Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders

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The adverse effects of prenatal alcohol exposure constitute a continuum of disabilities (fetal alcohol spectrum disorders [FASD]). In 1996, the Institute of Medicine established diagnostic categories delineating the spectrum but not specifying clinical criteria by which diagnoses could be assigned. In 2005, the authors published practical guidelines operationalizing the Institute of Medicine categories, allowing for standardization of FASD diagnoses in clinical settings. The purpose of the current report is to present updated diagnostic guidelines based on a thorough review of the literature and the authors’ combined expertise based on the evaluation of >10 000 children for potential FASD in clinical settings and in epidemiologic studies in conjunction with National Institute on Alcohol Abuse and Alcoholism–funded studies, the Collaborative Initiative on Fetal Alcohol Spectrum Disorders, and the Collaboration on FASD Prevalence. The guidelines were formulated through conference calls and meetings held at National Institute on Alcohol Abuse and Alcoholism offices in Rockville, MD. Specific areas addressed include the following: precise definition of documented prenatal alcohol exposure; neurobehavioral criteria for diagnosis of fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopmental disorder; revised diagnostic criteria for alcohol-related birth defects; an updated comprehensive research dysmorphology scoring system; and a new lip/philtrum guide for the white population, incorporating a 45-degree view. The guidelines reflect consensus among a large and experienced cadre of FASD investigators in the fields of dysmorphology, epidemiology, neurology, psychology, developmental/behavioral pediatrics, and educational diagnostics. Their improved clarity and specificity will guide clinicians in accurate diagnosis of infants and children prenatally exposed to alcohol.
Medicine (IOM) described 4 distinct diagnostic categories within FASD: FAS, partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD). However, the task force did not specify the clinical process by which individual children could be assigned to the groups. Since that time, a number of diagnostic systems have been proposed.\textsuperscript{4-10} In 2005, Hoyne et al\textsuperscript{4} described specific clinical guidelines that allowed for assigning diagnoses within the 1996 IOM classification. Subsequently, the authors have evaluated >10,000 children for potential FASD in clinical settings and epidemiologic studies as part of National Institute on Alcohol Abuse and Alcoholism (NIAAA) supported studies, the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), and the Collaboration on FASD Prevalence (CoFASP). CIFASD was established by NIAAA in 2003 to investigate data-driven methods for complete diagnosis of the continuum of FASD, prevention of the adverse effects of prenatal alcohol exposure, and effective interventions for affected individuals.\textsuperscript{11,12} CoFASP seeks to establish the prevalence of FASD among school-age children in US communities by using active case ascertainment methodology.\textsuperscript{12} Based on this broad multidisciplinary experience, the purpose of this special article is to propose updated clinical guidelines for diagnosing FASD that clarify and expand on the original 2005 guidelines. These updated diagnostic criteria have been formulated, reviewed, and accepted by the investigators and collaborating sites of CoFASP and the administrative core of CIFASD. They do not necessarily represent the policy of the American Academy of Pediatrics.

**BACKGROUND AND SCOPE OF THE PROBLEM**

FASDs are the leading cause of preventable developmental disabilities in the world. Recent school-based studies in the United States estimate the prevalence of FASD to be much higher than previously thought. May et al\textsuperscript{13} recently recorded combined rates of FAS and PFAS of 10.9 to 25.2 per 1000 (1.1%-2.5%) in a Rocky Mountain community, whereas the complete continuum of FASD (including ARND) was observed to be 24 to 48 per 1000 (2.4%-4.8%) in a community in the Northern Plains.\textsuperscript{14} In the mixed race population of the Western Cape Province in South Africa, the highest prevalence rates of FASD in the world have been documented, 135.1 to 207.5 per 1000 (13.5%-20.8%).\textsuperscript{15} The World Health Organization (WHO) is currently planning prevalence studies in several countries in Europe, Asia, Africa, and North America, which should lead to global data about the frequency of this continuum of disabilities.\textsuperscript{16}

The high prevalence of FASD produces an immense burden to society in financial terms, unrealized productivity, and human suffering. In the United States, annual cost estimates have ranged from $74.6 million in 1984\textsuperscript{17} to $4.0 billion in 1998.\textsuperscript{18} In 2007, the estimated annual cost of FASD in Canada was CAD $5.3 billion.\textsuperscript{19} The soaring prevalence and burden of FASD in children recently led the American Academy of Pediatrics to stress the following: no amount of alcohol intake during pregnancy can be considered safe; there is no safe trimester to drink alcohol; all forms of alcohol pose a similar risk; and binge drinking poses a dose-related risk to the fetus.\textsuperscript{20}

**PREPARATION OF UPDATED DIAGNOSTIC GUIDELINES**

These guidelines were formulated by the authors over a 12-month period, through a series of conference calls and face-to-face meetings at the offices of NIAAA in Rockville, MD. The following working subgroups of investigators were organized to revisit diagnostic criteria: dysmorphology evaluation, neurobehavioral assessment, and definition of significant documented prenatal alcohol exposure. Recommendations from the working committees were brought back to the larger group for discussion and revision. The guidelines presented herein are the result of a thorough review of the literature and the longstanding collective expertise of the authors. The updated clinical guidelines for diagnosis of FASD are set forth in Table 1.

**APPLICATION OF THE GUIDELINES IN THE DIAGNOSIS OF FASD**

An FASD diagnostic algorithm incorporating the updated diagnostic guidelines is depicted in Fig 1.

**Optimal Diagnostic Setting and the Role of the Pediatrician**

Assignment of an FASD diagnosis is a complex medical diagnostic process best accomplished through a structured multidisciplinary approach by a clinical team comprising members with varied but complementary experience, qualifications, and skills. The assessment of individuals prenatally exposed to alcohol requires a medical assessment and team leadership by a pediatrician or clinical geneticist/dysmorphologist with expertise in the full range of human malformation syndromes and the dysmorphology evaluation of children with FASD. In addition, exposed children should have expert psychological/neuropsychological assessment, and a skilled interviewer should evaluate prenatal maternal alcohol intake. Other team members may include developmental behavioral pediatricians, psychiatrists, speech pathologists, occupational therapists, physical therapists, special
TABLE 1 Updated Criteria for the Diagnosis of FASD

(See Table 2 for definition of documented prenatal alcohol exposure)

I. FAS
(With or without documented prenatal alcohol exposure)

A diagnosis of FAS requires all features, A–D:

A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
   1. Short palpebral fissures (≤10th centile)
   2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
   3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)

B. Prenatal and/or postnatal growth deficiency
   1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available)

C. Deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, including ≥1 of the following:
   1. Head circumference ≤10th percentile
   2. Structural brain anomalies
   3. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)

D. Neurobehavioral impairment*
   1. For children ≥3 y of age (a or b):
      a. WITH COGNITIVE IMPAIRMENT:
         --Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
         OR
         --Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
      b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
         --Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
   2. For children <3 y of age:
      --Evidence of developmental delay ≥1.5 SD below the mean

II. PFAS
-For children with documented prenatal alcohol exposure, a diagnosis of PFAS requires features A and B:

A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
   1. Short palpebral fissures (≤10th centile)
   2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
   3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)

B. Neurobehavioral impairment*
   1. For children ≥3 y of age (a or b):
      a. WITH COGNITIVE IMPAIRMENT:
         --Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
         OR
         --Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
      b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
         --Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
   2. For children <3 y of age:
      --Evidence of developmental delay ≥1.5 SD below the mean

-For children without documented prenatal alcohol exposure, a diagnosis of PFAS requires all features, A–C:

A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
   1. Short palpebral fissures (≤10th centile)
   2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
   3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)

B. Growth deficiency or deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology
   1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available), or:
   2. Deficient brain growth, abnormal morphogenesis or neurophysiology, including ≥1 of the following:
      a. Head circumference ≤10th percentile
      b. Structural brain anomalies
      c. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)

C. Neurobehavioral impairment*
   1. For children ≥3 y of age (a or b):
      a. WITH COGNITIVE IMPAIRMENT:
         --Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
         OR
         --Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment, or visual-spatial impairment)
b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
− Evidence of behavioral deficit in at least 1 domain ≥ 1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
2. For children <3 y of age:
− Evidence of developmental delay ≥ 1.5 SD below the mean

III. ARND
Requires features A and B (this diagnosis cannot be made definitively in children <3 y of age):
A. Documented prenatal alcohol exposure
B. Neurobehavioral impairment
For children ≥3 y of age (a or b):
1. WITH COGNITIVE IMPAIRMENT:
− Evidence of global impairment (general conceptual ability ≥ 1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥ 1.5 SD)
OR
− Evidence of deficit in at least 2 neurobehavioral domains ≥ 1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
2. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
− Evidence of behavioral deficit in at least 2 domains ≥ 1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)

IV. ARBD
Requires features A and B:
A. Documented prenatal alcohol exposure
B. One or more specific major malformations demonstrated in animal models and human studies to be the result of prenatal alcohol exposure: cardiac: atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects; skeletal: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis; renal: aplastic/hypoplastic/dysplastic kidneys, “horseshoe” kidneys/ureteral duplications; eyes: strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia; ears: conductive hearing loss, neurosensory hearing loss

Diagnostic Caveats: The assignment of an FASD is a complex medical diagnostic process best accomplished through a multidisciplinary approach. As is the case with many medical conditions, sound clinical judgment must be used. Differential diagnoses should always include genetic disorders or conditions arising from other teratogens. Additionally, because head circumference, growth, and many cognitive and behavioral characteristics have moderate to high degrees of heritability, when information is available about the biological parents, these data should be considered in the final diagnostic decision.

*Adaptive skills should be assessed, but such deficits cannot stand alone for diagnosis.

### FIGURE 1
FASD diagnostic algorithm. See text for complete discussion. A positive dysmorphology facial evaluation requires 2 of the 3 cardinal facial features of FASD (short palpebral fissures, smooth philtrum, and this vermilion border of the upper lip). Cutoffs for neuropsychological testing are −1.5 SD. Cutoffs for stature, weight, and head circumference are at the 10th percentile.
edcuators, audiologists, and/or ophthalmologists. 10, 21 – 23

The essential role of the pediatrician in the identification and care of children with FASD cannot be overstated. Pediatricians are among the most likely practitioners to first encounter children with prenatal alcohol exposure who are potentially at risk for FASD. Jones et al 24 demonstrated the accuracy of pediatricians in recognizing FAS on the basis of physical and other common associated features after a relatively short training session. In addition, once a diagnosis is assigned, pediatricians are called on to provide a medical home for affected children, coordinate mental health services, and manage other comorbid mental health disorders. Pediatricians also play an important role in the prevention of future alcohol-exposed pregnancies through counseling women with affected children. 25

Documentation of Significant Prenatal Alcohol Exposure

Assessment of maternal prenatal alcohol intake is an essential part of the diagnostic process and is the first step in the diagnostic algorithm outlined in Fig 1. It is best measured by quantity of alcohol consumed per occasion (standard drinks per drinking day), frequency that it is consumed (eg, daily, times per week), and timing during gestation, because timing of significant exposure (even in the early weeks of pregnancy) can produce different physical and neurobehavioral phenotypes. 26 – 30 Binge drinking (3–5 drinks or more per occasion) has been shown in animal and human studies to be the most detrimental to fetal development. 26, 31 Asking about use of other potential teratogens during pregnancy is also important because, in addition to their own potential teratogenicity, women who abuse drugs are more likely to use alcohol during pregnancy. 13, 14, 32 Because in many populations it is likely that prenatal alcohol use will be denied completely or be significantly underreported, 13, 14, 33 – 35 biomarkers can assist in documenting prenatal alcohol exposure. Most frequently, alcohol exposure information is collected retrospectively. It is well documented that accurate information on a particular pregnancy can be obtained from a willing respondent years after the birth of a child 36 – 38 or from the medical or social service records or a collateral informant (eg, spouse, close relative, or friend) who had regular contact with the mother during pregnancy. 15, 26

In maternal interviews, because of potential stigmatization associated with prenatal alcohol use, and for accuracy, questions should be asked in a timeline followback manner, 39, 40 progressing from the broader context of health history (childbearing, general illness, nutrition, and dietary intake 26, 41, 42) to the more sensitive alcohol use questions. It is important to also consider the overall drinking pattern immediately before pregnancy recognition, as it is common for the drinking pattern of 3 months before pregnancy to persist into early pregnancy. 13, 14, 43 – 49

A consensus definition of significant prenatal alcohol exposure is set forth in Table 2. Note that although certain circumstances permit the diagnosis of FAS or PFAS without firm documentation of gestational alcohol use (Table 1), positive confirmation of alcohol exposure must be available for the diagnosis of ARND or ARBD to be assigned.

Dysmorphology Evaluation

After assessing prenatal alcohol exposure, the presence or absence of the characteristic structural features of FASD must be evaluated. For the dysmorphology examination, height, weight, and head circumference should first be measured and plotted by using population-specific growth curves. In the United States, the authors advise following the Centers for Disease Control and Prevention (CDC) recommendations: use the

<table>
<thead>
<tr>
<th>TABLE 2 Definition of Documented Prenatal Alcohol Exposure (as Applied to the Diagnostic Categories Set Forth in Table 1)</th>
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<tr>
<td>One or more of the following conditions must be met to constitute documented prenatal alcohol exposure during pregnancy (including drinking levels reported by the mother 3 mo before her report of pregnancy recognition or a positive pregnancy test documented in the medical record). The information must be obtained from the biological mother or a reliable collateral source (eg, family member, social service agency, or medical record):</td>
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<tr>
<td>– ≥6 drinks/wk for ≥2 wk during pregnancy</td>
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<tr>
<td>– ≥3 drinks per occasion on ≥2 occasions during pregnancy</td>
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<td>– Documentation of alcohol-related social or legal problems in proximity to (before or during) the index pregnancy (eg, history of citation[s] for driving while intoxicated or history of treatment of an alcohol-related condition)</td>
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<tr>
<td>– Documentation of intoxication during pregnancy by blood, breath, or urine alcohol content testing</td>
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<tr>
<td>– Positive testing with established alcohol-exposure biomarker(s) during pregnancy or at birth (eg, analysis of fatty acid ethyl esters, phosphatidylethanol, and/or ethyl glucuronide in maternal hair; fingernails, urine, or blood, or placenta, or meconium) 26 – 50</td>
</tr>
<tr>
<td>– Increased prenatal risk associated with drinking during pregnancy as assessed by a validated screening tool of, for example, T-ACE (tolerance, annoyance, cut down, eye-opener) or AUDIT (alcohol use disorders identification test) 55</td>
</tr>
<tr>
<td>Assignment of documented prenatal alcohol exposure to any individual case requires the sound judgment of an experienced clinician.</td>
</tr>
<tr>
<td>これらは母陽性の妊娠例におけるアルコール摂取の検査キット（例えばT-ACE（tolerance, annoyance, cut down, eye-opener）またはAUDIT（alcohol use disorders identification test））による評価に基づいて、妊娠中のアルコール摂取のリスクの増加として適用されます。</td>
</tr>
<tr>
<td>Assignment of documented prenatal alcohol exposure to any individual case requires the sound judgment of an experienced clinician.</td>
</tr>
<tr>
<td>* These criteria for maternal drinking are based on large epidemiologic studies that demonstrate adverse fetal effects from ≥3 drinks per occasion 26, 57 and others that indicate 1 drink/day as a threshold measure for FASD. 44 – 46</td>
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WHO growth charts for children from birth to 2 years to assess height and weight. (The WHO growth standards for children younger than 2 years have been adapted for use in the United States.) Use the CDC growth charts for children and teenagers aged 2 to 19 years. In other countries, we recommend using more-specific population-normed charts, if available. If growth curves specific to the population studied are not available, we endorse the recommendations of the CDC for US children. Prenatal growth restriction can be determined from reference data published by Oken et al by gestational age. In these diagnostic guidelines, we define growth deficiency as \( \leq 10^{\text{th}} \) centile. The presence or absence of the 3 cardinal facial characteristics of FASD must next be objectively assessed: short palpebral fissures, smooth philtrum, and thin vermilion border of the upper lip (Fig 2).

Neurodevelopmental Assessment and Neuropsychology Evaluation

Because the primary manifestations of the teratogenic effects of alcohol are demonstrated by changes in brain structure and/or function, comprehensive neurodevelopmental assessment is essential. Although the dysmorphology assessment of infants and small children for the growth and facial characteristics of FASD is feasible, a comprehensive cognitive/developmental evaluation may not be possible by using conventional assessment tools until after age 3 years. However, the cognitive and neurobehavioral phenotype of affected children evolves predictably over time and can be correlated smaller than those measured live. Similarly, Astley found the norm for palpebral fissure measured from 2-dimensional photographic software to fall 1.6 SDs below the mean on a palpebral fissure chart derived from live examinations. Figure 3 A and B depicts the technique for direct measurement of palpebral fissure length, and Fig 3C demonstrates why, in our experience, 2-dimensional photographic assessment of palpebral fissure length is prone to inaccuracy because of individual variation in the zygomatic angle that cannot be corrected for by a single mathematical adjustment. However, it should be noted that investigators disagree on the method that results in the most accurate measurement of palpebral fissure length. The morphology of the philtrum and the vermilion border of the upper lip are objectively scored by comparison with a racially normed lip/philtrum guide (Fig 4). Scores of 4 or 5 are consistent with the effects of prenatal alcohol exposure. If 2 of the 3 cardinal facial characteristics are present (short palpebral fissures, smooth philtrum, and/or thin vermilion border of the upper lip) the child is classified as having a positive dysmorphology facial evaluation for FASD.

FIGURE 2
Typical child with FAS. The 3 cardinal facial features are evident: short palpebral fissures, smooth philtrum, and relatively thin vermilion border of the upper lip. Midface hypoplasia is also apparent.
with areas of brain vulnerability (Table 3).

The authors promote the use of standardized tests that were developed by using normative groups that are representative of the population being tested. Therefore, in the updated guidelines, $\geq 1.5 \text{ SD}$ below the mean refers to the mean of the normative group on which the tests were standardized. Therefore, both groups (alcohol-exposed children as well as unexposed children) are tested by using the same well-normed testing battery, thereby making the comparisons appropriate.

**Multidisciplinary Case Conference**

Once the prenatal exposure history, dysmorphology assessment, and neuropsychological testing have been obtained, a multidisciplinary case conference offers the best opportunity for full discussion of the case before assignment of an FASD or other diagnosis (Fig 1).

**Phenocopies of FASD**

Clinicians should be aware that the facial phenotype of FAS, although most commonly associated with prenatal alcohol exposure, is also observed in a variety of genetic and teratogenic conditions (Table 4).

Therefore, physicians should use a low threshold for ordering additional genetic testing of children with potential FASD. A chromosome microarray has been shown to be the highest-yield diagnostic test when a genetic phenocopy of FASD is being considered.$^{77,78}$

**DISCUSSION**

In the decade since the original operationalized IOM diagnostic criteria$^4$ were published, extensive international research on the teratogenic effects of alcohol and the authors’ broad clinical experience have allowed for the development of further clarity and specificity in the diagnostic guidelines presented in this article. However, it should be noted that agreement on a universal diagnostic system for FASD is lacking among investigators in the field of FASD, especially concerning some of the features of the diagnostic guidelines set forth in Table 1. A discussion of the debated elements follows.

**Diagnostic Categories Within the Continuum of FASD**

It is the authors’ assertion that the 4 original IOM diagnostic categories$^3$ within the continuum of FASD remain the most apt descriptors of the range of disabilities observed. These longstanding categories have heretofore been accepted by many of the diagnostic systems,$^{48,9}$ and we see no need to introduce additional confusion into a field in which diagnostic consensus is critical. In addition, classification of individuals into 1 of the existing specific IOM categories allows for determination of prognosis and treatment planning. We also assert that the category of ARBDs, although uncommon, remains necessary, especially in epidemiologic studies.$^{82,83}$ Our extensive database of alcohol-exposed children reveals many examples of affected children not fitting into 1 of the other categories who display 1 of the major malformations set forth in Table 1 and whose mothers binged during the embryonic stage critical to the developmental pathology of the malformation.

It should be noted that the Canadian diagnostic guideline for FASD recently was updated, collapsing the diagnostic categories under the diagnosis of “fetal alcohol spectrum disorder”$^7$ to 2: FASD with sentinel facial features and FASD without...
sentinel facial features. Whether this simplified diagnostic scheme will result in practical improvements in the clinical care of affected individuals and more accurate epidemiologic studies estimating the prevalence of FASD remains to be demonstrated.

**Sensitivity Versus Specificity in Clinical Diagnosis**

Similar to others, our goals in the formulation of FASD diagnostic guidelines have been improved sensitivity and greater inclusion of children in the complete continuum of FASD; thus, we have set cutoff levels for growth deficiency, head circumference, and palpebral fissure length at ≤10th centile and required 2, rather than 3, cardinal facial features for a diagnosis of FAS and PFAS. Because we advocate for a structured expert-led multidisciplinary diagnostic approach to the diagnosis of FASD, casting a broad net early in the diagnostic process and later using the case conference to carefully assign diagnoses has been our standard. Other diagnostic systems advocate for more stringent cutoffs: growth deficiency, head circumference, and palpebral fissure length less than or equal to the third centile and requiring all 3 of the cardinal facial features for alcohol-related diagnoses. Sensitivity and specificity are 2 sides of a diagnostic coin. Theoretically, the guidelines presented here demonstrating increased sensitivity could lead to overdiagnosis; thus, our advocacy for a structured expert multidisciplinary approach. On the other hand, strict diagnostic cutoffs associated with increased specificity could lead to underdiagnosis of affected children. Children with FASD are subject to a host of societal, educational, health, and judicial problems, all of which are affected by the time of diagnosis. Because early diagnosis and initiation of intervention should be of paramount importance, the guidelines presented here are intended to maximize both sensitivity and specificity for the detection of FASD.
importance, the authors assert that improved, sensitive, and inclusive diagnostic criteria for FASD should continue to be imperatives in the diagnostic process.

**Deficient Brain Growth, Abnormal Morphogenesis, or Abnormal Neurophysiology**

In the updated criteria, we have added documentation of recurrent nonfebrile seizures to the potential assignment of children to the diagnostic categories of FAS or PFAS. A child with FAS must now exhibit deficient brain growth, structure, or neurophysiology. This modification was prompted by a growing body of research that indicates that epilepsy is a frequent accompaniment of FASD. More commonly observed in children with FASD, a small head circumference is a reliable, easily obtained proxy for decreased brain volume. Finally, a number of structural brain abnormalities have been observed in imaging studies in animals and human subjects with FASD. Although no specific anatomic region of the brain is preferentially affected, malformations resulting from migration abnormalities, changes in size and shape of the corpus callosum, cerebellar vermis hypoplasia, and hypoplasia of the basal ganglia and hippocampus have been documented.

The 4-digit diagnostic code assesses these features as “structural evidence of central nervous system damage,” and the updated Canadian guideline for diagnosis of FASD includes a similar category (abnormal neuroanatomy/neurophysiology) as 1 of the 10 central nervous system domains that may be impaired, although this category is not a universal part of other diagnostic systems.

**Other Minor Anomalies in Children With FASD**

In dysmorphology, clinical diagnoses are based on recognizable patterns of major and minor anomalies. Although the dysmorphology contribution to FASD diagnoses is derived from objective evaluation of the face, a number of other minor anomalies have been observed consistently and more commonly in children prenatally exposed to alcohol than in nonexposed controls. The clinical assessment of the presence or absence of these features should be part of the dysmorphology evaluation of children with potential FASD. The overall dysmorphic variation in any individual child can be quantified by calculation of a dysmorphology score (an updated dysmorphology scoring system based on objective observations of growth and minor anomalies in 370 children with FAS is presented in Table 5). The dysmorphology score allows for objective comparison among groups of children with FASD and has proven to be a valuable research tool. It is also a useful instrument to review as part of the differential diagnostic process when assessing features of genetic or other teratogenic disorders that may mimic FASD (Table 4). The score has been observed to correlate significantly with prenatal maternal alcohol intake, as well as with the cognitive and neurobehavioral characteristics of the affected child.

**Specificity of Neurobehavioral Impairment**

The updated guidelines now require that all children assigned FASD diagnoses (with the exception of those with ARBD) must display neurobehavioral impairment (cognitive impairment or behavioral impairment without cognitive impairment). The original guidelines allowed for children with the requisite facial features, growth restriction, and/or microcephaly to be assigned an FASD diagnosis in the absence of significant neurobehavioral impairment. However, because neurocognitive impairment and abnormal behavior are the principal sources of disability in FASD, assignment of children with prenatal alcohol exposure into an FASD category without neurobehavioral impairment has no practical utility for either the child or the child’s family.

The definition of neurobehavioral impairment in FASD has become more specific over the past decade. The original 1996 IOM criteria and the 2005 guidelines defined neurobehavioral impairment as “evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone.” Although the 2005 criteria outlined areas of marked neurobehavioral impairment, levels of deficit and affected functional domains were not clearly articulated. The guidelines set forth in Table 1 clearly delineate domains of functioning to be assessed and levels of deficit to be reached to meet the diagnostic criteria for FAS, PFAS, and ARND.

The domains of function outlined in the updated criteria encompass the following: (1) global intellectual ability (full-scale, verbal, performance, or spatial IQ), (2) cognition (executive functioning, learning, memory, and visual-spatial skills), (3) behavior and self-regulation (mood, behavioral regulation, attention, and impulse control), and (4) adaptive skills.
<table>
<thead>
<tr>
<th>Areas of Brain Vulnerability in FASD</th>
<th>Neurocognitive</th>
<th>Behavioral Deficits Associated With Developmental Stage</th>
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<tbody>
<tr>
<td>Infancy: 0–2 y</td>
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<tr>
<td>• Cortical synaptogenesis</td>
<td>Neurocognitive</td>
<td>• Delayed cognitive development or global development delay</td>
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<td>• Development of cortical gray matter</td>
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<tr>
<td>• Myelination of sensory pathways</td>
<td>Self-Regulation</td>
<td>• Tremulousness, increased jitteriness</td>
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<td>• Maturation of the limbic system</td>
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<td>• Difficulty with self-soothing, and being soothed</td>
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<tr>
<td>• Myelination of motor pathways</td>
<td>Adaptive</td>
<td>• Emotional withdrawal, decreased infant affective functioning</td>
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<td>• Emotion withdrawal, decreased infant affective functioning</td>
<td></td>
<td>• Impaired stress reactivity, deficits in pain regulation</td>
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<td>• Complex play</td>
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<td>• Less complex play</td>
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<tr>
<td>• Delayed gross and fine motor milestones</td>
<td>Adaptive</td>
<td>• Poor feeding; poor sucking; easily fatigued</td>
</tr>
<tr>
<td>Toddler/Preschool: 3–5 y</td>
<td>Neurocognitive</td>
<td>• Delayed cognitive development or global developmental delay</td>
</tr>
<tr>
<td>• Synaptogenesis</td>
<td>Self-Regulation</td>
<td>• Attention: difficulties with attention regulation, hyperactivity and impulsivity; difficulty shifting attention; impaired visual and auditory attention; difficulty with sustained attention</td>
</tr>
<tr>
<td>• Development of cortical gray matter</td>
<td></td>
<td>• Executive function: difficulty encoding information; difficulty with multistep directions; difficulty with planning and organization; poor understanding of consequences</td>
</tr>
<tr>
<td>• Development of prefrontal cortex</td>
<td>Adaptive</td>
<td>• Sleep deficits: shortened sleep duration; increased sleep anxiety; parasomnias</td>
</tr>
<tr>
<td>• Development of temporal lobes</td>
<td></td>
<td>• Sensory processing: difficulty modulating sensory input; sensory seeking</td>
</tr>
<tr>
<td>• Development of dorsal motor cortex</td>
<td>Adaptive</td>
<td>• Delayed gross motor function: balance, coordination problems; &quot;clumsiness&quot;</td>
</tr>
<tr>
<td>• Development of temporal lobes</td>
<td></td>
<td>• Poor fine motor skills: difficulty with writing/drawing, poor dexterity; visual-spatial deficits; impaired visual-motor coordination</td>
</tr>
<tr>
<td>School-age: 6–12 y</td>
<td>Neurocognitive</td>
<td>• Delayed auditory processing; central auditory delay</td>
</tr>
<tr>
<td>• Decreased intracranial volume: Neurocognitive</td>
<td></td>
<td>• Speech and language deficits: difficulties with language acquisition; receptive, expressive language delays; deficits in word processing/word recognition; articulation errors; deficits in social pragmatics</td>
</tr>
<tr>
<td>• Decreased volume of parietal and temporal lobes</td>
<td>Self-Regulation</td>
<td>• Memory deficits: difficulty remembering things previously learned</td>
</tr>
<tr>
<td>• Prefrontal cortex</td>
<td>Adaptive</td>
<td>• Attention deficits: hyperactivity; impulsivity</td>
</tr>
<tr>
<td>• Temporal lobe</td>
<td></td>
<td>• Language deficits in higher order language processing</td>
</tr>
<tr>
<td>• Parietal lobe</td>
<td>Neurocognitive</td>
<td>• Social pragmatics: deficits in social cognition: inappropriate social initiation/social interaction; inappropriate sexual behaviors</td>
</tr>
<tr>
<td>Adolescent: 13–21 y</td>
<td>Self-Regulation</td>
<td>• Memory: difficulty encoding/consolidating new memory</td>
</tr>
<tr>
<td>• Decreased intracranial volume: Neurocognitive</td>
<td></td>
<td>• Language processing: impaired gestural communication; deficits in social perception</td>
</tr>
<tr>
<td>• Decreased volume of parietal and temporal lobes</td>
<td>Adaptive</td>
<td>• Visual-spatial: deficits in spatial processing; poor handwriting; impaired visual-motor integration</td>
</tr>
<tr>
<td>• White matter abnormalities</td>
<td></td>
<td>• Lower intellectual quotient</td>
</tr>
</tbody>
</table>

TABLE 3 Developmental Emergence of Neurocognitive and Behavioral Deficits Associated With FASD
These functional domains were selected based on the empirical evidence of deficits in children prenatally exposed to alcohol and/or who have been given a diagnosis of FASD.\textsuperscript{32,95-107}

For children >3 years of age, diagnoses of FAS or PFAS require evidence of global cognitive impairment (reflected in a deficit of $\geq 1.5$ SDs below the mean on a measure of global intelligence [full-scale IQ score] or performance, verbal, or visual/spatial IQ) or evidence of behavioral deficit $\geq 1.5$ SDs below the mean in $\geq 1$ domain in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control). A diagnosis of ARND can be made only if there is confirmed prenatal alcohol exposure and global cognitive impairment, reflected in a deficit of $\geq 1.5$ SDs below the mean on a measure of global intelligence (full-scale IQ score) or performance, verbal, or visual/spatial IQ. If cognitive impairment is not present (often the case with individuals prenatally exposed to alcohol), cognitive deficits in at least 2 additional neurobehavioral domains (executive functioning, specific learning, memory, or visual/spatial) are required at $\geq 1.5$ SDs below the mean. Additionally, the new guidelines provide for an ARND diagnosis based on behavioral impairment without cognitive impairment, as evidenced by deficits at $\geq 1.5$ SDs below the mean in at least 2 behavioral domains: mood or behavioral regulation, attention deficit, or impulse control. Adaptive skills also should be assessed.\textsuperscript{108-110}

The adaptive scores can be used to assist with the diagnosis; however, specific cutoffs and adaptive behavior requirements are not included in the diagnostic criteria.

For children who are $\leq 3$ years of age, a diagnosis of FAS and PFAS can be made if there is evidence of developmental delay $\geq 1.5$ SDs below the mean on a standardized measure of developmental trajectory. However, for ARND, a definitive diagnosis cannot be made before 3 years of age.

The neurobehavioral criteria for diagnoses within the FASD continuum differ from those proposed by other investigators\textsuperscript{5,9,10} (our guidelines require: cutoffs of $-1.5$ SDs rather than $-2$ SDs, for neurobehavioral assessment and less stringent neurobehavioral criteria for those affected children who demonstrate the requisite dysmorphology allowing classification into the categories of FAS and PFAS). Our previously published data confirm that because the dysmorphology score has the highest correlation with confirmed diagnoses in the FASD continuum, confidence in an FAS or PFAS diagnosis can be ensured with impairment in fewer neurobehavioral domains.\textsuperscript{26,94}

### Differentiation Between ARND and Neurobehavioral Disorder With Prenatal Alcohol Exposure

These updated criteria continue to include ARND as a necessary diagnostic category. With the introduction of Neurobehavioral Disorder with Prenatal Alcohol Exposure (ND-PAE) into the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition as a “condition in need of further study,”\textsuperscript{7} there has been significant confusion about the necessity of retaining both ARND and ND-PAE as diagnostic entities. To be clear, ARND is a complex medical diagnosis, best assigned as part of a multidisciplinary team evaluation for FASD. It has been widely applied in epidemiologic studies\textsuperscript{14,93} and in clinical settings and has been found to accurately describe the end of the continuum of FASD without dysmorphology.\textsuperscript{111,112} In contrast, ND-PAE is an experimental mental health diagnostic code that is intended to be used in clinical settings by clinicians from a variety...
The Revised Dysmorphology Score was derived from analysis of growth and structural data from 370 children with CHD, congenital heart disease; ICD, intercanthal distance; IPD, interpupillary distance; OFC, occipitofrontal (head) circumference; PFL, palpebral fissure length.

The Revised Dysmorphology Score was derived from analysis of growth and structural data from 370 children with CHD, congenital heart disease; ICD, intercanthal distance; IPD, interpupillary distance; OFC, occipitofrontal (head) circumference; PFL, palpebral fissure length.

The cardinal diagnostic features (small head circumference, growth restriction [height and weight combined], short PFL, limited elbow supination, camptodactyly, thin vermilion border of the upper lip) were assigned a score of 3. Other features observed in ≥100 children were assigned a score of 2. Features observed in <100 children received a score of 1. The score provides an objective method of quantifying dysmorphic features and comparing the structural phenotype of FASD among affected children; it is not used in assigning FASD diagnoses. However, compilation of the minor anomalies cataloged in the score is useful in differentiating children with FASD from genetic and teratogenic phenocopies (Table 5).

This list is not comprehensive. OMIM, Online Mendelian Inheritance in Man. 56

**TABLE 5** Revised Dysmorphology Scoring System (Based on Quantitative Analysis of Growth Restriction and Minor Anomalies in 370 Children With FAS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. Affected</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFC ≤10%</td>
<td>354</td>
<td>3</td>
</tr>
<tr>
<td>Growth deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height ≤10%</td>
<td>327</td>
<td>2</td>
</tr>
<tr>
<td>Weight ≤10%</td>
<td>322</td>
<td>2</td>
</tr>
<tr>
<td>Short PFL (≤10%)</td>
<td>313</td>
<td>2</td>
</tr>
<tr>
<td>Smooth philtrum</td>
<td>307</td>
<td>2</td>
</tr>
<tr>
<td>Thin vermilion</td>
<td>293</td>
<td>2</td>
</tr>
<tr>
<td>Hypoplastic midface</td>
<td>216</td>
<td>2</td>
</tr>
<tr>
<td>Epicanthal folds</td>
<td>204</td>
<td>2</td>
</tr>
<tr>
<td>Decreased IPD/ICD (≤25%)</td>
<td>202/104</td>
<td>2</td>
</tr>
<tr>
<td>Flat nasal bridge</td>
<td>179</td>
<td>2</td>
</tr>
<tr>
<td>Altered palmar crease</td>
<td>173</td>
<td>2</td>
</tr>
<tr>
<td>5th finger clinodactyly</td>
<td>149</td>
<td>2</td>
</tr>
<tr>
<td>Long philtrum (≥90%)</td>
<td>122</td>
<td>2</td>
</tr>
<tr>
<td>Anteverted nares</td>
<td>118</td>
<td>2</td>
</tr>
<tr>
<td>Camptodactyly</td>
<td>114</td>
<td>2</td>
</tr>
<tr>
<td>P rosa</td>
<td>64</td>
<td>2</td>
</tr>
<tr>
<td>“Railroad track” ears</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Heart murmur/confirmed CHD</td>
<td>50/6</td>
<td>2</td>
</tr>
<tr>
<td>Strabismus</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Limited elbow supination</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Hypoplastic nails</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Total possible score</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>
areas in need of further study are the following: potential use of improved and more practical 3-dimensional photographic imaging as an accurate proxy for live facial anthropometric measurements; improved noninvasive biomarkers for alcohol exposure throughout pregnancy and postnatally; postnatal epigenetic markers as a proxy for documentation of prenatal maternal alcohol intake, improved definition of which fetal and postnatal growth patterns are most consistent with the teratogenic effects of alcohol; and a more precise definition of what constitutes minimal criteria for adverse fetal alcohol exposure during gestation. Finally, other diagnostic approaches to FASD that can be readily applied in resource-poor settings should be explored.

CONCLUSIONS

FASD continues to represent a pressing global public health challenge. The first step in addressing this dilemma is to recognize the magnitude of the problem through careful case definition. Since the authors’ diagnostic guidelines were published in 2005, considerable progress has been made in further specifying the anatomic and neurobehavioral characteristics of FASD. These updated guidelines reflect consensus among a large and experienced cadre of FASD investigators in the fields of dysmorphology, epidemiology, neurology, psychology, developmental/behavioral pediatrics, and educational diagnostics. They do not necessarily represent the policy of the American Academy of Pediatrics. The improved specificity of these guidelines will aid clinicians in assignment of more accurate diagnoses of alcohol-exposed infants and children, thereby leading to more widespread early intervention and improved prevention efforts.

Dr Hoyme was the first author of the original diagnostic guidelines for fetal alcohol spectrum disorders (FASD) published in Pediatrics in 2005, conceptualized and designed the study, and drafted the initial document; Ms Kalberg with Dr Coles formulated the psychological testing battery used for the subjects and assisted in assignment of FASD diagnoses, along with Drs Elliott and Coles she was charged with clarifying the definition of alcohol-related neurodevelopmental disorder, and she revised the document; Dr Elliott assisted with assignment of FASD diagnoses, along with Ms Kalberg and Dr Coles she was charged with clarifying the definition of alcohol-related neurodevelopmental disorder, and she revised the document; Dr Blankenship and Mr Buckley comprised the data analysis group for the FASD team collaboration, they oversaw the gathering, storing, and analysis of sensitive subject data, and produced tables and figures for the manuscript; Dr Blankenship died before submission of the paper; Mr Buckley revised the document; Ms Marais coordinated the multidisciplinary diagnostic case conferences on the children from whom the data for this report were collected and revised the document; Drs Manning, Robinson, Adam, Abdul-Rahman, Jewett, and Jones examined all of the children in the studies on which the updated criteria are based, assigned diagnostic categories to the subjects, aided in crafting the definitions of the updated diagnostic criteria, and revised the document; Dr Coles contributed significantly to the clarification of alcohol-related neurodevelopmental disorder and revised the manuscript; Dr Chambers contributed significantly to the development of the overall diagnostic scheme for FASD and revised the manuscript; Dr Adams developed the psychological and neuropsychological testing battery and oversaw the testing of the large South African cohort of children examined over the past decade, participated in developing the neuropsychological criteria set forth in the article, and revised the document; Dr Shah authored the sections on the natural history of the neurobehavioral phenotype of FASD over the life span, and revised the document; Drs Riley and Charness added significantly to the formulation of the specific revised diagnostic guidelines and revised the document; Dr Warren is the driving force behind the epidemiological investigations that form the basis of the revised guidelines, participated in formulating the specific guidelines, and edited the document; Dr May is principal investigator of the school-based population studies in South Africa, Italy, and the United States on which this manuscript is based, and revised the document; and all authors agree to be accountable for all aspects of the work and approved the final manuscript as submitted.

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