NCC Pediatrics Continuity Clinic Curriculum:
Development II: Atypical Development
Faculty Guide

Pre-Meeting Preparation:

Please read or skim the following enclosures and click on the video links below:

- "Intellectual Disabilities" *(PIR, June 2018)*
- "Autism, Language Disorder, and Social (Pragmatic) Communication Disorder: DSM-V and Differential Diagnoses" *(PIR, August 2015)*
- Autism Spectrum Disorder: DSMV Fact Sheet *(APA, 2013—updates PIR terms)*
- *Excerpts from* "A Rational Approach to the Medical Evaluation of a Child with Developmental Delay"*(Contemporary Pediatrics, 2004)*
- Key Points and Figures From "AAP: Hearing Assessment in Infants and Children: Recommendations Beyond Neonatal Screening *(Pediatrics, 2009)*
- **CDC Autism Case Study Video Library** (no login required)

Conference Agenda

- *Review* Development II Quiz
- Complete Development II Cases
- Development II Board Review
- **"Autism Speaks" Reflections**:
  - Which videos were particularly impactful. What were the major differences between "typical" and "atypical" children?
  - Do these videos resonate with your clinical experiences? Think about patients you follow with "atypical development", not only including ASDs.

Extra-Credit:

- "Developmental Delay: When and How to Screen" *(AAFP, 2017)*
- "Current evidence-based recommendations on investigating children with global developmental delay" *(BJM, 2017)*
- "Evaluation of the child with global developmental delay and intellectual disability" *(CanPaedSoc, 2018)*
- "Intellectual Disability (Mental Retardation)" *(PIR—2012)*
- "Language & Speech Disorders in Preschool Children" *(PIR—2005)*
- "Recognition of Autism Before Age 2 Years" *(PIR—2008)*
- "Identification & Evaluation of Children with ASDs" *(AAP Clinical Report- 2007)*
- "Sugar Coaters and Straight Talkers: Communicating About Developmental Delays in Primary Care" *(Pediatrics, 2009)*

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Intellectual Disabilities

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Education Gaps

1. Pediatricians must have knowledge of the diagnostic criteria and levels of severity of intellectual disability (ID).
2. Pediatricians should be informed about current developments in the evaluation of a child with ID.
3. Pediatricians must be familiar with treatment and resources for children with ID.

Objectives

After completing this article, readers should be able to:

1. Formulate a plan for the evaluation of children with intellectual disability (ID) both in terms of coming to a diagnosis (evaluation of cognitive and adaptive skills) and performing a diagnostic evaluation.
2. Formulate treatment options and referral for services for children with ID.

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ABBREVIATIONS

AAIDD	American Association of Intellectual and Developmental Disabilities
AAP	American Academy of Pediatrics
CDC	Centers for Disease Control and Prevention
CT	computed tomographic
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
GDD	global developmental delay
ID	intellectual disability
IEP	Individualized Education Program
MRI	magnetic resonance imaging
WISC-V	Wechsler Intelligence Scale in Children-V
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence-IV

Intellectual disability (ID) is a neurodevelopmental disorder that is characterized by deficits in both intellectual functioning and adaptive functioning, whose onset is in the developmental period. (1) It affects approximately 1% to 3% of the population. (2) *Intellectual disability* has replaced the former term, *mental retardation,* through a federal statute (Rosa's Law, Public Law 111-256). *Global developmental delay (GDD)* is the term used to describe children aged 0 to 5 years with significant delays in 2 or more areas of development. (1) Although these delays may be transient, it is estimated that approximately two-thirds of children diagnosed as having GDD would eventually carry the diagnosis of ID after 5 years of age. (3)

As part of routine health-care visits, the American Academy of Pediatrics (AAP) recommends developmental surveillance at every well-child visit and formal developmental screening at ages 9, 18, and 24 or 30 months. (4) Screening instruments such as the Ages and Stages Questionnaire, the Pediatric Evaluation of Developmental Skills, and the Denver Developmental Screening Test-II help to identify children who will require more formal developmental assessments, where a child's developmental skills are more thoroughly evaluated and that will likely include testing of cognitive abilities.

PRESENTATION

Intellectual disability may present in various ways and at different ages in the pediatric patient. The more severe the impairment, the more likely ID is to present and be diagnosed earlier. Correspondingly, the milder the impairment, the more likely it is to manifest at an older age. It is possible that milder forms of ID may go unrecognized until the school-age years. A child with ID may present initially with receptive and expressive language delays, adaptive skills delays (eg, toileting, dressing), fine motor deficits, difficulties in problem-solving skills, social immaturity, and behavioral difficulties. It is important to consider that intelligence/developmental tests during the first 3 years of life involve many sensorimotor tasks that may affect the accurate measurement of the cognitive level of a child with a motor problem (eg, cerebral palsy, hypotonia) or sensory impairment (visual and auditory). Among the different areas of development monitored in early childhood (language, problem-solving, gross/fine motor, personal-social skills), gross motor skills are the least correlated with ID.

ASSESSMENT

Assessment of Intellectual Functioning

Intellectual functioning is measured by standardized instruments such as the Wechsler Intelligence Scale in Children-V (WISC-V), the Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV), and the Stanford-Binet Intelligence Scales-V. These are generally performed by a certified psychologist or special educator. These instruments are designed to measure a child's general intellectual ability and include verbal and nonverbal subtests. Persons with ID exhibit deficits in both verbal and nonverbal domains, although not necessarily to the same degree. An overall full-scale IQ score is derived from the combination of verbal and nonverbal IQ scores.

The WISC-V and WPPSI-IV include the following indices: verbal comprehension index, visuospatial index, fluid reasoning, working memory, and processing speed. The Stanford-Binet subtests include knowledge, quantitative reasoning, visuospatial reasoning, working memory, and fluid reasoning. These instruments can be administered in children as early as approximately age 2 years (Stanford Binet-V) to 2½ years (WPPSI-IV), although it is important to note that intelligence scores become more stable after 5 years of age. (5)(6)(7) People with intelligence scores more than 2 SD below the mean are considered to fall in the ID range. Using the normal curve to delineate levels of intelligence with a mean IQ score of 100 and a standard deviation of 15, it is estimated that approximately 2.5% of the population would fall in the ID range with IQ scores less than 70 (2 SD below the mean). Those with IQ scores of 70 to 84 are considered to have borderline intelligence. In school, children with borderline intelligence may be considered "slow learners" but not to the same degree as children with ID. Making a diagnosis of ID is not always straightforward; it may require a few visits to fully assess a child, and ongoing follow-up may be necessary.

Assessment of Adaptive Functioning

Adaptive functioning is measured through questionnaires such as the Vineland Adaptive Behavior Scales and the Adaptive Behavior Assessment System, (5) which are administered by certified clinicians such as psychologists or social workers with information obtained from the patient's primary caregivers. In the *Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition,* adaptive functioning is operationalized in terms of 3 domains: the conceptual domain (eg, competence in memory, language, academics, judgment), the social domain (eg, social awareness, interpersonal communication skills, friendships), and the practical domain (eg, learning and self-management). Impairment in at least 1 of these domains, wherein ongoing support is needed, should be present to meet the definition of ID. (1)

The American Association of Intellectual and Developmental Disabilities (AAIDD), the oldest interdisciplinary professional organization that has been instrumental in the definition and recognition of ID and its earlier iterations, uses a similar definition of ID as the *DSM-V*. The AAIDD defines ID as a disability characterized by "significant limitations in both intellectual functioning and adaptive behavior" with the onset of deficits before 18 years of age. (8)

LEVELS OF SEVERITY

The *DSM-V* and the AAIDD characterize the severity of ID based on a person's adaptive functioning and the amount of support a person needs. These are described and summarized in the following subsections (Table 1). (1)(6)

Mild ID

A person with mild ID may manifest difficulties in late preschool or the early school-age years. They may have difficulties in the academic setting (early reading, writing, arithmetic, time, and money) and seem more socially immature compared with other children their age. Communication and thinking may be more concrete and less mature than that of their peers. Although they may function

TABLE 1. **Levels of Severity of Intellectual Disability (ID)**

LEVEL OF ID (% CHILDREN WITH ID)	LEVEL OF SUPPORT (IN CONCEPTUAL, SOCIAL, PRACTICAL DOMAINS)	ASSOCIATED ESTIMATED IQ SCORE	PROJECTED ULTIMATE ACADEMIC ACHIEVEMENT
Mild (85%)	Intermittent	55–70	Up to sixth-grade level
Moderate (10%)	Limited	40–55	Up to second-grade level
Severe (3%–4%)	Extensive	25–40	Preschool level
Profound (1%–2%)	Pervasive	<25	–

Note: The level of severity is based on the level of adaptive functioning and support. (1)(6)

appropriately in matters of personal care and many even eventually live independently, they may need support intermittently, particularly in complex daily living situations. Some may be able to reach a sixth-grade level in academic functioning.

Moderate ID

A person with moderate ID generally presents earlier than those with mild ID, manifesting with learning and language difficulties in the preschool years and deficits in social and communication behavior, which require limited although possibly substantial support. Those affected may ultimately be able to perform basic tasks for personal care (eg, dress, toilet, and eat independently), but significant amounts of support time and teaching may be needed. During adulthood, they may be employed in jobs that require minimal communication and cognitive skills and may be able to participate in all household tasks but with ongoing support and teaching. Some may be able to reach a second-grade level in academic functioning.

Severe ID

A person with severe ID has limited capacity to understand written language and the concepts of numbers and time and would need extensive support from caretakers throughout life. Spoken language is also very limited, and they may have limited understanding of speech/language and gestural communication. Children with severe ID would require extensive support and supervision for all activities of daily living. Some may reach the pre-K level in academic functioning.

Profound ID

A person with profound ID has conceptual skills that do not go beyond the concrete, and ability mainly involves manipulation of objects, at best. They have very limited understanding of symbolic language, although they may be able to understand basic instructions. A person with profound ID requires pervasive support and is dependent in all aspects of personal care and daily living.

In the *DSM-IV* and *DSM-IV-TR*, the previous editions of the *DSM*, (9) levels of ID were extrapolated by increasing standard deviations from the mean IQ; thus, mild ID was defined as IQ scores between 2 and 3 SD below the mean of 100 (IQ scores from 50–55 to approximately 70); moderate ID corresponded to IQ scores between 3 and 4 SD below 100 (IQ scores from 35–40 to 50–55); severe ID was defined as IQ scores between 20 to 25 and 35 to 40; and profound ID corresponded to IQ scores less than 20 to 25. Although this classification may still be useful, using IQ scores solely does not accurately and completely reflect how well an individual is able to function, hence the shift in the classification of the levels of ID based on the individual's level of adaptive function.

ETIOLOGY

There are many different etiologies for ID: genetic disorders (eg, chromosomal disorders, including X chromosome disorders, contiguous gene deletions, and single-gene disorders), environmental causes (eg, alcohol and other teratogens, prenatal infections), traumatic brain injury, neurologic/brain disorders, nutritional deficiencies, and inborn errors of metabolism. A significant number of people with ID have no identifiable cause (Table 2). It is more likely to identify a biological cause in more significant forms of ID (such as moderate, severe, and profound ID) than in mild ID, which may be influenced by cultural, linguistic, and societal difficulties. (5)

Genetic Causes of ID

Online Mendelian Inheritance in Man (10) lists approximately 800 genetic syndromes associated with ID. These syndromes may have X-linked, autosomal dominant, or

TABLE 2. **Causes of Intellectual Disability**

Genetic syndromes
Chromosomal disorders, eg, Down syndrome
Contiguous gene deletions, eg, Williams syndrome, Angelman syndrome
Single-gene deletions, eg, fragile X syndrome, Rett syndrome
Environmental causes
Alcohol and other teratogens
Prenatal infections
Early childhood central nervous system infections
Traumatic brain injury
Central nervous system disorders/malformations
Inborn errors of metabolism
Nutritional (eg, severe malnutrition, chronic iron deficiency)
Not known

autosomal recessive inheritance. Medical evaluation for those with syndromic forms of ID will be based on known clinical manifestations of the genetic syndrome. (10)(11)(12) Table 3 summarizes some of the more common genetic syndromes associated with ID.

Down syndrome is the most common genetic cause of ID, with prevalence of 1 in 800, with 95% of cases due to trisomy 21, 4% to 5% due to an unbalanced translocation between chromosome 21 and another chromosome (usually chromosome 14), and 1% attributed to mosaicism. The clinical phenotype is very well-known and includes a distinct facies, congenital heart disease, hypothyroidism, gastrointestinal disorders, and hypotonia. Intelligence is usually in the mild-moderate range of ID, with verbal skills weaker than nonverbal skills. It is also associated with early Alzheimer disease and depression. The AAP has published health maintenance guidelines for children with Down syndrome. (13)

Fragile X syndrome is a trinucleotide repeat disorder (CGG) and is the most common inherited cause of ID, affecting 1 in 4,000 individuals. Although it is much more common in males, fragile X syndrome may be diagnosed in girls as well. Fully affected males (with triplet repeats >200) manifest with significant ID as well as clinical features that may include relative macrocephaly, an elongated face, prominent ears, hyperextensible joints, and large testes in postpubertal individuals. Females with fragile X syndrome may present with milder forms of cognitive impairment. Fragile X syndrome also has a well-recognized association with autism spectrum disorders. (2)

Rett syndrome is due to a mutation of the *MECP2* gene found in the X chromosome. It is primarily seen in girls (although it has also been identified in boys), where the clinical presentation includes a deceleration in the rate of head growth during the second year of life, hand-wringing and handwashing movements, language deficits/regression, and ID. It is more likely that males with *MECP2* mutations present with neonatal encephalopathy than with GDD/ID. (2)

Certain contiguous gene disorders are also associated with ID. (10)(11)(12) Williams syndrome is caused by a deletion in chromosome 7q11 and presents with elfinlike facial features, mild to moderate ID (with nonverbal function being a significant weakness), and cardiac and renal manifestations. Angelman and Prader-Willi syndromes are a result of genetic imprinting, where clinical manifestations depend on which parent contributes to the deletion in chromosome 15q11.2-q13. Less commonly, these syndromes can also be attributed to uniparental disomy (2 copies of a chromosome from the same parent). Angelman syndrome is due to a maternally derived deletion (or paternal disomy) and is associated with severe-profound ID, microcephaly, prognathism, and abnormal hand movements, whereas Prader-Willi syndrome is caused by a deletion in the paternally derived chromosome (or maternal disomy). The clinical course of patients with Prader-Willi syndrome is unique and consists of hypotonia and feeding difficulties in the neonatal period and obesity, atypical facial features, some degree of ID (low average to moderate ID), and psychiatric conditions (eg, obsessive compulsive disorder, skin picking) starting in toddlerhood or the preschool years. Smith-Magenis syndrome is caused by a deletion in the short arm of chromosome 17 (17p11.2) and is characterized by facial features such as midface hypoplasia and a broad nasal bridge, short stature, medical conditions such as visual problems, peripheral neuropathy, mild-moderate ID, sleep disturbances, and stereotypic and self-injurious behaviors. Miller-Dieker syndrome is due to a deletion in chromosome 17 and is associated with significant ID, microcephaly, and lissencephaly, where the brain is small and smooth due to a paucity of gyri and sulci.

Single-gene deletions associated with ID, aside from fragile X syndrome and Rett syndrome, include Rubinstein-Taybi syndrome (ID, short stature, microcephaly, abnormalities of the thumbs and toes) and tuberous sclerosis (skin manifestations, ID, autism, seizures, particularly infantile spasms). (10)(11)(12)

Environmental Causes of ID

Environmental causes of ID may also present with a set of symptoms that compose a syndrome. Fetal alcohol spectrum disorder results from prenatal exposure to alcohol and

TABLE 3. **Common Genetic Syndromes Associated with Intellectual Disability (ID)**

SYNDROME	GENETIC ABNORMALITY	DEVELOPMENTAL PROFILE	COMMON PHYSICAL FINDINGS
Down	Trisomy 21 (95%) Translocation (4%) Mosaicism (1%)	Mild to moderate ID (Verbal - low) Hypotonia Early Alzheimer disease	Down facies Congenital heart disease Hypothyroidism Gastrointestinal abnormalities
Fragile X	CGG trinucleotide repeat (>200)	ID (typically moderate) Learning disorders Autism spectrum disorder	Elongated face Macrocephaly Prominent ears Hyperextensible joints Enlarged testes (postpuberty)
Rett	*MECP2* deletion	ID Stereotypic hand mannerisms Language regression	Deceleration in head growth Gait abnormalities
Williams	7q11 deletion	Mild to moderate ID (nonverbal - low)	Elfinlike facial features Cardiac (eg, supravalvular aortic stenosis) Renal abnormalities Hypertension
Angelman	Maternally derived deletion 15q (or paternal disomy)	Severe to profound ID Atypical hand mannerisms	Microcephaly Prognathism
Prader-Willi	Paternally derived deletion 15q (or maternal disomy)	ID (variable levels) Psychiatric conditions	Neonate: hypotonia/feeding difficulties Toddler: obesity, excessive appetite

is characterized by alcohol-related birth defects, microcephaly and growth retardation, facial features such as short palpebral fissures, thin upper lip, smooth philtrum, neurocognitive problems such as ID and ADHD, and behavioral difficulties. (14) Intrauterine infections (TORCH) may present with developmental disabilities, growth defects, retinopathy, intracranial calcifications, and abnormalities in head size such as microcephaly (eg, cytomegalovirus) or macrocephaly (eg, toxoplasmosis associated with hydrocephalus). Most recently, congenital Zika infection has been implicated in causing significant microcephaly and other brain abnormalities in infants, which may likely lead to ID. (15)

Significant hypoxic-ischemic injury in the neonate may present early on with significant GDDs, motor impairment such as muscle hypertonicity/spasticity, microcephaly or poor head growth, and seizures. Many children with severe hypoxic-ischemic encephalopathy will eventually be diagnosed as having ID as well as cerebral palsy. Prematurity, especially for children with younger gestational age and more complicated courses, also places a child at risk for intellectual impairment and developmental disorders. (16)

In the United States, there has been a significant decrease in the levels of environmental lead due to successful public health efforts implemented during the past few decades. Consequently, there has been a dramatic decrease in blood lead levels in children. Mildly elevated lead levels are still detected, and these have been shown to be associated with mild cognitive delays. Lead toxicity has been associated with a decline of 1 to 2 IQ points (measured at 5 years or older) for every 10-point increase in lead level (17)(18) and a decrease of more than 7 IQ points for the first 10 μg/dL. (19) The AAP recommends further research to look more closely into these associations, through studies where confounders such as socioeconomic factors are better controlled for. (17)

Through newborn screening, conditions that may have led to ID if left untreated are being identified. These conditions include phenylketonuria and congenital hypothyroidism. In 2006, the American College of Medical Genetics Newborn Screening Expert Group recommended that 29 treatable conditions be universally screened in the newborn. (20) There are variations in each state as to the complete set of disorders that are being tested for. Pediatricians should be familiar with the conditions that are tested for in their state and ensure that each newborn undergoes the state's newborn screening. The AAP has provided recommendations for pediatricians and medical homes as newborn screening has expanded. (21)

APPROACH TO EVALUATION

The approach to the evaluation for the etiology of the ID includes a thorough history, focused physical and neurologic

examinations, and appropriate laboratory testing as warranted. (2)(7) History and physical examination together can identify the etiology in approximately 17% to 34% of cases of developmental delay. (7) Based on the history and physical examination findings, initial evaluation, including laboratory testing, genetic testing, and imaging, is determined.

History

The medical history includes a child's current developmental functioning and a chronology of attainment of developmental milestones, a history of educational interventions, and a detailed prenatal/perinatal/neonatal history, which should include any history of maternal medical conditions and outcomes of previous pregnancies, maternal infections, medication intake and substance use/abuse, and a review of the newborn metabolic and hearing screens. A 3-generation family history of developmental problems; ID; learning deficits; neurologic, metabolic, or genetic conditions; and consanguinity should be explored. The child's medical history should include any previous head injuries, central nervous system infections (such as meningitis or encephalitis), seizures and other neurologic conditions, and regression in skills.

Physical and Neurologic Examination

The physical examination focuses on growth parameters (especially head circumference), a thorough skin examination looking for lesions that may signify a neurocutaneous syndrome, a full neurologic examination, and evaluation for dysmorphic features that may suggest a genetic syndrome.

Evaluation of Head Size. Microcephaly, or a head circumference less than the third percentile for age, is highly associated with ID and is a manifestation of many disorders. Macrocephaly or a head circumference greater than the 97th percentile for age is associated with ID in the setting of certain genetic syndromes, such as fragile X syndrome and Sotos syndrome, as well as in patients with hydrocephalus. Autism spectrum disorder has also been associated with an enlarged head, especially in the first 5 years of life, (22) and in some of these cases, ID may be present.

Examination of the Skin. Neurocutaneous syndromes may also be associated with ID. (10)(11) Tuberous sclerosis is associated with skin findings such as ash leaf spots (hypopigmented macules), shagreen patches ("peau d' orange"–textured skin lesions), and facial angiofibromas. Neurofibromatosis, which is associated with attention-deficit/hyperactivity disorder, learning disorders, and, less commonly, ID, is characterized by café au lait spots, inguinal and axillary freckling, Lisch nodules on eye examinations, and neurofibromas in the body.

Dysmorphic Features. The clinician should take note of dysmorphic features and atypical features that may be manifestations of certain genetic syndromes as described previously.

LABORATORY EVALUATION

Evaluation of Syndromic Forms of ID

If the clinician suspects a specific syndrome as an etiology for the ID/GDD, laboratory tests to confirm or rule out this syndrome should be performed. This may include chromosome analysis for Down syndrome and fluorescence in situ hybridization testing when specific genetic disorders are suspected, such as Prader-Willi/Angelman syndrome, Smith-Magenis syndrome, Williams syndrome, 22q11 deletion, Miller-Dieker syndrome, cri du chat syndrome, and Wolf-Hirschhorn syndrome.

For patients with suspected TORCH and Zika infections, serologic testing, neuroimaging, eye examination, and hearing tests are recommended. (23) A referral to a genetics specialist may be considered for further evaluation of dysmorphic features.

Evaluation of Nonsyndromic ID of Unknown Etiology

The American Academy of Neurology has released reports with recommendations for the evaluation of nonsyndromic GDD/ID of unknown etiology. (7)(24) It is widely regarded among clinical geneticists that chromosomal microarray analysis, with a yield of approximately 15% to 20%, (25) should be the first-line cytogenetic test for these cases. There has been less universal consensus for fragile X testing, but many experts recommend fragile X testing in boys and girls with ID who have clinical features of fragile X syndrome (macrocephaly, prominent ears, hyperextensible joints, perseverative speech, enlarged testes in pubertal boys), as well as unexplained GDD/ID (in both sexes) if there is a family history of ID. Many geneticists also recommend fragile X testing for unexplained ID if the microarray result is normal. Karyotyping is recommended if there is a suspicion of aneuploidy (presence of an abnormal number of chromosomes in a cell) such as Down syndrome, a history of many miscarriages, or a family history of chromosomal abnormalities. Some clinicians recommend all 3—chromosomal microarray analysis, fragile X testing, and karyotyping—as the first-line evaluation for both boys and girls with nonsyndromic ID of unknown etiology considering the yield of approximately 2% for fragile X testing and 4% for karyotyping for these cases. (24) Microarray analysis does not detect balanced translocations (which a karyotype is able to), point mutations, or low level of mosaicism. (25) If microarray

analysis reveals an abnormality, further genetic testing of the parents may be recommended. For females with severe to profound ID, testing for Rett syndrome (*MECP2* gene) is recommended. (24)(25)

Consultation and collaboration with a clinical geneticist may be very useful in the evaluation of children with ID, especially those with unexplained ID, syndromic ID, or more severe levels of ID. Clinical geneticists and genetic counselors may also be helpful in the interpretation of the results of genetic testing. (25) A newer form of genetic testing, whole exome sequencing, may be able to identify a genetic cause in up to 40% of patients with unexplained ID; however, it is not widely available at this time, and the implications of using whole exome sequencing in the routine evaluation of all children with ID, wherein other genetic abnormalities not related to ID may be unearthed, is still not fully understood and must be explored further. (2)(25)

Inborn errors of metabolism account for a small percentage (approximately 0%–5%) of children with unexplained ID. (2)(7)(26) Testing for these conditions has been recommended for cases that are clinically suggestive of a metabolic disorder. Most of these conditions are associated with neurologic symptoms (ie, hypotonia, ataxia, dementia, epilepsy, spasticity), sensory deficits (visual and hearing impairment), and nonneurologic features, such as gastrointestinal symptoms, dermatologic findings, atypical odor, and problems in growth. Specific metabolic testing includes acylcarnitine profile, amino acids and urine organic acids, glycosaminoglycans, oligosaccharides, serum total homocysteine, purines, pyrimidines, and GAA/creating metabolites. (2) Recent reports have identified 89 inborn errors of metabolism associated with ID that are amenable to treatment. In line with this, a 2-tiered algorithm in testing for treatable forms of inborn errors of metabolism in a person with ID has been proposed. (26) Further studies are needed to fully comprehend the efficacy and implications of this approach in the evaluation of a child with unexplained ID. (7)(27)

Magnetic resonance imaging (MRI) may be helpful in the evaluation of children with nonsyndromic ID/GDD in the setting of abnormal neurologic findings such as microcephaly, macrocephaly, or focal neurologic signs, (28) with the likelihood of finding a structural abnormality increasing to 28% from a rate of 7.5% if the GDD/ID was isolated and not associated with abnormalities in head size or focal neurologic findings. The risk in the use of sedation or anesthesia in MRI studies, although low, should also be weighed in the evaluation of these children. An MRI is preferred over computed tomographic (CT) scan in identifying abnormal brain architecture and myelination and in the evaluation of deeper brain centers. A CT scan is useful to visualize calcifications, which may be present in prenatal infections such as toxoplasmosis and cytomegalovirus.

DIFFERENTIAL DIAGNOSES

In the evaluation of persons suspected of having ID, it is important to differentiate ID from neurodegenerative disorders, specific learning disorders, receptive/expressive language disorders, autism spectrum disorders, and sensory deficits (visual impairment and hearing impairment).

Neurodegenerative disorders present with significant regression in different aspects of functioning due to a progressive neurologic condition. This is in contrast to ID, whose etiology is nonprogressive (eg, genetic abnormality or a nonprogressive brain lesion). Specific learning disorders are neurodevelopmental disorders characterized by persistent difficulties in learning (eg, reading, mathematics, and/or written expression) that are not explained by and are not commensurate with one's cognitive potential. Children with specific learning disorders can be differentiated from those with ID in that they may have impairment in specific areas of learning (eg, reading/phonological skills) but have age-appropriate adaptive skills and cognitive skills, whereas children with ID will have global impairment in cognitive and adaptive skills. Language deficits may also be present in ID, but in ID there are also significant nonverbal deficits, leading to a more global impairment in function. Autism spectrum disorder is frequently associated with ID but is a separate disorder characterized by persistent social-communication and social interaction deficits, restricted/repetitive patterns of behavior, and atypical sensory reactivities. (1) The cognitive level of children with autism may range from significant ID to normal intelligence. Last, in the evaluation of a child with suspected ID, it is important to rule out any significant visual and hearing impairment that may contribute to the child's deficits in functioning.

MANAGEMENT

Special Education and Early Intervention

The mainstay of treatment and management of children with ID/GDD is the utilization of special education and early intervention programs. (6)(29) The Individuals with Disabilities Education Act provides individuals with ID/GDD the right to receive free and appropriate public education with goals and services as specified in their Individualized Education Program (IEP) or Individualized Family Service Plan (for children <3 years old). Studies have shown that early childhood education programs have long-term beneficial effects on cognition, language, academics (reading and

math), and youth behavior. (30)(31) There has been research as well showing that participation of children with ID (eg, Down syndrome) in early childhood educational programs may, at the very least, minimize the decline of intellectual functioning that occurs in these children. (32)(33)

During well-child visits, the pediatrician may detect developmental differences and delays through developmental surveillance or screening. Children who are suspected of having ID/GDD or other neurodevelopmental disorders should be referred to the state early intervention program (for children 0–3 years old) or to the Board of Education's Committee on Preschool Special Education (for children 3–5 years old) or Committee on Special Education (for children 5–21 years old) for evaluation and services.

The Individuals with Disabilities Education Act stipulates that children with disabilities receive their educational services in the least restrictive environment that is possible and appropriate to address their educational needs. Because of this, there has been a thrust toward mainstreaming wherein children with disabilities, even those with ID, may participate in more typical school environments for most or part of the school day. An inclusion or collaborative team teaching classroom is such a setting where children with special needs participate in the same classroom as typically developing children under the tutelage of 1 main teacher and 1 or more special education teachers. Children with disabilities may also receive related services such as speech/language therapy, occupational therapy, physical therapy, and counseling. In addition, classroom modifications and accommodations may be given to children with learning or intellectual disabilities through Section 504 of the Rehabilitation Act, (6) a federal law that protects individuals with disabilities from discrimination in various settings, including the public school system. Enhancing a person with ID's ability to communicate, not only through speech/language therapy but also through the use of a picture exchange communication system or augmentative communication devices, may be an important aspect of a child with ID's educational plan. Compared with typically developing children, children with ID learn at a much slower pace and may require more frequent repetitions before mastering a skill. Furthermore, the gap between these 2 groups will be increasingly wider as the years go by—an important tenet when counseling parents.

For children with more severe impairment, such as those with moderate to profound ID, a self-contained classroom may be needed wherein there is a small student to teacher ratio and the provision of individual or group paraprofessionals as needed. The child's IEP should reflect appropriate goals, which may be educational, vocational, or adaptive, while taking into consideration one's strengths and weaknesses. As the child reaches 16 years of age, the development of an Individualized Transition Plan would ensure continued support, beyond the educational realm, in areas such as employment, adult living skills, and recreation. (29)

Throughout this educational process, pediatricians play a key role, starting with the timely referral and identification of individuals with ID/GDD to being important advocates for their patients to receive services and interventions until they transition into adulthood. The Center for Parent Information and Resources (funded by the US Department of Education) offers helpful online information for pediatricians and parents about ID and the educational process, including the IEP and Individualized Transition Plan (http://www.parentcenterhub.org/intellectual/#school and http://www.parentcenterhub.org/transitionadult/).

Medical Home

The AAP and the US Department of Health and Human Services through its Healthy People 2010 have recommended that children, especially those with special health-care needs, which includes ID, receive "regular, ongoing, comprehensive care within a medical home." (34) In the medical home model of care, the pediatrician in collaboration with other medical subspecialists and professionals such as social workers and community health workers work as a team in the care of children with special needs, who, in addition to their primary disability, may have significant comorbid medical and psychiatric conditions and family challenges. The involvement of the family and addressing its needs are important components of the medical home.

Management of Comorbid Medical Conditions. Individuals with ID, especially those with moderate to profound ID, may have comorbid medical conditions such as seizure disorders, cerebral palsy, gastrointestinal disorders, and respiratory problems, which may have a significant effect on their daily functioning, progress, and need for additional support. (1)(5) Other important medical issues to explore in the care of people with ID are matters of sexuality and abuse, obesity and nutrition, physical activity and fitness, dental issues, and pain management. In addition to referring to appropriate subspecialists, the pediatrician has a role in providing information and resources to families about the child's disability, recommending healthy lifestyle options for diet and recreation, assuming the role of a conduit between the family and medical subspecialists, and being advocates for services that may address a patient's and family's needs. Online resources from the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/intellectualdisability.pdf and https://www.cdc.gov/ncbddd/disabilityandhealth/healthyliving.html) and Parent Center

Hub (http://www.parentcenterhub.org/find-your-center/) are examples of resources that may aid the pediatrician in this role.

Management of Comorbid Mental Health Conditions. Thirty percent of individuals with ID may have comorbid mental health conditions. (35) This rate is significantly higher than the rate observed in the general population. These mental health conditions include attention-deficit/hyperactivity disorder, depression, mood disorders, aggressive behaviors, and self-injurious behaviors. Behavioral interventions should be implemented in those with major behavioral difficulties, such as hyperactivity, aggressive behaviors, and self-injury. These interventions may be implemented in the home or school setting, with carryover to other settings to provide maximal benefit. Treatment with appropriate psychopharmacologic medications, based on target symptoms (eg, hyperactivity, aggressive behavior, self-injury), should be considered in those not fully controlled by behavioral measures, and referral to a child psychiatrist for medication management may be necessary.

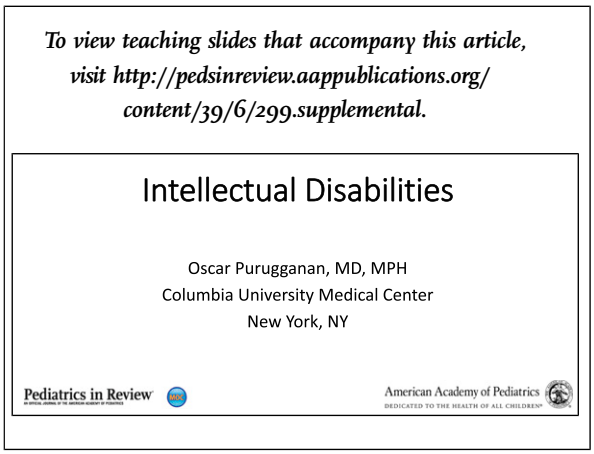
Referral to State/Community Programs and Family Supports. It is important for the pediatrician to be aware of the state and community programs that are available for persons with ID and other developmental disabilities in their community. A social worker, who may be consulted within the practice (if available) or in community agencies, may be an invaluable resource in providing support for families and in directing them to the appropriate community programs. In New York State, children with significant ID and other developmental disabilities, such as autism, are directed to the New York State Office for People with Developmental Disabilities (https://opwdd.ny.gov/). After undergoing an eligibility evaluation, each child with a disability is assigned a service coordinator who assists the family in obtaining access to community programs, respite services, home care support and after-school programs, behavior-management training, transportation services, crisis intervention, etc. (36)(37) The pediatrician or social worker may also refer the child to entitlement programs such as Social Security and Medicaid, which may provide invaluable supports for families.

As a child with ID reaches adulthood, issues such as legal guardianship, transitioning to an adult health-care provider, and employment come to the forefront and must be addressed. There is growing research that shows that given appropriate support and guidance, persons with ID may strive for competitive or supportive employment. (29) With these educational, medical, and community interventions, the ultimate goal is for persons with ID to reach their maximum potential as individuals and as members of the community.

Summary

- According to the definition, intellectual disability (ID) is a neurodevelopmental disorder that is characterized by deficits in both intellectual functioning and adaptive functioning (>2 SD below the mean as measured by standardized tests and questionnaires), with onset in the developmental period or younger than 18 years of age. The severity of ID is based on a person's adaptive functioning and level of supports. (1)
- Based on some research evidence as well as consensus, the initial approach to the evaluation for the etiology of the ID includes a thorough history, a detailed physical examination, and a focused evaluation based on the history and physical examination findings, which may include laboratory testing, genetic testing, and imaging. (7)
- Based on some research evidence as well as consensus, the recommendation for the evaluation of nonsyndromic ID of unknown etiology includes genetic testing with chromosomal microarray analysis, fragile X testing, and karyotyping. For females with severe-profound ID, testing for Rett syndrome is also recommended. (24)
- Based on some research evidence as well as consensus, the mainstay of treatment and management of ID/global developmental delay is the utilization of special education and early intervention programs through the Individuals with Disabilities Education Act. Individuals with ID, especially those with moderate to profound ID, should also be evaluated for comorbid medical and mental health conditions, which are more prevalent in this population than in the healthy population. Finally, children with ID, as with other children with special health-care needs, are best followed in a medical home–type setting where there is collaboration between the pediatrician, other health professionals, community workers, and the child's family. (6)(29)(30)

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/6/299.supplemental.



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Autism, Language Disorder, and Social (Pragmatic) Communication Disorder: DSM-V and Differential Diagnoses

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Educational Gap

The recent revision of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) included refinements to the diagnostic criteria for autism spectrum disorders and language disorders and introduced a new entity, social (pragmatic) communication disorder. Clinicians should become familiar with these changes and understand how to apply this new knowledge in clinical practice.

Objectives After completing this article, readers should be able to:

1. Know the revised criteria for autistic spectrum disorders and language disorders and the diagnostic criteria for social (pragmatic) communication disorder.
2. Understand the clinical similarities and difference of these disorders.
3. Know the differences in the long-term prognosis of these disorders.
4. Be familiar with some relatively common "nonspecific" behaviors that should not be confused with specific developmental disorders.

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INTRODUCTION

The past decade has witnessed an explosion in public and professional awareness of autism and autistic spectrum disorders (ASDs). Once considered to be a rare disorder, ASD now has a reported prevalence rate of slightly more than 1% among United States children. (1) Although the cause of this increased prevalence is not certain, greater awareness has likely resulted in improved recognition. This has been accompanied by increased research on autism focused on its cause and effective interventions for young children. Autism treatment programs are now widely available in school and community settings.

At the same time, childhood language disorders, which are more common than ASDs, have remained relatively unknown publicly and professionally. At kindergarten entry, approximately 7% to 8% of children have evidence of a language impairment (2) and are at significant risk for difficulty with language-based learning

tasks and social adaptation as they progress through school. The most recent revision of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) introduced social (pragmatic) communication disorder (SPCD) as a distinct disorder of communication affecting a broad range of social interactions. (3) Although recognized by speech-language pathologists for many years, pragmatic language impairment is likely to be an unfamiliar construct to most other clinicians. Symptoms of this disorder are usually present in children with autism and may be part of a broader language disorder. However, SPCD also may be seen in children who use fluent and complex language.

Because children with ASD, language disorder, or SPCD often share some common features, differential diagnosis may be difficult in very young children. However, by the time most children enter kindergarten, distinguishing among these disorders should be possible. As discussed in this article, outcomes of these conditions differ substantially. Accurate diagnosis is necessary for both directing children and families to appropriate treatments and counseling families about children's prognoses and future needs.

AUTISTIC SPECTRUM DISORDERS

In 1943, Kanner noted that individuals with autism had severely impaired ability to relate to other people and situations "in an ordinary way," preferring to be alone. They were unable to "use language to convey meaning to others," although their rote memory was excellent. Kanner also noted that their spontaneous activities were limited in variety, and their behavior was "governed by an anxiously obsessive desire for the maintenance of sameness that nobody but the child himself may disrupt on rare occasions."(4) These original observations have served as the basis for the diagnosis of autism and other "pervasive developmental disorders." In May 2013, DSM-V provided a revised definition of ASD that focused on symptom severity in two core dimensions: social (social communication and social interaction) and nonsocial (restricted, repetitive patterns of behaviors, interests, or activities) (Table 1). This new definition helps to distinguish individuals with a primary lack of social interest (ASD) from those whose social difficulties are due to their deficits in communication abilities.

Children with autism may be oblivious to peers or parents and not notice when others are distressed or in need of assistance (ie, lack empathy). In many children, inflexible adherence to very specific and apparently nonfunctional routines or rituals and marked resistance to any type of change in these patterns furthers their isolation from their surroundings and presents a major challenge to learning and social integration with peers. In the past, autism had often been associated with generalized cognitive impairments. More recent surveillance data have identified that most affected children (62%) have intellectual abilities in the normal range (intelligence quotient [IQ] > 70). (1) Restricted interests may manifest as an extraordinary focus on a limited range of topics (eg, dinosaurs, bathroom fixtures, United States Presidents, origami designs) to the exclusion of most other subjects.

Prevalence

According to statistics compiled by the Centers for Disease Control and Prevention Autism and Developmental Disabilities Monitoring Network, the prevalence of autism among children age 8 years has increased from approximately 1:150 in 2000 to 1:68 in 2010, with a male-to-female ratio of 4.5:1. This represents an increase of approximately 78% over the 8-year reporting period. The greatest increases were seen in Hispanic children, non-Hispanic black children, and those without co-occurring intellectual impairment. (1)

Causative Factors

Genetic factors appear to play a significant role in autism. For example, a known genetic or chromosomal condition (eg, Down syndrome, fragile X syndrome, tuberous sclerosis) is identified in approximately 10% of people with autism. Heredity also plays a significant role: a couple who has one child with autism has a 2% to 18% chance of having a second affected child. (5) In twin studies, if one identical twin has autism, the other will be similarly affected 36% to 95% of the time. (6) Other biologic risk factors for autism include children born to older parents (7) and children born preterm or with low birthweight. (8)(9)

Developmental Trajectory

The earliest symptoms of ASD may include a lack of social interaction in the first year after birth and delay in language developmental milestones. Affected infants typically "fail to connect" with their parents and caretakers due to very limited joint attention behaviors. In both retrospective and prospective studies, infants and toddlers diagnosed with ASD demonstrated impairments or delays in visual behaviors (atypical tracking and fixation on objects), motor development (decreased activity levels, delayed fine or gross motor ability, atypical motor mannerisms), play (limited imitative play, odd or repetitive play patterns), social communication (lack of interest in faces, poor eye contact, lack of social smiling or responsiveness to others), language

TABLE 1. **Autism Spectrum Disorder: DSM-V Definition**

Diagnostic Criteria
A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):
1) Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2) Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3) Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior.
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive):
1) Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2) Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
3) Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
4) Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior.
C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

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(especially social babbling, verbal comprehension, use of words or gestures to communicate), and general cognitive development. (10)(11) In many of these infants, early difficulty with sleep patterns and emotional regulation (atypical responsiveness to internal or external stimuli) were present.

A pattern of gradual or rapid regression involving loss of previously acquired speech and social-emotional connectedness, usually before 18 months of age, has been reported in 20% to 50% of children diagnosed with ASD. Odd and repetitive behaviors typically emerge after the second year of age, and the intensity of sensory and behavioral responses to stimuli (eg, extreme resistance to any change) increases with age. As they enter their adult years, very few individuals with ASD can live and work independently; most continue to require support and supervision. (12)(13)(14)(15) Those individuals with intact intellectual and language abilities often remain socially isolated but may be able to find a niche that conforms to their unique skills and interests.

CHILDHOOD LANGUAGE DISORDERS

Language provides a shared convention for communicating with others. It also serves as a medium through which learning and social interactions occur. In the broadest sense, communication abilities encompass all of the actions and skills involved in exchanging information, thoughts, and feelings with others. As such, communication skills have both verbal and nonverbal components. More specifically, language abilities refer to the use and understanding of words and sentences. At the most basic level, the essential structural components of language include sound production (phonemes), word meaning (semantics), grammar (syntax), and rhythm and intonation of speech (prosody). Higher-order

language abilities involve appropriate functional use of verbal and nonverbal skills for effective communication (pragmatics). A disorder of language development not due to intellectual or physical disability is often referred to in the literature as specific language impairment (SLI).

Prevalence

The prevalence of language delay in children varies with age and the criteria used. In addition, there is no uniform pattern to the deficits exhibited by children with language disorders. DSM-V defines childhood language disorder as persistent difficulty "in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production" that are "substantially and quantifiably" below age expectations (Table 2). Although DSM-V does not provide quantitative guidelines to assist with the diagnosis, SLI is defined in most research settings by a composite language measure that falls 2 or more standard deviations (SD) below the mean (16) (or scores of 1.25 SD below the mean on two or more subscales(2)) on omnibus language tests in the presence of normal nonverbal intellectual ability (performance IQ > 85). At 24 months of age, up to 17% of children are delayed in meeting what are considered typical language milestones. (17) Although many preschoolers resolve their language delays over time, by kindergarten entry, approximately 7.4% of children continue to be delayed in language development, despite having normal nonverbal cognitive ability and no other explanation for their delay. (2)

TABLE 2. Language Disorder: DSM-V Definition

Diagnostic Criteria
A. Persistent difficulties in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production that include the following:
1) Reduced vocabulary (word knowledge and use).
2) Limited sentence structure (ability to put words and word endings together to form sentences based on the rules of grammar and morphology).
3) Impairments in discourse (ability to use vocabulary and connect sentences to explain or describe a topic or series of events or have a conversation).
B. Language abilities are substantially and quantifiably below those expected for age, resulting in functional limitations in effective communication, social participation, academic achievement, or occupational performance, individually or in any combination.
C. Onset of symptoms in the early developmental period
D. The difficulties are not attributable to hearing or other sensory impairment, motor dysfunction, or another medical or neurological condition and are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

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Causative Factors

A large number of social, environmental, and health factors have been associated with language development in children. (18) Genetic factors appear to play a major role, as indicated by language disorders frequently clustering in families (19) and having a very high concordance rate in monozygotic twins. (20) Language disorders are significantly more common in boys than girls, with sex ratios varying from 1.3 to 5.9:1. (21)

Developmental Trajectory

Most children who are later diagnosed with SLI display a delay in onset or use of words up to 3 years of age. In some cases, they attempt to compensate for an inability to use words by relying on gestures and other body language, but frustration and tantrums are common. Although many preschool children use routines and schedules to help negotiate their daily activities and experiences, those with language impairments may have a greater need for routine and may exhibit more resistance or stress in new or unfamiliar situations. In general, as language skills improve, there is a corresponding improvement in social behavior and ability to adapt to change. As children with SLI start to use words, they may repeat phrases or dialog from movies or stories in an echolalic manner. Echolalia can be immediate or delayed. Immediate echolalia consists of unmodified repetition (one word or more) of what another person has just said; delayed echolalia refers to repetition that happens after a significant time delay. For example, a child may say, "You want juice?" after being asked whether he wants juice (immediate echolalia) or he may use a sentence he has heard previously, "You want juice?" to indicate that he is thirsty (delayed echolalia). In both examples, echolalia clearly serves a communicative function. Typically, the linguistic sophistication of the echolalic utterances exceeds what the child typically says. Echolalia reflects a specific weakness in understanding and using grammatical knowledge, resulting in an inability to combine words spontaneously to form sentences, even though the children comprehend the overall meaning (gist) of the phrases. Reliance on repeating large chunks of language reflects a holistic "top-down" pattern of language development in children who do not know how to construct sentences from the "bottom up." Although children who have SLI have limited receptive and expressive language abilities, their nonverbal and visual abilities are

generally intact. Imitation and pretend play are typically preserved, but their peer interactions may be adversely affected by their communication difficulty. (17)

Both immediate and delayed echolalia are often associated with autism, but as noted by Tager-Flusberg et al, they are not "synonymous with or unique to this syndrome [ie, ASD]."(22) Idiosyncratic or noncommunicative use of echolalia (for self-stimulation, self-regulation of behaviors, or apparently private meanings not shared by others) seems to distinguish individuals with autism from those with SLI. (23) For both children with SLI and autism, echolalia is replaced by spontaneously created phrases and sentences as mastery of language improves. (24)

Children with SLI generally respond positively to speech-language therapy, and they may master the basic language skills of grammar and word knowledge by the time they enter kindergarten. In some cases, they may be dropped from further therapy because they no longer qualify for services. Despite this period of "illusory recovery,"(25) children with an early history of language delay remain at high risk for academic difficulty. (26) Prospective studies of both clinically referred and community samples have found that language impairments and social-emotional difficulties of some degree persist into adulthood in approximately 50% to 80% of affected individuals. (27)(28) Many children appear to improve significantly in basic language abilities, only to experience learning difficulties with literacy (word reading, reading comprehension, and writing skills) and with mathematics as they progress through school. (25)(29) In the few published prospective studies of adults diagnosed with language disorders in childhood, most functioned independently, married, and had families. (12) Adults with persistent deficits in basic language abilities tended to work in professions that did not demand high language and literacy levels. In one very small study, adult males with severe language disorders had a relatively poor prognosis, exhibiting a decline in nonverbal cognitive abilities over time, and a significant minority struggled to find and maintain steady employment. (30)

SOCIAL (PRAGMATIC) COMMUNICATION DISORDER

DSM-V identifies SPCD as a form of communication disorder affecting the use of language for social exchanges, ability of individuals to adapt their communication style to the context of the interaction, ability to follow conventional and cultural norms (rules) for conversation, and ability to understand implicit or ambiguous language (Table 3). As noted by Staikova et al, "(Pragmatics) is the domain of language that manages how other aspects of language are used in conversational contexts."(31) Disorders of the pragmatic aspects of language have been recognized since the 1980s, (32) and SPCD represents a refinement of this diagnostic category. (33) Although pragmatic language difficulties can be part of a more general language disorder, ASD, or genetic/neurologic syndromes (eg, Williams syndrome, spina bifida/hydrocephalus), research demonstrates that SPCD can present in the absence of other conditions. (31)(34)(35) Because of frequent diagnostic overlap, social-pragmatic skills are best viewed as one dissociable dimension of language and communication ability. SPCD should be considered when there is a significant discrepancy between the individual's social-pragmatic skills and structural language abilities. The prevalence of SPCD in the general population has not yet been determined.

Children with SPCD frequently misinterpret what other people say and do. They have difficulty expressing themselves, verbally and nonverbally, in ways that are

TABLE 3. **Social (Pragmatic) Communication Disorder: DSM-V Definition**

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

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appropriate to the situation. (36) They may also struggle with understanding and using idioms, humor, slang, metaphor, irony, and sarcasm appropriately. Individuals with weak pragmatic abilities often appear to be socially awkward, inappropriate, or odd. Further, overreliance on literal interpretation of language and inability to make correct inferences may impair their ability to interact with peers and lead to social isolation, anxiety, and frustration.

Developmental Trajectory

Because language is used socially to initiate and maintain relationships, deficits in pragmatic language usually become noticeable by age 4 or 5 years. In school settings, children with SPCD may be socially ostracized or bullied. Social naiveté may also make them vulnerable to being taken advantage of by more socially savvy peers. In a recent community sample of 4-year-old children, Ketelaars et al found pragmatic difficulty strongly associated with peer problems, emotional problems, conduct problems, and hyperactivity/inattention. (37) However, in a longitudinal follow-up study, young adults who had been diagnosed with pragmatic language impairment generally progressed furthest academically and were more likely to work in skilled professions than individuals who had been diagnosed with either ASD or SLI as children. (12)

APPROACH TO DIFFERENTIAL DIAGNOSES

The challenge for the clinician confronting a young child who is delayed in talking or who has difficulty interacting with adults or other children is to distinguish among several possible diagnostic explanations. Many early symptoms of ASD and language disorders are nonspecific and may be related to the child's level of cognitive developmental or difficulty with emotional regulation. For example, atypical emotional reactivity or gaze avoidance may be an early sign of ASD but could also be due to extreme shyness or anxiety, visual or auditory impairments, severe cognitive delay, or nonautistic communication disorders. Children with symptoms of attention-deficit/hyperactivity disorder (ADHD) and comorbid language impairment may present special diagnostic challenges because their inattention may be related to both their lack of understanding of language and their impulsive and hyperactive behavior style. In addition, children with ADHD have deficits in social and pragmatic language skills, even after controlling for their general language abilities. (30)(36)(38) Finally, delayed emergence of expressive language skills may be a normal variation (so-called "late talker syndrome"). (17)

Accurate differential diagnosis should start with a determination of the child's overall pattern of cognitive and communication abilities. The gold standard for such evaluation is formal assessment by a multidisciplinary team of professionals that might include a child psychologist, speech-language pathologist, developmental pediatrician, child psychiatrist, and education specialist. However, a child's developmental and functional levels can be assessed in a pediatric setting through a variety of means. For example, a careful history from the parents and caretakers, focusing specifically on the child's speech and language, motor, social, and play skills and augmented by structured questionnaires and rating forms completed by adults familiar with the child can provide very accurate information. Observation of the child's skills in the clinical environment may be helpful but cannot be relied upon because children may not demonstrate their capabilities in an unfamiliar setting. Ultimately, a correct diagnosis depends on both quantitative and qualitative comparisons of the child with typical developmental milestones and on the clinician's knowledge of normal variations and nonspecific behaviors often seen in young children. (39)

Nonspecific Behaviors

The presence of restricted, repetitive patterns of behaviors, interests, or activities presents a diagnostic challenge. Rather than being specific for ASDs, these behaviors may occur in typically developing children at certain ages or as part of a set of behaviors common in individuals with moderate-to-severe intellectual impairment. (40) For example, Evans et al found that approximately 60% of otherwise typically developing children between the ages of 2 and 6 years exhibited a variety of compulsive and "just right" behaviors (eg, arranging objects until they satisfy some sensory-perceptual criteria for being "just right") and repetitive behaviors with insistence on sameness (eg, "prefers the same household schedule or routine every day," "acts out the same thing over and over in pretend play," "repeats certain actions over and over," and "has strong preferences for certain foods"). (41) Similarly, motor stereotypies, which are movements that combine into rhythmic (eg, arm flapping, waving, or shaking; head nodding; fluttering of fingers in front of the face) or complex sequences of motor movements, may be found in children and adults who do not have autistic or intellectual disorders. These behaviors typically begin at 1 year of age and frequently persist into adulthood. A family history of stereotypical movements is noted in up to 25% of such individuals. (42) Of note, motor stereotypies are often indistinguishable in individuals with and without autism. (43)

DIFFERENTIATING LANGUAGE DISORDER, SOCIAL (PRAGMATIC) COMMUNICATION DISORDER, AND AUTISM SPECTRUM DISORDER

Language skills are delayed and disordered in both language disorders and ASD, and children with either disorder may demonstrate immediate or delayed echolalia. The major distinctions between these conditions involve social and imaginative behaviors (Table 4). Children with language disorder display a social drive that is significantly reduced in ASD. Early signs of social drive include spontaneous and sustained affective exchanges with parents and caretakers. Young children with language disorder initiate social interaction by showing and sharing what they see, do, and find (joint attention) and are effective in using nonverbal behaviors to communicate (gestures, facial expressions) until they have appropriate language skills. Their difficulty interacting socially with others is largely due to their limited language skills. As toddlers, children with language disorder engage in imitation and pretend play; in contrast, children with ASD display little or no interest in emulating others' actions or in playing with toys in a symbolic manner. (44)(45) The child with a language disorder may rely on routines as a means of organizing and understanding his or her surroundings and as a method of transitioning from one activity to another. In contrast, children with ASD engage in stereotypical and repetitive behaviors for the purposes of self-stimulation or relief from stress. The distinguishing factor in the autistic individual is the abnormal intensity or focus of these behaviors. (46) For example, a toddler strongly attached to odd objects (eg, paper clips), or an older child or adult who spends hours writing out timetables is more likely to have ASD than a preschool child who insists on a specific bedtime ritual or who wants to watch certain videos repeatedly.

Children with SPCD resemble those with ASD in some aspects of social difficulty, but they lack the restricted and repetitive behaviors and interests that are seen in ASD. (18)(20) On a more elemental level, children with SPCD have good imagination and pretend play skills and appear to have a desire to interact with their peers, but they lack skills to be effective communicators. In contrast, children with ASD are more aloof and exhibit fewer prosocial and more atypical behaviors than those with SPCD. (33)

CONCLUSION

Differential diagnosis of social and communication difficulties is challenging in the preschool years. Major diagnostic considerations include ASD, language disorder, SPCD, and a variation on normal development. The revisions of DSM-V may help to clarify the distinctions among these disorders.

Few individual symptoms are unique to any specific disorder. Therefore, the child's symptoms should be considered in the context of his or her profile of cognitive and verbal abilities. In addition, clinicians should consider whether the behaviors of concern may serve a functional purpose in helping the child adapt to his or her situation.

TABLE 4. **Comparison of Specific Language Impairment (SLI), Social (Pragmatic) Communication Disorder (SPCD), and Autism Spectrum Disorder (ASD)**

	SLI	SPCD	ASD
Social	• Strong interest • Joint attention • Affective reciprocity • Difficulties may be due to deficits in basic language abilities	• Strong interest • Inappropriate interactions that are not due to deficits in basic language abilities	• Little interest • Limited/absent joint attention • Limited/absent affective reciprocity
Play	• Imitation • Pretending	• Imitation • Pretending	• Very limited imitation • No symbolic play • Attachment to odd objects
Routines	• No restricted, repetitive patterns of behavior, interests, or activities	• No restricted, repetitive patterns of behavior, interests, or activities	• Rigid and ritualized behavior that does not seem to serve any functional purpose
Behavior Patterns	• Frustrated because of lack of understanding or inability to communicate	• Frustrated because of lack of success in social interactions	• Stereotypic behaviors • Unusual responses to stimuli

Medical Evaluation of a Child with Developmental Delay

TABLE 1

Risk factors for developmental delay that can be identified on the developmental assessment

Area	Age	Findings
Motor	4½ mo	Does not pull up to sit
	5 mo	Does not roll over
	7–8 mo	Does not sit without support
	9–10 mo	Does not stand while holding on
	15 mo	Not walking
	2 yr	Not climbing up or down stairs
	2½ yr	Not jumping with both feet
	3 yr	Unable to stand on one foot momentarily
	4 yr	Not hopping
	5 yr	Unable to walk a straight line back and forth or balance on one foot for 5 to 10 sec
Fine motor	3½ mo	Persistence of grasp reflex
	4–5 mo	Unable to hold rattle
	7 mo	Unable to hold an object in each hand
	10–11 mo	Absence of pincer grasp
	15 mo	Unable to put in or take out
	20 mo	Unable to remove socks or gloves by self
	2 yr	Unable to stack 5 blocks or not scribbling
	2½ yr	Not turning a single page of a book
	3 yr	Unable to stack 8 blocks or draw a straight line
	4 yr	Unable to stack 10 blocks or copy a circle
	4½ yr	Unable to copy a square
	5 yr	Unable to build a staircase of blocks or copy a cross
Language	5–6 mo	Not babbling
	8–9 mo	Not saying "da" or "ba"
	10–11 mo	Not saying "dada" or "baba"
	18 mo	Has <3 words with meaning
	2 yr	No 2-word phrases or repetition of phrases
	2½ yr	Not using at least 1 personal pronoun
	3½ yr	Speech only half-understandable
	4 yr	Does not understand prepositions
	5 yr	Not using proper syntax in short sentences
Cognitive	2–3 mo	Not alert to mother, with special interest
	6–7 mo	Not searching for dropped object
	8–9 mo	No interest in peek-a-boo
	12 mo	Does not search for hidden object
	15–18 mo	No interest in cause-and-effect games
	2 yr	Does not categorize similarities (e.g., animals vs. vehicles)
	3 yr	Does not know own full name
	4 yr	Cannot pick shorter or longer of two lines
	4½ yr	Cannot count sequentially
	5 yr	Does not know colors or any letters
	5½ yr	Does not know own birthday or address
Psychosocial	3 mo	Not smiling socially
	6–8 mo	Not laughing in playful situations
	1 yr	Hard to console, stiffens when approached
	2 yr	Kicks, bites, and screams easily and without provocation
		Rocks back and forth in crib
		No eye contact or engagement with other children or adults
	3–5 yr	In constant motion
		Resists discipline
		Does not play with other children

Source: First LR, Palfrey JS: The infant or young child with developmental delay. *N Engl J Med* 1994;330:478–483. Copyright © 1994 Massachusetts Medical Society. All rights reserved. Reprinted with permission.

Unexplained Global Developmental Delay / Intellectual Disability

A) Detailed medical and developmental history, including prior diagnostic testing, especially newborn screening labs
B) Three-generation family history
C) Complete physical and neurological examination with attention to dysmorphism
D) Consider EEG testing if history concerning for epileptic seizures or encephalopathy
E) Consider psychoeducational testing, vision testing, and hearing testing
F) Consider referral to a clinician with relevant expertise if child appears to have an unrecognized genetic syndrome

Specific Etiology Suspected?

Yes

A) Genetic syndrome: single gene tests
B) XLID. XLID gene testing
C) Structural abnormality: MRI
D) Metabolic disorder: screening tests

A) All seventies and genders:
Microarray if possible
Otherwise: karyotype and SfFISH
B) Moderate to severe and female: *MeCP2* testing
C) Mild and either gender: *FMR1* testing

Abnormal

Test parents and siblings as appropriate
Refer for genetic counseling

Normal

Neuroimaging: Head MRI
If available, consider MRS

Diagnostic

Specific testing as appropriate

Non-diagnostic

Metabolic testing, based on clinical judgment:
A) Plasma amino acids, ammonia, acylcarnitines
B) Serum uric acid
C) Urine organic acids
D) Urine and plasma creatine, creatinine, and guanidinoacetic acid
E) Appropriate testing for CGDs
F) Plasma VLCFA, pipecolic acid, phytanic acid, and RBC plasmalogens
G) Serum 7-dehydrocholesterol
H) Urine mucopolysaccharides and sialic acid
I) Blood or fibroblast screening for lysosomal enzyme deficiencies
J) CSF glucose, lactate, pyruvate, glycine, organic acids, folate, and neurotransmitter metabolites

Abnormal

Specific testing as appropriate

Normal

Ongoing follow-up
Consider further evaluation as warranted

Fig. 43-1 **Algorithm for the evaluation of the child with unexplained global developmental delay or intellectual disability.** A detailed history, a complete physical examination, psychoeducational testing, and screening tests for visual and hearing deficits are recommended for all children with GDD/ID. EEG is recommended when there is concern about seizures or an epileptic encephalopathy. In children with features suggesting a specific etiology, genetic testing, neuroimaging, and metabolic testing may be useful for confirmation. For children without features suggesting a specific etiology, testing can be done in a stepwise or parallel manner for genetic abnormalities, structural brain abnormalities, and metabolic abnormalities. Although an extensive list of metabolic tests is provided in this algorithm, there is insufficient evidence to make specific recommendations as to which testing sequence would have the greatest diagnostic yield. The algorithm is explained in greater detail in the Clinical Context section of this guideline. CGD = congenital disorder of glycosylation, CSF = cerebrospinal fluid, EEG = electroencephalogram, RBC = red blood cell, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, VLCFA = very long chain fatty acids, XLID = X-linked intellectual disability. This algorithm is based on data contained in an evidence-based review on this topic [Michelson et al, 2011].

(Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2011, in press.)

Hearing Assessment in Infants and Children: Recommendations Beyond Neonatal Screening

Allen D. Buz Harlor, Jr, Charles Bower

KEY POINTS

1. Every child with 1 or more risk factors on the hearing risk assessment should have ongoing developmentally appropriate hearing screening and at least 1 diagnostic audiology assessment by 24 to 30 months of age.
2. Periodic objective hearing screening of all children should be performed according to the recommendations for preventive periodic health care.
3. Any parental concern about hearing loss should be taken seriously and requires objective hearing screening of the patient.
4. All providers of pediatric health care should be proficient with pneumatic otoscopy and tympanometry. However, it is important to remember that these methods do not assess hearing.
5. Developmental abnormalities, level of functioning, and behavioral problems (ie, autism/developmental delay) may preclude accurate results on routine audiometric screening and testing. In this situation, referral to an otorhinolaryngologist and a pediatric audiologist who has the necessary equipment and expertise to test infants and young children should be made.
6. The results of abnormal screening should be explained carefully to parents, and the child's medical record should be flagged to facilitate tracking and follow-up.
7. Any abnormal objective screening result requires audiology referral and definitive testing.
8. A failed infant hearing screening or a failed screening in an older child should always be confirmed by further testing.
9. Abnormal hearing test results require intervention and clinically appropriate referral, including otolaryngology, audiology, speech language pathology, genetics, and early intervention.

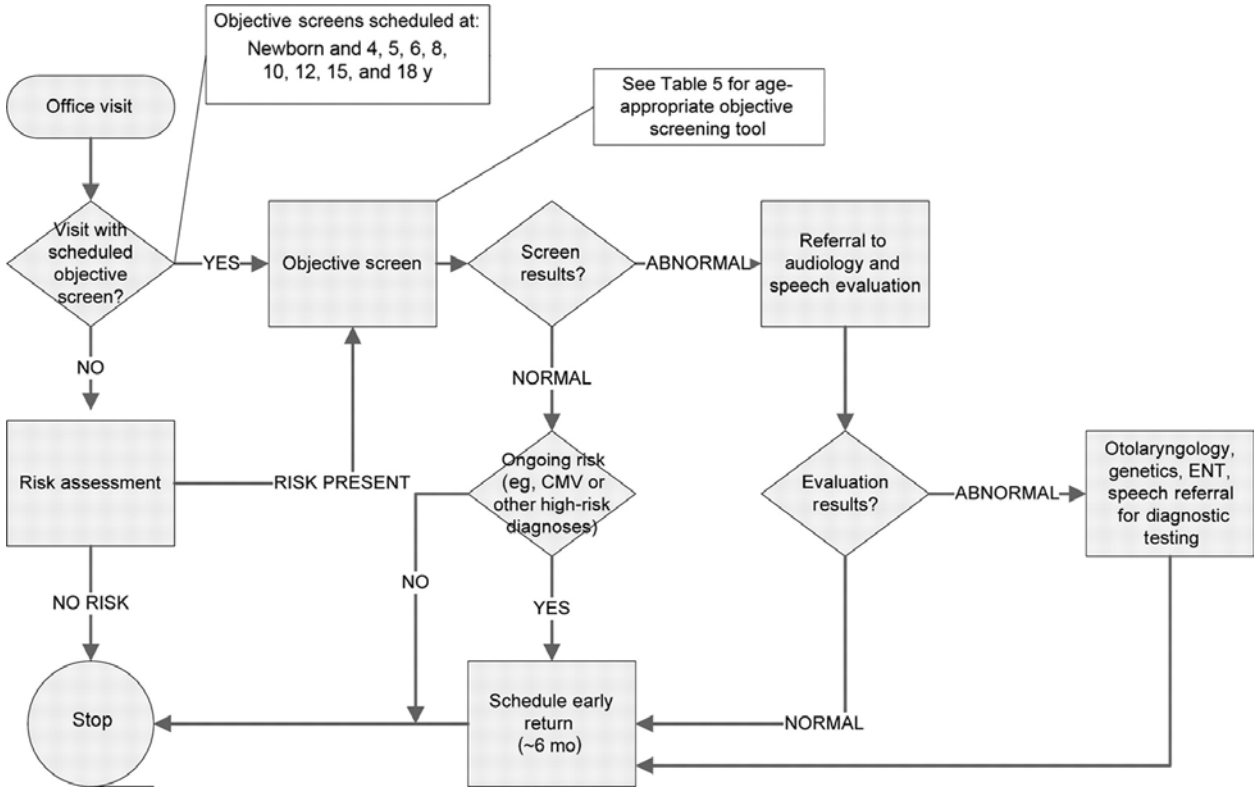


TABLE 3 American Academy of Pediatrics Joint Committee on Infant Hearing Year 2007 Position Statement[5]: Risk Indicators Associated With Permanent Congenital, Delayed-Onset, and/or Progressive Hearing Loss in Childhood

1	Caregiver concern[a] regarding hearing, speech, language, or developmental delay.
2	Family history[a] of permanent childhood hearing loss.
3	Neonatal intensive care of more than 5 days or any of the following regardless of length of stay: ECMO[a], assisted ventilation, exposure to ototoxic medications (gentamicin and tobramycin) or loop diuretics (furosemide/Lasix), and hyperbilirubinemia[19] that requires exchange transfusion.
4	In utero infections such as CMV[a], herpes, rubella, syphilis, and toxoplasmosis.
5	Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies.
6	Physical findings, such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss.
7	Syndromes associated with hearing loss or progressive or late-onset hearing loss[a], such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielson.
8	Neurodegenerative disorders[a], such as Hunter syndrome, or sensory motor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth syndrome.
9	Culture-positive postnatal infections associated with sensorineural hearing loss[a], including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis.
10	Head trauma, especially basal skull/temporal bone fracture[a] that requires hospitalization.
11	Chemotherapy[a].
12	Recurrent or persistent otitis media for at least 3 months.

Risk indicators that are marked with [a] are of greater concern for delayed onset hearing loss. ECMO indicates extracorporeal membrane oxygenation; CMV, cytomegalovirus.

Reproduced with permission from: American Academy of Pediatrics, Joint Committee on Infant Hearing. *Pediatrics*. 2007; 120(4):898–921.

TABLE 5 Audiologic Tests for Infants and Children

Developmental Age of Child	Auditory Test/ Average Time	Type of Measurement	Test Procedures	Advantages	Limitations
All ages	Evoked OAEs/10-min test	Physiologic test specifically measuring cochlear (outer hair cell) response to presentation of a stimulus; stimuli may be clicks (transient evoked OAEs) or tone pairs (distortion product OAEs)	Small probe containing a sensitive microphone is placed in the ear canal for stimulus delivery and response detection	Ear-specific results; not dependent on whether patient is asleep or awake; quick test time; screening test	Infant or child must be relatively inactive during the test; not a comprehensive test of hearing, because it does not assess cortical processing of sound; OAEs are very sensitive to middle-ear effusions and cerumen or vernix in the ear canal
Birth to 9 mo	Automated ABR/15-min test	Electrophysiologic measurement of activity in auditory nerve and brainstem pathways	Placement of electrodes on child's head detects neurologic response to auditory stimuli presented through earphones or ear inserts 1 ear at a time	Ear-specific results; responses not dependent on patient cooperation; screening test	Infant or child must remain quiet during the test (sedation is often required); not a comprehensive test of hearing, because it does not assess cortical processing of sound
9 mo to 2.5 y	VRA/15- to 30-min test	Behavioral tests measuring responses of the child to speech and frequency-specific stimuli presented through speakers or insert earphones	Technique conditions the child to associate speech or frequency-specific stimuli with a reinforcer, such as a lighted toy or video clips; VRA requires a calibrated, sound-treated room	Assesses auditory perception of child; diagnostic test.	When performed with speakers, only assesses hearing of the better ear; not ear specific; if VRA is performed with insert, earphones can rule out a unilateral hearing loss
2.5 to 4 y	Play audiometry/ 15–30 min	Behavioral test of auditory thresholds in response to speech and frequency-specific stimuli presented through earphones and/ or bone vibrator	Child is conditioned to respond when stimulus tone is heard, such as to put a peg in a pegboard or drop a block in a box	Ear-specific results; assesses auditory perception of child; screening or diagnostic test.	Attention span of child may limit the amount of information obtained
4 y to adolescence	Conventional audiometry/ 15- to 30-min test	Behavioral test measuring auditory thresholds in response to speech and frequency-specific stimuli presented through earphones and/ or bone vibrator	Patient is instructed to raise his or her hand when stimulus is heard	Ear-specific results; assesses auditory perception of patient; screening or diagnostic test	Depends on the level of understanding and cooperation of the child
All ages	Diagnostic ABR	Electrophysiologic measurement of activity in auditory nerve and brainstem pathways	Placement of electrodes on child's head detects auditory stimuli presented through insert earphones 1 ear at a time	Ear-specific results; multiple frequencies are tested, creating a map of hearing loss similar to an audiogram; responses not dependent on patient cooperation; diagnostic test	Infant or child must remain quiet during the test (sedation is often required); not a true test of hearing, because it does not assess cortical processing of sound
All ages	Tympanometry	Relative change in middle-ear compliance as air pressure is varied in the external auditory canal	Small probe placed in the ear canal and pressure varied in the ear canal	Tests for possible middle-ear pathology and pressure-equalization tube function	Not a test of hearing; depends on ear canal seal; high-frequency tone probe needed for infants younger than 6 mo

Adapted with permission from: Bachmann KR, Arvedson JC. *Pediatr Rev.* 1998;19(5):155–165.

Development II Quiz:

1. Intellectual Disability (IQ<, or 2 SD below the mean IQ) is found in **2.5%** of the population. Autism Spectrum Disorder is found in **1.5%** of the population.

2. Complete the following table, related to Intellectual Disability:

TABLE 1. **Levels of Severity of Intellectual Disability (ID)**

LEVEL OF ID (% CHILDREN WITH ID)	LEVEL OF SUPPORT (IN CONCEPTUAL, SOCIAL, PRACTICAL DOMAINS)	ASSOCIATED ESTIMATED IQ SCORE	PROJECTED ULTIMATE ACADEMIC ACHIEVEMENT
Mild (85%)	Intermittent	55–70	Up to sixth-grade level
Moderate (10%)	Limited	40–55	Up to second-grade level
Severe (3%–4%)	Extensive	25–40	Preschool level
Profound (1%–2%)	Pervasive	<25	–

Note: The level of severity is based on the level of adaptive functioning and support. (1)(6)

True or False?

3. A good history and physical exam can identify the etiology of up to a third of cases of developmental delay. **TRUE** . Studies show 17-34% of the time a specific cause of developmental delay is evident with history and physical exam alone.

4. Most children with ASD also have ID. **FALSE.** 62% of children with ASD have an IQ > 70 and are therefore not intellectually disabled.

5. Whole exome sequencing has approximately twice the diagnostic yield as chromosomal microarray in evaluating unexplained intellectual disability. **TRUE.** (approximately 40% versus 15-20%.)

6. Instruments for identifying intellectual disability (e.g. Stanford-Binet-V and WPPSI-IV) can not be administered until 5 years of age. **FALSE.** They can be administered at 2 to 2.5 years but the scores become more stable after 5 years of age.

7. Restrictive, repetitive, or "just right" behaviors, interests, or activities in 2 to 6 year olds are usually associated with autism spectrum disorder. **FALSE.** Approximately 60% of typically developing children will exhibit a variety of compulsive behaviors during this age range.

8. According to the "Medical Evaluation" flow chart, what is the minimum medical work-up for a child with global developmental delay and normal physical exam? Chromosomal analysis, Fragile X, and referral to developmental pediatrician.

***** In Oct 2010, President Obama signed into law "Rosa's Law" which changed references in federal law from *mental retardation* to *intellectual disability*, and references to *a mentally retarded individual* to *an individual with an intellectual disability*. Read about the campaign to "Spread the Word to End the Word", which started in MD.

Development II Cases:

Case 1:

Joshua, a 2 year old male, presents to your clinic for his well baby check. His family is new to the military and has never been seen in this clinic before. He lives in a household with his parents and grandparents; his parents speak English and Taiwanese, and his grandparents speak purely Taiwanese. Joshua seems like a "bright" toddler to his mother because he is so social – he enjoys being the center of attention. He seems to understand the language of others and can follow 2-step commands without gesture. He points to body parts when asked. However, he only has about a 25-word expressive vocabulary in English, and says approx 25 words in Taiwanese. Mother relates that he does try to imitate his older cousin's speech in both English and Taiwanese. She also relates that she's 'not concerned about his talking because a lot of boys on my husband's side of the family had trouble with talking.'

Does his language and social development concern you? Why or why not?

- Language: Concerning. As discussed in *Devo I*, by 24 months, bilingual children should have a **100-200 word combined English and Taiwanese vocabulary**, using the standard listed for monolingual 24 month-olds (*see table below*)

Age Range	Receptive Language	Expressive Language
18 to 24 months	Points to body parts Understands personal pronouns Carries out two directions with objects	Imitates speech Uses "mine" or "me" Uses jargon and words to relate experiences Has 100- to 200-word vocabulary
24 to 36 months	Follows two-step directives Responds to yes/no questions Understands concept of "one"	Has up to 900-word vocabulary Uses three- or four-word phrases 50% to 75% of speech is understood

Adapted from *A Quick Reference Guide to Your Child's Speech and Language Development*. Marcus Family Speech and Hearing Center, Children's Hospital of Wisconsin.

- Social: Not concerning. He seems appropriate (*see table below*).

AGE IN MONTHS	EMOTIONAL	SOCIAL
21–24	Beginning "socialization" of emotional expression by social/cultural influences • modulation of emotion • masking of emotion Infant's reaction to ambiguous events is shaped by emotional reactions of others	Imitates others to please them Recursive nature of social thought (ie, thinking about "How I behave to you and you to me") Parallel play Tolerates separation; will continue activity

If his language concerns you, how would you classify his 'atypical pattern of development'?

- Broadly speaking, he appears to have a **specific language impairment (SLI)**. An SLI describes children with normally developed *non-verbal cognitive abilities*, but significant language problems—in the absence of obvious neurologic insult or hearing impairment. Nearly **20% of 2-year-olds** have delayed onset of speech.
- According to the DSM-V, SPCD (social pragmatic communication disorder) is a form of communication disorder affecting the use of language for social exchanges, ability of individuals to adapt their communication style to the context of the interaction, ability to follow conventional and cultural norms (rules) for conversation, and ability to understand implicit or ambiguous language. Joshua has no evidence of SPCD which is usually diagnosed in school aged children.

Is his paternal family hx relevant? Does that decrease your concern for language disorder?

- SLIs tend to cluster in certain families at a much higher rate than in a general population (**30% of 1st degree pro-band relatives** vs. 3% in general population).
- There is an entity called **familial late-talker syndrome**, in which males, often from the paternal side, are delayed in expressive language, while otherwise excelling cognitively and academically. *Children who are familial late-talkers have excellent comprehension and social skills, and eventually have normal expressive language abilities.*
- That said, it is hard to evaluate receptive/expressive language without the help of a SLP, and the consequences of missing a language delay/disorder diagnosis can be disastrous.

Does Joshua require hearing screening?

- Due to Joshua's speech delay and parental concern for this, he has a risk factor for hearing loss and should be evaluated. If your clinic has the ability to appropriately screen a 2 year old infant, in-clinic screening is indicated. If not, referral to audiology for formal evaluation is appropriate.
- Per AAP guidelines, children should be screened for hearing loss even if they do not have risk factors in the newborn period as well as ages 4, 5, 6, 8, 10, 12, 15, and 18 years.

Would you refer this patient? If so, to whom?

- It would be appropriate to refer this patient for a formal **speech assessment**. If that assessment showed delay, **early intervention services** should be initiated. It might also be appropriate to refer this patient for a formal **audiology evaluation**.
- Strictly speaking, the table below (from PIR) lists absolute indications for referral, which this patient actually exceeds. . . *Residents and preceptors can discuss their approaches*:

Indications for Referral for Delays and Disorders of Language and Speech

Age	Finding
24 months	Vocabulary less than 50 words No two-word phrases Less than 50% of speech intelligible to strangers

After presenting your A/P to Joshua's mother, she adds that she has been using Baby Signs since Josh was 9-months to help him "overcome or compensate" for his language delay. **Applying what you know about language development, do you think signing helped or hindered him?**

This is **controversial:**

- Proponents of baby sign language point out the gap between toddlers' desire to communicate and ability to do so, which often leads to frustration and tantrums. Since hand-eye coordination develops sooner than acquisition of verbal skills, infants can learn simple signs for common words before they are able to produce speech.
- Alternatively, opponents of baby-signing question whether formalized symbolic gesturing will delay the onset of speech.

➢ Research appears to favor the former: in several studies, babies taught sign language ultimately showed larger expressive and receptive spoken language vocabularies, as well as a reduction in problematic behaviors like temper tantrums. (See AAP Answer, here).

Case 2:

Katelynn is a 2 year old healthy female presenting for a well child visit. She comes into your office, immediately sits in a small chair on the opposite side of the room from her mother, and begins playing with the toy train on the table. As you conduct the interview, you note that her play with the train does not change; she runs the train in a circle again and again. In asking mom about this behavior, she relates that Katelynn also arranges her dolls in a specific order on her bed, and she gets very upset when the order has been altered. You also uncover that the child is rather 'quiet and shy' and only says ten words (although she seems to understand nearly everything she hears).

What language milestones would you expect of a 2 year old?

- 2-to-3-word phrases
- 50% intelligible
- Understanding pronouns
- >50 words in vocabulary (usually many more)

What other questions would you elicit in the developmental history?

In general, elicit information about the **3 DSM-*V* criteria for ASDs:** (1) delayed and disordered communication; (2) restricted and repetitive behaviors; (3) deficits in social reciprocity.

- Meeting motor milestones?
- Birth history?
- Seem to understand facial expressions?
- Other stereotyped behavior?
- Plays cooperatively with others? Other social skills?
- Family history of MR, difficulties in school, personality disorders, etc?
- Does the child display any emotional reciprocity?
- Does the child have proto-declarative and proto-imperative pointing?
- Does the child make eye contact?

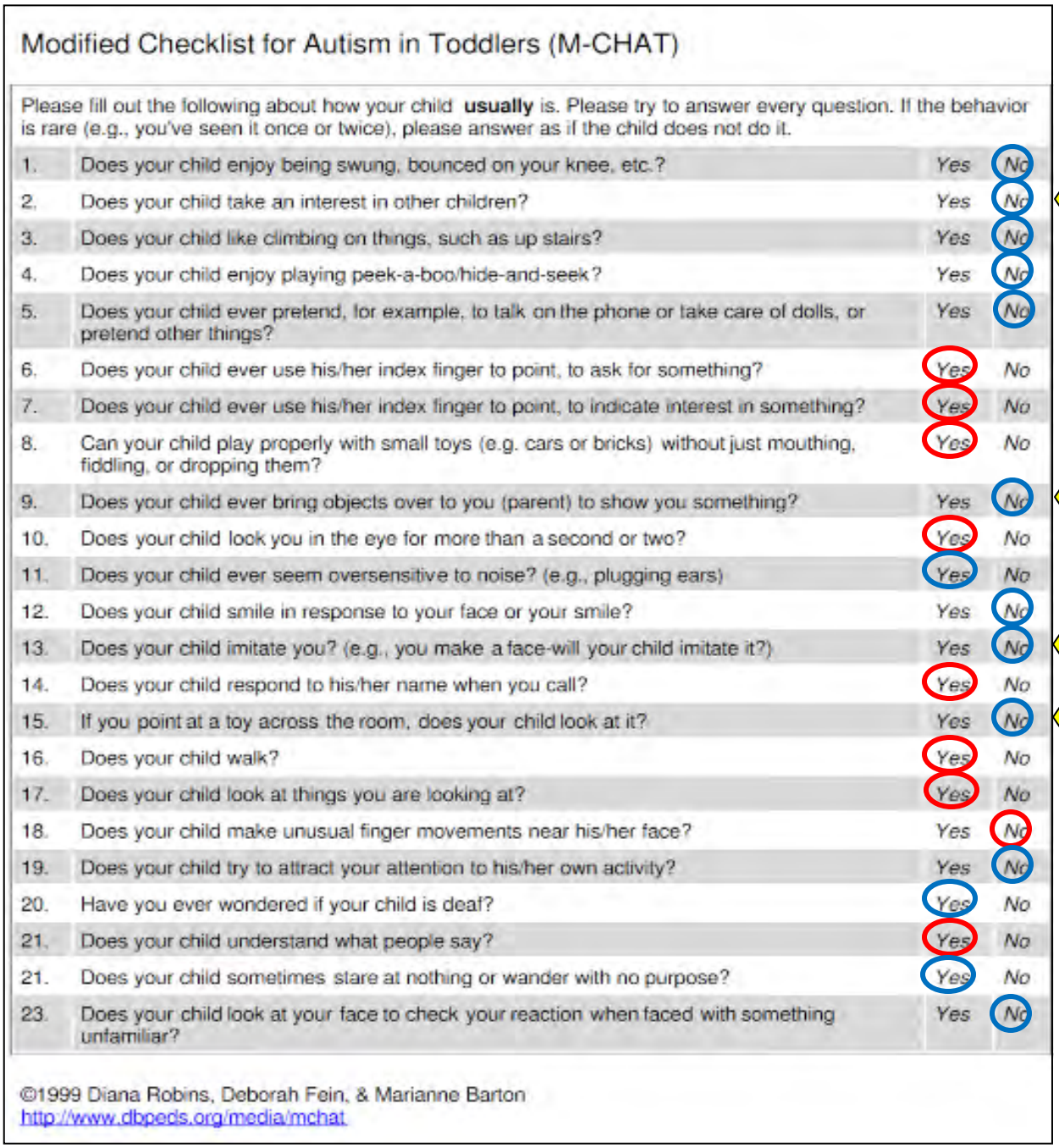
You administer the M-CHAT shown on the next page. Score it and answer the next questions: **Are you concerned? If so, will you refer the patient? Would you do any further work-up?**

- M-CHAT indicates risk of autism (failure of 14 items-**blue**; and 4 critical items-arrows
- **Referrals** to audiology, developmental peds, speech-language pathology, and early intervention; later may need EFMP enrollment
- **No lab evaluation** for autism unless coexisting MR, dysmorphic features on exam, or positive family history of Fragile X.

MCHAT or POSI?
from Tufts:
" the POSI's internal reliability was high and sensitivity of the POSI compared favorably to that of the M-CHAT. More children scored positive on the POSI than on the MCHAT, and best evidence from population samples suggests that the MCHAT is more specific than the POSI."

Once she has heard the likely diagnosis, mother reveals to you that she is 12 weeks pregnant and wonders if the unborn child has a higher risk of autism. **She wonders if there is a 'genetic test' that via amniocentesis to diagnose the unborn child. What is your response?**

- Increased risk of autism in siblings of autistic pts (10x higher than general population). Also increased risk of cognitive defects, social disorders, etc.
- No specific lab test can diagnose autism spectrum disorders. Parents are encouraged to watch for "early signs" throughout a child's first 2 years. *(see "Med Eval" Table I).*



Modified Checklist for Autism in Toddlers (M-CHAT)

Please fill out the following about how your child **usually** is. Please try to answer every question. If the behavior is rare (e.g., you've seen it once or twice), please answer as if the child does not do it.

1.	Does your child enjoy being swung, bounced on your knee, etc.?	Yes	No
2.	Does your child take an interest in other children?	Yes	No
3.	Does your child like climbing on things, such as up stairs?	Yes	No
4.	Does your child enjoy playing peek-a-boo/hide-and-seek?	Yes	No
5.	Does your child ever pretend, for example, to talk on the phone or take care of dolls, or pretend other things?	Yes	No
6.	Does your child ever use his/her index finger to point, to ask for something?	Yes	No
7.	Does your child ever use his/her index finger to point, to indicate interest in something?	Yes	No
8.	Can your child play properly with small toys (e.g. cars or bricks) without just mouthing, fiddling, or dropping them?	Yes	No
9.	Does your child ever bring objects over to you (parent) to show you something?	Yes	No
10.	Does your child look you in the eye for more than a second or two?	Yes	No
11.	Does your child ever seem oversensitive to noise? (e.g., plugging ears)	Yes	No
12.	Does your child smile in response to your face or your smile?	Yes	No
13.	Does your child imitate you? (e.g., you make a face-will your child imitate it?)	Yes	No
14.	Does your child respond to his/her name when you call?	Yes	No
15.	If you point at a toy across the room, does your child look at it?	Yes	No
16.	Does your child walk?	Yes	No
17.	Does your child look at things you are looking at?	Yes	No
18.	Does your child make unusual finger movements near his/her face?	Yes	No
19.	Does your child try to attract your attention to his/her own activity?	Yes	No
20.	Have you ever wondered if your child is deaf?	Yes	No
21.	Does your child understand what people say?	Yes	No
21.	Does your child sometimes stare at nothing or wander with no purpose?	Yes	No
23.	Does your child look at your face to check your reaction when faced with something unfamiliar?	Yes	No

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http://www.dbpeds.org/media/mchat

Katelynn's mother seems understandably overwhelmed at the end of your appointment. You give her your card and offer to add Katelynn to your continuity panel. The next day, you see the following T-con in AHLTA: *"question about immunizations, per mom"*. You call mother back, and she reports that she has done some internet research.

Did any of the immunizations Katelynn received cause her autism? Do any immunizations contain thimerosal? (Flashback: Immunizations)

- Current scientific evidence does not support a link between the MMR vaccine or any combination of vaccines and ASD. There is also no scientific proof to support a link between thimerosal (mercury preservative). See Consensus Report from IOM.
- Most **flu vaccines** contain thimerosal, although, there are some thimerosal-free flu vaccines (more expensive) available, including at WR-B.

Development II Board Review:

1. An infant born at 34 weeks' gestation comes in for her 1-month-old evaluation. Her neonatal course was uncomplicated. Her parents ask if she will have delayed development due to her prematurity.

Of the following, the MOST appropriate response is that healthy preterm infants
A. have age-appropriate language skills by the time they are 12 months of age
B. have an increased risk of mild motor impairment
C. born at 32 to 36 weeks' gestation have a fourfold increase in intellectual disabilities
D. should have their developmental age corrected for the degree of prematurity until 4 years of age
E. show hand preference at an earlier age than term infants

Some factors that lead to greater risk of neurological/behavioral problems among preterm infants (those born at <37 weeks' gestation) include low birthweight (<2,500 g), intrauterine growth restriction, and a history of maternal prenatal drug use. Medical complications that could affect the infant's development include intraventricular hemorrhage (IVH), cardiac lesions, bronchopulmonary dysplasia, feeding problems, and retinopathy of prematurity. A preterm infant who has either a grade 3 or 4 IVH has a 35% to 90% increased risk of a neurodevelopmental disability.

A 34 weeks' gestation infant who has an uncomplicated neonatal course, such as the child described in the vignette, has an increased risk of mild motor impairment, referred to as a developmental coordination disorder. Most experts agree that preterm infants should have their developmental ages corrected for the degree of prematurity at least for the first 12 months after birth; many clinicians continue to use a full correction until 24 months of age. However, age correction up to 4 years of age is not necessary.

Preterm infants born at 32 to 36 weeks' gestation have a 1.4-fold increased risk of intellectual disabilities over term infants, although the risk increases to 7-fold for children born prior to 32 weeks' gestation. Healthy preterm infants may not develop age-appropriate language skills until they are older than 12 months of age, which is why their developmental level must be corrected for their level of prematurity. A preterm infant should not routinely have early hand preference; such a finding may be indicative of cerebral palsy.

2. You care for a 7-year-old boy who has moderate intellectual disability and autistic behavior. Molecular genetic testing has confirmed that he has findings consistent with classic fragile X syndrome. His pregnant mother has undergone prenatal testing, which revealed that she is carrying a female fetus that also has fragile X syndrome.

Of the following, the MOST accurate statement regarding fragile X syndrome in females is that
A. their affected sons have more severe intellectual disability than their affected brothers
B. they can have normal intelligence
C. they do not exhibit autistic behaviors
D. they typically are affected as severely as males who have fragile X syndrome
E. they usually are infertile

Fragile X syndrome is an X-linked disorder of dysmorphic features and intellectual disability (usually moderate) with autistic features that is estimated to occur in 1 in 4,000 males. Fragile X syndrome is one of a group of disorders caused by progressive expansion, through generations, of a trinucleotide repeat sequence (in this case, CGG) that leads to disruption of gene function. Other conditions caused by trinucleotide repeat expansion include myotonic dystrophy and Huntington disease. The gene that is disrupted in fragile X syndrome is *FMR1*.

To predict the result of *FMR1* disruption for an individual, it is important to know the average number of CGG repeats in the general population as well as the phenotypes associated with various expansion sizes. Typically, humans have 5 to 40 CGG repeats in exon 1 of the *FMR1* gene. An "intermediate" allele size of approximately 41 to 58 repeats is not associated with an unusual phenotype and is of unclear significance; rarely, alleles of this size have been reported to expand in subsequent generations. Allele sizes of approximately 59 to 200 repeats are referred to as "premutation" alleles, and individuals who are premutation carriers usually have normal intelligence but may have some features of fragile X syndrome; they also may be at increased risk for fragile X-associated tremor/ataxia

syndrome (FXTAS) or premature ovarian failure. Allele sizes of more than 200 repeats are referred to as "full mutations." Once the allele reaches this size, it is methylated, which effectively silences *FMR1* expression, resulting in fragile X syndrome.

The clinical presentation of fragile X syndrome in males varies according to age. Prepubertal boys may be large for age (in both height and weight) and have relative macrocephaly. They often exhibit hypotonia and may have gastroesophageal reflux and recurrent otitis media. They have motor and speech delays and display behaviors such as hand-flapping and wrist-biting. They are almost always intellectually disabled, with abilities falling within the moderate range of intellectual deficit. As they grow, their faces elongate, and the prominence of the forehead, ears, and jaw becomes more noticeable. After puberty, they have striking macroorchidism.

Females who have fragile X syndrome have highly variable presentations. Approximately 50% of those who have a full fragile X mutation are intellectually disabled, with features and behaviors similar to those of affected boys, although they typically are less severely affected than males who have equivalent mutations. The other 50% are intellectually normal. The leading theory as to the cause of intellectual variability in affected females is that the ratio of active "normal" Xs to active Xs with the *FMR1* mutation in brain cells predicts intellectual ability; a predominance of active, "normal" Xs is associated with normal intellectual ability.

The term "anticipation" refers to the increasing severity of a disease as it is passed from generation to generation. Disease anticipation occurs in fragile X syndrome, but it is not possible to predict an expansion of the CGG sequence each time a conception takes place. Also, because the *FMR1* gene is silenced when there are greater than 200 repeats, the person who has 300 repeats is not expected to be more severely affected than the person who has 200 repeats. Therefore, women who have full mutations are not expected to have children who are more severely affected than their full-mutation brothers. Approximately 20% of female premutation carriers have premature ovarian failure, but female full mutation carriers typically have normal fertility.

3. During the health supervision visit for an 18-month-old boy, his parents express concern that he is vocalizing but not saying any real words. He is holding a small piece of string that he moves back and forth repeatedly. When you call his name, he does not respond. You point to the light in the room and say "look," but he continues to look at the string with a sideways glance. You try to get him to look at you, but he avoids eye contact.

Of the following, the MOST likely diagnosis for this boy is
A. Asperger disorder
B. autistic disorder
C. expressive/receptive language disorder
D. obsessive-compulsive disorder
E. Rett syndrome

The child described in the vignette shows clinical features of an autistic disorder, a heterogeneous neurodevelopmental disorder. Affected individuals have impairments in three specific areas: reciprocal social interactions, verbal and nonverbal communication, and range of activities or interests. The clinical presentation is specific to the child, with differing degrees of impairment in each of the three core symptom areas.

The hallmark of autism is abnormal social interactions. Children lack the ability to share interests with others (joint attention skills) using verbal or nonverbal communication. They commonly show weakness in eye contact. Their interaction may range from aloofness and an unawareness of other people to having varied or odd interaction with others. Language development commonly is delayed, and children may have immediate or delayed echolalia, unusual intonation, and repetitive speech. Children who have autism may engage in repetitive play and show little imaginative play. They may focus on sensory aspects of objects or develop obsessions about unusual objects (stop signs, elevators). They often have difficulty handling transitions and may engage in repetitive hand or body movements. Many affected children have cognitive impairment. Children who have subthreshold clinical features (some but not all of the features) may receive the diagnosis of pervasive development disorder-not otherwise specified within the autism spectrum.

Red flags of development that warrant further evaluation for possible autism include:
• No babbling by 9 months

• No gesturing by 12 months
• No single words by 16 months
• No functional nonecholalic 2-word phrases by 24 months
• Any loss of language or social skills at any age

Neither a diagnosis of expressive language disorder nor obsessive-compulsive disorder would account for the impaired social engagement exhibited by the boy in the vignette. Individuals who have Asperger syndrome (Asperger disorder in DSM-IV TR) have impairments in social interaction and restricted interests and activities, but they have relatively preserved cognitive and language functioning, in contrast to the delays in developing language reported for the child in the vignette. Rett syndrome almost exclusively affects females and presents with a slowing of motor development between 6 and 18 months of age. Between ages 1 and 4 years, the child exhibits a decline in social interactions, cognitive abilities, purposeful hand movements, and speech.

4. A 5-year-old girl recently was diagnosed with an autistic disorder and mental retardation. Her parents are upset by her lack of progress in her special education program and seek your guidance in treating her autism. At a parent support group, they were told about the use of complementary and alternative medical approaches to therapy. They ask whether they should pursue these interventions.

Of the following, your BEST response is to
A. explain to the parents that alternative treatments have been demonstrated to be ineffective
B. explain to the parents that they must consider the benefits, risks, and efficacy for each treatment
C. refer the parents for psychological counseling to deal with their guilt feelings
D. suggest the parents discuss the alternative treatments with the special education teachers
E. tell the parents that they should not expect much progress because their daughter has both mental retardation and autism

Complementary and alternative medicine (CAM) is used frequently among children who have chronic illness or disability such as mental retardation or autism. Many parents become frustrated with biomedical therapies due to uncertainty of a cure and lack of an active role in the care plan. They also may be attracted to an approach that they perceive to be more "natural."

A number of CAM therapies have been advocated for children with developmental disabilities, including those who have autism, but to date no results from controlled trials support their efficacy. For example, there is no scientific evidence that vision therapy (eye exercise) or "patterning" (series of exercises promoted to enhance development) is effective in remediating pediatric developmental and neurologic conditions. Sensory integration therapy also lacks evidence-based research, although parents may report benefit for a child who has a high degree of sensory defensiveness. Other CAM therapies with no proven efficacy such as the use of hyperbaric oxygen or chelation may involve potential risks to the child as well.

The pediatrician is in a unique situation to help families evaluate CAM therapies and provide guidance regarding their benefits, risks, and evidence of efficacy. In particular, families should be informed about placebo effects and the need for controlled studies, as well as potential adverse effects. Discussion of CAM should not be referred to the child's special education teacher. Dismissal of CAM therapies as generally ineffective may be interpreted as a lack of sensitivity. Referring the family to a counselor may help them discuss frustrations but would not address their question regarding the use of alternative therapies. Although the child has both mental retardation and autism, the clinician should be sensitive to the family's desire to have the child meet her cognitive potential.

5. During the health supervision visit for a 4-year-old girl, her father reports that she has developed a stutter over the past 9 months. He explains that she is a little frustrated by the difficulty in expressing herself but otherwise seems happy and well-adjusted. In talking with the father, you also note that he has a mild stutter. He speaks to the child slowly and deliberately and encourages her to take her time when speaking to you.

Of the following, the risk factor that MOST strongly suggests the need for speech therapy for this girl is the
A. age of onset
B. child's reaction to stuttering
C. child's sex

D. father's stutter
E. time since onset

The onset of stuttering typically occurs during the period of intense speech and language development as the child progresses from two-word utterances to the use of complex sentences, generally between the ages of 2 and 5 years but sometimes as early as 18 months.

About 5% of all children go through a period of stuttering that lasts 6 months or more. The sex ratio for stuttering appears to be equal at the onset of the disorder, but studies indicate that three to four times as many boys continue to stutter. Between 75% and 80% of children who start to stutter stop within 12 to 24 months without speech therapy. Children who begin stuttering before the age of 3.5 years and girls are more likely to outgrow stuttering. Strong evidence shows that almost all children who stutter have a family member who stutters.

Studies have shown that individuals who stutter have a large degree of within-word dysfluencies compared with their typical peers. Examples are: 1) repetition of individual sounds or syllables such as "W-w-w-what is he doing?", 2) prolongation of words such as "Wwwwwwhat is he doing?, and 3) blocks or pauses such as ". . . What is he doing?" Such dysfluencies may be associated with eyelid closing and physical tension around the lips. The standard criteria for diagnosing a child who has stuttering or is at risk to develop stuttering is an average of at least three within-word dysfluencies in 100 words of conversation.

Although the girl described in the vignette does not have a strong negative reaction to her speech impediment, her father stutters, placing her at risk for problematic stuttering and indicating the need for speech therapy. Referral should be made for children who have severe stuttering problems, those who have mild stuttering problems that do not improve markedly within 6 to 8 weeks, or those whose parents are very concerned. Referral also is indicated for children who have associated behaviors (eg, head, body, or limb movement; audible breathing prior to the disfluencies; and observable muscle tension in the orofacial region). In time, such children may develop anxiety about stuttering that could contribute to the chronicity of the disorder.

6. A 2-month-old infant has lost the vision in both of his eyes due to bilateral retinoblastoma. His distressed parents ask how the infant's blindness will affect his behavior and development.

Of the following, the child MOST likely will
A. begin saying single words at 16 to 20 months
B. begin walking between 18 and 22 months
C. display behaviors of an autism spectrum disorder
D. have a language-based learning disorder
E. have significant cognitive impairments

Legal blindness is defined as central visual acuity with corrective lenses of 20/200 or less in the strongest eye or a limited visual field that extends to an angle of 20 degrees. Congenital blindness occurs in 30 per 100,000 births. More than 50% of children who have visual impairment also have developmental disabilities, such as cognitive-adaptive disability, seizures, hearing impairments, and learning disorders. In many of these cases, the disabilities result from central nervous system pathology.

Postnatal blindness, which accounts for approximately 8% to 11% of all childhood blindness, can be caused by infections, trauma, or tumors. Retinoblastoma is the most common primary malignant intraocular tumo.r of childhood. The initial finding in most cases is a white pupillary reflex (leukokoria). Advanced tumors may be treated with enucleation.

Children who have congenital or acquired (eg, due to retinoblastoma) blindness without associated neurologic abnormalities should not be at increased risk for motor or cognitive impairment. They are not at increased risk for language-based learning disabilities or autism spectrum disorders. However, children who have significant visual impairment may begin to walk at an older age (18 to 22 months) than sighted children due to different exposure to motor exploration. They typically develop language skills at the same time (12 months) as sighted children. Children who have visual impairments should be provided with much physical contact that includes hugging and comforting. They should be encouraged to partake in self-help skills and exploration of their environment.