WA State FAS Diagnostic & Prevention Network (FAS DPN)


Validation of FASD Diagnostic Systems

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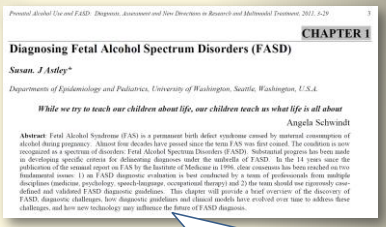
## Diagnosing FASD: 2011 Chapter

*Prenatal Alcohol Use and FASD: Diagnosis, Assessment and New Directions in Research and Multimodal Treatment, 2011, 3-29* 3

CHAPTER 1

**Diagnosing Fetal Alcohol Spectrum Disorders (FASD)**

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

Angela Schwindt

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

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http://depts.washington.edu/fasdpn/pdfs/astley-FASD-chapter2011.pdf

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## Diagnosing FASD: Chapter (Astley, 2011)

FAS

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

| | 4-Digit Code (2004)[38] | CDC (2004) [36] | Canadian (2005) [37] | Hoyme (2005)[39] | IOM (1996)[E1] |
|---|---|---|---|---|---|
| Growth | Prenatal and/or postnatal height or weight ≤ 10th percentile<br>(Growth Ranks 2-4) | Prenatal and/or postnatal height or weight ≤ 10th percentile<br>(Growth Ranks 2-4) | At least 1 of the following:<br>• Prenatal and/or postnatal height or weight ≤ 10th percentile<br>• Weight-to-height ratio (≤ 10th percentile)<br>(Growth Ranks 2-4) | Prenatal and/or postnatal height or weight ≤ 10th percentile<br>(Growth Ranks 2-4) | At least 1 of the following:<br>• Low birth weight<br>• Low weight for height<br>• Decelerating weight<br>(Growth Ranks 1-4) |
| Face | All 3 of the following at any age:<br>• PFL ≤ 3rd percentile<br>• Smooth philtrum Rank 4 or 5<br>• Thin upper lip Rank 4 or 5<br>(Face Rank 4) | All 3 of the following:<br>• PFL ≤ 10th percentile<br>• Smooth philtrum Rank 4 or 5<br>• Thin upper lip Rank 4 or 5<br>(Face Ranks 3-4) | All 3 of the following at any age:<br>• PFL ≤ 3rd percentile<br>• Smooth philtrum Rank 4 or 5<br>• Thin upper lip Rank 4 or 5<br>(Face Rank 4) | 2 or more of the following:<br>• PFL ≤ 10th percentile<br>• Smooth philtrum Rank 4 or 5<br>• Thin upper lip Rank 4 or 5<br>(Face Ranks 2-4) | Characteristic pattern that includes features such as short PFL, flat upper lip, flattened philtrum, and flat midface.<br>(Face Ranks 1-4) |
| CNS | At least 1 of the following:<br>• Structural/Neurological (e.g., OFC ≤ 3rd percentile, abnormal structure, seizure disorder, hard signs)<br>• Severe Dysfunction (3 or more domains* of function with impairment 2 or more SDs below the norm)<br>(CNS Rank 3 and/or 4) | At least 1 of the following:<br>• Structural/Neurological (e.g., OFC ≤ 10th percentile, abnormal structure, seizure disorder, hard-soft signs)<br>• Dysfunction*<br>○ 3 or more domains of function with impairment 1 or more SDs below the norm<br>○ Global deficit (2 or more SDs below the norm)<br>(CNS Ranks 3-4) | At least 1 of the following:<br>Structure/Neurological/Functional domains with impairment*<br>• Hard-soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication.<br>(CNS Ranks 3 and/or 4) | At least 1 of the following:<br>• Structural<br>○ OFC ≤ 10th percentile<br>○ Abnormal structure<br>(CNS Rank 1 or 4) | At least 1 of the following:<br>• Structural/Neurological:<br>○ Decreased cranial size at birth<br>○ Abnormal structure (e.g., microcephaly, partial/complete agenesis of the corpus callosum, cerebellar hypoplasia)<br>○ Neurological hard-soft signs<br>(CNS Rank 4?) |
| Alcohol | Confirmed or Unknown<br>(Alcohol Ranks 2-3 or 4) | Confirmed or Unknown<br>(Alcohol Ranks 2-3 or 4) | Confirmed or Unknown<br>(Alcohol Ranks 2-3 or 4) | Confirmed-excessive or Unknown<br>(Alcohol Ranks 2 or 4) | Confirmed-excessive or Unknown<br>(Alcohol Ranks 2 or 4) |

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## Examples of Contrasts between the Diagnostic Guidelines

An example where the Revised IOM Guidelines differ from the other FASD Diagnostic Guidelines.

| Patient Outcomes (10 years old) | |
|---|---|
| Growth: | Height 10th percentile, weight 95th percentile |
| Face: | PFL 10th percentile |
| | Somewhat smooth philtrum, Rank 4 |
| | Thick upper lip, Rank 1 |
| CNS: | OFC 10th percentile, IQ 100, No evidence of dysfunction |
| Alcohol: | Unknown |
| **Diagnostic Classifications** | |
| IOM: | Unable to classify. Not sufficiently case-defined |
| 4-Digit Code: | Not FASD, Code 2212 |
| Canadian: | Not FASD |
| CDC: | Not FAS |
| Revised IOM (Hoyme): | FAS / Alcohol Unknown |

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## Examples of Contrasts between the Diagnostic Systems

An example where the Canadian Guidelines differ from the other FASD Diagnostic Guidelines.

| Patient Outcomes (2 years old) | |
|---|---|
| Growth: | Height 1st percentile, weight 1st percentile |
| Face: | PFL 1st percentile |
| | Smooth philtrum, Rank 5 |
| | Thin upper lip, Rank 5 |
| CNS: | OFC 1st percentile, BSID outcomes low-normal |
| Alcohol: | Intoxicated weekly throughout pregnancy |
| **Diagnostic Classifications** | |
| IOM: | FAS/PFAS |
| 4-Digit Code: | FAS / Alcohol Exposed (Code = 4444) |
| Canadian: | Not FASD |
| CDC: | FAS / Alcohol Exposed |
| Revised IOM (Hoyme): | FAS / Alcohol Exposed |

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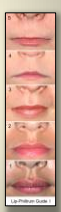
## Examples of Contrasts between the Diagnostic Systems

An example where the 4-Digit Code differs from the other FASD Diagnostic Guidelines.

| Patient Outcomes (10 years old) | |
|---|---|
| Growth: | Height 50th percentile, weight 50th percentile |
| Face: | Normal PFL, 50th percentile |
| | Normal philtrum, Rank 2 |
| | Normal upper lip, Rank 2 |
| CNS: | 2 Domains of significant dysfunction (ADHD, Memory) No CNS structural or neurological abnormalities. |
| Alcohol: | 1 glass wine /day throughout pregnancy. |
| **Diagnostic Classifications** | |
| IOM: | Not FASD |
| 4-Digit Code: | Neurobehavioral Disorder/Alcohol Exposed (Code = 1123) |
| Canadian: | Not FASD |
| CDC: | Not FAS |
| Revised IOM (Hoyme): | Not FASD |



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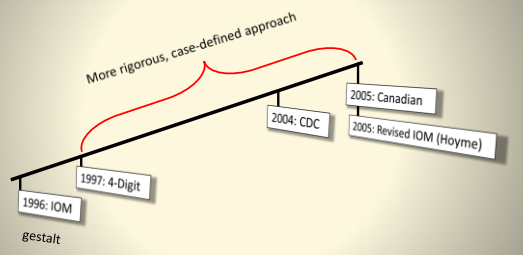
## FAS/D Diagnostic Guidelines: Timeline

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## FASD 4-Digit Diagnostic Code


**All Diagnostic Tools and Courses available at cost or free on the web.**
**www.fasdpn.org**

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## Abbreviated Case-Definitions of 4-Digit Code

| Rank | Growth (3) | Face (4) | CNS (3) | Alcohol (4) |
|---|---|---|---|---|
| 4 | ≤ 2 % | All 3 features | Structural / Neurological Abnormalities | Confirmed High |
| 3 | 3 - 5 % | 2.5 features | Severe Dysfunction | Confirmed Moderate |
| 2 | 6 -10 % | 1-2 features | Moderate Dysfunction | Unknown |
| 1 | > 10 % | No features | No Dysfunction | Confirmed Absent |

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**3434 is one of twelve 4-Digit Codes for FAS**

## Example of 4-Digit Codes for FAS and PFAS

A **FAS (alcohol exposed)**

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

B **FAS (alcohol exposure unknown)**

| | | |
|---|---|---|
| 2432 | 3432 | 4432 |
| 2442 | 3442 | 4442 |

C **Partial FAS (alcohol exposed)**

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

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## 4-Digit Code produces 4 Diagnostic Subgroups (not 256!)

| Diagnosis | | Growth | FAS Face | CNS | | Alcohol |
|---|---|---|---|---|---|---|
| 1. FAS | | growth | face | severe | | alc |
| 2. PFAS | Partial FAS | | face | severe | | alc |
| 3. SE/AE | Static Encephalopathy / Alc Exposed | | | severe | | alc |
| 4. ND/AE | Neurobehavioral Disorder / Alc Exposed | | | | moderate | alc |

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## 4-Digit Code produces 4 Diagnostic Subgroups (not 256!)

| Diagnosis | | Growth | FAS Face | CNS | | Alcohol |
|---|---|---|---|---|---|---|
| 1. FAS | | growth | face | severe | | alc |
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| 3. SE/AE | Static Encephalopathy / Alc Exposed | | | severe | | alc |
| 4. ND/AE | Neurobehavioral Disorder / Alc Exposed | | | | moderate | alc |

SE/AE = severe "ARND"
ND/AE = moderate "ARND"

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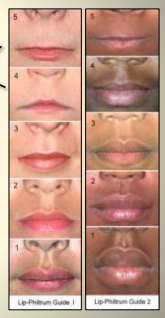
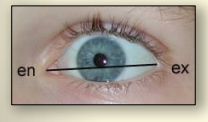
## 4-Digit Code FAS Face

| | |
|---|---|
| 1) Short PFL | ≤ -2 SD |
| 2) Smooth Philtrum | Rank 4 or 5 |
| 3) Thin Upper Lip | Rank 4 or 5 |

FAS




Palpebral fissure length (PFL) = endocanthion to exocanthion

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## Assessing a Diagnostic Tool's Performance

Precision: A precise measure is one that is nearly the same value each time it is measured. It is reproducible. It is reliable.

- Measure PFL 3 times, get 27 mm each time.

Accuracy: The degree to which a measurement actually represents the true value.

- If the true PFL = 28 mm, the measures above are precise, but inaccurate.

Validity: How well an instrument measures what it purports to measure.

- Do the guidelines produce clinically distinct subgroups?
- Do subjects who meet the criteria for FAS actually have FAS?
- Are the brains of FAS distinct from the brains of ARND?
- Is the FAS facial phenotype specific to prenatal alcohol exposure (only observed in subjects with prenatal alcohol exposure)?
- Does face predict brain?
- Do alcohol exposure patterns differ between FAS and ARND?
- Do two clinics using the same Guidelines derive the same diagnoses?

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## Interpretation of Validity

Validity is not an all-or-nothing characteristic of an instrument. An instrument cannot really be said to possess or lack validity; it is a question of degree.

Furthermore, although the process of testing the validity of an instrument is referred to as validation, it is inappropriate to speak of the process as yielding proof of validity.

Like all tests of hypotheses, the testing of an instrument's validity is not proved, established, or verified, but rather supported to a greater or lesser degree by evidence.

Validation is a never-ending process. The more evidence that can be gathered that an instrument is measuring what it is supposed to be measuring, the more confidence individuals will have in its validity.

The performance (validity) of a FASD Diagnostic System should be rigorously assessed, not assumed.

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## The Performance of FASD 4-Digit Code was Tested before it was Published

| | |
|---|---|
| 1993 | University of Washington FAS DPN interdisciplinary diagnostic clinic opened. |
| 1993-96 | A gestalt approach to FASD diagnosis was used. |
| 1995 | Began development of the 4-Digit Code. |
| | The performance of the code was tested retrospectively on 598 patients previously diagnosed by gestalt and 100 patients prospectively, prior to release of the Code. |
| 1997 | The 1st edition of the Code was printed . |
| | The FAS DPN clinics stopped using the gestalt method and started using the 4-Digit Code. |
| 1999 | The 2nd edition of the Code was printed. |
| 2000 | A formal scientific study was published to compare gestalt and 4-Digit Code outcomes of 454 patients diagnosed in the FAS DPN clinic. |
| 2004 | The 3rd edition of the Code was printed. |
| 2009-10 | The Code continues to be tested, most notably through the MRI/MRS/fMRI and Profile studies. |

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## A Sample of the Evidence Supporting the Validation of the FASD 4-Digit Code

1. FAS Face confirmed to be highly specific (>95%) to FAS and alcohol.
2. Face predicts brain. The more severe the face, the more severe the brain.
3. The CNS Dysfunction Rank predicts brain. The more severe the CNS dysfunction Rank (1,2,3), the smaller the caudate.
4. The diagnoses FAS, PFAS, SE/AE, and ND/AE are clinically and statistically distinct .
   A. Only FAS/PFAS have the FAS face, small frontal lobes, reduced choline.
   B. Only FAS/PFAS and SE/AE have small caudates.
   C. FAS/PFAS have more severe CNS dysfunction than SE/AE.
   D. ND/AE have CNS structural abnormalities underlying their moderate CNS dysfunction.
5. Alcohol exposure patterns predict outcomes.
   A. Exposure patterns among FAS/PFAS distinct from SE/AE and ND/AE.
6. The 4-Digit Code is reproducible across clinics. Of 687 patients diagnosed at the WA Network Clinics, 91% received a diagnosis that matched the diagnosis rendered at the Univ WA Clinic.

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## 4-Digit Code vs Gestalt: Initial Evidence of Improved Performance

454 patients diagnosed by both Gestalt and 4-Digit Code:

Gestalt produced a highly variable FAS group.

52 patients received a gestalt diagnosis of FAS.
In the absence of rigorous guidelines, this group was very heterogeneous.

Of the 52 subjects with a gestalt diagnosis of FAS:
- only 17 had growth deficiency (<10th percentile)
- only 14 had the Rank 4 FAS face.
- only 27 had significant CNS structural/functional abnormalities.

When the more rigorous 4-Digit Code guidelines were applied:
- Only 10 of the 52 retained a diagnosis of FAS

4-Digit Code produced expected correlations; Gestalt did not.
- Face was NOT correlated with brain when the gestalt method was used.
- Face was highly correlated with brain when the 4-Digit Code was used.

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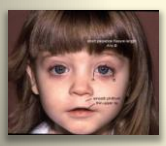
## 4-Digit Code (Rank 4) FAS Face is highly specific to FAS/Alcohol

| Rank 4 FAS Facial Phenotype | |
|---|---|
| Short PFL | ≤ -2 SD (≤ 2%) |
| Smooth Philtrum | Rank 4 or 5 |
| Thin Upper Lip | Rank 4 or 5 |



F
A
S

1. The Rank 4 FAS Facial Phenotype is so specific to FAS and prenatal alcohol exposure (>95%) it is used to screen for FAS in foster care and serves to confirm exposure when exposure history unknown.
2. The Rank 4 FAS Face has never been observed in a child with no prenatal alcohol exposure.
3. The Rank 4 FAS face was derived empirically through a scientific study, not through clinical opinion.
4. When these facial criteria are relaxed, the face is no longer specific to FAS and alcohol.

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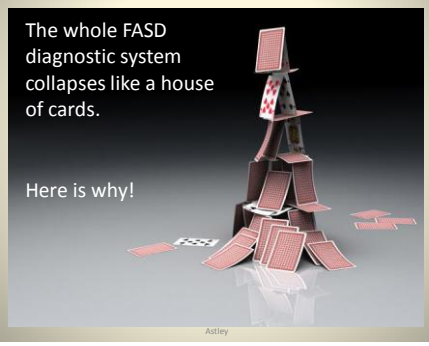
## What happens when the FAS face is not Specific to FAS and Prenatal Alcohol Exposure?

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## The Quintessential Role of the FAS Facial Phenotype

**Why are the criteria used to define the FAS facial phenotype so important to the medical validity of all FASD diagnoses?**

- When one makes a diagnosis of FAS, one is stating implicitly that the individual has a syndrome caused by prenatal alcohol exposure.
- One is also stating implicitly that the biological mother drank alcohol during pregnancy and, as a result, harmed her child.
- These are bold conclusions to draw and are not without medical and ethical consequences.

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## The Quintessential Role of the FAS Facial Phenotype

If the FAS Facial Phenotype is not CONFIRMED to be highly specific to FAS and alcohol exposure
the entire FASD diagnostic system breaks down.

1. The term (FAS) is rendered invalid.
   Since no feature is specific to (caused only by) alcohol, you can no longer call it FAS. You can no longer confirm alcohol is causally linked to any of the outcomes in an individual patient.
2. The diagnosis (FAS/alcohol exposure unknown) is also rendered invalid.
   The FAS face can no longer be used as a proxy measure of alcohol exposure when the exposure history is unknown.
3. FAS is no longer distinct from ARND.
   ARND is FAS without the face. But if there is no face, there is no distinction. Thus, one can no longer justify classifying FAS and ARND separately.
4. 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.

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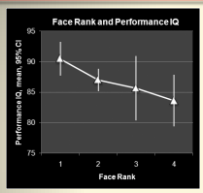
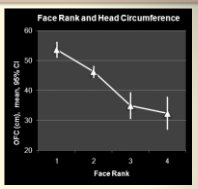
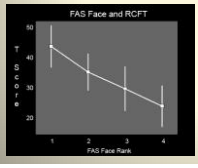
## Strong correlations between the 4-Digit FAS Face and brain support the validity of the 4-Digit Code Rank 4 FAS Facial Phenotype




- The FAS facial phenotype presents along a clinically meaningful continuum. It is not simply present or absent.
- The more severe the FAS face, the more severe the CNS structural/functional abnormality.

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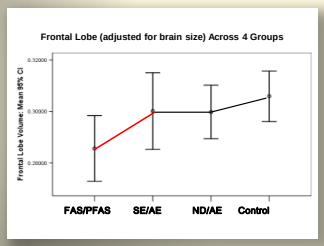
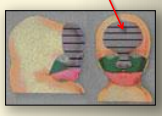
## Only those with the Rank 4 FAS Face have Disproportionately Smaller Frontal Lobe Volumes




This is particularly compelling since the morphogenesis of the middle and upper face is heavily influenced by signals emanating from the forebrain to the frontonasal prominence



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## Evidence that the FAS PFL criteria should be kept at 2%, not relaxed to 10%

Feldman et al., 2012 (study of 922 subjects)

- 1st trimester alcohol exposure correlated with smooth philtrum and thin upper lip.
- No pattern of prenatal alcohol exposure correlated with PFL ≤10%. (this was an unexpected finding).

Astley (study of 1,400 subjects).

- When a "short" PFL was defined as ≤ 10%, NO correlations were found with any pattern of prenatal alcohol exposure.
- When a short PFL was defined as ≤ 2%, strong, significant correlations were found with many patterns of alcohol exposure (1st trimester, binge, 5 days/wk).

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## Evidence that the FAS Facial criteria require all 3 features, not just 2 of the 3

The Revised-IOM criteria for the FAS phenotype relax the PFL to the 10th percentile and require only 2 of the 3 facial features be present.

A 2006 study confirmed these relaxations in the criteria rendered the Revised-IOM FAS facial phenotype non-specific to FAS and prenatal alcohol exposure.

The Revised-IOM FAS facial criteria were applied to a population of :

- Healthy, high functioning children (mean IQ = 120)
- With confirmed absence of prenatal alcohol exposure.

25% met the Revised-IOM criteria for the full FAS facial phenotype.

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## Lets look at the 4-Digit Code's Method for Classifying CNS Dysfunction

CNS Ranks 1, 2, and 3

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## CNS Dysfunction is Ranked on a 3-Point Scale

| Rank | Growth (3) | Face (4) | CNS (3) | Alcohol (4) | Rank |
|---|---|---|---|---|---|
| 4 | ≤ 2 % | All 3 features | Structural / Neurological Abnormalities | Confirmed High | 4 |
| 3 | 3 - 5 % | 2.5 features | 3. Severe Dysfunction | Confirmed Moderate | 3 |
| 2 | 6 -10 % | 1-2 features | 2. Moderate Dysfunction | Unknown | 2 |
| 1 | > 10 % | No features | 1. No Dysfunction | Confirmed Absent | 1 |

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## The 3 CNS Ranks were designed to predict increasing likelihood of underlying structural brain abnormality.

| CNS Rank | Label | Case-Definition | Likelihood of underlying structural brain abnormality |
|---|---|---|---|
| 3 | Severe Dysfunction | 3 or more domains, 2 SDs below the mean | Probable |
| 2 | Moderate Dysfunction | 1-2 domains , 2 SDs below the mean | Possible |
| 1 | No Dysfunction | No evidence of dysfunction | Unlikely |

Do they?

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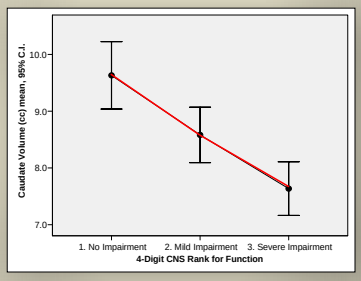
## YES!

## CNS Ranks 1, 2, 3 Correlate with Decreasing Caudate Volume




MRI Study: Caudate volume decreases significantly as CNS Functional Rank increases from 1) no impairment, to 2) mild impairment, to 3) severe impairment.

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Does the 4-Digit Code produce diagnostic subgroups with significantly distinct CNS structural/functional abnormalities?

## Yes!

FAS, PFAS, SE/AE, and ND/AE are clinically and statistically distinct.

1. Only FAS/PFAS have the FAS face, small frontal lobes, reduced choline.
2. Only FAS/PFAS and SE/AE have small caudates.
3. FAS/PFAS have more severe CNS dysfunction than SE/AE.
4. ND/AE have CNS structural abnormalities underlying their moderate CNS dysfunction.

Here is the evidence….

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## Sociodemographic Profile of 1,400 Patients with FASD in the WA FAS DPN clinics

| Characteristic | | N | % |
|---|---|---|---|
| **Gender:** | male | 812 | 58 |
| **Race:** | White | 684 | 49 |
| | Black | 92 | 7 |
| | American Indian/Native Alaskan | 115 | 8 |
| | Other | 509 | 36 |
| **Age** at diagnosis (yrs): | 0-3 | 258 | 18 |
| | 4-5 | 233 | 17 |
| | 6-10 | 482 | 34 |
| | 11-15 | 286 | 20 |
| | 16+ | 141 | 10 |
| **Annual Income** less than $35,0000 | | 385 | 65 |

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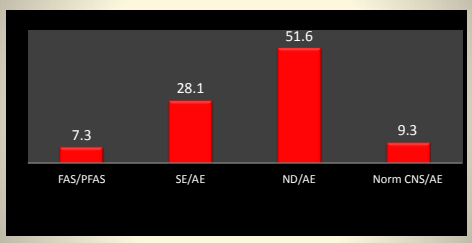
## FASD Diagnostic Outcomes for 1,400 Patients

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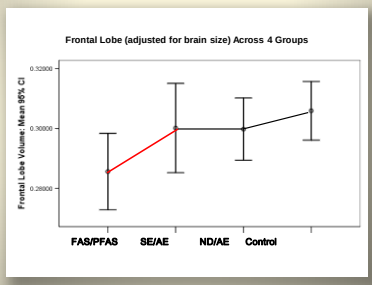
## Only those with FAS/PFAS had disproportionately smaller frontal lobe volumes

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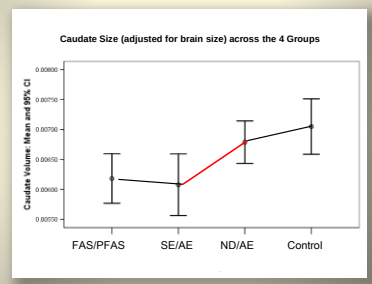
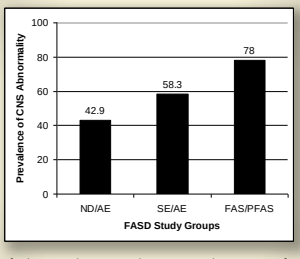
## Those with FAS/PFAS and SE/AE had disproportionately smaller caudate volumes




What FAS/PFAS and SE/AE have in common is severe CNS dysfunction (CNS Rank 3).

Astley

## Prevalence of CNS Structural Abnormalities increases with increasing severity of FASD diagnosis.



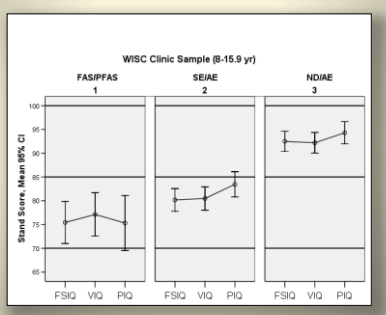

The prevalence of subjects with 1 or more brain regions that were significantly smaller than a healthy unexposed control group increased as severity of FASD diagnostic classification increased.

Even the ND/AE group with moderate dysfunction (CNS Rank 2) had structural abnormalities!

Astley

## WISC IQ decreases with increasing severity of FASD diagnosis

WISC

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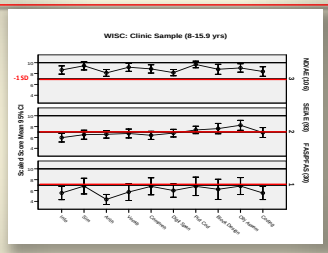
## WISC subtest scores decrease with increasing severity of FASD diagnosis.

WISC




FAS/PFAS and SE/AE must meet the same diagnostic threshold for severe dysfunction.
That said ….
Those who meet that threshold and have the FAS Face (FAS/PFAS) have more severe dysfunction than those who meet that threshold and do not have the FAS face (SE/AE).

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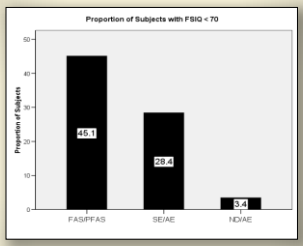
## Proportion of subjects with FSIQ < 70 increases with increasing severity of FASD diagnosis.

FSIQ




FAS/PFAS and SE/AE must meet the same diagnostic threshold for severe dysfunction.
That said ….
Those who meet that threshold and have the FAS Face (FAS/PFAS) have more severe dysfunction than those who meet that threshold and do not have the FAS face (SE/AE).

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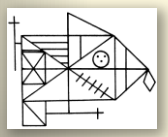
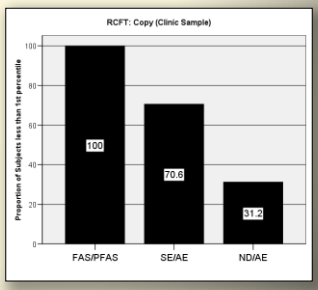
Proportion of subjects who fail the RCFT increases with increasing severity of FASD diagnosis.

Rey Complex Figure Test



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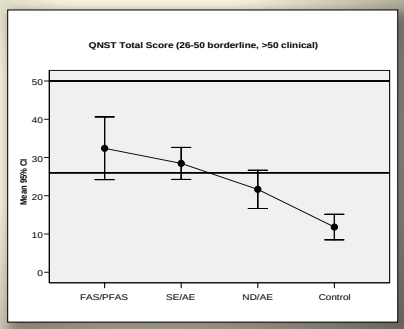
Performance on the Quick Neurological Screen Test decreases with increasing severity of FASD diagnosis.

Quick Neurological Screen Test

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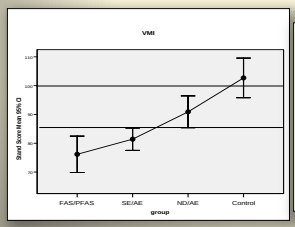
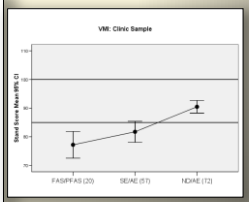
Performance on Visual Motor Integration decreases with increasing severity of FASD diagnosis.

Visual Motor Integration

MRI Study




Clinic Sample

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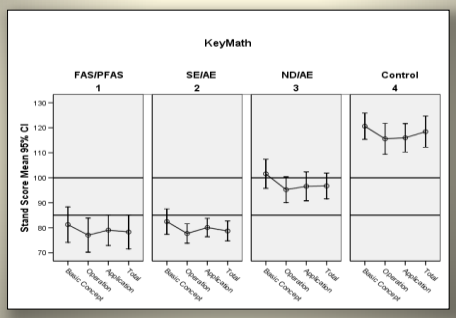
Performance on KeyMath comparably impaired among FAS/PFAS and SE/AE.

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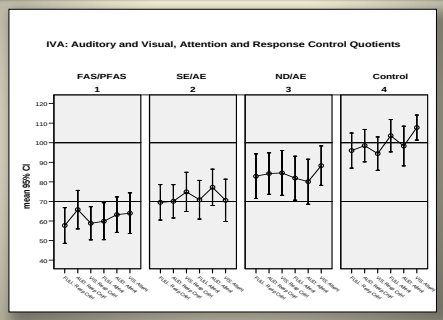
Performance on Continuous Performance Test (IVA) decreases with increasing severity of FASD diagnosis.

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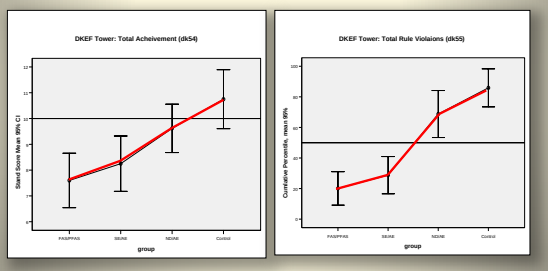
Performance on Executive Function task decreases with increasing severity of FASD diagnosis.

Delis-Kaplan Executive Function System: Tower Test

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## Significant Differences between FAS/PFAS and SE/AE

FAS/PFAS and SE/AE must meet the same diagnostic threshold for severe dysfunction.
That said ....
Those who meet that threshold and have the FAS Face (FAS/PFAS) have more severe outcomes than those who meet that threshold and do not have the FAS face (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 | 2.8 | 6.5 |
| Key Math estimation | 5 | 6.4 |
| VMI | 77 | 89 |
| RCFT Copy (raw) | 11 | 18 |
| IVA Full Response Quot. | 58 | 70 |

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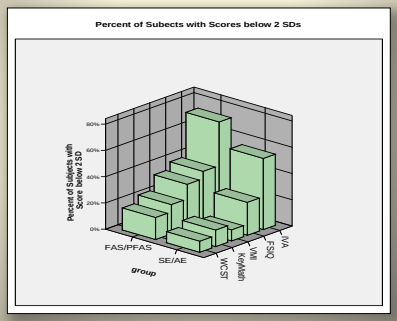
## FAS/PFAS significantly more severe than SE/AE

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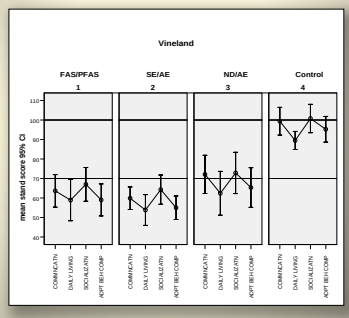
## One domain in which FAS/AE, SE/AE, and ND/AE are Comparably Impaired:
Adaptive Function

Vineland Adaptive Behavior Scales

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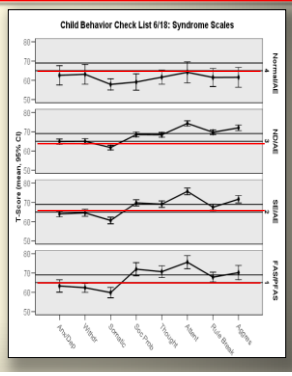
## Parent's Report of Child's Behavior: CBCL

Parents report child's behavior is comparably impaired across all 3 groups

(FAS/PFAS, SE/AE and ND/AE)

All 3 groups score in the clinical range.

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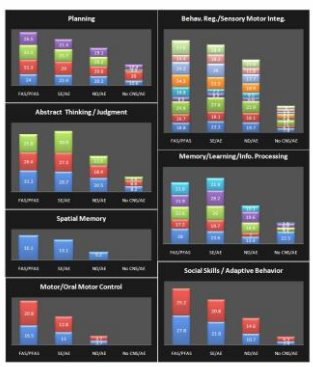
## Parent's Report of Child's Behavior via Parent Interview with Psychologist and MD

Note: this is before parent and clinicians know the child's FASD diagnostic outcome.

In contrast to CBCL, differences do exist between FASD groups




Parent interview (page 6) of the Diagnostic Form

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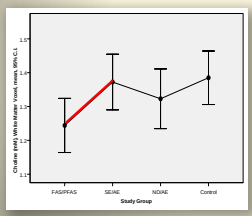
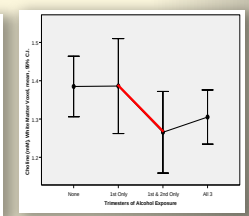
## Choline Significantly Lower among FAS/PFAS

- Choline is significantly lower among FAS / PFAS (may be a marker for white matter deficit).
- Choline lower among those with alcohol exposure through the 2nd or 3rd trimesters.




Choline lower in FAS/PFAS




Choline lower with longer exposure

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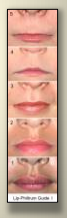
## Lets revisit the issue about microcephaly as a CNS criteria for FAS

The Canadian Guidelines are the only guidelines that require severe CNS dysfunction be present to render a diagnosis of FAS.

Microcephaly alone is not sufficient.

| Patient Outcomes (2 years old) | |
|---|---|
| Growth: | Height 1st percentile, weight 1st percentile |
| Face: | PFL 1st percentile |
| | Smooth philtrum, Rank 5 |
| | Thin upper lip, Rank 5 |
| CNS: | OFC 1st percentile, BSID outcomes low-normal |
| Alcohol: | Intoxicated weekly throughout pregnancy |
| **Diagnostic Classifications** | |
| IOM: | FAS/PFAS |
| 4-Digit Code: | FAS / Alcohol Exposed (Code = 4444) |
| Canadian: | Not FASD |
| CDC: | FAS / Alcohol Exposed |
| Revised IOM (Hoyme): | FAS / Alcohol Exposed |



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## Evidence that microcephaly (≤ 3%tile) is sufficient for FAS

- The 4-Digit Code's CNS criteria for FAS requires evidence of structural and/or functional abnormality. Microcephaly alone IS sufficient.
- The Canadian CNS criteria for FAS requires evidence of functional abnormality. Microcephaly alone is NOT sufficient.
  - This prevents a diagnosis of FAS from being rendered in a child under the age of 6 years (because they are too young to engage in the required functional assessments). But children with FAS are born with FAS.
  - Why is microcephaly alone not sufficient? The concern is microcephaly may not be sufficiently predictive of CNS dysfunction.
  - Delaying a diagnosis of FAS until 6 years of age will adversely impact early intervention, prevention, and surveillance efforts.

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## Evidence that microcephaly (≤ 3%) plus the Rank 4 FAS Face is highly predictive of severe CNS impairment

Among 50 patients 1-23 years of age with FAS and microcephaly:

- Growth (≤ 10th percentile)
- Full FAS face (Rank 4)
- Microcephaly (≤ 3rd percentile)
- Alcohol exposed

All over the age of 7 years had severe CNS dysfunction (CNS Rank 3)

| Brain Function | 0-6 years old | 7-23 years old |
|---|---|---|
| CNS 1: "normal" | 67% | 0% |
| CNS 2: moderate dysfunction | 18% | 0% |
| CNS 3: severe dysfunction | 15% | 100% |

"normal" function in the 0-6 year olds was based on developmental assessments using tools like the Bayley Scales of Infant Development.

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Evidence that microcephaly (≤ 3%) plus the Rank 4 FAS Face is highly predictive of severe CNS impairment

Among 50 patients 1-23 years of age with FAS and microcephaly:

- Growth (≤ 10th percentile)
- Full FAS face (Rank 4)
- Microcephaly (≤ 3rd percentile)
- Alcohol exposed

Microcephaly alone should be sufficient CNS evidence to render a diagnosis of FAS in children under age 6 who present with the Rank 4 FAS facial phenotype.

All over the age of 7 years had severe CNS dysfunction (CNS Rank 3)

| Brain Function | 0-6 years old | 7-23 years old |
|---|---|---|
| CNS 1: normal | 68% | 0% |
| CNS 2: moderate dysfunction | 18% | 0% |
| CNS 3: severe dysfunction | 15% | 100% |

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Does the Diagnostic System provide an objective method for recording prenatal alcohol exposure?

Can the Diagnostic System detect distinct patterns of alcohol exposure between FAS and ARND?

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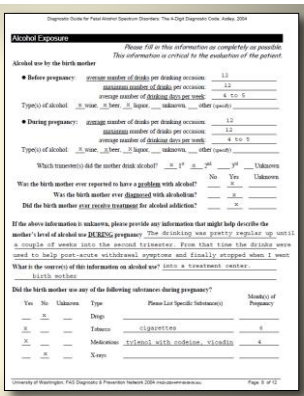
Form Used to Document "Reported" Alcohol Exposure


Posted online
www.fasdpn.org



Alcohol Exposure

*Please fill in this information as completely as possible. This information is critical to the evaluation of the patient.*

**Alcohol use by the birth mother**

- **Before pregnancy:** average number of drinks per drinking occasion: 12; maximum number of drinks per occasion: 12; average number of drinking days per week: 4 to 5
  Type(s) of alcohol: X wine, ___ beer, X liquor, ___ unknown, ___ other (specify)
- **During pregnancy:** average number of drinks per drinking occasion: 12; maximum number of drinks per occasion: 12; average number of drinking days per week: 4 to 5
  Type(s) of alcohol: X wine, ___ beer, X liquor, ___ unknown, ___ other (specify)

Which trimester(s) did the mother drink alcohol? X 1st X 2nd ___ 3rd ___ Unknown

| | No | Yes | Unknown |
|---|---|---|---|
| Was the birth mother ever reported to have a problem with alcohol? | ___ | X | ___ |
| Was the birth mother ever diagnosed with alcoholism? | ___ | X | ___ |
| Did the birth mother ever receive treatment for alcohol addiction? | ___ | X | ___ |

If the above information is unknown, please provide any information that might help describe the mother's level of alcohol use DURING pregnancy: The drinking was pretty regular up until a couple of weeks into the second trimester. From that time the drinks were used to help post-acute withdrawal symptoms and finally stopped when I went into a treatment center.

What is the source(s) of this information on alcohol use? birth mother

**Did the birth mother use any of the following substances during pregnancy?**

| Yes | No | Unknown | Type | Please List Specific Substance(s) | Month(s) of Pregnancy |
|---|---|---|---|---|---|
| ___ | X | ___ | Drugs | | |
| X | ___ | ___ | Tobacco | cigarettes | 6 |
| X | ___ | ___ | Medications | tylenol with codeine, vicodin | 4 |
| ___ | X | ___ | X-rays | | |

University of Washington, FAS Diagnostic & Prevention Network 2004 [illegible] Page 9 of 12

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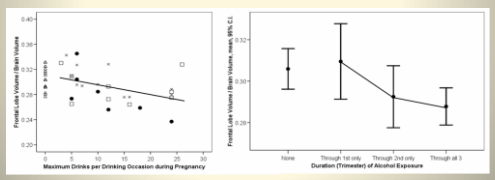
## Frontal Lobe Volume and Alcohol Exposure

4-Digit Code method for documenting prenatal alcohol exposure allows identification of important at-risk patterns of exposure.

The frontal lobe volume decreases significantly with increasing number of drinks and increasing duration of prenatal alcohol exposure.




Number of Drinks Trimesters of Exposure

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## Significant Differences in Alcohol Exposure Patterns exist between FAS/PFAS and SE/AE

FAS/PFAS and SE/AE must meet the same diagnostic threshold for severe dysfunction. That said ....

Those who meet that threshold and have the FAS Face (FAS/PFAS) have significantly

more days/week of alcohol exposure
and
are more likely to have exposure all 3 trimesters

than those who meet that threshold and do not have the FAS face (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% |

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Are the guidelines confirmed to be reproducible?

If two clinics use the guidelines, do they render the same diagnoses?

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## The 4-Digit Code is reproducible across clinics.


Of 687 patients diagnosed across the
4 Washington State FASD Diagnostic Network Clinics
in Everett, Spokane, Pullman and Yakima

91% received a diagnosis that matched the diagnosis rendered by the Seattle Clinic.

When it did not match, the most common reason was the face was measured by hand rather than with the software.

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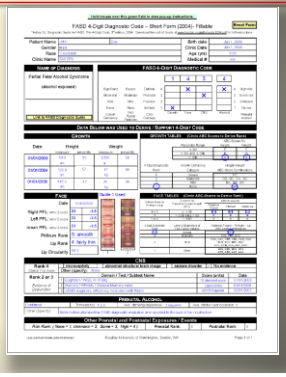
## The WA FASD Clinics use the 1-Page Electronic 4-Digit Code Form.


Available free online
http://depts.washington.edu/fasdpn/pdfs/FASD-4digit-shortform-fillable-2004-052508.pdf



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## As you assess the performance of FASD Diagnostic Guidelines, ask the following questions:

1. Have properly designed studies been conducted to confirm the FAS Face is highly specific (>95%) to FAS and alcohol?
2. Individuals are born with FAS/D. Can the diagnostic system identify FAS/D at birth?
3. Growth, face, brain, and alcohol exposure all present along clinically meaningful continuums. The FAS face is not just present or absent. The brain is not just normal or abnormal. Do the Guidelines recognize/incorporate these important continuums?
4. Do the guidelines produce diagnostic subgroups (FAS, PFAS, ARND, SE/AE, ND/AE) that are clinically and statistically distinct?
   A. Do MRI 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?
5. Can the guidelines detect unique alcohol exposure patterns between the FASD subgroups?
6. Are the guidelines confirmed to be reproducible? If two clinics use the guidelines, do they render the same diagnoses?

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## Conclusion (Astley, 2011)

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 (eg, treatment, prevention, communication among specialists, and qualification for services), the process of rendering a diagnosis can sometimes be influenced by those different purposes. The only diagnosis that serves all purposes most effectively is a correct diagnosis. Access to services should be based on an individual's disabilities and not on what caused their disabilities. Therefore, services should be available for individuals across the full continuum of FASD and not just those with FAS.

Astley

## Key References


Astley SJ. Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the WA State Fetal Alcohol Syndrome Diagnostic & Prevention Network. Can J Clin Pharmacol .Vol 17(1) Winter 2010:e132-e164; March 26, 2010.

Astley et al., Neuropsychological and behavioral outcomes from a comprehensive magnetic resonance study of children with FASD, Canadian J Clinical Pharmacology, 2009;16(1):e178-201.

Astley et al., MRI outcomes from a comprehensive magnetic resonance study of children with FASD, Alcoholism: Clinical Experimental Research 2009;33(10).

Astley et al., MRS outcomes from a comprehensive magnetic resonance study of children with FASD, Magnetic Resonance Imaging Magnetic Resonance Imaging, 2009;27:760-778.

Astley et al., fMRI outcomes from a comprehensive magnetic resonance study of children with FASD, J Neurodevelopmental Disorder 2009;1:61-80.

Astley SJ. Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code, 3rd edition, University of Washington Publication Services, Seattle WA, 2004.

Astley SJ, Clarren SK. A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrome, J Peds. 1996;129:33-41.

Astley SJ, Clarren SK. Measuring the facial phenotype of individuals with prenatal alcohol exposure: correlations with brain dysfunction Alc Alc, 2001;36(20:147-159.

Astley SJ, Comparison of the 4-Digit Diagnostic Code and the Hoyme Diagnostic Guidelines for FASD, Pediatrics 2006;118(4):1532.

Astley SJ. Graphic cognitive/behavioral/psychiatric profiles of FASD. Slide show presented to NIAAA/CDC in 2009.

Astley SJ. Diagnosing FASD. In: Prenatal Alcohol Use and FASD: Diagnosis, Assesment and New Directions in Research and Multimodal Treatment. Eds Adubato and Cohen, Bentham, 2011


All literature referenced in this presentation can be obtained at the following weblinks:
www.fasdpn.org/htmls/literature.htm
www.fasdpn.org/pdfs/astley-graphicprofile-2009secure.pdf

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