VALIDATION OF THE FETAL ALCOHOL SPECTRUM DISORDER (FASD) 4-DIGIT DIAGNOSTIC CODE

Susan J Astley
Professor of Epidemiology and Pediatrics, University of Washington, Seattle WA

ABSTRACT

Background
The fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code has been used by interdisciplinary diagnostic teams worldwide for 17 years. It was created to improve the ease, accuracy, and reproducibility of diagnoses across the full spectrum of FASD. Over the years, a number of FAS/D diagnostic guidelines have been proposed. As the field of FASD moves forward, it will be important to adopt a single set of diagnostic guidelines worldwide. To achieve this, the performance (validity) of current diagnostic guidelines must be rigorously assessed and reported.

Objective
To summarize the body of evidence that has amassed over 20 years that validates the performance of the FASD 4-Digit Diagnostic Code.

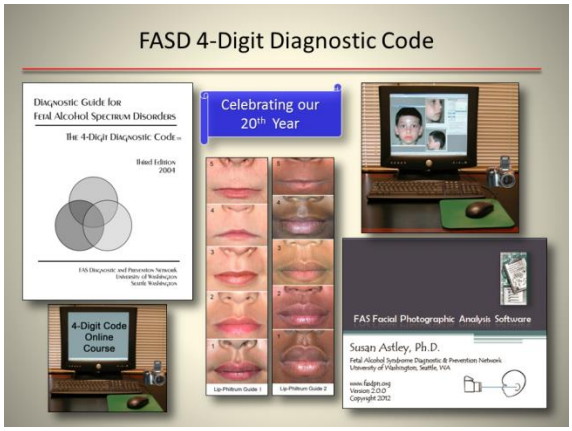
Methods
The evidence validating the 4-Digit Code is documented across 35 studies published between 1992 and 2012, including new information presented in this report. These studies and data sources include the delineation of the FAS facial phenotype; creation of the 4-Digit Code (1997-2004); our 10-year, foster-care FAS screening program; our MRI/fMRI/MRS studies; analysis of 2,550 individuals evaluated for FASD over 20 years in the WA State FASDPN clinics, and analysis of 622 patient satisfaction/follow-up surveys; surveys of 10,000 professionals attending the University of Washington FASD diagnostic clinic trainings; and surveys of over 700 professionals worldwide who completed the 4-Digit Code Online Course.

Conclusion
The 4-Digit Code is a simple, comprehensive, evidence-based, validated diagnostic system. It has served as the cornerstone of a fully integrated FASD screening, diagnostic, intervention, prevention, and surveillance program in Washington State for the past 20 years.

Key Words: *Fetal alcohol spectrum disorders (FASD), fetal alcohol syndrome (FAS), diagnosis, validity, 4-Digit Diagnostic Code, FAS Diagnostic & Prevention Network (FASDPN)*

The fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code has been used by interdisciplinary diagnostic teams worldwide for 17 years (Figure 1).[1-3] It was created to improve the ease, accuracy, and reproducibility of diagnoses across the full spectrum of FASD.[4] Over the years, a number of FAS/D diagnostic guidelines have been proposed.[5-8] As the field of FASD moves forward, it will be important to adopt a single set of diagnostic guidelines worldwide.[9] To achieve this, the performance (validity) of current diagnostic guidelines must be empirically assessed and reported. The purpose of this report is to pull together the body of evidence that has amassed over 20 years that validates the performance of the FASD 4-Digit Diagnostic Code. This report highlights key evidence, directing readers to the source publications for more details.

FIG. 1 A. The FASD 4-Digit Diagnostic Code is supported by a number of tools including the Guidelines, Lip-Philtrum Guides, FAS Facial Photographic Analysis Software, and Online Course. All are distributed free or at cost on the FASDPN website. B. Interdisciplinary diagnostic team.



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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.[5,10-13] 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 and preventable cause of intellectual disabilities in the Western World.[14] The prevalence of FAS is estimated to be 1 to 3 per 1,000 live births[5] in the general U.S. 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.[15]

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.[16-19] 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), Static Encephalopathy / Alcohol Exposed (SE/AE), and Neurobehavioral Disorder / Alcohol Exposed (ND/AE) fall under the umbrella of FASD[4].

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.[20] 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, events, and conditions.

In the absence of objective, accurate, and reproducible methods for measuring and recording the severity of exposures and outcomes in individual patients, diagnoses use to vary widely from clinic to clinic.[4,5,21-23] From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities, and missed opportunities for primary prevention.[4] From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence.[4,5,8,23] 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.[4,15,24] 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.[4,16,25,26] Non-standardized diagnostic methods also thwart valid efforts to compare outcomes between research studies.[16,17,27]

FASD Diagnostic Guidelines

FASD diagnostic guidelines have evolved over time since the term FAS was first coined in the medical literature in 1973.[9] Early guidelines were gestalt (purposely broad and conceptual) in nature and administered primarily by geneticists and dysmorphologists.[4,9] The Institute of Medicine (IOM) FASD guidelines[5] published in 1996 would be the last in this line of gestalt approaches to diagnosis. In 1997, the FASD 4-Digit Diagnostic Code was introduced to overcome the limitations of the gestalt approach to diagnosis.[1] It proposed an interdisciplinary approach to diagnosis guided by rigorously and empirically case-defined criteria.[20] In 2004-2005, three additional FAS/D diagnostic guidelines were published: the CDC FAS guidelines[6] in July 2004; the Revised IOM FASD guidelines[8] in January 2005, and the Canadian FASD guidelines[7] in March 2005. The 4-Digit Code was subsequently updated in January, 1999[2] and November 2004.[3] 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.[9] 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 large clinical sample of 1,014 individuals of all races and ages (birth to 51 years of age).[4] Empirical methods were used both to develop[28-30] and validate the performance of the 4-Digit Code.[4,9,15-17,23-26] The CDC[6] and Canadian[7] guidelines were federally mandated and commanded a more consensus-driven process. These guidelines were not empirically validated prior to publication. The Revised IOM[8] 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 gestalt guidelines: the 1996 IOM Guidelines. All four of these guidelines have been compared/contrasted in detail by Astley in 2010.[9] In Astley's summary remarks, she reports "*The field should strive to adopt a single set of diagnostic guidelines for FASD*". This same conclusion was drawn at a recent meeting of FASD diagnostic guideline authors at the March 2013 International FASD conference in Vancouver British Columbia. It is important to note that the process of selection has long been underway by clinicians worldwide. It is clinicians who will ultimately decide which diagnostic guidelines best meet their needs and the needs of their patients and families. To guide this selection process, it will be essential for the authors of the various guidelines to validate (assess the performance) of their guidelines. Validity must be confirmed, not assumed, through properly designed empirical studies.[5]

Assessing a Diagnostic Tool's Performance (Validity)

Validity is the degree to which a tool (or diagnostic system) is measuring what it purports to measure.[31] Validity is not determined by a single statistic, but by a body of research that demonstrates the relationship between the diagnostic system and the condition it is intended to measure. There are three overarching forms of validity: **content validity, criterion validity, and construct validity**. **Content Validity** is a measure of how well the items in the diagnostic system represent the entire range of possible items the diagnostic system should cover. **Criterion validity** is a measure of a diagnostic tool's accuracy relative to a gold standard. **Construct validity** refers to the degree to which a test measures what it claims, or purports, to be measuring. It refers to the ability of a measurement tool to measure the physiological concept being assessed. Convergent and discriminant validity are two subtypes of construct validity. **Convergent validity** refers to the degree to which two measures of constructs that theoretically should be related are in fact related. In contrast, **discriminant validity** tests whether concepts or measurements that are supposed to be unrelated are in fact unrelated. An important aspect of clinical research is the inference that an association represents a cause-effect relationship. Features of associations that support causation include: the strength of the association; the consistency of observed evidence; specificity of the relationship; temporality of the relationship; the biological gradient of dose-response, biological plausibility; and experimental confirmation. **Predictive validity** refers to a tool's ability to predict something is should theoretically be able to predict. **Precision (Accuracy)** is the degree to which a measurement procedure produces the correct answer. **Reliability (Reproducibility)** is the degree to which a measurement procedure produces the same result each time. **Test-Retest Reliability** is the variation in measurements taken by a single person on the same item and under the same conditions**. Inter-rater Reliability** is used to assess the consistency of a test across two or more raters. **Intra-rater Reliability** is the degree of agreement among multiple repetitions of a diagnostic test performed by a single rater. Statistical measures used to assess these constructs include linear correlation coefficients, tests for trends, and Kappa statistics. Fundamental measures of diagnostic accuracy include sensitivity and specificity. The **sensitivity** of a test is the proportion of people with the condition who test positive for it (the true positive rate). The **specificity** of a test is the proportion of people who do not have the condition who test negative for it (the true-negative rate). **Positive Predictive Value (PPV)** is the probability that a patient with a positive test result really does have the condition. **Negative Predictive Value (NPV)** is the probability that a patient with a negative test result really does not have the condition. The body of research presented below that validates the performance of the FASD 4-Digit Code utilized all of these measures.

Introduction to the FASD 4-Digit Code

The FASD 4-Digit Code is described in full by Astley.[3] 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 (Figure 2A). 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. There are a total of 102 4-Digit Codes that fall broadly under the umbrella of FASD (Table 2). These codes cluster under four clinically meaningful FASD diagnostic subcategories: fetal alcohol syndrome (FAS): Diagnostic Categories A and B; Partial FAS (PFAS): Diagnostic Category C; Static Encephalopathy/Alcohol-Exposed (SE/AE): Diagnostic Categories E and F; and Neurobehavioral Disorder/Alcohol-Exposed (ND/AE): Diagnostic Categories G and H (Figure 2B). The attributes of the 4-Digit Code are summarized in Table 3

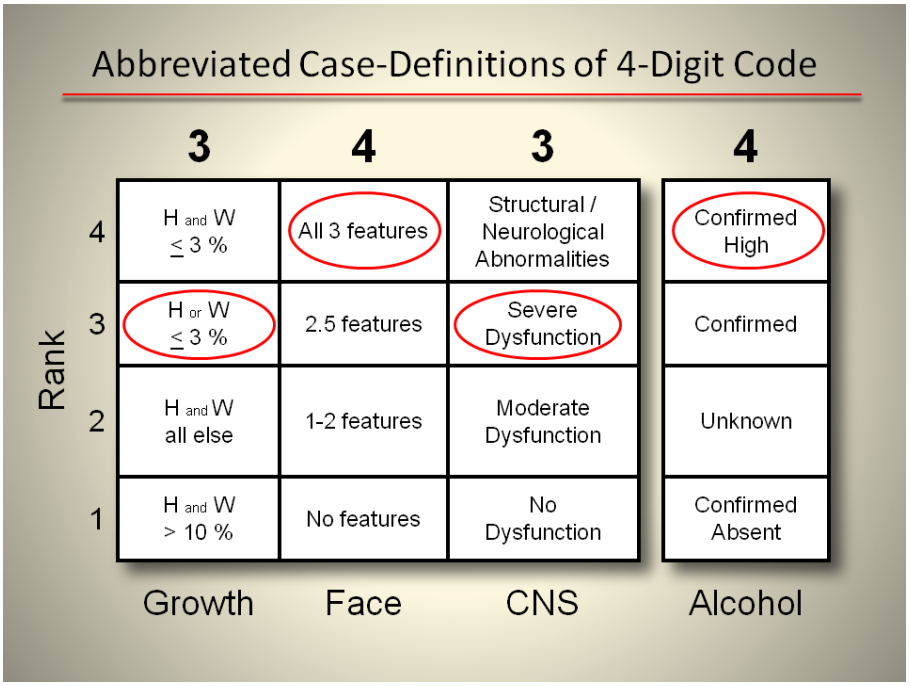
A Validation Guide

As clinicians assess the performance of FAS/D Diagnostic Guidelines, they may find the list of questions presented in Table 1 a helpful guide.

TABLE 1: As clinicians assess the performance of FASD diagnostic guidelines, clinicians should ask the following questions. The answer to all of these questions is 'yes' for the FASD 4-Digit Diagnostic Code.

1. Have properly designed studies been published to confirm the case definition for the FAS facial phenotype is highly specific (>95%) to FAS and alcohol (e.g. observed only among individuals with prenatal alcohol exposure and FAS)?
2. Was data used to empirically derive the diagnostic guidelines? Was the data drawn from a large, representative, population-base?
3. Has the performance of the guidelines been empirically assessed (validated)?
4. Individuals are born with FAS/D. Can the diagnostic system identify FAS/D at birth and across the lifespan?
5. Growth deficiency, the FAS facial phenotype, CNS abnormalities, and alcohol exposure all present along clinically meaningful continuums. The FAS facial phenotype is not just present or absent. The brain is not just normal or abnormal. Do the Guidelines recognize/incorporate these important continuums?
6. Do the guidelines produce clinically distinct subgroups across the full spectrum (FAS, PFAS, SE/AE, ND/AE)?
    A. Do brain imaging studies identify statistically significant contrasts between the FASD subgroups?
    B. Individuals with FAS have more severe CNS dysfunction than individuals with "ARND". Do the Guidelines generate FAS and "ARND" groups that demonstrate this important contrast?
    C. Do individuals who meet the criteria for FAS actually have FAS?
7. Can the guidelines detect unique alcohol exposure patterns between the FASD subgroups?
8. Can the diagnostic system be effectively and efficiently taught to interdisciplinary teams?
9. Are the guidelines confirmed to be reproducible? If two clinics use the guidelines, do they render the same diagnoses?
10. Do families report high satisfaction/confidence with the diagnostic process/outcome?
11. Are the names of the diagnoses (FAS, PFAS, SE/AE, ND/AE) medically valid? Do they imply causality between alcohol and outcome that cannot be confirmed in the individual patient?
12. Do diagnoses under the umbrella of FASD qualify patients for intervention services that lead to improved outcomes?

FIG. 2 A. Abbreviated case-definitions of the FASD 4-Digit Code.[3] The 4-Digit Code 3434 is one of 12 Codes that fall under the diagnostic category FAS (Table 2). B. The 4-Digit Code produces four diagnostic subgroups under the umbrella of FASD: FAS, PFAS, SE/AE, and ND/AE.[16,26] The 4-Digit Code uses the terms SE/AE and ND/AE in place of the term ARND.



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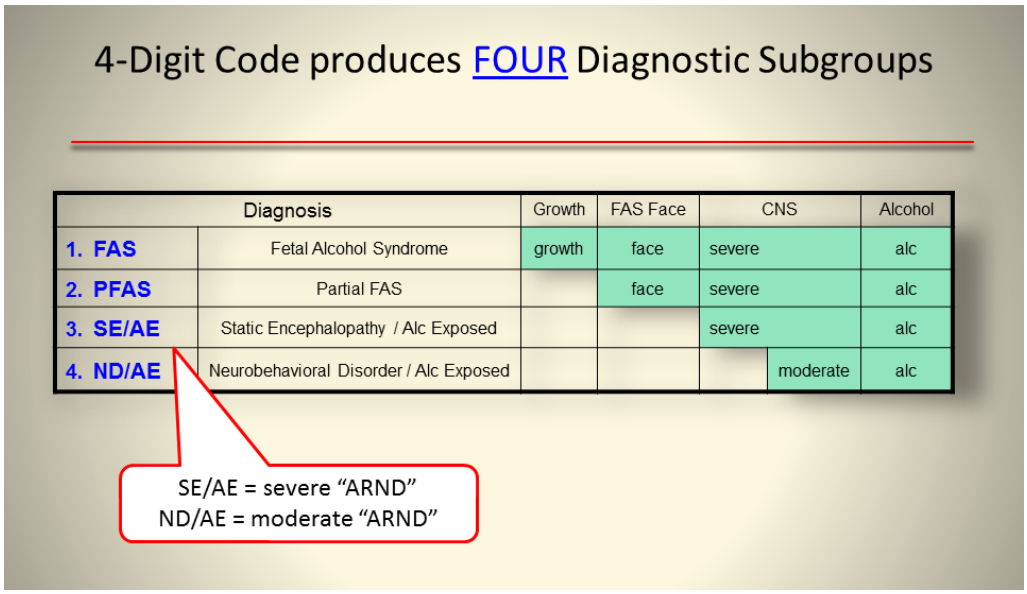

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TABLE 2 4-Digit Diagnostic Codes within each FASD Diagnostic Category (2004)[3]

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
1334	1434	2334	3334
1343	1443	2343	3343
1344	1444	2344	3344

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

TABLE 3 Key Attributes of the FASD 4-Digit Diagnostic Code.[4]

1. Greatly increases diagnostic precision and accuracy through the development of objective, quantitative measurement scales (e.g., Lip-Philtrum Guides), facial analysis software, and specific, operational case definitions.
2. Diagnoses the full spectrum of outcomes across the lifespan.
3. Was developed empirically using a large, representative, population-base.
4. Offers 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.
5. Uses the universal language of numbers, thus facilitating ease of reporting worldwide. The numeric base also allows rapid and easy update of large datasets as diagnostic criteria are refined.
6. Establishes 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.
7. Establishes diagnostic subclassifications that capture the full spectrum of FASD without inferring alcohol is the sole causal agent.
8. Documents all other prenatal and postnatal adverse exposures and events that can also impact outcome.
9. Provides a quantitative measurement and reporting system (the 4-Digit Code) that can be used independent of the diagnostic nomenclature.
10. Has received extensive assessment/validation of its performance.
11. Was designed for use by an interdisciplinary FASD diagnostic team.
12. Is readily taught to interdisciplinary teams through an Online Course, thus greatly expanding the availability of diagnostic services worldwide.
13. Qualifies patients for intervention services that produce improved outcomes.
14. Receives high satisfaction/confidence ratings from families and clinicians

Data sources used to assess/validate the FASD 4-Digit Diagnostic Code

The 4-Digit Code is a simple, comprehensive, evidence-based, validated diagnostic system (Figure 1).[9] The performance of the 4-Digit Code was assessed (validated) prior to its initial release in 1997 and extensively thereafter. The evidence supporting the validation of the 4-Digit Code is documented across over 35 studies published between 1992 and 2012, including new information presented in this report. These studies include the empirical delineation of the FAS facial phenotype (1992-2001)[25,28-30,32]; the creation and updates of the 4-Digit Code (1997-2004)[1-3]; a 10-year population-based FAS active screening/surveillance study of foster care using 2D facial photographs and the FAS Facial Photographic Analysis Software (1999-2009)[15,24,33]; WA State Pregnancy Risk Assessment Monitory System (PRAMS) public health surveillance data documenting annual maternal use of alcohol during pregnancy (1993-99)[34]; the MRI/fMRI/MRS studies (2002-2007)[16,17,27,35]; analysis of over 2,000 fields of data

on over 2,550 alcohol-exposed individuals evaluated for FASD over the course of 20 years in the seven WA State FASDPN clinics (1993-2013)[26], analysis of 577 patient satisfaction/follow-up surveys over 20 years[26]; surveys of over 10,000 professionals attending the UW FASD diagnostic clinic trainings (1993-2013); and surveys of over 700 professionals worldwide who completed the 4-Digit Code Online Course (2004-2013).

A synopsis of the published evidence validating the performance of the 4-Digit Code is presented in Table 4. Each entry in Table 4 is described in full in the body of this report, identified numerically to match the entry in Table 4.

TABLE 4 Synopsis of published evidence validating the performance of the FASD 4-Digit Code. Each entry in this Table is described in full in the body of this report.

1. The 4-Digit Code was created in 1997 to overcome the limitations of the gestalt approach to FASD diagnosis used from 1973-1996. Its advanced performance was empirically confirmed prior to its publication. The 4-Digit Code:
    A. Produced more accurate, homogeneous diagnostic subgroups.
    B. Detected clinically important correlations between growth, face, brain, and alcohol that the gestalt method failed to detect.
    C. Demonstrated high inter- and intra-rater reliability.
    D. Had a FAS facial phenotype with confirmed high sensitivity and specificity to FAS and prenatal alcohol exposure.
2. The Quintessential Role of the FAS Facial Phenotype
    A. The full FAS Facial Phenotype (Rank 4):
        1. Is confirmed to be highly sensitive and specific (>95%) to FAS and alcohol and does not vary by race, gender or age.
        2. Serves as the most efficient/effective way to screen for FAS in population-based samples
        3. Is uniquely correlated with significantly and disproportionately smaller frontal lobe volumes which is consistent with midventral forebrain deficiencies associated with facial dysmorphia observed in animal studies of alcohol teratogenicity.
        4. Is quintessential to the validity of all diagnoses under the umbrella of FASD, not just FAS.
    B. The FAS Facial Phenotype presents on a Continuum:
        1. Presents on a continuum that is significantly correlated with (predictive of) abnormal brain structure and function.
        2. Can be measured easily and accurately from a 2D photo using the FAS Facial Photographic Analysis Software.
3. The 4-Digit Code's method for case-defining the highly variable CNS dysfunction that typifies FASD demonstrates high construct validity.
    A. The 4-Digit Code's method for classifying CNS dysfunction (CNS Ranks 1, 2, and 3) successfully predicts underlying CNS structural abnormality, as it was designed to do. For example, the more severe the CNS dysfunction (CNS Ranks 1,2 and 3), the smaller the caudate volume.
    B. Microcephaly predicts severe CNS dysfunction among infants/toddlers who present with the full Rank 4 FAS facial phenotype.
4. The 4-Digit Code generates four distinct diagnostic subgroups (FAS, PFAS, SE/AE, and ND/AE), under the umbrella of FASD.

A. The 4 diagnoses are clinically and statistically distinct and span the full continuum of FASD.

1. Individuals with FAS have growth deficiency, those with PFAS do not.
2. Only FAS/PFAS have the FAS face, small frontal lobe volumes, and reduced choline levels.
3. Only FAS/PFAS and SE/AE have small caudate volumes.
4. FAS/PFAS have more severe CNS dysfunction than SE/AE.
5. SE/AE have more severe CNS structural/functional abnormalities than ND/AE.
6. ND/AE have CNS structural abnormalities underlying their moderate CNS dysfunction.
7. Even families detect/report clear distinctions between the diagnostic subgroups.

B. Extensive evidence validates the inclusion of individuals with moderate dysfunction (ND/AE) under the umbrella of FASD.

C. The term ARND (like Fetal Alcohol Effects) should be abandoned and replaced with medically valid terms like SE/AE and ND/AE that do not imply causation.

5. The 4-Digit Code's method of documenting prenatal alcohol exposure not only detects significant correlations between exposure and outcomes, but also detects exposure patterns that distinguish the diagnostic subgroups.

A. The 1-page standardized form used to record prenatal alcohol exposure patterns effectively addresses the challenges of documenting exposure. Full information is rarely available. Despite this, the 4-Digit Code method can:

1. Detect significant correlations between alcohol exposure and measures of growth, face, and CNS abnormalities.
2. Identify exposure patterns among FAS/PFAS that are distinct from SE/AE and ND/AE.

B. The prevalence of maternal alcohol use during pregnancy correlates with the prevalence of FAS as defined by the 4-Digit Code.

C. An 'excessive' alcohol exposure history should not be required for a diagnosis under the umbrella of FASD for the following reasons:

1. As tools become more sensitive, our ability to detect adverse outcomes improves.
2. Risk varies among individuals, even between twins.
3. Sends the wrong public health message "moderate exposure is safe?"
4. Reliable histories on quantity/frequency/timing of exposure are rarely available.
5. Only allowing high exposures to be associated with adverse outcomes prevents identifying the true dose-response relationship between alcohol and adverse outcomes.

6. The 4-Digit Code has been effectively and efficiently taught to interdisciplinary FASD diagnostic teams worldwide through an inexpensive Online Course.

7. The 4-Digit Code is reproducible across clinics. Of 677 patients diagnosed across 7 WA FASD Clinics, >93% received a diagnosis that matched the diagnosis rendered by the core clinic at the University of Washington.

8. Families report high satisfaction and confidence with the interdisciplinary approach to FASD diagnosis using the 4-Digit Code.

9. Patient follow-up surveys confirm all FASD diagnoses (FAS, PFAS, SE/AE, and ND/AE) provided equal access to intervention services that led to improved outcomes.

1 The 4-Digit Code was created in 1997 to overcome the limitations of the gestalt approach to FASD diagnosis. Its advanced performance relative to the gestalt approach was empirically confirmed prior to its publication.

When the University of Washington CDC-sponsored FASD diagnostic clinic first opened in January 1993, it was the first to propose/implement an interdisciplinary approach to diagnosis.[20,36-38] The interdisciplinary team (medical doctor, psychologist, speech language pathologist, occupational therapist, social worker, and family advocate) used the most current FASD diagnostic guidelines available at that time; the 1989 gestalt diagnostic criteria published by Sokol and Clarren.[13] In 1996, the IOM published an updated set of FASD diagnostic guidelines[5], but continued to propose a gestalt approach. The gestalt approach to diagnosis presented with many limitations as outlined in Astley & Clarren.[1,4] The 4-Digit Code was created in 1997 to overcome these limitations.[1] The medical/research records of the first 1,014 patients diagnosed at the Washington State FAS Diagnostic and Prevention Network of clinics were used to develop the 4-Digit Diagnostic Code.[4] Importantly, this was a representative statewide population of patients spanning all ages and races. To assess the performance of the 4-Digit Code, the subset of 454 patients who had received a gestalt diagnosis under the umbrella of FASD (FAS, atypical FAS, or possible fetal alcohol effect (PFAE)) were retroactively coded on the 4-Digit Code to empirically compare the FASD classification outcomes of the two diagnostic systems.[4] The superior performance of the 4-Digit Code relative to the gestalt approach to diagnosis is briefly summarized below.

1A The 4-Digit Code produced homogeneous FASD diagnostic subgroups. The gestalt method of diagnosis produced highly variable FASD diagnostic subgroups.

For example, of the first 454 patients who received a gestalt diagnosis under the umbrella of FASD, 69 were classified as FAS. In the absence of rigorous guidelines, this group was very heterogeneous.[4] Of the 69 subjects with a gestalt diagnosis of FAS: only 32 had growth deficiency ($\leq$10th percentile); only 27 had the Rank 4 FAS face; and only 40 had significant CNS structural/functional abnormalities. When the more rigorous 4-Digit Code was applied to the 69 with a gestalt diagnosis of FAS only 9 of the 69 retained a diagnosis of FAS. Twelve were reclassified to Partial FAS; 18 were reclassified to Static Encephalopathy /Alcohol Exposed (SE/AE); 26 were reclassified to Neurobehavioral Disorder / Alcohol Exposed (ND/AE); and 4 were not even on the spectrum (exposure unknown).

1B The 4-Digit Code detected clinically important correlations between growth, face, brain, and alcohol that the gestalt method failed to detect.

Inter-correlations between growth, face, brain, and alcohol, confirmed to exist in laboratory-based studies of alcohol teratogenicity[29,39], were completely absent in our clinical population when the gestalt method was used, and strongly significant when the 4-Digit Code was used. For example, the hypothesis that the full-scale intelligence quotient (FSIQ) decreases with increasing magnitude of expression of the FAS facial phenotype was tested among 216 patients who had been diagnosed by both the gestalt and 4-Digit diagnostic systems.[4] Of the 216 patients, 31 were identified as having the gestalt FAS facial phenotype. The difference in the mean FSIQ between the patients with and without the gestalt FAS facial phenotype (82.3 and 85.0 respectively) was not statistically significant ($t = -1.56$, $p = 0.13$). In contrast, when the same 216 patients were classified by their 4-point Likert rank reflecting the magnitude of expression of the 4-Digit Code FAS facial phenotype, the difference in the mean FSIQ between the patients with and without the full FAS facial phenotype (78.5 and 87.7 respectively) was statistically significant ($t = 2.3$, $p = 0.02$). More importantly, a statistically significant, inverse, linear association was revealed. The mean FSIQs among the patients

with FAS Facial Ranks of 4 (severe), 3 (moderate), 2 (mild), and 1 (absent) were 78.5, 83.8, 84.8 and 87.7 respectively ($f = 4.1$, $p = 0.04$). Thus, a clinically important linear association between face and brain that was detected by the 4- Digit Code, failed to be detected by the gestalt method of diagnosis. This illustrates two important points: First, in the absence of specific case definitions, the gestalt approach results in diagnostic misclassification. This explains why the mean FSIQs for the groups with and without the gestalt FAS facial phenotype did not differ significantly. Individuals who truly did not have the FAS facial phenotype were misclassified as having the gestalt FAS face. Their inclusion in the gestalt FAS group erringly elevated the mean FSIQ for that group. Note the mean FSIQ for the gestalt FAS facial group was 82.8 while the mean FSIQ for the 4-Digit Rank 4 FAS facial group was 78.5. Second, the gestalt method of diagnosis records the FAS facial phenotype on a dichotomous scale (present, absent). The 4-Digit Code records the FAS facial phenotype on a 4-point Likert scale (Rank 1. Absent; Rank 2. mildly present; Rank 3. moderately present; Rank 4. severely present). In reality, growth, face, brain and alcohol all present along clinically meaningful continuums. The 4-Digit Code captures all outcomes and exposures on ordinal or continuous scales. Ordinal and continuous scales have far greater statistical power than dichotomous (e.g., present, absent) scales to detect important correlations that will not only advance our understanding of FASD, but provide us with more sensitive diagnostic tools. For example, one challenge in FASD diagnosis is to confirm or rule-out CNS dysfunction in children too young to participate in comprehensive neuropsychological testing. We now know that the subset of young children at greatest risk for CNS dysfunction is the subset who present with a Rank 2, 3 or 4 FAS facial phenotype. The higher the facial rank, the higher the risk.[9,25] The face is such a strong predictor of underlying CNS dysfunction, we recommend these children receive early intervention based on the presence of this physical risk factor. Postponing intervention until CNS dysfunction manifests would deny the child access to the benefits of early intervention. The correlation between the magnitude of expression of the 4-Digit FAS facial phenotype and CNS abnormality is presented more fully in section 2B.

1C The 4-Digit Code had confirmed high inter-rater and intra-rater reliability.

A core goal of the 4-Digit Code was to establish a diagnostic system that was reproducible (reliable) across clinicians and clinics. No matter where a patient was seen, they would receive the same FASD diagnostic outcome. This diagnostic precision and accuracy were achieved through the development of objective, quantitative measurement scales (e.g. Lip-Philtrum Guides) and specific, operational case definitions. The creation of the FAS Facial Photographic Analysis Software[33,40], web-based instructional videos and animations, and the FASD 4-Digit Code Online accredited course[41] further enhanced diagnostic precision and accuracy. This rigorous, case-defined approach is what sets the 4-Digit Code apart from the gestalt approach to diagnosis. The Code's reliability was confirmed to be high prior to its publication.[4] The 4-Digit Codes of 20 randomly selected patient files were re-derived independently by two clinicians, while masked to the original 4-Digit code that had been derived 1-4 years ago by the University of Washington diagnostic team. The re-derived codes matched the original 4-Digit Codes across all four digits for all 20 subjects (inter- and intra-rater reliability was 100%, ($Kappa = 1.0$, $p = 0.000$). The 4-Digit Codes for the 20 randomly selected patients spanned the entire spectrum of Neurobehavioral Disorder to Partial FAS (1124 to 1444). Inter-rater reliability between the six FASDPN regional clinics and the University of Washington FASDPN Core clinic resulted in an exact match across all four digits on 15 of 16 (94%) patients ($Kappa = 0.93$, $p = 0.000$) and an exact match on Diagnostic Category on all 16 (100%) of the patients ($Kappa = 1.0$, $p = 0.000$). The one 4-Digit code that did not match was coded by the regional FASDPN clinic as 1223 and the University FASDPN clinic as 1123. The mismatch in the facial score was due to the network physician not pulling the epicanthal fold back before measuring

the palpebral fissure length resulting in an underestimate of the length. Diagnostic inter-rater reliability between the six FASDPN regional clinics and the University of Washington FASDPN Core clinic continues to be high (93% match in FASD Diagnostic Category across 677 patients over the next 18 years (Kappa = 0.92, p = 0.000)).

1D The Rank 4 FAS facial phenotype was confirmed to have high sensitivity and specificity to FAS and prenatal alcohol exposure.

Prior to the creation of the 4-Digit Code, a decade of research was conducted to empirically identify and case-define the cluster of minor facial anomalies that were most sensitive and specific (>95%) to FAS and prenatal alcohol exposure.[15,25,28-30,32] This is described more fully below.

2 The quintessential role of the FAS facial phenotype.

The FAS facial phenotype is the cornerstone of FASD diagnostic guidelines (Table 5). Two core principles are important to understand: 1) The high sensitivity and specificity of the full FAS facial phenotype is essential to the validity of all diagnoses under the umbrella of FASD, not just the diagnosis labeled FAS. 2) The FAS face is not simply present or absent. It presents on a clinically meaningful continuum that is highly predictive of underlying structural and functional brain abnormalities. Each of these principals is discussed more fully below.

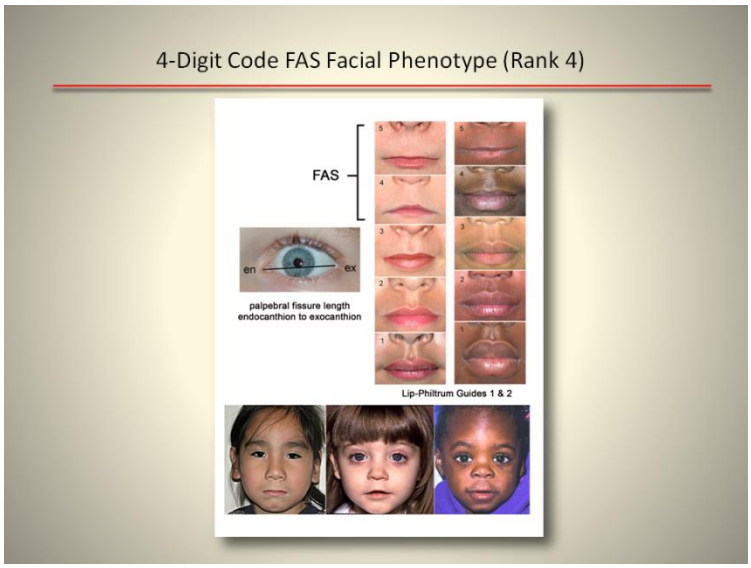
TABLE 5 4-Digit Code FAS facial phenotype fundamentals.

1. Empirically identified and case-defined 18 years ago.
2. Presents along a clinically meaningful continuum (absent, mild, moderate, severe: Facial Ranks 1,2, 3, 4 respectively).
3. This continuum is significantly correlated with (predictive of) brain abnormality. The more severe the face, the more severe the underlying structural and functional brain abnormality.
4. This face can be identified across all ages and races and does not diminish with age.
5. The Rank 4 FAS Face is confirmed to be highly sensitive and specific (>95%) to FAS and prenatal alcohol exposure. This high specificity is the only reason a diagnosis of FAS to be rendered when alcohol exposure is unknown.
6. If the criteria for the FAS facial phenotype are relaxed, sensitivity and specificity are substantially reduced.
7. A diagnosis of (FAS/Alcohol Exposure Unknown) cannot be made if the FAS facial phenotype used to render that diagnosis is not highly specific to prenatal alcohol exposure. Specificity must be empirically confirmed, not assumed.
8. The full continuum of the 4-Digit Code FAS facial phenotype is easily and accurately measured from a 2D digital photo using a $60 piece of software (FAS Facial Photographic Analysis Software). This ease, accuracy, and low cost of measurement is why 2D was selected over 3D.
9. The most accurate and efficient method to screen for full FAS is to identify the Rank 4 facial phenotype from a 2D digital facial photo (as demonstrated by the 10-year foster care FAS screening program in Seattle).

2A The full (Rank 4) FAS facial phenotype.

The full (Rank 4) FAS facial phenotype, as defined by the 4-Digit Code, is the simultaneous expression of the following three minor facial anomalies: 1) short palpebral fissure lengths (PFL) (2 or more SDs below the mean ($\leq$ 2.5th percentile)); 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) (Figure 3).[4]

FIG. 3 The full (Rank 4) FAS facial phenotype, as defined by the 4-Digit Code, is the simultaneous expression of the following three minor facial anomalies: 1) short palpebral fissure lengths (PFL) (2 or more SDs below the mean); 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)[3]. The FAS facial phenotype does not vary by race, as demonstrated in photos of three children with the Rank 4 FAS facial phenotype (Native American, Caucasian, and African American).



2A.1 The full FAS facial phenotype (Rank 4) is highly sensitive and specific (>95%) to FAS and prenatal alcohol exposure and does not vary by race, gender or age.

If the Rank 4 FAS facial phenotype 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) this facial phenotype would be highly sensitive to FAS (e.g., individuals with FAS would have the FAS facial phenotype), 2) this face would be highly specific to FAS (e.g., individuals without FAS would not have the FAS facial phenotype), and 3) this face would be highly specific to prenatal alcohol exposure (e.g., individuals with confirmed absence of 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. [24,25,28-30]

Empirical studies were conducted over the course of 10 years to identify and case-define the cluster of minor facial anomalies that had the highest sensitivity and specificity to FAS.[15,25,28-30,32,42] The Rank 4 FAS facial phenotype is > 95% sensitive and specific to FAS and prenatal alcohol exposure.[28,30] Sensitivity and specificity were

confirmed to be unaffected by race, gender, and age.[25] The Rank 4 FAS facial phenotype presents across all races, is identifiable at birth, and does not diminish with age.[9] Twenty years of FASD clinic and 10 years of FAS screening in foster care bear this out. This FAS facial phenotype has been accurately measured and diagnostically classified in thousands of individuals across every race (e.g., 1,958 Caucasian, 596 African American, 360 Native American, 254 Hispanic, 48 Asian) and combination of race without limitation This is achieved by using measurement scales normalized to race, gender, and age, as appropriate. And, although it has been a long held belief in this field "*that some FAS craniofacial anomalies may be less evident at birth, become more conspicuous during early infancy and childhood, and often diminish or even disappear during adolescence and adulthood"*[5], our experience over 20 years confirms this does not hold true.[26] This belief stemmed largely from three studies published in the 1980s and 90s that assessed the qualitative change in facial features among children who presented with gestalt features of FAS.[43-45] Back then an ever growing list of minor facial anomalies was being attributed to FAS. Most of the features that were reported to diminish with age (flat nasal bridge, epicanthal folds, short upturned nose, and retrognathia): had never been confirmed to be sensitive or specific to prenatal alcohol exposure; and were remarkably consistent with descriptions of normal facial growth. Enlow and Hans[46] report that when one compares the face of a normal child to that of a normal adult, the child's nose is short and upturned, the nasal bridge is low, often resulting in epicanthal folds, and the mandible is small and retrusively placed. Interestingly, the FAS features reported not to change with age (short PFL, smooth philtrum, and a thin upper lip) are the only features that the 4-Digit Code will subsequently confirm to be sensitive and specific to prenatal alcohol exposure, and match the features originally identified as defining the face of FAS by David Smith, M.D. back in 1979. As stated by Smith.[47] "*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*." Further evidence that the FAS facial phenotype (as defined by the 4-Digit Code) does not diminish with age stems from our experience conducting FASD diagnostic evaluations on thousands of individuals over 20 years.[26] Although we typically see individuals just once to render a diagnosis, we have seen over 100 children at two time points, typically as toddlers and again as adolescents. No child had a FAS facial phenotype that diminished with age when measured using reliable measurement techniques (eg. Lip-Philtrum Guides and FAS Facial Photographic Analysis Software[33]). We also routinely request childhood (or younger) facial photos of all patients requesting an FASD diagnostic evaluation. Among the 1,279 patients providing us with younger pictures of themselves, again, we have never seen the FAS facial phenotype (as defined by the 4-Digit Code) diminish with age.

When the diagnostic criteria for the FAS facial phenotype are relaxed, the phenotype is no longer sufficiently sensitive and specific to FAS and prenatal alcohol exposure. If the specificity falls below 95%, two fundamental problems arise. First, the diagnostic label FAS is rendered medically invalid. If you label the patient's outcome FAS, you are declaring a patient has a syndrome caused by their mother's consumption of alcohol during pregnancy.[9] But if the face is not specific to alcohol, you have no medical or scientific evidence to support this declaration of causation in an individual patient. Second, a diagnosis of FAS can no longer be made in the absence of a confirmed prenatal alcohol exposure. All current FASD diagnostic guidelines allow a

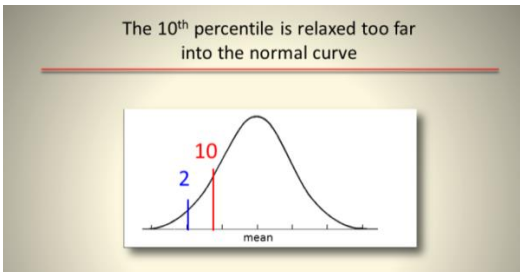
diagnosis of FAS to be rendered when prenatal alcohol exposure is unknown because the guidelines assume the FAS facial phenotype is specific to alcohol and thus can serve as confirmation of exposure. But the specificity cannot be assumed. It has to be confirmed and it has to be confirmed high. The 4-Digit Code Rank 4 face is the only FAS facial phenotype with sufficiently high specificity (>95%) to allow the outcome to be labeled FAS and allow the diagnosis to be rendered in the absence of confirmed exposure.

Two FAS/D diagnostic guidelines published subsequent to the 4-Digit Code (CDC[6] and the revised IOM[8]) relaxed the criteria for the FAS facial phenotype. Both guidelines relaxed the PFL criteria from $\leq 2^{nd}$ percentile to $\leq 10^{th}$ percentile. The revised IOM went one step further, reducing the number of required facial features from 3 to 2. Although relaxation of the criteria will reduce the specificity of the facial phenotype to FAS and prenatal alcohol exposure, neither guideline reported the specificity of their relaxed FAS facial phenotypes.

Evidence that the FAS PFL criteria should be kept at $\leq 2^{nd}$ percentile, not relaxed to $\leq 10^{th}$ percentile.

In a recently published study of 922 patients with documented prenatal exposure histories, who were evaluated by a dysmorphologist between 1978 and 2005; 1st trimester alcohol exposure correlated significantly with the presence of a smooth philtrum and thin upper lip.[48] No pattern of prenatal alcohol exposure correlated with a PFL $\leq$ 10%. The authors noted this later finding was unexpected. We too were surprised to see no correlation between short PFLs and prenatal alcohol exposure because we have always found strong correlations between these two variables. One plausible explanation for the absence of a correlation was the criterion they used to define a short PFL. The 4-Digit Code defines a short PFL as $\leq 2^{nd}$ percentile. Feldman used a more relaxed criterion; $\leq 10^{th}$ percentile. This relaxation may have relaxed the PFL too far into the normal curve (Figure 4A). To test this hypothesis, we replicated this analysis using our dataset of 1,400 patients with confirmed prenatal alcohol exposure who had undergone a FASD evaluation in the WA State FASDPN between 1993 and 2005 (Figure 4B). When the definition of a "short" PFL was relaxed to $\leq$ 10%, no correlations were found with any pattern of prenatal alcohol exposure. When the definition of a "short" PFL was set back to $\leq$ 2% (the criteria used by the 4-Digit Code), strong, significant correlations were found with quantity, frequency, and duration of alcohol exposure (Figure 4B). This provides strong evidence that the PFL criterion for the FAS facial phenotype should be set at $\leq 2^{nd}$ percentile, not relaxed to $\leq 10^{th}$ percentile.

FIG. 4AB When a short PFL is defined as ≤ 2nd percentile (as reflected in the 4-Digit Code), significant correlations are detected with prenatal alcohol exposure. When the definition is relaxed to ≤ 10th percentile (as reflected in the CDC and Revised IOM guidelines), no correlations with prenatal alcohol exposure are detected. These findings were reported by Feldman, et al[48] and replicated here using our FASDPN dataset.



A

Prenatal alcohol exposure not correlated with PFL when criteria relaxed to ≤ 10th percentile

		4-Digit PFL		CDC & Revised IOM PFL	
Prenatal Alcohol Exposure		≤ 2%	> 2%	≤ 10%	> 10%
Days / Week	n	534	324	673	185
	Mean (SD)	4.6 (2.3)	4.2 (2.4)	4.4 (2.4)	4.4 (2.4)
	F (p-value)	3.7 (.04)		.03 (.83)	
Max. Drinks / Week	n	359	222	456	125
	Mean (SD)	64.9 (92)	50.1 (59)	60.7 (86)	53.9 (60)
	F (p-value)	2.3 (.02)		.80 (.41)	
Trimesters	All 3: n (%)	533 (64)	301 (36)	661 (79)	173 (21)
	1 to 2: n (%)	203 (56)	157 (44)	267 (74)	93 (26)
	Chi Square, Yates (p-value)	5.7 (.02)		3.5 (.07)	

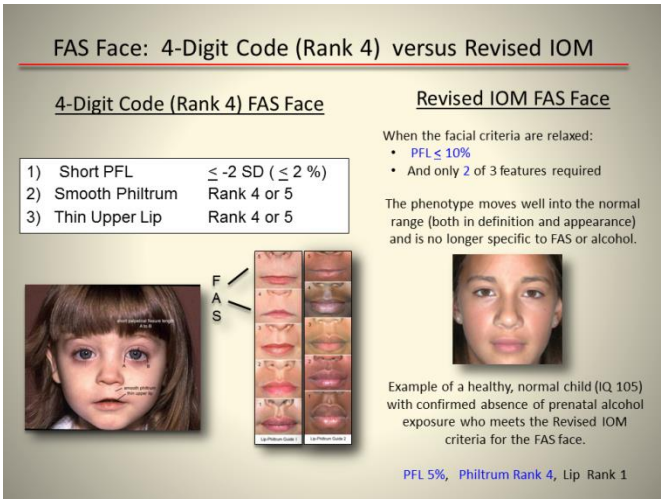
B

Evidence that the FAS facial criteria require all 3 features, not just 2 of the 3.

The Revised-IOM[8] criteria for the FAS facial phenotype relaxed the PFL to ≤ 10th percentile and requires only 2 of the 3 facial features be present. A 2006 study[23] confirmed these relaxations in the facial criteria rendered the Revised-IOM FAS facial phenotype non-specific to both prenatal alcohol exposure (specificity 75%) and FAS (specificity 68%). For reference, a specificity of 50% is equivalent to random chance; the predictive equivalent of flipping a coin. The specificity of the 4-Digit Code FAS facial phenotype to FAS and prenatal alcohol exposure is >95%. In the 2006 study, the performance of the Revised-IOM FAS criteria was assessed by applying them to two populations: 1) 952 alcohol-exposed patients evaluated in the WA FASDPN clinics, and 2) 16 healthy, high-functioning children with confirmed absence of prenatal alcohol exposure enrolled as controls in a magnetic resonance study. In this study a substantial number of patients in the FASD clinics met the Revised-IOM criteria for the full FAS facial phenotype (35%; 330 of 952 subjects), but very few of them met the Revised-IOM criteria for a diagnosis of FAS (11.8%; 39 of 330 subjects). If the Revised-IOM 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. But just the opposite was observed. The vast majority of those with the FAS face (88.2%; 291 of 330 subjects) did not

have FAS. If the Revised-IOM 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 high-functioning children with confirmed absence of prenatal alcohol exposure met the criteria for the Revised-IOM FAS face. When the facial criteria are relaxed as specified in the Revised IOM criteria, the phenotype moves well into the normal range (both in definition and appearance) and is no longer specific to FAS or prenatal alcohol exposure (Figure 5).

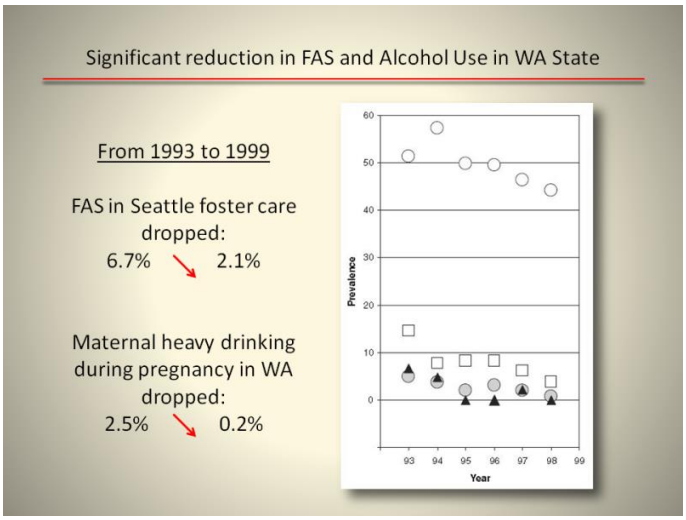
FIG. 5 When the FAS facial phenotype is relaxed[8] (photo on the right), the phenotype moves well into the normal range (both in definition and appearance) and is no longer specific to FAS or prenatal alcohol exposure.



2A.2. The Rank 4 face is so specific to FAS, it alone was used to accurately screen for FAS in a 10-year, foster care FAS screening program. This, in turn, allowed us to track the prevalence and prevention of FAS in WA State.

The high specificity of the Rank 4 FAS facial phenotype to FAS and prenatal alcohol exposure was further confirmed through a 10-year, active case-ascertainment, foster care FAS screening program conducted in Seattle.[15] If the Rank 4 FAS facial phenotype is truly highly specific to FAS and prenatal alcohol exposure, then one should be able to screen for FAS using nothing more than a facial photograph. Our 10-year foster care FAS screening program confirmed this to be true. All children entering a foster care program had their 2D digital facial photograph analyzed with the FAS Facial Photographic Analysis Software.[33,40] All children with the Rank 4 FAS facial phenotype were classified as screen-positive for FAS and received an interdisciplinary FASD diagnostic evaluation using the 4-Digit Code. The screening tool (presence of the Rank 4 FAS facial phenotype in a 2D facial photograph) performed with 100% sensitivity, 99.8% specificity, 85.9% predictive value positive and 100% predictive value negative for FAS. Over 2,500 children were screened over a period of 10 years (1999-2009) with 98% participation. This 10 year active-case-ascertainment screening program confirmed 1/100 children in foster care in the Seattle area had FAS. Data from this study would go on to confirm that the prevalence of FAS in this foster care population decreased significantly (6.7% to 2.1%)[24,34] (across successive birth cohorts) as the prevalence of heavy maternal drinking during pregnancy in WA State decreased significantly (2.5% to 0.2%) in those same years[24] (Figure 6).

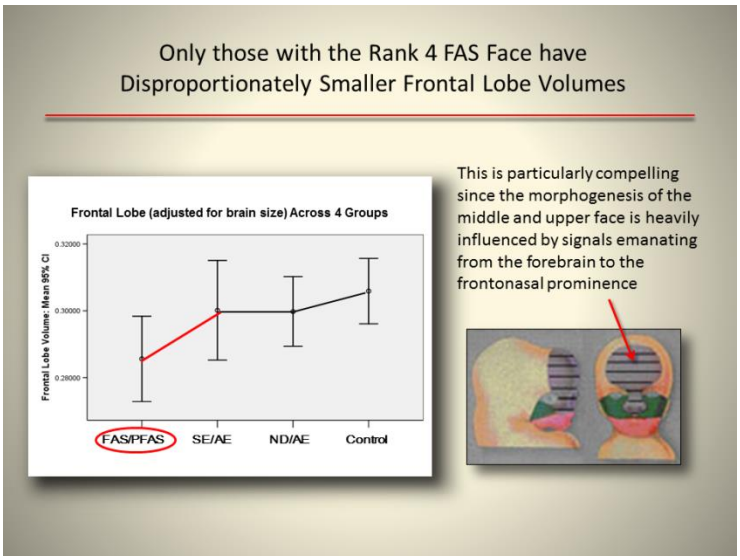
FIG. 6 The prevalence of FAS dropped significantly from 6.7% to 2.1% among children in Seattle foster care born between 1993 and 1999. This correlated with a significant decline (2.5% to 0.2%) in the prevalence of women drinking during pregnancy in WA State during those same years[24]. Key: Decline in the prevalence of alcohol use by women in Washington State from 1993 to 1998: (○) Any level of alcohol use 3 months prior to pregnancy; (□) Any level of alcohol use in the third trimester of pregnancy; (●) Heavy alcohol use (>14 drinks/week) 3 months prior to pregnancy.[34] (▲) Prevalence of FAS among children in a Seattle foster care program born from 1993 to 1998.[24]



<u>2A.3</u>. Individuals with the Rank 4 FAS face have significantly and disproportionately smaller frontal lobe volumes. This is particularly compelling since the forebrain plays an important role in the normal morphogenesis of the midline facial features and laboratory studies of alcohol teratogenesis report midventral forebrain deficiencies associated with facial dysmorphia in both mice and primates.

In an MRI study comparing brain volumes among children with 4-Digit Code diagnostic classifications of FAS/PFAS, SE/AE, and ND/AE, and a healthy, unexposed control group, the mean volume of the frontal lobe was significantly and disproportionately smaller in the FAS/PFAS group compared with each of the other groups.[16] (Figure 7). The FAS/PFAS group was the only group with the full Rank 4 FAS facial phenotype. This is a particularly compelling and validating finding when one considers the morphogenesis of the middle and upper face is heavily influenced by signals emanating from the forebrain to the frontonasal prominence.[49] The correlation between median facial malformations and underlying brain malformation has been known for decades.[50] The FAS facial features (short palpebral fissure lengths, a smooth philtrum and a thin upper lip) are midline anomalies derived from the anterior frontal neural crest primordia of the early forebrain.[51] Deficiencies in the numbers of crest cells most frequently affect development of the frontonasal derivatives and are usually associated with defective forebrain and eye development.[51] It has long been speculated that some extreme forms of midline facial anomalies (i.e., cyclopia, holoprosencephaly, arhinencephaly) are pathognomonic of brain malformation.[50] This speculation was further supported by the presence of a proportional increase in midventral forebrain deficiencies and the severity of facial dysmorphia in mice[52-54], nonhuman primates[29,55], and now humans.[16]

FIG. 7 The mean volume of the frontal lobe was significantly ($p < 0.05$) and disproportionately smaller in the FAS/PFAS group compared with each of the other study groups (SE/AE, ND/AE and unexposed healthy controls).[16] The FAS⁄PFAS group is the only group with the full FAS facial phenotype. Morphogenesis of the middle and upper face is heavily influenced by signals emanating from the forebrain to the frontonasal prominence.[49] The frontonasal prominence is the striped region in the insert depicting a 5-week (left) and 10-week (right) fetus.[56]



2A.4. The high specificity of the Rank 4 FAS facial phenotype is quintessential to the validity of all diagnoses under the umbrella of FASD, not just those labeled FAS.

Why are the criteria used to define the FAS facial phenotype so important to the medical validity of all diagnoses under the umbrella of FASD, not just the diagnosis of FAS? When one makes a diagnosis of FAS, one is stating implicitly that the individual has a syndrome caused by prenatal alcohol exposure.[9] 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, ethical, and even legal consequences. What happens when the FAS face is not at least 95% specific to FAS and prenatal alcohol exposure? The whole FASD diagnostic system collapses like a house of cards. Here is why.

a. The term FAS is rendered invalid. If the face is not specific to (caused only by) alcohol, it is no longer medically valid or medically ethical to label the condition fetal alcohol syndrome. You can no longer confirm alcohol is causally linked to any of the outcomes (growth, brain, or face) in an individual patient.
b. The diagnosis FAS/alcohol-exposure-unknown is also rendered invalid. If the face is not specific to (caused only by) alcohol, the FAS face can no longer serve as the confirmation of alcohol exposure when the exposure history is unknown.
c. FAS is no longer distinct from ARND. ARND is "FAS without the face". But if there is no FAS face, there is no distinction between FAS and ARND. Thus, you can no longer justify classifying FAS and ARND separately.
d. The term "ARND" remains invalid. Since ARND has no feature specific to prenatal alcohol, you are in no position to declare the Neurodevelopmental Disorder is "Alcohol-Related" (ARND) in an individual patient. This is discussed more fully below.

2B. Principle 2: The FAS facial phenotype presents along a clinically meaningful continuum.

2B.1. The FAS facial phenotype is not just present or absent. It presents along a continuum that is significantly correlated with (predictive of) abnormal brain structure and function.

The more severe the FAS face, the more severe the CNS structural/functional abnormality (Figure 8); growth deficiency (Figure 9), and duration of alcohol exposure (Figure 10).[9,26,27] We predicted back in 1999[29] that if the FAS facial phenotype was measured on a continuum, it would serve as a more sensitive indicator of teratogenic outcome than the previous practice of recording the FAS facial phenotype as simply present or absent as documented in the IOM FASD guidelines.[5] Figures 8 and 9 clearly confirm this to be true. The statistically significant linear correlations observed between the magnitude of expression of the FAS facial phenotype and brain structure and function: 1) further validate that short PFLs, a smooth philtrum, and a thin upper lip are the key diagnostic facial features, 2) are consistent with the clinical literature that midline facial defects predict underlying brain dysfunction[4,25,29,30,47,50], and 3) provide evidence that an intermediate expression of the FAS facial phenotype serves as an important clinical risk factor for brain damage caused by prenatal alcohol exposure. This continuum is important in predicting the risk for CNS dysfunction among young children who present with some or all of the FAS facial features, but are too young to engage in a comprehensive assessment of brain function.[9] The correlations between face and brain (Figure 8) also demonstrate that individuals with the full FAS facial features do have CNS structural and functional abnormalities that are significantly more severe than individuals with milder expressions of the FAS facial phenotype.[16] This is not an artifact of the criteria used to define the different FASD diagnostic subgroups. In accordance with the 4-Digit Code, FAS/PFAS and SE/AE must meet the same diagnostic threshold for severe dysfunction (CNS Rank 3 and/or 4). That said; those who meet that threshold and have the FAS facial phenotype (FAS/PFAS) have significantly more severe dysfunction, on average, than those who meet that threshold and do not have the FAS facial phenotype (SE/AE) (Fig 17). Not all published studies identify statistically significant contrasts in CNS abnormality between alcohol-exposed individuals with and without the FAS facial phenotype. This may be a reflection of the criteria used to define the FAS facial features in those studies.[57-60] We too failed to observe any correlation between face and brain when we used less rigorous methods of defining and measuring the face (e.g., the gestalt FAS facial phenotype) prior to the establishment of the 4-Digit Code.[4] When the facial criteria of the 4-Digit Code are used, significant contrasts are observed between alcohol-exposed groups with and without the FAS facial phenotype.[61]

FIG. 8 Data from the WA FASDPN clinics[26] and the MRI studies[16] confirm that the more severe the FAS facial phenotype (4-Digit Code Facial Rank 1 = no features, 2 = mild features; 3 = moderate features; 4 = severe features, presented on the x axis) the more severe the abnormalities in CNS structure and function (FSIQ; head circumference centile; visual motor integration standard score; Quick Neurological Screen Test score; prevalence of significant developmental delay; and number of significantly impaired domains of function, presented on the y axis). These statistically significant linear correlations serve to validate the 4-Digit Code FAS facial phenotype.

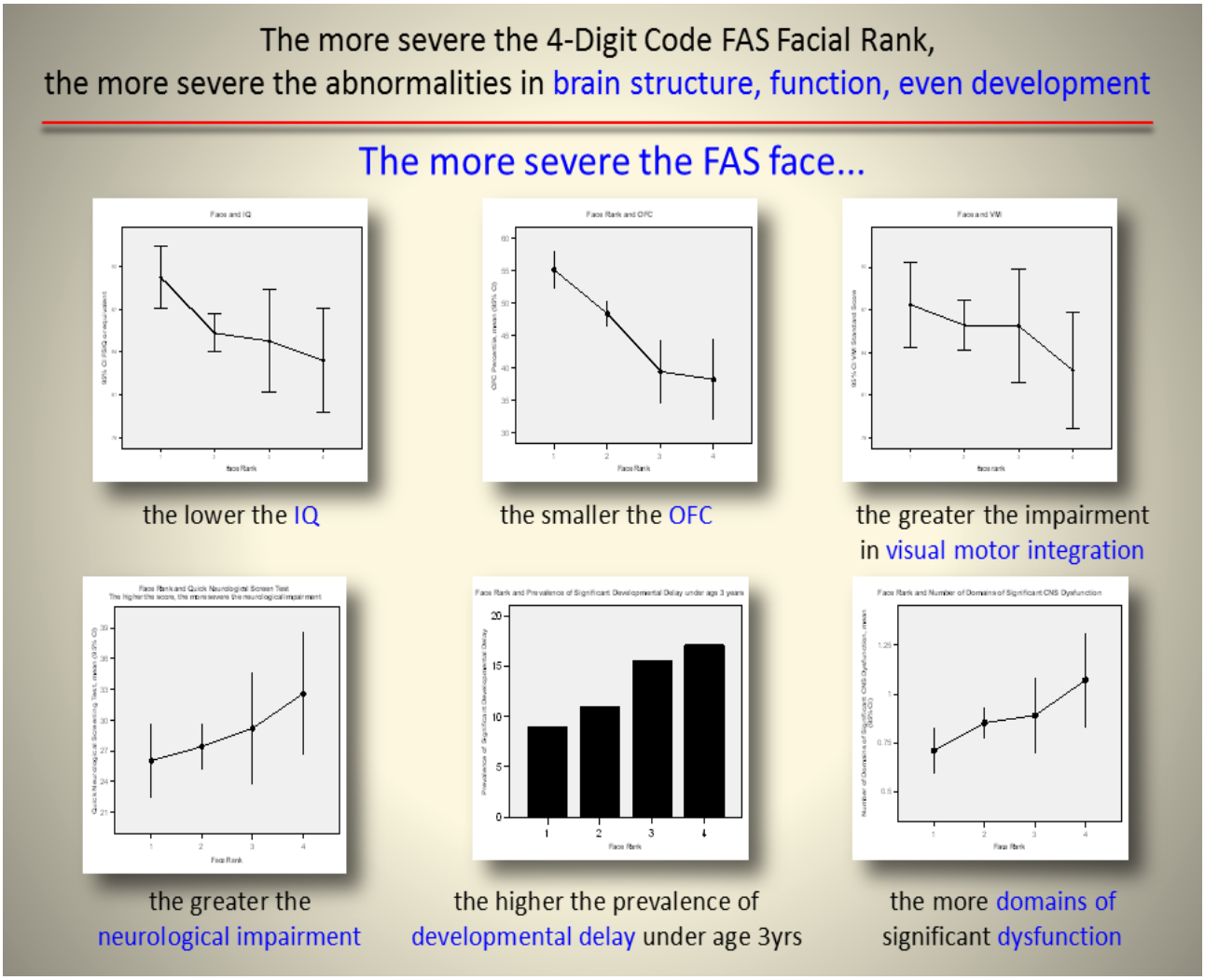


FIG. 9. Data from the WA FASDPN clinics[26] document the more severe the 4-Digit FAS facial phenotype (Facial Ranks 1-4), the more severe the growth deficiency (birth weight and length percentiles as well as weight and height percentiles at the time of the FASD diagnostic evaluation. Pictured are statistically significant linear trends.

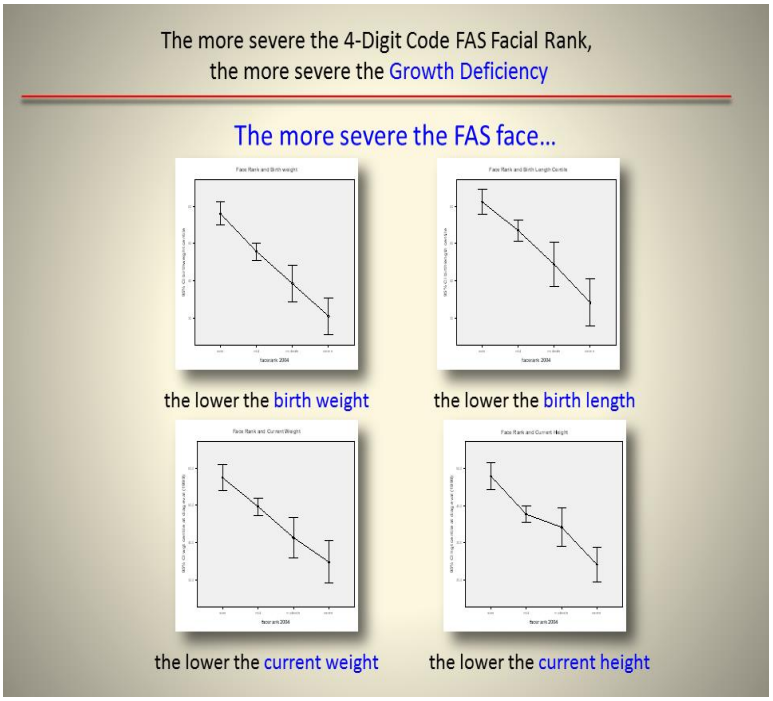
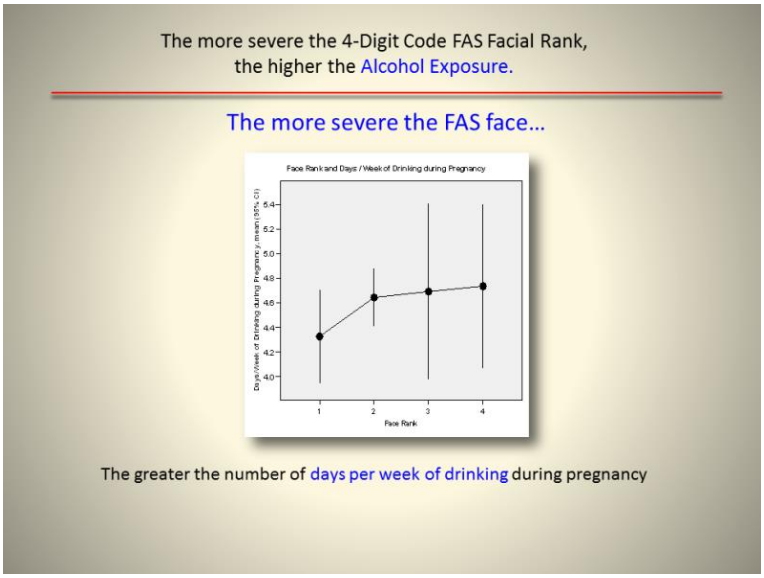


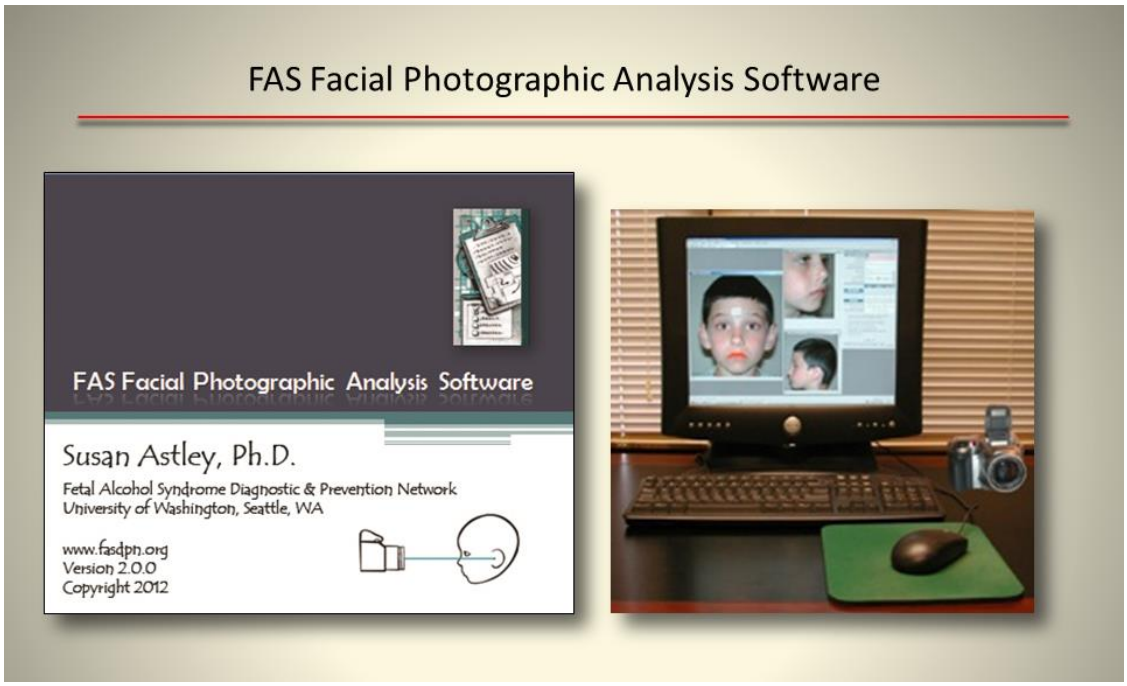
FIG. 10 Data from the WA FASDPN clinics[26] document the more severe the 4-Digit FAS facial phenotype (Facial Ranks 1-4), the greater the number of days/week of drinking during pregnancy (significant linear trend, F=10.7, p = 0.001).



2B.2. The FAS facial features can be accurately measured from a 2D digital photo using the FAS Facial Photographic Analysis Software.

The full continuum of the FAS facial features can be easily and accurately measured from 2D digital facial photographs using the FAS Facial Photographic Analysis Software.[33,40] (Figure 11). This Windows-based software is both inexpensive ($60 USD) and User friendly. This ease, accuracy, and low cost of measurement are why a 2-dimentional (2D) format was selected over a 3D format back in 2004. This software has been used to measure and diagnostically classify the facial features of all patients (> 2,550) evaluated in the WA State FASD clinics over the past 20 years.[26] It was also used to screen over 2,000 children participating in a 10-year foster care FAS screening program in Seattle.[15] The software was used to generate the Canadian PFL normal growth charts in 2010.[62] These Canadian PFL charts were subsequently incorporated into Version 2.0 of the software in 2012.[33] The software is currently in use worldwide. A video demonstration of the software is posted on the FASDPN website.

FIG. 11 The FAS Facial Photographic Analysis Software (Version 2.0)[33] is a Windows-based program that provides accurate measurement of FAS facial features from a 2D digital facial photograph. The software has been distributed worldwide since 2004.

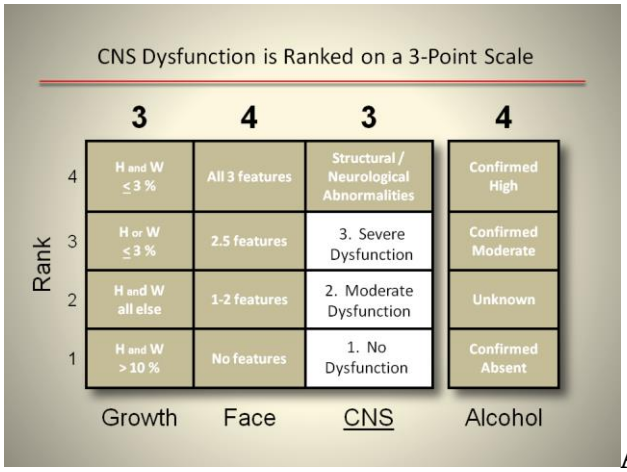


3. The 4-Digit Code's method for case-defining the highly variable CNS dysfunction that typifies FASD demonstrates high construct validity.

3A. The 4-Digit Code's method for classifying CNS dysfunction (CNS Ranks 1, 2, and 3) successfully predicts underlying CNS structural abnormality as it was designed to do.

An important contribution of the 4-Digit Code was the method used to case-define the highly variable, nonspecific CNS dysfunction that typifies FASD. It was important to establish a method that quantified the breadth and magnitude of dysfunction (e.g., the number of domains of function 2 or more SDs below the mean as measured by standardized psychometric tools administered by a clinician) without unduly constraining which domains must be impaired. CNS dysfunction is ranked on a 3-Point likert scale (Figure 12A). Ranks 1, 2, and 3 reflect none, 1 to 2, and 3 or more domains of dysfunction respectively. The 3 CNS Ranks in the 4-Digit Code were case-defined to predict increasing likelihood of underlying structural brain abnormality[4,9,16,26] (Figure 12B). Alcohol is a teratogen that interferes with the structural development of the fetal brain. This, in turn, can lead to abnormal function. We postulated in 1997… "*The greater the dysfunction, the higher the probability of underlying structural brain abnormality*".[1] In 2009, our MRI study confirmed this to be true![16] Many significant correlations were identified between CNS dysfunction and brain region volumes, but perhaps most striking was the significant, inverse, linear correlation between increasing CNS dysfunction (CNS Ranks 1,2 and 3) and decreasing caudate volume (Figure 12C). This is powerful evidence (construct validity) that the CNS Ranking system used by the 4-Digit Code is clinically and scientifically valid.

FIG. 12 A. The 4-Digit Code ranks CNS dysfunction on a 3-point scale (none, moderate, severe). B. The 3 CNS Ranks were case-defined to predict increasing likelihood of underlying structural brain abnormality.[4] C. MRI confirmed this to be true.[16] The more severe the CNS dysfunction (Rank 1, 2, 3), the smaller the caudate volume (significant linear trend F=13.5; p<.001; Duncan range test confirms each CNS group is significantly distinct from the others).



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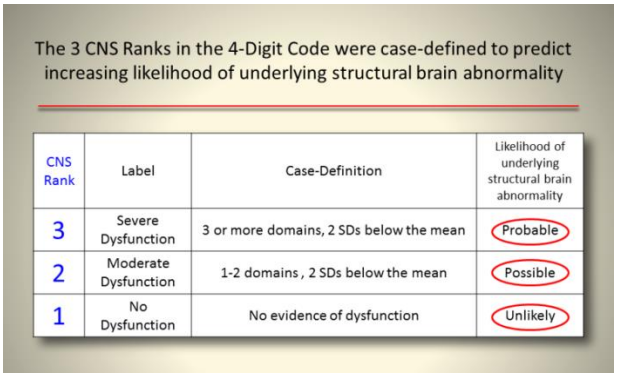

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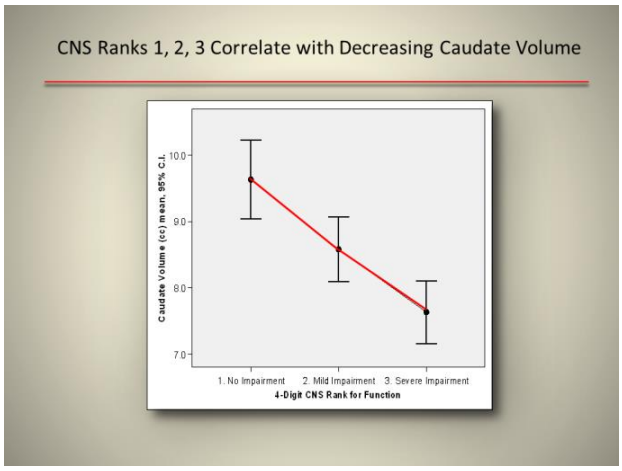
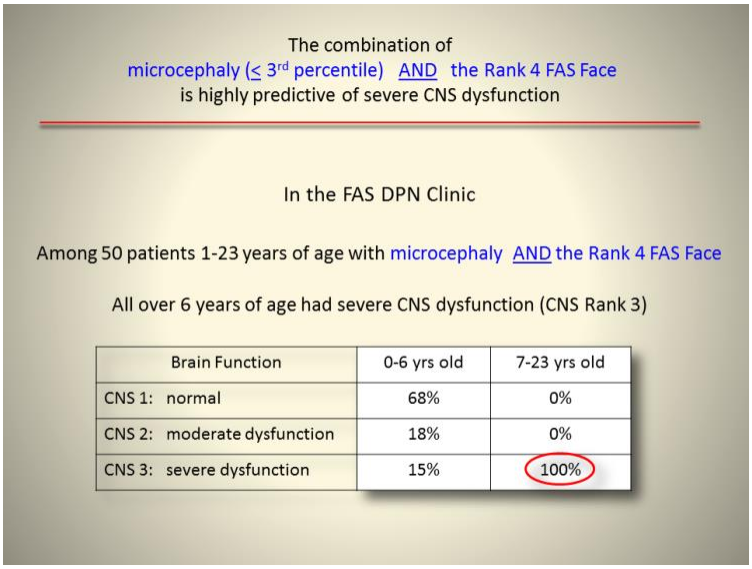


C

3B. Microcephaly predicts severe CNS dysfunction among infants/toddlers who present with the full Rank 4 FAS facial phenotype.

One area of discordance between current FASD diagnostic guidelines is the CNS criteria for FAS.[9] Some guidelines allow microcephaly alone to meet the CNS criteria, some guidelines do not. If severe functional abnormality is required, a diagnosis of FAS cannot be rendered in a child who is too young (typically < 6 years old) to participate in a comprehensive assessment of function (IQ, language, memory, executive function, etc). Is it clinically cogent to render a diagnosis of FAS in an infant who presents with structural evidence of CNS abnormality (microcephaly), but is too young to assess and confirm the presence of CNS dysfunction? Is the presence of microcephaly (an occipital frontal circumference (OFC) 2 or more SDs below the mean) in an infant with the Rank 4 FAS facial phenotype predictive of brain dysfunction that will not be revealed until the infant is old enough to participate in higher level functional assessments? The answers to both questions are yes.[9,26] In a cross sectional look at the first 1,400 patients evaluated in the WA FASDPN, 154 patients were diagnosed with FAS/PFAS.[26] Of the 154 patients, 69 (44.8%) had microcephaly. Of the 69 with microcephaly, 36 (52%) had no evidence of brain dysfunction (Rank 1), 14 (20%) had moderate (Rank 2) brain dysfunction, and 19 (28%) had severe (Rank 3) brain dysfunction. Did the 52% with no evidence of brain dysfunction, truly have normal function, or were they too young to accurately/comprehensively assess function? The data would suggest they were too young to assess. The subset with no evidence of brain dysfunction (Rank 1) had a mean age of 4.7 (6.0 SD) years. The subset with Rank 2 moderate dysfunction had a mean age of 7.5 (5.9 SD) years. And the subset with Rank 3 severe dysfunction had a mean age of 10.3 (5.9 SD) years. The older the patient, the more likely they revealed evidence of moderate to severe dysfunction (ANOVA $F=5.8$ (df 2), $p=.005$). Another way to look at this using our current dataset of 2,550 patients with FASD is as follows. Of all 50 patients, 1-23 years of age, who presented with microcephaly and the Rank 4 FAS facial phenotype, only 15% of the group $\leq$ 6 years of age presented with severe dysfunction (CNS Rank 3), but 100% > 6 years of age had severe CNS dysfunction (Figure 13). These analyses strongly support that rendering a diagnosis of FAS in a newborn/infant that presents with microcephaly, but is too young to assess/confirm brain dysfunction, is clinically sound. The combined presence of the Rank 4 FAS facial phenotype, microcephaly ($\leq 3^{rd}$ percentile), and prenatal alcohol exposure are highly predictive of brain dysfunction. The significant linear correlations between increasing magnitude of expression of the 4-Digit FAS facial phenotype and 1) increasing CNS dysfunction, and 2) decreasing head circumference further support this (Figure 8). Children with FAS are born with FAS. Early diagnosis affords early intervention. Postponing an FAS diagnosis in children with microcephaly, who were not old enough to participate in higher-level functional assessments, could lead to missed opportunities for early intervention.[63]

FIG. 13 Is microcephaly a sufficient measure of brain abnormality in children too young to assess for brain dysfunction? Data from the WA FASDPN clinics confirm that the combination of microcephaly and the Rank 4 FAS facial phenotype in children ≤ 6 years old is highly predictive of severe CNS dysfunction that will be evident later in childhood/adolescence once they are old enough to assess.



4. The 4-Digit Code generates four distinct diagnostic subgroups (FAS, PFAS, SE/AE, and ND/AE) under the umbrella of FASD.

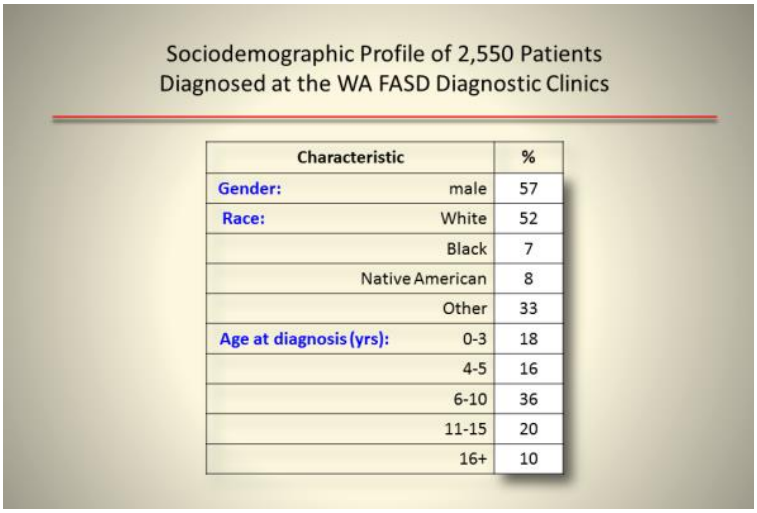
4A. FAS, PFAS, SE/AE and ND/AE are clinically distinct diagnostic subgroups that span the full continuum of FASD:

The WA FASDPN clinics have conducted FASD diagnostic evaluations on 2,550 patients with prenatal alcohol exposure over 20 years (Figures 2, 14).[26] They range in age from newborn (2 days old) to adult (53 years old), with the vast majority being school-aged. The 4-Digit Code produces diagnostic subgroups (FAS, PFAS, SE/AE, and ND/AE) that are confirmed to be clinically and statistically distinct.[9,16,26,27,35] (Figures 14-17). For example, FAS presents with growth deficiency (height and/or weight ≤ 10th percentile); PFAS does not. Only FAS/PFAS have the FAS facial phenotype, significantly ($p < 0.05$) smaller frontal lobe volumes[16] (Fig 15a), and reduced choline neurometabolite levels[35] (Fig 16). Only FAS/PFAS and SE/AE (the only two groups with severe CNS dysfunction (Ranks 3) have significantly ($p < 0.05$) smaller caudate volumes.[16] (Fig 15b). FAS/PFAS have, on average, more severe CNS structural and functional abnormalities than SE/AE even though FAS/PFAS and SE/AE must meet the same diagnostic threshold for severe dysfunction (CNS Rank 3 or 4).[16] (Figures 15, 17). Those who meet that threshold and have the FAS facial phenotype (FAS/PFAS) have more severe outcomes than those who meet that threshold and do not have the FAS facial phenotype (SE/AE). SE/AE has more severe CNS dysfunction than ND/AE (Figures 15). SE/AE have more severe CNS dysfunction and a higher prevalence of CNS structural abnormalities (58%) than ND/AE. And 43% of ND/AE have, on average, one or more significantly small brain region volumes, despite their more moderate CNS dysfunction.[16] (Figure 15c).

Although functional impairment typically becomes more severe as one advances from ND/AE to SE/AE to FAS/PFAS, the one domain that is comparably and significantly impaired

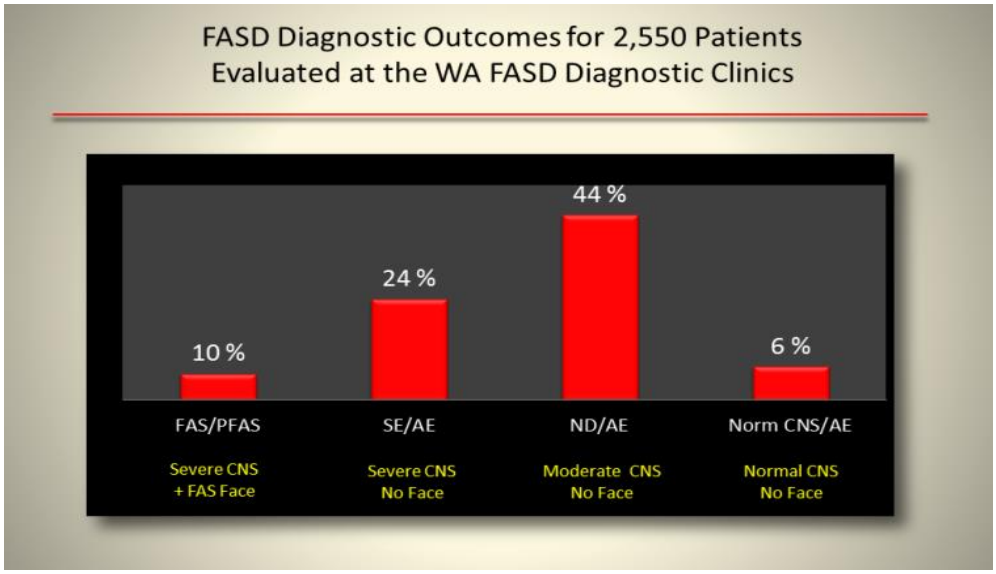
across all diagnostic subgroups is adaptive function.[26] (Figure 18). Not only are the diagnostic subgroups distinct based on standardized measures of CNS structure and function, even caregivers can distinguish between these diagnostic subgroups.[26] (Figure 19). A structured 2-hour interview is conducted with the caregivers by the medical doctor paired with the psychologist or social worker. The 4-Digit Code Caregiver Interview Form (p.6 of the Diagnostic Form[3]) is used. The interview takes place before a diagnosis has been rendered and before the clinicians have even met the child. Thus the results are not biased. The outcomes presented in Figure 19 serve to validate the clinical utility of the semi-structured caregiver interview developed and used by the 4-Digit Code.

FIG. 14. A) Sociodemographic profile and B) distribution of FASD 4-Digit Code diagnostic outcomes of the 2,550 patients with prenatal alcohol exposure evaluated in the WA FASDPN Clinics over the past 20 years.



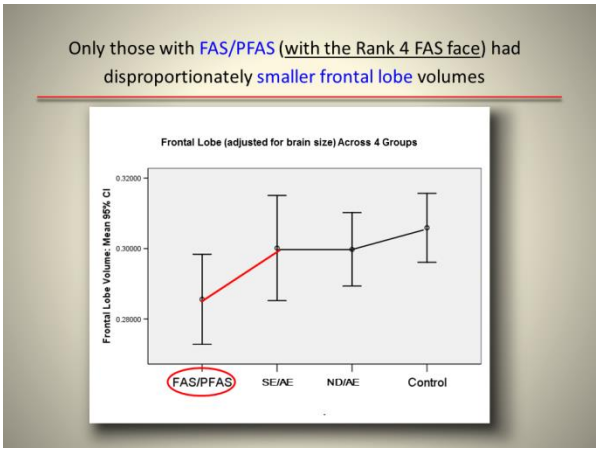
Characteristic		%
Gender:	male	57
Race:	White	52
	Black	7
	Native American	8
	Other	33
Age at diagnosis (yrs):	0-3	18
	4-5	16
	6-10	36
	11-15	20
	16+	10

A



B

FIG. 15 FAS, PFAS, SE/AE, and ND/AE are clinically and statistically distinct diagnostic subgroups that span the full continuum of FASD. Individuals with the FAS facial phenotype (FAS/PFAS) have more severe CNS dysfunction than individuals without the facial phenotype (SE/AE).



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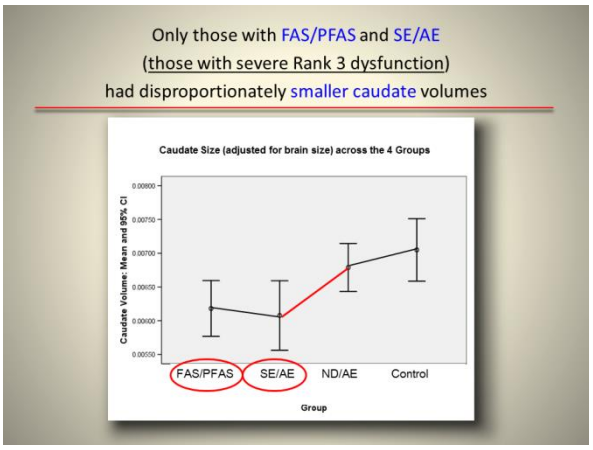

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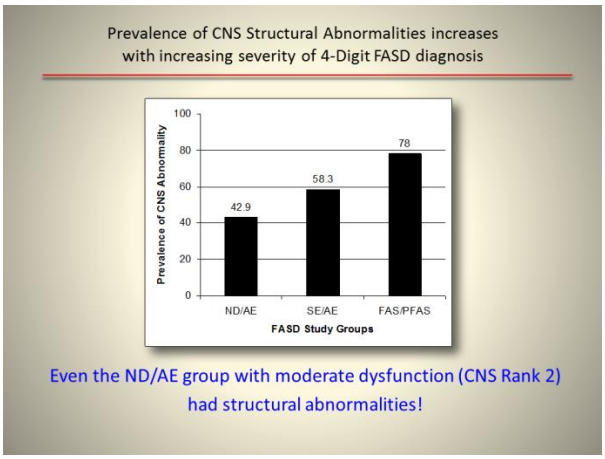

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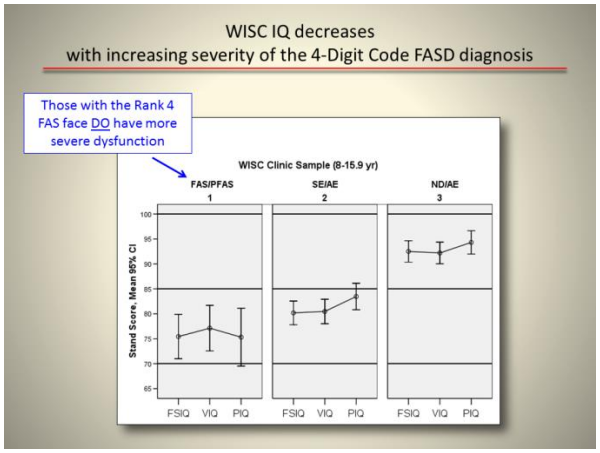

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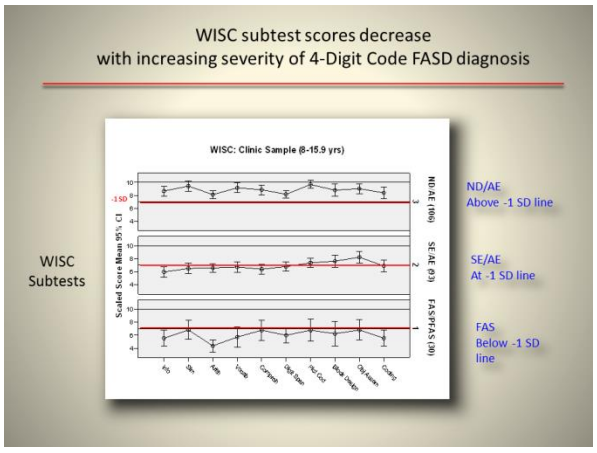

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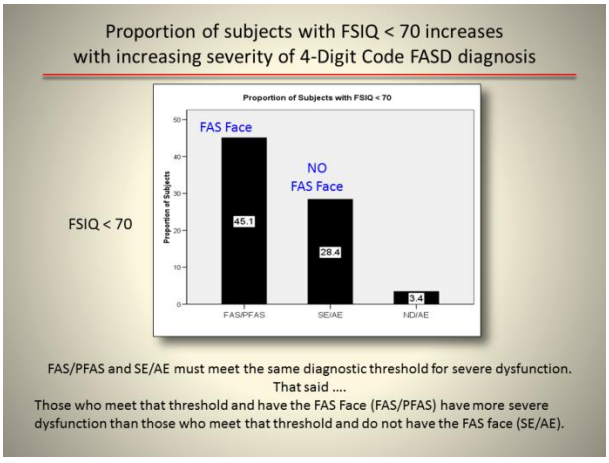

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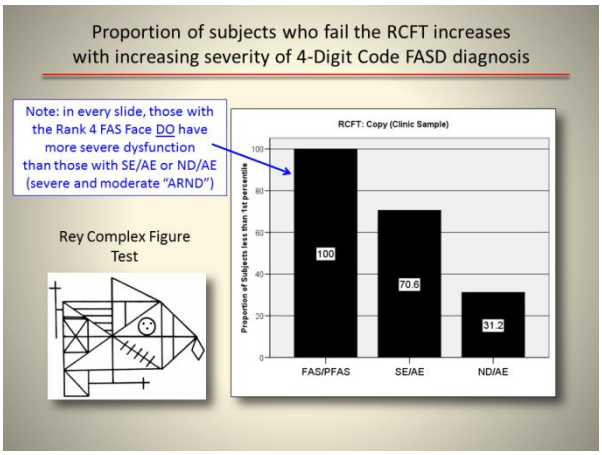

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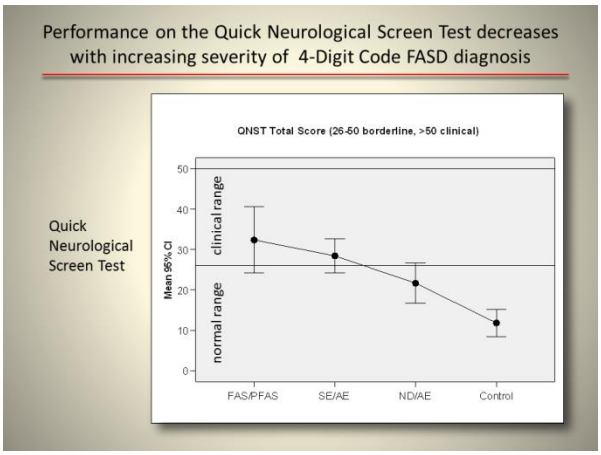

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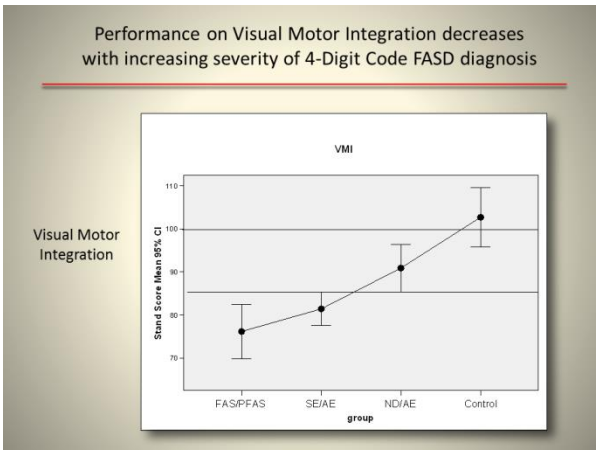

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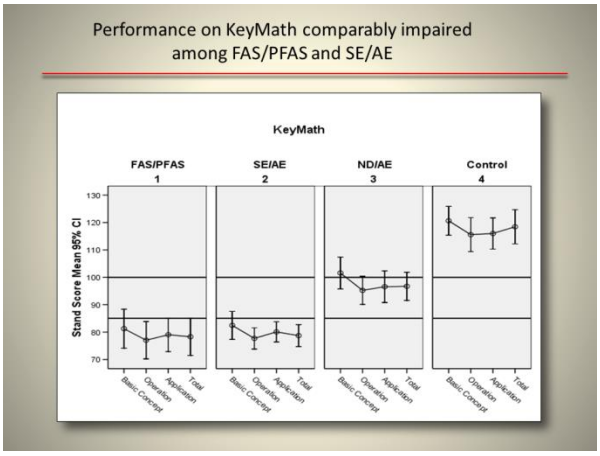

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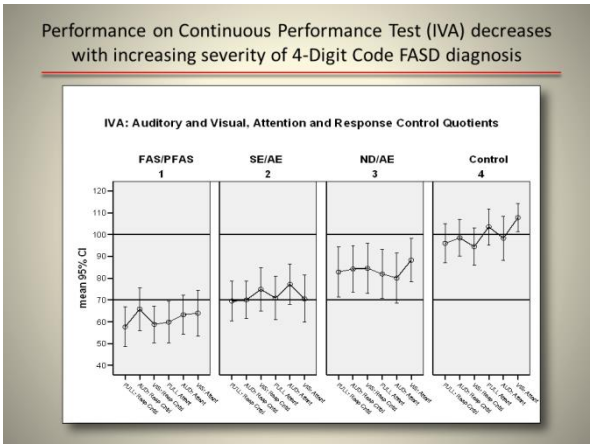

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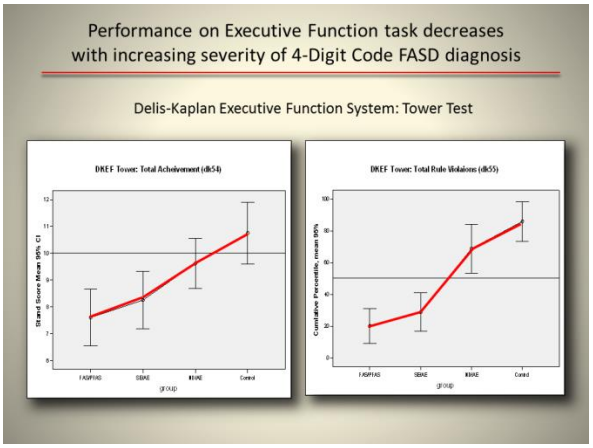


L

FIG. 16 An MRS study[35] confirmed the neurometabolite choline was significantly ($p<0.05$) lower among the FAS/PFAS group and significantly ($p<0.05$) lower among those with longer durations of prenatal alcohol exposure.

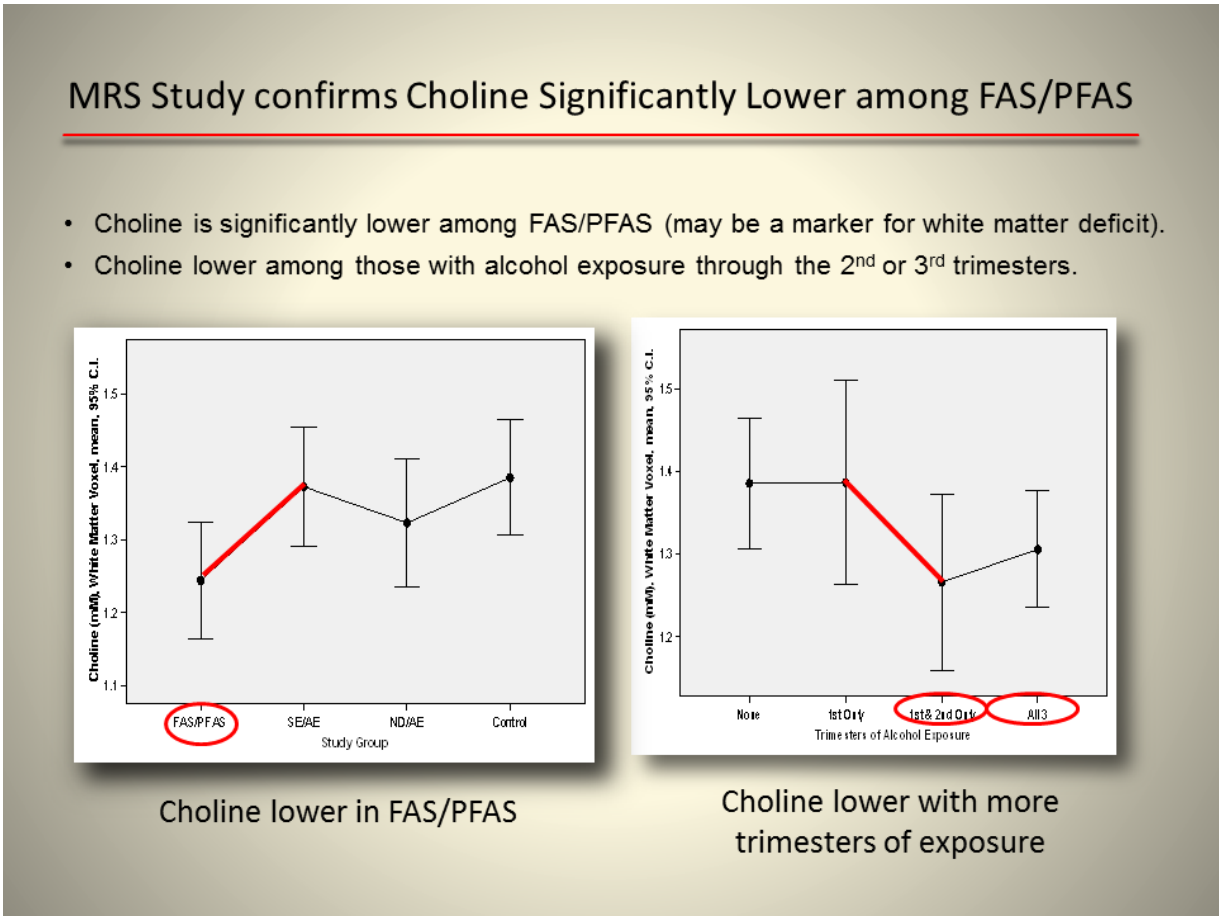
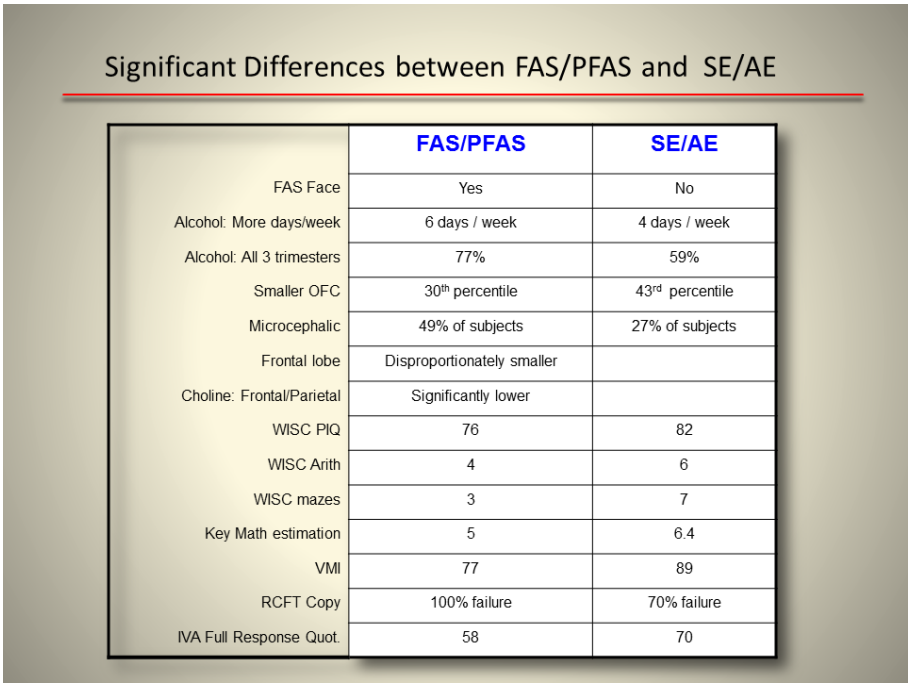


FIG. 17 Despite the fact that the CNS diagnostic criteria for FAS/PFAS and SE/AE are identical (CNS Ranks 3 and/or 4), those who meet that threshold and have the FAS facial phenotype (FAS/PFAS) have significantly more severe CNS abnormalities than those who meet that threshold and do not have the FAS facial phenotype (SE/AE).[16,26] A. Tabular presentation. B. Graphical presentation.



Significant Differences between FAS/PFAS and SE/AE

	FAS/PFAS	SE/AE
FAS Face	Yes	No
Alcohol: More days/week	6 days / week	4 days / week
Alcohol: All 3 trimesters	77%	59%
Smaller OFC	30th percentile	43rd percentile
Microcephalic	49% of subjects	27% of subjects
Frontal lobe	Disproportionately smaller	
Choline: Frontal/Parietal	Significantly lower	
WISC PIQ	76	82
WISC Arith	4	6
WISC mazes	3	7
Key Math estimation	5	6.4
VMI	77	89
RCFT Copy	100% failure	70% failure
IVA Full Response Quot.	58	70

A

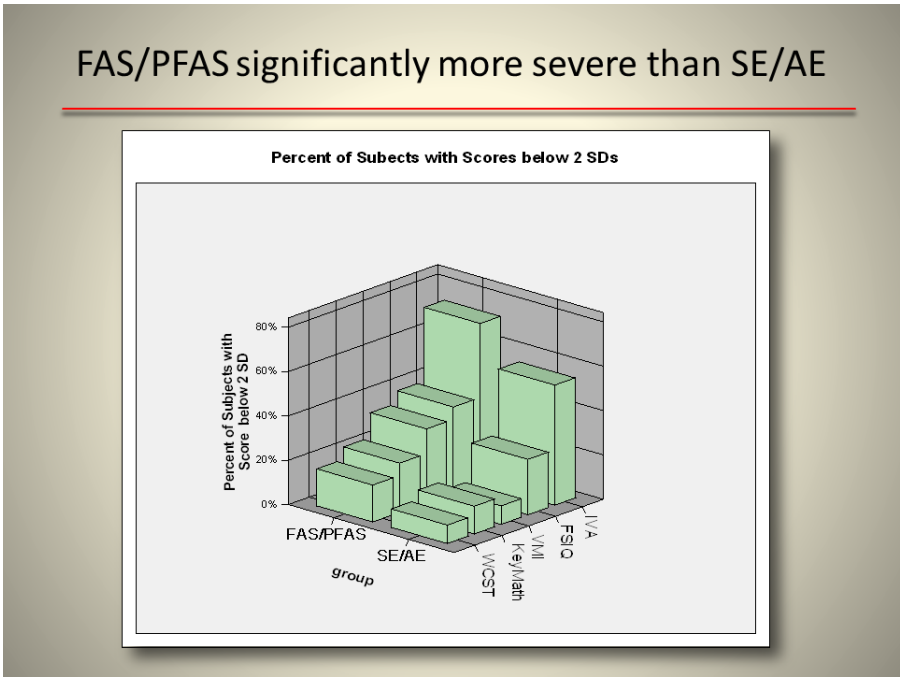


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FIG. 18 Although functional impairment typically becomes more severe as one advances from ND/AE to SE/AE to FAS/PFAS, the one domain that is comparably and significantly impaired across all diagnostic subgroups is adaptive function.[26]

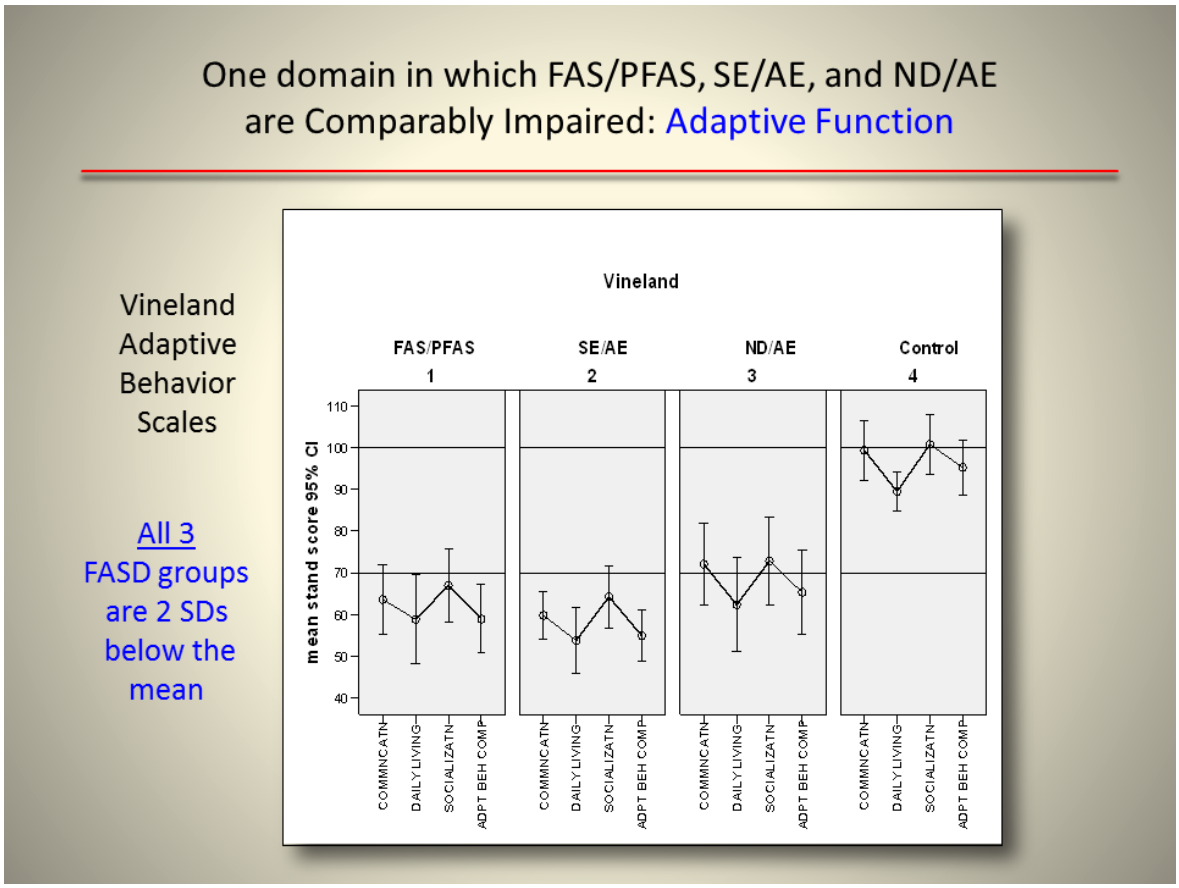
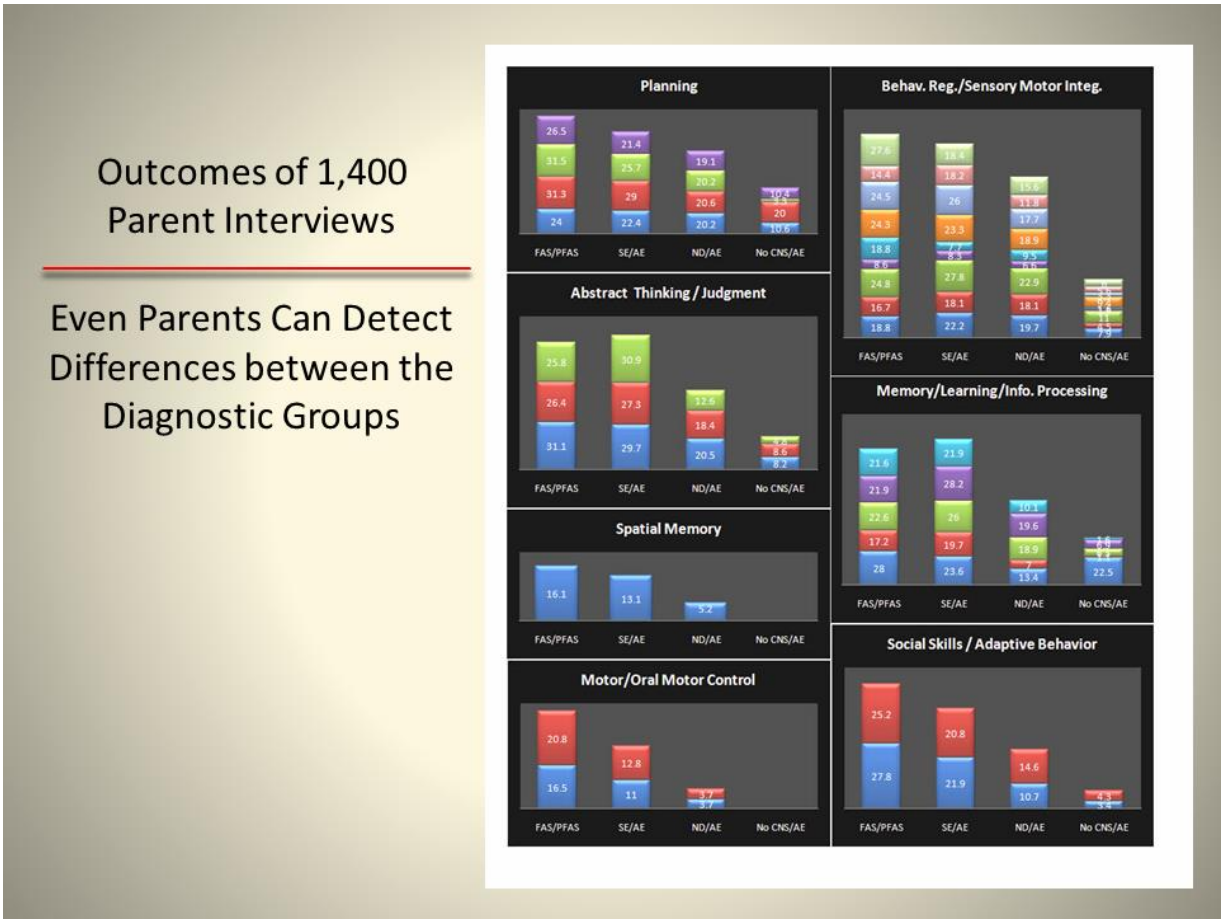


FIG. 19 Even caregivers can detect behavioral differences between the 4-Digit Code Diagnoses FAS/PFAS, SE/AE, and ND/AE.[26] A structured 2-hour interview is conducted with the caregivers by the medical doctor and psychologist using the 4-Digit Code Caregiver Interview Form (p.6 of the Diagnostic Form). The higher the bar, the more severe the child's behavioral problem reported by the caregiver.



4B. Extensive evidence supports the inclusion of individuals with moderate dysfunction (ND/AE) under the umbrella of FASD.

Prenatal alcohol exposure causes the full spectrum of CNS dysfunction from moderate to severe.[17,26,64] Individuals that present with CNS dysfunction, but no physical features of FAS, are often referred to as having Alcohol-Related Neurodevelopmental Disorder (ARND).[5] The Canadian[7] and Revised IOM[8] guidelines use the term ARND to classify individuals who present with severe CNS dysfunction. Neither guideline includes a diagnostic category for individuals that present with moderate dysfunction. In contrast, the 4-Digit Code[3] has two diagnostic categories to capture the full spectrum of dysfunction: 1) Neurobehavioral Disorder/Alcohol Exposed (ND/AE) for moderate dysfunction (CNS Rank 2), and 2) Static Encephalopathy/Alcohol Exposed (SE/AE) for severe dysfunction (CNS Ranks 3 and/or 4). The evidence that supports inclusion of ND/AE (moderate dysfunction) under the umbrella of FASD is as follows. First, and most importantly, thousands of laboratory-based studies, including our nonhuman primate studies[65,66], confirm prenatal alcohol exposure causes moderate dysfunction. Not only does it cause moderate dysfunction, but moderate dysfunction is the most common outcome. Of the

2,550 alcohol-exposed patients evaluated at the WA FASDPN clinics over the past 20 years, 44% met the criteria for ND/AE[26] (Figure 20). ND/AE was the most common outcome, exceeding the prevalence of FAS/PFAS (10%) and SE/AE (24%) combined. It is important to note that alcohol is not the only risk factor contributing to adverse outcomes in our patient population.[26] (Figure 21). So what would the diagnostic distribution look like if alcohol was the only risk factor? To answer that question, we applied the 4-Digit Code to the outcomes observed in our primate model of FASD[66] (Figure 20). Remarkably, the distribution of FAS/PFAS (4%), SD/AE (30%) and ND/AE (57%) was near identical to that observed in our FASD clinical population with ND/AE being the most common outcome. And just like in our primate model, individuals with ND/AE have alcohol exposures as high as those with FAS/PFAS and SE/AE.[26] (Figure 22). Are these moderate impairments in brain function associated with underlying CNS structural abnormalities? Again, the answer is yes. Our MRI study confirmed at least 43% of individuals with ND/AE have significant CNS structural abnormalities.[16] (Figure 15C). Our extensive experience in the WA FASDPN confirms that it is the children with moderate dysfunction that fair the worst and are often in most need of diagnostic identification and intervention. These are the children that typically slip through the cracks. Their disabilities are often not severe enough in the cognitive domain to qualify them for services (only 3% have an IQ less than 70)[26], but severe enough across many other domains (Figure 23) to adversely impact their ability to fully engage in school and live productive, independent lives. Children with ND/AE received as many intervention recommendations as children with FAS/PFAS and SE/AE.[67] (Figure 24) and caregivers reported the interventions worked as well for their children as did caregivers of children with FAS/PFAS and SE/AE.[26] (Figure 31). It is important to clarify that, when we report above that there is extensive evidence to support inclusion of ND/AE under the umbrella of FASD, we are not stating that all individuals who meet the criteria for ND/AE have FASD. By definition all individuals with Fetal Alcohol Spectrum Disorder have a disorder caused, at least in part, by their prenatal alcohol exposure. But not all individuals with ND/AE necessarily have a FASD. Only the subset of individuals whose neurobehavioral disorder was caused, at least in part, by their prenatal alcohol exposure, have a FASD. This is a current inherent weakness in the umbrella term FASD. In the absence of a biomarker that can causally link an individual's alcohol exposure with their neurodevelopmental disorder, there is no way to identify which individuals with ND/AE have FASD. This same argument applies to the diagnostic classification of SE/AE and ARND. Not all individuals who meet the criteria for SE/AE (or meet the criteria for ARND using the IOM or Canadian Guidelines) necessarily have FASD. Only the subset of individuals whose CNS abnormalities were caused, at least in part, by their prenatal alcohol exposure has FASD. And once again the field of FASD currently has no way (no biomarker) to identify this subset. Until such a biomarker is identified, if such a biomarker exists, the 4-Digit Code elects to label these categories with terms that do not imply causality.

FIG. 20 Individuals with moderate dysfunction (ND/AE) make up the majority of patients (44%) seen in the WA FASDPN clinics. Alcohol is capable of causing moderate dysfunction, as demonstrated in our primate study of alcohol teratogenicity.[66] When the 4-Digit Code was applied to the outcomes in the primate study, ND/AE was the most prevalent outcome (57%). The distribution of diagnostic outcomes observed in the primate study were near identical to the distribution observed in our clinical population.

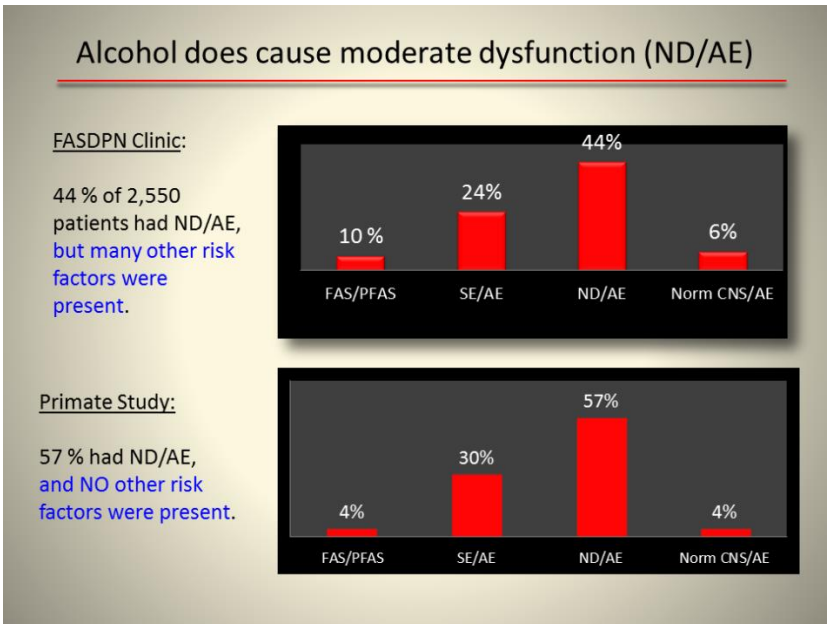


FIG. 21 Alcohol is never the only risk factor for abnormal development in a FASD clinical population. The prevalence of other risk factors among the 2,550 patients evaluated at the WA FASDPN clinics is substantial.[26]

Risk Factors Among 2,550 FASD Patients	
Prenatal alcohol exposure	100%
No prenatal care	31 %
Maternal learning disabilities	36 %
Other adverse prenatal exposures	93 %
Prenatal tobacco	62 %
Prenatal crack/cocaine	37 %
Perinatal difficulties	53 %
Foster/adoptive care	85 %
Physical abuse	34 %
Sexual abuse	24 %
Neglect	64 %
Home placements (average #)	3

FIG. 22 Among the first 1,400 alcohol-exposed patients evaluated in the WA FASDPN clinics, those with moderate CNS dysfunction (ND/AE) had alcohol exposures as high as those with severe CNS dysfunction (FAS/PFAS and SE/AE).[26]

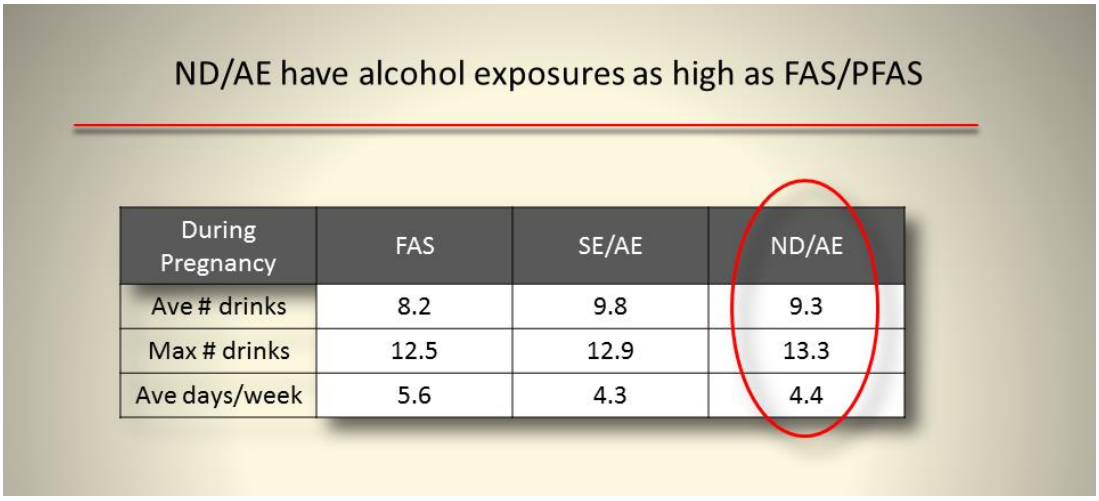


FIG. 23 Although individuals with ND/AE have less severe CNS dysfunction than FAS/PFAS or SE/AE, their disabilities span the full continuum. Their disabilities are often not severe enough in the cognitive domain to qualify them for services (only 3% have an IQ less than 70)[26], but severe enough across many other domains to adversely impact their ability to fully engage in school and live productive, independent lives.[26]

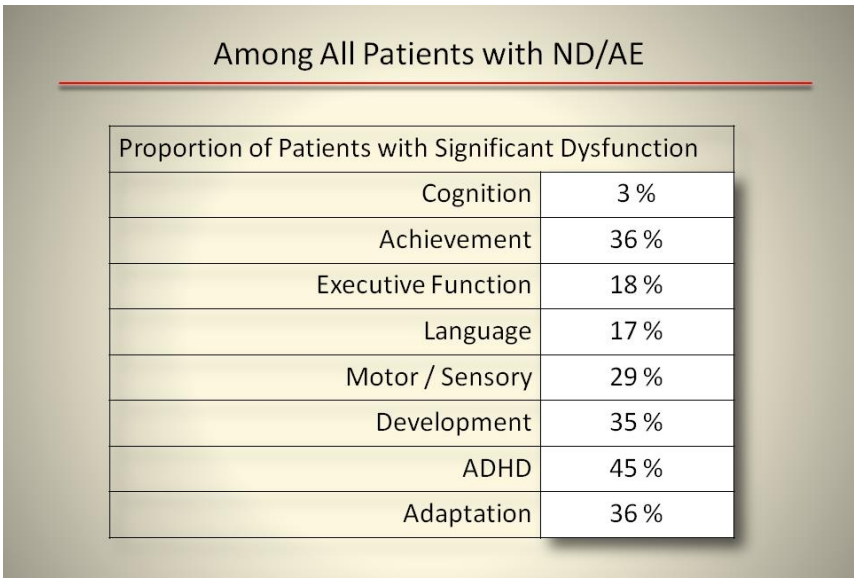
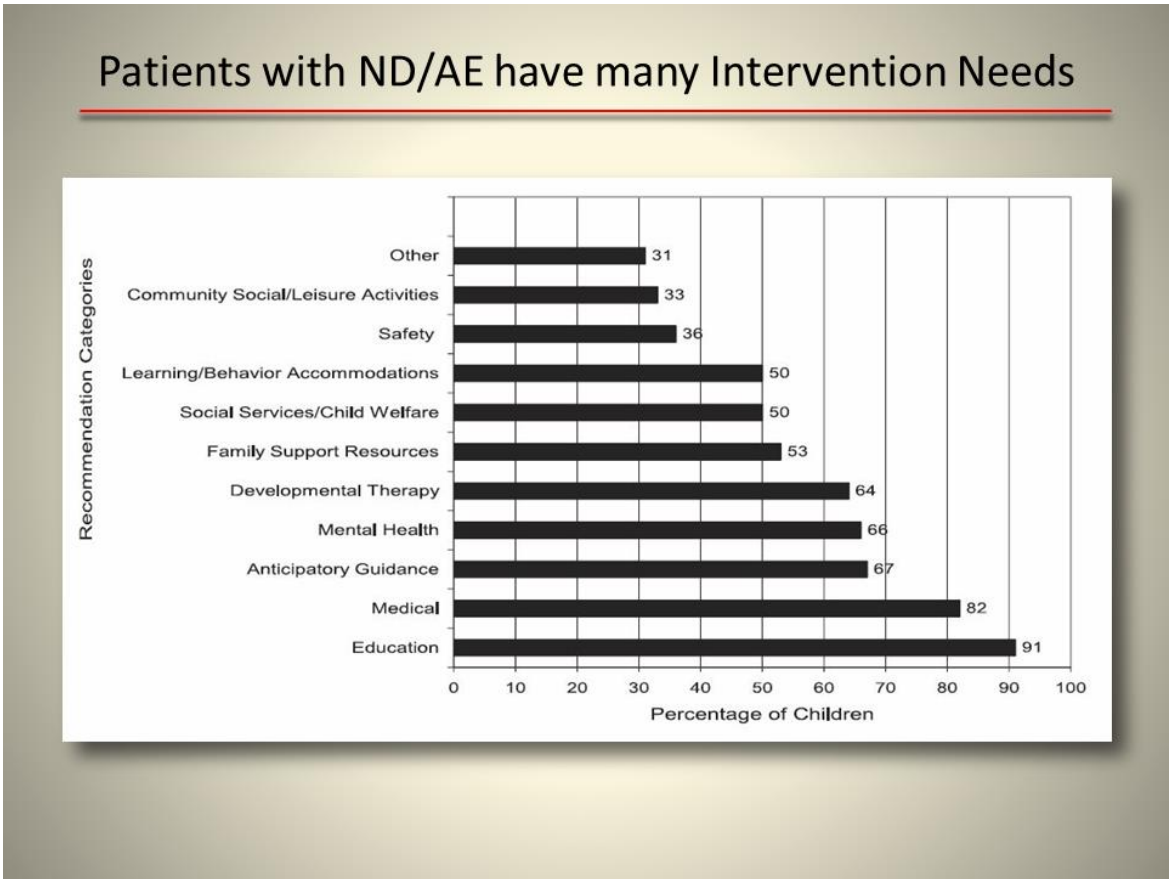


FIG. 24 Among patients evaluated in the WA FASDPN clinics, those with ND/AE received as many intervention recommendations as those with FAS/PFAS and SE/AE.[67]



<u>4C.</u> The term ARND (like Fetal Alcohol Effects (FAE)) should be abandoned and replaced with medically valid terms like SE/AE and ND/AE.

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.[9] The problem with the diagnostic terms used to date (Fetal Alcohol Effects (FAE)[12] and Alcohol-Related Neurodevelopmental Disorder (ARND)[5]) is they imply that the patient's outcomes are *alcohol effects or alcohol-related.* They imply *alcohol caused the patient's* outcomes. But this presumption in an individual patient is medically invalid because the CNS abnormalities are not specific to (caused only by) prenatal alcohol exposure. There are many other known and 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 causal role of alcohol in an *individual patient*. And it is never just alcohol. There are many other known and unknown risk factors that may be partly or even fully responsible for the patient's outcome.[26] (Figure 21).

The solution to this problem is to replace the term ARND with ND/AE and SE/AE. In 1995, Aase, Jones, & Clarren proposed discontinuation of the term Fetal Alcohol Effects (FAE). "*We propose abandoning the clinical use of the term FAE with its implications of causation. A diagnosis that implies causation should not be applied unless the relationship can be proven. 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. Several*

unfortunate consequences may result from inappropriately using the term FAE: Women are stigmatized for having damaged their children by drinking during pregnancy when it is by no means certain that they have done so."[21] But, in 1996, the term Alcohol Related Neurodevelopmental Disorder (ARND) was introduced with all the same limitations of FAE.[5] In 1997, the 4-Digit Code introduced the following terms to replace ARND[1] ND/AE Neurobehavioral Disorder / Alcohol Exposed and SE/AE Static Encephalopathy / Alcohol Exposed One need not confirm a causal link between a patient's alcohol exposure and neurobehavioral disorder to provide effective intervention [26,27,63,67,68] and prevention.[24,38] Access to services should be based on a person's disability, not on what caused their disability.[9,21] Most recently, the DSM-5[69] included this FASD diagnostic subgroup under conditions for further study and chose to label it Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE). And the recently published recommendations for the Australian FASD diagnostic guidelines chose to label this group Neurodevelopmental Disorder-Alcohol Exposed (ND-AE).[70]

When one uses a term like ARND, one finds themself wanting/needing to require an excessive exposure to alcohol to increase the odds that the child's impairments might in fact be caused, at least in part, by their alcohol exposure. This is a dangerous road to go down. 1) Setting a threshold of excessive exposure for Alcohol-Related Neurodevelopmental Disorder (ARND) does not confirm the patient's alcohol exposure is related to their neurodevelopmental disorder. 2) Alcohol is never the only risk contributing to the neurodevelopmental disorder (Figure 21). 3) One is sending a dangerous message that lower levels of alcohol exposure are safe. 4) And one is blaming a woman for harming her child, when they have no ability to make/defend such a claim. These claims have medical, ethical and even legal consequences.

The WA FASDPN has effectively case-defined, diagnosed, and referred children with "ARND" for intervention services using the 4-Digit Code for 20 years, without calling it ARND. Of the 2, 550 patients with FASD diagnosed in the first 20 years.[26]

- 1,122 were diagnosed with ND/AE (moderate "ARND)
- 612 were diagnosed with SE/AE (severe "ARND)
- 100% have confirmed alcohol exposure, most with exposures as high as those with FAS (Figure 22).
- All risk factors are documented and reported in the medical record, not just the alcohol exposure (Figures 25, 26).
- All receive comprehensive intervention recommendations (Figure 24).[67]
- It is a child's disability, not their exposure that qualifies them for services.
- 84% of families report the intervention services met all or most of their needs. (Figure 31)

The term ARND is not needed to qualify a patient for services. There tends to be a strong belief among some families and clinicians that the only diagnosis that will qualify a child for services is FAS. Along the same lines, it is also believed that the outcome must be blamed on (linked to) the alcohol (e.g., ARND) for a child to qualify for services. Twenty years of family surveys in the WA State FASD clinics confirm that a diagnosis of FAS or ARND is not required to access and benefit from services. Families whose children received a diagnosis of SE/AE or ND/AE were as likely to access and benefit from services as families whose children received a diagnosis of FAS or PFAS.[26] (Figure 31)

FIG. 25 The 4-Digit Code provides generic descriptions of all FASD diagnostic subgroups, including the text above for SE/AE.[3] It is a standard of practice with the 4-Digit Code to clearly state that alcohol is not the only risk factor that could be contributing to a patient's outcomes.

Medical Summary

Final Diagnosis: Static encephalopathy / Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found so the patient does not have FAS, but there was evidence of significant CNS damage/dysfunction as you will see noted on the attached pages. There was also a clear history of exposure to significant amounts of alcohol during gestation. In this situation, we use the term "static encephalopathy" to describe the patient's condition. On the attached sheets are the specific findings in this patient's case that led us to this conclusion. The diagnosis of static encephalopathy does not mean that alcohol is the only 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. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy face.

Individuals with significant CNS abnormalities have structural, neurological, and/or cognitive/behavioral evidence of CNS damage/dysfunction, and should be viewed as individuals with disabilities. The diagnosis of static encephalopathy has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

5. The 4-Digit Code's method of documenting prenatal alcohol exposure not only detects significant correlations between exposure and outcomes, but also detects exposure patterns that distinguish the diagnostic subgroups.

5A. The 4-Digit Code form used to document prenatal alcohol exposure is both effective and sensitive.

The 1-page standardized form (Figure 26) used to record prenatal alcohol exposure effectively addresses the challenges inherent in obtaining these exposure histories.[3] Full, accurate exposure information is rarely available in a FASD diagnostic clinical setting (Figure 29). Nevertheless, significant correlations are detected between prenatal alcohol exposure and measures of growth deficiency, facial phenotype, and CNS structural and functional abnormalities.[26] For example, frontal lobe volume was found to decrease significantly with increasing number of drinks per drinking occasion and duration of exposure during pregnancy.[16] (Figure 27A). Even patterns that significantly distinguish FAS/PFAS from SE/AE are detected.[9,26] (Figure 27B). And when measures of prenatal alcohol exposure among the 2,550 patients evaluated at the FASDPN clinics over the past year are assessed, the prevalence of drinking all three trimesters declines significantly when plotted across the patients' 30 birth cohorts dating back to 1980 (Figure 27C). As noted above, when the gestalt method of diagnosis[13] was practiced in the FASDPN in the early 1990's, no correlations between alcohol and patient outcomes were detected.[4]

FIG. 26 The 4-Digit Code provides a 1-page standardized form (page 8 of the Diagnostic Form) to record prenatal alcohol exposure that effectively addresses the challenges inherent in obtaining these exposure histories.[3]

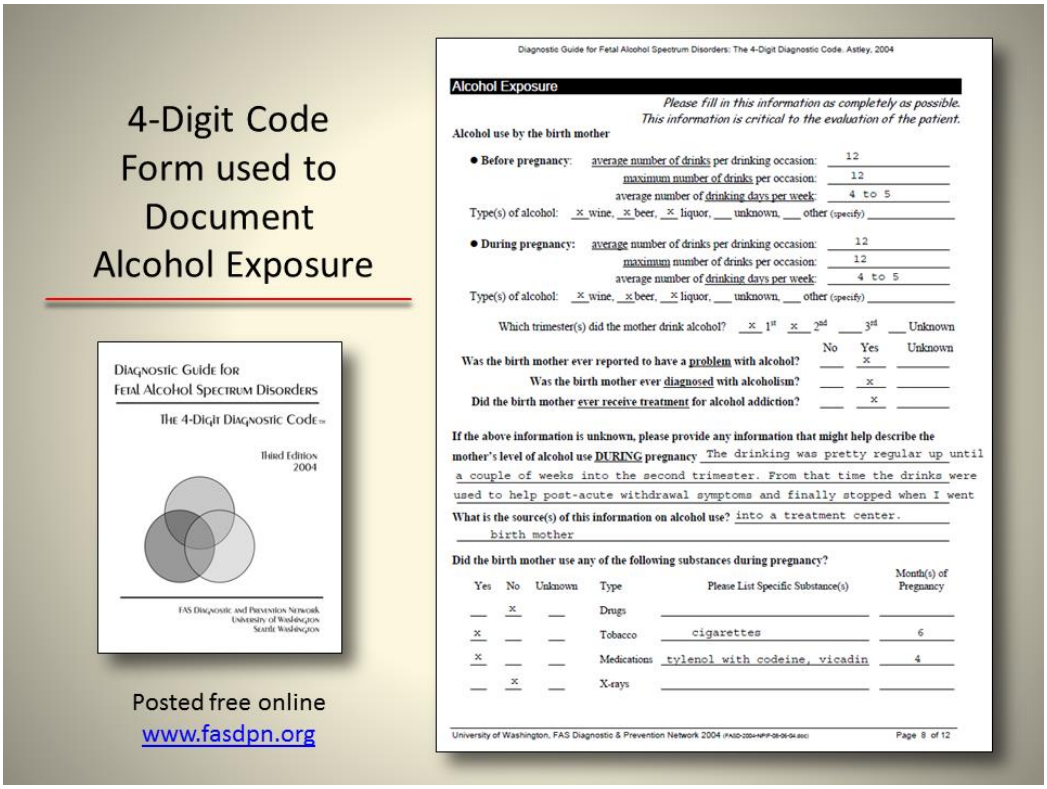
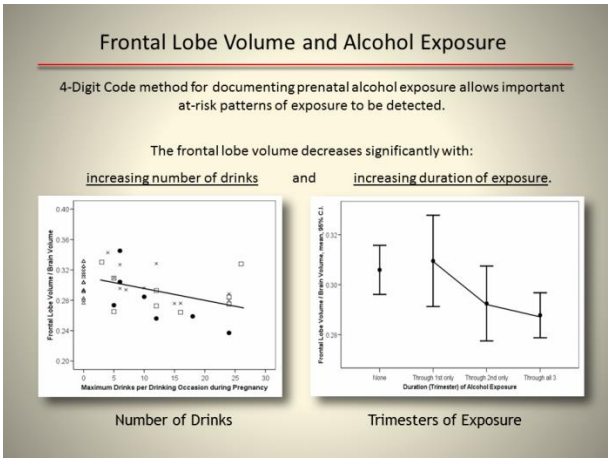
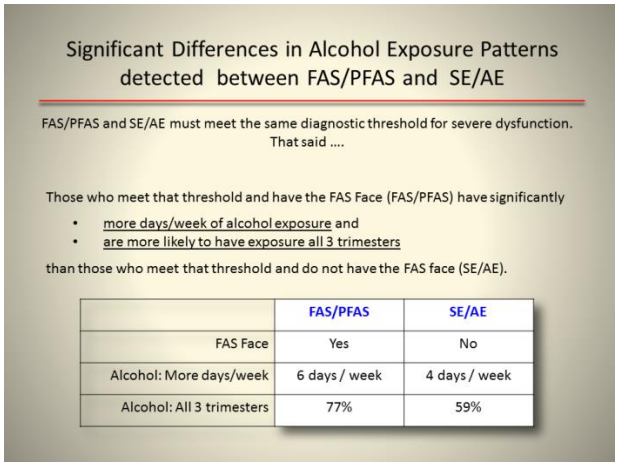


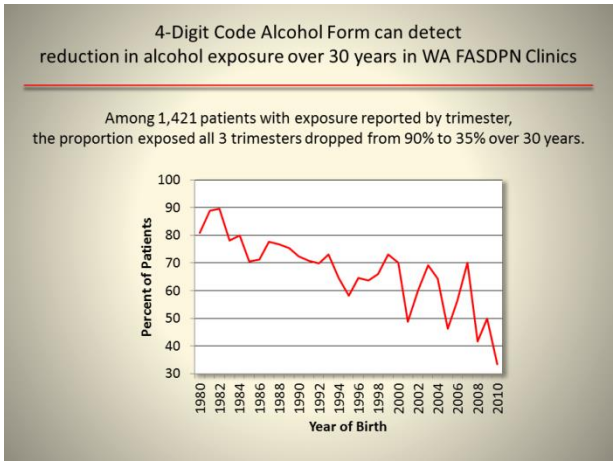
FIG. 27 The 4-Digit Code's method of documenting prenatal alcohol exposure: (A) not only detects statistically significant correlations between exposure and outcomes[16], but also (B) detects statistically significant exposure patterns that distinguish the diagnostic subgroups[26], and (C) detects significant declines in exposure over time.



A



B

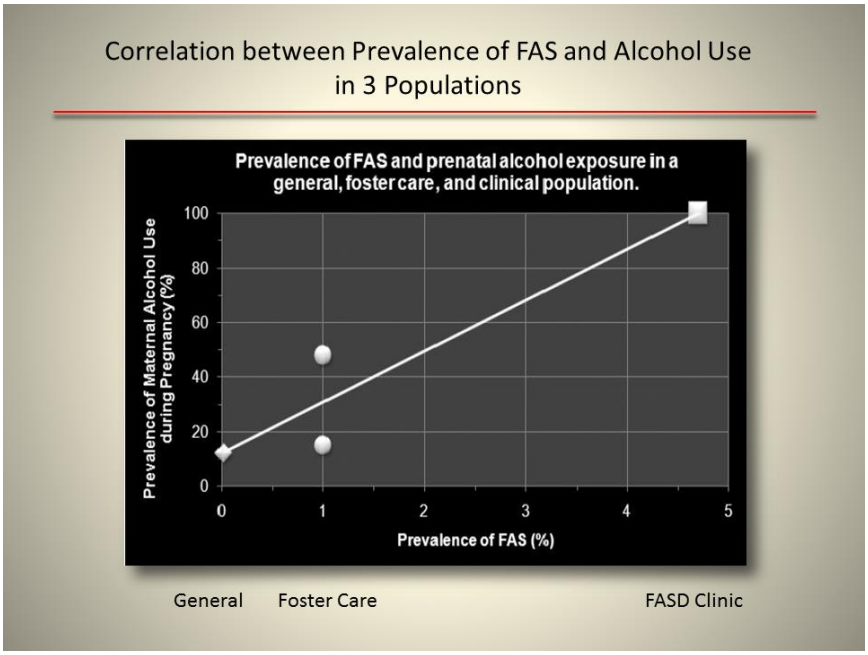


C

5B. The prevalence of maternal alcohol use during pregnancy correlates with the prevalence of FAS as defined by the 4-Digit Code

Two studies document a significant correlation between the prevalence of maternal alcohol use during pregnancy and prevalence of FAS as defined by the 4-Digit Code. In a 10-year active case-ascertainment FAS screening program of foster care in Seattle, WA, the prevalence of maternal drinking during pregnancy in Washington State measured through PRAMS declined significantly (p <0.001) from 1993 to 1998 as did the prevalence of fetal alcohol syndrome among foster children born across those same years (P <0.03) (Figure 6).[24] In a second study, the correlation between the prevalence of FAS to the prevalence of prenatal alcohol exposure across three population bases (the FASDPN clinic, a Seattle foster care program, and the general U.S. population), a significant linear trend was revealed (Figure 28).[26]

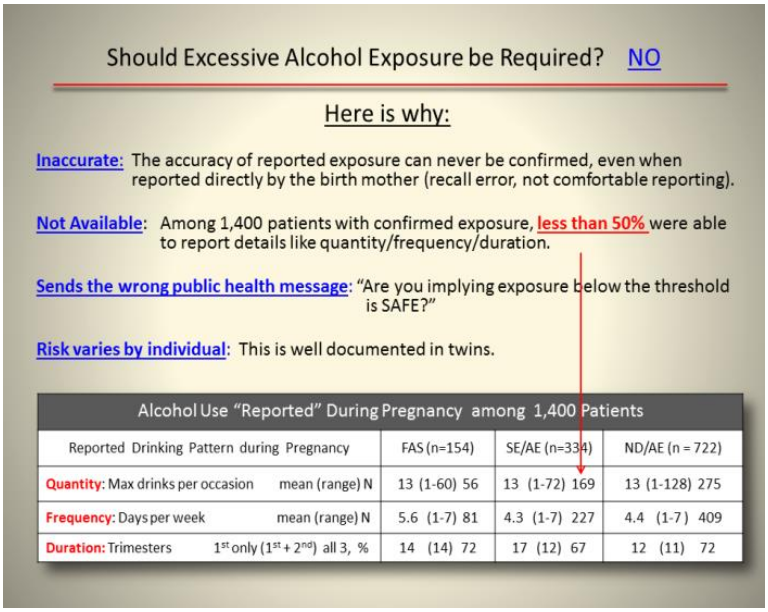
FIG. 28 Prevalence of FAS and prevalence of maternal alcohol use during pregnancy in three populations.[26] ◆General U.S. population (FAS = 0.2%[70], alcohol use = 12.2%). ●King County WA foster care population (FAS = 1%, alcohol use = 15% to 48%).[24] ■ WA FASDPN clinical population (FAS = 4.7%, alcohol use = 100%).[26] Best fit linear trend line: y = 18.989x + 12.352; R-squared = 0.89.



5C. An 'excessive' alcohol exposure history should not be required for a diagnosis 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.[9] 1.) As our tools for measuring outcome become more sensitive, our ability to identify adverse outcomes at lower exposures increases.[72] 2.) Risk from alcohol exposure varies between fetuses[73], even between fraternal twins with ostensibly identical exposure.[74,75] 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 who? 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.) 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. Even a birth mother can have difficulty accurately recalling her alcohol use during a pregnancy, especially if that pregnancy was years ago. Among the first 1,400 patients with a confirmed prenatal alcohol exposure evaluated in the WA FASDPN clinics, less than half had measures of quantity, frequency, and duration of alcohol exposure available.[26] This information would be required if an excessive exposure history had to be confirmed. "Excessive"alcohol exposures should not be required for FASD diagnoses (Figure 29). To minimize incorrectly linking a prenatal alcohol exposure to an outcome in an individual patient, diagnostic guidelines should confirm their definition of the FAS facial phenotype is highly specific to prenatal alcohol exposure, avoid use of terms like ARND that imply causality, and report all risk factors that may be contributing to an individual's outcomes, not just the alcohol.

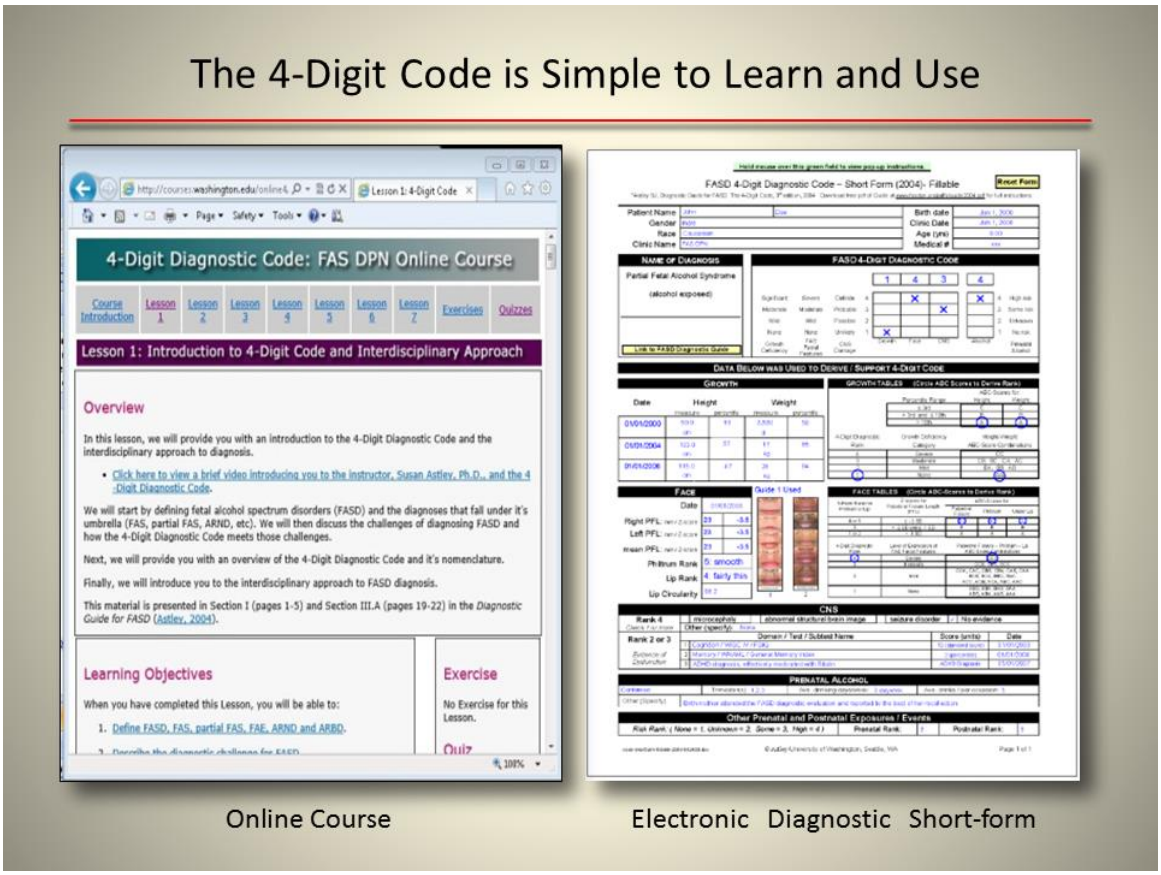
FIG. 29 Four reasons why an FASD diagnostic guidelines should not require 'excessive' prenatal alcohol exposure.[9]



6. The 4-Digit Code has been effectively and efficiently taught to interdisciplinary FASD diagnostic teams worldwide through an inexpensive Online Course.

Clinicians report high satisfaction with the 4-Digit Code. The 4-Digit Code was designed to be a self-taught coding system that could be implemented by simply following the directions provided in the FASD 4-Digit Diagnostic Guide.[1-3] For clinical teams who prefer a more comprehensive introduction to FASD diagnosis and instruction on the use of the 4-Digit Code, the FASD 4-Digit Code Online Course was developed in 2004.[41] (Figure 30A). The Online course is an individual-start, self-paced, fully online program that includes readings, exercises, self-grading quizzes and videos of an entire FASD diagnostic evaluation conducted by the UW FASD interdisciplinary team. Over 700 professionals worldwide have completed the accredited course. Surveys of hundreds of clinicians over 20 years confirm: 93% of professionals describe the 4-Digit Code as clear and 99% of professionals report they would recommend it to others. The 4-Digit Diagnostic Code is practical to use. The Code can be administered using nothing more than the Lip-Philtrum Guides and the 1-page 4-Digit Code Short Form programmed to derive the 4-Digit Code from data entered (Figure 30b) (available free online).

FIG. 30 A. The FASD 4-Digit Code Online Course.[41] B. The 4-Digit Code Short Form is a free pdf posted online that is programmed to generate the 4-Digit Code from data entered into the form.



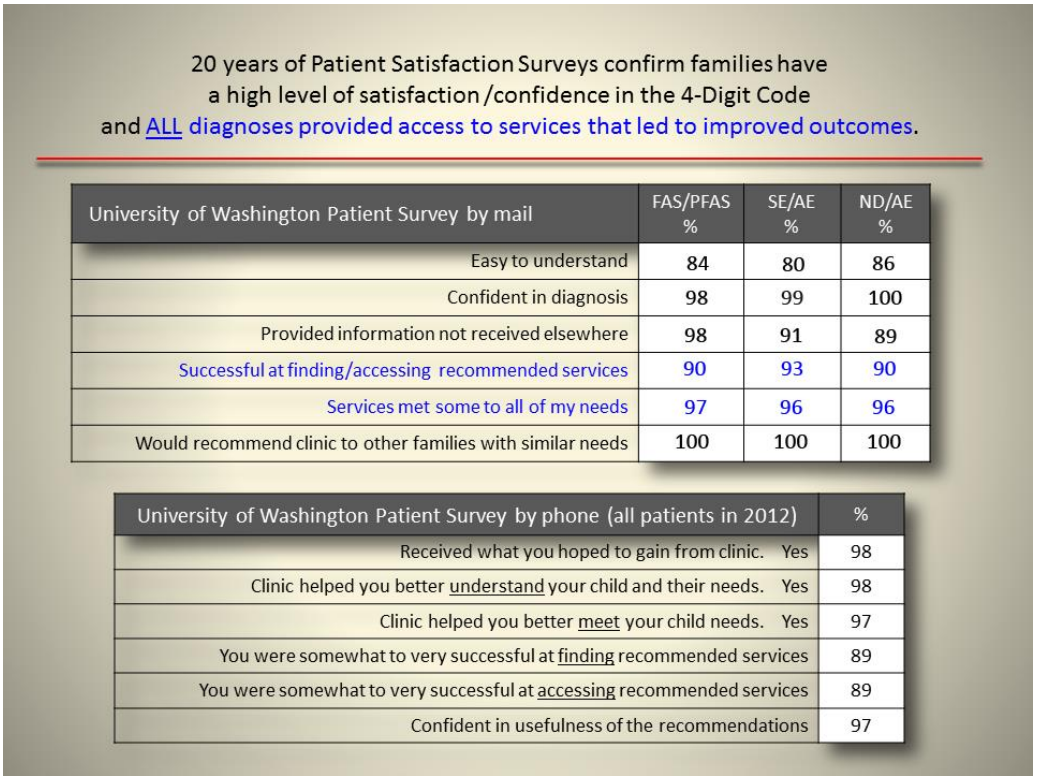
7. The 4-Digit Code has high inter-rater reliability (reproducible) across clinics.

Inter-rater reliability was confirmed to be high prior to the release of the 4-Digit Code, as described above in section 1D, and continued to be high over the next 18 years. Inter-rater reliability between the seven WA FASD Network clinics and the University of Washington Core clinic resulted in an exact match on diagnostic category for 93% of the 677 FASD diagnostic evaluations they conducted over 18 years (Kappa = 0.92, p = 0.000). The most common source of error was facial measurement when the FAS Facial Photographic Analysis software was not used. For example, when clinician's used the six inch plastic ruler to measure the PFL, their measures were on average 1 to 2 mms below the measure derived using the FAS Facial Photographic Analysis Software. This is the direction of error that would be expected due to the slight curvature of the facial plane as demonstrated in an animation on the FASDPN website. A 1-2 mm error can have a significant impact on diagnostic classification accuracy. For example, if a 7 year old girl had PFLs that were truly well within the normal range (25 mm; only 0.4 SDs below the population mean for girls her age[76]), a 1 mm under-estimate (24 mm) would make the PFLs falsely appear to be 1.3 SDs below the mean and thus falsely appear to meet the PFL criteria for the FAS facial phenotype using the CDC or Revised IOM FASD guidelines ($\leq 10^{th}$ percentile or $\geq$ 1.28 SDs below the mean). A 2 mm under-estimate (23 mm) would make the PFLs falsely appear to be 2.1 SDs below the mean and thus falsely appear to meet the PFL criteria for the FAS facial phenotype using the 4-Digit Code ($\leq$ 2 SDs below the mean). Measuring PFLs with a handheld ruler has been confirmed to be highly inaccurate and variable based on data collected over 20 years at the WA FAS DPN. Among eight clinicians measuring PFLs directly with a ruler on 52 to 322 patients each, 12% to 50% of their measurements were 1 or more mm above or below the PFL measured from the child's facial photo using the Facial Software. Six clinicians routinely under-estimated the PFL, two routinely over-estimated the PFL, and one was as likely to overestimate the PFL as underestimate the PFL. The FAS Facial Photographic Analysis Software[33] was developed to overcome these measurement errors and is used by the WA FASDPN as a standard of medical practice for all diagnostic evaluations.

8. Families report high satisfaction and confidence with the interdisciplinary approach to FASD diagnosis using the 4-Digit Code.

Twenty years of patient satisfaction surveys confirm families have a very high level of satisfaction and confidence in the 4-Digit Code administered by an interdisciplinary team.[26] (Figure 31). A 10-question patient satisfaction survey has been sent to all patients evaluated at the UW FASDPN clinic since 1993. The survey may be completed anonymously and comes with a stamped, addressed return envelope to maximize participation in the survey. Patients universally expressed high satisfaction for the FASD diagnostic services provided by the University of Washington (Figure 31). One hundred percent would recommend the Clinic to other families with similar needs. Overall, 92% said they received information they were unable to obtain elsewhere, despite the fact the clinic is located in a large metropolitan area (Seattle) with many genetic, neurodevelopmental, and psychological evaluation services available. Overall, 83% found the explanation of the diagnosis using the 4- Digit Code easy to understand.

FIG. 31 Twenty years of patient satisfaction surveys confirm families have a very high level of satisfaction and confidence in the 4-Digit Code administered by the University of Washington interdisciplinary diagnostic team.[26] Family's whose child received a diagnosis of SE/AE or ND/AE were as likely to report successfully accessing and benefiting from recommended intervention services as family's whose child received a diagnosis of FAS/PFAS.



9. Patient follow-up surveys report all FASD diagnoses (FAS, PFAS, SE/AE, and ND/AE) provided equal access to intervention services that led to improved outcomes.

Perhaps most informative; family's whose child received a diagnosis of SE/AE or ND/AE were as likely to report successfully accessing and benefiting from recommended intervention services as family's whose child received a diagnosis of FAS/PFAS.[26] (Figure 31). This is in contrast to the oft stated belief that a family will not qualify for services if the diagnosis is not FAS/PFAS or at least given a name that implies alcohol is the causal agent (e.g., ARND). Overall, 82.1% of families reported being somewhat to very successful in finding the recommended intervention services and 83.7% reported these services met some to all of their needs.

CONCLUSION

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 diagnosis. A diagnosis reflects the condition of a patient; however, because a diagnosis serves many purposes (e.g., 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. Services should be available for individuals across the full continuum of FASD, not just those with FAS.

Acknowledgments

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Corresponding Author: astley@uw.edu

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