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Prenatal Alcohol Use and Fetal Alcohol Spectrum Disorders

Diagnosis, Assessment and New Directions in Research and Multimodal Treatment

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CHAPTER 1

Diagnosing Fetal Alcohol Spectrum Disorders (FASD)

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While we try to teach our children about life, our children teach us what life is all about

Angela Schwindt

Abstract: Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. Almost four decades have passed since the term FAS was first coined. The condition is now recognized as a spectrum of disorders: Fetal Alcohol Spectrum Disorders (FASD). Substantial progress has been made in developing specific criteria for delineating diagnoses under the umbrella of FASD. In the 14 years since the publication of the seminal report on FAS by the Institute of Medicine in 1996, clear consensus has been reached on two fundamental issues: 1) an FASD diagnostic evaluation is best conducted by a team of professionals from multiple disciplines (medicine, psychology, speech-language, occupational therapy) and 2) the team should use rigorously case-defined and validated FASD diagnostic guidelines. This chapter will provide a brief overview of the discovery of FASD, diagnostic challenges, how diagnostic guidelines and clinical models have evolved over time to address these challenges, and how new technology may influence the future of FASD diagnosis.

INTRODUCTION

What is FASD?

Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of FAS has changed little since the 1970's when the condition was first described and refined [1-5]. The condition has been broadly characterized by prenatal and/or postnatal growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) abnormalities. FAS is the leading known preventable cause of intellectual disabilities in the Western World [6]. The prevalence of FAS is estimated to be 1 to 3 per 1,000 live births [1] in the general population, but has been documented to be as high as 10 to 15 per 1,000 in some higher-risk populations such as children residing in foster care [7,8].

The physical, cognitive, and behavioral deficits observed among individuals with prenatal alcohol exposure are not dichotomous, that is either normal or clearly abnormal. Rather, the outcomes, and the prenatal alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive [9-12]. This full range of outcomes observed among individuals with prenatal alcohol exposure has come to be called Fetal Alcohol Spectrum Disorders (FASD). Diagnoses like FAS, Partial FAS (PFAS), and Alcohol-Related Neurodevelopmental Disorder (ARND) fall under the umbrella of FASD.

The Diagnostic Challenge

FASD can present a daunting, but not insurmountable challenge for diagnosis. Individuals with prenatal alcohol exposure present with a wide range of outcomes, most of which are not specific to prenatal alcohol exposure and often manifest differently across the lifespan. Professionals from multiple disciplines (medicine, psychology, speech-language pathology, occupational therapy, etc.) are needed to assess and interpret accurately the broad array of outcomes that define the diagnoses. The pattern and severity of outcomes are dependent on the timing, frequency, and quantity of alcohol exposure (which is rarely known with any level of accuracy), and is frequently confounded by other adverse prenatal and postnatal exposures and events.

In the absence of objective, accurate, and reproducible methods for measuring and recording the severity of exposures and outcomes in individual patients, diagnoses have varied widely from clinic to clinic [1,13-16]. From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary

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disabilities [17], and missed opportunities for primary prevention [18]. From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence [1,14,16,19]. Inaccurate estimates thwart efforts to allocate sufficient social, educational, and health care services to this high-risk population, and preclude accurate assessment of primary prevention intervention efforts. From a clinical research perspective, diagnostic misclassification reduces the power to identify clinically meaningful contrasts between FAS and control groups and between FASD clinical subgroups like FAS and ARND [9,14,20]. Non-standardized diagnostic methods also thwart valid efforts to compare outcomes between research studies [9,10, 21].

DISCOVERY OF FETAL ALCOHOL SYNDROME

Reference to the harmful effects of maternal drinking on infant outcome date back to biblical times (Behold, thou shalt conceive, and bear a son; and now drink no wine or strong drink…Judges 13:7) [22], with several remarkably comprehensive descriptions by physician groups in the 1700s and 1800s [23-25]. But several hundred years would go by before another entry would be made to the medical literature. In 1968 Lemoine and colleagues from France published an article describing 147 patients [26]. In 1970, unaware of the Lemoine publication, Ulleland and colleagues from Seattle, Washington published similar observations describing a small group of alcohol-exposed infants admitted to several high-risk maternal-child health clinics at the University of Washington [27,28]. Dr. Ulleland's findings were accepted for presentation at the American Pediatric Society-Society for Pediatric Research meeting, held in Atlantic City New Jersey in 1970 [27]. Through a presentation to the University of Washington pediatric faculty, David Smith, M.D., a dysmorphologist, became interested in Dr. Ulleland's research. This would eventually lead to a collaborative publication in 1973 describing the pattern of outcome associated with prenatal alcohol exposure [29] and the publication that coined the term FAS [2].

Initial FAS Diagnostic Guidelines (1973-89)

Progress in refining the FAS diagnosis can be traced by reviewing Clarren and Smith [4], who summarized the available clinical reports from 1973 to 1976, and the reports from the fetal alcohol workshops of the Research Society of Alcoholism in 1980 and 1989 [3,5].

IOM FAS Diagnostic Guidelines (1996)

In recognition of the seriousness of FAS for the individual and society, the U.S. Congress mandated (in Section 705 of Public Law 102-321, the ADAMHA Reorganization Act) the Institute of Medicine (IOM) of the National Academy of Sciences to conduct a study of FAS and related birth defects. A seminal report was published in 1996 covering the full spectrum of issues from prevalence, diagnosis, prevention, to treatment [1]. A chapter entitled "Diagnosis and Clinical Evaluation of FAS" was included. The committee was charged with evaluating existing diagnostic criteria and formulating the best possible diagnostic guidelines reflective of current knowledge. The IOM diagnostic guidelines for FASD are presented in their entirety across Tables 1-4, as they represent an important baseline from which current guidelines evolved. The IOM committee recognized the following issues as central to delineating FASD:

1. Should a documented history of exposure to alcohol be required for a diagnosis of FAS?
2. Which physical features should be used to define the disorder?
3. Can behavioral or cognitive features be used to define the disorder?
4. Is there a role for ancillary measures (e.g., magnetic resonance imaging [MRI] in making the diagnosis?
5. Can criteria be designed to be used across the lifespan?
6. What is the relationship of so-called fetal alcohol effects to fetal alcohol syndrome?

These issues will be discussed later in this chapter as they relate to both the IOM guidelines and current guidelines.

While the IOM guidelines reflected an important advancement in FASD diagnosis: 1) the IOM committee felt "a medical diagnosis of FAS remained the purview of dysmorphologists and clinical geneticists" (page 79), and 2) the guidelines remained intentionally broad and conceptual (e.g., gestalt) rather than specific and operational (e.g., case-defined) [1].

Table 1. FAS diagnostic criteria: Comparison across the five most current FAS/D diagnostic guidelines.

	4-Digit Code (2004)[38]	CDC (2004) [36]	Canadian (2005) [37]	Hoyme (2005)[19]	IOM (1996)[1]
Growth	Prenatal and/or postnatal height or weight ≤ 10th percentile (Growth Ranks 2-4)	Prenatal and/or postnatal height or weight ≤ 10th percentile (Growth Ranks 2-4)	At least 1 of the following: • Prenatal and/or postnatal height or weight ≤ 10th percentile • Weight-to-height ratio (≤10th percentile) (Growth Ranks 2-4)	Prenatal and/or postnatal height or weight ≤ 10th percentile (Growth Ranks 2-4)	At least 1 of the following: • Low birth weight • Low weight for height • Decelerating weight (Growth Ranks 1-4)
Face	All 3 of the following at any age: • PFL ≤ 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Rank 4)	All 3 of the following: • PFL ≤ 10th percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 3-4)	All 3 of the following at any age: • PFL ≤ 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Rank 4)	2 or more of the following: • PFL ≤ 10th percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 2-4)	Characteristic pattern that includes features such as short PFL, flat upper lip, flattened philtrum, and flat midface. (Face Ranks 1-4)
CNS	At least 1 of the following: • Structural/Neurological: (e.g., OFC ≤ 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domains[a] of function with impairment 2 or more SDs below the mean) (CNS Rank 3 and/or 4)	At least 1 of the following: • Structural/Neurological: (e.g., OFC ≤ 10th percentile, abnormal structure, seizure disorder, hard/soft signs) • Dysfunction[b]: ○ 3 or more domains of function with impairment 1 or more SDs below the mean ○ Global deficit (2 or more SDs below the mean) (CNS Ranks 2-4)	At least 3 of the following Structure/Neurological/ Functional domains with impairment[c]: • Hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication (CNS Ranks 3 and/or 4)	At least 1 of the following: • Structural ○ OFC ≤ 10th percentile ○ Abnormal structure (CNS Rank 1 or 4)	At least 1 of the following: • Structural/Neurological: ○ Decreased cranial size at birth ○ Abnormal structure (e.g., microcephaly, partial/complete agenesis of the corpus callosum, cerebellar hypoplasia) ○ Neurological hard/soft signs (CNS Rank 4?)
Alcohol	Confirmed or Unknown (Alcohol Ranks 2,3 or 4)	Confirmed or Unknown (Alcohol Ranks 2,3 or 4)	Confirmed or Unknown (Alcohol Ranks 2,3 or 4)	Confirmed-excessive or Unknown (Alcohol Ranks 2 or 4)	Confirmed-excessive or Unknown (Alcohol Ranks 2 or 4)

a. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level.

b. CDC: Performance substantially below that expected for an individual's age, schooling, or circumstances, as evidenced by: 1. Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing) or 2. Functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains: a) cognitive or developmental deficits or discrepancies b) executive functioning deficits c) motor functioning delays d) problems with attention or hyperactivity e) social skills f) other, such as sensory problems, pragmatic language problems, memory deficits, etc.

c. Canadian: Impairment indicates scores ≥ 2 SDs below the mean, discrepancies of 1.5-2 SDs among subtests, or ≥ 1 SD discrepancy between subdomains.

The equivalent 4-Digit Ranks for Growth, Face, CNS and Alcohol are inserted in red font to facilitate comparison across the guidelines.

FASD diagnosis has now advanced beyond the 1996 IOM FASD diagnostic guidelines. While areas of debate still exist, the field has reached consensus on two fundamental issues: 1) an FASD diagnostic evaluation is best conducted by an interdisciplinary team of professionals, and 2) the team should use rigorously case-defined and validated FASD diagnostic guidelines.

Interdisciplinary Diagnostic Approach

The University of Washington FAS Diagnostic & Prevention Network (FAS DPN) first introduced an interdisciplinary approach to FASD diagnosis through a CDC-sponsored FAS prevention project conducted in 1992-97 [18,30-32]. Because of the complexity and broad array of outcomes observed in individuals with prenatal alcohol exposure, an interdisciplinary team is essential for an accurate and comprehensive diagnosis and treatment plan. An interdisciplinary FASD diagnostic team typically includes a medical doctor, psychologist, speech language pathologist, occupational therapist, social worker, and family advocate. Other members of the interdisciplinary team may include, but are not limited to, psychiatrists, neuropsychologists, geneticists, public health nurses, and mental health specialists.

Interdisciplinary models will necessarily vary to accommodate site-specific factors like funding, location (rural versus urban), access to services, target population, etc. The model used by the University of Washington FAS DPN diagnostic clinic targets both a general population and a high-risk foster care population. Individuals from the general population (birth to adult) are referred to the clinic by a broad array of community professionals (medical, educational, social-service, justice). In addition, all children who screen positive for the full FAS facial phenotype from the FAS DPN-Foster Care Passport Program FAS screening program [7,8] are also referred to the clinic.

The patient population served by the FAS DPN has expressed strong preference for an evaluation that can be completed in a single visit. Thus, two patients are evaluated per day, one in the morning and one in the afternoon. The interdisciplinary team includes a pediatrician, two psychologists, a speech-language pathologist, an occupational therapist, a social worker, and a family advocate. Prior to an evaluation, previous medical, school, and social records are collected by the clinic coordinator and reviewed by the lead psychologist. On the day of the evaluation, the lead psychologist presents the case to the team. The child is then assessed by the second psychologist, speech language pathologist, and occupational therapist while the caregivers are interviewed by the pediatrician and lead psychologist. Upon completion of the interview, the pediatrician conducts a physical exam of the patient. The team reconvenes to derive the FASD 4-Digit Code and compose an intervention plan. The team shares the diagnostic results and intervention plan with the family at the end of the 4-hour appointment. A single comprehensive report documenting the diagnostic outcome, all data used to derive the diagnostic outcome, and intervention recommendations are submitted to the patient's medical record.

A more detailed description of the interdisciplinary diagnostic approach used by the University of Washington FAS DPN is presented in Clarren et al., [32]. A short video of an interdisciplinary diagnostic team conducting an FASD diagnostic evaluation can be viewed by clicking on http://depts.washington.edu/fasdpn/htmls/diagteamvideo.htm (Fig. 1)

Figure. 1: This video segment portrays an interdisciplinary team conducting an FASD diagnostic evaluation using the FASD 4-Digit Code. The video is a live recording of an actual FASD diagnostic evaluation. The patient is an adolescent adopted from Russia. The interdisciplinary team includes a pediatrician, two psychologists, a speech-language pathologist, an occupational therapist, a social worker, a family advocate, and a public health professional. The child will receive a 4-Digit Code of 4442 (FAS / Alcohol Exposure Unknown). The team conducted a 2-hour interview with the adoptive parents and a 2-hour evaluation of the child. The team has already derived the first two digits of the 4-Digit Code (the Growth and Face Ranks). This segment portrays the team's derivation of the last two digits of the 4-Digit Code (the CNS and Alcohol Ranks). The team will also document all other prenatal and postnatal risk factors that may have contributed to the child's outcomes. This video segment is one of several presented in the FASD 4-Digit Diagnostic Code Online Course offered at the FAS DPN at the University of Washington.[33] Copyright: Susan Astley, University of Washington, Seattle, WA

Current FAS/D Guidelines (1997 2005)

Four FAS/D diagnostic guidelines have been published since the IOM Guidelines in 1996 [1]: the FASD 4-Digit Code in March 1997 [34,35]; the CDC FAS guidelines in July 2004 [36]; the Hoyme FASD guidelines in January 2005 [19], and the Canadian FASD guidelines in March 2005 [37]. The 4-Digit Code was subsequently updated in January, 1999 [34] and November 2004 [38]. All four guidelines are in current use. This is not to imply the 1996

IOM guidelines are not in use. But each of the four new guidelines purports to have been created to replace or augment the 1996 IOM guidelines.

Table 2: Partial FAS diagnostic criteria. Comparison across the five most current FAS/D diagnostic guidelines.

	4-Digit Code (1997-2004)[38]	CDC[a] (2004) [36]	Canadian (2005)[37]	Hoyme (2005)[19]	IOM (1996)[1]
Growth	Prenatal or postnatal height or weight ≤ 10th percentile (Growth Ranks 1-4)	--	No growth deficiency (Growth Rank 1)	Prenatal and/or postnatal height or weight ≤ 10th percentile (Growth Ranks 2-4)	At least 1 of the following: • Low birth weight • Low weight for height • Decelerating weight (Growth Ranks 1-4)
Face	All 3 of the following at any age: • PFL ≤ 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 3 or 4)*	--	2 of the following at any age: • PFL ≤ 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 2 or 3)	2 or more of the following: • PFL ≤ 10th percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 2-4)	Some components of the pattern of FAS characteristic facial anomalies. (Face Ranks 1-4)
CNS	At least 1 of the following: • Structural/Neurological: (e.g., OFC ≤ 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domains[b] of function with impairment 2 or more SDs below the mean) (CNS Rank 3 and/or 4)	--	At least 3 of the following Structure/Neurological/Functional domains with significant impairment[c]: • Hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication (CNS Rank 3 and/or 4)	At least 1 of the following: • Structural ○ OFC ≤ 10th percentile ○ Abnormal structure • Dysfunction ○ Complex pattern[d] of behavior / cognitive abnormalities (CNS Ranks 1-4)	At least 1 of the following: • Structural/Neurological : ○ Decreased cranial size at birth ○ Abnormal structure ○ Hard/soft signs • Dysfunction ○ Complex pattern[e] of behavior / cognitive abnormalities (CNS Ranks 2-4)
Additional Criteria	PFAS requires the CNS and Alcohol criteria to be met and allows the Growth and/or the Face criteria to be relaxed just slightly. • *One facial feature may be relaxed as follows: (PFL ≤ 1 SD, or Philtrum Rank 3, or Lip Rank 3) or • Growth can be relaxed to normal.	--	None	PFAS requires the Face and Alcohol criteria to be met and only one of the following additional criteria : • Growth • CNS Structural • CNS dysfunction	PFAS requires the Face and Alcohol criteria to be met and only one of the following additional criteria : • Growth • CNS Structural / Neurological • CNS dysfunction
Alcohol	Confirmed (Alcohol Ranks 3 or 4)	--	Confirmed (Alcohol Ranks 3 or 4)	Confirmed-excessive or Unknown (Alcohol Ranks 2 or 4)	Confirmed-excessive (Alcohol Rank 4)

a. The CDC Guidelines only address FAS.

b. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level.

c. Canadian: Impairment indicates scores ≥ 2 SDs below the mean, discrepancies of 1.5-2 SDs among subtests, or ≥ 1 SD discrepancy between subdomains.

d. Hoyme: Marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction).

e. IOM: Complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone: e.g., learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention or judgment.

The equivalent 4-Digit Ranks for Growth, Face, CNS and Alcohol are inserted in red font to facilitate comparison across the guidelines.

Why are there four separate guidelines? Their existence reflects the ongoing debate on how best to approach FASD diagnosis. All present with strengths and limitations. Each was developed under different circumstances that influenced their outcome. The 4-Digit Code was investigator initiated in a statewide clinical/research arena using a clinical sample of 1,014 individuals of all races and ages (birth to 51 years of age) [14]. Empirical methods were used both to develop [20,39] and validate the performance of the 4-Digit Code [7-9,14,20,39]. The CDC [36] and Canadian [37] guidelines were federally mandated and commanded a more consensus-driven process. These guidelines were not empirically validated prior to publication. The Hoyme [19] guidelines were also investigator initiated in a clinical/research arena, using a clinical sample of 164 Native American and South African children to augment an existing set of guidelines: the IOM Guidelines.

Table 3. ARND (or its equivalent: Static Encephalopathy/Alcohol Exposed or Neurobehavioral Disorder/Alcohol Exposed) diagnostic criteria. Comparison across the five most current FAS/D diagnostic guidelines.

	4-Digit Code (1997-2004)[38]	CDC[a] (2004)[36]	Canadian (2005)[37]	Hoyme (2005)[19]	IOM (1996)[1]
Growth	Normal to deficient (Growth Ranks 1-4)	--	No growth deficiency (Growth Rank 1)	No growth deficiency (Growth Rank 1)	No growth deficiency (Growth Rank 1)
Face	No more than 1 of the following: • PFL ≤ 3rd percentile • Philtrum Rank 4 or 5 • Lip Rank 4 or 5 (Face Ranks 1-2)	--	No FAS facial phenotype (Face Rank 1)	No FAS facial phenotype (Face Rank 1)	Presumably no components of the pattern of FAS characteristic facial anomalies. (Face Rank 1)
CNS	Criteria for "Static Encephalopathy" At least 1 of the following: • Structural/Neurological: (e.g., OFC ≤ 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domains[b] of function with impairment 2 or more SDs below the mean) (CNS Rank 3 and/or 4) Criteria for "Neurobehavioral Disorder"[c] • No Structural/Neurological abnormalities. • Moderate Dysfunction: (1-2 domains[b] of function with impairment ≥ 1.5 SDs below the mean) (CNS Rank 2)	--	At least 3 of the following Structure/Neurological/ Functional domains with significant impairment[c]: • Hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication (CNS Ranks 3-4)	At least 1 of the following: • Structural ○ OFC ≤ 10th percentile ○ Abnormal structure • Dysfunction ○ Complex pattern[d] of behavior / cognitive abnormalities (CNS Ranks 1-4)	At least 1 of the following: • Structural/Neurological: ○ Decreased cranial size at birth ○ Abnormal structure ○ Hard/soft signs • Dysfunction ○ Complex pattern[e] of behavior / cognitive abnormalities (CNS Ranks 2-4)
Additional Criteria	The term ARND is not used. The following terms are used in lieu of ARND: Static Encephalopathy (Severe dysfunction) Neurobehavioral Disorder (Moderate dysfunction)	--	--	--	--
Alcohol	Confirmed (Alcohol Ranks 3 or 4)	--	Confirmed (Alcohol Ranks 3 or 4)	Confirmed-excessive (Alcohol Rank 4)	Confirmed-excessive (Alcohol Rank 4)

a. The CDC Guidelines only address FAS.

b. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level. MRI research confirms Neurobehavioral Disorder/Alcohol Exposed is a distinct, clinically meaningful subclassification under the umbrella of FASD [9]

c. Canadian: Impairment indicates scores ≥ 2 SDs below the mean, discrepancies of 1.5-2 SDs among subtests, or ≥ 1 SD discrepancy between subdomains.

d. Hoyme: Marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction)

e. IOM: Complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone: e.g., learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention or judgment.

The equivalent 4-Digit Ranks for Growth, Face, CNS and Alcohol are inserted in red font to facilitate comparison across the guidelines.

Each guideline is introduced below. Since the circumstances that surrounded the development of each guideline influenced its outcome, it seemed most appropriate to let each guideline introduce itself (the published abstract or executive summary of each is presented below, with permission).

Table 4. ARBD diagnostic criteria. Comparison across the five most current FAS/D diagnostic guidelines.

	4-Digit Code[a] (1997-2004) [38]	CDC[b] (2004) [36]	Canadian[a] (2005) [37]	Hoyme (2005) [19]	IOM (1996) [1]
Growth	--	--	--	Not specified (Growth Rank ?)	Not specified (Growth Rank ?)
Face	--	--	--	2 or more of the following: • PFL ≤ 10th percentile • Philtrum Rank 4 or 5 • Lip Rank 4 or 5 (Face Ranks 2-4)	Not specified (Face Rank ?)
CNS	--	--	--	Not specified (CNS Rank ?)	Not specified (CNS Rank ?)
Congenital Defects	--	--	--	1 or more of the following: • Cardiac: Atrial septal defects, Ventricular septal defects, Aberrant great vessels, Tetralogy of Fallot. • Skeletal: Hypoplastic nails, Shortened fifth digits, Radioulnar synostosis, Flexion contractures, Camptodactyly, Clinodactyly, Pectus excavatum and carinatum, Klippel-Feil syndrome, Hemivertebrae, Scoliosis. • Renal: Aplastic/dysplastic/hypoplastic kidneys, Horseshoe kidneys, Ureteral duplications, Hydronephrosis. • Ocular: Strabismus, Retinal vascular anomalies, Refractive problems secondary to small globes. • Auditory: Conductive hearing loss, Neurosensory hearing loss. • Other: Virtually every malformation has been described in some patient with FAS. The etiologic specificity of most of these anomalies to alcohol teratogenesis remains uncertain.	Congenital structural defects in 1 of the following categories, including malformations and dysplasias (if the patient displays minor anomalies only, 2 must be present): • Cardiac: Atrial septal defects, Ventricular septal defects, Aberrant great vessels, conotruncal heart defects. • Skeletal: Radioulnar synostosis, Vertebral segmentation defects, Large joint contractures, Scoliosis. • Renal: Aplastic/dysplastic/hypoplastic kidneys, "Horseshoe" kidney/ureteral duplications. • Eyes: Strabismus, Ptosis, Retinal vascular anomalies, Optic nerve hypoplasia. • Ears: Conductive hearing loss, Neurosensory hearing loss. • Minor Anomalies: Hypoplastic nails, Short fifth digits, Clinodactyly of fifth fingers, Pectus carinatum / excavatum, Camptodactyly, "Hockey stick" palmar creases, Refractive errors, "Railroad track" ears.
Alcohol	--	--	--	Confirmed-excessive (Alcohol Rank 4)	Confirmed-excessive (Alcohol Rank 4)

a. The 4-Digit Code and Canadian Guidelines do not recognize ARBD as a FASD diagnostic classification.

b. The CDC Guidelines only address FAS.

The equivalent 4-Digit Ranks for Growth, Face, CNS and Alcohol are inserted in red font to facilitate comparison across the guidelines.

To facilitate comparisons across the five guidelines, the FAS criteria used by the 4-Digit Code [38], CDC [36], Canadian [37], Hoyme [19], and IOM [1] guidelines are presented in Table 1. The same format is used to present the criteria for PFAS, ARND, and ARBD (Tables 2-4 respectively).

It is important to note that for the purposes of this chapter, the 4-Digit Code has been translated, as best as possible, into a text, rather than numeric, format across Tables 1-4. This was done to facilitate comparison to the other guidelines that publish their diagnostic criteria in text format. Diagnostic teams should not use the textual translations of the 4-Digit Code presented in Tables 1-4 to derive a 4-Digit Code. Diagnostic teams should use the numeric format presented in the 2004 Diagnostic Guide [38].

FASD 4-Digit Code (1997, 1999, Nov 2004) [34,35,38]

Rationale for the FASD 4-Digit Code

One year after the release of the 1996 IOM guidelines [1], the FASD 4-Digit Diagnostic Code was created [14,34,35,38] to address the following limitations in the extant gestalt approach to FASD diagnosis.

1. *There have been no standardized operational definitions for FAS or for any of the other diagnoses that fall under the umbrella of FASD. Rather, there have been diagnostic guidelines that physicians have been encouraged to follow, but the guidelines have not been sufficiently specific to assure diagnostic accuracy or precision.*

For example, according to the diagnostic guidelines published by Sokol and Clarren [5], which were a minor modification of the 1980 definition of FAS by the Fetal Alcohol Study Group of the Research Society for Alcoholism [3], which, in turn, were derived from the work of Clarren and Smith [4]: "The diagnosis of FAS can only be made when the patient has signs of abnormality in each of the three categories: 1) Prenatal and/or postnatal growth retardation [weight and/or length below the 10th percentile when corrected for gestational age], 2) central nervous system involvement (including neurological abnormality, developmental delay, behavioral dysfunction or deficit, intellectual impairment, and/or structural abnormalities, such as microcephaly [head circumference below the 3rd percentile or brain malformations found on imaging studies or autopsy] and 3) a characteristic face, currently qualitatively described as including short palpebral fissures, an elongated midface, a long and flattened philtrum, thin upper lip, and flattened maxilla."

The 1996 guidelines for the diagnosis of FAS proposed by the IOM [1] took a similar approach. The diagnosis of FAS can be made when the patient presents with: "1) Evidence of growth retardation, as in at least one of the following: a) low birth weight for gestational age; b) decelerating weight over time not due to nutrition; or c) disproportional low weight to height; 2) Evidence of a characteristic pattern of facial anomalies that includes features such as short palpebral fissures and abnormalities in the premaxillary zone (e.g., flat upper lip, flattened philtrum, and flat midface); and 3) Evidence of CNS neurodevelopmental abnormalities, as in at least one of the following: a) decreased cranial size at birth; b) structural brain abnormalities (e.g., microcephaly, partial or complete agenesis of the corpus callosum, cerebellar hypoplasia);c) neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination."

Although these descriptions do provide guidance, they are not sufficiently specific to assure diagnostic accuracy and precision. They reflect a gestalt approach to diagnosis. The guidelines for CNS abnormalities do not address how many areas of deficit must be present, how severe the deficits must be, or what level of documentation must exist to substantiate the presence of the deficit. The guidelines for the facial phenotype are equally nonspecific. How many facial features must be present, how severe must the features be, and what scale of measurement should be used to judge the severity? One need only read the clinical literature or review medical records, birth certificates, birth defect registries or ICD-9 codes to see how variably these criteria are interpreted, applied and reported [1,40-43].

2. *There has been a lack of objective, quantitative scales to measure and report the magnitude of expression of key diagnostic features*

For example, although a thin upper lip and smooth philtrum are key diagnostic features [1,2,4,39,44], quantitative measurement scales were never used to measure thinness or smoothness, and guidelines had never been established for how thin or smooth the features must be. Objective quantitative scales not only improve accuracy and precision, but also establish a common numeric language for communicating outcomes in medical records and in the medical literature.

3. *The term fetal alcohol effects (FAE) was broadly used and poorly defined.*

The term 'suspected fetal alcohol effects' was first introduced into the medical literature in 1978 and was defined as 'less complete partial expressions' of FAS in individuals with prenatal alcohol exposure [4]. Based on this definition, an individual whose mother drank a few glasses of wine intermittently throughout pregnancy and presented with attention deficit hyperactivity disorder would meet the criteria for FAE. So would an individual whose mother drank a fifth of vodka daily throughout pregnancy and presented with microcephaly, severe mental retardation, growth deficiency and no facial anomalies. The broad use of this term and the reluctance to abandon it points to the clear need to develop diagnostic terms for individuals with prenatal alcohol exposure who present with physical anomalies and/or cognitive/behavioral disabilities, but do not meet the criteria for FAS. New diagnostic terms that more finely differentiate the variable exposures and outcomes of individual patients, without implying alcohol as the sole causal agent, were needed.

4. *Clinical terms like FAE [4,5], alcohol-related birth defects (ARBD) [1] and alcohol-related neurodevelopmental disorder (ARND) [1] imply a causal link between alcohol exposure and outcome*

in a given individual that cannot be medically confirmed. Leading dysmorphologists in the field of FAS diagnosis have formally requested that the term FAE no longer be used for this reason[13].

With the likely exception of the full facial phenotype, no other physical anomalies or cognitive/behavioral disabilities observed in an individual with prenatal alcohol exposure are necessarily specific to (caused only by) their prenatal alcohol exposure [1]. Features such as microcephaly, neurological abnormalities, attention deficit, mental retardation, and growth deficiency frequently occur in individuals with prenatal alcohol exposure, and frequently occur in individuals with no prenatal alcohol exposure. The diagnostic terms ARBD and ARND introduce the same limitation as does FAE, namely, implying alcohol exposure caused the birth defect or neurobehavioral disorder in an individual patient.

5. *Too often diagnoses depicting FASD are reported in the medical records and scientific literature with no documentation of the method used to derive the diagnosis and little or no documentation of the data used to render/support the diagnosis.*

Failure to report this information can limit the patient's ability to qualify for and receive appropriate intervention services from subsequent health care, social service, and educational providers. For example, simply reporting that an individual has FAS does little to convey the individual's strengths and disabilities. Some individuals with FAS have low IQs, some have IQs in the normal range, some have attention deficits, some do not, some have problems with memory, while others have language deficits. From a public health perspective, failure to report these data also prevents surveillance efforts from accurately tracking the prevalence of FASD diagnoses in the population. The supportive data are needed to validate the diagnoses. Accurate surveillance is vital for setting public health policy and assessing the effectiveness of primary prevention efforts. The 4-Digit Code requires that data be collected not just to support the diagnosis, but to derive the diagnosis. The 4-Digit Code provides a comprehensive FASD Diagnostic Form for recording all supportive data and provides a numeric classification scheme that is readily incorporated into clinical, research, and surveillance databases.

6. *FAS is a medical diagnosis and thus has historically been diagnosed by a medical doctor (e.g., dysmorphologist, geneticist). There is now clear consensus that an interdisciplinary team approach is superior [32,35-37].*

Each of the above limitations was largely overcome with the development of the FASD 4-Digit Diagnostic Code in 1997[35]. Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: (1) growth deficiency, (2) FAS facial phenotype, (3) CNS structural/functional abnormalities, and (4) prenatal alcohol exposure (Figs. 2 and 3). The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined. For example if a patient received the following Ranks: Growth = 3, Face = 4, CNS = 4, Alcohol = 4; the resulting 4-Digit Code would be 3444. Code 3444 is one of twelve 4-Digit Codes that meet the criteria for FAS/Alcohol Exposed (Fig. 2). An interactive, electronic FASD 4-Digit Code Short Form [45] is provided (Fig. 4) to demonstrate the simple, numeric approach used by the 4-Digit Code to define and derive a diagnosis. There are 256 possible 4-digit diagnostic codes, ranging from 1111 (reflecting complete absence of growth deficiency, FAS facial features, CNS abnormalities, and alcohol exposure) to 4444 (reflecting the most severe presentation of FAS: severe growth deficiency, the full FAS facial phenotype, significant CNS abnormalities, and high exposure to alcohol). Each 4-Digit diagnostic code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall broadly under the umbrella of FASD (A. FAS/Alcohol Exposed B. FAS/Alcohol Exposure Unknown, C. Partial FAS/Alcohol Exposed, E-F. Static Encephalopathy/Alcohol Exposed, and G-H. Neurobehavioral Disorder/Alcohol Exposed) (Fig. 2).

The FASD 4-Digit Diagnostic Code was developed from the clinical records of 1,014 patients of all races and ages evaluated by the FAS DPN interdisciplinary team at the University of Washington. The purpose was not to redefine, but rather, more specifically case-define the key diagnostic components of FAS as presented across several previously published FAS diagnostic guidelines [1,3-5]. The performance of the 4-Digit Code was validated prior to

FASD 4-Digit Diagnostic Code

		3	4	4		4
RANK	4	Severe	Severe	Definite		High risk
	3	Moderate	Moderate	Probable		Some Risk
	2	Mild	Mild	Possible		Unknown
	1	None	None	Unlikely		No Risk
		Growth Deficiency	**FAS Facial Features**	**CNS Damage**		**Prenatal Alcohol**

Digit Diagnostic Codes within each FASD Diagnostic Category

A. FAS / Alcohol Exposed

2433 3433 4433
2434 3434 4434
2443 3443 4443
2444 3444 4444

B. FAS / Alcohol Exposure Unknown

2432 3432 4432
2442 3442 4442

C. Partial FAS /Alcohol Exposed

1333 1433 2333 3333 4333
1334 1434 2334 3334 4334
1343 1443 2343 3343 4343
1344 1444 2344 3344 4344

E. Sentinel Physical Finding(s) / Static Encephalopathy / Alcohol Exposed

3133 3233 4133 4233
3134 3234 4134 4234
3143 3243 4143 4243
3144 3244 4144 4244

F. Static Encephalopathy / Alcohol Exposed

1133 1233 2133 2233
1134 1234 2134 2234
1143 1243 2143 2243
1144 1244 2144 2244

G. Sentinel Physical Finding(s) / Neurobehavioral Disorder / Alcohol Exposed

1323 2323 3123 3323 4123 4323
1324 2324 3124 3324 4124 4324
1423 2423 3223 3423 4223 4423
1424 2424 3224 3424 4224 4424

H. Neurobehavioral Disorder / Alcohol Exposed

1123 1223 2123 2223
1124 1224 2124 2224

I. Sentinel Physical Finding(s) / Alcohol Exposed

1313 2313 3113 3313 4113 4313
1314 2314 3114 3314 4114 4314
1413 2413 3213 3413 4213 4413
1414 2414 3214 3414 4214 4414

J. No Physical Findings or CNS Abnormalities Detected / Alcohol Exposed

1113 1213 2113 2213
1114 1214 2114 2214

Figure 2: The 4-Digit Code is derived by ranking the severity of growth deficiency, FAS facial features, CNS abnormality, and alcohol exposure on 4-point Likert scales. Each rank is specifically case-defined [38]. The 4-Digit Code 3444 is one of twelve 4-Digit Codes that meet the diagnostic criteria for FAS / Alcohol Exposed.

its release [14]. Its performance was compared to the standard gestalt method of diagnosis on the first 454 patients who had received a gestalt diagnosis of FAS, PFAS or possible fetal alcohol effect (PFAE) prior to the development of the 4-Digit Code.

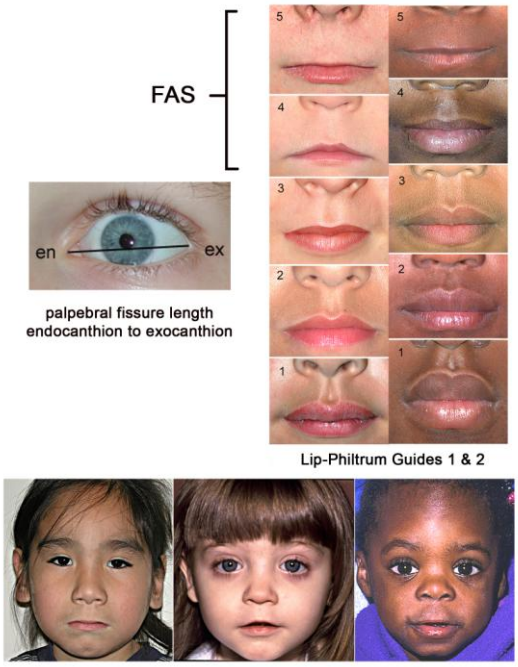
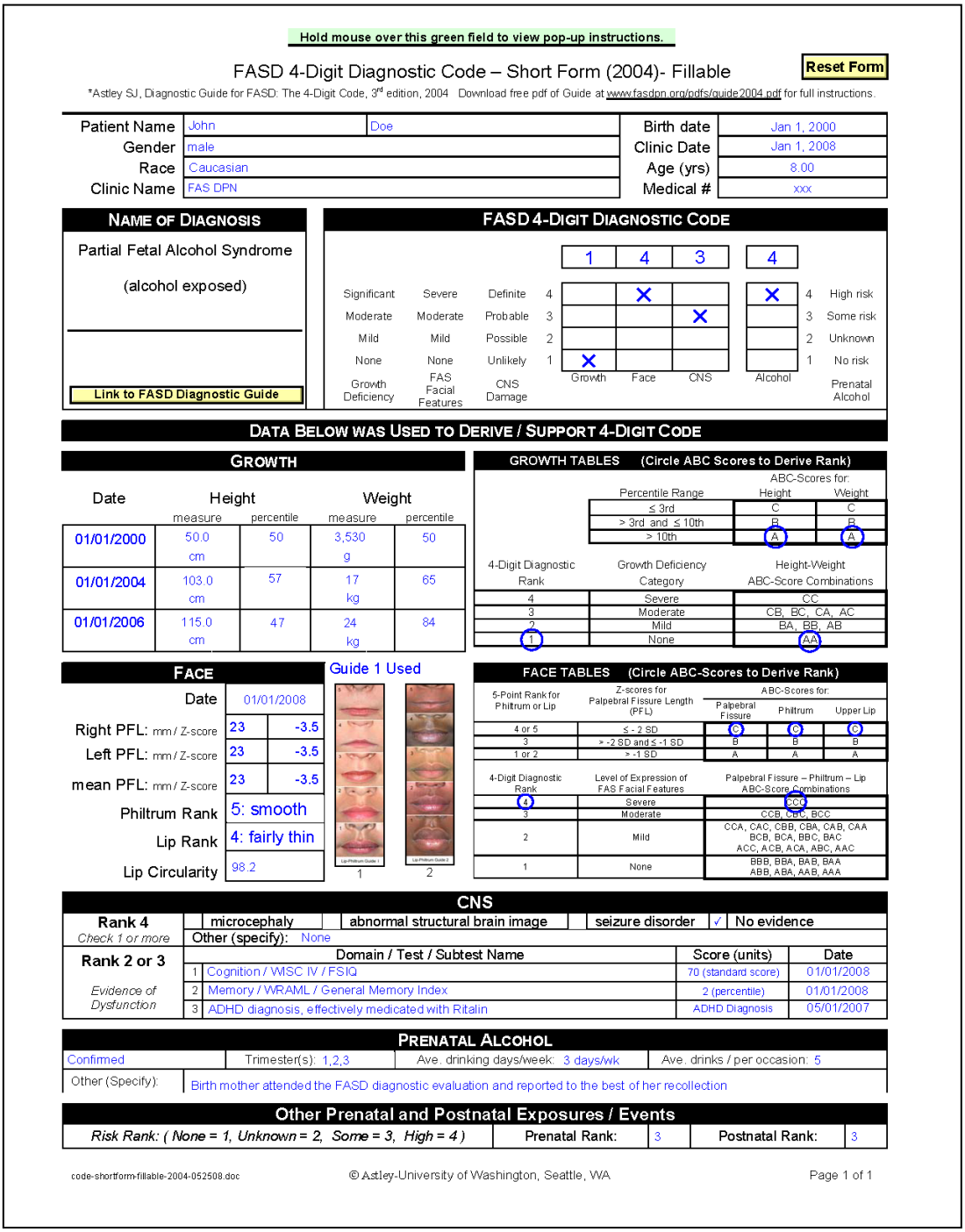


Figure 3: FASD 4-Digit Code FAS facial phenotype. The Rank 4 FAS facial phenotype determined with the 4-Digit Diagnostic Code requires the presence of all 3 of the following anomalies: (1) palpebral fissure length 2 or more standard deviations below the norm; (2) smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide), and (3) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide). Examples of the Rank 4 FAS facial phenotype for Native American, Caucasian, and African American children are shown. Copyright: Susan Astley, University of Washington, Seattle, WA.

The FASD 4-Digit Diagnostic Code:

1. Greatly increased diagnostic precision and accuracy through the development of objective, quantitative measurement scales (e.g., Lip-Philtrum Guides), facial analysis software, and specific case definitions.
2. Diagnosed the full spectrum of outcomes across the lifespan.
3. Offered an intuitively logical numeric approach to reporting outcomes and exposure that reflects the true diversity and continuum of disability observed in individuals with prenatal alcohol exposure.
4. Established a method for case-defining the highly variable, nonspecific CNS dysfunction that typifies FASD, by quantifying the breadth and magnitude of dysfunction (number of domains of function 2 or more SDs below the mean) without unduly constraining which domains must be impaired.
5. Established diagnostic subclassifications that captured the full spectrum of FASD without inferring alcohol is the sole causal agent.
6. Documents all other prenatal and postnatal adverse exposures and events that can also impact outcome.
7. Provides a quantitative measurement and reporting system (the 4-Digit Code) that can be used independent of the diagnostic nomenclature.
8. Has received extensive assessment/validation of its performance.
9. Was designed for use by an interdisciplinary FASD diagnostic team.
10. Is readily taught to a wide array of health care and social service providers (e.g., FASD 4-Digit Code Online Course[46]), thus greatly expanding the availability of diagnostic services.



Hold mouse over this green field to view pop-up instructions.

FASD 4-Digit Diagnostic Code – Short Form (2004)- Fillable

Reset Form

*Astley SJ, Diagnostic Guide for FASD: The 4-Digit Code, 3rd edition, 2004 Download free pdf of Guide at www.fasdpn.org/pdfs/guide2004.pdf for full instructions.

Patient Name	John Doe	Birth date	Jan 1, 2000
Gender	male	Clinic Date	Jan 1, 2008
Race	Caucasian	Age (yrs)	8.00
Clinic Name	FAS DPN	Medical #	xxx

NAME OF DIAGNOSIS

Partial Fetal Alcohol Syndrome

(alcohol exposed)

Link to FASD Diagnostic Guide

FASD 4-DIGIT DIAGNOSTIC CODE

1 4 3 4

	Growth	Face	CNS	Alcohol	
Significant / Severe / Definite		X		X	4 High risk
Moderate / Moderate / Probable			X		3 Some risk
Mild / Mild / Possible					2 Unknown
None / None / Unlikely	X				1 No risk
Growth Deficiency		FAS Facial Features	CNS Damage		Prenatal Alcohol

DATA BELOW WAS USED TO DERIVE / SUPPORT 4-DIGIT CODE

GROWTH

Date	Height measure	Height percentile	Weight measure	Weight percentile
01/01/2000	50.0 cm	50	3,530 g	50
01/01/2004	103.0 cm	57	17 kg	65
01/01/2006	115.0 cm	47	24 kg	84

GROWTH TABLES (Circle ABC Scores to Derive Rank)

Percentile Range	ABC-Scores for: Height	Weight
≤ 3rd	C	C
> 3rd and ≤ 10th	B	B
> 10th	(A)	(A)

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
(1)	None	(AA)

FACE

Guide 1 Used

Date	01/01/2008	
Right PFL: mm / Z-score	23	-3.5
Left PFL: mm / Z-score	23	-3.5
mean PFL: mm / Z-score	23	-3.5
Philtrum Rank	5: smooth	
Lip Rank	4: fairly thin	
Lip Circularity	98.2	

1 2

FACE TABLES (Circle ABC-Scores to Derive Rank)

5-Point Rank for Philtrum or Lip	Z-scores for Palpebral Fissure Length (PFL)	ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	(C)	(C)	(C)
3	> -2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure – Philtrum – Lip ABC-Score Combinations
(4)	Severe	(CCC)
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

CNS

Rank 4 *Check 1 or more*		microcephaly	abnormal structural brain image	seizure disorder	✓ No evidence
	Other (specify): None				

Rank 2 or 3 *Evidence of Dysfunction*

	Domain / Test / Subtest Name	Score (units)	Date
1	Cognition / WISC IV / FSIQ	70 (standard score)	01/01/2008
2	Memory / WRAML / General Memory Index	2 (percentile)	01/01/2008
3	ADHD diagnosis, effectively medicated with Ritalin	ADHD Diagnosis	05/01/2007

PRENATAL ALCOHOL

Confirmed	Trimester(s): 1,2,3	Ave. drinking days/week: 3 days/wk	Ave. drinks / per occasion: 5
Other (Specify):	Birth mother attended the FASD diagnostic evaluation and reported to the best of her recollection		

Other Prenatal and Postnatal Exposures / Events

Risk Rank: (None = 1, Unknown = 2, Some = 3, High = 4)	Prenatal Rank:	3	Postnatal Rank:	3

code-shortform-fillable-2004-052508.doc © Astley-University of Washington, Seattle, WA Page 1 of 1

Figure 4: FASD 4-Digit Diagnostic Code Short Form. In lieu of the more comprehensive 7-page FASD Diagnostic Form, some clinics may prefer to use the **1-page FASD 4-Digit Short Form**. The Short Form allows a clinician to record the minimum amount of data required to derive/support the 4-Digit Code. Diagnostic teams who do not have the time/capacity to complete the more comprehensive form will find this electronic, interactive, Short Form helpful.

The 4-Digit Code has served as the cornerstone of a fully integrated and highly successful screening, diagnostic, intervention, prevention, and surveillance program in Washington State for the past 17 years [7,8,18,1,47-49]. A comprehensive profile of all patients receiving an interdisciplinary FASD diagnostic evaluation using the 4-Digit Code at the Washington State FAS Diagnostic and Prevention network (WA FAS DPN) clinic in the first 12 years of operation is presented in the Astley paper [50]. Hundreds of FASD diagnostic teams have been trained worldwide to use this interdisciplinary FASD diagnostic system [46].

CDC FAS Guidelines, July 2004 [36]

In 2004 the CDC published the following Executive Summary to introduce the CDC FAS guidelines (p. vii-ix, with permission) [36]:

"As part of the fiscal year 2002 appropriations funding legislation, the U.S. Congress mandated that the Centers for Disease Control and Prevention (CDC), acting through the National Center on Birth Defects and Developmental Disabilities (NCBDDD) Fetal Alcohol Syndrome (FAS) Prevention Team and in coordination with the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect (NTFFAS/FAE), other federally funded FAS programs, and appropriate nongovernmental organizations, would:

Develop guidelines for the diagnosis of FAS and other negative birth outcomes resulting from prenatal exposure to alcohol,

Incorporate these guidelines into curricula for medical and allied health students and practitioners, and seek to have them fully recognized by professional organizations and accrediting boards, and

Disseminate curricula to and provide training for medical and allied health students and practitioners regarding these guidelines.

Through the coordinated efforts of CDC, the NTFFAS/FAE, and a scientific working group (SWG) of experts in FAS research, diagnosis, and treatment, the diagnostic criteria were developed over a 2-year period.

A primary goal of these guidelines is to provide standard diagnostic criteria for FAS so that consistency in the diagnosis can be established for clinicians, scientists, and service providers. The guidelines are based on state-of-the-art scientific research, clinical expertise, and family input regarding the physical and neuropsychological features of FAS. The SWG sought to harmonize these guidelines with other diagnostic systems currently in use in this country and others (e.g., Canada). The SWG strove to provide a balance between conservative and overly inclusive diagnostic systems. Differential diagnosis from other genetic, teratological, and behavioral disorders was emphasized.

These guidelines are not intended to be an endpoint in the discussion of diagnosing FAS. There is a great need to acquire science-based information that will facilitate diagnostic criteria for additional related disorders, such as Alcohol Related Neurodevelopmental Disorder (ARND). These guidelines conclude with a call for further research and continuous refinement of the diagnostic criteria for FAS and related conditions so that affected individuals and their families can receive important services that enable them to achieve healthy lives and reach their full potential."

Hoyme FASD Guidelines, January 2005 [19]

In 2005, Hoyme et al [19] published the following abstract (p. 39, with permission) to introduce their FASD guidelines:

"The adverse effects of alcohol on the developing human represent a spectrum of structural anomalies and behavioral and neurocognitive disabilities, most accurately termed fetal alcohol spectrum disorders (FASD). The first descriptions in the modern medical literature of a distinctly recognizable pattern of malformations associated with maternal alcohol abuse were reported in 1968 and 1973. Since that time, substantial progress has been made in developing specific criteria for defining and diagnosing this condition. Two sets of diagnostic criteria are now used most widely for evaluation of children with potential diagnoses in the FASD continuum, ie, the 1996 IOM [1] criteria and the Washington criteria. Although both approaches have improved the clinical delineation of FASD, both suffer from significant drawbacks in their practical application in pediatric practice. Objective. The purpose of this report is to present specific clarifications of the 1996 IOM criteria [1] for the diagnosis of FASD, to facilitate their practical application in clinical pediatric practice. A large cohort of children who were prenatally exposed to alcohol were identified, through active case-ascertainment methods, in 6 Native American communities in the United States and 1 community in the Western Cape Province of South Africa. The children and their families underwent standardized multidisciplinary evaluations, including a dysmorphology examination, developmental and neuropsychologic testing,

and a structured maternal interview, which gathered data about prenatal drinking practices and other demographic and family information. Data for these subjects were analyzed, and revisions and clarifications of the existing IOM FASD diagnostic categories were formulated on the basis of the results. The revised IOM method defined accurately and completely the spectrum of disabilities among the children in our study. On the basis of this experience, we propose specific diagnostic criteria for fetal alcohol syndrome and partial fetal alcohol syndrome. We also define alcohol-related birth defects and alcohol-related neurodevelopmental disorder from a practical standpoint. The 1996 IOM criteria [1] remain the most appropriate diagnostic approach for children prenatally exposed to alcohol. The proposed revisions presented here make these criteria applicable in clinical pediatric practice. "

Canadian FASD Guidelines, March 2005 [37]

In 2005 Chudley et al [37] published the following abstract (p. s1) to introduce the Canadian FASD guidelines:

"A subcommittee of the Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder reviewed, analyzed and integrated current approaches to diagnosis to reach agreement on a standard in Canada. The purpose of this paper is to review and clarify the use of current diagnostic systems and make recommendations on their application for diagnosis of FASD-related disabilities in people of all ages. The guidelines are based on widespread consultation of expert practitioners and partners in the field. The guidelines have been organized into 7 categories: screening and referral; the physical examination and differential diagnosis; the neurobehavioural assessment; and treatment and follow-up; maternal alcohol history in pregnancy; diagnostic criteria for fetal alcohol syndrome (FAS), partial FAS and alcohol-related neurodevelopmental disorder; and harmonization of Institute of Medicine and 4-Digit Diagnostic Code approaches. The diagnosis requires a comprehensive history and physical and neurobehavioural assessments; a multidisciplinary approach is necessary. These are the first Canadian guidelines for the diagnosis of FAS and its related disabilities, developed by broad-based consultation among experts in diagnosis."

Comparison of Current Guidelines

An interdisciplinary approach to FASD diagnosis using more rigorously case-defined guidelines, as originally proposed by the WA FAS DPN [14,32,35] was adopted in principal in all subsequent guidelines. Key contrasts do exist, however (Tables 1-4). Of the guidelines currently in use, the FASD 4-Digit Code[38] and Canadian FASD guidelines [37] are most similar. Both systems cover the full spectrum of diagnostic outcomes, use FAS facial criteria with confirmed high specificity to prenatal alcohol exposure, and adhere to strict criteria that use the standard medical/statistical definition of "abnormal" (2 or more SDs below the mean or its equivalent $\leq 2.5^{th}$ percentile) [51]. In contrast to the 4-Digit Code and Canadian guidelines, the CDC guidelines [36] address only FAS; have more relaxed facial criteria (with unknown specificity); and have more relaxed CNS criteria (using diagnostic cutoff values for "abnormal" of 1 SD below the mean or $\leq 10^{th}$ percentile). The Hoyme guidelines [19], while addressing the full spectrum of outcomes, diverge considerably from the 4-Digit Code, CDC, and Canadian guidelines, but are closely aligned with the IOM guidelines [1] from which they were derived. For the diagnosis of FAS, the Hoyme guidelines further relax the facial criteria requiring only 2 of the 3 diagnostic features be present while allowing the palpebral fissure length (PFL) to move further into the normal range ($\leq 10^{th}$ percentile). This results in facial criteria that are no longer specific to prenatal alcohol exposure [16]. The Hoyme guidelines for FAS also restrict the CNS criteria to structural abnormalities only; and relax the criterion for small head circumference from the medical definition of microcephaly ($\leq 2.5^{th}$ percentile) [52] to $\leq 10^{th}$ percentile. All 4 sets of guidelines require prenatal alcohol exposure to be documented, but allow a diagnosis of FAS to be rendered if prenatal alcohol exposure is unknown. The Hoyme guidelines, like the IOM guidelines, go further by requiring that the confirmed exposure be "excessive" (e.g., characterized by substantial regular intake or heavy episodic drinking). Features unique to each guideline are: 1) The 4-Digit Code does not use the term ARND and is the only guideline that measures all four features of FAS (growth, face, CNS, and alcohol exposure) on continuous scales; 2) The Canadian guidelines require severe CNS dysfunction be present for a diagnosis of FAS; and 3) The Hoyme guidelines use only physical features to define FAS.

Diagnostic Nomenclature

A number of terms have been established over the years to label the diagnostic subclassifications under the umbrella of FASD. These include FAS, PFAS ARND, Static Encephalopathy/Alcohol Exposed (SE/AE),

Neurodevelopmental Disorder/Alcohol Exposed (ND/AE), Alcohol Related Birth Defects (ARBD), and Fetal Alcohol Effects (FAE). Table 5 presents each term, the clinical features that delineate each term, and which guidelines use the terms.

Table 5: FASD diagnostic terms, the clinical features that define each term, and which FAS/D guidelines use each term.

FASD Diagnostic Terms	Clinical Features Present					Guidelines That Use the Term				
	Growth Deficiency	FAS Facial Phenotype	CNS Abnormality	Prenatal Alcohol Exposure	Other Congenital Defects	4-Digit[38]	CDC[a][36]	Canadian[37]	Hoyme[19]	IOM[1]
FAS	Yes	Yes	Yes	Yes or Unknown		■	■	■	■	■
PFAS	Yes or No	Yes (Full or Partial)	Yes or No[b]	Yes or Unknown[c]		■	-	■	■	■
ARND			Yes	Yes			-	■	■	■
SE/AE			Yes, Severe	Yes		■	-			
ND/AE			Yes, Moderate	Yes		■	-			
ARBD		Yes and No[d]		Yes	Yes		-		■	■
FAE[e]			Yes	Yes			-			

a. (-) CDC guidelines currently address only FAS.
b. The Hoyme and IOM guidelines allow PFAS to be diagnosed in the absence of CNS abnormality.
c. Only the Hoyme guidelines allow an unknown alcohol exposure for PFAS.
d. The Hoyme guidelines require the FAS facial phenotype be present for ARBD. The IOM guidelines do not.
e. Used in the Sokol & Clarren FASD guidelines [5]

Issues to Consider

The following issues are important to consider as one assesses the strengths/limitations of the current FAS/D diagnostic guidelines.

Why are the criteria used to define the FAS facial phenotype so important to the medical validity of a FAS diagnosis? When one makes a diagnosis of FAS, one is stating implicitly that the individual has a syndrome caused by prenatal alcohol exposure[16]. One is also stating implicitly that the biological mother drank alcohol during pregnancy and, as a result, harmed her child. These are bold conclusions to draw and are not without medical and ethical consequences. How confident can one be when one infers a causal link between an individual's prenatal alcohol exposure and his or her syndromic features, especially when 2 of the 3 diagnostic features of this syndrome (growth deficiency and CNS damage/dysfunction) are not specific to (caused only by) prenatal alcohol exposure. The validity of the diagnosis rests solely on the specificity of the facial phenotype to the exposure (alcohol) and to the outcome (FAS). If a cluster of facial features is truly unique to prenatal alcohol exposure (e.g., alcohol is the only agent that can cause this facial phenotype) and is unique to the diagnosis of FAS (e.g., this exact phenotype is not present in any other medical condition), then one would expect to observe the following: (1) the face would be highly sensitive to FAS (e.g., individuals with FAS would have the FAS facial phenotype), (2) the face would be highly specific to FAS (e.g., individuals without FAS would not have the FAS facial phenotype), and (3) the face would be highly specific to prenatal alcohol exposure (e.g., individuals without prenatal alcohol exposure would not have the FAS facial phenotype). The rank 4 FAS facial phenotype, as defined by the 4-Digit Code, demonstrates all three of these qualities [7,9,16,20,39].

A highly specific FAS facial phenotype validates the FAS diagnosis, because the presence of the face confirms that an individual was affected, at least in part, by their prenatal alcohol exposure. The face also confirms the individual was exposed to alcohol. The latter is used to render a diagnosis of FAS in the absence of confirmed prenatal alcohol exposure. If the face is truly specific to alcohol, then individuals cannot have the face if they were not exposed to alcohol. This is why all diagnostic guidelines allow FAS to be diagnosed, even when prenatal alcohol exposure is

unknown. When the face is confirmed to be highly specific to alcohol exposure, it can serve as a valid proxy measure for exposure. This is also why diagnostic guidelines cannot and do not allow ARND (or its equivalent) to be diagnosed when alcohol exposure is unknown. Since the FAS facial phenotype is not present in ARND, it cannot serve as a proxy measure for alcohol exposure. In the absence of a highly specific facial phenotype, the validity of the diagnostic process breaks down precipitously; an individual's outcome cannot be linked to their prenatal alcohol exposure, FAS becomes indistinguishable from ARND, and valid diagnoses cannot be made when alcohol exposure is unknown.

Considering the quintessential role the FAS facial phenotype plays in FAS diagnosis, its specificity cannot be assumed, it must be confirmed through properly designed empirical studies. The FAS facial criteria (Rank 4) used by the 4-Digit Code and Canadian Guidelines have confirmed, high sensitivity and specificity (> 95%) [39]. The CDC and Hoyme guidelines have not reported the sensitivity and specificity of their relaxed facial criteria. When the Hoyme criteria were applied to a sample of normal to high functioning children with confirmed absence of prenatal alcohol exposure, 4 of the 16 met the Hoyme criteria for the full FAS facial phenotype [16]. This demonstrates the facial criteria have been relaxed too far.

Should an 'excessive' alcohol exposure be required for diagnoses under the umbrella of FASD? There remains no clear scientific consensus on what quantity, frequency, and duration of exposure is toxic to the fetus. There are a multitude of reasons for this. 1.) As our tools for measuring outcome become more sensitive, our ability to identify adverse outcomes at lower exposures increases [53]. 2.) Risk from alcohol exposure varies between fetuses, even between fraternal twins with ostensibly identical exposure [54, 55]. It is not uncommon for one fraternal twin to have full FAS, while the other appears unaffected. Identical twins are typically identically affected. 3.) From a public health perspective, requiring excessive exposure implies lower levels of exposure are 'safe'. Safe for whom? 4.) From a research perspective, artificially linking outcome to a threshold level of high exposure prevents assessing the true relationship between exposure and outcome. 5.) Finally, from a clinical perspective, if an "excessive" exposure is required, it would be difficult to rationalize why an individual with all the features of FAS would receive a diagnosis of FAS if their exposure was unknown, but would fail to receive a diagnosis of FAS if their exposure was confirmed, but reportedly not excessive. This implies that practitioners have the ability to confirm the accuracy of exposure histories. They do not. "Excessive" alcohol exposures should not be required for FASD diagnoses.

FAE and ARND: The field continues to struggle with what to label the condition characterized by prenatal alcohol exposure and CNS abnormalities when the FAS facial phenotype is absent. The problem with the diagnostic terms used to date (Fetal Alcohol Effects (FAE) and Alcohol-Related Neurodevelopmental Disorder (ARND) is they imply that the patient's outcomes are *alcohol effects* or *alcohol-related* outcomes. They imply alcohol caused the patient's outcomes. But this presumption in an *individual* patient is medically invalid because CNS abnormalities are not specific to (caused only by) prenatal alcohol exposure. There are many other known or unknown risk factors that may be partly or even fully responsible for the patient's outcome. In the absence of the FAS facial phenotype, current medical technology has no ability to confirm or rule-out the etiologic role of alcohol in an *individual* patient.

The term FAE (or more accurately, possible FAE) was first introduced by Clarren and Smith in 1978 [4]. In 1995, Aase, Jones, and Clarren argued effectively that clinical use of the term FAE, with its implications of causation, should be abandoned [13]. In 1996, the IOM [1] acknowledged the concerns expressed by Aase and colleagues [13] and introduced ARND (and ARBD) to replace FAE. But ARND (and ARBD) presented with all the same limitations as FAE. In 1997, the 4-Digit Code introduced Static Encephalopathy/Alcohol Exposed (SE/AE)) and Neurobehavioral Disorder/Alcohol Exposed (NDAE) to replace ARND [35]. These new clinical classifications divided ARND into two subgroups; 1) individuals with severe dysfunction (CNS Rank 3) and 2) individuals with moderate dysfunction (CNS Rank 2). A recent MRI study confirmed SE/AE and ND/AE are distinct clinical subclassifications with clear evidence of CNS structural abnormality detectable by MRI volumetric analyses [9]. Importantly, the terms neither confirm nor rule-out the causal role of alcohol. In 2005, the Hoyme [19] and Canadian [37] guidelines also acknowledged the concern expressed by Aase and colleagues [13], but chose to continue the use of the term ARND. The Hoyme guidelines expressed the following reservations about the SE/AE and ND/AE terms introduced by the 4-Digit Code. They raised a number of important issues that warrant discussion.

"The Washington criteria place much emphasis on the encephalopathy and neurobehavioral disorder present among affected children. These 2 findings are not specifically defined and, as general terms, they are not unique to the prenatal effects of alcohol on fetal development. In addition, the family and genetic background of the child is not adequately integrated into the criteria. Because this highly structured system seems all-encompassing, there is the potential for over-diagnosis of alcohol-related disabilities; any child with a disability who has been exposed to

alcohol prenatally can be assigned a diagnostic classification easily, even if the cause of the disability is genetic" (p. 41) [19].

To clarify, the 4-Digit Code cannot over-diagnose "alcohol-related" disabilities because the only "alcohol-related" diagnoses the 4-Digit Code generates are FAS and Partial FAS. The potential to over-diagnosis alcohol-related disabilities occurs with the use of the term Alcohol-Related Neurodevelopmental Disorder. The 4-Digit Code is the only FASD guideline that does not use this term. The 4-Digit Code does assign a diagnostic classification to all individuals who present with a disability. The classification reflects their disability; their *outcome* per se (e.g., FAS, PFAS, Static Encephalopathy, Neurobehavioral Disorder, etc). For example, if the individual presented with moderate impairment in memory and executive function, their disability would be classified as Neurodevelopmental Disorder. All children with or without a disability also have their prenatal alcohol exposure status reported. Their exposure is reported separate from their disability using the following naming convention: "disability/exposure" (eg., FAS / Alcohol Exposed, FAS / Alcohol Exposure Unknown, Neurobehavioral Disorder/ Confirmed Absence of Alcohol Exposure; No Sentinel Physical Findings or CNS Abnormalities Detected/Alcohol Exposed, etc). This naming convention neither implies nor rules-out a causal association between the outcome and the exposure in an individual patient. Hoyme and colleagues are correct in stating that static encephalopathy and neurobehavioral disorder are not unique to the prenatal effects of alcohol on fetal development. The same holds true for the neurodevelopmental disorder referenced in ARND. This is why it is so important that the nomenclature not assert the outcomes are unique (related to) the alcohol exposure. The use of a nomenclature that reports outcome separate from exposure is perhaps one of the most important features and strengths of the 4-Digit Code that distinguishes it from all other FASD diagnostic guidelines.

The 4-Digit Code was developed under the premise that a diagnosis should be based on verifiable facts, not supposition. The diagnostic nomenclature used by the 4-Digit Code reflects this. Growth deficiency and CNS damage/dysfunction are not specific to (caused only by) prenatal alcohol exposure. When an individual presents with prenatal alcohol exposure and CNS damage/ dysfunction, but does not have the FAS facial phenotype, the damage/dysfunction may be entirely attributable to the prenatal alcohol exposure, partially attributable to the prenatal alcohol exposure, or unrelated to the prenatal alcohol exposure. It is important to remember that even when a diagnosis of full FAS is rendered, one cannot necessarily attribute ALL of the individual's disabilities to their alcohol exposure. To the extent that other adverse risk factors are present, they too can, and likely will, contribute to the overall constellation of outcomes.

Current medical technology has no ability to confirm or rule-out the etiologic role of alcohol in an *individual* patient. This does not prevent one from effectively moving forward. An accurate diagnosis and effective intervention can proceed without confirming alcohol caused the person's disability. Access to services should be based on a person's disability, not on what caused their disability. Prevention can also proceed without linking outcome to exposure in an individual patient. In fact, on an empirical level, valid identification of causal associations requires exposures and outcomes to be documented separately.

When an individual presents with CNS damage/dysfunction and prenatal alcohol exposure, the 4-Digit Code calls it what it is; Static Encephalopathy/Alcohol Exposed if the CNS damage/dysfunction is severe or Neurobehavioral Disorder/Alcohol Exposed if the CSN dysfunction is moderate. The medical definition of static encephalopathy is *"any significant abnormal condition of the structure or function of brain tissue that is neither progressing nor regressing*" [56]. Including the phrase "Alcohol Exposed" in the diagnostic name serves to alert clinical providers that the individual was exposed to a teratogen and therefore is at risk for underlying brain damage. Knowledge of this risk is important, because the presence of underlying brain damage should influence a clinician's approach to ongoing care and intervention.

Aase and colleagues [13] urged "*simple recording of the verifiable conclusions. . . . If prenatal alcohol exposure has taken place, but FAS cannot be substantiated, the exposure still should be indicated, and any nonspecific abnormalities or problems noted*." (p. 49) This is the approach taken by the 4-Digit Code. The clinical summary templates for SE/AE and ND/AE include the following statement: "The diagnosis of Static Encephalopathy/Alcohol Exposed (or Neurobehavioral Disorder/Alcohol Exposed) does not mean that alcohol is the cause of the problem. A number of other factors could be contributing to the present issues, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth" [14, 38]. The 4-Digit Code also devotes a chapter and 4-Digit ranking system to documentation of other prenatal (including genetic) and postnatal exposures and events that frequently occur with prenatal alcohol exposure and likely contribute to the outcomes observed for individuals [38]. In fact, the vast majority of the 1,400 patients with prenatal alcohol exposure

diagnosed in the WA FAS DPN between 1993-2005 presented with multiple risk factors (93% were exposed to tobacco or illicit drugs in utero, 31% had no prenatal care, 36% had confirmed physical and/or sexual abuse, and 70% were in foster/ adoptive care) [50]. The impact of prenatal alcohol exposure is rarely if ever assessed in isolation from other risk factors.

The Hoyme guidelines [19] state, "FASD must always be a diagnosis of exclusion. Many genetic and malformation syndromes have some of the other clinical characteristics of FAS. If there is no indication of another genetic or malformation syndrome, then the revised IOM criteria can be applied to categorize a diagnosis within the FASD continuum" (quotes from pp. 45-46). Overlap between individual symptoms/anomalies is common throughout medicine. An astute clinician would not mistake FAS for William's syndrome simply because the two have some, but not all features in common. It is the constellation of features that distinguish the two syndromes. FAS is not a diagnosis of exclusion. Alcohol is a teratogen to all developing fetuses, including those with other genetic disorders or syndromes. It is worth noting that one child diagnosed with FAS in the WA FAS DPN also had Down syndrome. The child presented with growth deficiency below the 2nd percentile on a growth chart for children with Down syndrome. The child presented with the facial features of Down syndrome and FAS. The facial features of Down syndrome are distinct from the facial features of FAS. The two phenotypes were readily apparent and easily distinguished. The child presented with microcephaly (3 SDs below the mean for children with normal development, 1 SD below the mean for children with Down syndrome). The child presented with Bayley[57] Motor and Mental Index scores below 50; a level of developmental delay that can be observed in both Down syndrome and FAS. The birth mother was reported to have consumed alcohol daily throughout pregnancy. A FASD diagnostic team should consider alternative or co-occurring syndromic diagnoses and medical conditions at all times. The prevalence of other syndromes among 1,400 patients with prenatal alcohol exposure receiving a FASD diagnostic evaluation in a WA FAS DPN clinic is 1.8% [50]

Hoyme and colleagues [19] expressed concern that SE/AE and ND/AE are not specifically defined. The growth, face, CNS, and alcohol criteria are specifically defined for SE/AE and ND/AE (Table 3). The CNS functional criteria specify which functional domains may be impaired, how many must be impaired, and how severely (in SDs) each must be impaired. Most of the current guidelines (4-Digit Code [38], CDC [36], and Canadian [37] now provide this enhanced level of detail when defining the CNS functional criteria for their FAS, PFAS and ARND classifications.

ARBD: The term Alcohol-Related Birth Defects (ARBD) was introduced by the IOM [1] with the caveat that "*virtually every malformation has been described in some patient with FAS. The etiologic specificity of most of the anomalies to alcohol teratogenesis remains uncertain*". This statement remains true today. For this reason, the 4-Digit Code[38] and Canadian [37] Guidelines do not include ARBD as a diagnostic classification. The 4-Digit Code and Canadian guidelines require the reporting of all birth defects; they simply do not support labeling them as ARBD. The Hoyme [19] guidelines do include ARBD as a diagnostic classification, but require the FAS facial phenotype to be present. Inclusion of the FAS facial phenotype may help increase the chance that the birth defect may be related to the alcohol exposure, but only if the etiologic specificity of the guideline's FAS facial criteria is confirmed to be high.

Are Lip-Philtrum Guides Needed for each Race? All guidelines published subsequent to the 4-Digit Code have adopted the use of the University of Washington Lip-Philtrum Guides for measuring philtrum smoothness and upper lip thinness (Fig. 3). There are currently two Lip-Philtrum Guides; one normalized to Caucasians and one normalized to African Americans (Fig. 3). The Guides are purposely labeled Guide 1 and Guide 2, respectively, for they were created for use on more than just Caucasian and African American individuals. Guide 1 is intended for use on all races (or racial combinations) that indigenously have lips similar in thickness to Caucasians. Guide 2 is intended for use on all races (or racial combinations) that indigenously have lips similar in thickness to African Americans. The Guide that best matches the indigenous phenotype of the patient's race(s) should be used. It is essential that the patient's medical record document which Guide was used for their diagnostic evaluation.

While it may seem obligatory to create a Lip-Philtrum Guide for every race, there are two fundamental reasons why this is neither feasible nor clinically necessary. First, racial categories are more a social-political construct than scientific or anthropological classifications. Racial categories are not sufficiently case-defined to classify individuals accurately into discrete groups and a large portion of the population is multiracial. Finally, race rarely translates into one homogeneous phenotype. For example, there is tremendous phenotypic variability between American Indian tribes, thus creation of an "American Indian" Lip-Philtrum Guide would be clinically invalid. Second, the magnitude of difference that would differentiate lips of the same rank across more than two "racially-normed" guides would become imperceptibly small. The magnitude of difference would become clinically irrelevant and below the level of

accurate detection. To demonstrate this, look at how little difference there is between the Rank 5 lips on Guides 1 and 2 (Fig. 3). Now imagine the Rank 5 lip on a Lip-Philtrum Guide for a race that falls between Guides 1 and 2.

Can an accurate diagnosis be rendered at any age? The answer depends on the diagnosis and the guidelines. If a diagnostic classification requires standardized psychometric evidence of *higher level* dysfunction across multiple domains like language, memory, executive function, and/or cognition, then a patient must be old enough to engage in this higher level assessment (generally > 7 years old) to confirm or rule-out dysfunction. This is not to say a diagnostic evaluation should be postponed until after age 7. There is tremendous benefit to early diagnosis and intervention [17,48,58]. The 4-Digit Code explicitly states that a diagnosis rendered at an early age could change (upgrade to a more severe classification) as the child ages and higher level cognitive impairments emerge. As an example, if a 10 year old child presented with the following features (growth deficiency, the FAS facial phenotype, a normal head size, severe dysfunction in memory, executive function, and attention, and prenatal alcohol exposure), she would receive a diagnosis of FAS (4-Digit Code 4434). If she had received a diagnostic evaluation at 1 year of age, her severe functional impairments would not yet be apparent. They may only manifest as moderate developmental delays on a Bayley Scales of Infant Development [57], resulting in a 4-Digit Code of 4424 (sentinel physical findings, neurobehavioral disorder, alcohol exposed). Her true diagnosis would be FAS, but at 1 year of age, she would not be old enough to reveal the true magnitude of her CNS dysfunction. She benefits nonetheless from her early diagnosis in two ways: 1) she receives early intervention, and 2) her high risk status is documented in her medical record with recommendations to monitor her closely over time. If and when she presents with more severe CNS dysfunction, she would receive a FASD diagnostic re-evaluation to upgrade her diagnostic classification appropriately.

Can an accurate diagnosis be rendered in an adult? Yes. Adults often present with more complex life histories and competing risks (traumatic head injury, their own alcohol and drug abuse, and mental health problems). Confirmation of exposure can also be more challenging. But the same diagnostic criteria and interdisciplinary approach are utilized. The interdisciplinary team will need expertise in adult psychological assessment and knowledge of community services available to adults. While adults will not have benefited from early intervention, an accurate diagnosis will lead to a better understanding of their disability and improved access to disability assistance and services.

Before leaving this topic, one additional question regarding age and diagnosis is often asked: **Does the face of FAS change with age?** Literature from the 80's and 90's [59-61] would lead one to believe that infants and adults are less likely to present with the full FAS facial phenotype than school-aged children. But the data were largely anecdotal and focused on facial features that are no longer regarded as diagnostic of the FAS facial phenotype [20]. Data from 1,400 patients evaluated for FASD in the WA FAS DPN document just the opposite. The proportion of subjects who presented with the full FAS facial phenotype (Rank 4) by age group was as follows: birth to 3.9 yrs (14%), 4 to 16.9 years (7.7%), and 17 to 53 years (9.5%). The age group with the highest prevalence of the FAS facial phenotype was infants under one year of age (23%) [50]. It is certainly possible for the facial features to change with age. Although, in our experience, when change occurs it has always been quite subtle. In the event that facial features do change over time, most diagnostic guidelines address this by stating that the features may be present at *any* age. For example, if an adult presents with some, but not all of the FAS facial features, but childhood photos document the full FAS facial phenotype, then the adult would meet the full FAS facial criteria based on their childhood photos.

Overall, diagnostic evaluations for FASD can be conducted across the lifespan (newborn to adult). The diagnostic criteria do not change with age. The most accurate diagnosis can be rendered in childhood when the child is old enough to engage in all levels of assessment, but a diagnostic evaluation should not be postponed for this reason. Infants may require re-assessment. Adults present with unique challenges, but benefit nonetheless.

Validation of FASD Guidelines. It is imperative that the performance (reliability, accuracy, specificity, and validity) of diagnostic guidelines be confirmed through properly designed empirical studies [1]. A number of empirical studies have been published confirming the performance of the measurement tools, case-definitions, and diagnostic subclassifications used by the 4-Digit Code [7,9,10,14,16,20,21,39,50,62]. A recently completed MRI/fMRI/MRS study of children with FASD identified significant differences in neuropsychological outcomes [10], neurostructural outcomes [9], neuroactivation levels [21], and neurometabolite levels [63] between the FAS/PFAS, SE/AE and ND/AE clinical subgroups. Significant correlations were observed between size of brain regions and level of prenatal alcohol exposure, magnitude of FAS facial phenotype, and level of CNS dysfunction (Fig. 5). These findings confirm the 4-Digit Code produces three clinically distinct and increasingly more affected diagnostic subclassifications (FAS/PFAS, SE/AE, and ND/AE) under the umbrella of FASD.

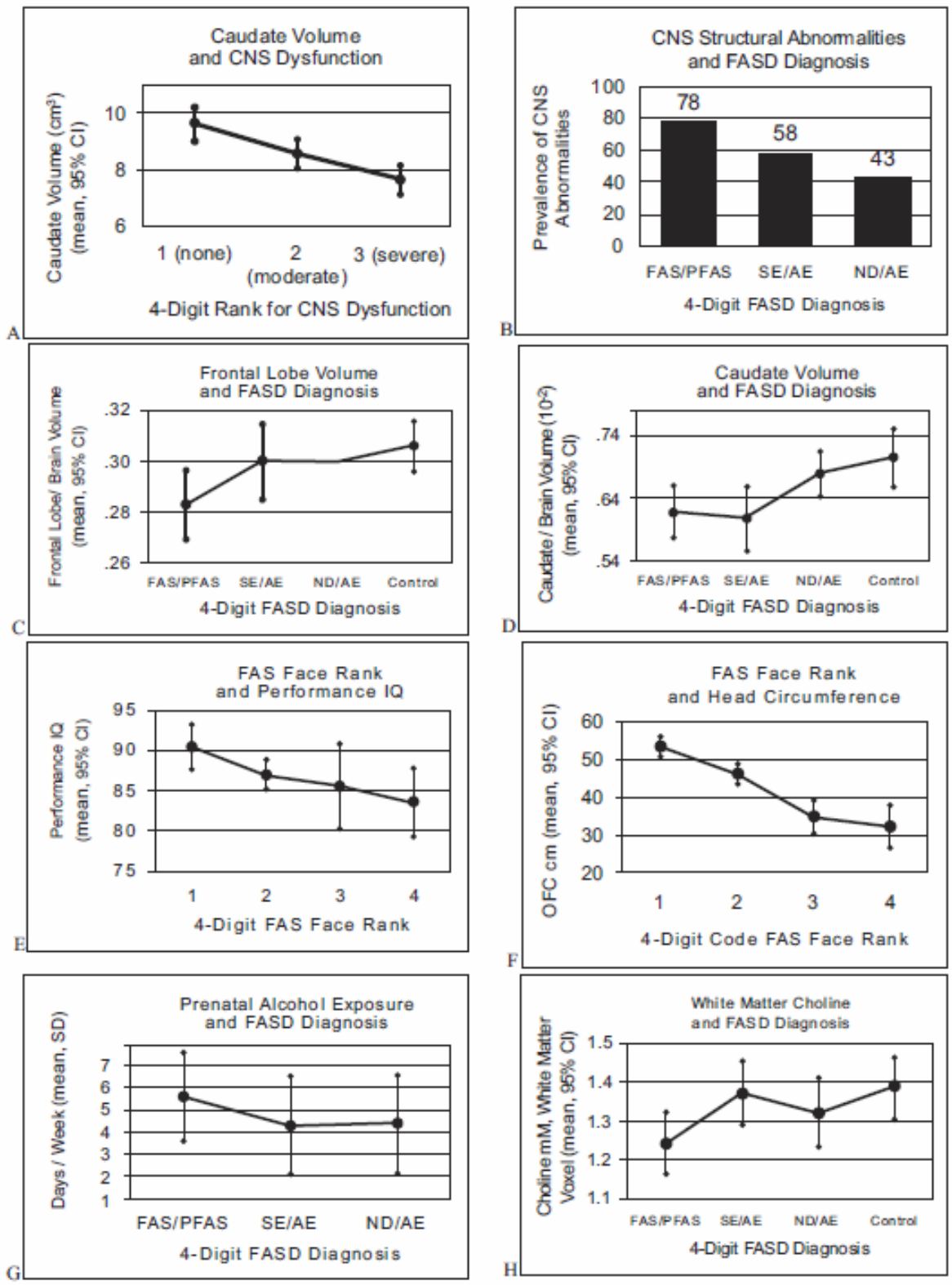


Figure 5: Examples of some of the many significant, empirical findings that serve to validate the performance of the FASD 4-Digit Diagnostic Code [9.10.50.63].

Patient Examples that Exemplify Key Contrasts between the Guidelines.

One practical method to assess the performance of the guidelines is to compare/contrast how they classify cases across the spectrum. Below are four hypothetical patient examples and the diagnostic classifications each would receive from the five most current FAS/D diagnostic guidelines [IOM [1], 4-Digit Code[38], Canadian[37], CDC[36], and Hoyme[19]]. These examples were selected to exemplify key contrasts between the guidelines. There are certainly many other examples that would result in identical diagnostic classifications across all five guidelines.

PATIENT EXAMPLE 1 (10 years old):

Growth: Hgt 10th percentile, wgt 95th percentile
Face: PFL 10th percentile;
Somewhat smooth philtrum, Rank 4;
Thick upper lip, Rank 1
CNS: OFC 10th percentile, FSIQ 120, No evidence of dysfunction.
Alcohol: Unknown

Diagnostic Classifications:

IOM: Unable to definitively classify. The IOM criteria are not sufficiently case-defined.
4-Digit Code: No sentinel physical findings or CNS abnormalities detected / Alcohol Unknown (4-Digit Code = 2212), Not FASD
Canadian: Not FASD
CDC: Not FAS
Hoyme: FAS / Alcohol Unknown

PATIENT EXAMPLE 2 (10 years old)

Growth: Hgt 2nd percentile, wgt 2nd percentile
Face: Small PFL, 2nd percentile,
Smooth philtrum, Rank 5,
Thin upper lip, Rank 5
CNS: OFC 30th percentile, No CNS structural/neurological abnormalities, FSIQ 50 (1st percentile). Severe dysfunction across all domains.
Alcohol: Intoxicated weekly throughout pregnancy

Diagnostic Classifications

IOM: Partial FAS? (This diagnostic classification is in question because the IOM growth deficiency criteria are not strictly met)
4-Digit Code: FAS/Alcohol Exposed (Code = 4434)
Canadian: FAS/Alcohol Exposed
CDC: FAS/Alcohol Exposed
Hoyme: Partial FAS/Alcohol Exposed

PATIENT EXAMPLE 3 (10 years old)

Growth: Hgt 50th percentile, wgt 50th percentile
Face: Normal PFL 50th percentile,
Normal philtrum Rank 2,
Normal upper lip Rank 2
CNS: OFC 50th percentile, No CNS structural/neurological abnormalities. ADHD, Significant memory impairment, All other domains of function within normal range.
Alcohol: One glass of wine nightly throughout pregnancy. No reports of binge drinking, intoxication, or problems with alcohol use.

Diagnostic Classifications:

IOM: Not FASD
4-Digit Code: Neurobehavioral Disorder / Alcohol Exposed (Code = 1123)
Canadian: Not FASD
CDC: Not FAS.
Hoyme: Not FASD

PATIENT EXAMPLE 4: (2 years old)

Growth: Hgt 1st percentile, wgt 1st percentile
Face: Small PFL 1st percentile,
Smooth philtrum, Rank 5,
Thin upper lip, Rank 5
CNS: OFC 1st percentile, Bayley Scales of Infant Development outcomes within low-normal range.
Alcohol: Intoxicated weekly throughout pregnancy

Diagnostic Classifications:

IOM: Partial FAS? (This diagnosis is in question because the IOM growth deficiency criteria are not strictly met)
4-Digit Code: FAS/Alcohol Exposed (Code = 4444)
Canadian: Not FASD
CDC: FAS/Alcohol Exposed
Hoyme: FAS/Alcohol Exposed

FUTURE DIRECTIONS

Without doubt, the one emerging arena that will have the greatest impact on the future of FASD diagnosis is brain imaging. All diagnostic guidelines include "evidence of abnormal brain structure (e.g., abnormal MRI, microcephaly)" as a key diagnostic criteria for FAS, PFAS, and ARND (or its equivalent). Detection of abnormal structure currently relies on radiologist review (visual inspection) of brain images. But MRI technology can now produce accurate measures of size/shape/and tissue composition of brain regions that provide far more sensitive measures of structural abnormality [9, 64-66]. For example, in a recently completed FASD MRI study, none of the 23 children with ND/AE were identified as having an abnormal MRI by radiologist review, yet 43% of the subjects had one or more brain regions, two or more standard deviations below the mean size observed in the healthy Control group using MRI volumetric analysis [9]. Does this mean 43% of these children now meet the diagnostic criteria for having an "abnormal MRI"? Not necessarily. Norms for the size of brain regions, by gender and age, must be established using large, representative, population-based samples, rather than small, convenient research control samples. The National Institutes of Health MRI Study of Normal Brain Development [67, 68] is a landmark study that is documenting structural brain development and behavior longitudinally from birth to young adulthood in a large population-based sample of healthy children targeted to the United States 2000 census distribution. Thus, we will soon have "normal growth charts" for the size of brain regions, much like we have normal growth charts for height, weight, and head circumference. If microcephaly meets the FASD criteria for a structural brain abnormality, should a significantly small frontal lobe or caudate volume meet the criteria? The answer will likely depend, in part, on how size correlates with function. Decreasing head circumference is correlated with increasing severity of dysfunction [9, 69]. A rapidly growing literature documents similar correlations exist between regional brain volumes and function [9, 65,70] (Fig. 5A). If brain imaging technology is adopted into the FASD diagnostic evaluation process, the prevalence of FAS/D will increase, simply by virtue of increased sensitivity to detect structural brain abnormality.

SUMMARY REMARKS

1. An FASD diagnostic evaluation is most accurately conducted by an interdisciplinary team.

2. The field should strive to adopt a single set of diagnostic guidelines for FASD.

3. Guidelines should undergo rigorous assessment of their accuracy, reliability, specificity, and validity to confirm their high performance, preferably before their release.

4. Use of the terms ARND and ARBD, like FAE, should be discontinued. They should be replaced by terminology that does not imply or rule-out a causal association between outcome and exposure in an individual patient.

5. Exposure and outcome should be assessed and reported separately.

6. The FAS facial phenotype must by highly specific to prenatal alcohol exposure and FAS to render a valid diagnosis of FAS, especially in the absence of a confirmed prenatal alcohol exposure. Specificity must be confirmed through properly designed empirical studies.

7. Diagnostic criteria should not require 'excessive' levels of alcohol exposure because a safe level of exposure has not been confirmed for all individuals and the accuracy of an exposure history can never be verified.

8. The report summarizing the outcome of an FASD diagnostic evaluation should report the FASD diagnostic classification, which diagnostic guidelines were used, all data required to confirm the diagnostic criteria were met and all recommendations documented.

9. Access to intervention services should be based on a patient's disability, not on what caused their disability.

CONCLUSIONS

Accurate, reliable, diagnoses across the full continuum of FASD have been available to families and clinicians for over a decade. As medical technology and our understanding of FASD advance, so must our diagnostic methods and tools. It is imperative that advancements in diagnostic methods be guided by an evidence base of rigorously designed, implemented, and peer-reviewed research. When a diagnosis under the umbrella of FASD is made, two individuals are affected directly; the child and the birth mother. The consequences of an incorrect diagnosis for both mother and child must be considered carefully. Diagnostic guidelines should guide professionals in rendering an accurate medical diagnosis. A diagnosis reflects the condition of a patient; however, because a diagnosis serves many purposes (eg, treatment, prevention, communication among specialists, and qualification for services), the process of rendering a diagnosis can sometimes be influenced by those different purposes. The only diagnosis that serves all purposes most effectively is a correct diagnosis. Access to services should be based on an individual's disabilities and not on what caused their disabilities. Therefore, services should be available for individuals across the full continuum of FASD and not just those with FAS.

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