American Academy of Pediatrics
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CLINICAL REPORT

Identification and Evaluation of Children With Autism Spectrum Disorders

Guidance for the Clinician in Rendering Pediatric Care

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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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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 article[16] 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-TR[4] (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 multisite, 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 diagnostic 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-IV[3] 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-

TR[4] 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 1990[57] 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 proportion 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), fibroangiomata, 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.
- Phenylketonuria[118]: 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 syndrome[119]: 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 syndrome[131]: 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* gene[132]) 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 disorders[137] and psoriasis[138]); 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 al[150] 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) vaccine[153] and mercury-containing vaccines.[154–156] In 2001, the Institute of Medicine[157] 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 neuroimaging 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 periphery[167];
- 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 findings[187] 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 referencing[222] 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-Cohen[230] coined the term "mindblindedness" 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 rotely 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 "language" 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 prespeech 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-TR[4] 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 stereotypies. Stereotypies are repetitive, nonfunctional, atypical behaviors such as hand flapping, finger movements, rocking, or twirling.[3,4,203] Although most stereotypies are harmless, they are problematic in that they may prevent the child from accomplishing a task or learning new skills. Although stereotypies 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 stereotypies. Even typically developing toddlers, especially before the onset of fluent language, may flap their arms briefly when they are excited or frustrated. Stereotypies associated with ASDs often do not appear until after 3 years of age[232] 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 algorithm[246]).

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 called[252]; 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 jargoning; 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

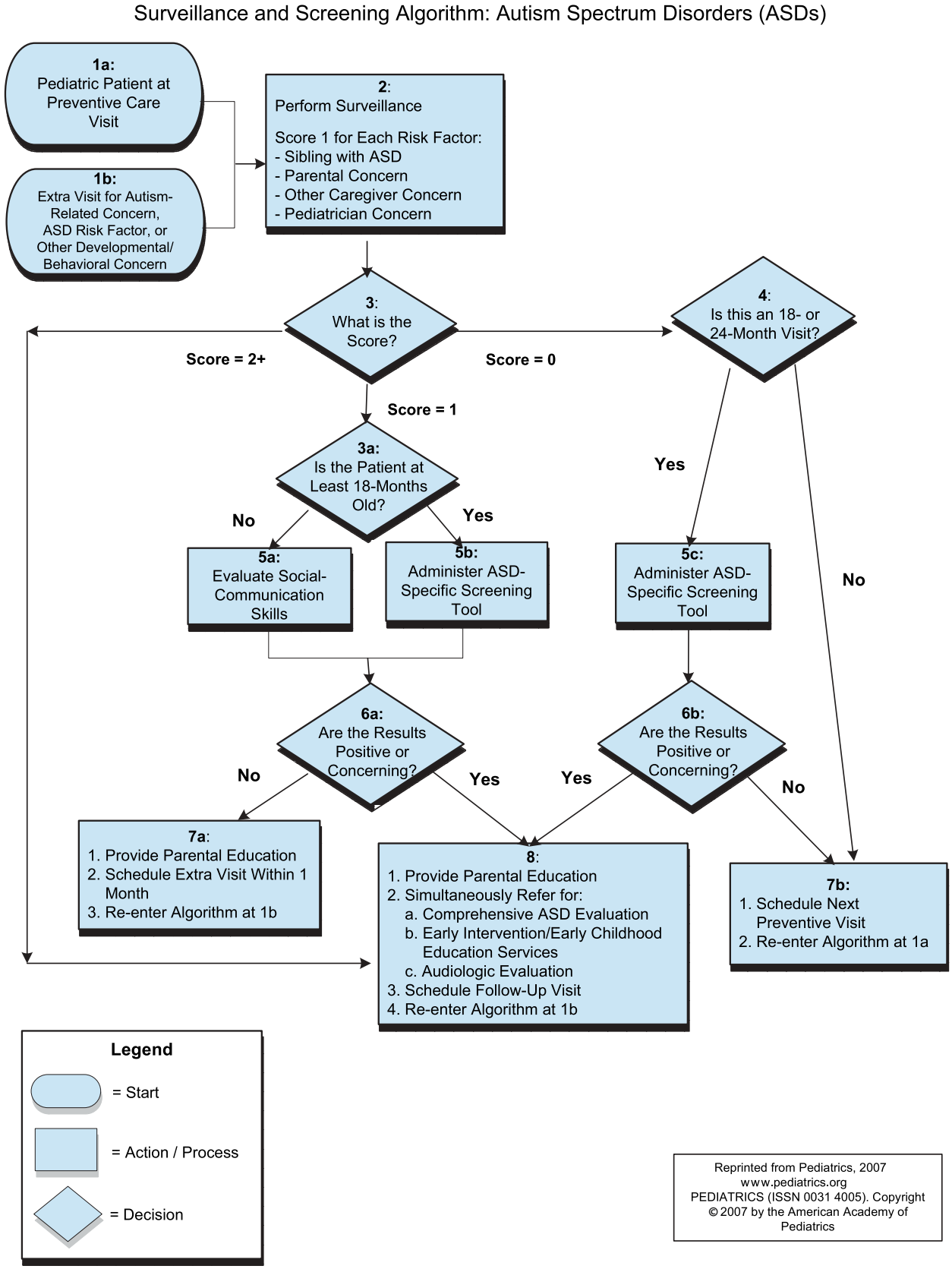

FIGURE 1
Surveillance and screening algorithm: ASDs.

Surveillance and Screening Algorithm: Autism Spectrum Disorders (ASDs)

1a: Pediatric Patient at Preventive Care Visit

1a - Developmental concerns, including those about social skill deficits, should be included as one of several health topics addressed at each pediatric preventive care visit through the first 5 years of life. *(Go to step 2)*

1b: Extra Visit for Autism-Related Concern, ASD Risk Factor, or Other Developmental/ Behavioral Concern

1b – At the parents' request, or when a concern is identified in a previous visit, a child may be scheduled for a "problem-targeted" clinic visit because of concerns about ASD. Parent concerns may be based on observed behaviors, social or language deficits, issues raised by other caregivers, or heightened anxiety produced by ASD coverage in the media. *(Go to step 2)*

2:
Perform Surveillance

Score 1 for Each Risk Factor:
- Sibling with ASD
- Parental Concern
- Other Caregiver Concern
- Pediatrician Concern

2 - Developmental surveillance is a flexible, longitudinal, continuous, and cumulative process whereby health care professionals identify children who may have developmental problems. There are 5 components of developmental surveillance: eliciting and attending to the parents' concerns about their child's development, documenting and maintaining a developmental history, making accurate observations of the child, identifying the risk and protective factors, and maintaining an accurate record and documenting the process and findings. The concerns of parents, other caregivers, and pediatricians all should be included in determining whether surveillance suggests that the child may be at risk of an ASD. In addition, younger siblings of children with an ASD should also be considered at risk, because they are 10 times more likely to develop symptoms of an ASD than children without a sibling with an ASD. Scoring risk factors will help determine the next steps. *(Go to step 3)*

For more information on developmental surveillance, see "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening" (*Pediatrics* 2006;118:405-420).

3: What is the Score?

3 - Scoring risk factors:
- If the child does not have a sibling with an ASD and there are no concerns from the parents, other caregivers, or pediatrician: Score=0 *(Go to step 4)*
- If the child has only 1 risk factor, either a sibling with ASD or the concern of a parent, caregiver, or pediatrician: Score=1 *(Go to step 3a)*
- If the child has 2 or more risk factors: Score=2+ *(Go to step 8)*

3a: Is the Patient at Least 18-Months Old?

3a –
- If the child's age is <18 months, *Go to step 5a*
- If the child's age is ≥18 months, *Go to step 5b*

4: Is this an 18- or 24-Month Visit?

4 – In the absence of established risk factors and parental/provider concerns (score=0), a level-1 ASD-specific tool should be administered at the 18- and 24-month visits. *(Go to step 5c)* If this is not an 18- or 24-month visit, *(Go to step 7b).*

Note: In the AAP policy, "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening", a general developmental screen is recommended at the 9-, 18-, and 24-or 30-month visits and an ASD screening is recommended at the 18-month visit. This clinical report also recommends an ASD screening at the 24-month visit to identify children who may regress after 18 months of age.

5a: Evaluate Social-Communication Skills

5a - If the child's age is <18 months, the pediatrician should use a tool that specifically addresses the clinical characteristics of ASDs, such as those that target social-communication skills. *(Go to step 6a)*

5b: Administer ASD-Specific Screening Tool

5b - If the child's age is ≥18 months, the pediatrician should use an ASD-specific screening tool. *(Go to step 6a)*

5c: Administer ASD-Specific Screening Tool

5c – For all children ages 18 or 24 months (regardless of risk factors), the pediatrician should use an ASD-specific screening tool. *(Go to step 6b)*

AAP-recommended strategies for using ASD screening tools: *"Autism: Caring for Children with Autism Spectrum Disorders: A Resource Toolkit for Clinicians" (in press)**

6a: Are the Results Positive or Concerning?

6a – When the result of the screening is *negative*, *Go to step 7a*

When the result of the screening is *positive*, *Go to step 8*

6b: Are the Results Positive or Concerning?

6b – When the result of the ASD screening (at 18- and 24-month visits) is *negative, Go to step 7b*

When the result of the ASD screening (at 18- and 24-month visits) is *positive*, *Go to step 8*

7a:
1. Provide Parental Education
2. Schedule Extra Visit Within 1 Month
3. Re-enter Algorithm at 1b

7a – If the child demonstrates risk but has a negative screening result, information about ASDs should be provided to parents. The pediatrician should schedule an extra visit within 1 month to address any residual ASD concerns or additional developmental/ behavioral concerns after a negative screening result. The child will then re-enter the algorithm at 1b. A "wait-and-see" approach is discouraged. If the only risk factor is a sibling with an ASD, the pediatrician should maintain a higher index of suspicion and address ASD symptoms at each preventive care visit, but an early follow-up within 1 month is not necessary unless a parental concern subsequently arises.

7b:
1. Schedule Next Preventive Visit
2. Re-enter Algorithm at 1a

7b – If this is not an 18- or 24-month visit, or when the result of the ASD screening is *negative*, the pediatrician can inform the parents and schedule the next routine preventive visit. The child will then re-enter the algorithm at 1a.

8:
1. Provide Parental Education
2. Simultaneously Refer for:
   a. Comprehensive ASD Evaluation
   b. Early Intervention/Early Childhood Education Services
   c. Audiologic Evaluation
3. Schedule Follow-up Visit
4. Re-enter Algorithm at 1b

8 – If the screening result is *positive* for possible ASD in step 6a or 6b, the pediatrician should provide peer reviewed and/or consensus-developed ASD materials. Because a positive screening result does not determine a diagnosis of ASD, the child should be referred for a comprehensive ASD evaluation, to early intervention/early childhood education services (depending on child's age), and an audiologic evaluation. A categorical diagnosis is not needed to access intervention services. These programs often provide evaluations and other services even before a medical evaluation is complete. A referral to intervention services or school also is indicated when other developmental/behavioral concerns exist, even though the ASD screening result is negative. The child should be scheduled for a follow-up visit and will then re-enter the algorithm at 1b. All communication between the referral sources and the pediatrician should be coordinated.

AAP information for parents about ASDs includes: "*Is Your One-Year-Old Communicating with You*?*" and *"Understanding Autism Spectrum Disorders.**"

*Available at www.aap.org

FIGURE 1
Continued

Child Neurology Society practice parameter on screening and diagnosis of autism[107] 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-

mentary[260] 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 Profile[261] (which can be downloaded at www.brookespublishing.com/store/books/wetherby-csbsdp/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[268]	Download: www.dbpeds.org/media/mchat.pdf or www.firstsigns.org/downloads/m-chat.pdf; for scoring: www.firstsigns.org/downloads/m-chat_scoring.PDF
Pervasive Developmental Disorders Screening Test-II, Primary Care Screener (PDDST-II PCS)	18–48 mo	Questionnaire completed by parent (22)	10–15	0.92[c]	0.91[c]	Siegel[269]	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)
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]	Download: www.autismresearchcentre.com/tests/aq_adolescent_test.asp
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]	Questions are included as an appendix in 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]	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 Arick,[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 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; 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 myelinization 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 myelinization 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-unturned" 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, neuroligin 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 24[260] 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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RESOURCE FOR FAMILIES

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