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Comparison of the 4-Digit Diagnostic Code and the Hoyme Diagnostic Guidelines for Fetal Alcohol Spectrum Disorders

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ABSTRACT

OBJECTIVE. The 4-Digit Diagnostic Code for fetal alcohol spectrum disorders and the Hoyme fetal alcohol spectrum disorders diagnostic guidelines differ markedly. The performances of the 2 diagnostic systems were compared.

METHODS. The fetal alcohol syndrome diagnostic criteria from the 4-Digit Code and Hoyme guidelines were applied to 952 patients who had received an interdisciplinary, fetal alcohol spectrum disorders, diagnostic evaluation at the University of Washington with the 4-Digit Diagnostic Code and 16 children with confirmed absence of prenatal alcohol exposure.

RESULTS. The prevalence of fetal alcohol syndrome was 3.7% with the 4-Digit Code and 4.1% with the Hoyme guidelines. Although the prevalences were similar, the patients identified were not. Only 17 individuals met the fetal alcohol syndrome criteria for both systems. An extraordinary number of patients (35%) met the Hoyme criteria for the fetal alcohol syndrome facial phenotype, but only 39 of those 330 patients met the Hoyme criteria for fetal alcohol syndrome. Even some children with no alcohol exposure (25%) had the Hoyme fetal alcohol syndrome face. The specificities of the Hoyme fetal alcohol syndrome face for the Hoyme fetal alcohol syndrome diagnosis and prenatal alcohol exposure were low in these populations.

CONCLUSIONS. Without a specific facial phenotype, a valid diagnosis of fetal alcohol syndrome cannot be rendered for patients with prenatal alcohol exposure, because a causal link between their outcomes and exposure cannot be established, and a valid diagnosis of fetal alcohol syndrome cannot be rendered for patients with unknown alcohol exposure, because the face cannot serve as a valid proxy measure for alcohol exposure. Diagnostic guidelines must confirm the specificity of their fetal alcohol syndrome facial criteria to validate their diagnostic criteria.

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Key Words
diagnostic methods, fetal alcohol syndrome, fetal alcohol spectrum disorders, evaluation, guidelines

Abbreviations
FASD—fetal alcohol spectrum disorders
FAS—fetal alcohol syndrome
OFC—occipital frontal circumference
PFL—palpebral fissure length
IOM—Institute of Medicine
CDC—Centers for Disease Control and Prevention
ARND—alcohol-related neurodevelopmental disorder
ARBD—alcohol-related birth defects
CNS—central nervous system
DPN—Diagnostic and Prevention Network
CI—confidence interval

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FETAL ALCOHOL SPECTRUM disorders (FASD) is a general term used to describe the full spectrum of adverse outcomes observed among individuals with prenatal alcohol exposure. Fetal alcohol syndrome (FAS) and partial FAS are 2 of several medical diagnoses that fall under the designation of FASD. In the past 10 years, several diagnostic guidelines for FASD have been published, including the Institute of Medicine (IOM) FASD guidelines in 1996,[1] the FASD 4-Digit Diagnostic Code (Fig 1) in 1997, 1999, and 2004,[2–5] the Centers for Disease Control and Prevention (CDC) FAS guidelines in 2004,[6] the Canadian FASD guidelines in 2005,[7] and the Hoyme FASD guidelines in 2005.[8] An interdisciplinary approach to diagnosis, with a more case-defined approach, as proposed originally by Astley and Clarren and colleagues,[4,9,10] was adopted in principal in all subsequent guidelines. Key contrasts do exist, however (Table 1). Of all guidelines published after the 4-Digit Code, the Canadian guidelines are most similar to the 4-Digit Code. Both systems cover the full spectrum of diagnostic outcomes and adhere to strict criteria that use the standard medical statistical definition of "abnormal" as ≥2 SDs below the mean or its equivalent, ≤2.5th percentile. The criteria used by the 2 systems to define each diagnosis under the designation of FASD are nearly identical.

In contrast to the 4-Digit Code and Canadian guidelines, the CDC guidelines address only FAS and have more-relaxed facial and central nervous system (CNS) criteria, using diagnostic cutoff values of ≥1 SD below the mean or ≤10th percentile. By definition, the 10th percentile and −1 SD are both within the normal range. One standard deviation below the mean is equivalent to the 16th percentile. The 10th percentile is equivalent to 1.3 SDs below the mean.

The Hoyme guidelines, while addressing the full spectrum of outcomes, diverge considerably from the 4-Digit Code, the CDC guidelines, and the Canadian guidelines. For the diagnosis of FAS, the Hoyme guidelines further relax the facial criteria, requiring only 2 of the 3 diagnostic features specified by the CDC; restrict the CNS criteria to structural abnormalities only; and relax the criterion for small head circumference from the medical definition of microcephaly (≤2.5th percentile) to ≤10th percentile. Hoyme et al[8] referred to their FASD diagnostic guidelines as a clarification of the 1996 IOM criteria. The 2 sets of guidelines are authored by separate groups, however.

All 4 sets of guidelines require prenatal alcohol exposure to be confirmed but allow a diagnosis of FAS to be rendered if prenatal alcohol exposure is unknown. The Hoyme guidelines go farther by requiring that the confirmed exposure be excessive. The 4-Digit Code does not require confirmation of excessive exposure because (1) there is no known threshold of exposure below which all fetuses are not at risk for FAS; (2) requiring excessive exposure may send an unsafe message that only high levels of alcohol use are damaging to the fetus; and (3) it is rarely, if ever, possible to confirm the accuracy of the quantity, frequency, and timing of exposure reported to a diagnostic clinic. There are many potential threats to the reliability of a prenatal alcohol exposure history. Birth mothers may be reluctant to report that they drank during pregnancy. They may be unable to recall accurately how much they drank, because the child's diagnostic evaluation is often conducted several years after the pregnancy. Furthermore, frequently the birth mother is not present at the time of the child's diagnostic evaluation. Eighty-one percent of children diagnosed at Washington State FAS Diagnostic and Prevention Network (DPN) clinics are in foster or adoptive care; therefore, information on maternal alcohol exposure is obtained frequently from indirect sources. The 4-Digit Code has demonstrated, however, that rendering a diagnosis of FAS, as defined by the 4-Digit Code, when alcohol exposure is unknown is medically valid. This is because the rank 4 FAS facial phenotype (Fig 2), as defined by the 4-Digit Code, is so specific to FAS (99.8%)[11–14] that it serves as a valid proxy measure of prenatal alcohol exposure. The sensitivity (100%) and specificity (99.8%) of the rank 4 FAS facial phenotype to the 4-Digit diagnosis of FAS have been derived from properly designed split-half empirical studies[12,13] and validated through population-based screening and surveillance programs.[11,14] As the FAS facial criteria are relaxed,

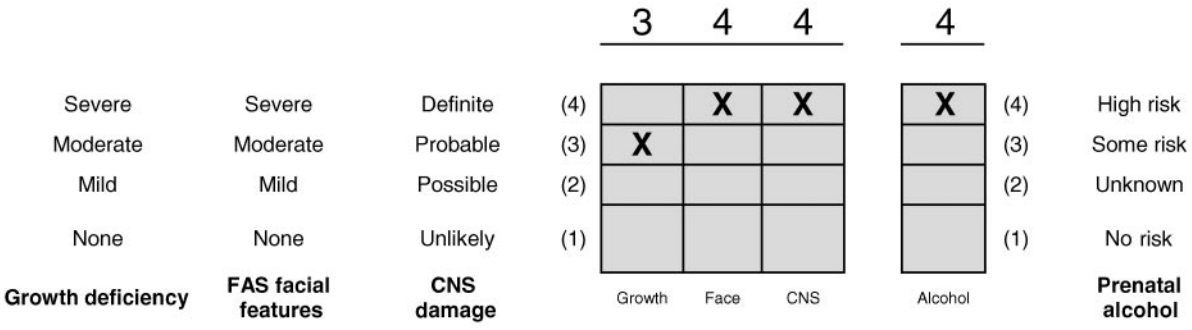


FIGURE 1
Four-Digit Diagnostic Code grid. The 4-Digit Code (3444) that is inserted in the grid is 1 of 12 codes that meet the diagnostic criteria for FAS.[5]

TABLE 1 **Comparison of Key FAS Diagnostic Criteria Across 5 FASD Diagnostic Guidelines**

	IOM (1996)	4-Digit Code (2004)	CDC (2004)	Canadian (2005)	Hoyme (2005)
Growth	At least 1 of the following: low weight for height, low birth weight, or decelerating weight	Prenatal or postnatal height or weight of ≤10th percentile (growth ranks 2, 3, or 4)	Prenatal or postnatal height or weight of ≤10th percentile	At least 1 of the following: prenatal or postnatal height or weight of ≤10th percentile or low weight-to-height ratio (10th percentile)	Prenatal or postnatal height or weight of ≤10th percentile
Face	Characteristic pattern that includes features such as short PFL, flat upper lip, flattened philtrum, and flat midface	All 3 of the following (facial rank 4; Fig 3): PFL of ≤3rd percentile, philtrum rank 4 or 5, and lip rank 4 or 5	All 3 of the following: PFL of ≤10th percentile, philtrum rank 4 or 5, and lip rank 4 or 5	All 3 of the following: PFL of ≤3rd percentile, philtrum rank 4 or 5, and lip rank 4 or 5	Two of the following 3: PFL of ≤10th percentile, philtrum rank 4 or 5, and lip rank 4 or 5
CNS	At least 1 of the following: OFC of ≤3rd percentile (microcephaly), abnormal structure, or hard/soft signs	At least 1 of the following (brain rank 3 or 4): OFC of ≤3rd percentile (microcephaly), abnormal structure, seizure disorder, hard signs, ≥3 domains with impairment ≥2 SDs below the mean (domains may include but are not limited to cognition, memory, language, executive functioning, and attention-deficit/hyperactivity disorder), or global deficits	At least 1 of the following: OFC of ≤10th percentile, abnormal structure, seizure disorder, hard/soft signs, ≥3 domains (cognitive or developmental, executive functioning, motor, attention-deficit/hyperactivity disorder, social, or other) with impairment ≥1 SD below the mean, or global deficits	Impairment[a] in ≥3 of the following domains: hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, attention-deficit/hyperactivity disorder, adaptive behavior, social skills, and social communication	At least 1 of the following: OFC of ≤10th percentile or abnormal structure
Alcohol	Confirmed or unknown	Confirmed (alcohol rank 3 or 4) or unknown (alcohol rank 2)	Confirmed or unknown	Confirmed or unknown	Confirmed to be excessive or unknown

[a] Impairment indicates scores ≥2 SDs below the mean, discrepancies of 1.5 to 2 SDs among subtests, or ≥1 SD discrepancy between subdomains.

their sensitivity and specificity for FAS decrease markedly. Neither the CDC guidelines nor the Hoyme guidelines assessed or reported the sensitivity or specificity of their relaxed criteria for the FAS facial phenotype as their criteria for a FAS diagnosis.

The Hoyme diagnostic criteria for FAS also differ from the 4-Digit Code, CDC guidelines, and Canadian guidelines in that the diagnosis is based solely on physical features of growth, facial anomalies, and structural brain abnormalities. Therefore, an interdisciplinary clinical team (eg, psychologist, occupational therapist, and speech/language pathologist) would have no role in the derivation of a FAS diagnosis. Typically, the most disabling feature of FAS is the cognitive/behavioral impairment. With the Hoyme guidelines, a child would meet the CNS criteria for FAS by having nothing more than an occipital frontal circumference (OFC) in the 10th percentile, even in the presence of normal or above-normal cognitive/behavioral function. An OFC in the 10th percentile does not meet the medical definition of microcephaly (≤2.5th percentile). By definition, 10% of the general population has an OFC of ≤10th percentile. In contrast, a child who presents with severe mental retardation (IQ of 55) but no evidence of structural brain abnormalities would fail to meet the Hoyme diagnostic criteria for FAS, because brain dysfunction is not included as a diagnostic feature of FAS in the Hoyme guidelines.

Because of concerns regarding the Hoyme FAS diagnostic criteria, namely, (1) they relax the FAS facial phenotype criteria without confirming the phenotype's specificity for FAS or prenatal alcohol exposure, (2) they allow FAS to be diagnosed when prenatal alcohol exposure is unknown, with the use of FAS facial criteria of unknown specificity for prenatal alcohol exposure, (3) they require confirmation of excessive prenatal alcohol exposure, when documentation of prenatal alcohol exposure is typically unreliable, (4) they include only structural/morphologic measures of CNS damage and exclude functional and neurologic measures of CNS damage, (5) they allow a single structural abnormality to serve as evidence of CNS damage, while relaxing the criterion for one of the key structural features (OFC) into the normal range (≤10th percentile), and (6) the diagnostic guidelines were created by using a nonrepresentative population base (South Africans and Native Americans) and invalid application of a measurement tool (white lip-philtrum guide), this study was conducted to assess the performance of the Hoyme FAS diagnostic criteria when applied to 2 populations, namely, the University of Washington FASD clinical population (a large population that is highly representative of a US population seeking FASD diagnostic services) and a group of high-functioning children with confirmed absence of prenatal alcohol exposure, enrolled as control subjects in a research study. The specific aims of this study were (1)

A

5-point Likert Rank for philtrum and lip	*z* score[a] for palpebral fissure length	Circle the ABC scores for: Palpebral fissure length	Philtrum smoothness	Upper-lip thinness
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**

B

4-digit facial 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

FIGURE 2
The 4-Digit facial rank[5] (rank of 1–4) is calculated by deriving the facial ABC-Score, which reflects the PFL, philtrum smoothness, and upper lip thinness (A), and converting the facial ABC-Score to the 4-digit rank for face (B). For example, an individual with PFL of −3 SD, philtrum rank 3, and lip rank 1 would receive a facial ABC-Score of CBA and a 4-Digit facial rank of 2. [a]The *z* score reflects how many SDs above or below the mean the patient's PFL is.

to assess the specificity of the Hoyme FAS facial phenotype for the Hoyme FAS diagnosis when the Hoyme guidelines were applied to the University of Washington FASD clinical population, (2) to assess the specificity of the Hoyme FAS facial phenotype to prenatal alcohol exposure when the Hoyme diagnostic guidelines were applied to a study population with confirmed absence of prenatal alcohol exposure, (3) to compare the prevalence of FAS (with and without confirmed prenatal alcohol exposure) between the Hoyme and 4-Digit Code criteria for FAS, when the 2 sets of criteria were applied to the University of Washington FASD clinical population, and (4) to compare, on a case-by-case basis, which patients did and did not receive a diagnosis of FAS when the Hoyme and 4-Digit Code FAS criteria were applied to the University of Washington FASD clinical population.

METHODS

FASD Clinical Population

The target clinical population for this study included all patients diagnosed to date at the University of Washington FAS DPN clinic. A comprehensive set of data (>2000 fields of information, documenting prenatal and lifetime exposures and outcomes, including standardized facial photographs) is collected and entered into a database for each patient who receives a FASD diagnostic evaluation at the FAS DPN clinic, with informed consent and University of Washington Human Subjects Review Board approval. More than 98% of patients provide consent; therefore, the data set is highly representative of the entire University of Washington FAS DPN patient population. All FAS DPN patients have been diagnosed by an interdisciplinary clinical team[10] with the 1997, 1999, or 2004 version of the 4-Digit Diagnostic Code.[2–5] The records of all patients who met the inclusion criteria were included in this study; there were no exclusion criteria. The inclusion criteria were as follows: (1) the patient received an interdisciplinary FASD diagnostic evaluation at the University of Washington FAS DPN clinic with the FASD 4-Digit Diagnostic Code; (2) the patient gave consent for use of the FAS DPN clinical data for research purposes; and (3) all data required to render a FAS diagnosis with the Hoyme guidelines (ie, measures of growth, face, brain growth and/or morphogenesis, and prenatal alcohol exposure) were available in the patient's record.

Research Population With No Alcohol Exposure

The records of 16 children with confirmed absence of prenatal alcohol exposure, who were enrolled as control subjects in a recently completed MRI research study, were also included in this study.[15] The MRI study was

conducted with subject consent and University of Washington Human Subjects Review Board approval. Because only 4 of the 952 patients in the FASD clinical population had a confirmed absence of prenatal alcohol exposure, this larger data set of unexposed subjects was included for better assessment of the specificity of the Hoyme FAS facial phenotype for prenatal alcohol exposure. If the Hoyme FAS facial phenotype is specific to (caused only by) prenatal alcohol exposure, then none of these children should have the FAS facial phenotype. The 16 children in this study population were 8 to 15 years of age; 8 were female, 13 were white, 2 were black, and 1 was Asian American. Their Wechsler Intelligence Scale for Children-III full-scale IQs ranged from 112 to 133.

Hoyme FASD Diagnostic Guidelines

The Hoyme criteria (Table 2) for the diagnostic classifications of FAS with confirmed maternal alcohol exposure and FAS without confirmed maternal alcohol exposure were applied to the 2 study populations. These criteria were used to generate 2 outcome variables, namely, Hoyme FAS facial phenotype (present or absent) and Hoyme FAS diagnosis with or without confirmed maternal alcohol use (present or absent). Because the criteria for these diagnostic outcomes are based solely on physical features measured on numeric scales (eg, height, weight, palpebral fissure length [PFL], and head circumference), computer algorithms were written and applied to the electronic data sets to generate the outcome variables. This eliminated any potential for human error, bias, or interrater discordance.

FASD 4-Digit Diagnostic Code (2004)

All patients in the clinical study population (n = 952) had been diagnosed previously by the University of Washington interdisciplinary FASD diagnostic team. Their 4-Digit Diagnostic Codes and all exposure and outcome data collected for their diagnostic evaluations were recorded in the FAS DPN clinical database. The FASD 4-Digit Diagnostic Code was first printed in 1997 and was updated in 1999 and 2004. For the purposes of this study, all FASD 4-Digit Codes were updated to reflect the 2004 version of the FASD 4-Digit Diagnostic Code.[5] These updates included use of the black lip-philtrum guide and black PFL normative values[16] for all black patients, use of the upper lip circularity tables to rank lip thinness, use of the new growth rank tables, and coding of full-scale IQ of ≤60 as CNS rank 3 rather than rank 4. Because all updates were simply numeric transformations of existing numeric data, the 4-Digit Codes were updated to the 2004 criteria by writing computer transformation algorithms and applying them to the existing data set. Therefore, there was no risk of human error, bias, or interrater discordance in the updating process. All subjects in the MRI study population received a 2004, 4-Digit Diagnostic Code at the time of the MRI study. Therefore, their 4-Digit Codes did not require updating.

The 4 digits of the diagnostic 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 abnormalities, and (4) prenatal alcohol exposure (Figs 1–3). A detailed description of the 4-Digit Code is presented in the *Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions: The 4-Digit Diagnostic Code*.[5] Briefly, the magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Each Likert rank is specifically case defined. There are 256 possible 4-digit diagnostic codes, ranging from 1111 to 4444. Each 4-digit diagnostic code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Eight of the 22 diagnostic categories (categories A–C and E–I) fall broadly under the designation of FASD. This study focuses on diagnostic categories A and B, that is, FAS (alcohol exposed) and FAS (alcohol exposure unknown), respectively. The 2004 criteria for these 2 diagnostic categories are presented in Table 3 in a format to facilitate direct comparison with the Hoyme FAS criteria in Table 2. This study also focuses on the FAS facial phenotype. The 4-point ranking system for the 4-Digit Code FAS facial phenotype is presented in Figs 2 and 3. The 4-point ranking system for growth deficiency is as follows: rank 1, height and weight of >10th percentile; rank 2, height or weight of ≤10th percentile but >3rd percentile; rank 3, height or weight of ≤3rd percentile; rank 4, height and weight of ≤3rd percentile. The 4-point ranking system for the CNS is as follows: rank 1, no evidence of dysfunction/delay; rank 2, evidence of

TABLE 2 Hoyme Diagnostic Criteria for FAS With or Without Confirmed Maternal Alcohol Exposure[8]

FAS with confirmed maternal alcohol exposure requires all features A–D
- A Evidence of prenatal and/or postnatal growth retardation
  1. Height or weight of ≤10th percentile, corrected for racial normative values, if possible
- B. Evidence of a characteristic pattern of minor facial anomalies, including ≥2 of the following:
  1. Short palpebral fissures (≤10th percentile, equivalent to ≥1.28 SDs below the mean)
  2. Thin vermilion border of upper lip (score 4 or 5 on the Lip-Philtrum Guide)
  3. Smooth philtrum (score 4 or 5 on the Lip-Philtrum Guide)
- C. Evidence of deficient brain growth or abnormal morphogenesis, including ≥1 of the following:
  1. Structural brain abnormalities
  2. Head circumference of ≤10th percentile
- D. Confirmed maternal alcohol exposure; a pattern of excessive intake characterized by substantial regular intake or heavy episodic drinking

FAS without confirmed maternal alcohol exposure requires features A, B, and C

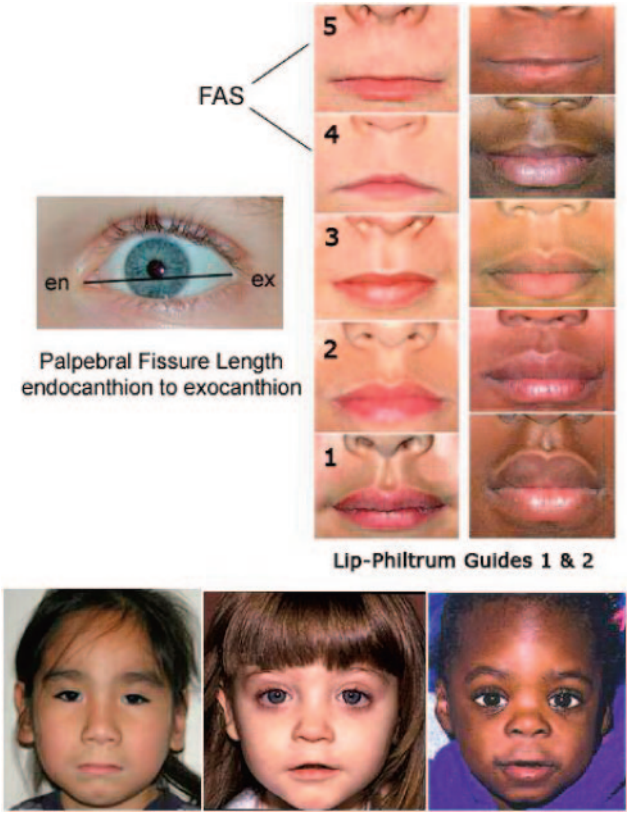


FIGURE 3
Four-Digit Code FAS facial phenotype. The rank 4 FAS facial phenotype determined with the 4-Digit Diagnostic Code[5] requires the presence of the following 3 anomalies: (1) PFL below −2 SD, (2) smooth philtrum (rank 4 or 5 on the Lip-Philtrum Guide), and (3) thin upper lip (rank 4 or 5 on the Lip-Philtrum Guide). Examples of the rank 4 FAS facial phenotype for Native American, white, and black children are shown. The endocanthion and exocanthion are standardized facial landmarks.

moderate dysfunction; rank 3, evidence of severe dysfunction; rank 4, evidence of structural or neurologic damage. The 4-point ranking system for prenatal alcohol exposure is as follows: rank 1, confirmed absence of alcohol exposure from conception to birth; rank 2, alcohol exposure unknown; rank 3, exposure is confirmed and the level of exposure is low-moderate or unknown; rank 4, exposure is confirmed and level is high. More-detailed case definitions of these ranks have been published.[5]

This study did not compare the other diagnoses (partial FAS, alcohol-related neurodevelopmental disorder [ARND], and alcohol-related birth defects [ARBD]) under the designation of FASD across the 2 diagnostic systems, for the following reasons. The Hoyme criteria for partial FAS and ARND include "evidence of a complex pattern of behavioral or cognitive abnormalities," but the Hoyme description of this complex pattern is not specific enough for reliable application of the criteria to the FAS DPN data set. For example, the Hoyme guidelines do not define how severe the abnormalities must be (1 SD below the mean? 2 SDs below the mean?) or how many domains of function must be impaired (2 domains? 3 domains?) to constitute a complex pattern. In contrast, the 4-Digit Code, CDC guidelines, and Canadian guidelines provide specific thresholds (eg, ≥3 domains of function, ≥2 SDs below the mean) (Table 1). The Hoyme criteria for ARBD could not be compared across the 2 systems because, like the CDC guidelines and the Canadian guidelines, the 4-Digit Code does not recognize ARBD as a medical diagnostic classification.

Analysis

The prevalence of FAS in the FASD clinical population was computed by using the 2004, 4-Digit Code and Hoyme criteria for FAS (with and without confirmed prenatal alcohol exposure). The number of patients who met the Hoyme criteria for the FAS facial phenotype was computed for both study populations. The specificity of the Hoyme FAS facial phenotype for the Hoyme FAS diagnosis was computed as follows: number of patients without the Hoyme FAS facial phenotype divided by number of patients without a Hoyme diagnosis of FAS. The specificity of the Hoyme FAS facial phenotype for prenatal alcohol exposure was computed as follows: number of patients without the Hoyme FAS facial phenotype divided by number of patients with a confirmed absence of prenatal alcohol exposure. Each estimate of specificity was accompanied by a 95% confidence interval (CI). Specificity refers to the ability of a test or outcome to indicate nondisease when no disease is present. If an outcome is not specific, then it indicates falsely the presence of disease in nondiseased subjects. A binomial test was used to compare the observed frequency of the Hoyme FAS facial phenotype with the expected frequency (0%) among the 16 children with confirmed absence of prenatal alcohol exposure.

RESULTS

Hoyme Guidelines Applied to the FASD Clinical Population

Study Group

Of the 956 patients diagnosed to date in the FAS DPN Clinic, 952 (99.6%) met the inclusion criteria for this study (Table 4). Therefore, this study population is highly representative of the entire FAS DPN patient population seen over 13 years. The study population represents a racially diverse group, ranging in age from 0.2 and 50.8 years of age at the time of the FASD diagnostic evaluation. A total of 732 of the patients (77%) had 2004, 4-Digit Codes that fell under the general designation of FASD. An additional 147 (15%) had growth, facial, and/or CNS abnormalities but their prenatal alcohol exposures were unknown. An additional 4 patients had a confirmed absence of prenatal alcohol exposure. Therefore, this patient population reflects the range of outcomes and exposures encountered typically by a FASD diagnostic clinic; not all patients referred to

TABLE 3 **Four-Digit Code Diagnostic Criteria for FAS With and Without Confirmed Prenatal Alcohol Exposure[5]**

FAS with confirmed prenatal alcohol exposure requires all features A–D[a]

- A. Evidence of prenatal and/or postnatal growth retardation (growth rank 2, 3, or 4); height and/or weight of ≤10th percentile, corrected for race and midparental height when possible
- B. Presence of all 3 of the following minor facial anomalies (facial rank 4):
  1. Short palpebral fissures (≥2 SDs below the mean, equivalent to ≤2.5th percentile)
  2. Thin upper lip (rank 4 or 5 on Lip-Philtrum Guide 1 or 2, as appropriate for race)
  3. Smooth philtrum (rank 4 or 5 on Lip-Philtrum Guide 1 or 2, as appropriate for race)
- C. Evidence of ≥1 of the following (CNS rank 3 or 4):
  1. Structural brain abnormalities
     a. Structural brain abnormalities (as may be viewed by brain imaging)
     b. Microcephaly (head circumference ≥2 SDs below the mean, equivalent to ≤2.5th percentile)
  2. Neurologic abnormalities
     a. Seizure disorder of prenatal origin
     b. Hard neurologic signs (eg, cerebral palsy)
  3. Significant brain dysfunction
     a. Three or more domains of brain function, ≥2 SDs below the mean, when assessed with validated, standardized, psychometric tools; domains may include but are not limited to executive function, memory, cognition, and language
- D. Confirmed prenatal alcohol exposure (alcohol rank 3 or 4); a specific pattern or level of exposure is not required because it is rarely known when this information has been obtained reliably in a clinical setting and the risk of a specific pattern of exposure is not identical across all fetuses

FAS without confirmed prenatal alcohol exposure requires features A, B, and C, with prenatal alcohol exposure not confirmed to be present and not confirmed to be absent[b]

[a] These criteria reflect the following 2004, 4-Digit Diagnostic Codes: 2433, 2434, 2443, 2444, 3433, 3434, 3443, 3444, 4433, 4434, 4443, and 4444.
[b] These criteria reflect the following 2004, 4-Digit Diagnostic Codes: 2432, 2442, 3432, 3442, 4432, and 4442.

the clinic receive a diagnosis under the designation of FASD.

Specific Aim 1

Thirty-five percent of the patients (330 of 952 patients) met the Hoyme criteria for the full FAS facial phenotype. Only 39 (11.8%) of the 330 patients with the Hoyme FAS facial phenotype met the Hoyme criteria for a diagnosis of FAS (with or without confirmed maternal alcohol use). The specificity of the Hoyme FAS facial phenotype for the Hoyme FAS diagnosis in this clinical population was 68% (622 of 913 patients; 95% CI: 65%–71%). Of the 330 patients with the Hoyme FAS facial phenotype, most did not present with other features of FAS; 60% presented with no growth deficiency (height and weight percentiles of >10th percentile), 74% did not have the 4-digit FAS facial phenotype (rank 4), 82% did not have microcephaly (OFC of ≤2.5th percentile), 77% had an OFC of >10th percentile; 89% of the 32 clinically indicated MRI studies were normal; and 64% of subjects did not have confirmed, excessive, prenatal alcohol exposure. It is worth noting that an additional 84 (25%) of the 330 patients would likely meet the Hoyme criteria for partial FAS (with or without confirmed maternal alcohol use). This is based on the assumption that the Hoyme criteria for a complex pattern of behavioral or cognitive abnormalities are comparable to the 4-digit CNS rank 3. However, 24 of these 84 children had no evidence of brain damage/dysfunction. Their only impairment was growth deficiency. If the specificity of the Hoyme FAS facial phenotype is computed for the Hoyme diagnoses of FAS plus partial FAS, then specificity increases, but only to 75% (622 of 829 subjects; 95% CI: 72%–78%).

Specific Aim 3

The prevalence of FAS (with or without confirmed prenatal alcohol exposure) determined with the 2004, 4-Digit Code was 3.7% (35 of 952 subjects). The prevalence of FAS (with or without confirmed maternal alcohol use) determined with the Hoyme FASD guidelines was 4.1% (39 of 952 subjects). Although the prevalences were similar, the patients identified with the 2 systems were not. Only 17 patients met both the 4-Digit Code and Hoyme criteria for FAS.

Specific Aim 4

Of the 39 patients who met the Hoyme criteria for FAS, 22 (56.4%) did not meet the 4-Digit Code criteria for FAS. The 22 patients ranged in age from 0.8 to 21.4 years and were racially diverse (white, 64%; black, 14%; Native American, 0%; other, 22%). They did not meet the 4-Digit Code criteria for FAS for ≥1 of the following reasons. Thirteen (59%) had facial phenotypes within the normal range (facial rank 2), as defined with the 4-Digit Code. Two had unknown prenatal alcohol exposures and facial features that were too mild (rank 2 or 3, not sufficiently specific for FAS) to allow labeling of the outcome as FAS in the absence of confirmed exposure. Seven (32%) met the 4-Digit Code for Partial FAS.

To portray just how different the Hoyme and 4-Digit Code criteria for FAS are, the outcomes for 1 of the 22

TABLE 4 **Sociodemographic and Clinical Profile of University of Washington FAS DPN Clinical Study Population**

Characteristic	Total Sample ($N = 952$)
Female gender, *n* (%)	416 (43.8)
Race, *n* (%)	
White	490 (51.5)
Black	53 (5.6)
Native American	59 (6.2)
Hispanic (full or mixed race)	107 (11.2)
Asian (full or mixed race)	15 (1.6)
Other (full or mixed race)	228 (23.9)
Age at time of diagnosis, y	
Mean ± SD	10.2 ± 7.4
Range	0.2–50.8
Age distribution, *n* (%)	
0–2.9 y	101 (10.6)
3–10 y	452 (47.9)
11–17 y	295 (31.0)
≥18 y	100 (10.5)
2004, 4-Digit Diagnostic Categories, *n* (%)	
A (FAS; alcohol exposed)[a]	29 (3.0)
B (FAS; alcohol exposure unknown)[a]	6 (0.6)
C (partial FAS; alcohol exposed)[a]	46 (4.8)
E (physical findings/static encephalopathy; alcohol exposed)[a]	58 (6.1)
F (static encephalopathy; alcohol exposed)[a]	163 (17.1)
G (physical findings/neurobehavioral disorder; alcohol exposed)[a]	87 (9.1)
H (neurobehavioral disorder; alcohol exposed)[a]	323 (33.9)
I (physical findings; alcohol exposed)	20 (2.1)
J (no physical findings or CNS abnormalities detected; alcohol exposed)	58 (6.1)
K (physical features/static encephalopathy; alcohol exposure unknown)	16 (1.7)
L (static encephalopathy; alcohol exposure unknown)	39 (4.1)
M (physical findings/neurobehavioral disorder; alcohol exposure unknown)	26 (2.7)
N (neurobehavioral disorder; alcohol exposure unknown)	66 (6.9)
P (no physical findings or CNS abnormalities detected; alcohol exposure unknown)	11 (1.2)
Q (physical findings/static encephalopathy; confirmed absence of exposure)	1 (0.1)
R (static encephalopathy; confirmed absence of exposure)	1 (0.1)
S (physical findings/neurobehavioral disorder; confirmed absence of exposure)	1 (0.1)
T (neurobehavioral disorder; confirmed absence of exposure)	1 (0.1)

[a] These categories fit under the designation FASD.

children (a 14-year-old white youth) who met the Hoyme criteria for FAS but not the 4-Digit criteria for FAS are presented in Fig 4. The 4-Digit Code did not classify this child as having FAS or any diagnosis under the designation of FASD, because alcohol exposure was unknown and the outcomes observed in this child (short stature and microcephaly) were not specific to FAS. Because the Hoyme guidelines require that only 2 of the 3 FAS facial features be present (in this case, PFL in the 1st percentile and philtrum rank 4), this child can and does present with a very thick upper lip (Lip-Philtrum Guide rank 1). This results in a facial phenotype that neither looks dysmorphic nor resembles FAS (Fig 4). The facial features of this child were measured at the time of diagnosis, directly by 2 clinicians and through photographic analysis, with concordance across all 3 measurements. Photographic examples of the rank 4 FAS facial phenotype, as defined with the 4-Digit Code, are presented for comparison in Fig 3.

Conversely, of the 35 patients who met the 4-Digit Code criteria for FAS, 18 (51.4%) did not meet the Hoyme criteria for FAS. The 18 patients ranged in age from 1.5 to 24.3 years and were racially diverse (white, 39%; black, 11%; Native American, 0%; other, 50%). They did not meet the Hoyme criteria for FAS for ≥1 of the following reasons. Seven (39%) did not have evidence of structural brain anomalies, but all 7 had evidence of significant brain dysfunction (4-Digit Code CNS rank 3) (Table 1), including 3 with IQ scores between 56 and 64. Twelve (67%) had confirmed prenatal alcohol exposure (4-Digit Code alcohol rank 3), but information was not available to confirm that exposure was excessive (4-Digit Code alcohol rank 4). Six of these 12 children had 4-digit codes of 4443, which demonstrates clearly that confirmed excessive exposure is not required for a child to present with the most severe end of the spectrum for growth deficiency, FAS facial features, and CNS damage. Six children (33%) likely would have met the Hoyme criteria for partial FAS. These individuals had significant brain dysfunction (4-Digit CNS rank 3) but no known evidence of structural brain anomalies.

Hoyme Guidelines Applied to the Population With Confirmed Absence of Prenatal Alcohol Exposure

Specific Aims 2 and 3

When the Hoyme criteria for the FAS facial phenotype were applied to the 16 children with confirmed absence of prenatal alcohol exposure who were enrolled as control subjects in a MRI research study, 4 (25%) of the 16 children met the Hoyme criteria for the FAS facial phenotype. This observed frequency of 25% was significantly greater than the expected frequency of 0% (binomial test, $P < .001$). The specificity of the Hoyme FAS facial phenotype for prenatal alcohol exposure in this study population was 75% (12 of 16 children; 95% CI: 50%–89%). All 4 subjects had normal growth, normal facial phenotypes according to the 4-Digit Code (facial rank 2), normal OFCs, normal cranial MRI results, and neuropsychological performance significantly above average, including full-scale IQ scores between 124 and 128. None of the 16 children met the 4-Digit Code criteria for the FAS facial phenotype (rank 4). The sole purpose of including these 16 children in this study was to assess the specificity of the FAS facial phenotype for prenatal alcohol exposure. For the sake of completeness,

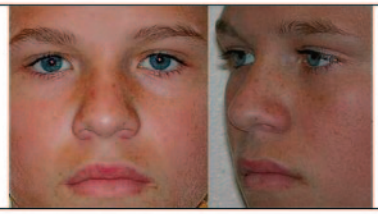
Features		4-Digit Code
Growth	[a]Height 1st percentile (parental heights unknown) Weight 12th percentile	Rank 3
Face	[a]PFL: 1st percentile (-2.9 SD) [a]Philtrum: somewhat smooth: rank 4 Lip: thick: rank 1 No other facial anomalies present 	Rank 2
CNS	[a]OFC 1st percentile (-2.2 SD) Brain function in the low-normal range, including an FSIQ = 95	Rank 4 Rank 2
Alcohol	[a]Unknown	Rank 2
4-digit code diagnosis	Sentinel physical findings/static encephalopathy/alcohol exposure unknown	3242
Hoyme diagnosis	FAS (unknown maternal alcohol exposure)	

FIGURE 4
Example of a 14-year-old child who met the Hoyme FAS criteria but not the 4-Digit Code FAS criteria. [a]Features that allowed the child to meet the Hoyme criteria for FAS (maternal alcohol exposure unknown). FSIQ indicates full-scale IQ.

it could be stated that none of the 16 children met the Hoyme or 4-Digit criteria for a diagnosis of FAS, but this was known from the start. By definition, an individual who was not exposed to alcohol cannot be at risk for FAS.

It is interesting to note that, although only 4 of the 952 patients in the FASD clinical population had a confirmed absence of prenatal alcohol exposure, 1 (25%) of those 4 also met the Hoyme criteria for the full FAS facial phenotype. The child had a normal facial phenotype according to the 4-Digit Code (rank 2) and was growth deficient (rank 4). This observation also reflects a specificity of 75%.

DISCUSSION

Specificity of the FAS Facial Phenotype and Its Impact on Diagnosis

This study demonstrated that an extraordinary number of patients in the FAS DPN clinic met the Hoyme criteria for the full FAS facial phenotype (35%; 330 of 952 subjects), whereas very few of them met the Hoyme criteria for a diagnosis of FAS (11.8%; 39 of 330 subjects). If the Hoyme FAS facial phenotype were specific to FAS, then it would be expected that the vast majority of those with the FAS face would have FAS; the opposite was observed, however. The vast majority of those with the FAS face (88.2%; 291 of 330 subjects) did not have FAS. If the Hoyme FAS face were specific to (caused only by) prenatal alcohol exposure, then individuals could not have the FAS face if they had not been exposed to alcohol. However, this study found that 25% of the children with confirmed absence of prenatal alcohol exposure, in both study populations, met the criteria for the Hoyme FAS face.

Although these results are concerning, they were not unexpected. By relaxing 1 of the facial criteria into the normal range (PFL of ≤10th percentile), requiring only 2 of 3 features to be present, and allowing the 2 features to be expressed at the mildest end of the spectrum (for example, a white subject with a PFL in the 10th percentile with a somewhat smooth philtrum [rank 4] but a very thick upper lip [rank 1]), the diagnostic criteria identify many individuals with normal facial phenotypes. One hundred fifty of the 330 patients with the Hoyme FAS facial phenotype had facial phenotypes that were only rank 2 according to the 4-Digit Code. Rank 2 (by definition) is well within the normal range for the general population.

Although the primary focus of this study was on the diagnosis of FAS, the relaxed Hoyme FAS facial criteria also jeopardize the clinical validity of the Hoyme criteria for partial FAS. The Hoyme criteria for partial FAS use the same relaxed criteria for the FAS facial phenotype and require only 1 other feature to be present (growth deficiency, deficient brain growth or abnormal morphogenesis, or evidence of a complex pattern of behavioral or cognitive abnormalities). Confirmed prenatal alcohol exposure is not required. Therefore, a white individual who presents with the following features would meet the Hoyme criteria for partial FAS: growth, height in the 10th percentile and weight in the 95th percentile; face, PFL in the 10th percentile, somewhat smooth philtrum (rank 4), and very thick upper lip (rank 1); CNS, normal structure and function; alcohol, unknown exposure. With the 4-Digit Code, this child would not even fall under the designation of FASD, because the outcomes are in the normal to very mildly impaired range, the only impaired outcome (height in the 10th percentile) is not specific for prenatal alcohol exposure, and alcohol exposure is unknown. In contrast to the Hoyme guidelines, the 4-Digit Code requires confirmed prenatal alcohol exposure for partial FAS, because the 4-Digit diag-

nosis of Partial FAS allows the facial criteria to be relaxed to facial rank 3 in some instances. Facial rank 3 is less specific for FAS and prenatal alcohol exposure; therefore, the 4-Digit Code does not allow it to be used as a proxy measure of prenatal alcohol exposure for partial FAS when prenatal alcohol exposure is unknown.

Why are the sensitivity and specificity of the FAS facial phenotype so important for the medical validity of a diagnosis of FAS? When we make a diagnosis of FAS, we are stating implicitly that the individual has a syndrome caused by prenatal alcohol exposure. We are also stating implicitly that the birth 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 are we when we infer 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 for the exposure (alcohol) and the outcome (FAS). If a cluster of facial features truly is unique to prenatal alcohol exposure (meaning that alcohol is the only agent that can cause this facial phenotype) and is unique to the diagnosis of FAS (meaning that this exact phenotype is not present in any other medical condition), then we would expect to observe the following: (1) the face would be highly sensitive for FAS (individuals with FAS would have the FAS facial phenotype), (2) the face would be highly specific for FAS (individuals without FAS would not have the FAS facial phenotype), and (3) the face would be highly specific for prenatal alcohol exposure (individuals without prenatal alcohol exposure would not have the FAS facial phenotype). The rank 4 FAS facial phenotype, as defined with the 4-digit code, demonstrates all 3 of these qualities.[4,11–14] A highly specific FAS facial phenotype validates the FAS diagnosis, because the presence of the face confirms that individuals were affected by their prenatal alcohol exposure. The face not only confirms that individuals were affected by prenatal alcohol exposure but also confirms that they were exposed to alcohol. We depend on the latter when we 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 can and do allow FAS to be diagnosed even when prenatal alcohol exposure is unknown. The face is so specific for alcohol exposure that it serves as a valid proxy measure for exposure. This is also why all diagnostic guidelines cannot and do not allow ARND (or its equivalent) to be diagnosed when alcohol exposure is unknown. Because 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; individuals' outcomes cannot be linked to their prenatal alcohol exposure, FAS becomes indistinguishable from ARND/fetal alcohol effects, and diagnoses cannot be made when alcohol exposure is unknown. Considering the fundamental role that the FAS facial phenotype plays in FAS diagnosis, its specificity cannot be assumed and must be confirmed through properly designed empirical studies.

The Evidence Base Underlying the FAS Facial Phenotype

A series of empirical laboratory,[17] clinical,[4,12,13] and population-based screening and surveillance[11,14] studies were conducted by Astley, Clarren, and colleagues over the course of 10 years, to establish the evidence base that supports the diagnostic validity of the 4-Digit Code rank 4 FAS facial phenotype. In 2004, the CDC incorporated the 3 facial anomalies into their FAS guidelines but relaxed the PFL criterion from ≤2.5th percentile to ≤10th percentile. The CDC did not report measures of sensitivity or specificity to validate their relaxed facial criteria. The CDC guidelines[6] cite a series of studies that are intended to support their FAS facial phenotype criteria, but relaxation of the PFL criterion actually goes against the evidence-based literature. For example, the CDC guidelines report, "Use of these three cardinal features (smooth philtrum, thin vermilion, and small palpebral fissures) to assess whether an individual's dysmorphia is consistent with FAS is compatible with the IOM report and other diagnostic systems currently in use."[6] The 3 features are "compatible" with the IOM and 4-Digit Code guidelines, but the magnitude of expression of the PFL is not. The IOM guidelines state, "In this area, the palpebral fissures (eye slits) are short, usually measuring well below −2 SD (standard deviation) for age."[1] The mean PFL among all patients diagnosed as having FAS in the Washington State FAS DPN clinic was −4.0 SD (±1.3 SD).[13] Both the IOM and FAS DPN PFL references are substantially below the 10th percentile (or its equivalent, −1.28 SD) criterion set by the CDC. The CDC does report that use of the 3rd percentile cutoff value for the PFL reduces potential false-positive results for the diagnosis. The CDC guidelines also reported that, "Using anthropometric measurements of all facial features, clinical researchers have confirmed the midline feature abnormalities.[18]"[6] In actuality, the study by Moore et al[18] did not include all facial features. Two of the 3 key midline facial features (philtrum smoothness and lip thinness) were never assessed, and the mean PFL among the 41 alcohol-exposed subjects was −3.6 SD (±1.6 SD), again well below the 10th percentile set by the CDC. Finally, the CDC guidelines reported, "Studies of clinic-referred samples also support these features as discriminant for FAS.[13,19]"[6] But Astley and Clarren[13] did not report that these features are discriminant for FAS

when the PFL is relaxed to the 10th percentile. Coles et al[19] did not include a study group diagnosed as having FAS, did not report what facial features were assessed, and did not conduct a discriminant analysis to delineate the FAS facial phenotype.

In 2005, the Hoyme criteria[8] further relaxed the diagnostic criteria for the FAS facial phenotype to ≥2 of the 3 CDC facial criteria. Like the CDC, Hoyme et al[8] did not provide measures of sensitivity or specificity to validate their relaxed criteria. They also did not report what methods they used (eg, discriminant analyses) to conclude that the facial criteria should be relaxed to 2 features. It is interesting to note that these relaxed criteria are no longer consistent with the facial criteria defined by David Smith, who originally coined the term FAS. In 1979, Smith[20] reported,

> As far as the diagnosis is concerned, perhaps the most important point to emerge in the last few years is that the facial abnormalities seen in affected infants are the key cluster of features that tend to make FAS a clinically discernible entity. Many disorders result in mental and growth deficiency, but in FAS the deficiencies are typically present in a patient whose face has short palpebral fissures, a hypoplastic upper lip with a thinned vermilion border, and a smoothed or absent philtrum. Up to now, the descriptions of the facial features of FAS that have appeared in the literature have not always emphasized the same abnormalities. This has led to some confusion, but inspection of the photographs accompanying these reports leaves no doubt about the facial similarities of FAS patients.

Strengths and Limitations That Affect Validity

The study design and methods used by Hoyme et al[8] to formulate their diagnostic guidelines present both strengths and limitations. Key strengths include the use of skilled multidisciplinary teams led by experts in the field of FASD diagnosis; use of standardized objective measurement tools to enhance reliability; and access to a reasonably large, population-based, study sample. Several limitations, however, jeopardize the validity of the guidelines. (1) Hoyme et al[8] reported that the objective of their study was to formulate more-precise clarifications of the 1996 IOM diagnostic guidelines[1] for "general pediatric practice." However, the racial distribution of their study population (92 South Africans[21] and 72 Native Americans[22]) is not representative of their intended target population (general pediatric practice). (2) Hoyme et al[8] used data for previously diagnosed South African and Native American patients (1998–2003)[22] to formulate their diagnostic criteria. However, an incorrect lip-philtrum guide (white) was used to measure lip thinness in their South African population. Use of a white Lip-Philtrum Guide for a predominantly South African population would result in substantial diagnostic misclassification. The direction of error would be to underestimate the prevalence of the FAS facial phenotype. Creation of diagnostic criteria from a data set predominated by subjects who had a key facial feature measured with an incorrect tool would jeopardize the clinical validity of those criteria. Hoyme et al[8] reported, "A weakness of the proposed diagnostic approach is that the normative values currently used for growth and facial morphologic features are based largely on white populations." The black Lip-Philtrum Guide was made available to clinicians in 2003, before the publication of the Hoyme diagnostic guidelines in 2005. Because the black Lip-Philtrum Guide was not available at the time the South African population was being diagnosed, the South African population may not have been an appropriate population to include in the formulation of the Hoyme guidelines. (3) The Hoyme guidelines described the Lip-Philtrum Guide as follows: "A score of 1 is considered completely normal, whereas a score of 5 is most indicative of FAS."[8] This is incorrect; a score of 1 is highly abnormal. The Lip-Philtrum Guide reflects a normal curve in which rank 3 is the mean (50th percentile) and ranks 1 and 5 reflect the extreme ends of the normal curve (<2.5th percentile and >97.5th percentile, respectively). Rank 4 for the lips and philtrum is not 4 ranks above normal but only 1 rank above normal. Therefore, relaxation of the facial criteria to just 2 of the 3 features, while allowing the 2 features to be expressed near or within the normal range (rank 4 or 10th percentile), would identify a preponderance of individuals with normal facial phenotypes. This is exactly what occurred when the Hoyme FAS facial criteria were applied to the FAS DPN clinical population and a control population of children with confirmed absence of prenatal alcohol exposure. (4) Finally, Hoyme et al[8] reported, "Our aim was to improve both the reliability and validity of diagnoses within the FASD continuum." They concluded, "Application of our guidelines to our extensive database of children prenatally exposed to alcohol demonstrated that the method was rigorous and accurate."[8] The authors convey an important point, that is, guidelines should undergo rigorous evaluation of their performance. However, the authors did not report standardized measures of reliability (eg, test-retest and interrater reliability), validity (eg, construct validity, convergent validity, and criterion validity), or accuracy (eg, sensitivity, specificity, and positive and negative predictive values). These measures have been assessed, confirmed to be high, and published for the 4-Digit Code.[4,11–14]

Hoyme et al[8] used data for 164 children to formulate their FASD diagnostic guidelines. These children were diagnosed originally by May and colleagues[21,22] between 1998 and 2003, with a gestalt approach to diagnosis. Hoyme et al[8] reported that 97 of the 164 children received an original gestalt diagnosis of FAS. When Hoyme et al[8] applied their 2005 guidelines to the 164 children, only 59 of the 97 children retained their diagnosis of FAS. Ten of the 59 children did not have confirmed

prenatal alcohol exposures. The remaining 38 received revised diagnoses across the entire spectrum of FASD, documenting the magnitude and prevalence of errors in the original FAS diagnoses. Sixteen of those who were diagnosed originally as having FAS were reclassified as having ARND (ie, reclassified from the full FAS facial phenotype to a complete absence of the FAS facial phenotype). The inaccurate and highly variable diagnostic outcomes that result from the gestalt approach to diagnosis were demonstrated in 2000 by Astley and Clarren.[4] When the 1997 version of the 4-Digit Code was applied to 69 patients who had received previously a gestalt diagnosis of FAS at the University of Washington FAS DPN clinic, only 9 maintained their FAS diagnosis. Sixty lost their diagnosis of FAS because 37 had no evidence of growth deficiency, 27 had only 1 of the 3 FAS facial features, 29 had no psychometric or structural evidence of brain damage, and 5 had unknown exposure to alcohol. The extraordinarily high FAS prevalence rates (40.5–46.4 cases per 1000 subjects) reported by May et al[21] for a South African community were based on FAS diagnoses that Hoyme et al[8] reported were inaccurate and overestimated.

The Potential to Overdiagnose Alcohol-Related Disabilities

Another marked contrast between the 4-Digit Code and the Hoyme guidelines is in the use of the terms ARND and ARBD. The Hoyme guidelines use the terms, and the 4-Digit Code does not. Both sets of guidelines acknowledge that growth deficiency and CNS damage/dysfunction are not specific to prenatal alcohol exposure, a fact that has been accepted in the field of FASD from the start.[20] With regard to the diagnosis of individuals who present with prenatal alcohol exposure and CNS damage/dysfunction but no FAS facial phenotype, Hoyme et al[8] expressed the following concern about the 4-Digit Code.

> 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.

To the contrary, the 4-Digit Code cannot overdiagnose alcohol-related disabilities because the 4-Digit Code does not render "alcohol-related" diagnoses. The only diagnoses that the 4-Digit Code links causally (or relates) to prenatal alcohol exposure are FAS and Partial FAS. This is the most important feature of the 4-Digit Code that distinguishes it from all other FASD diagnostic guidelines. The 4-Digit Code was developed with 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 in a clinic 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. Current medical technology is unable to confirm or to exclude the etiologic role of alcohol for an individual patient. This does not pose a problem, however. An accurate diagnosis and effective intervention can proceed without confirmation of an etiologic role of alcohol. When an individual presents with CNS damage/dysfunction and prenatal alcohol exposure, the 4-Digit Code names it exactly what it is, that is, static encephalopathy/alcohol exposed if the CNS damage/dysfunction is severe or neurobehavioral disorder/alcohol exposed if the CSN dysfunction is less severe. The terms do not state or imply a causal association between the exposure and outcomes. Rather, including the phrase "alcohol exposed" in the diagnostic terms serves to alert clinical providers that the individual was exposed to a teratogen and thus is at risk for underlying brain damage. Knowledge of this risk is important, because the presence of underlying brain damage could affect the clinician's future care and intervention efforts for that patient. In contrast to the 4-Digit Code, when an individual presents with CNS damage/dysfunction and prenatal alcohol exposure but no FAS facial phenotype, the Hoyme FASD guidelines label the condition alcohol-related neurobehavioral disorder, stating that the patient's neurobehavioral disorder is related to their alcohol exposure. Aase et al[23] argued effectively that clinical use of the term fetal alcohol effects, with its implications of causation, should be abandoned. Those same arguments apply to ARND and ARBD. Clinicians new to the field of FASD diagnosis are encouraged to read that seminal article. Aase et al[23] 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." This is exactly what the 4-digit code does. To convey more completely this important and unique feature of the 4-Digit Code, the guidelines provide clinical summary templates for static encephalopathy/alcohol exposed and neurobehavioral disorder/alcohol exposed, which include the following statement: "The diagnosis of static encephalopathy (or neurobehavioral disorder) 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 ex-

posures or problems during pregnancy, and various experiences since birth."[3,5] The 4-Digit Code devotes an entire chapter and 4-Digit ranking system to documentation of other prenatal (including genetic) and postnatal exposures and events that occur frequently with prenatal alcohol exposure and likely contribute to the outcomes observed for individuals.[3,5] In fact, the vast majority of the 952 patients seen in the University of Washington FAS DPN clinic presented with multiple risk factors (81% were exposed to illicit drugs in utero, 25% had poor prenatal care, 29% had other complications during pregnancy, 2% had other syndromes, 25% were physically or sexually abused, and 70% were in foster/adoptive care). The impact of prenatal alcohol exposure is never assessed in isolation from other risk factors. The Hoyme guidelines 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."[8] Overlap between individual symptoms/anomalies is common throughout medicine. An astute clinician would not mistake FAS for William's syndrome simply because the 2 have some but not all features in common, because it is the constellation of features that distinguish the 2 syndromes. The statement that FASD diagnostic criteria should be applied only if there is no indication of another genetic syndrome implies that alcohol is not a teratogen to a child born with another syndrome. Clearly this is not true. A FASD diagnostic team should consider alternative or co-occurring syndromic diagnoses and medical conditions at all times.

CONCLUSIONS

Accurate, reliable, medical diagnoses across the full continuum of FASD have been available to families and clinicians for almost 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 designation of FASD is made, 2 individuals are affected directly, namely, 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.

It is critical to identify all individuals at risk for FASD. This is achieved through screening and not through relaxation of diagnostic criteria. Screening criteria typically use relaxed diagnostic criteria to identify correctly all individuals with the disease (true-positive results). However, this comes at the risk of incorrectly identifying some individuals who do not have the disease (false-positive results). All subjects identified as screen-positive receive a comprehensive diagnostic evaluation. It is at that time that accurate diagnoses are rendered and the false-positive screens are confirmed to be false-positive results. Through this process, an individual may receive a false-positive screening outcome. No one should receive a false-positive diagnosis, however.

Patients and their families deserve accurate diagnoses. Effective intervention and prevention require accurate diagnoses. Professionals now have access to several FASD diagnostic guidelines. Ultimately they will decide which guidelines are adopted into practice. Their decision will be influenced in large part by a measure of validity that is not easily quantified, namely, construct validity, the extent to which the guidelines produce meaningful results that are commensurate with their clinical impression.

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