



Practice parameter: Screening and diagnosis of autism

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society

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Article abstract—Autism is a common disorder of childhood, affecting 1 in 500 children. Yet, it often remains unrecognized and undiagnosed until or after late preschool age because appropriate tools for routine developmental screening and screening specifically for autism have not been available. Early identification of children with autism and intensive, early intervention during the toddler and preschool years improves outcome for most young children with autism. This practice parameter reviews the available empirical evidence and gives specific recommendations for the identification of children with autism. This approach requires a dual process: 1) routine developmental surveillance and screening specifically for autism to be performed on all children to first identify those at risk for any type of atypical development, and to identify those specifically at risk for autism; and 2) to diagnose and evaluate autism, to differentiate autism from other developmental disorders.

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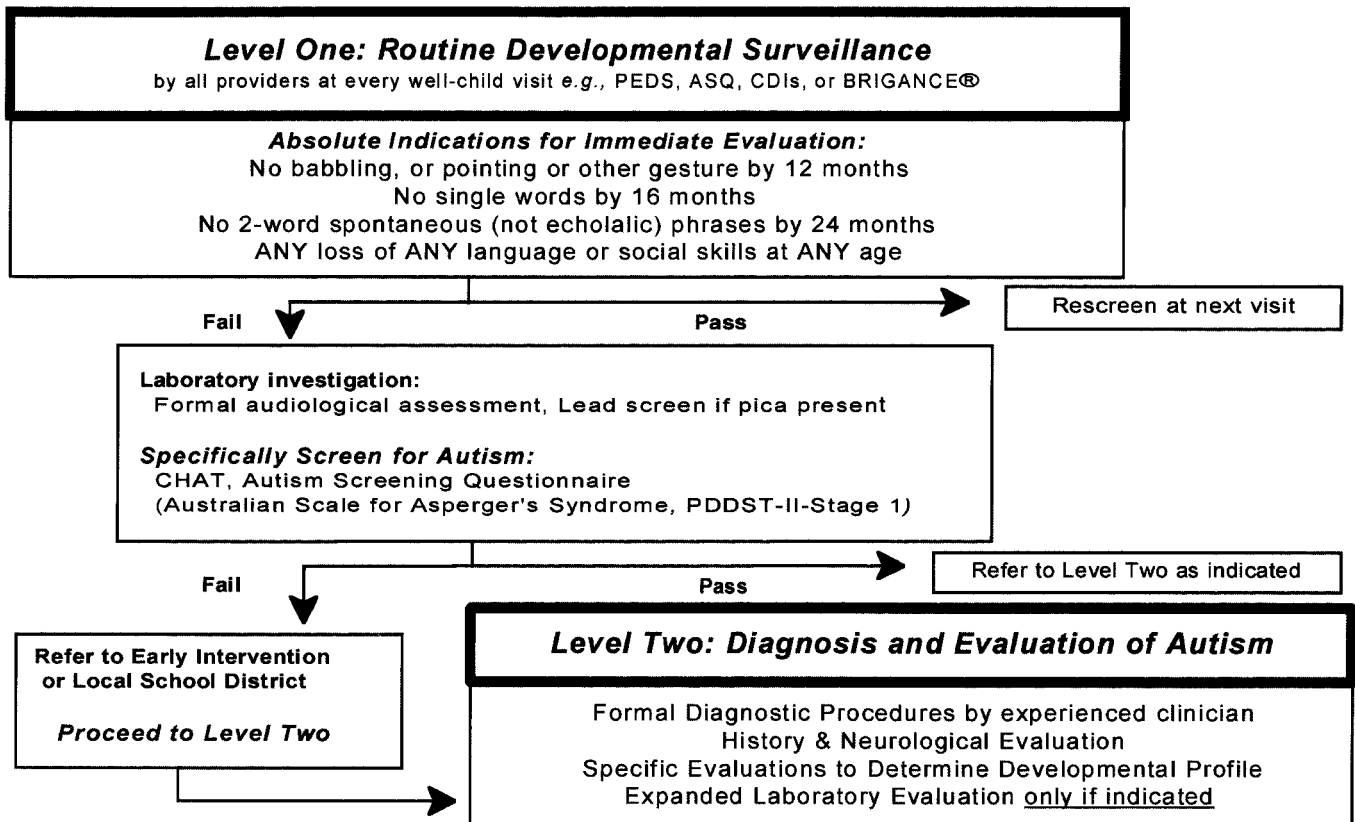


Figure. Practice parameter algorithm.

Autism, autistic spectrum, and pervasive developmental disorders encompass a wide continuum of associated cognitive and neurobehavioral disorders, including the core-defining features of impaired socialization, impaired verbal and nonverbal communication, and restricted and repetitive patterns of behavior (table).¹ Between 60,000 and 115,000 children under 15 years of age in the United States meet diagnostic criteria for autism based on recent prevalence estimates of 10 to 20 cases per 10,000 people. In 1,300 families recently surveyed, the average age at diagnosis of autism was about 6 years, despite the fact that most parents felt something was wrong by 18 months of age and usually sought medical assistance by age 2 years.² Fewer than 10% of the children were diagnosed at initial presentation; another 10% were either told to return if their worries persisted, or that their child “would grow out of it.” The rest were referred to another professional (at a mean age of 40 months), of which only 40% were given a formal diagnosis, 25% were told “not to worry,” and 25% were referred to a third or fourth professional. Almost 20% reported that they either had to exert considerable pressure to obtain the referrals or pay privately. Over 30% of parents referred to subsequent professionals reported that no help was offered (e.g., with education, therapy, or referrals to parent support groups), and only about 10% reported that a professional explained their child’s problems. Almost

half of the families reported that the school system and other parents were the major source of assistance over time, rather than the medical health care community.

The diagnosis of autism often is not made until 2 to 3 years after symptoms are recognized, primarily because of concerns about labeling or incorrectly diagnosing the child. Identifying children with autism and initiating intensive, early intervention during the preschool years results in improved outcomes for most young children with autism.³⁻⁷ Early diagnosis of autism and early intervention facilitates earlier educational planning, provisions for family supports and education, management of family stress and anguish, and delivery of appropriate medical care and treatment.³⁻⁷

Clinically identifying children with autism requires two levels of investigation, each addressing a distinct component of patient management (figure).¹ The first level, *Routine Developmental Surveillance and Screening Specifically for Autism*, should be performed on all children and involves first identifying those at risk for any type of atypical development, followed by identifying those specifically at risk for autism. Mental retardation or other medical or neurodevelopmental conditions require separate evaluations and are not within the scope of this document.

The second level, *Diagnosis and Evaluation of Autism*, involves a more in-depth investigation of already identified children and differentiates autism from other developmental disorders. In-depth diagnosis and

Table Diagnostic Criteria for 299.00 Autistic Disorder

A. A total of six (or more) items from (1), (2), and (3), with two from (1), and at least one each from (2) and (3):

1. Qualitative impairment in social interaction, manifest by at least two of the following:
 - 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
 - Failure to develop peer relationships appropriate to developmental level
 - Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by lack of showing, bringing, or pointing out objects of interest)
 - Lack of social or emotional reciprocity
2. Qualitative impairment in communication, as manifest by at least one of the following:
 - 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)
 - In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
 - Stereotyped and repetitive use of language, or idiosyncratic language
 - Lack of varied, spontaneous make-believe, or social imitative play appropriate to developmental level
3. Restrictive repetitive and stereotypic patterns of behavior, interests, and activities, as manifested by at least one of the following:
 - Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
 - Apparently inflexible adherence to specific nonfunctional routines or rituals
 - Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
 - Persistent preoccupation with parts of objects.

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:

1. Social interaction
2. Language as used in social communication
3. Symbolic or imaginative play

C. The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.

The other pervasive developmental disorders include Asperger's disorder, Rett syndrome, childhood disintegrative disorder, pervasive developmental disorder—not otherwise specified (PDD-NOS), or atypical autism.

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Detailed information on other PDD diagnoses can be found in the comprehensive background paper.¹

evaluation are important in determining optimal interventional strategies based on the child's profile of strengths and weaknesses. For these two areas of in-

vestigation, specific clinical questions were defined (see Appendix 2), clinical evidence was summarized, and diagnostic recommendations were developed.

Evidence and recommendations are presented in three sections. The first two sections, *Level One: Routine Developmental Surveillance and Screening Specifically for Autism*, and *Level Two: Diagnosis and Evaluation of Autism*, first present the empiric data for each question and are followed by recommendations linked to the specific evidence. Each is followed by a section on *Recommendations for Research*. The third section, *Consensus-Based General Principles of Management*, presents additional recommendations based on broad consensus. Additional information about autism, including behavioral aspects associated with the core defining deficits, methodology, and clinical evidence are described in the background paper.¹ Specific information about the recommended developmental screening and diagnostic tools can be found at <http://www.aan.com> under *AAN Resources: Practice Statements: Official AAN Practice Statements: Autism, Screening and diagnosis of*.

Description of the process. Experts in the surveillance/screening and diagnosis of autism were selected by 11 professional organizations (see Appendix 1) and convened in June 1998 and January 1999. They reviewed and evaluated the quality of the evidence from the published literature, developed a consensus of evidence-based management recommendations, and published a comprehensive background paper on the surveillance, screening, and diagnosis of autism.¹ Evidence reviewed for this parameter was identified through literature searches using MEDLINE and PsychINFO. Relevant articles were included from all languages using the following search terms: autistic; OR autism; OR pervasive, and NOT treatment. This search produced over 4,000 citations, from which 2,750 studies met the following inclusion criteria: clinical papers published since 1990; review papers and meta-analyses developed for DSM-IV; and the overview of the *National Institutes of Health State of the Science Conference on Autism in 1995*. Relevant book chapters and books were also included, as identified by the expert panel.

The strength of the evidence for each relevant article and book chapter was ranked using the defined criteria shown in Appendix 3. Recommendations were thereby derived based on the strength of the evidence and stratified (**Standard**, **Guideline**, or **Practice Option**) as defined in Appendix 3.

Level one: routine developmental surveillance and screening specifically for autism. *Analysis of the evidence.* When and how often should developmental surveillance/screening be performed? Approximately 25% of children in any primary care practice show developmental issues. However, fewer than 30% of primary care providers conduct standardized screening tests at well-child appointments.⁸⁻¹⁰ The American Academy of Pediatrics (AAP) stresses the

importance of a flexible, continual developmental surveillance process at each well-child visit, and recommends eliciting and valuing parental concerns, probing regarding age-appropriate skills in each developmental domain, and observing each child.¹¹

What are the appropriate developmental screening questionnaires that provide sensitive and specific information? Developmental screening tools have been formulated based on screening of large populations of children with standardized test items. Sensitive and specific developmental screening instruments include: the Ages and Stages Questionnaire, the BRIGANCE® Screens, the Child Development Inventories, and the Parents' Evaluations of Developmental Status.¹

The Denver-II (DDST-II, formerly the Denver Developmental Screening Test-Revised) has been the traditional tool used for developmental screening, but research has found that it is insensitive and lacks specificity. The Revised Denver Pre-Screening Developmental Questionnaire (R-DPDQ) was designed to identify a subset of children who needed further screening. However, studies have shown that it detected only 30% of children with language impairments and 50% of children with mental retardation.¹²⁻¹⁵

How are conventional developmental milestones defined? Conventional developmental language milestones are based on normative data from numerous standardized language instruments for infants.¹⁶⁻¹⁹ Lack of acquisition of the following milestones within known accepted and established ranges is considered abnormal: no babbling by 12 months; no gesturing (e.g., pointing, waving bye-bye) by 12 months; no single words by 16 months; no 2-word spontaneous (not just echolalic) phrases by 24 months; and any loss of any language or social skills at any age. Failure to meet these milestones is associated with a high probability of a developmental disability.

Do parents provide reliable information regarding their child's development? Several studies encompassing 737 children showed that parental concerns about speech and language development, behavior, or other developmental issues were highly sensitive (i.e., 75% to 83%) and specific (79% to 81%) in detecting global developmental deficits.²⁰⁻²² However, the absence of such concerns had modest specificity in detecting normal development (47%).²⁰ An additional study that combined parental concern with a standardized parental report found this to be effective for early behavioral and developmental screening in the primary care setting.²³

Can autism be reliably diagnosed before 36 months of age? Because there are no biological markers for autism, screening must focus on behavior. Recent studies comparing 109 autistic and 33 typically developing children demonstrated that problems with eye contact, orienting to one's name, joint attention, pretend play, imitation, nonverbal communication, and language development are measurable by 18 months of age.²⁴⁻²⁷ These symptoms are stable in children from toddler age through preschool

age. Retrospective analysis of home videotapes have also identified behaviors that distinguish infants with autism from other developmental disabilities as early as 8 months of age.²⁸⁻³⁰

Current screening methods may not identify children with milder variants of autism, those without mental retardation or language delay, such as verbal individuals with high-functioning autism and Asperger's disorder, or older children, adolescents, and young adults.

Is there an increased risk of having another child with autism (recurrence)? The incidence of autism in the general population is 0.2%, but the risk of having a second (or additional) autistic child increases almost 50-fold to approximately 10 to 20%.³¹⁻³⁴

What tools are available with appropriate psychometric properties to specifically screen for autism? Appropriately sensitive and specific autism screening tools for infants and toddlers have only recently been developed, and this continues to be the current focus of many research centers. The Checklist for Autism in Toddlers (CHAT) for 18-month-old infants, and the Autism Screening Questionnaire for children 4 years of age and older, have been validated on large populations of children. However, it should be noted that the CHAT is less sensitive to milder symptoms of autism, as children later diagnosed with PDD-NOS, Asperger's, or atypical autism did not routinely fail the CHAT at 18 months.^{27,35}

The Pervasive Developmental Disorders Screening Test-II (PDDST-II) for infants from birth to 3 years of age, the Modified Checklist for Autism in Toddlers (M-CHAT) for infants at 2 years of age, and the Australian Scale for Asperger's Syndrome for older verbal children, are currently under development or validation phases.¹

What screening laboratory investigations are available for developmental delay, with or without suspicion of autism? *Formal audiologic evaluation.* The Committee on Infant Hearing of the American Speech-Language-Hearing Association developed guidelines for the audiologic assessment of children from birth through 36 months of age.³⁶ They recommended that all children with developmental delays, particularly those with delays in social and language development, have a formal audiologic hearing evaluation. Three studies have documented that conductive, sensorineural, or mixed hearing loss can co-occur with autism, and that some children with autism may be incorrectly thought to have peripheral hearing loss.^{37,38} In addition, transient conductive hearing loss associated with otitis media with effusion can also occur in children with autism.

Audiologic assessment of such children requires modifications of traditional test techniques and environments (e.g., operant test procedures).^{39,40} Electrophysiologic procedures are useful for estimating hearing sensitivity and for examining middle ear, cochlear, and VIIIth nerve or auditory brainstem pathway integrity.^{41,42} Evoked otoacoustic emissions are useful for examining cochlear (sensory) function,

and is a frequency-specific, as well as a time- and cost-efficient procedure.⁴³ Frequency-specific auditory brainstem response (ABR) is the single most useful electrophysiologic procedure for use in estimating hearing thresholds, and has been demonstrated to be highly correlated with behavioral hearing thresholds in children who hear normally and in children who have sensorineural hearing loss.⁴²

Lead screening. Children with developmental delays who spend an extended period in the oral-motor stage of play (where everything “goes into their mouths”) are at increased risk for lead toxicity, especially in certain environments. The prevalence of pica in this group can result in high rates of substantial or recurrent exposure to lead. The National Center for Environmental Health of the Centers for Disease Control and Prevention recommends that children with developmental delays, even without frank pica, should be screened for lead poisoning.⁴⁴ Blood lead levels in children with autism are elevated.¹ In one study, the mean blood lead level in 18 autistic children was higher than in 16 nonautistic “psychotic” children or in 10 normal siblings; 44% of the autistic and psychotic children had lead levels significantly above the mean compared with control subjects.⁴⁵ In a more recent study, 17 autistic children treated for lead poisoning were compared with 30 children without autism. The autistic children were older at diagnosis, had higher lead levels, and most were reexposed despite close monitoring of their environment.⁴⁶

Level one evidence-based recommendations.

Clinical practice recommendations.

1. Developmental surveillance should be performed at all well-child visits from infancy through school-age, and at any age thereafter if concerns are raised about social acceptance, learning, or behavior (**Guideline**).
2. Recommended developmental screening tools include the Ages and Stages Questionnaire, the BRIGANCE® Screens, the Child Development Inventories, and the Parents' Evaluations of Developmental Status (**Guideline**).
3. Because of the lack of sensitivity and specificity, the Denver-II (DDST-II) and the Revised Denver Pre-Screening Developmental Questionnaire (R-DPDQ) are not recommended for appropriate primary-care developmental surveillance (**Guideline**).
4. Further developmental evaluation is required whenever a child fails to meet any of the following milestones (**Guideline**): babbling by 12 months; gesturing (e.g., pointing, waving bye-bye) by 12 months; single words by 16 months; two-word spontaneous (not just echolalic) phrases by 24 months; loss of any language or social skills at any age.
5. Siblings of children with autism should be carefully monitored for acquisition of social, communi-

cation, and play skills, and the occurrence of maladaptive behaviors. Screening should be performed not only for autism-related symptoms but also for language delays, learning difficulties, social problems, and anxiety or depressive symptoms (**Guideline**).

6. Screening specifically for autism should be performed on all children failing routine developmental surveillance procedures using one of the validated instruments—the CHAT or the Autism Screening Questionnaire (**Guideline**).
7. Laboratory investigations recommended for any child with developmental delay and/or autism include audiologic assessment and lead screening (**Guideline**). Early referral for a formal audiologic assessment should include behavioral audiometric measures, assessment of middle ear function, and electrophysiologic procedures using experienced pediatric audiologists with current audiologic testing methods and technologies (**Guideline**). Lead screening should be performed in any child with developmental delay and pica. Additional periodic screening should be considered if the pica persists (**Guideline**).

Recommendations for research.

1. Develop and validate appropriate autism screening tools with adequate sensitivity and specificity in children younger than 1 year of age that could be used by a wide range of practitioners.
2. Current methods of screening for autism may not identify: 1) children with milder variants of the disorder; 2) children without mental retardation or language delay, such as verbal individuals with high functioning autism and Asperger's disorder; or 3) older children, adolescents, and young adults. Additional tools are needed to help identify and evaluate these groups of patients.
3. Studies are needed to provide insight into the emergence of early auditory behaviors that are considered atypical and may be prevalent in children with autism. Studies are also needed on the audiologic characteristics of individuals with autism to help assess peripheral hearing sensitivity and suprathreshold responses.

Level two: diagnosis and evaluation of autism.

Analysis of the evidence. Who should diagnose autism? Although educators, parents, and other health care professionals identify signs and symptoms characteristic of autism, a clinician experienced in the diagnosis and treatment of autism is usually necessary for accurate and appropriate diagnosis.^{25,47,48} Clinicians must rely on their clinical judgment, aided by guides to diagnosis, such as DSM-IV and the *Tenth Edition of the International Classification of Diseases* (ICD-10), as well as by the results of various assessment instruments, rating scales, and checklists. These instruments and criteria should be used by practitioners not as experienced in the diagnosis of autism.

What are the medical and neurologic concerns in evaluating children with autism? Familial prevalence. Family studies have shown that there is a 50-fold to 100-fold increase in the rate of autism in first-degree relatives of autistic children. Within these families, there are also elevated rates of social difficulties; higher incidences of cognitive, communication, learning and executive function deficits; increased stereotyped behaviors; and anxiety, affective, language, and pragmatic disorders.^{33,49-55} Monozygotic twin pair studies have also shown a high concordance rate (60%) for DSM-IV Autistic Disorder, 71% for the broader autistic spectrum phenotype, and 92% for an even broader phenotype of social and communication deficits with stereotyped behaviors that nonetheless were clearly differentiated from normal. In contrast, no concordance for autism was noted in dizygotic twin pairs and only 10% were concordant for some form of cognitive, social or language deficit.^{56,57}

Large head circumference without frank neuropathology. Children with autism have a larger head circumference; only a small proportion have frank macrocephaly.^{33,57-61} Large head size may not necessarily be present at birth, but may appear in early to mid-childhood, perhaps indicating an increased rate of brain growth. Neuroimaging studies in autism also found larger brain volumes without associated neuropathology.^{62,63}

Association with tuberous sclerosis complex (TSC) and less often with Fragile X (FraX) syndrome. Seventeen to over 60% of mentally retarded individuals with TSC are also autistic, and these patients commonly have epilepsy.⁶⁴⁻⁶⁷ In contrast, the number of autistic individuals with TSC has been estimated to be between 0.4% and 3%.⁶⁶ This rate increases to 8% to 14% if epilepsy is also present.⁶⁶

Clinical studies report that 3% to 25% of patients with FraX have autism.⁶⁸⁻⁷⁰ However, no evidence of FraX in autistic individuals was found using cytogenetic (not DNA analysis) techniques;⁷¹ with molecular genetic analyses, only a few autistic individuals were shown to have FraX.⁷²

What are the specific deficits of the autistic child's developmental profile? Speech, language, and verbal and nonverbal communication. Verbal and nonverbal communication deficits seen in autism are far more complex than simple speech delay, but overlap with developmental language disorders or specific language impairments. Expressive language function ranges from complete mutism (as often seen in children 2 to 3 years of age) to verbal fluency, though verbal abilities are often accompanied by many errors in word meaning (semantics) or language and communicative deficits in social contexts (social-pragmatics).⁷³⁻⁷⁵

Cognitive deficits. Many autistic individuals demonstrate a particular pattern on intellectual tests that is characteristic of autism, i.e., performance IQ (PIQ) higher than verbal IQ (VIQ), and specific intersubtest scatter, with Block Design typically the highest subtest and Comprehension usually

the lowest. However, the PIQ-VIQ split is severity dependent. When Full Scale IQ (FSIQ) and VIQ are both above 70, 80% of autistic individuals will have no significant VIQ-PIQ disparity, and the remainder are evenly divided between those with PIQ > VIQ and those with PIQ < VIQ.⁷⁶

The DSM-IV defines the diagnosis of mental retardation as the combination of subaverage intellectual functioning (IQ < 70) and concurrent deficits in adaptive functioning. Autistic individuals have poorer adaptive function than would be predicted by IQ alone.⁷⁷

Sensorimotor deficits. Impairments of gross and fine motor function are reported as being common in autistic individuals, and are recognized as hypotonia, limb apraxia, or motor stereotypies. Motor deficits are more severe in individuals with lower IQ scores.⁷⁸ Hand or finger mannerisms, body rocking, or unusual posturing are reported in 37% to 95% of individuals, and often manifest during the preschool years.^{24,58,78} Sensory processing abilities are aberrant in 42% to 88% of autistic individuals and include preoccupation with sensory features of objects, over- or underresponsiveness to environmental stimuli, or paradoxical responses to sensory stimuli.⁷⁹

Neuropsychological, behavioral, and academic impairments. Specific neuropsychological impairments can be identified, even in young children with autism, that correlate with the severity of autistic symptoms.⁸⁰ Performance on tasks that rely on rote, mechanical, or perceptual processes are typically spared; deficient performance exists on tasks requiring higher-order conceptual processes, reasoning, interpretation, integration, or abstraction. Dissociations between simple and complex processing are reported in the areas of language, memory, executive function, motor function, reading, mathematics, and perspective-taking.⁸⁰⁻⁸³ There is no reported evidence that confirms or excludes a diagnosis of autism based on these cognitive patterns alone.

When and what laboratory investigations are indicated for the diagnosis of autism? Genetic testing. A chromosomal abnormality reported in possibly more than 1% of autistic individuals involves the proximal long arm of chromosome 15 (15q11-q13), which is a greater frequency than other currently identifiable chromosomal disorders.⁸⁴⁻⁸⁶ Those with the 15q abnormalities typically have moderate to profound mental retardation. The duplication is usually maternally inherited, either pseudodicentric 15 (inverted duplication 15) or other atypical marker chromosomes, with one or two extra copies of the area roughly corresponding to the typical Angelman syndrome (AS)/Prader Willi Syndrome (PWS) deletion region of approximately four million base pairs. Conversely, AS is usually due to a deletion of maternally inherited 15q11-q13 material and has been found in patients with autism and profound mental retardation.^{85,87}

Metabolic testing. Inborn errors in amino acid, carbohydrate, purine, peptide, and mitochondrial metabolism, as well as toxicologic studies have been

studied, but the percentage of children with autism who have a metabolic disorder is probably less (and some experts agree that it is considerably less) than 5%.^{88,89}

Electrophysiologic testing. The prevalence of epilepsy in autistic children has been estimated at 7%⁹⁰ to 14%,⁹¹ whereas the cumulative prevalence by adulthood is estimated at 20% to 35%.^{90,91} Seizure onset peaks in early childhood and again in adolescence. Mental retardation, with or without motor abnormalities and family history of epilepsy, was a significant risk factor for the development of seizures in autistic individuals.⁹²⁻⁹⁵

It is unclear whether there is a relationship between autism and an early regressive course (before 36 months), childhood disintegrative disorder ([CDD] after 36 months), Landau-Kleffner syndrome, and electrical status epilepticus during slow wave sleep (ESES). Autism with regression and CDD have both been associated with seizures or epileptiform sleep-deprived EEG (with adequate sampling of slow wave sleep).⁹⁶⁻⁹⁸ A higher incidence of epileptiform EEG abnormalities in autistic children with a history of regression has been reported when compared to autistic children with clinical epilepsy.⁹⁷ Seizures or epileptiform discharges were more prevalent in children with regression who demonstrated cognitive deficits. Regression in cognition and language in adolescence associated with seizure onset has also been observed, but little is known about its cause or prevalence. There may be a causal relationship between a subgroup of children with autistic regression and EEG-defined "benign focal epilepsies."⁹⁹ There is insufficient evidence to suggest a role for event-related potentials or magnetoencephalography in the evaluation of autism.

Neuroimaging. CT studies, ordered as standard assessments of children diagnosed with autism during the 1970s and 1980s, reported a wide range of brain imaging abnormalities and suggested that there was an underlying structural disorder in patients with autism. This view changed when Damasio et al.¹⁰⁰ demonstrated that such abnormalities were incidental to coexisting anatomic disorders unrelated to autism. A very low prevalence of focal lesions or other structural abnormalities was found; their inconsistent localization marked them as coincidental. Prevalence of lesions on MRI in children with autism is similar to normal control subjects.¹⁰¹ CT and MRI studies of autistic subjects screened to exclude those with disorders other than autism confirmed the absence of significant structural brain abnormalities.⁶³

Functional imaging modalities such as functional MRI (fMRI), single-photon emission CT (SPECT), or positron-emission tomography (PET) are currently only research tools in the evaluation of autism. There is no evidence to support a role for functional neuroimaging studies in the clinical diagnosis of autism at the present time.¹

Other tests. There is insufficient evidence to support the use of other tests such as hair analysis for

trace elements, celiac antibodies, allergy testing (particularly food allergies for gluten, casein, candida, and other molds), immunologic or neurochemical abnormalities, micronutrients such as vitamin levels, intestinal permeability studies, stool analysis, urinary peptides, mitochondrial disorders (including lactate and pyruvate), thyroid function tests, or erythrocyte glutathione peroxidase studies.¹

Level two: evidence-based recommendations.

Clinical practice recommendations.

1. Genetic testing in children with autism, specifically high resolution chromosome studies (karyotype) and DNA analysis for FraX, should be performed in the presence of mental retardation (or if mental retardation cannot be excluded), if there is a family history of FraX or undiagnosed mental retardation, or if dysmorphic features are present (**Standard**). However, there is little likelihood of positive karyotype or FraX testing in the presence of high-functioning autism.
2. Selective metabolic testing (**Standard**) should be initiated by the presence of suggestive clinical and physical findings such as the following: if lethargy, cyclic vomiting, or early seizures are evident; the presence of dysmorphic or coarse features; evidence of mental retardation or if mental retardation cannot be ruled out; or if occurrence or adequacy of newborn screening for a birth is questionable.
3. There is inadequate evidence at the present time to recommend an EEG study in all individuals with autism. Indications for an adequate sleep-deprived EEG with appropriate sampling of slow wave sleep include (**Guideline**) clinical seizures or suspicion of subclinical seizures, and a history of regression (clinically significant loss of social and communicative function) at any age, but especially in toddlers and preschoolers.
4. Recording of event-related potentials and magnetoencephalography are research tools at the present time, without evidence of routine clinical utility (**Guideline**).
5. There is no clinical evidence to support the role of routine clinical neuroimaging in the diagnostic evaluation of autism, even in the presence of megalencephaly (**Guideline**).
6. There is inadequate supporting evidence for hair analysis, celiac antibodies, allergy testing (particularly food allergies for gluten, casein, candida, and other molds), immunologic or neurochemical abnormalities, micronutrients such as vitamin levels, intestinal permeability studies, stool analysis, urinary peptides, mitochondrial disorders (including lactate and pyruvate), thyroid function tests, or erythrocyte glutathione peroxidase studies (**Guideline**).

Recommendations for research.

1. Studies are needed to further identify the usefulness of electrophysiologic techniques to clarify the

role of epilepsy in autism, especially in children with a history of regression.

2. Additional studies to examine potential genetic and/or environmental factors and their relationship to the etiology of autism are needed.
3. Continuing efforts might focus on identifying contributing genes to determine whether the behavioral syndromes (which constitute the basis of DSM-IV and ICD-10) have actual biological validity.
4. Evaluation of environmental factors (e.g., nonspecific infections or other immunologically mediated events) that might contribute to triggering the expression of autistic symptoms or regression requires additional study.

Consensus-based general principles of management. The following recommendations are based on consensus agreement by the participating organizations involved in the development of this parameter.¹

Surveillance and screening. In the United States, states must follow federal Public Law 105-17: the Individuals with Disabilities Education Act Amendments of 1997–IDEA'97, which mandates immediate referral for a free appropriate public education for eligible children with disabilities from the age of 36 months, and early intervention services for infants and toddlers with disabilities from birth through 35 months of age.

Diagnosis. The diagnosis of autism should include the use of a diagnostic instrument with at least moderate sensitivity and good specificity for autism. Sufficient time should be planned for standardized parent interviews regarding current concerns and behavioral history related to autism, and direct, structured observation of social and communicative behavior and play. Recommended instruments include¹:

Diagnostic parental interviews

- The Gilliam Autism Rating Scale
- The Parent Interview for Autism
- The Pervasive Developmental Disorders Screening Test–Stage 3
- The Autism Diagnostic Interview–Revised

Diagnostic observation instruments

- The Childhood Autism Rating Scale
- The Screening Tool for Autism in Two-Year-Olds
- The Autism Diagnostic Observation Schedule–Generic

Medical and neurologic evaluation. Perinatal and developmental history should include milestones; regression in early childhood or later in life; encephalopathic events; attentional deficits; seizure disorder (absence or generalized); depression or mania; and behaviors such as irritability, self-injury, sleep and eating disturbances, and pica. The physical and neurologic examination should include: longitudinal measurements of head circumference and examination for unusual features (facial, limb, stature, etc.) suggesting the need for genetic evaluation;

neurocutaneous abnormalities (requiring an ultraviolet [Wood's] lamp examination); gait; tone; reflexes; cranial nerves; and determination of mental status, including verbal and nonverbal language and play.

Evaluation and monitoring of autism. The immediate and long-term evaluation and monitoring of autistic individuals requires a comprehensive multidisciplinary approach, and can include one or more of the following professionals: psychologists, neurologists, speech–language pathologists and audiologists, pediatricians, child psychiatrists, occupational therapists, and physical therapists, as well as educators and special educators. Individuals with mild autism should also receive adequate assessments and appropriate diagnoses.

Reevaluation within 1 year of initial diagnosis and continued monitoring is an expected aspect of clinical practice because relatively small changes in the developmental level affect the impact of autism in the preschool years. In general, there is no need to repeat extensive diagnostic testing; however, follow-up visits can be helpful to address behavioral, environmental, and other developmental concerns.

Speech, language, and communication evaluation. A comprehensive speech–language–communication evaluation should be performed on all children who fail language developmental screening procedures by a speech–language pathologist with training and expertise in evaluating children with developmental disabilities. Comprehensive assessments of both preverbal and verbal individuals should account for age, cognitive level, and socioemotional abilities, and should include assessment of receptive language and communication, expressive language and communication, voice and speech production, and in verbal individuals, a collection and analysis of spontaneous language samples to supplement scores on formal language tests.

Cognitive and adaptive behavior evaluations. Cognitive evaluations should be performed in all children with autism by a psychologist or other trained professional. Cognitive instruments should be appropriate for the mental and chronologic age, provide a full range (in the lower direction) of standard scores and current norms independent of social ability, include independent measures of verbal and nonverbal abilities, and provide an overall index of ability. A measure of adaptive functioning should be collected for any child evaluated for an associated cognitive handicap. Consensus-based recommendations for using specific instruments include the Vineland Adaptive Behavior Scales and the Scales of Independent Behavior–Revised.¹

Sensorimotor and occupational therapy evaluations. Evaluation of sensorimotor skills by a qualified experienced professional (occupational therapist or physical therapist) should be considered, including assessment of gross and fine motor skills, praxis, sensory processing abilities, unusual or stereotyped mannerisms, and the impact of these components on the autistic person's life. An occupational therapy

evaluation is indicated when deficits exist in functional skills or occupational performance in the areas of play or leisure, self-maintenance through activities of daily living, or productive school and work tasks. Although not routinely warranted as part of all evaluations of children with autism, the Sensory Integration and Praxis Tests may be used on an individual basis to detect specific patterns of sensory integrative dysfunction.

Neuropsychological, behavioral, and academic assessments. These assessments should be performed as needed, in addition to the cognitive assessment, to include social skills and relationships, educational functioning, problematic behaviors, learning style, motivation and reinforcement, sensory functioning, and self-regulation. Assessment of family resources should be performed by appropriate psychologists or other qualified health care professionals and should include assessment of parents' level of understanding of their child's condition, family (parent and sibling) strengths, talents, stressors and adaptation, resources and supports, as well as offer appropriate counseling and education.

Disclaimer. The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) seeks to develop scientifically sound, clinically relevant practice parameters for the practice of neurology. Practice parameters are strategies for patient management that assist physicians in clinical decision making. A practice parameter is one or more specific recommendations based on analysis of evidence of a specific clinical problem. These might include diagnosis, symptoms, treatment, or procedure evaluation. This evidence-based review addresses the major management issues health care providers face in surveying, screening, and diagnosing children with autism. The clinical evidence is reviewed, management recommendations provided, and areas of continued research identified. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Appendix 1

Participating Organizations and Authors

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Representatives were named from the following associations: Barbara Cutler, EdD, and Susan Goodman, JD (Autism National Committee); Cheryl Trepagnier, PhD (Autism Society of America); Daniel H. Geschwind, MD, PhD (Cure Autism Now); and Charles T. Gordon, MD (National Alliance for Autism Research). The National Institutes of Health also named liaisons to serve on this committee, including Marie Bristol–Power, PhD (National Institute of Child Health and Human Development); Judith Cooper, PhD (National Institute of Deafness and Communication Disorders); Judith Rumsey, PhD (National Institute of Mental Health); and Giovanna Spinella, MD (National Institute of Neurological Disorders and Stroke).

Appendix 2

Clinical questions addressed for surveillance, screening and diagnosing children with autism

Routine developmental surveillance and screening for autism

1. When and how often should developmental surveillance/screening be performed?
2. What are the appropriate developmental screening questionnaires that provide sensitive and specific information?
3. How are conventional developmental milestones defined?
4. Do parents provide reliable information regarding their child's development?
5. Can autism can be reliably diagnosed before 36 months of age?
6. Is there an increased risk of having another child with autism (recurrence)?
7. What screening laboratory investigations are available for developmental delay, with or without suspicion of autism?
8. What tools are available with appropriate psychometric properties to specifically screen for autism?

Diagnosis and evaluation of autism

1. Who should diagnose autism?
2. What are the medical and neurologic concerns in evaluating children with autism?
3. What are the specific deficits of the autistic child's developmental profile?
4. When and what laboratory investigations are indicated for the diagnosis of autism?

Appendix 3

Definitions for strength of the evidence

Class I. Must have all of a through d. a) Prospective study of a well-defined cohort which includes a description of the nature of the population, the inclusion/exclusion criteria, demographic characteristics such as age and sex, and seizure type. b) The sample size must be adequate with enough statistical power to justify a conclusion or for identification of subgroups for whom testing does

or does not yield significant information. c) The interpretation of evaluations performed must be done blinded to outcome. d) There must be a satisfactory description of the technology used for evaluations (e.g., EEG, MRI).

Class II. Must have a or b. a) Retrospective study of a well-defined cohort which otherwise meets criteria for class 1a, b and 1d. b) Prospective or retrospective study which lacks any of the following: adequate sample size, adequate methodology, a description of inclusion/exclusion criteria, and information such as age, sex and characteristics of the seizure.

Class III. Must have a or b. a) A small cohort or case report. b) Relevant expert opinion, consensus, or survey.

A cost-benefit analysis or a meta-analysis may be class I, II, or III, depending on the strength of the data upon which the analysis is based.

Definitions for strength of the recommendations

Standard. A principle for patient management that reflects a high degree of clinical certainty (usually requires one or more Class I studies that directly address the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).

Guideline. A recommendation for patient management that reflects moderate clinical certainty (usually requires one or more Class II studies or a strong consensus of Class III evidence).

Practice option. Strategy for patient management for which clinical utility is uncertain (inconclusive or conflicting evidence or opinion).

Appendix 4

American Academy of Neurology Quality Standards Subcommittee Members: Gary Franklin, MD, MPH—Co-Chair; Catherine A. Zahn, MD—Co-Chair; Milton Alter, MD, PhD; Stephen Ashwal, MD (facilitator); John Calverley, MD; Richard Dubinsky, MD; Jacqueline French, MD; Michael Glantz, MD; Michael K. Greenberg, MD; Gary Gronseth, MD; Deborah Hirtz, MD; Robert G. Miller, MD; James Stevens, MD; William Weiner, MD; and Wendy Edlund, AAN Manager, Clinical Practice Guidelines.

References

- Filipek PA, Accardo PJ, Baranek GT, et al. The screening and diagnosis of autistic spectrum disorders. *J Autism Dev Disord* 1999;29:437–482.
- Howlin P, Moore A. Diagnosis of autism. A survey of over 1200 patients in the UK. *Autism* 1997;1:135–162. (Class II).
- Rogers SJ. Empirically supported comprehensive treatments for young children with autism. *J Clin Child Psychol* 1998;27:168–179. (Class III).
- Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. *J Consult Clin Psychol* 1987;55:3–9. (Class II).
- McEachin JJ, Smith T, Lovaas OI. Long-term outcome for children with autism who received early intensive behavioral treatment. *Am J Ment Retard* 1993;97:359–372. (Class II).
- Ozonoff S, Cathcart K. Effectiveness of a home program intervention for young children with autism. *J Autism Dev Disord* 1998;28:25–32. (Class II).
- Sheinkopf SJ, Siegel B. Home-based behavioral treatment of young children with autism. *J Autism Dev Disord* 1998;28:15–23. (Class III).
- Majnemer A, Rosenblatt B. Reliability of parental recall of developmental milestones. *Pediatr Neurol* 1994;10:304–308. (Class II).
- Dworkin PH. British and American recommendations for developmental monitoring: the role of surveillance. *Pediatrics* 1989;84:1000–1010. (Class III).
- Glascoe FP, Dworkin PH. Obstacles to effective developmental surveillance: errors in clinical reasoning. *J Dev Behav Pediatr* 1993;14:344–349. (Class III).
- American Academy of Pediatrics Committee on Children with Disabilities. Screening infants and young children for developmental disabilities. *Pediatrics* 1994;93:863–5. (Class III).
- Glascoe FP, Byrne KE, Ashford LG, Johnson KL, Chang B, Strickland B. Accuracy of the Denver-II in developmental screening. *Pediatrics* 1992;89:1221–1225. (Class I).
- Greer S, Bauchner H, Zuckerman B. The Denver Developmental Screening Test: how good is its predictive validity? *Dev Med Child Neurol* 1989;31:774–781. (Class II).
- Diamond KE. Predicting school problems from preschool developmental screening: A four-year followup of the Revised Denver Developmental Screening test and the role of parent report. *J Div Early Child* 1987;11:247–253. (Class I).
- Sciarillo WG, Brown MM, Robinson NM, Bennett FC, Sells CJ. Effectiveness of the Denver Developmental Screening Test with biologically vulnerable infants. *J Dev Behav Pediatr* 1986;7:77–83. (Class I).
- Fenson L, Dale P, Reznick S, et al. MacArthur communicative development inventories. San Diego, CA: Singular Publishing, 1993.
- Hedrick DL, Prather EM, Tobin AR. Sequenced inventory of communication development—revised edition. Seattle, WA: University of Washington Press, 1984.
- Iretton H, Glascoe FP. Assessing children's development using parents' reports. The Child Development Inventory. *Clin Pediatr* 1995;34:248–255. (Class I).
- Bricker D, Squires J. The ages & stages questionnaires, second edition. Baltimore, MD: Paul H. Brookes Publishing Company, 1999.
- Glascoe FP. It's not what it seems. The relationship between parents' concerns and children with global delays. *Clin Pediatr* 1994;33:292–296. (Class I).
- Glascoe FP, Sandler H. Value of parents' estimates of children's developmental ages. *J Pediatr* 1995;127:831–835. (Class I).
- Glascoe FP. Parents' concerns about children's development: prescreening technique or screening test? *Pediatrics* 1997;99:522–528. (Class I).
- Glascoe FP, Dworkin PH. The role of parents in the detection of developmental and behavioral problems. *Pediatrics* 1995;95:829–836. (Class III).
- Lord C. Follow-up of two-year-olds referred for possible autism. *J Child Psychol Psychiatry* 1995;36:1365–1382. (Class II).
- Stone WL, Lee EB, Ashford L, Brissie J, Hepburn SL, Coonrod EE, Weiss BH. Can autism be diagnosed accurately in children under three years? *J Child Psychol Psychiatry* 1999;40:219–226. (Class II).
- Charman T, Swettenham J, Baron-Cohen S, Cox A, Baird G, Drew A. Infants with autism: An investigation of empathy, pretend play, joint attention, and imitation. *Dev Psychol* 1997;33:781–789. (Class II).
- Cox A, Klein K, Charman T, et al. The early diagnosis of autism spectrum disorders: use of the autism diagnostic interview—revised at 20 months and 42 months of age. *J Child Psychol Psychiatry* 1999;40:705–718. (Class II).
- Mars AE, Mauk JE, Dowrick P. Symptoms of pervasive developmental disorders as observed in prediagnostic home videos of infants and toddlers. *J Pediatr* 1998;132:500–504. (Class II).
- Werner E, Dawson G, Osterling J, Dinno J. Recognition of autism spectrum disorders before 1 year of age. A retrospective study based on home videotapes. *J Autism Dev Disord* 2000;30:157–162. (Class II).
- Baranek GT. Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9-12 months of age. *J Autism Dev Disord* 1999;29:213–224. (Class II).
- Szatmari P, Jones MB, Tuff L, Bartolucci G, Fisman S, Mahoney W. Lack of cognitive impairment in first-degree relatives of children with pervasive developmental disorders. *J Am Acad Child Adolesc Psychiatry* 1993;32:1264–1273. (Class II).
- Jorde LB, Mason-Brothers A, Waldmann R, et al. The UCLA—University of Utah epidemiologic survey of autism: genealogical analysis of familial aggregation. *Am J Med Genet* 1990;36:85–88. (Class I).
- Bolton P, Macdonald H, Pickles A, et al. A case-control family history study of autism. *J Child Psychol Psychiatry* 1994;35:877–900. (Class I).
- Piven J, Gayle J, Chase GA, Fink B, Landa R, Wzorek MM, Folstein SE. A family history study of neuropsychiatric disorders in the adult siblings of autistic individuals. *J Am Acad Child Adolesc Psychiatry* 1990;29:177–183. (Class II).

35. Charman T, Swettenham J, Baron-Cohen S, Cox A, Baird G, Drew A. An experimental investigation of social-cognitive abilities in infants with autism: Clinical implications. *Infant Mental Health Journal* 1998;19:260-275.
36. American Speech-Language-Hearing Association. Guidelines for the audiologic assessment of children from birth through 36 months of age. Committee on Infant Hearing. American Speech-Language-Hearing Association (ASHA) 1991;33(suppl 5):37-43. (Class III).
37. Jure R, Rapin I, Tuchman RF. Hearing-impaired autistic children. *Dev Med Child Neurol* 1991;33:1062-1072. (Class II).
38. Klin A. Auditory brainstem responses in autism: brainstem dysfunction or peripheral hearing loss? *J Autism Dev Disord* 1993;23:15-35. (Class II).
39. Gravel JS, Kurtzberg D, Stapells D, Vaughan H, Wallace I. Case studies. Seminars in hearing 1989;10:272-287. (Class III).
40. Verpoorten RA, Emmen JG. A tactile-auditory conditioning procedure for the hearing assessment of persons with autism and mental retardation. *Scand Audiol Suppl* 1995;41:49-50. (Class II).
41. Gorga MP, Kaminski JR, Beauchaine KL, Jesteadt W, Neely ST. Auditory brainstem responses from children three months to three years of age. *J Speech Hear Res* 1989;32:281-288. (Class II).
42. Stapells DR, Gravel JS, Martin BA. Thresholds for auditory brain stem responses to tones in notched noise from infants and young children with normal hearing or sensorineural hearing loss. *Ear Hear* 1995;16:361-371. (Class I).
43. Grewe TS, Danhauer JL, Danhauer KJ, Thornton AR. Clinical use of otoacoustic emissions in children with autism. *International J Pediatr Otorhinolaryngol* 1994;30:123-132. (Class III).
44. Centers for Disease Control and Prevention. Screening young children for lead poisoning: Guidance for state and local public health officials. Atlanta, GA: Centers for Disease Control and Prevention-National Center for Environmental Health, November 1997. (Class III).
45. Cohen DJ, Johnson WT, Caparulo BK. Pica and elevated blood lead level in autistic and atypical children. *Am J Dis Child* 1976;130:47-48. (Class II).
46. Shannon M, Graef JW. Lead intoxication in children with pervasive developmental disorders. *J Toxicol Clin Toxicol* 1997;34:177-182. (Class II).
47. Volkmar FR, Klin A, Siegel B, Szatmari P, Lord C, Campbell M, Freeman BJ, Cicchetti DV, Rutter M, Kline W, et al. Field trial for autistic disorder in DSM-IV. *Am J Psychiatry* 1994;151:1361-1367. (Class I).
48. Lord C, Storoschuk S, Rutter M, Pickles A. Using the ADI-R to diagnose autism in preschool children. *Infant Mental Hlth J* 1993;14:234-252. (Class I).
49. Piven J, Wzorek M, Landa R, Lainhart J, Bolton P, Chase GA, Folstein S. Personality characteristics of the parents of autistic individuals. *Psychol Med* 1994;24:783-795. (Class I).
50. DeLong R. Children with autistic spectrum disorder and a family history of affective disorder. *Dev Med Child Neurol* 1994;36:674-687. (Class II).
51. DeLong R, Nohria C. Psychiatric family history and neurological disease in autistic spectrum disorders. *Dev Med Child Neurol* 1994;36:441-448. (Class II).
52. Piven J, Palmer P, Landa R, Santangelo S, Jacobi D, Childress D. Personality and language characteristics in parents from multiple-incidence autism families. *Am J Med Genet* 1997;74:398-411. (Class I).
53. Hughes C, Leboyer M, Bouvard M. Executive function in parents of children with autism. *Psychol Med* 1997;27:209-220. (Class II).
54. Piven J, Palmer P, Jacobi D, Childress D, Arndt S. Broader autism phenotype: evidence from a family history study of multiple-incidence autism families. *Am J Psychiatry* 1997;154:185-190. (Class I).
55. Fombonne E, Bolton P, Prior J, Jordan H, Rutter M. A family study of autism: Cognitive patterns and levels in parents and siblings. *J Child Psychol Psychiatry* 1997;38:667-683. (Class I).
56. Le Couteur A, Bailey A, Goode S, Pickles A, Robertson S, Gottesman I, Rutter M. A broader phenotype of autism: the clinical spectrum in twins. *J Child Psychol Psychiatry* 1996;37:785-801. (Class I).
57. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med* 1995;25:63-77. (Class I).
58. Rapin I. Neurological examination. In: Rapin I, ed. *Preschool children with inadequate communication: developmental language disorder, autism, low IQ*. London, UK: MacKeith Press, 1996:98-122. (Class I).
59. Lainhart JE, Piven J, Wzorek M, Landa R, Santangelo SL, Coon H, Folstein SE. Macrocephaly in children and adults with autism. *J Am Acad Child Adolesc Psychiatry* 1997;36:282-290. (Class II).
60. Davidovitch M, Patterson B, Gartside P. Head circumference measurements in children with autism. *J Child Neurol* 1996;11:389-393. (Class II).
61. Woodhouse W, Bailey A, Rutter M, Bolton P, Baird G, Le Couteur A. Head circumference in autism and other pervasive developmental disorders. *J Child Psychol Psychiatry* 1996;37:665-671. (Class II).
62. Piven J, Arndt S, Bailey J, Andreasen N. Regional brain enlargement in autism: a magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry* 1996;35:530-536. (Class II).
63. Filipek PA. Neuroimaging in the developmental disorders: The state of the science. *J Child Psychol Psychiatry* 1999;40:113-128. (Class II).
64. Gillberg IC, Gillberg C, Ahlsen G. Autistic behaviour and attention deficits in tuberous sclerosis: a population-based study. *Dev Med Child Neurol* 1994;36:50-56. (Class II).
65. Hunt A, Shepherd C. A prevalence study of autism in tuberous sclerosis. *J Autism Dev Disord* 1993;23:323-339. (Class II).
66. Smalley SL, Tanguay PE, Smith M, Gutierrez G. Autism and tuberous sclerosis. *J Autism Dev Disord* 1992;22:339-355. (Class II).
67. Curatolo P, Cusmai R, Cortesi F, Chiron C, Jambeque I, Dulac O. Neuropsychiatric aspects of tuberous sclerosis. New York Academy of Sciences and the National Tuberous Sclerosis Association Conference: Tuberous sclerosis and allied disorders (1990, Bethesda, Maryland). *Ann NY Acad Sci* 1991;615:8-16. (Class III).
68. Piven J, Gayle J, Landa R, Wzorek M, Folstein S. The prevalence of fragile X in a sample of autistic individuals diagnosed using a standardized interview. *J Am Acad Child Adolesc Psychiatry* 1991;30:825-830. (Class II).
69. Bolton P, Rutter M. Genetic influences in autism. *Int Rev Psychiatr* 1990;2:67-80. (Class II).
70. Bailey A, Bolton P, Butler L, et al. Prevalence of the fragile X anomaly amongst autistic twins and singletons. *J Child Psychol Psychiatry* 1993;34:673-688. (Class I).
71. Hashimoto O, Shimizu Y, Kawasaki Y. Brief report: low frequency of the fragile X syndrome among Japanese autistic subjects. *J Autism Dev Disord* 1993;23:201-209. (Class III).
72. Klauck SM, Munstermann E, Bieber-Martig B, et al. Molecular genetic analysis of the FMR-1 gene in a large collection of autistic patients. *Hum Genet* 1997;100:224-229. (Class I).
73. Wetherby AM, Prizant BM, Hutchinson T. Communicative, social-affective, and symbolic profiles of young children with autism and pervasive developmental disorder. *Am J Speech-Language Pathol* 1998;7:79-91. (Class II).
74. Stone WL, Ousley OY, Yoder PJ, Hogan KL, Hepburn SL. Nonverbal communication in two- and three-year-old children with autism. *J Autism Dev Disord* 1997;27:677-696. (Class II).
75. Rapin I. *Preschool Children with Inadequate Communication: developmental language disorder, autism, low IQ*. London, UK: MacKeith Press, 1996. (Class I).
76. Siegel DJ, Minshew NJ, Goldstein G. Wechsler IQ profiles in diagnosis of high-functioning autism. *J Autism Dev Disord* 1996;26:389-406. (Class II).
77. Volkmar FR, Carter A, Sparrow SS, Cicchetti DV. Quantifying social development in autism. *J Am Acad Child Adolesc Psychiatry* 1993;32:627-632. (Class II).
78. Rogers SJ, Bennetto L, McEvoy R, Pennington BF. Imitation and pantomime in high-functioning adolescents with autism

- spectrum disorders. *Child Dev* 1996;67:2060–2073. (Class II).
79. Kientz MA, Dunn W. A comparison of the performance of children with and without autism on the Sensory Profile. *Am J Occup Ther* 1997;51:530–537. (Class II).
 80. Dawson G, Meltzoff AN, Osterling J, Rinaldi J. Neuropsychological correlates of early symptoms of autism. *Child Dev* 1998;69:1276–1285. (Class II).
 81. Minshew NJ, Goldstein G, Taylor HG, Siegel DJ. Academic achievement in high functioning autistic individuals. *J Clin Exp Neuropsychol* 1994;16:261–270. (Class I).
 82. Ozonoff S, Pennington BF, Rogers SJ. Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. *J Child Psychol Psychiatry* 1991;32:1081–1105. (Class II).
 83. Minshew NJ, Goldstein G, Siegel DJ. Neuropsychologic functioning in autism: profile of a complex information processing disorder. *J Int Neuropsychol Soc* 1997;3:303–316. (Class II).
 84. Cook EH Jr, Lindgren V, Leventhal BL, et al. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am J Hum Genet* 1997;60:928–934.
 85. Schroer RJ, Phelan MC, Michaelis RC, et al. Autism and maternally derived aberrations of chromosome 15q. *Am J Med Genet* 1998;76:327–336. (Class II).
 86. Weidmer-Mikhail E, Sheldon S, Ghaziuddin M. Chromosomes in autism and related pervasive developmental disorders: a cytogenetic study. *J Intellect Disabil Res* 1998;42:8–12. (Class II).
 87. Steffenburg S, Gillberg CL, Steffenburg U, Kyllerman M. Autism in Angelman syndrome: a population-based study. *Pediatr Neurol* 1996;14:131–136. (Class II).
 88. Dykens EM, Volkmar FR. Medical conditions associated with autism. In: Cohen DJ, Volkmar FR, eds. *Handbook of autism and pervasive developmental disorders*, second edition. New York, NY: John Wiley & Sons, 1997:388–410. (Class III).
 89. Rutter M, Bailey A, Simonoff E, Pickles A. Genetic influences and autism. In: Cohen DJ, Volkmar FR, eds. *Handbook of autism and pervasive developmental disorders*, second edition. New York, NY: John Wiley & Sons, 1997:370–387. (Class III).
 90. Rapin I. Historical data. In: Rapin I, ed. *Preschool children with inadequate communication: developmental language disorder, autism, low IQ*. London, UK: MacKeith Press, 1996: 58–97. (Class I).
 91. Tuchman RF, Rapin I, Shinnar S. Autistic and dysphasic children. II. Epilepsy. *Pediatrics* 1991;88:1219–1225. (Class II).
 92. Gillberg C, Steffenburg S. Outcome and prognostic factors in infantile autism and similar conditions: a population-based study of 46 cases followed through puberty. *J Autism Dev Disord* 1987;17:273–287. (Class II).
 93. Rossi PG, Parmeggiani A, Bach V, Santucci M, Visconti P. EEG features and epilepsy in patients with autism. *Brain Dev* 1995;17:169–174. (Class II).
 94. Volkmar FR, Nelson DS. Seizure disorders in autism. *J Am Acad Child Adolesc Psychiatry* 1990;29:127–129. (Class II).
 95. Wong V. Epilepsy in children with autistic spectrum disorder. *J Child Neurol* 1993;8:316–322. (Class II).
 96. Rapin I. Autism. *N Engl J Med* 1997;337:97–104. (Class III).
 97. Tuchman RF, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. *Pediatrics* 1997;99:560–566. (Class II).
 98. Tuchman RF. Regression in pervasive developmental disorders: Is there a relationship with Landau-Kleffner Syndrome? *Ann Neurol* 1995;38:526. Abstract. (Class II).
 99. Nass R, Gross A, Devinsky O. Autism and autistic epileptiform regression with occipital spikes. *Dev Med Child Neurol* 1998;40:453–458. (Class III).
 100. Damasio H, Maurer R, Damasio AR, Chui H. Computerized tomographic scan findings in patients with autistic behavior. *Arch Neurol* 1980;37:504–510. (Class II).
 101. Filipek PA, Richelme C, Kennedy DN, Rademacher J, Pitcher DA, Zidel SY, Caviness VS. Morphometric analysis of the brain in developmental language disorders and autism. *Ann Neurol* 1992;32:475. Abstract. (Class II).