather than degree of atypicality (autistic symptoms). However, within the subgroup of children with normal intelligence, the degree of atypicality then becomes more important in determining prognosis. Many believe that people with AS have better outcomes than those with other ASDs. This may be true, because by definition, all those with AS have normal intelligence. One adult outcome study found that although those with AS tend to have a greater likelihood of earning a college degree than those with high-functioning autism/PDD-NOS, the college education did not significantly affect employment or marriage status.^{331,334}

Genetic Counseling

Genetic counseling regarding recurrence risk in siblings is important even when the etiologic evaluation is negative, because the recurrence risk is approximately 5% to 6% (range: 2%–8%) in a family with 1 child with an idiopathic ASD.^{67,68} The prevalence of abnormality in siblings is even higher, perhaps 20%, when the broader phenotype or milder constellation of similar social, communication, and behavioral abnormalities is considered.⁶⁸ If there are already 2 siblings with ASDs in a family, it is likely that the recurrence risk for a strictly defined ASD in subsequent offspring is well above 8% and may approach 25%, but there is insufficient evidence to be more precise.⁶⁸ It is important to discuss the recurrence risk promptly after diagnosis to provide parents with this information before they conceive another child.⁶⁷ When an etiology is determined, the recurrence risk may be lower or higher than the risk in idiopathic ASD, depending on the syndrome or condition identified, and prenatal diagnosis may be possible.

GUIDANCE FOR PEDIATRICIANS REGARDING THE IDENTIFICATION AND EVALUATION OF CHILDREN WITH ASDs

In summary, most PCPs can expect to care for several children with ASDs in the context of the medical home.⁵ No two children with ASDs will be exactly alike; each will have his or her own constellation of diagnostic and management challenges. The PCP has an important role

in the early identification of children with ASDs. PCPs should do the following:

1. Conduct surveillance at every well-child visit. Be a good listener and recognize the early subtle red flags that indicate the possibility of an ASD. Be especially vigilant for younger siblings of a child who has already been diagnosed with an ASD.²⁵³
2. Screen at 18^{246,260} and 24²⁶⁰ months and any other time when parents raise a concern about a possible ASD. Although no screening tool is perfect, choose and become comfortable with at least 1 tool for each age group and use it consistently. Before 18 months of age, screening tools that target social and communication skills may be helpful in systematically looking for early signs of ASDs.²⁶¹
3. If an ASD-specific screening result is negative but either the parents or the PCP remain somewhat concerned, then the PCP should schedule the child for an early, targeted clinic visit to address these persistent concerns.
4. Act on a positive screening result or when a child demonstrates 2 or more risk factors. Do not take a “wait-and-see” approach. Depending on the age of the child, simultaneously refer for all 3: comprehensive ASD evaluation; early intervention/early childhood education services; and an audiologic evaluation. Do not wait for a definitive diagnosis of an ASD to refer for developmental services; early intervention can be beneficial even if it targets the child’s unique deficits. The intervention strategy can be modified if needed when the child is determined to have an ASD.

The science of ASDs is expanding rapidly. Newer tools are under development and should become available to clinicians so that children can be screened and evaluated more efficiently and with greater accuracy in the future.

The reader is referred to the accompanying AAP clinical report, “Management of Children With Autism Spectrum Disorders,”³⁰³ to learn more about specific techniques and challenges in caring for children with ASDs within the context of a pediatric medical home.

APPENDIX 1: REIMBURSEMENT FOR SCREENING ACTIVITIES

Reimbursement for the administration of developmental and ASD-specific screening tools is an important aspect of screening. Developmental screening tests, including ASD-specific tests that are completed by a parent or nonphysician staff member and are reviewed and interpreted by the physician, can be billed appropriately by using *Current Procedural Terminology* (CPT) code 96110.²⁴⁶

Tools that include a direct clinical observation component have the benefit of providing some potentially more objective information, and aspects of behavior that parents may not have noticed can be sampled. Extended

screening tests that include a direct testing component can be billed appropriately by using CPT code 96111.²⁴⁶

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REFERENCES

1. American Academy of Pediatrics, Committee on Children With Disabilities. The pediatrician's role in the diagnosis and management of autistic spectrum disorder in children. *Pediatrics*. 2001;107:1221–1226
2. American Academy of Pediatrics, Committee on Children With Disabilities. Technical report: the pediatrician's role in the diagnosis and management of autistic spectrum disorder in children. *Pediatrics*. 2001;107(5). Available at: www.pediatrics.org/cgi/content/full/107/5/e85
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)*. Washington, DC: American Psychiatric Publishing; 1994
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Publishing; 2000
5. Dosreis S, Weiner CL, Johnson L, Newschaffer CJ. Autism spectrum disorder screening and management practices among general pediatric providers. *J Dev Behav Pediatr*. 2006; 27:S88–S94
6. Heidgerken AD, Geffken G, Modi A, Frakey L. A survey of autism knowledge in a health care setting. *J Autism Dev Disord*. 2005;35:323–330
7. National Research Council, Committee on Interventions for Children With Autism. *Educating Children With Autism*. Washington, DC: National Academies Press; 2001
8. Fein D, Dixon P, Paul J, Levin H. Brief report: pervasive developmental disorder can evolve into ADHD: case illustrations. *J Autism Dev Disord*. 2005;35:525–534
9. Sallows GO, Graupner TD. Intensive behavioral treatment for children with autism: four-year outcome and predictors. *Am J Ment Retard*. 2005;110:417–438
10. Kasari C, Freeman S, Paparella T. Joint attention and symbolic play in young children with autism: a randomized controlled intervention study. *J Child Psychol Psychiatry*. 2006;47: 611–620
11. Kelley E, Paul JJ, Fein D, Naigles LR. Residual language deficits in optimal outcome children with a history of autism. *J Autism Dev Disord*. 2006;36:807–828
12. Johnson CP. New tool helps physicians diagnose autism early. *AAP News*. 2004;24:74
13. American Academy of Pediatrics. *Is Your One-Year-Old Communicating With You?* Elk Grove Village, IL: American Academy of Pediatrics; 2004
14. American Academy of Pediatrics. *Understanding Autism Spectrum Disorders*. Elk Grove Village, IL: American Academy of Pediatrics; 2005
15. Kanner L. Autistic disturbances of affective contact. *Nerv Child*. 1943;2:217–250
16. Asperger H. Die "autistischen psychopathen" im Kindesalter. *Arch Psychiatr Nervenkr*. 1944;117:76–136
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III)*. Washington, DC: American Psychiatric Association; 1980
18. Volkmar FR, Klin A. Issues in the classification of autism and related conditions. In: Volkmar FR, Paul R, Klin A, Cohen DL, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. Vol 1. Hoboken, NJ: John Wiley & Sons; 2005:5–41
19. Baird G, Charman T, Baron-Cohen S. A screening instrument for autism at 18 months of age: a 6-year follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2000;39:694–702
20. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children. *JAMA*. 2001;285:3093–3099
21. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children: confirmation of high prevalence. *Am J Psychiatry*. 2005;162:1133–1141
22. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsop M, DeCoufle P. Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. *Pediatrics*. 2001;108:1155–1161
23. Fombonne E, Simmons H, Ford T. Prevalence of pervasive developmental disorders in the British nationwide survey of child mental health. *J Am Acad Child Adolesc Psychiatry*. 2001; 40:820–827
24. Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord*. 2003;33:365–382
25. Tidmarsh L, Volkmar FR. Diagnosis and epidemiology of autism spectrum disorders. *Can J Psychiatry*. 2003;48:517–525
26. Centers for Disease Control and Prevention. Mental health in the United States: parental report of diagnosed autism in children aged 4–17 years—United States, 2003–2004. *MMWR Morb Mortal Wkly Rep*. 2006;55:481–486
27. 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
28. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2000 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders: Autism and Developmental Disabilities Monitoring Network, Six Sites, United States, 2000. *MMWR Surveill Summ*. 2007;56(1):1–11
 29. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders: Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2002. *MMWR Surveill Summ*. 2007;56(1):12–28
 30. Van Naarden Braun K, Pettygrove S, Daniels J, et al. Evaluation of a methodology for a collaborative multiple source surveillance network for autism spectrum disorders: Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2002. *MMWR Surveill Summ*. 2007;56(1):29–40
 31. Rice C, Baio J, Van Naarden Braun K, et al. A public health collaboration for the surveillance of autism spectrum disorders. *Paediatr Perinat Epidemiol*. 2007;21:179–190
 32. Charman T, Baird G. Practitioner review: diagnosis of autism spectrum disorder in 2- and 3-year-old children. *J Child Psychol Psychiatry*. 2002;43:289–305
 33. Fombonne E. Epidemiology of autistic disorder and other pervasive development disorders. *J Clin Psychiatry*. 2005;66(suppl 10):3–8
 34. Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. *JAMA*. 2003;289:49–55
 35. Wiggins LD, Baio J, Rice C. Examination of the time between first evaluation and first autism spectrum diagnosis in a population-based sample. *J Dev Behav Pediatr*. 2006;27:S79–S87
 36. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. The incidence of autism in Olmsted County, Minnesota, 1976–1997: results from a population-based study. *Arch Pediatr Adolesc Med*. 2005;159:37–44
 37. Gernsbacher MA, Dissanayake C, Goldsmith HH, Mundy PC, Rogers SJ, Sigman M. Autism and deficits in attachment behavior. *Science*. 2005;307:1201–1203
 38. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM-III-R)*. Washington, DC: American Psychiatric Association; 1987
 39. Factor DC, Freeman NL, Kardash A. Brief report: a comparison of DSM-III and DSM-III-R criteria for autism. *J Autism Dev Disord*. 1989;19:637–640
 40. Volkmar FR, Klin A, Siegel B, et al. Field trial for autistic disorder in DSM-IV. *Am J Psychiatry*. 1994;151:1361–1367
 41. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*. Vol 1–3. Geneva, Switzerland: World Health Organization; 1994
 42. Individuals With Disabilities Education Act Amendments. Pub L No. 101-476 (1990)
 43. Eagle RS. Commentary: further commentary on the debate regarding increase in autism in California. *J Autism Dev Disord*. 2004;34:87–88
 44. Gurney JG, Fritz MS, Ness KK, Sievers P, Newschaffer CJ, Shapiro EG. Analysis of prevalence trends of autism spectrum disorder in Minnesota. *Arch Pediatr Adolesc Med*. 2003;157:622–627
 45. Laidler JR. How “educational assessments” skew autism prevalence rates. Available at: www.autism-watch.org/general/edu.shtml. Accessed March 19, 2007
 46. Laidler JR. US Department of education data on “autism” are not reliable for tracking autism prevalence. *Pediatrics*. 2005;116(1). Available at: www.pediatrics.org/cgi/content/full/116/1/e120
 47. Shattuck PT. The contribution of diagnostic substitution to the growing administrative prevalence of autism in US special education data. *Pediatrics*. 2006;117:1028–1037
 48. Newschaffer CJ. Investigating diagnostic substitution and autism prevalence trends. *Pediatrics*. 2006;117:1436–1437
 49. Mandell DS, Novak MM, Zubritsky CD. Factors associated with age of diagnosis among children with autism spectrum disorders. *Pediatrics*. 2005;116:1480–1486
 50. Individuals With Disabilities Education Act Amendments. Pub L No. 105-17 (1997)
 51. Individuals With Disabilities Education Improvement Act of 2004. Pub L No. 108-446 (2004)
 52. Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. *J Autism Dev Disord*. 2002;32:207–215
 53. M.I.N.D. Institute. *Report to the Legislature on the Principal Findings From the Epidemiology of Autism in California: A Comprehensive Pilot Study*. Davis, CA: University of California Davis; 2002. Available at: www.ucdmc.ucdavis.edu/mindinstitute/newsroom/study_final.pdf. Accessed March 14, 2007
 54. Blaxill MF, Baskin DS, Spitzer WO. Commentary: Blaxill, Baskin, Spitzer on Croen et al. (2002), the changing prevalence of autism in California. *J Autism Dev Disord*. 2003;33:223–226
 55. Newschaffer CJ, Falb MD, Gurney JG. National autism prevalence trends from United States special education data. *Pediatrics*. 2005;115(3). Available at: www.pediatrics.org/cgi/content/full/115/3/e277
 56. Palmer RF, Blanchard S, Jean CR, Mandell DS. School district resources and identification of children with autistic disorder. *Am J Public Health*. 2005;95:125–130
 57. Americans With Disabilities Act of 1990. Pub L No. 101-336 (1990)
 58. Kent L, Evans J, Paul M, Sharp M. Comorbidity of autistic spectrum disorders in children with Down syndrome. *Dev Med Child Neurol*. 1999;41:153–158
 59. Starr EM, Berument SK, Tomlins M, Papanikolaou K, Rutter M. Brief report: autism in individuals with Down syndrome. *J Autism Dev Disord*. 2005;35:665–673
 60. Johansson M, Rastam M, Billstedt E. Autism spectrum disorders and underlying brain pathology in CHARGE association. *Dev Med Child Neurol*. 2006;48:40–50
 61. Bishop DV, Maybery M, Wong D, Maley A, Hallmayer J. Characteristics of the broader phenotype in autism: a study of siblings using the Children’s Communication Checklist-2. *Am J Med Genet B Neuropsychiatr Genet*. 2006;141:117–122
 62. Lotter V. Epidemiology of autistic conditions in young children. *Soc Psychiatry Psychiatr Epidemiol*. 1966;1:124–135
 63. Volkmar F, Chawarska K, Klin A. Autism in infancy and early childhood. *Annu Rev Psychol*. 2005;56:315–336
 64. Bailey A, Phillips W, Rutter M. Autism: towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *J Child Psychol Psychiatry*. 1996;37:89–126
 65. Risch N, Spiker D, Lotspeich L, et al. A genomic screen of autism: evidence for a multilocus etiology. *Am J Hum Genet*. 1999;65:493–507
 66. Asherson PJ, Curran S. Approaches to gene mapping in complex disorders and their application in child psychiatry and psychology. *Br J Psychiatry*. 2001;179:122–128
 67. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics*. 2004;113(5). Available at: www.pediatrics.org/cgi/content/full/113/5/e472
 68. Rutter M. Genetic influences and autism. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive*

- Developmental Disorders*. 3rd ed. Vol 1. Hoboken, NJ: John Wiley & Sons; 2005:425–452
69. Bailey A, Le Couteur A, Gottesman I. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med*. 1995;25:63–77
 70. Reichenberg A, Gross R, Weiser M, et al. Advancing paternal age and autism. *Arch Gen Psychiatry*. 2006;63:1026–1032
 71. Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. *Arch Pediatr Adolesc Med*. 2007;161:334–340
 72. Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism. *Arch Pediatr Adolesc Med*. 2007;161:326–333
 73. Arndt T, Stodgell CJ, Rodier PM. The teratology of autism. *Int J Dev Neurosci*. 2005;23:189–199
 74. Lopez-Rangel E, Lewis ME. Loud and clear evidence for gene silencing by epigenetic mechanisms in autism spectrum and related neurodevelopmental disorders. *Clin Genet*. 2006;69:21–22
 75. Veenstra-Vanderweele J, Christian SL, Cook EH Jr. Autism as a paradigmatic complex genetic disorder. *Annu Rev Genomics Hum Genet*. 2004;5:379–405
 76. Goldson E. Autism spectrum disorders: an overview. *Adv Pediatr*. 2004;51:63–109
 77. Monaco AP, Bailey AJ. Autism: the search for susceptibility genes. *Lancet*. 2001;358(suppl):S3
 78. Ylisaukko-oja T, Alarcón M, Cantor RM, et al. Search for autism loci by combined analysis of Autism Genetic Resource Exchange and Finnish families. *Ann Neurol*. 2006;59:145–155
 79. Buxbaum JD. The genetics of autism spectrum disorders. *Medscape Psychiatry Ment Health*. 2005;10(2). Available at: www.medscape.com/viewarticle/520013. Accessed March 15, 2007
 80. McDougle CJ, Erickson CA, Stigler KA, Posey DJ. Neurochemistry in the pathophysiology of autism. *J Clin Psychiatry*. 2005;66(suppl 10):9–18
 81. International Molecular Genetic Study of Autism Consortium. A full genome screen for autism with evidence for linkage to a region on chromosome 7q. *Hum Mol Genet*. 1998;7:571–578
 82. International Molecular Genetic Study of Autism Consortium (IMGSAC). A genomewide screen for autism: strong evidence for linkage to chromosomes 2g, 7q, and 16p. *Am J Hum Genet*. 2001;69:570–581
 83. Cook EH. Genetics of autism. *Child Adolesc Psychiatr Clin N Am*. 2001;10:333–350
 84. Yonan AL, Alarcon M, Cheng R, et al. A genome-wide screen of 345 families for autism-susceptibility loci. *Am J Hum Genet*. 2003;73:886–897
 85. Cook EH Jr, Courchesne RY, Cox NJ, et al. Linkage-disequilibrium mapping of autistic disorder, with 15q11-13 markers. *Am J Hum Genet*. 1998;62:1077–1083
 86. Gillberg C. Asperger syndrome and high functioning autism. *Br J Psychiatry*. 1998;172:200–209
 87. Korvatska E, Van de Water J, Anders TF, Gershwin ME. Genetic and immunologic considerations in autism [published correction appears in *Neurobiol Dis*. 2002;10:69]. *Neurobiol Dis*. 2002;9:107–125
 88. Volkmar FR, Lord C, Bailey A, Schultz RT, Klin A. Autism and pervasive developmental disorders. *J Child Psychol Psychiatry*. 2004;45:135–170
 89. Battaglia A, Bonaglia MC. The yield of subtelomeric FISH analysis in the evaluation of autistic spectrum disorders. *Am J Med Genet C Semin Med Genet*. 2006;142:8–12
 90. Dawson G. Despite major challenges, autism research continues to offer hope. *Arch Pediatr Adolesc Med*. 2007;161:411–412
 91. Cook EH Jr, Lindgren V, Leventhal BL, et al. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am J Hum Genet*. 1997;60:928–934
 92. Nurmi EL, Dowd M, Tadevosyan-Leyfer O, Haines JL, Folstein SE, Sutcliffe JS. Exploratory subsetting of autism families based on savant skills improves evidence of genetic linkage to 15q11–q13. *J Am Acad Child Adolesc Psychiatry*. 2003;42:856–863
 93. Wolpert CM, Menold MM, Bass MP, et al. Three probands with autistic disorder and isodicentric chromosome 15. *Am J Med Genet*. 2000;96:365–372
 94. Bolton PF, Dennis NR, Browne CE, et al. The phenotypic manifestations of interstitial duplications of proximal 15q with special reference to the autistic spectrum disorders. *Am J Med Genet*. 2001;105:675–685
 95. Rutter M. Incidence of autism spectrum disorders: changes over time and their meaning. *Acta Paediatr*. 2005;94:2–15
 96. Barton M, Volkmar F. How commonly are known medical conditions associated with autism? *J Autism Dev Disord*. 1998;28:273–278
 97. Rutter M, Bailey A, Bolton P, Le Couteur A. Autism and known medical conditions: myth and substance. *J Child Psychol Psychiatry*. 1994;35:311–322
 98. Rutter M. Genetic studies of autism: from the 1970s into the millennium. *J Abnorm Child Psychol*. 2000;28:3–14
 99. Fombonne E. Epidemiological studies of pervasive developmental disorders. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. Vol 1. Hoboken, NJ: John Wiley & Sons; 2005:42–69
 100. Fombonne E. Epidemiological trends in rates of autism. *Mol Psychiatry*. 2002;7(suppl 2):S4–S6
 101. Battaglia A, Carey JC. Etiologic yield of autistic spectrum disorders: a prospective study. *Am J Med Genet C Semin Med Genet*. 2006;142:3–7
 102. Demark JL, Feldman MA, Holden JJ. Behavioral relationship between autism and fragile X syndrome. *Am J Ment Retard*. 2003;108:314–326
 103. Honda H, Shimizu Y, Rutter M. No effect of MMR withdrawal on the incidence of autism: a total population study. *J Child Psychol Psychiatry*. 2005;46:572–579
 104. Shevell M, Ashwal S, Donley D, et al. 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;60:367–380
 105. Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M. Etiologic yield of autistic spectrum disorders: a prospective study. *J Child Neurol*. 2001;16:509–512
 106. Filipek PA, Accardo PJ, Baranek GT, et al. The screening and diagnosis of autism spectrum disorders [published correction appears in *J Autism Dev Disord*. 2000;30:81]. *J Autism Dev Disord*. 1999;29:439–484
 107. 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;55:468–479
 108. Miles JH, Hillman RE. Value of a clinical morphology examination in autism. *Am J Med Genet*. 2000;91:245–253
 109. Hagerman PJ, Hagerman RJ. The fragile X premutation: a maturing perspective [published correction appears in *Am J Hum Genet*. 2004;75:352]. *Am J Hum Genet*. 2004;74:805–816
 110. Rogers SJ, Wehner DE, Hagerman R. The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *J Dev Behav Pediatr*. 2001;22:409–417
 111. Watson MS, Leckman JF, Annen B, et al. Fragile X in a survey of 75 autistic males. *N Engl J Med*. 1984;310:1462

112. Smalley SL. Autism and tuberous sclerosis. *J Autism Dev Disord.* 1998;28:407–414
113. Baker P, Piven J, Sato Y. Autism and tuberous sclerosis complex: prevalence and clinical features. *J Autism Dev Disord.* 1998;28:279–285
114. Wiznitzer M. Autism and tuberous sclerosis. *J Child Neurol.* 2004;19:675–679
115. Curatolo P, Porfirio M, Manzi B, Seri S. Autism in tuberous sclerosis. *Eur J Paediatr Neurol.* 2004;8:327–332
116. Curatolo P. Tuberous sclerosis: genes, brain, and behavior. *Dev Med Child Neurol.* 2006;48:404
117. Lauritsen M, Ewald H. The genetics of autism. *Acta Psychiatr Scand.* 2001;103:411–427
118. Baieli S, Pavone L, Meli C, Fiumara A, Coleman M. Autism and phenylketonuria. *J Autism Dev Disord.* 2003;33:201–204
119. Aronson M, Hagberg B, Gillberg C. Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: a follow-up study. *Dev Med Child Neurol.* 1997;39:583–587
120. Clayton-Smith J, Laan L. Angelman syndrome: a review of the clinical and genetic aspects. *J Med Genet.* 2003;40:87–95
121. Thatcher KN, Peddada S, Yasui DH, LaSalle JM. Homologous pairing of 15q11-13 imprinted domains in brain is developmentally regulated but deficient in Rett and autism samples. *Hum Mol Genet.* 2005;14:785–797
122. Lopez-Rangel E, Lewis ME. Do other methyl-binding proteins play a role in autism? *Clin Genet.* 2006;69:25
123. Niemitz EL, Feinberg AP. Epigenetics and assisted reproductive technology: a call for investigation. *Am J Hum Genet.* 2004;74:599–609
124. Ham AL, Kumar A, Deeter R, Schanen NC. Does genotype predict phenotype in Rett syndrome? *J Child Neurol.* 2005;20:768–778
125. Kerr AM, Ravine D. Review article: breaking new ground with Rett syndrome. *J Intellect Disabil Res.* 2003;47:580–587
126. Kerr AM, Prescott RJ. Predictive value of the early clinical signs in Rett disorder. *Brain Dev.* 2005;27(suppl 1):S20–S24
127. Kerr A. Annotation: Rett syndrome—recent progress and implications for research and clinical practice. *J Child Psychol Psychiatry.* 2002;43:277–287
128. Einspieler C, Kerr AM, Prechtel HF. Abnormal general movements in girls with Rett disorder: the first four months of life. *Brain Dev.* 2005;27(suppl 1):S8–S13
129. Ravn K, Nielsen JB, Uldall P, Hansen FJ, Schwartz M. No correlation between phenotype and genotype in boys with a truncating *MECP2* mutation. *J Med Genet.* 2003;40:e5
130. Moog U, Smeets EE, van Roozendaal KE, et al. Neurodevelopmental disorders in males related to the gene causing Rett syndrome in females (*MECP2*). *Eur J Paediatr Neurol.* 2003;7:5–12
131. Elias E, Giampietro P. Autism may be caused by Smith-Lemli-Opitz syndrome (SLOS). Presented at: annual Clinical Genetics meeting; March 17–20, 2005; Dallas, TX
132. Vissers LE, van Ravenswaaij CM, Admiraal R, et al. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet.* 2004;36:955–957
133. Filipek PA, Juranek J, Nguyen MT, Cummings C, Gargus JJ. Relative carnitine deficiency in autism. *J Autism Dev Disord.* 2004;34:615–623
134. Connolly AM, Chez M, Streif EM, et al. Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. *Biol Psychiatry.* 2006;59:354–363
135. Stern L, Francoeur MJ, Primeau MN, Sommerville W, Fombonne E, Mazer BD. Immune function in autistic children. *Ann Allergy Asthma Immunol.* 2005;95:558–565
136. Ashwood P, Van de Water J. Is autism an autoimmune disease? *Autoimmun Rev.* 2004;3:557–562
137. Molloy CA, Morrow AL, Meinzen-Derr J, et al. Familial autoimmune thyroid disease as a risk factor for regression in children with autism spectrum disorder: a CEPA study. *J Autism Dev Disord.* 2006;36:317–324
138. Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorder: a case-control study. *Arch Pediatr Adolesc Med.* 2005;159:151–157
139. Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J Child Neurol.* 1999;14:388–394
140. Lawler CP, Croen LA, Grether JK, Van de Water J. Identifying environmental contributions to autism: provocative clues and false leads. *Ment Retard Dev Disabil Res Rev.* 2004;10:292–302
141. Bristol MM, Cohen DJ, Costello EJ. State of the science in autism: report to the National Institutes of Health. *J Autism Dev Disord.* 1996;26:121–154
142. Kemper TL, Bauman M. Neuropathology of infantile autism. *J Neuropathol Exp Neurol.* 1998;57:645–652
143. Chess S. Follow-up report on autism in congenital rubella. *J Autism Child Schizophr.* 1977;7:69–81
144. Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. *Am J Epidemiol.* 2005;161:916–925
145. Knickmeyer R, Baron-Cohen S, Raggatt P, Taylor K. Foetal testosterone, social relationships, and restricted interests in children. *J Child Psychol Psychiatry.* 2005;46:198–210
146. Badawi N, Kurinczuk U, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ.* 1998;317:1549–1553
147. Badawi N, Kurinczuk U, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the western Australian case-control study. *BMJ.* 1998;317:1554–1558
148. Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. *Pediatrics.* 2001;107(4). Available at: www.pediatrics.org/cgi/content/full/107/4/e63
149. Klug MG, Burd L, Kerbeshian J, Benz B, Martsof JT. A comparison of the effects of parental risk markers on pre- and perinatal variables in multiple patient cohorts with fetal alcohol syndrome, autism, Tourette syndrome, and sudden death syndrome: an enviromic analysis. *Neurotoxicol Teratol.* 2003;25:707–717
150. Badawi N, Dixon G, Felix JF, et al. Autism following a history of newborn encephalopathy: more than a coincidence? *Dev Med Child Neurol.* 2006;48:85–89
151. Glasson EJ, Bower C, Petterson B, De Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. *Arch Gen Psychiatry.* 2004;61:618–627
152. Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. *Am J Epidemiol.* 2005;161:916–928; discussion 926–928
153. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet.* 1998;351:637–641
154. Blaxill MF, Redwood L, Bernard S. Thimerosal and autism? A plausible hypothesis that should not be dismissed. *Med Hypotheses.* 2004;62:788–794
155. Geier DA, Geier MR. Early downward trends in neurodevelopmental disorders following removal of thimerosal-containing vaccines. *J Am Physicians Surg.* 2006;11:8–13

156. Kirby D. *Evidence of Harm: Mercury in Vaccines and the Autism Epidemic—A Medical Controversy*. New York, NY: St Martin's Press; 2005
157. Institute of Medicine, Immunization Safety Review Committee. *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism*. Stratton K, Gable A, Shetty P, McCormick M, eds. Washington, DC: National Academies Press; 2001
158. Richler J, Luyster R, Risi S, et al. Is there a "regressive phenotype" of autism spectrum disorder associated with the measles-mumps-rubella vaccine? A CPEA study. *J Autism Dev Disord*. 2006;36:299–316
159. D'Souza Y, Fombonne E, Ward BJ. No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder [published correction appears in *Pediatrics*. 2006;118:2608]. *Pediatrics*. 2006;118:1664–1675
160. Katz SL. Has the measles-mumps-rubella vaccine been fully exonerated? *Pediatrics*. 2006;118:1744–1745
161. DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsop M, Boyle C. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. *Pediatrics*. 2004;113:259–266
162. Stehr-Green P, Tull P, Stellfeld M, Mortensen PB, Simpson D. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. *Am J Prev Med*. 2003;25:101–106
163. Nelson KB, Bauman ML. Thimerosal and autism? *Pediatrics*. 2003;111:674–679
164. Institute of Medicine, Immunization Safety Review Committee. *Immunization Safety Review: Vaccines and Autism*. Washington, DC: National Academies Press; 2004
165. Harrington JA, Rosen L, Garneco A, Patrick PA. Parental perceptions and use of complementary and alternative medicine practices for children with autistic spectrum disorders in private practice. *J Dev Behav Pediatr*. 2006;27(2 suppl):S156–S161
166. Bauman ML, Kemper TL. Structural brain anatomy in autism: what is the evidence? In: Bauman ML, Kemper TL, eds. *The Neurobiology of Autism*. 2nd ed. Baltimore, MD: Johns Hopkins University Press; 2005:121–135
167. Casanova MF, Buxhoeveden DP, Switala AE, Roy E. Minicolumnar pathology in autism. *Neurology*. 2002;58:428–432
168. Pickett J, London E. The neuropathology of autism: a review. *J Neuropathol Exp Neurol*. 2005;64:925–935
169. Moldin SO, Rubenstein JL, Hyman SE. Can autism speak to neuroscience? *J Neurosci*. 2006;26:6893–6896
170. DiCicco-Bloom E, Lord C, Zwaigenbaum L, et al. The developmental neurobiology of autism spectrum disorder. *J Neurosci*. 2006;26:6897–6906
171. Rodier PM, Arndt TL. The brainstem in autism. In: Bauman ML, Kemper TL, eds. *The Neurobiology of Autism*. 2nd ed. Baltimore, MD: Johns Hopkins University Press; 2005:136–149
172. McCaffery P, Deutsch CK. Macrocephaly and the control of brain growth in autistic disorders. *Prog Neurobiol*. 2005;77:38–56
173. Nelson KB, Nelson PG. Size of the head and brain in autism: clue to underlying biologic mechanisms? In: Bauman ML, Kemper TL, eds. *The Neurobiology of Autism*. 2nd ed. Baltimore, MD: Johns Hopkins University Press; 2005:23–33
174. Courchesne E, Karns CM, Davis HR, et al. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology*. 2001;57:245–254
175. Sparks BF, Friedman SD, Shaw DW, et al. Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*. 2002;59:184–192
176. Courchesne E, Carper R, Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. *JAMA*. 2003;290:337–344
177. Dementieva YA, Vance DD, Donnelly SL, et al. Accelerated head growth in early development of individuals with autism. *Pediatr Neurol*. 2005;32:102–108
178. Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. Effects of age on brain volume and head circumference in autism. *Neurology*. 2002;59:175–183
179. Redcay E, Courchesne E. When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biol Psychiatry*. 2005;58:1–9
180. Nelson KB, Grether JK, Croen LA, et al. Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. *Ann Neurol*. 2001;49:597–606
181. Chugani DC, Muzik O, Behen M, et al. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Ann Neurol*. 1999;45:287–295
182. Lainhart JE. Advances in autism neuroimaging research for the clinician and geneticist. *Am J Med Genet C Semin Med Genet*. 2006;142:33–39
183. Sokol DK, Edwards-Brown M. Neuroimaging in autistic spectrum disorder (ASD). *J Neuroimaging*. 2004;14:8–15
184. Toal F, Murphy DG, Murphy KC. Autistic-spectrum disorders: lessons from neuroimaging. *Br J Psychiatry*. 2005;187:395–397
185. Levitt JG, Blanton RE, Smalley S, et al. Cortical sulcal maps in autism. *Cereb Cortex*. 2003;13:728–735
186. Hardan AY, Jou RJ, Keshavan MS, Varma R, Minshew NJ. Increased frontal cortical folding in autism: a preliminary MRI study. *Psychiatr Res*. 2004;131:263–268
187. Schultz RT. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. *Int J Dev Neurosci*. 2005;23:125–141
188. Brambilla P, Hardan AY, di Nemi SU, et al. The functional neuroanatomy of autism. *Funct Neurol*. 2004;19:9–17
189. Dalton KM, Nacewicz BM, Johnstone T, et al. Gaze fixation and the neural circuitry of face processing in autism. *Nat Neurosci*. 2005;8:519–526
190. Castelli F, Frith C, Happe F, Frith U. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain*. 2002;125:1839–1849
191. Just MA, Cherkassky VL, Keller TA, Minshew NJ. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain*. 2004;127:1811–1821
192. Koshino H, Carpenter PA, Mishew NJ, Cherkassky VL, Keller TA, Just MA. Functional connectivity in an fMRI working memory task in high-functioning autism. *Neuroimage*. 2005;24:810–821
193. Ramachandran VS, Oberman LM. Broken mirrors. *Sci Am*. 2006;295(5):62–69
194. Filipek PA. Neuroimaging in the developmental disorders: the state of the science. *J Child Psychol Psychiatry*. 1999;40:113–128
195. Howlin P, Moorf A. Diagnosis in autism: a survey of over 1200 patients in the UK. *Autism*. 1997;1:135–162
196. Howlin P, Asgharian A. The diagnosis of autism and Asperger syndrome: findings from a survey of 770 families. *Dev Med Child Neurol*. 1999;41:834–839
197. Wetherby AM, Prizant BM, Schuler AL. Understanding the nature of communication and language impairments. In: Wetherby AM, Prizant BM, eds. *Autism Spectrum Disorders*. Baltimore, MD: Paul H. Brookes; 2000:109–141
198. Mundy P, Markus J. On the nature of communication and language impairment in autism. *Ment Retard Dev Disabil Res Rev*. 1997;3:343–349
199. Tuchman RF, Rapin I. Regression in pervasive developmental

- disorders: seizures and epileptiform electroencephalogram correlates. *Pediatrics*. 1997;99:560–566
200. Werner E, Dawson G. Validation of the phenomenon of autistic regression using home videotapes. *Arch Gen Psychiatry*. 2005;62:889–895
 201. Sigman M, Dijamco A, Gratier M, Rozga A. Early detection of core deficits in autism. *Ment Retard Dev Disabil Res Rev*. 2004;10:221–233
 202. Johnson CP. Early clinical characteristics of children with autism. In: Gupta VB, ed. *Autism Spectrum Disorders in Children*. New York, NY: Marcell Dekker; 2004:85–123
 203. Chawarska K, Volkmar FR. Autism in infancy and early childhood. In: Volkmar FR, Klin A, Paul R, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. Vol I. Hoboken, NJ: John Wiley & Sons; 2005:223–246
 204. Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. *Int J Dev Neurosci*. 2005;23:143–152
 205. Maestro S, Muratori F, Cesari A, Pecini C, Apicella F, Stern D. A view to regressive autism through home movies: is early development really normal? *Acta Psychiatr Scand*. 2006;113:68–72
 206. Mitchell S, Brian J, Zwaigenbaum L, Roberts W, Szatmari P, Smith I, Bryson S. Early language and communication development of infants later diagnosed with autism spectrum disorder. *J Dev Behav Pediatr*. 2006;27(2 suppl):S69–S78
 207. Rogers SJ, Bennetto L. Intersubjectivity in autism. In: Wetherby AM, Prizant BM, eds. *Autism Spectrum Disorders*. Baltimore, MD: Paul H. Brookes; 2000:79–107
 208. Turner LM, Stone WL, Pozdol SL, Coonrod EE. Follow-up of children with autism spectrum disorders from age 2 to age 9. *Autism*. 2006;10:243–265
 209. Charman T. Why is joint attention a pivotal skill in autism? *Philos Trans R Soc Lond B Biol Sci*. 2003;358:315–324
 210. Chawarska K, Klin A, Volkmar FR. Automatic attention cueing through eye movement in 2-year-old children with autism. *Child Dev*. 2003;74:1108–1122
 211. Dawson G, Munson J, Estes A. Neurocognitive function and joint attention ability in young children with autism spectrum disorder versus developmental delay. *Child Dev*. 2002;73:345–358
 212. Klin A, Saulnier C, Tsatsanis K, Volkmar FR. Clinical evaluation in autism spectrum disorders: psychological assessment within a transdisciplinary framework. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. Vol II. Hoboken, NJ: John Wiley & Sons; 2005:772–798
 213. Wetherby AM, Woods J, Allen L, Cleary J, Dickinson H, Lord C. Early indicators of autism spectrum disorders in the second year of life. *J Autism Dev Disord*. 2004;34:473–493
 214. Wetherby A, Watt N, Morgan L, Shumway S. Social communication profiles of children with autism spectrum disorders in the second year of life. *J Autism Dev Disord*. 2007;37:960–975
 215. Leekam SR, Ramsden CA. Dyadic orienting and joint attention in preschool children with autism. *J Autism Dev Disord*. 2006;36:185–197
 216. MacDonald R, Anderson J, Dube WV, et al. Behavioral assessment of joint attention: a methodological report. *Res Dev Disabil*. 2006;27:138–150
 217. Mundy P, Card J, Fox N. EEG correlates of the development of infant joint attention skills. *Dev Psychobiol*. 2000;36:325–338
 218. Paparella T, Kasari C. Joint attention skills and language development in special needs populations: translating research to practice. *Infants Young Child*. 2004;17:269–280
 219. Lord C. Follow-up of two-year-olds referred for possible autism. *J Child Psychol Psychiatry*. 1995;36:1365–1382
 220. Mundy P. Joint attention and social-emotional approach behavior in children with autism. *Dev Psychopathol*. 1995;7:63–82
 221. Leekam S, Lopez B. Attention and joint attention in preschool children with autism. *Dev Psychol*. 2000;36:261–273
 222. Wetherby AM, Prizant BM, Hutchinson TA. Communicative, social/affective, and symbolic profiles of young children with autism and pervasive developmental disorders. *Am J Speech Lang Pathol*. 1998;7:79–91
 223. Dawson G, Hill D, Spencer A, Galpert L, Watson L. Affective exchanges between young autistic children and their mothers. *J Abnorm Child Psychol*. 1990;18:335–345
 224. Happé F. Studying weak central coherence at log levels: children with autism do not succumb to visual illusions—a research note. *J Child Psychol Psychiatry*. 1996;37:873–877
 225. Briskman J, Happé F, Frith U. Exploring the cognitive phenotype of autism: weak “central coherence” in parents and siblings of children with autism: II. Real life skills and preferences. *J Child Psychol Psychiatry*. 2001;42:309–316
 226. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a “theory of mind”? *Cognition*. 1985;21:37–46
 227. Twachtman-Cullen D. More able children with autism spectrum disorders. In: Wetherby AM, Prizant BM, eds. *Autism Spectrum Disorders*. Baltimore, MD: Paul H. Brookes; 2000:225–249
 228. Astington JW, Barriault T. Children’s theory of mind: how young children come to understand that people have thoughts and feelings. *Infants Young Child*. 2001;13:1–12
 229. Yirmiya N, Erel O, Shaked M, Solomonica-Levi D. Meta-analysis comparing theory of mind abilities of individual with autism, individuals with mental retardation, and normally developing individuals. *Psychol Bull*. 1998;124:283–307
 230. Baron-Cohen S. *Mindblindness: An Essay on Autism and Theory of Mind*. Cambridge, MA: MIT Press; 1995
 231. Arik JR, Krug DA, Fullerton A, Loos L, Falco R. School-based programs. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. vol 2. Hoboken, NJ: John Wiley & Sons; 2005:1003–1028
 232. Stone WL, Lee EB, Ashford L, et al. Can autism be diagnosed accurately in children under 3 years? *J Child Psychol Psychiatry*. 1999;40:219–226
 233. Schroeder SR, Oster-Granite ML, Berkson G, et al. Self-injurious behavior. *Ment Retard Dev Disabil Res Rev*. 2001;7:3–11
 234. Volkmar F, Cook EH Jr, Pomeroy J, Realmuto G, Tanguay P. Practice parameters for the assessment and treatment of children, adolescents, and adults with autism and other pervasive developmental disorders. American Academy of Child and Adolescent Psychiatry, Working Group on Quality Issues [published correction appears in *J Am Acad Child Adolesc Psychiatry*. 2000;39:938]. *J Am Acad Child Adolesc Psychiatry*. 1999;38(12 suppl):32S–54S
 235. Williams DL, Goldstein G, Carpenter PA, Minschew NJ. Verbal and spatial working memory in autism. *J Autism Dev Disord*. 2005;35:747–756
 236. Grandin T, Scariano MM. *Emergence, Labeled Autistic*. Novato, CA: Arena Press; 1986
 237. CBS News. A school, a team, a dream. March 2, 2006. Available at: <http://www.cbsnews.com/stories/2006/03/02/eveningnews/main1364675.shtml>. Accessed March 19, 2007
 238. Treffert DA. The autistic artist, “special faculties,” and savant syndrome. *Arch Pediatr Adolesc Med*. 2007;161:32
 239. Rogers SJ, Ozonoff S. Annotation: what do we know about sensory dysfunction in autism? A critical review of the empirical evidence. *J Child Psychol Psychiatry*. 2005;46:1255–1268

240. Anzalone ME, Williamson GG. Sensory processing and motor performance in autism spectrum disorders. In: Wetherby AM, Prizant BM, eds. *Autism Spectrum Disorders*. Baltimore, MD: Paul H. Brookes; 2000:143–166
241. Iarocci G, McDonald J. Sensory integration and the perceptual experience of persons with autism. *J Autism Dev Disord*. 2006;36:77–90
242. Gillberg C, Kadesjo B. Why bother about clumsiness? The implications of having developmental coordination disorder (DCD). *Neural Plast*. 2003;10:59–68
243. Gadow KD, DeVincent CJ, Pomeroy J. ADHD symptom subtypes in children with pervasive developmental disorder. *J Autism Dev Disord*. 2006;36:271–283
244. Frith U, Soares I. Research into earliest detectable signs of autism: what parents say. *Communication*. 1993;27:17–18
245. Siegel B, Pliner C, Eschler J, Elliott GR. How children with autism are diagnosed: difficulties in identification of children with multiple developmental delays. *J Dev Behav Pediatr*. 1988;9:199–204
246. American Academy of Pediatrics, Council on Children With Disabilities, Section on Developmental and 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;119:1808–1809]. *Pediatrics*. 2006;118:405–420
247. Glascoe FP. Evidence-based approach to developmental and behavioural surveillance using parents' concerns. *Child Care Health Dev*. 2000;26:137–149
248. Glascoe FP, Dworkin PH. The role of parents in the detection of developmental and behavioral problems. *Pediatrics*. 1995;95:829–836
249. Young KT, Davis K, Schoen C, Parker S. Listening to parents: a national survey of parents with young children. *Arch Pediatr Adolesc Med*. 1998;152:255–262
250. King TM, Glascoe FP. Developmental surveillance of infants and young children in pediatric primary care. *Curr Opin Pediatr*. 2003;15:624–629
251. Palomo R, Belinchon M, Ozonoff S. Autism and family home movies: a comprehensive review. *J Dev Behav Pediatr*. 2006;27(2 suppl):S59–S68
252. Nadig AS, Ozonoff S, Young GS, Rozga A, Sigman M, Rogers SJ. A prospective study of response to name in infants at risk for autism. *Arch Pediatr Adolesc Med*. 2007;161:378–383
253. Stone WL, McMahon CR, Yoder PJ, Walden TA. Early social-communicative and cognitive development of younger siblings of children with autism spectrum disorders. *Arch Pediatr Adolesc Med*. 2007;161:384–390
254. Johnson CP, Blasco PA. Infant growth and development. *Pediatr Rev*. 1997;18:224–242
255. Johnson CP. Recognition of autism spectrum disorders before age 2 years. *Pediatr Rev*. 2008; In press
256. Smith RD. The use of developmental screening tests by primary care pediatricians. *J Pediatr*. 1978;93:524–527
257. Werner EE, Honzik MP, Smith RS. Prediction of intelligence and achievement at ten years from twenty months pediatric and psychologic evaluations. *Child Dev*. 1968;39:1063–1075
258. Sand N, Silverstein M, Glascoe FP, Gupta VB, Tonniges TP, O'Connor KG. Pediatricians' reported practices regarding developmental screening: do guidelines work? Do they help? *Pediatrics*. 2005;116:174–179
259. Sices L, Feudtner C, McLaughlin J, Drotar D, Williams M. How do primary care physicians identify young children with developmental delays? A national survey. *J Dev Behav Pediatr*. 2003;24:409–417
260. Gupta VB, Hyman SL, Johnson CP, et al. Identifying children with autism early [published correction appears in *Pediatrics*. 2007;119:867]. *Pediatrics*. 2007;119:152–153
261. Wetherby AM, Prizant BM. *Communication and Symbolic Behavior Scales Developmental Profile (CSBS DP): First Normed Edition*. Baltimore, MD: Paul H. Brookes; 2002
262. Dietz C, Swinkels S, van Daalen E, van Engeland H, Buitelaar JK. Screening for autistic spectrum disorder in children aged 14–15 months. II: population screening with the Early Screening of Autistic Traits Questionnaire (ESAT)—design and general findings. *J Autism Dev Disord*. 2006;36:713–722
263. Swinkels SH, Dietz C, van Daalen E, Kerkhof IH, van Engeland H, Buitelaar JK. Screening for autistic spectrum disorder in children aged 14 to 15 months. I: The development of the Early Screening of Autistic Traits Questionnaire (ESAT). *J Autism Dev Disord*. 2006;36:723–732
264. Coonrod EE, Stone WL. Screening for autism in young children. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. Vol 2. Hoboken, NJ: John Wiley & Sons; 2005:707–729
265. Lord C, Corsello C. Diagnostic instruments in autistic spectrum disorders. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. Vol II. Hoboken, NJ: John Wiley & Sons; 2005:730–771
266. Camp BW. What the clinician really wants to know: questioning the clinical usefulness of sensitivity and specificity in studies of screening tests. *J Dev Behav Pediatr*. 2006;27:226–230
267. Baron-Cohen S, Allen J, Gillberg C. Can autism be detected at 18 months? The needle, the haystack, and the CHAT. *Br J Psychiatry*. 1992;161:839–843
268. Robins D, Fein D, Barton M, Green JA. The Modified-Checklist for Autism in Toddlers (M-CHAT): an initial investigation in the early detection of autism and pervasive developmental disorders. *J Autism Dev Disord*. 2001;31:131–144
269. Siegel B. *The Pervasive Developmental Disorders Screening Test II (PDDST-II)*. San Antonio, TX: Harcourt Assessment; 2004
270. Campbell JM. Diagnostic assessment of Asperger's disorder: a review of five third-party rating scales. *J Autism Dev Disord*. 2005;35:25–35
271. Williams J, Scott F, Stott C, et al. The CAST (Childhood Asperger Syndrome Test): test accuracy. *Autism*. 2005;9:45–68
272. Baron-Cohen S, Cox A, Baird G. Psychological markers in the detection of autism in infancy in a large population. *Br J Psychiatry*. 1996;168:158–163
273. Scambler D, Rogers SJ, Wehner EA. Can the Checklist for Autism in Toddlers differentiate young children with autism from those with developmental delays? *J Am Acad Child Adolesc Psychiatry*. 2001;40:1457–1463
274. Wong V, Hui LH, Lee WC, et al. A modified screening tool for autism (Checklist for Autism in Toddlers [CHAT-23]) for Chinese children. *Pediatrics*. 2004;114(2). Available at: www.pediatrics.org/cgi/content/full/114/2/e166
275. Scott FJ, Baron-Cohen S, Bolton P, Brayne C. The CAST (Childhood Asperger Syndrome Test): preliminary development of a UK screen for mainstream primary-school age children. *Autism*. 2002;6:9–31
276. Williams J, Allison C, Scott F, et al. The Childhood Asperger Syndrome Test (CAST): test-retest reliability. *Autism*. 2006;10:415–427
277. Dumont-Mathieu T, Fein D. Screening for autism in young children: the Modified Checklist for Autism in Toddlers (M-CHAT) and other measures. *Ment Retard Dev Disabil Res Rev*. 2005;11:253–262
278. Myles B, Bock S, Simpson R. *Asperger Syndrome Diagnostic Scale*. Los Angeles, CA: Western Psychological Services; 2001

279. Krug DA, Arick J, Almond P. Behavior checklist for identifying severely handicapped individuals with high levels of autistic behavior. *J Child Psychol Psychiatry*. 1980;21:221–229
280. Baron-Cohen S, Hoekstra RA, Knickmeyer R, Wheelwright S. The Autism-Spectrum Quotient (AQ): adolescent version. *J Autism Dev Disord*. 2006;36:343–350
281. Ehlers S, Gillberg C, Wing L. A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. *J Autism Dev Disord*. 1999;29:129–141
282. Eaves RC, Milner B. The criterion-related validity of the Childhood Autism Rating Scale and the Autism Behavior Checklist. *J Abnorm Child Psychol*. 1993;21:481–491
283. Perry A, Condillac RA, Freeman NL, Dunn-Geier J, Belair J. Multi-site study of the Childhood Autism Rating Scale (CARS) in five clinical groups of young children. *J Autism Dev Disord*. 2005;35:625–634
284. Schopler E, Reichler RJ, Rochen Renner B. *The Childhood Autism Rating Scale (CARS)*. Los Angeles, CA: Western Psychological Services; 1988
285. Sevin JA, Matson JL, Coe DA, Fee VE, Sevin BM. A comparison and evaluation of three commonly used autism scales. *J Autism Dev Disord*. 1991;21:417–432
286. Gilliam JE. *Gilliam Asperger's Disorder Scale (GADS)*. Austin, TX: Pro-Ed; 2001
287. Gilliam JE. *Gilliam Autism Rating Scale 2nd Edition (GARS-2)*. Austin, TX: Pro-Ed; 2006
288. Krug DA, Arick JR. *Krug Asperger's Disorder Index (KADI)*. Austin, TX: Pro-Ed; 2003
289. Stone WL, Coonrod EE, Ousley OY. Brief report: Screening Tool for Autism in Two-Year-Olds (STAT): development and preliminary data. *J Autism Dev Disord*. 2000;30:607–612
290. Stone WL, Coonrod EE, Turner LM, Pozdol SL. Psychometric properties of the STAT for early autism screening. *J Autism Dev Disord*. 2004;34:691–701
291. Berument SK, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. *Br J Psychiatry*. 1999;175:444–451
292. Rutter M, Bailey A, Lord C, et al. *The Social Communication Questionnaire (SCQ) Manual*. Los Angeles, CA: Western Psychological Services; 2003
293. Myers SM, Johnson CP. Autism spectrum disorders. In: Wolraich ML, Dworkin PH, Drotar DD, Perrin EC, eds. *Developmental and Behavioral Pediatrics*. Philadelphia, PA: Elsevier; 2007: In press
294. American Speech-Language-Hearing Association. Position statement: roles and responsibilities of speech-language pathologists in diagnosis, assessment, and treatment of autism spectrum disorders across the life span. Available at: www.asha.org/NR/rdonlyres/4C2593BF-6920-4B44-BD0D-6067A65AEDDB/0/v3PS_autismL.Span.pdf. Accessed March 19, 2007
295. American Speech-Language-Hearing Association. Technical Report: principles for speech-language pathologists in diagnosis, assessment, and treatment of autism spectrum disorders across the life span. Available at: www.asha.org/NR/rdonlyres/D0370FEA-98EF-48EE-A9B6-952913FB131B/0/v3TR_autismL.Span.pdf. Accessed March 19, 2007
296. Moeschler JB, Shevell M; American Academy of Pediatrics, Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. *Pediatrics*. 2006;117:2304–2316
297. Filipek PA. Medical aspects of autism. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. Vol 1. Hoboken, NJ: John Wiley & Sons; 2005:534–581
298. Scahill L. Diagnosis and evaluation of pervasive developmental disorders. *J Clin Psychiatry*. 2005;66:19–25
299. Voigt RG, Childers DO, Dickerson CL, et al. Early pediatric neurodevelopmental profile of children with autistic spectrum disorders. *Clin Pediatr (Phila)*. 2000;39:663–668
300. Barbaresi WJ, Katusic SK, Voigt RG. Autism: a review of the state of the science for pediatric primary health care clinicians. *Arch Pediatr Adolesc Med*. 2006;160:1167–1175
301. McMahon WM, Baty BJ, Botkin J. Genetic counseling and ethical issues for autism. *Am J Med Genet C Semin Med Genet*. 2006;142:52–57
302. Challman TD, Barbaresi WJ, Katusic SK, Weaver A. The yield of the medical evaluation of children with pervasive developmental disorders. *J Autism Dev Disord*. 2003;33:187–192
303. Myers SM, Johnson CP; American Academy of Pediatrics, Council on Children With Disabilities. Management of children with autism spectrum disorders. *Pediatrics*. 2007;120:1162–1182
304. Srour M, Mazer B, Shevell MI. Analysis of clinical features predicting etiologic yield in the assessment of global developmental delay. *Pediatrics*. 2006;118:139–145
305. Keller K, Williams C, Wharton P, et al. Routine cytogenetic and FISH studies for 17p11/15q11 duplications and subtelomeric rearrangement studies in children with autism spectrum disorders. *Am J Med Genet A*. 2003;117:105–111
306. Lobo-Menendez F, Sossey-Alaoui K, Bell JM, et al. Absence of *McCP2* mutations in patients from the South Carolina autism project. *Am J Med Genet B Neuropsychiatr Genet*. 2003;117:97–101
307. Gillberg C. Subgroups in autism: are there behavioural phenotypes typical of underlying medical conditions? *J Intellect Disabil Res*. 1992;36:201–214
308. Gillberg C, Coleman M. Autism and medical disorders: a review of the literature. *Dev Med Child Neurol*. 1996;38:191–202
309. Schaefer GB, Lutz RE. Diagnostic yield in the clinical genetic evaluation of autism spectrum disorders. *Genet Med*. 2006;8:549–556
310. Abdul-Rahman OA, Hudgins L. The diagnostic utility of a genetics evaluation in children with pervasive developmental disorders. *Genet Med*. 2006;8:50–54
311. Curry CJ, Stevenson RE, Aughton D, et al. Evaluation of mental retardation: recommendations of a consensus conference: American College of Medical Genetics. *Am J Med Genet*. 1997;72:468–477
312. Roberts G, Palfrey J, Bridgemohan C. A rational approach to the medical evaluation of a child with developmental delay. *Contemp Pediatr*. 2004;21:76–100
313. Ravnani JB, Tepperberg JH, Papenhausen P, et al. Subtelomere FISH analysis of 11 688 cases: an evaluation of the frequency and pattern of subtelomere rearrangements in individuals with developmental disabilities. *J Med Genet*. 2006;43:478–489
314. Manning MA, Cassidy SB, Clericuzio C, et al. Terminal 22q deletion syndrome: a newly recognized cause of speech and language disability in the autism spectrum. *Pediatrics*. 2004;114:451–457
315. Fine SE, Weissman A, Gerdes M, et al. Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. *J Autism Dev Disord*. 2005;35:461–470
316. Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy Behav*. 2006;8:267–271
317. Kagan-Kushnir T, Roberts SW, Snead OC. Screening electroencephalograms in autism spectrum disorders: evidence-based guideline. *J Child Neurol*. 2005;20:197–206

318. Mantovani J. Regression and seizures. Presented at: the Spectrum of Developmental Disabilities XXVIII: Autism—From Kanner to Current; March 27–29, 2006; Baltimore, MD
319. Mao R, Pevsner J. The use of genomic microarrays to study chromosomal abnormalities in mental retardation. *Ment Retard Dev Disabil Res Rev*. 2005;11:279–285
320. Charman T, Taylor E, Drew A, Cockerill H, Brown JA, Baird G. Outcome at 7 years of children diagnosed with autism at age 2: predictive validity of assessments conducted at 2 and 3 years of age and pattern of symptom change over time. *J Child Psychol Psychiatry*. 2005;46:500–513
321. Sigman M, McGovern CW. Improvement in cognitive and language skills from preschool to adolescence in autism. *J Autism Dev Disord*. 2005;35:15–23
322. Lotter V. Follow-up studies. In: Rutter M, Schopler E, eds. *Autism: A Reappraisal of Concepts and Treatment*. New York, NY: Plenum Press; 1978:475–495
323. Gillberg C, Steffenburg S. Outcome and prognostic factors in infantile autism and similar conditions: a population-based study of 46 cases followed through puberty. *J Autism Dev Disord*. 1987;17:273–287
324. Stevens MC, Fein DA, Dunn M, et al. Subgroups of children with autism by cluster analysis: a longitudinal examination. *J Am Acad Child Adolesc Psychiatry*. 2000;39:346–352
325. Coplan J. Counseling parents regarding prognosis in autistic spectrum disorder. *Pediatrics*. 2000;105(5). Available at: www.pediatrics.org/cgi/content/full/105/5/e65
326. Szatmari P, Merette C, Bryson SE, et al. Quantifying dimensions in autism: a factor analytic study. *J Am Acad Child Adolesc Psychiatry*. 2002;41:467–474
327. Seltzer MM, Krauss MW, Shattuck PT, Orsmond G, Swe A, Lord C. The symptoms of autism spectrum disorders in adolescence and adulthood. *J Autism Dev Disord*. 2003;33:565–581
328. Coplan J. Atypicality, intelligence, and age: a conceptual model of autistic spectrum disorder. *Dev Med Child Neurol*. 2003;45:712–716
329. Howlin P, Goode S, Hutton J, Rutter M. Adult outcome for children with autism. *J Child Psychol Psychiatry*. 2004;45:212–229
330. Seltzer MM, Shattuck P, Abbeduto L, Greenberg JS. Trajectory of development in adolescents and adults with autism. *Ment Retard Dev Disabil Res Rev*. 2004;10:234–247
331. Howlin P, Goode S. Outcome in adult life for people with autism and Asperger's syndrome. In: Volkmar FR, ed. *Autism and Pervasive Developmental Disorders*. New York, NY: Cambridge University Press; 1998:209–241
332. Szatmari P, Bryson SE, Boyle MH, Streiner DL, Duku E. Predictors of outcome among high functioning children with autism and Asperger syndrome. *J Child Psychol Psychiatry*. 2003;44:520–528
333. Coplan J, Jawad AF. Modeling clinical outcome of children with autistic spectrum disorders. *Pediatrics*. 2005;116:117–122
334. Howlin P. Outcome in high-functioning adults with autism with and without early language delays: implications for the differentiation between autism and Asperger syndrome. *J Autism Dev Disord*. 2003;33:3–13

RESOURCE FOR FAMILIES

American Academy of Pediatrics. *Autism: Caring for Children With Autism Spectrum Disorders: A Resource Toolkit for Clinicians*. Elk Grove Village, IL: American Academy of Pediatrics; 2007

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