Autism spectrum disorders: a pediatric overview and update

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Purpose of review
To provide an updated overview of autism spectrum disorders (ASDs), with particular attention to the pediatrician's role in assessing and managing patients with ASDs.

Recent findings
Clinical perspectives on ASDs continue to evolve. The prevalence of ASDs in the United States continues to rise, and pediatricians are being tasked with the responsibility for universal screening. Further changes in its epidemiology will undoubtedly result from anticipated changes in the diagnostic criteria put forth in the upcoming revision to the *Diagnostic and Statistical Manual* (5th edition). Although there have been considerable advances in identifying a genetic cause in many more cases, the cause remains elusive in most cases. Recent studies of concordant twins suggest there is a stronger environmental component than previously believed. Research suggests earlier diagnosis may be feasible in some cases, and a new treatment approach has been shown to be effective in very young children. Although there have not been any large-scale advances in the medical treatment, some isolated successes have been reported and other promising therapies are now being investigated.

Summary
Clinical guidelines for ASDs are evolving, with updated diagnostic criteria expected and revised recommendations for evaluation also imminent. This article provides pediatricians with a clinical overview of ASD – with an emphasis on the clinical considerations relating to screening, evaluation, and management.

Keywords
autism spectrum disorders, cause, diagnosis, pervasive developmental disorders

INTRODUCTION

Twenty-six years ago, a colleague wrote: 'In recent years, no other childhood disorder has received as much attention, generated more controversy, or left educators and parents in more confusion about what to do than the condition known as hyperactivity. The vagueness of the term has resulted in an ''epidemic'' of cases, causes, and cures' [1]. Although this observation might well still apply to attention deficit hyperactivity disorder (ADHD), others could reasonably argue that it applies equally well to the field of autism spectrum disorders (ASDs). Although we lack answers for far too many important questions and controversy swirls around every aspect of this diagnostic category, it is important that pediatricians fully understand the issues related to early identification, evaluation, treatment, and outcome of ASDs.

PREVALENCE

ASDs are one of the most prevalent neurodevelopmental disorders among children today. More children are diagnosed with ASDs each year in the United States than AIDS, cancer, and diabetes combined [2]. ASDs, synonymous with pervasive developmental disorders (PDDs), encompass a group of neurodevelopmental disorders along a

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KEY POINTS

- Pediatricians play an essential role in the early identification and management of children with autism spectrum disorders.
- Early identification of ASDs is important because it may reduce ASD severity, though this is more challenging for milder forms of ASD.
- Imminent release of the newest edition of the *Diagnostic and Statistical Manual* (DSM-5) will provide a revised nosology with stricter criteria for ASD diagnosis.
- Advances in molecular genetic testing have identified a genetic cause in more cases of ASD; however, there is a growing body of research supporting an epigenetic cause of ASD in many cases. Current recommendations for laboratory testing are summarized.
- Although developmental therapies are the backbone of treatment (with recent research supporting a refined developmental approach), there will likely be an expanded role for medical treatments in the years ahead.

spectrum, with each ASD subtype characterized by varying degrees of difficulties with social interaction, communication (verbal and nonverbal), and unusual, repetitive behaviors [3]. Currently, ASDs affect 1 in 88 children in the United States and are four times more prevalent in males than females (1 in 54 boys affected compared with 1 in 252 girls affected) [4]. While prevalence estimates of ASDs have increased significantly in the recent years, from 1 in 150 in the year 2000 to 1 in 88 in the year 2008, it is unclear to what extent this is a true increase or a product of expanded diagnostic criteria [5].

DEFINITION AND NOSOLOGY

'Autism' received its own classification in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-3) in 1980 [6]. When the DSM-4 was updated in 1994, 'autistic disorder' was subsumed under a new umbrella category of 'Pervasive Developmental Disorders' (PDDs), which included four other disorders: Asperger's disorder, childhood-onset disintegrative disorder (CODD), Rett syndrome, and PDD-Not Otherwise Specified (PDD-NOS). Although each of these conditions had some shared elements, the DSM-4 tried to delineate these different conditions with respect to age of onset, symptom severity, prognosis, and associated features [3]. While these disorders are now generally known as ASDs, they were never labeled as such in the DSM-4.

The current DSM-4 criteria have been criticized from both a clinical and an epidemiologic standpoint. Inconsistent diagnoses over time and among physicians have influenced DSM-5 developers to minimize diagnostic ambiguities by consolidating the constituent disorders. When the DSM-5 is released in May 2013, autistic disorder, PDD-NOS, CODD, and Asperger's disorder will no longer be distinct conditions; instead, they will collectively be defined as 'Autism Spectrum Disorder' – formally recognizing what has been the de-facto umbrella term in recent years.

As proposed, the diagnostic criteria for 'ASD' will reflect several other major changes. The three domains defining ASDs in the DSM-4 are condensed into two domains: 'social and communication deficits' and 'fixed interests and repetitive behaviors' [7]. Social and communication deficits are combined because they are seen as being clinically linked (if not inseparable) and to improve diagnostic specificity without compromising sensitivity. It is hoped that numerical severity levels will enhance specificity. Data analyses suggest the revised criteria will have the highest kappa coefficient yet of 0.69 [7,8].

ASD diagnosis will now require children to exhibit all three symptoms in social communication and interaction (a) and two of four symptoms in repetitive behavior domain (b); the symptoms must present in early childhood (c) and limit everyday functioning (d). Experts disagree about the impact of these changes on prevalence. Some proponents of the new changes believe it will reduce the overdiagnosis of ASDs; on the other hand, some (including advocacy groups) are concerned the DSM-5 criteria will lead to a decrease in cases, and that high-functioning individuals with a 'mild ASD' (e.g., PDD-NOS or Asperger's disorder) will no longer meet the criteria and potentially lose some services, accommodation, and supports. The most thorough case analysis to date examining the effect of the proposed DSM-5 criteria on patients currently diagnosed with ASD suggests that 91% of these patients will retain their diagnosis under the proposed DSM-5 criteria [9].

CAUSE

The most perplexing aspect of ASDs remains their cause. The suspected causes of ASDs are as diverse as the spectrum itself, and presumably reflect a child's early life environment and genetic endowment. In some cases, identifying a cause can not only allay familial guilt and anxiety, but also allow more meaningful family counseling, medical evaluation or monitoring, and treatment [10].

Genetics

Advances in genetic testing – for example, comparative genomic hybridization and other new, sophisticated techniques – have enabled researchers to identify numerous candidate genes and loci on nearly every chromosome [11–14]. Fernandez *et al.*'s [15] initial implication of copy number variations (CNVs – an abnormal number of copies of a DNA segment) on the contactin (CNTN) 4 gene has led to research linking other CNTN family candidate genes involved in central nervous system function (e.g., CNTNAP2) to small populations with ASDs [16].

Interest in the genetic heritability of ASDs originated with Folstein and Rutter's first twin study reporting a striking difference between monozygotic and dizygotic twins [17]; their subsequent studies reported increasingly higher monozygotic concordance rates and nearly 0% dizygotic concordance [18]. In the past decade, genetic susceptibility to ASDs has been a main focus of research, with studies reporting concordance rates as high as 90% in monozygotic twins and as low as 10% in dizygotic twins [19]. Genetic research had collectively implied a strong genetic component to ASDs – attributing almost all variances in phenotypic expression to heritable factors [18].

Last year, the results of the largest ever ASD twin study, the California Autism Twin Study, found ASD concordance rates to be much lower than previously expected [20▪]. A total of 192 twin pairs born between 1987 and 2004 were identified where at least one twin had either autistic disorder or a milder ASD. For autistic disorder (and not other ASDs), probandwise concordance for male twins was 0.58 for 40 monozygotic pairs and 0.21 for 31 dizygotic pairs, and for female twins 0.60 for seven monozygotic pairs and 0.27 for 10 dizygotic pairs. Much higher concordance was observed when the entire spectrum of ASDs was included. Probandwise concordance for male twins was 0.77 for 45 monozygotic pairs and 0.31 for 45 dizygotic pairs, and for female twins 0.50 for nine monozygotic pairs and 0.36 for 13 dizygotic pairs. Results indicated that ASD was 55% attributable to the environmental factors shared by twins, a much greater percentage than predicted by earlier twin studies [20▪]. Given the California twin population was ethnically, demographically, and socioeconomically diverse, these results were interpreted as convincing evidence for environmental influences on ASDs.

Immunological

Several different lines of recent research suggest an association between ASDs and the immunological response; unfortunately, the relevance and implications of these different associations are not well understood. While some studies suggest maternal immune response to prenatal infection may be responsible for many cases of ASDs, other studies have identified altered immune responses in children with ASDs.

Prenatal immune influences have been suggested by large-scale epidemiologic studies that demonstrate an increased risk of ASD in the offspring of women who had a viral or bacterial infection during pregnancy. Researchers believe that ASD is not a consequence of the infection itself, but rather the maternal immune response to that infection. This hypothesis was supported by a recent animal study. When pregnant mice were injected with a viral mimic that initiated the same type of immune response as a viral infection, the offspring demonstrated the equivalent of core behavioral and neuropathological symptoms associated with ASD. Moreover, the 'ASD mice' no longer exhibited stereotyped/repetitive and anxiety-like behaviors when irradiated and given an immunologically normal bone-marrow transplant. Such immune system dysregulation could be a promising target for ASD treatment in at least one-third of the ASD population. Further testing in mice models is needed before considering immunological treatments in humans [21].

Other recent studies have suggested that the immune system of children with ASD is more highly activated. For example, several investigators have demonstrated increased cytokine levels in children with ASD, with one recent study finding the greatest elevation in children with a history of regressive autism [22,23]. These findings, if replicated, have implications not only for the clinical diagnosis of ASD, but also for its treatment. We believe it is likely that researchers will make rapid and substantial gains in teasing out prenatal and postnatal immune influences in the next few years.

Environmental

One of the most contentious environmental concerns centers on childhood vaccines. Dr Andrew Wakefield stirred this fear in parents when he released an article implying a link between the measles, mumps, and rubella (MMR) vaccine and 'a new syndrome of autism and bowel disease' [24]. While the study was retracted for methodological concerns of sample bias, it was later revealed that Wakefield falsified the data [25]. Despite public renouncement of this study, many parents were influenced by this putative 'connection' between childhood vaccines and the development of ASDs.

Once the MMR vaccine was dismissed as a cause of ASDs, thimerosal, the mercury-containing preservative in vaccines, became the new target. To ease concerns over potential neurotoxic effects of the mercury, essentially all vaccinations for young children are now thimerosal-free [26]. Unfortunately, ASD incidence has not dropped – validating the opinion of experts that thimerosal was not responsible for the increased incidence of ASDs [27,28].

In October 2007, Dr Robert Sears published *The Vaccine Book: Making the Right Decision for Your Child*, encouraging alternative and selective vaccine schedules for concerned parents. Sears proposed giving a child the 'bare minimum' and increasing vaccination intervals. Dr Sears raised concerns about many vaccine ingredients – namely fetal bovine serum and human blood products (presumably albumin). However, his fears are generally predicated on faulty logic and misinformation. For example, his rationale for spacing out vaccinations is to avoid exposure to high levels of aluminum. In fact, by 6 months of age, infants typically ingest far greater amounts of aluminum from breast milk or formula than is contained in vaccines [29]. Refer to Offit and Moser's broader critique of Sears' ideology for more information [28].

Although valid scientific evidence linking vaccinations to ASDs has yet to be produced, anxious parents continue to express concerns about vaccine safety. Unfortunately, each time research dispels concerns about one aspect of the vaccine regimen, fears are raised about another theoretical risk. At this time, many in the scientific community are frustrated that limited resources continue to be expended refuting scientifically tenuous or fallacious reasoning; on the other hand, it is important to maintain public confidence in the recommended vaccine regimen.

Given the recent reports that ASD concordance rates were severely underestimated for dizygotic twins in the past, research is now focused on the potential prenatal and postnatal environmental triggers [30]. Future research will likely analyze the shared environment, or experiences common to both twins, prior to the second year of life [30]. Suspect environmental factors include parental age [31], maternal infections during pregnancy [32], multiple births [33], and low birth weight [34].

EARLY IDENTIFICATION OF AUTISM SPECTRUM DISORDER

As most ASDs are diagnosed in early childhood, the pediatrician plays a crucial role in identifying toddlers at risk for an ASD, and ultimately searching for the underlying cause of a child's ASD. Clinical guidelines exist for highlighting the key behaviors and signs that should alert a pediatrician to an ASD. The American Academy of Pediatrics (AAP)'s most recent guidelines [35] provide pediatricians with a 'toolbox' of recommended tests to screen for ASDs and guidelines for the medical evaluation of children for whom there are clinical concerns. Specifically, the AAP developed an 'Algorithm for Developmental Surveillance and Screening', with the expectation that pediatricians screen with standardized developmental tools at the 9, 18, and 24 or 30 month visits, and that an ASD-specific screening tool be used at the 18 and 24 month visits to maximize the early detection of ASDs [35]. The Modified Checklist for Autism in Toddlers (M-CHAT) is a helpful (but imperfect) screening tool that can be administered to all children in a primary care setting at no cost to the practitioner [36].

To insure the most favorable outcome, increased emphasis is being placed on early identification of ASDs. As signs are sometimes present before 12 months of age, pediatricians may wish to more formally assess older infants. The AAP's Autism Toolkit includes a copy of the Communication and Symbolic Behavior Scales Developmental Profile (CSBS DP), a 24-item parent checklist with norms extending down to 6 months of age. Researchers just reported on the positive-predictive value of another screening tool, the First Year Inventory (FYI) – a parent-report measure designed to identify 12-month-old infants at risk for ASDs [37▪]. A longitudinal follow-up study found that 31% of children classified as at risk for ASD on the FYI at 12 months received a confirmed diagnosis by 3 years old, with 85% of the at-risk children having a developmental disability or concern by 3 years old. As most ASD-specific screening by pediatricians is currently done between 18 and 24 months old, instruments like the FYI or the CSBS DP may allow children at high risk for ASD to receive early intervention even sooner.

MEDICAL EVALUATION

Diagnostic medical testing of children with ASD or an intellectual disability (formerly mental retardation) has focused on four main areas – genetic testing, neuroimaging, EEG, and metabolic screening. In recent years, there have been significant changes in the recommended diagnostic approach to evaluating children with ASD or intellectual disability. Some conventional tests have been deemed unnecessary because of their very low diagnostic yield and others have been rendered 'obsolete' with the development of more sophisticated alternatives.

Genetic testing

Advances in molecular genetic testing have radically transformed the clinical approach to etiologic evaluation of children with autism and intellectual disability. Chromosomal karyotypes – routine G-banding or when testing for fragility of the X chromosome – have now been replaced by molecular genetic techniques that have a higher yield. Chromosomal microarray analysis (CMA), otherwise known as comparative genomic hybridization, is the most robust test available to clinicians for identifying a genetic basis for ASD or intellectual disability [38–40]. Whereas G-banded karyotype would identify a genetic abnormality in fewer than 3% of cases, CMA – with its ability to detect clinically significant copy-number variants with 100 times greater resolution than standard karyotyping – has identified clinically significant abnormalities in 8% or more of ASD cases. Although the AAP's 2007 guidelines did not recommend routine CMA testing, a recent AAP publication detailed the advantages of CMA over karyotypes [38]. The AAP's most recent recommendations to physicians regarding the initial medical evaluation of a child with ASD are outlined in the newly revised Autism Toolkit. There, the AAP recommends in its 'Physician Fact Sheet' that CMA be offered to all patients with ASD [41].

Many commercial laboratories offer CMA test batteries that focus on the genetic anomalies most commonly associated with ASD. Interestingly, researchers recently reported on the findings of a proprietary genetic test battery intended to predict ASDs. Focusing on the 237 genetic markers on 146 genes and related cellular pathways linked to ASDs, this test takes the novel approach of examining multiple genetic mutations and their additive contribution, while considering protective versus vulnerability single-nucleotide polymorphisms (SNPs) and the genetic differences between ethnicities. Investigators reported that the test correctly predicted ASDs in 72% of cases in two independent sets of central European-descending populations [42▪▪]. The outcome of ongoing evaluations among other ethnic groups will further determine the test's accuracy and specificity. Nonetheless, like some of the early screening parent questionnaires, this test may aid early detection of ASDs in some cases. Though not yet clinically available through commercial laboratories, exome sequencing has recently been reported to identify de-novo genetic mutations in about 15% of children with severe intellectual disability, some of whom also had autism [43]. This investigational technique will likely be available in the not-too-distant future. Ultimately, it is anticipated that whole-genome sequencing will become commercially available and will supplant all other genetic tests in the evaluation of children with severe developmental disability. A proof-of-concept study showed that whole-genome sequencing can be done in a clinical setting [44].

Although CMA testing is quite sensitive for some genetic defects, it does not detect Fragile X syndrome or Rett syndrome. The AAP recommends that DNA testing for Fragile X should also be offered to all patients with ASD. The index of suspicion for Fragile X will be heightened if phenotypic features or a positive family history are present; however, Fragile X testing is indicated even if the family history is negative or if the patient – especially a woman – is nonstigmatized. Genetic testing for Rett syndrome – MECP2 gene mutation and sequence analysis – should generally be limited to girls with microcephaly or deceleration of head growth and other features of Rett syndrome, or who present with stereotypical hand-wringing movements and developmental regression [41].

Even though chromosomal karyotypes should no longer be routinely ordered, a karyotype is indicated if a balanced translocation is suspected, as these will not be detected with CMA. Clinicians should suspect a balanced translocation if there is a history of more than two miscarriages. In children with ASD and macrocephaly (head circumference >2 standard deviations above the mean), PTEN gene mutation and sequence analysis should be considered, as affected patients (and some family members) are at increased risk for certain malignancies. This mutation should be considered especially in men with penile macules. Clinical consultation with a geneticist may be helpful regarding further evaluation or counseling. For example, if Angelman syndrome is suspected in a child with intellectual disability, happy affect, and hand waving and clapping, CMA may be negative in some cases and more sophisticated testing would be indicated [41].

Neuroimaging

Neuroimaging technologies have likewise become more sophisticated, with functional magnetic resonance imaging (fMRI) emerging as an effective research tool for isolating frequently disrupted neural systems that may underlie ASDs [41]. It is suspected that brain abnormalities found consistently among patients with ASDs are a product of underlying genetic mutations that influence the expression of key proteins in the brain, and thus result in inefficient neuronal migration, cortex organization, and overall neural circuitry [45▪].

Current studies are using neuroimaging to isolate these problem regions in the brains of people with and without ASDs, noting differences in gene expression, brain architecture, and displayed behaviors that characterize ASD [46,47▪▪]. Careful analysis of the structural and volumetric measures derived from brain MRIs has failed to identify a consistent pattern of early brain development in children with ASDs. Recent studies using diffusion tensor imaging (DTI, a technique that measures water diffusion within a tissue) suggest that there is a distinct white-matter fiber tract maturation pattern discernable in high-risk infants who eventually develop an ASD or ASD-like symptoms [41]. It is hoped that identification of ASD brain biomarkers will soon allow earlier and enhanced ASD-risk detection and that, with time, neuroimaging will provide an objective diagnostic test. At this time, 'isolated, stable macrocephaly' is not an indication for an MRI or CT scan. The AAP recommends that MRIs should only be considered in children with acute regression, microcephaly, midline facial defects, neurocutaneous lesions (with or without Wood lamp), or abnormalities on neurologic examination [41].

Electroencephalogram

Guidelines suggest that a sleep-deprived EEG with adequate sampling of slow-wave sleep should only be performed if there is a history of acute developmental regression, unexplained behavior change, clinical seizures, or suspicion of subclinical seizures [41,48].

Metabolic testing

Metabolic disorders, resulting from biological errors in amino acid, carbohydrate, purine, peptide, or mitochondrial metabolism, are the cause of an ASD in fewer than 5% of all cases. Metabolic testing should not be routinely performed. The AAP recommends that testing be limited to 'children with cyclic vomiting, hypotonia, lethargy (especially when associated with mild illnesses), poor growth, unusual odors, multiple organ involvement, ataxia or other movement disorder, or evidence of a storage disease (e.g., coarse features). Testing should include lactate, pyruvate, carnitine, acylcarnitine profile, liver and renal function, amino acids including testing for phenylketonuria, and urine organic acids'. Lead levels should be monitored in children with ASD and a history of pica, especially those living in a high-risk environment. Serum ferritin level may also be indicated to assess iron stores. According to the AAP, there is no evidence that hair analysis, micronutrient levels, intestinal permeability studies, stool analyses, urinary peptides, or mercury levels are helpful [41,48].

TREATMENT

Educational therapy focusing on behavior, communication, and social responsiveness remains the mainstay of treatment for ASDs. Medications, though not indicated for the treatment of ASDs themselves, are occasionally helpful in addressing different symptoms, including hyperactivity and irritability. A range of alternative therapies exist, though they generally have very little research to support their use.

Educational therapies

Educational therapies are the primary form of intervention for ASDs in children. Although many different techniques are available, only some of these approaches are considered 'evidence based'. Applied behavior analysis (ABA) and the Early Start Denver Model (ESDM) are best supported by well-designed research; however, pediatricians should be familiar with other, widely known treatment approaches.

Applied behavior analysis

ABA encourages socially significant behaviors through a reinforcement learning technique that trains children with autism to engage in activities of daily living. ABA has been considered a successful behavioral intervention for the past five decades, yielding substantial gains for children with autism in intelligence quotient, language, academic performance, and adaptive behavior, with significantly better social behavior compared with children with autistic disorder in control groups [49].

The success of ABA has led to many different forms. In Lovaas' Young Autism Project, a discrete trial training (DTT) methodology was employed [50]. DTT is now the most widely recognized form of ABA. DTT fosters learning readiness by teaching fundamental skills such as attention, compliance, imitation, and discrimination learning as small, individually acquired tasks [49].

Like other forms of ABA, DTT has been questioned for its applicability in natural situations as it is conducted entirely in a structured teaching environment. To address these concerns, traditional ABA techniques have been modified in recent years via naturalization of these behavioral interventions [51]. Whereas traditional ABA has long been recognized as the educational treatment of choice for young children with autism, it is less clear whether this treatment paradigm is the optimal approach

for less severely affected, higher functioning individuals.

Early Start Denver Model

The ESDM is a novel developmental–behavioral intervention rooted in ABA that is designed for young children (toddlers) with signs of an ASD [52]. The ESDM was effective in randomized clinical trials for children as young as 12–18 months across all ASDs by teaching child-specific goals through play activities [53]. The ESDM model has now been adapted for experimental use in infants as young as 6 months with signs of ASD [54].

'Floortime'/developmental individual-difference relationship-based model

The developmental individual-difference relationship-based (DIR) model is a relationship-focused intervention often integrated with floortime play, in which adults engage with children by playing with them on the floor [55]. By allowing the child to lead floortime play activities, the child is challenged to work toward achieving social and emotional milestones. An independent pilot study training parents to use the Floortime/DIR model at home for 15 h/week over 8–12 months reported that 45.5% of children made substantial functional developmental progress, deeming it a potentially cost-effective intervention for young children with autism [56]. A recent study in Thailand found that adding Floortime/DIR intervention for 15.2 h/week for 3 months among preschool children with ASDs conferred on the intervention group significantly greater gains on three measures: Functional Emotional Assessment Scale, Childhood Autism Rating Scale, and the Functional Emotional Questionnaires [57]. Preliminary results of an ongoing randomized controlled Canadian trial of 51 preschool age children in either a DIR treatment group (2 h/week of therapy and parent coaching) or a community treatment group (3.9 h/week) suggest that children in the DIR treatment group made significantly greater gains in social interaction skills compared with the community treatment group [58]. Although these two comparative studies from 2011 demonstrated that DIR/Floortime significantly improved emotional development and reduced core ASD symptoms, it is unclear whether this treatment approach would be as effective in settings where more extensive treatments are provided.

Pivotal response treatment

Pivotal response treatment (PRT) is another research-validated treatment for ASDs. PRT, also derived from ABA, trains parents to encourage their children to display pivotal developmental behaviors: attention, persistence, interest, initiation, cooperation, joint attention, and affect [49]. PRT reinforces positive social communication without disruptive self-stimulatory behaviors; it is mainly used with preschool and elementary school children, but also helps adolescents and young adults [59,60]. PRT is a fundamental component of the ESDM.

Relationship development intervention

Relationship development intervention (RDI) emphasizes the value of positive interaction by engaging the child in a social relationship that motivates the child to acquire the social skills to maintain such relationships [61]. RDI allows individuals with ASDs to develop 'dynamic intelligence', or flexible thinking, which allows them to cope with changes and new information. RDI is built from the perspective that ASDs are a deviation from typical development of social relationships because of an inability to think flexibly. RDI addresses this dysfunction by helping parents gradually build their relationship with their child. Although Greenspan found a positive result in a small sample of individuals with ASD receiving RDI [62], RDI efficacy has yet to be evaluated by independent empirical studies.

Training and education of autistic and related communication handicapped children

The training and education of autistic and related communication handicapped children (TEACCH) method is structure based, often called 'structured teaching', including organization of the physical environment, predictable sequences of activities, visual schedules, flexible routines, structured work and activity systems, and visually structured activities [63]. Emphasis lies on modifying the environment to accommodate a child's deficits and improve the child's individual skills [49]. Among children receiving TEACCH services, improvements in parent teaching skills and parent satisfaction have been reported, though not based on controlled studies of treatment outcomes. In a controlled study, children enrolled in a TEACCH-based home program for 4 months along with their local day treatment programs improved significantly more than those in the control group who only received local day treatment services [64].

Educational therapies in perspective

Given the expanded number of educational techniques to treat children with ASD – some with more empirical support than others – it is likely difficult

for a primary care pediatrician to appreciate the differences among these treatment approaches and make informed recommendations to families about what constitutes an optimal treatment for a specific child. Although it would be wonderful if parents and professionals had an evidence-based algorithm to clearly identify which treatment method is best for each child on the autism spectrum, no such algorithm exists. Realistically, selection of an educational approach for a child with ASD will be subject to clinical considerations as well as nonclinical factors – such as parent preference, cost, and accessibility.

Pharmacotherapy: medical treatments currently available

Although no medications are FDA approved to treat the core symptoms of ASDs, pharmacotherapy may be used in children with ASD to target commonly associated symptoms such as hyperactivity, impulsivity, inattention, aggression, irritability, anxiety, and withdrawal. The decision to prescribe medication should be on a case-by-case basis after reasonable nonpharmacologic interventions have been attempted. Two atypical antipsychotics are approved by the FDA for the treatment of irritability in children with autism – risperidone (age 5 and above) and aripiprazole (age 6 and above). These medications, though effective, often have side-effects and require careful monitoring. Increased appetite with significant weight gain is not uncommon. Although monitoring abdominal girth (waist circumference) may be helpful, BMI measurements at baseline and at follow-up provide a more precise metric. Insulin resistance with blood sugar elevation is also associated with the atypical antipsychotics. Although monitoring protocols vary considerably, many experts recommend baseline testing and then follow-up testing at 3 months, 6 months, and then every 6 months thereafter [65]. Baseline blood tests should include fasting plasma glucose, hemoglobin a1c, fasting lipids, liver function tests, prolactin, and thyroid stimulating hormone. Follow-up testing should include fasting glucose and lipids. Some guidelines also recommend monitoring insulin levels, though others suggest following high-density lipoprotein/triglyceride ratios, as triglyceride elevation is almost always present with insulin resistance. Prolactin levels should be monitored in cases where symptoms or signs of elevation are evident; likewise, a complete blood count may be included if there are concerns about neutropenia. Patients who have multiple risk factors for diabetes mellitus or who have gained *at least* 7% of their pretreatment weight should be monitored especially closely.

Hyperactivity and impulsivity are not uncommon in children with ASDs. Any of the FDA-approved ADHD medications can be used in children with ASDs. When prescribed for children with ASDs, stimulants typically have a somewhat smaller effect size; in addition, lower doses are often required and adverse events may be more common [66]. It must be remembered that children with ASDs may not be able to communicate side-effects such as stomachaches or headaches, so parents and clinicians must be especially attentive to dosing and clinical response. As children with ASDs often have difficulty with existing forms of long-acting stimulants (caplets, capsules, sprinkled beads, or transdermal patches), clinicians may find a newly approved, extended release liquid methylphenidate formulation to be especially helpful in some children. Atomoxetine or alpha-2 agonists may be used to treat hyperactivity or impulsivity, especially in children for whom stimulants are not effective and well tolerated.

In the past, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine have been used to treat repetitive behaviors or rigidity in children with ASD; however, studies suggest these medications may be effective in adults, but not children. Likewise, children with ASD are often very anxious, which can then lead to significant behavior problems. Although there are no studies demonstrating that SSRIs are effective in reducing anxiety in children with ASDs, these medications are sometimes prescribed based on their demonstrated efficacy in the non-ASD population [67].

Sleep problems are also common in children with ASDs. Although nonpharmacologic interventions should always be the initial treatment approach, melatonin has been shown to be effective when given before bedtime at doses ranging from 0.5 to 10 mg. As alpha-2 agonists and atomoxetine are also somewhat sedating in some children, nighttime administration of these medications may be helpful in children experiencing problems with sleep onset [67].

Although treatment with other medications (e.g., typical antipsychotics, mood stabilizers) is sometimes indicated, children with ASD needing more sophisticated or aggressive psychopharmacologic management should likely be referred to a pediatric subspecialist with expertise in this field – either pediatric neurologist, child psychiatrist, or developmental pediatrician [67].

Promising medical treatments

Genetic investigations of ASDs have led researchers to develop experimental medical treatments that

target these genetic abnormalities. For example, arbaclofen (an investigational drug for patients with Fragile X syndrome) has been shown to be a potential disease-modifying drug in preclinical models [68▪] and results in significant improvements in social impairment in clinical trial [69▪▪]. Given its preliminary success in treating a core symptom of autism, arbaclofen will be further tested in ongoing clinical trials, and could be the first effective medicine to treat Fragile X. Of course, it is hoped that, if arbaclofen can improve the social function of children with comorbid ASD and Fragile X, it may be effective in other ASD populations as well or lead to the development of other effective medications.

Enzyme replacement therapy is another investigational treatment that has been fast-tracked for clinical testing in the USA. This treatment is targeted at children with autism who are reported to have biomarkers suggesting enzyme deficiencies. These enzyme deficiencies then result in an inability to digest protein, which then compromises amino acid production. A proprietary high-protease enzyme replacement formulation (CM-AT) was just reported to be significantly more effective than placebo in treating core and noncore symptoms of children aged 3–8 years with autism in a randomized, double-blind, Phase III clinical trial [70,71].

Another potential therapeutic focuses on the patients with autism, intellectual disability, and seizures because of a defect of branched chain amino acid (BCAA) metabolism. Patients with this rare mutation have decreased levels of BCAAs. Novarino *et al.* [72] demonstrated in a genetically engineered 'knockout mice' model that abnormal brain amino acid profiles and neurobehavioral deficits respond to dietary supplementation. The researchers also took skin samples from patients with this gene defect and converted them into neural stem cells; these neural cells functioned normally in the presence of an environment rich in the depleted amino acids – suggesting that at least one very rare form of autism may be treatable.

New research suggests that other available medications may be helpful in treating children with ASD. Oral administration of N-acetylcysteine (NAC), an antioxidant and a glutamatergic modulator, displayed efficacy in treating disruptive symptoms in children with autistic disorder in a pilot study [73▪]. Further studies are needed to assess the feasibility of using NAC as a routine treatment option for disruptive behaviors from autistic disorder and for other disorders marked by repetition and compulsion (i.e. obsessive compulsive disorder and skin picking). Similarly, preliminary results of a large-scale, placebo-controlled, double-blind study suggest that nasally administered oxytocin has been found to improve core deficits of ASD in children and adolescents. Increased brain activity in regions known to process social information was observed following oxytocin treatment, translating behaviorally to greater social engagement [74]. Again, additional studies are needed to determine whether these available medications are indeed well tolerated and effective for use in children with ASD.

COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES

Studies indicate that 50–75% of children with ASDs are treated with complementary and alternative medicine (CAM) [75,76]; these percentages are even higher in children with severe autism or comorbid intellectual disability. Such therapies are easily accessible and perhaps more psychologically comforting for parents given that they are generally less invasive [76]. Unfortunately, the scope of this article does not allow discussion of the dozens of CAM therapies for ASD; instead, we will briefly discuss some of the more popular, intriguing, and controversial interventions.

Dietary changes are often made to enhance or alleviate common symptoms in children with ASD. The most common dietary intervention is a gluten-free/casein-free diet, which families pursue in the hope that it will alleviate suspect gastrointestinal problems thought to aggravate ASD symptoms [77]. Although many gluten-free foods are now available, the gluten-free/casein-free elimination diet can be difficult to implement. More importantly, in a methodologically rigorous, well-controlled study of children with ASDs on the gluten-free/casein-free diet for at least 1 month, there were no significant changes in attention, activity, sleep, or bowel habits [78]. Pediatricians should counsel families about this latest research finding – recognizing at the same time that many parents will be encouraged by anecdotal reports and try the gluten-free/casein-free diet nonetheless.

Supplementation with omega-3 fatty acids is also not uncommon. A randomized, double-blind, placebo-controlled, 6-week pilot trial [79] examined the effects of 1.5 g/day of omega-3 fatty acids (0.84 g/day eicosapentaenoic acid and 0.7 g/day docosahexaenoic acid) supplementation on children with ASDs. In this pilot study of 13 children (aged 5–17 years) with autistic disorders accompanied by severe tantrums, aggression, or self-injurious behavior, investigators noted decreased hyperactivity and stereotypy (each with a large effect size) and no significant adverse effects. Although replicating these findings in larger samples is needed, there is

likely little harm in families considering an empiric trial of fish oil supplementation.

Many other dietary supplements have been promoted, though few have credible research to support their use. In a pair of controlled studies by the investigators at Arizona State University, investigators noted children with autistic disorder to have various nutritional deficiencies [80] and that vitamin and mineral supplements led to improvements on nutritional, metabolic, and clinical outcome measures [81]. Despite longstanding claims that Vitamin B6 and magnesium supplementation is helpful, a recent Cochrane review noted there were few studies available, the samples were small, and the results inconclusive. It concluded that research does not support this form of treatment [82]. Methyl B12 injections have been used to prevent oxidative stress often linked to ASDs, with only anecdotal reports of improvement [83]. Studies looking at the nutritional status of children with ASD and treatment opportunities are actively being pursued; hopefully, research will soon clarify which dietary and nutritional interventions can be considered well tolerated and effective.

Hyperbaric oxygen therapy (HBOT), which uses pressurized oxygen to increase blood flow and oxygen to the brain and decrease inflammation, has been suggested as a treatment for ASD. At this point, there are very few well-controlled trials and the results are inconsistent. Experts have recommended that methodologically rigorous studies be conducted with meticulous attention to sham control conditions. Pending further evidence to suggest efficacy, HBOT is not recommended for children with ASD [84].

Chemical chelation has been a popular yet controversial intervention among families who believe heavy metal poisoning (e.g., mercury) is responsible for their child's ASD symptoms. In two internet-based surveys, 7–8% of parents of children with ASD indicated that they had tried chelation therapy. Although a few published studies provide weak evidence for chelation, there are no well-controlled studies to suggest it is either well tolerated or effective. A 2013 review article concludes that research does not support chelation as a treatment for ASD [85]. Pediatricians should also discourage families from pursuing craniosacral massage (most typically proffered by chiropractors) or auditory integration therapy.

Complementary and alternative medicine in perspective

From an emotional standpoint, it is understandable how families may feel compelled to explore CAM treatments. Pediatricians who want to practice evidence-based medicine must remember that novel therapies may be effective and that the absence of research does not necessarily mean absence of benefit. On the other hand, the benefits (if any) of most CAM treatments are overstated, and there are considerable risks if families pursue each and every CAM treatment available. A family's decision to pursue CAM may be acceptable as long as it does not present health risks to the child, preclude more effective therapies, or usurp limited family resources [86]. Integrative medicine, a blend of traditional and nontraditional treatments, is an emerging compromise between mainstream pediatricians who are skeptical and hopeful parents desperate to help their child.

Prognosis

Recent studies suggest that the outcome for children with ASD can be highly variable. Children with ASDs can differ considerably at baseline and at follow-up not just in terms of severity, but also with regard to associated developmental disabilities (e.g., intellectual disability), medical conditions, and comorbid psychiatric disorders. Efforts to model the diverse cases of ASDs have generated mathematical representations of typical outcomes along a path of defined functional level. Through a longitudinal developmental surveillance study of a large population of children with ASDs in California, six distinct trajectories in three functional domains (social, communication, and repetitive behavior) have been identified [87▪▪]. As can be seen in Fig. 1, each of these trajectories – high, medium-high, bloomers, medium, low-medium, and low – begins with a baseline ASD severity, which has been associated with the most common factors within the population. Socioeconomic status is implicated as a significant factor in ASD developmental outcome, as it encompasses variables inherent to home and neighborhood environment, including quality of treatment and education, and access to services and early interventions [87▪▪].

CONCLUSION

Years ago, Winston Churchill – in reference to the Russian foreign policy – lamented: 'It is a riddle, wrapped in a mystery, inside an enigma; but perhaps there is a key'. Undoubtedly, experts in child development would likely extend Churchill's famous words to ASDs. Although gains in understanding have been achieved, progress has been slow and researchers have far more questions than answers. Whereas causes were once viewed as either genetic

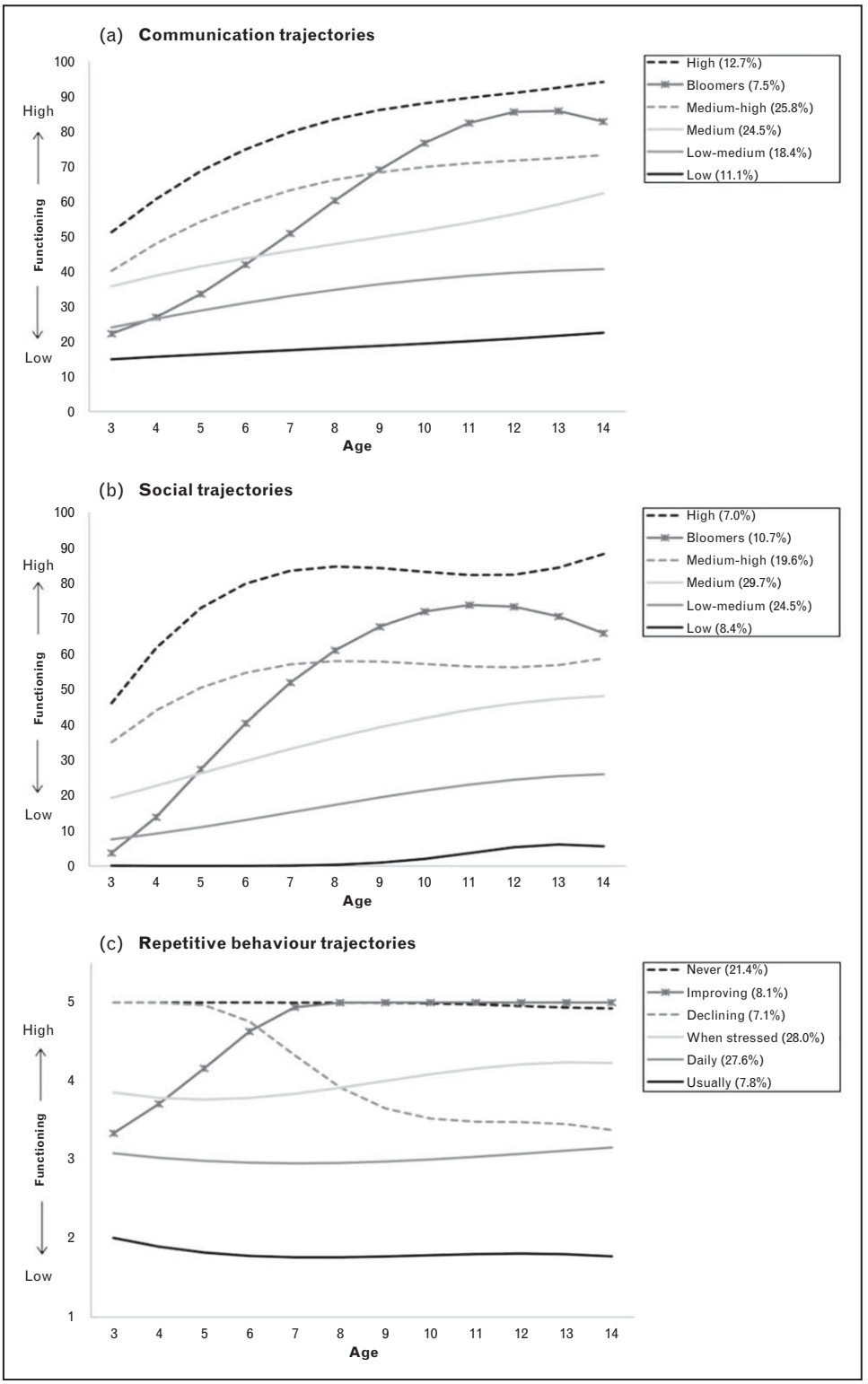

FIGURE 1. Modeled symptom trajectories by functionality versus age, for across autism spectrum disorder (ASD) diagnostic criteria: (a) communication, (b) social, and (c) repetitive behavior. Data from Fountain *et al.* [87▪▪].

or environmental, there is now greater appreciation of the phenomenon of epigenetics – in which environmental factors influence gene expression. As more epigenetic associations are explored, it is hoped the nature–nurture interaction underlying ASDs will be better understood.

Recent studies suggest that children with ASD can be identified at an early age and, indeed, benefit

from very early intervention. Although developmental/educational/behavioral treatments will continue to serve as the mainstay of treatment, new research suggests that one or more medical therapies may be a helpful adjunct. Hopefully, in the coming decade, sociocultural and medical interventions can target the genetic and overlying environmental factors associated with ASDs.

Pediatricians truly play a pivotal role regarding ASDs. It is incumbent on pediatricians to screen all young children as recommended and to refer patients for evaluation at the earliest sign of concern. For children diagnosed with an ASD, pediatricians should be a resource for families about the range of available treatments and should be an advocate for affected children to make sure that they receive all appropriate care and services. Hopefully, investigators will soon find one or more of the keys to which Winston Churchill alluded.

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Conflicts of interest

A.A. is a consultant to NextWave Pharmaceuticals. A.T. declares no conflicts of interest.

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