

# Comparison of the 4-Digit Code and Hoyme 2016 FASD Diagnostic Guidelines

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# Objectives

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1. Compare the tools and criteria used to render the diagnoses.
2. Compare the FASD diagnostic outcomes
  - Prevalence of FASD outcomes across patients
  - Diagnostic discordance/concordance within patients
3. Assess measures of validity.
4. Address ethical implications of the diagnostic nomenclature.

# Methods

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1. We used the records of 1,392 consecutive patients diagnosed at the University of Washington by an interdisciplinary team between 1993-2012 using the 4-Digit Code.
2. Facial features were measured using the FAS Facial Photographic Analysis Software.
3. PFL percentiles were computed using the Stromland PFL growth charts because they address birth through adult. These norms are generated from photo measures (thus are in accordance with Hoyme 2016 guideline recommendations).
4. The 4-Digit Code Lip-Philtrum Guide was used to measure lips and philtrum for the 4-Digit Code. The Hoyme North American Lip-Philtrum Guide was used to measure lips and philtrums for the Hoyme guidelines.
5. All patients ( $n = 130$ ) with one or both birth parents African American were excluded from the study because it was unclear which PFL norms to use when applying the Hoyme guidelines and it was unclear if the Hoyme South African Mixed Race Lip/Philtrum Guide was intended for use on an African American population.

# What is Fetal Alcohol Spectrum Disorder (FASD)?

FASD is an umbrella term.

FASD reflects the full range of outcomes caused by prenatal alcohol exposure.

The 4-Digit Code generates 4 diagnoses broadly under the umbrella of FASD:

Diagnosis		Growth	FAS Face	CNS		Alcohol
1. FAS	Fetal Alcohol Syndrome	growth	face	severe		alc / unk
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

\* Also referred to as:

- Alcohol Related Neurodevelopmental Disorder (ARND) or
- Neurodevelopmental Disorder Prenatal Alcohol Exposed (ND-PAE)



# Interdisciplinary FASD Diagnostic Clinic

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An FASD diagnosis is best conducted:

- by an interdisciplinary team
- using validated diagnostic guidelines.

Interdisciplinary team typically includes:

- Medical doctor
- Psychologist
- Speech Language Pathologist
- Occupational Therapist
- Social Worker
- Family Advocate



# 4-Digit Code FASD Diagnostic Tools

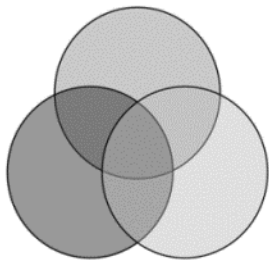
All tools available at  
[fasdpn.org](http://fasdpn.org)




## DIAGNOSTIC GUIDE FOR FETAL ALCOHOL SPECTRUM DISORDERS

### THE 4-DIGIT DIAGNOSTIC CODE™

Third Edition  
2004



FAS DIAGNOSTIC AND PREVENTION NETWORK  
UNIVERSITY OF WASHINGTON  
SEATTLE WASHINGTON




**FAS Facial Photographic Analysis Software**


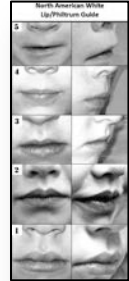
Susan Astley, Ph.D.

Fetal Alcohol Syndrome Diagnostic & Prevention Network  
University of Washington, Seattle, WA

[www.fasdpn.org](http://www.fasdpn.org)  
Version 2.1.0  
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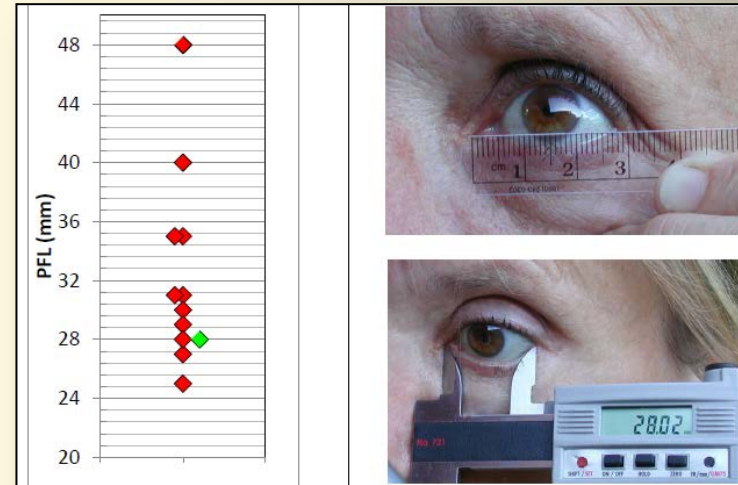
# Some Key **Contrasts** in 4-Digit Code & Hoyme 2016 FASD Criteria

Criteria	4-Digit 2004	Hoyme et al 2016
<b>Growth</b>	$\leq 10^{\text{th}}$ percentile Emphasis on short stature	$\leq 10^{\text{th}}$ percentile
<b>FAS Face</b>	<p>3 features PFL <math>\leq 3^{\text{rd}}</math> percentile 4-Digit Code Lip-Philtrum Guides Face: absent, mild, mod, severe Specificity: <math>\sim 95\%</math> Photo Software confirmed more accurate than direct exam.</p> 	<p>2 of 3 features PFL <math>\leq 10^{\text{th}}</math> percentile Hoyme Lip/Philtrum Guides Face: absent / present Specificity: <math>\sim 75\%</math> “we feel that direct exams are more practical in an office setting”</p> 
<b>Brain structure</b>	Structural/neurological abnormalities OFC $\leq 3^{\text{rd}}$ percentile	Structural/neurological abnormalities OFC $\leq 10^{\text{th}}$ percentile
<b>Brain function</b>	3 or more domains $\leq 2$ SD Function: (normal, moderate, severe)	1 or 2 domains $\leq 1.5$ SD Function: (normal / abnormal)
<b>Alcohol</b>	Confirmed Exposure (at any reported level or level unknown)  or Unknown Exposure (if 4-Digit FAS face present)	Significant Exposure ( $\geq 6$ drinks / wk for $\geq 2$ wks) ( $\geq 3$ drinks / occasion, $\geq 2$ occasions), etc  or Unknown Exposure (if Hoyme FAS face present)

# Published Empirical Study Confirms Accuracy of the FAS Facial Software and Inaccuracy of the Ruler (Astley, 2015)

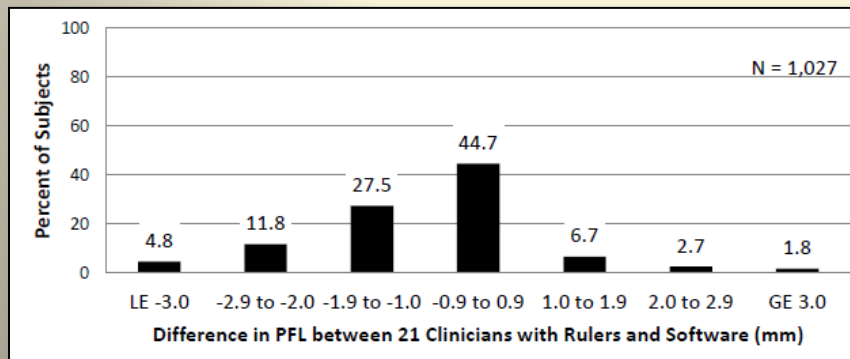
## Software Versus Gold Standard Caliper

The software derived PFLs that were identical to or within 0.2 mm of the caliper measure.



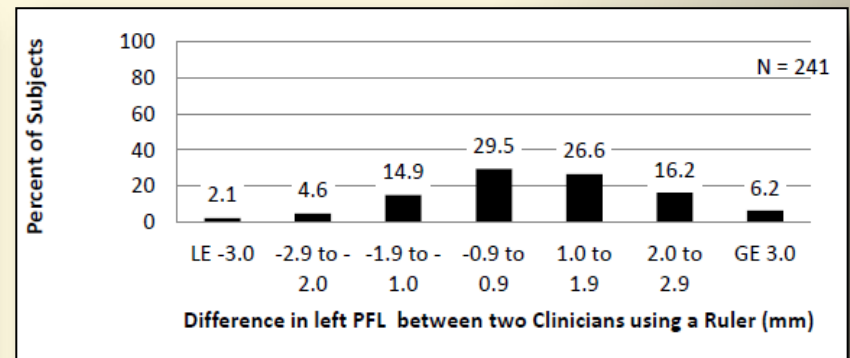
## 11 Clinicians with Rulers ♦ Versus Gold Standard Caliper ♦

Only 1 Clinician obtained the correct PFL (28mm). Others were off by 1-20 mm



## 21 Clinicians with Rulers Versus the Software

56% of ruler measures had 1-3 mm error



## Ruler used by 2 Clinicians

71% were 1-3 mm different



# Hoyme 2016 Alcohol Criteria

	Prenatal Alcohol Exposure	
	Exposure is Confirmed and Significant	Exposure is Unknown
FAS	Yes	Yes
pFAS	Yes	Yes
ARND	Yes	
ARBD	Yes	

**TABLE 2** Definition of Documented Prenatal Alcohol Exposure (as Applied to the Diagnostic Categories Set Forth in Table 1)

One or more of the following conditions must be met to constitute documented prenatal alcohol exposure during pregnancy (including drinking levels reported by the mother 3 mo before her report of pregnancy recognition or a positive pregnancy test documented in the medical record). The information must be obtained from the biological mother or a reliable collateral source (eg, family member, social service agency, or medical record):

- $\geq 6$  drinks/wk for  $\geq 2$  wk during pregnancy<sup>a</sup>
- $\geq 3$  drinks per occasion on  $\geq 2$  occasions during pregnancy<sup>a</sup>
- Documentation of alcohol-related social or legal problems in proximity to (before or during) the index pregnancy (eg, history of citation[s] for driving while intoxicated or history of treatment of an alcohol-related condition)
- Documentation of intoxication during pregnancy by blood, breath, or urine alcohol content testing
- Positive testing with established alcohol-exposure biomarker(s) during pregnancy or at birth (eg, analysis of fatty acid ethyl esters, phosphatidylethanol, and/or ethyl glucuronide in maternal hair, fingernails, urine, or blood, or placenta, or meconium)<sup>50–55</sup>
- Increased prenatal risk associated with drinking during pregnancy as assessed by a validated screening tool of, for example, TACE (tolerance, annoyance, cut down, eye-opener) or AUDIT (alcohol use disorders identification test)<sup>56</sup>

If exposure is confirmed, but the level is not significant (4 drinks/wk for  $> 2$  wk during pregnancy) than the exposure is neither Significant nor Unknown.

# FAS DOES occur when “reported” alcohol is less than threshold required by Hoyme Guidelines

An Actual Case of Full FAS (4443) in a 21 year old				
Growth	Rank 4	Height 1%, Weight 1%		
Face	FAS Rank 4 (CCC)	PFL 1%,	Philtrum Rank 4,	Lip Rank 4
CNS structure	CNS Rank 4	Microcephaly 2 %		
CNS dysfunction	CNS Rank 3, Severe	FSIQ 76, Adaptation 65, Math Calc 60, Core Lang 67, Memory 59		
Alcohol	Rank 3 Birth mother report	1 drink/wk for > 2 wk during pregnancy (all 3 trimesters) 1 drink per occasion on > 2 occasions during pregnancy		

Either the “report” above is inaccurate or exposure below the Hoyme threshold can cause FAS.

- If the exposure is inaccurate, then applying the criteria to it is meaningless.
- Setting a threshold also sends a dangerous public health message that drinking below the threshold is safe. Are we to turn away individuals who report less than the threshold?

**TABLE 2** Definition of Documented Prenatal Alcohol Exposure

One or more of the following conditions must be met to constitute documented prenatal alcohol exposure by the mother 3 mo before her report of pregnancy recognition obtained from the biological mother or a reliable collateral source:

- $\geq 6$  drinks/wk for  $\geq 2$  wk during pregnancy<sup>a</sup>
- $\geq 3$  drinks per occasion on  $\geq 2$  occasions during pregnancy<sup>a</sup>
- Documentation of alcohol-related social or legal problems in pre-pregnancy or history of treatment of an alcohol-related condition
- Documentation of intoxication during pregnancy by blood, breath, or urine
- Positive testing with established alcohol-exposure biomarker(s) such as ethyl glucuronide in maternal hair, fingernails, urine, or blood
- Increased prenatal risk associated with drinking during pregnancy (e.g., miscarriage, stillbirth, or AUDIT (alcohol use disorders identification test) score  $\geq 8$ )



# Contrasts in Diagnoses

## 4-Digit Code vs Hoyme 2016 FASD Guidelines

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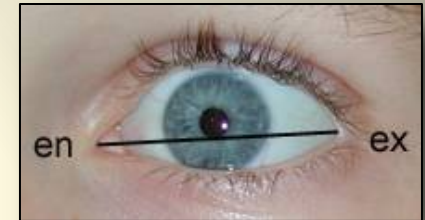
<u>4-Digit Code</u>	<u>Hoyme (2016)</u>
FAS / Confirmed Alcohol	FAS / Confirmed Alcohol
FAS / Unknown Alcohol	FAS / Unknown Alcohol
pFAS / Confirmed Alcohol	pFAS / Confirmed Alcohol
No	pFAS / Unknown Alcohol
Static Encephalopathy / Confirmed Alcohol	} ARND / Confirmed Alcohol
Neurobehavioral Disorder / Confirmed Alcohol	
No	ARBD / Confirmed Alcohol

# 4-Digit Code FAS Facial Phenotype

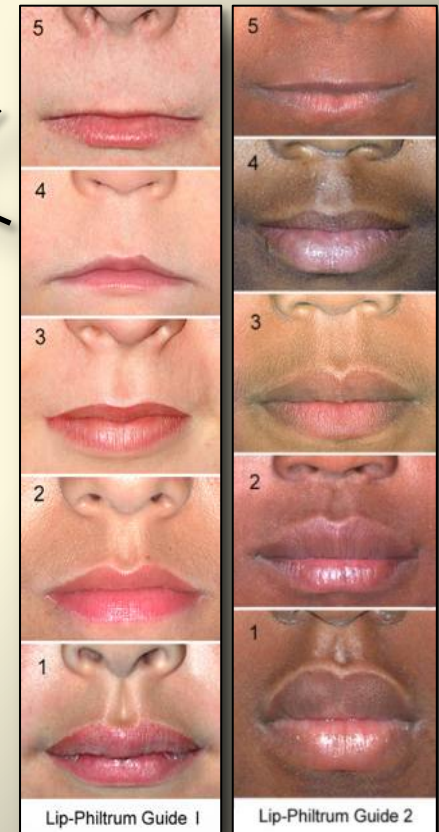
All 3 features must be present

- 1) Short PFL  $\leq 3^{\text{rd}}$  percentile
- 2) Smooth Philtrum Rank 4 or 5
- 3) Thin Upper Lip Rank 4 or 5

Palpebral fissure length (PFL) = endocanthion to exocanthion



FAS

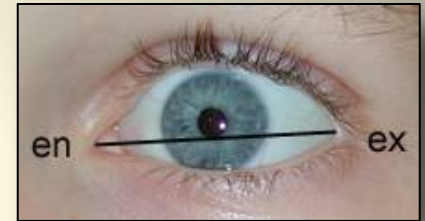


# Hoyme 2016 FAS Facial Phenotype

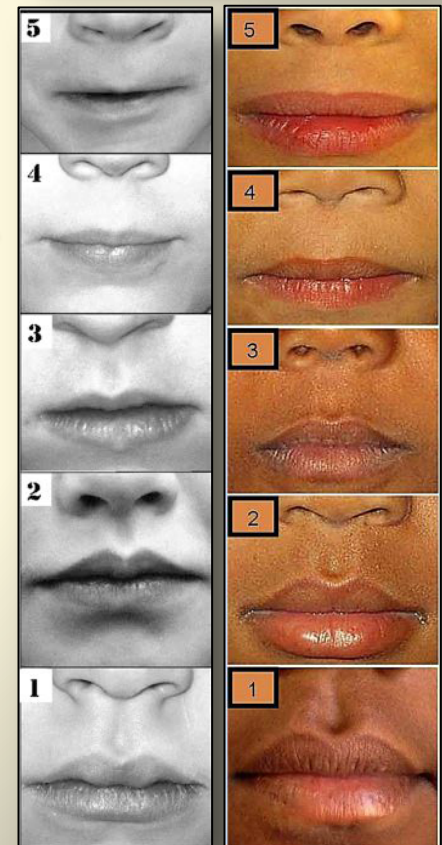
2 of the 3 features must be present

- 1) Short PFL  $\leq 10^{\text{th}}$  percentile
- 2) Smooth Philtrum Rank 4 or 5
- 3) Thin Upper Lip Rank 4 or 5

Palpebral fissure length (PFL) = endocanthion to exocanthion



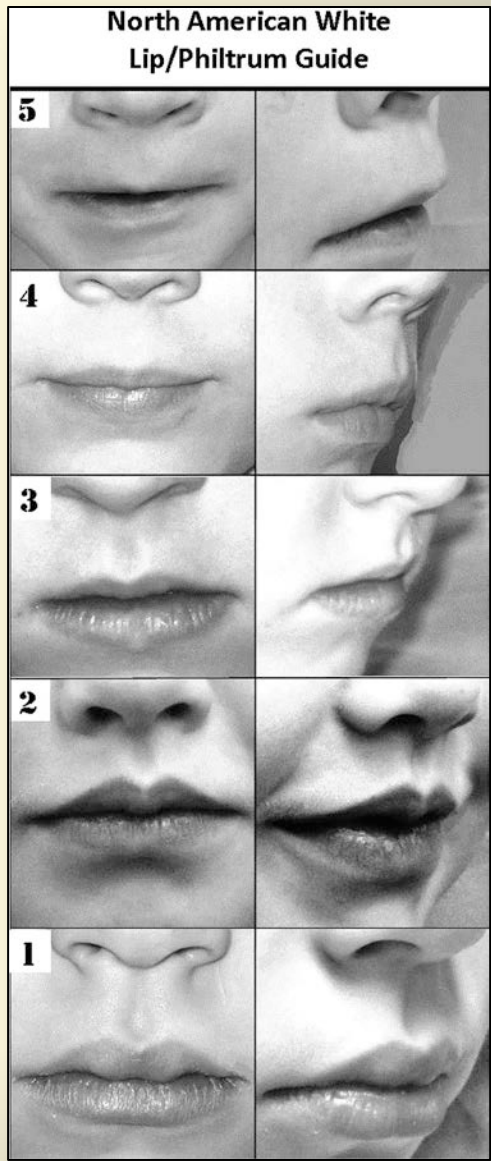
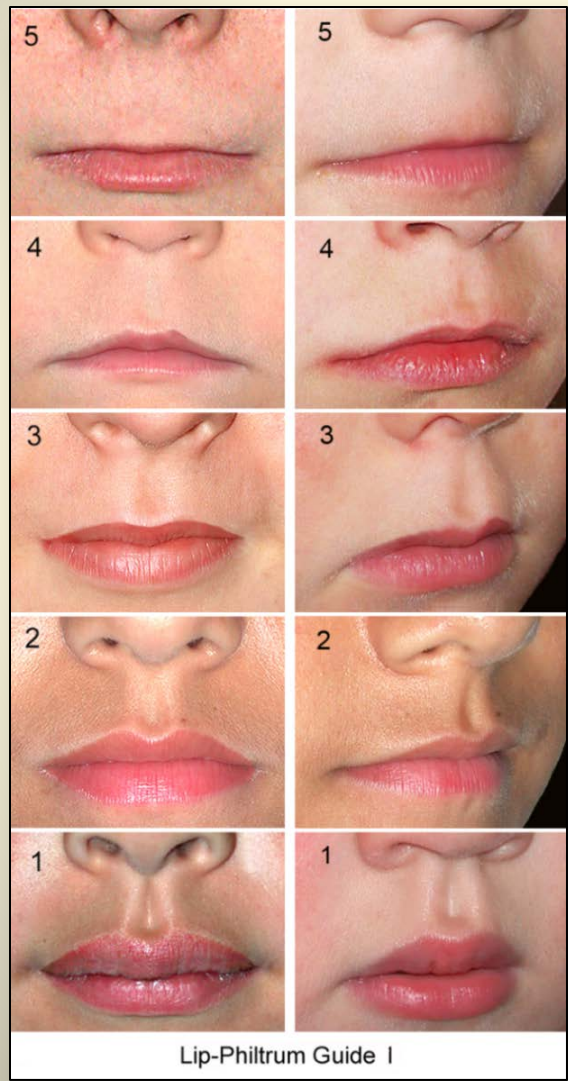
FAS





# 4-Digit and Hoyme Lip-Philtrum Guides Do Not Match

4-Digit Code



Hoyme 2016

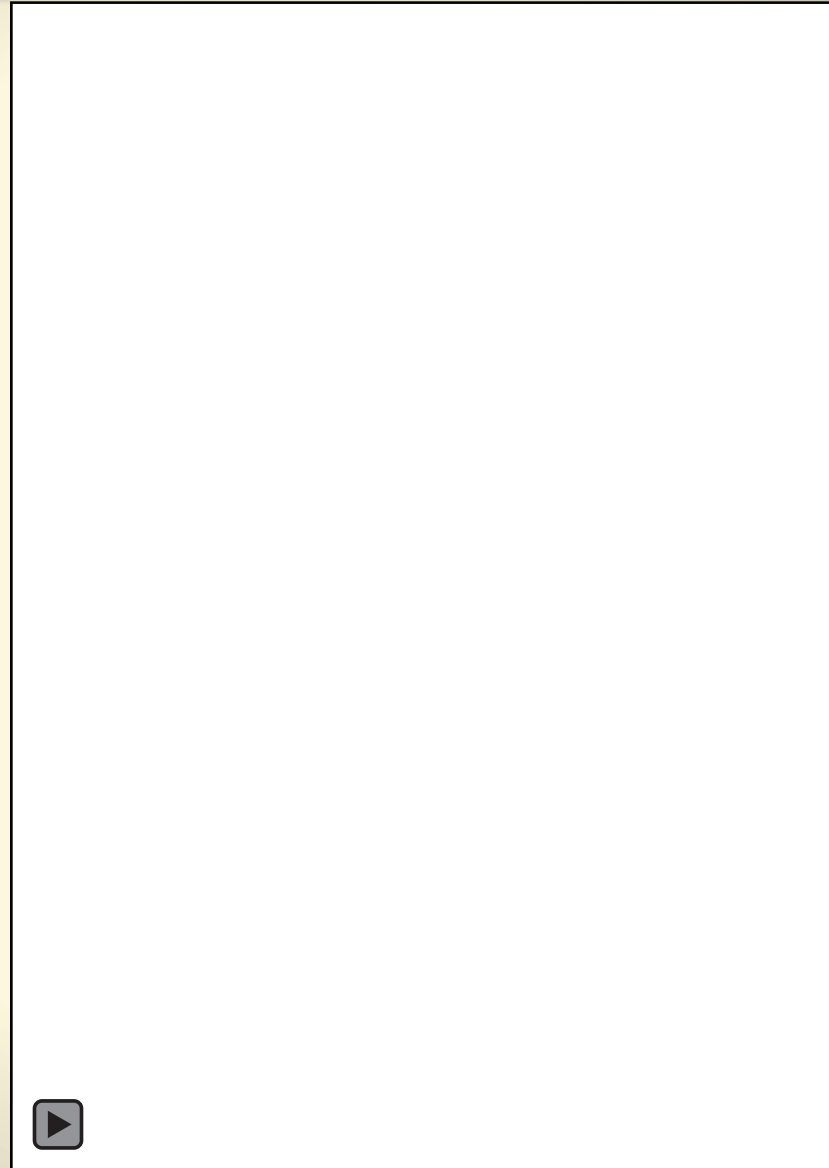
# Lip Circularity Demonstration using the FAS Facial Photographic Analysis Software

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Lip Circularity =  
 $\text{perimeter}^2 / \text{area}$

The thinner the lip  
\* \* \*

The larger the  
circularity



avi video file

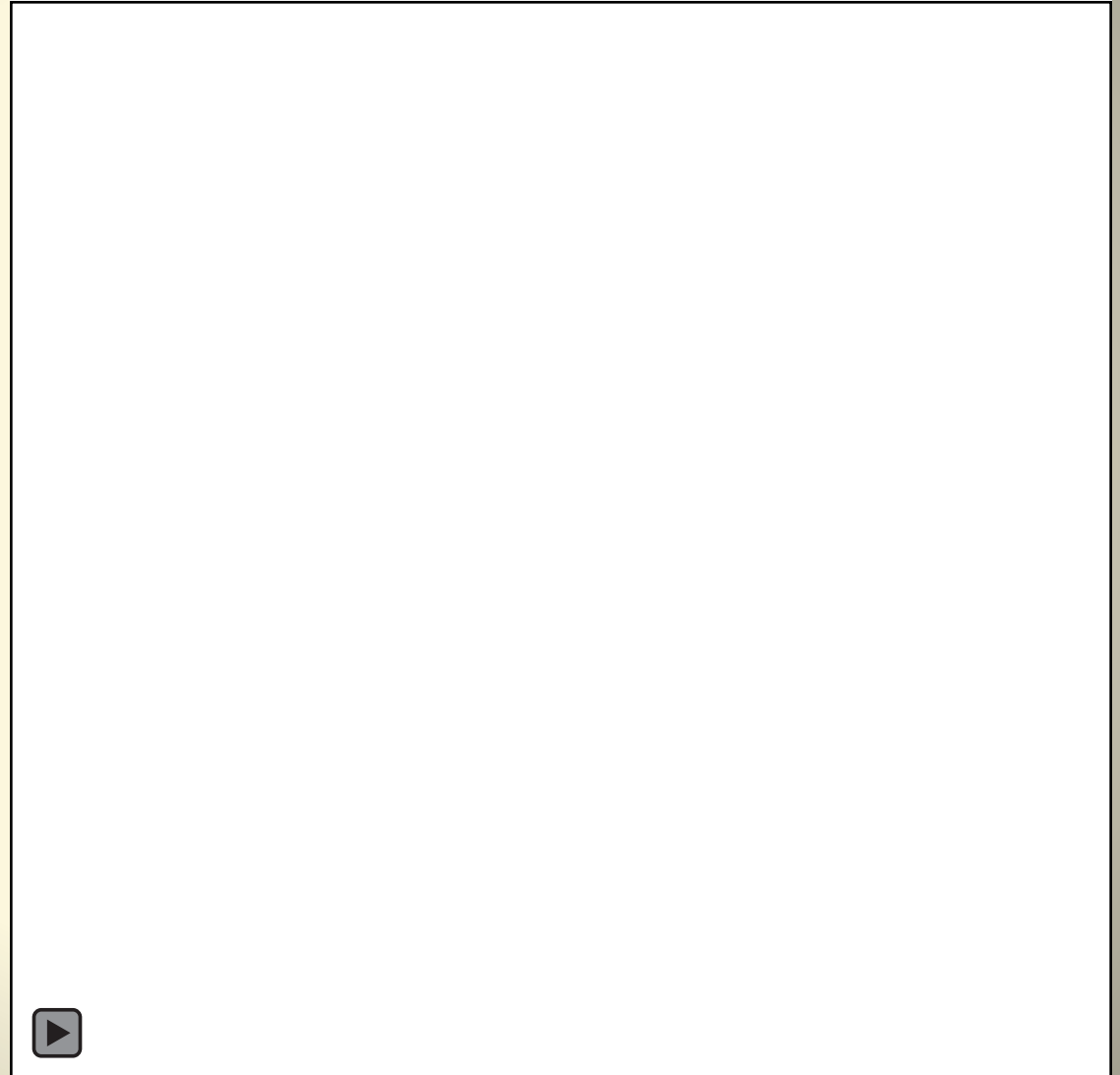
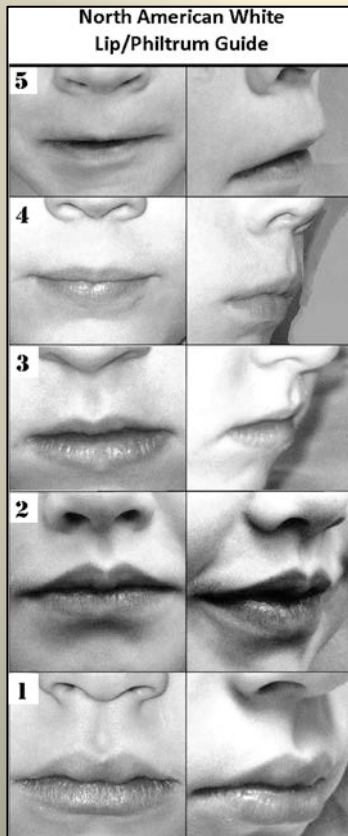
# Lip Circularity of Rank 4 Lip

## North American White: Hoyme 2016

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Hoyme (2016)  
Rank 4 Lip:

Circularity = 52.5



avi video file demonstrating lip circularity measure.





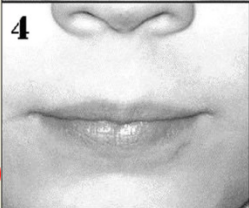




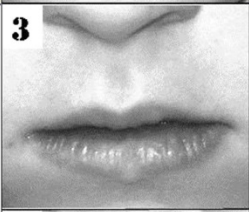
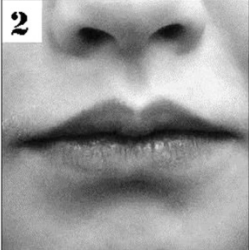
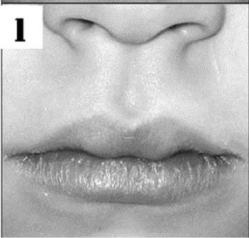
# 4-Digit Code Lip-Philtrum Guide with Hoyme Rank 4 Lip Overlay

Hoyme Rank 4 Lip is equivalent to 4-Digit Rank 2 Lip.

Hoyme Rank 4 Lip Overlaid on 4-Digit Guide			
Circularity			
178	5		5
	131.5		
85	4		4
	75.5		
65	3		3
	57.5		
50			2
	42.5		
35	1		1
Lip-Philtrum Guide I			

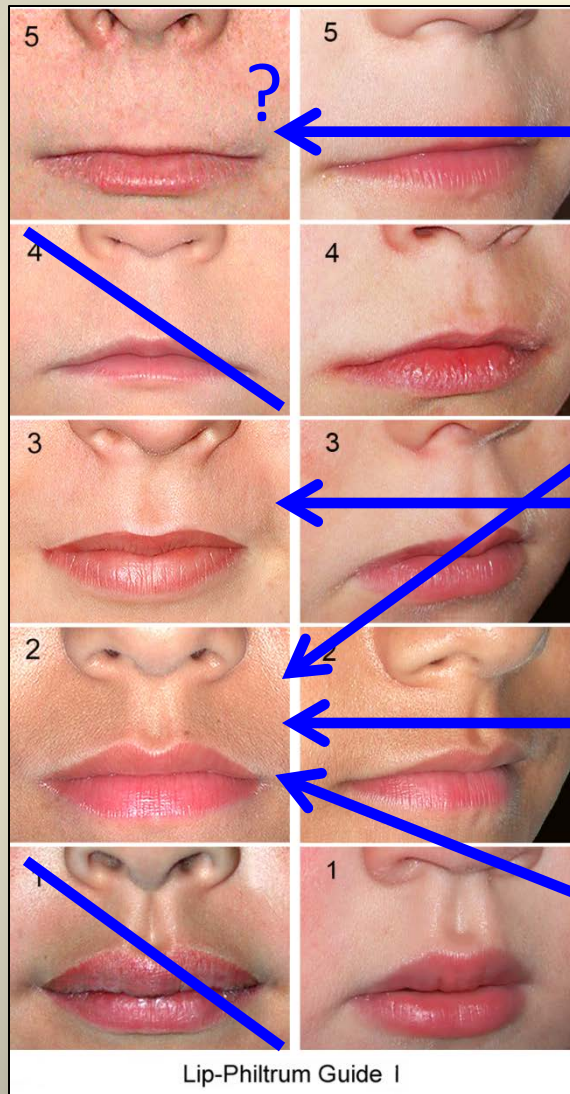
North American White Lip/Philtrum Guide			
5			
4			
3			
2			
1			





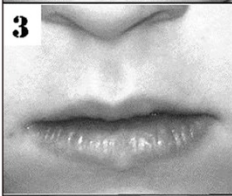

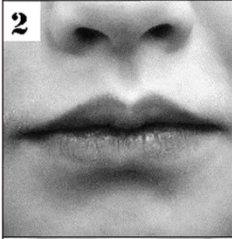
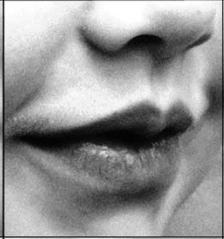
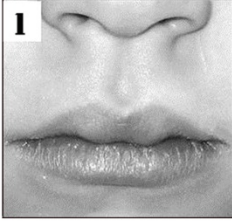
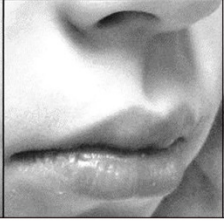
# Rank 4 Lip Circularity Cut-Off for 4-Digit And Hoyme Guides

Hoyme		Lip Circularity		4-Digit	FAS
5		unk	176	5 	
4		52.5	85	4 	
Rank 4 or 5 Circularity $\geq 52.5$			75.5	3 	
		59.0	65	2 	
		46.6	50	1 	
3					NOT FAS
2					
1		45.3	35		



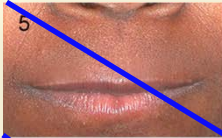

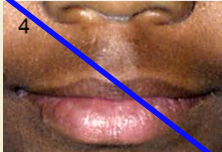


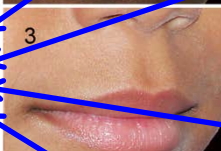


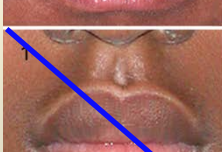

# 4-Digit and Hoyme Lip-Philtrum Guides Do Not Match






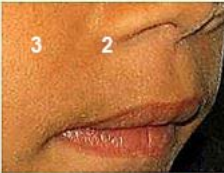




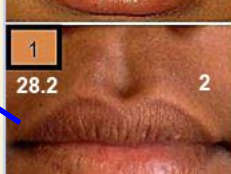

4-Digit Rank Equivalents	North American White Lip/Philtrum Guide	
5 ?		
2		
3		
2		
2		

# 4-Digit and Hoyme Lip-Philtrum Guides Do Not Match

## Circularity

> 62.1	80		
52.1 to 62.0	57		
30.1 to 52.0	39		
27.5 to 30.0	29		
< 27.4	25		

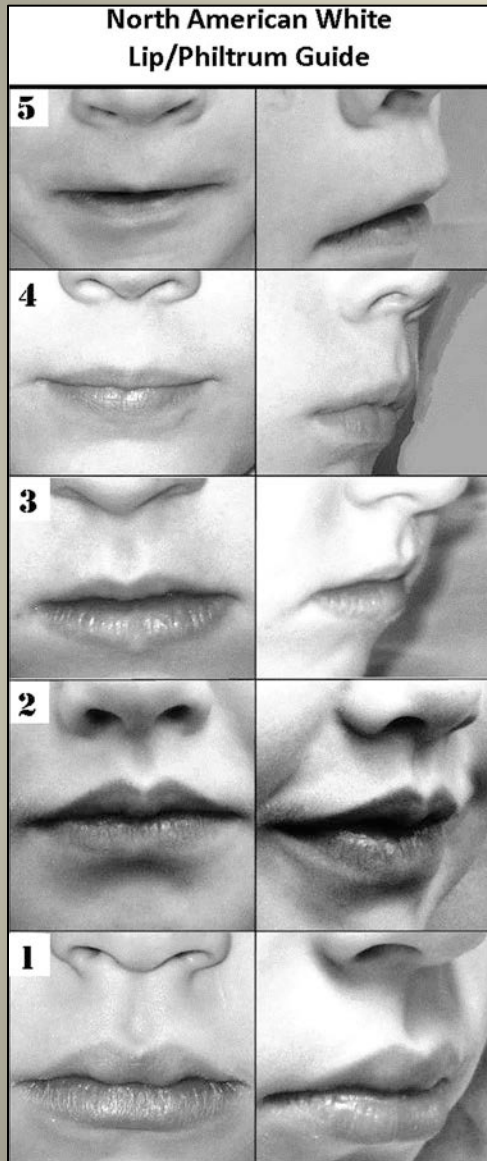
Lip-Philtrum Guide 2

South African Mixed Race			
Circularity	Lip/Philtrum Guide		
	Black	Mixed White	
5	3	2	1
40.1			
4	3	3	2
46.0			
3	3	2	1
36.2			
2	3	1	1
32.9			
1	2	1	1
28.2			



# Hoyme (2016) FAS Facial Phenotype

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**FIGURE 2**

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

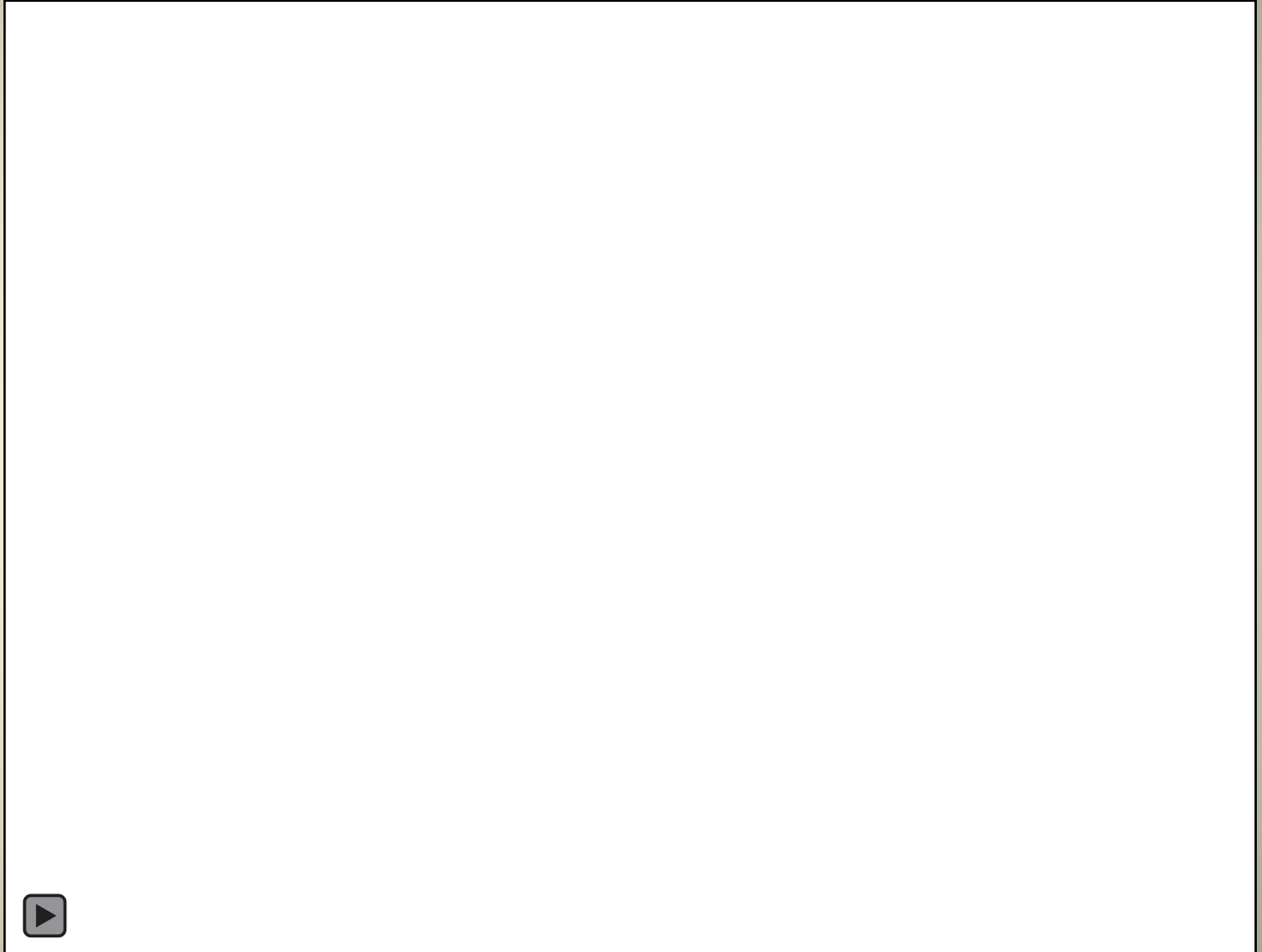
# Lip Thinness (Circularity) for Hoyme 2016 FAS Face

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Lip Circularity  
= 43.4

Equivalent to  
Rank 2 on  
4-Digit Guide.



avi video file

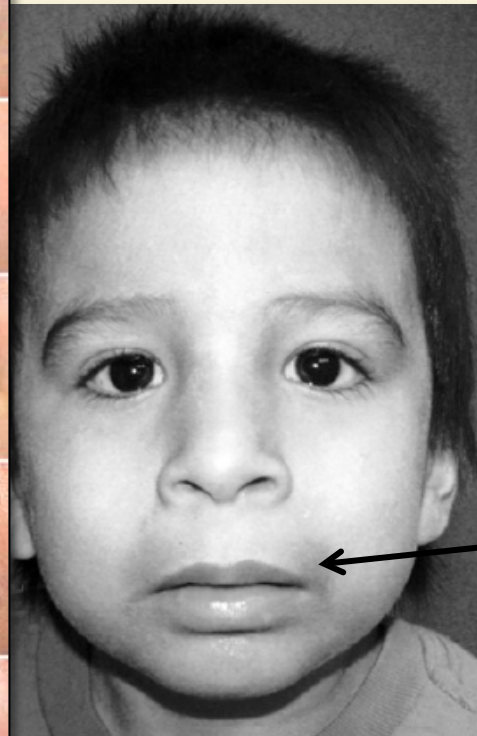


## 4-Digit Face



# FAS Facial Phenotype

## Hoyme 2016 Face



Rank 2 Lip:  
Lip Circularity  
43.4

Rank 2 Circularity  
57.4  
to  
42.5

## 4-Digit Face



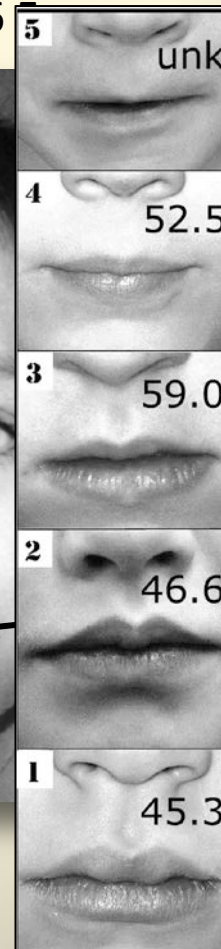
# FAS Facial Phenotype

Hoyme 2016



Rank 2 Circularity

57.4  
to  
42.5



Rank 2 Lip:  
Lip Circularity  
43.4







# FAS Facial Phenotype

## 4-Digit Code

3 Features Required.

1.  $PFL \leq 3^{rd} \%$
2. Philtrum Rank 4 or 5
3. Lip Rank 4 or 5

FACE TABLES				
5-Point Rank for Philtrum or Lip	Z-scores for Palpebral Fissure Length	ABC-Scores for:		
		Palpebral Fissure	Philtrum	Upper Lip
4 or 5	$\leq -2$ SD	C	C	C
3	$> -2$ SD and $\leq -1$ SD	B	B	B
1 or 2	$> -1$ SD	A	A	A

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



Lip  
Thinness



# FAS Facial Phenotype Hoyme 2016

Only 2 features required and  
2 of the 3 relaxed relative to 4-Digit Code.

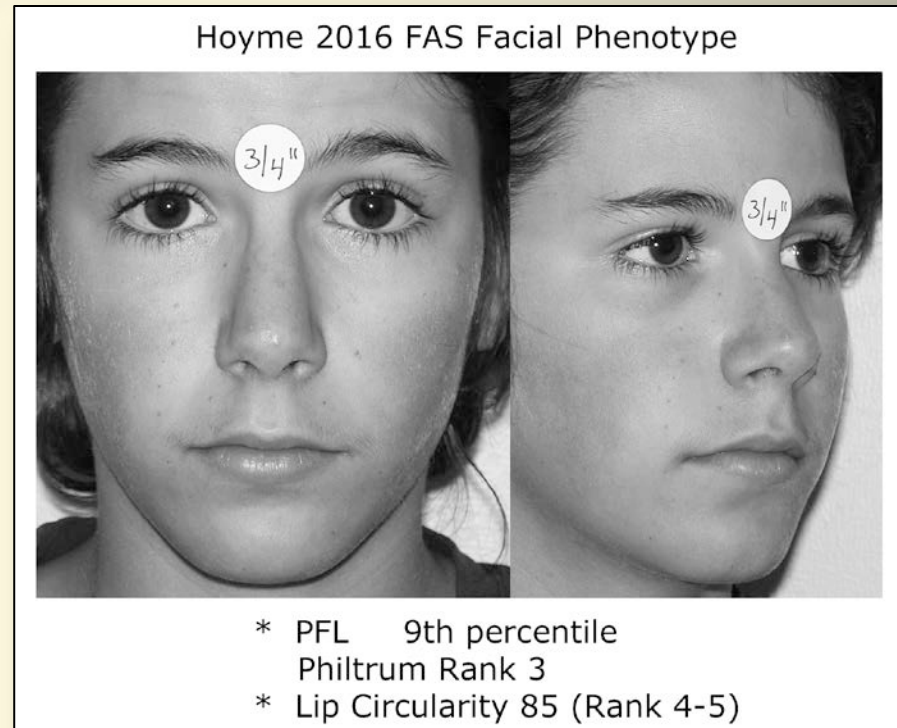
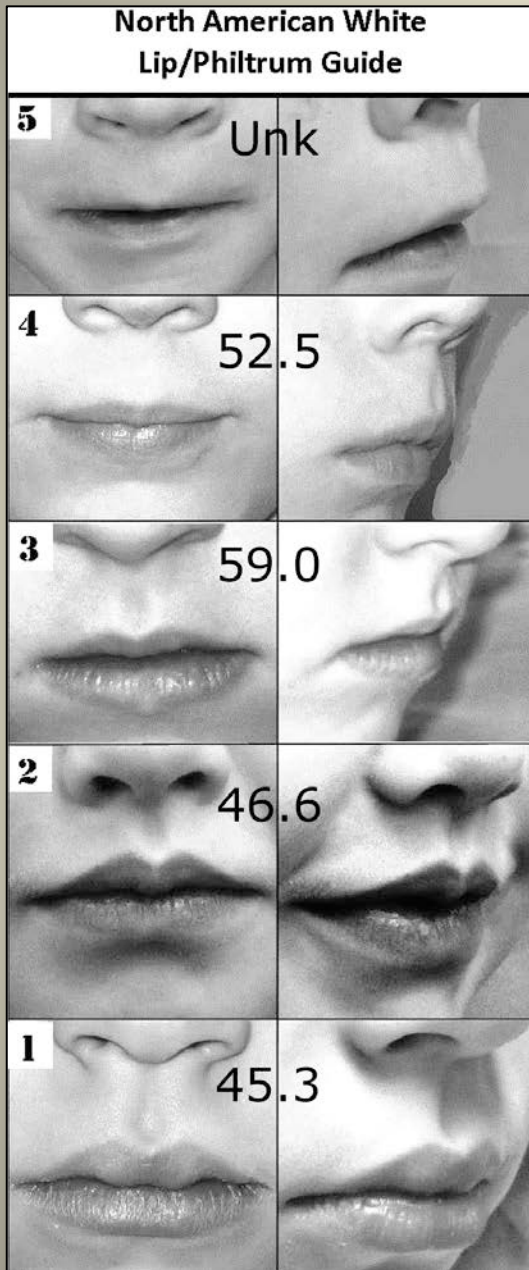
1.  $PFL \leq 10^{\text{th}} \%$
2. Philtrum Rank 4 or 5
3. Lip Ranks 2-5

FACE TABLES				
5-Point Rank for Philtrum or Lip	Z-scores for Palpebral Fissure Length	ABC-Scores for:		
		Palpebral Fissure	Philtrum	Upper Lip
4 or 5	$\leq -2 \text{ SD}$	C	C	C
3	$> -2 \text{ SD and } \leq -1 \text{ SD}$	B	B	B
1 or 2	$> -1 \text{ SD}$	A	A	A

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

# FAS Facial Phenotype, Hoyme 2016



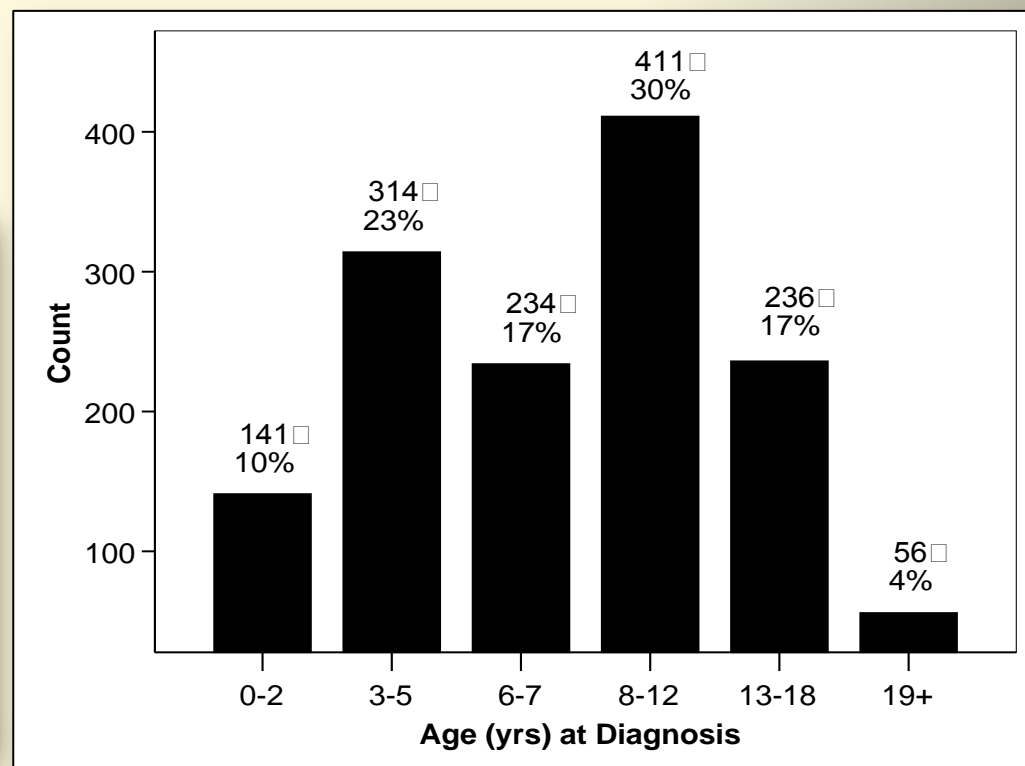
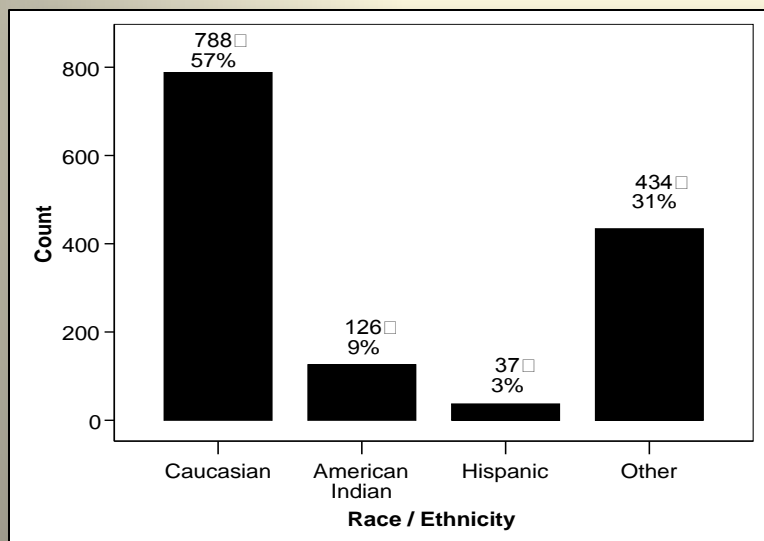
	FAS Face	PFL	Philtrum	Lip
Hoyme	Yes	Yes	No	Yes
4-Digit	No	No	No	Yes
	Rank 2	B	B	C

Confirmed absence of Prenatal Alcohol, FSIQ 123



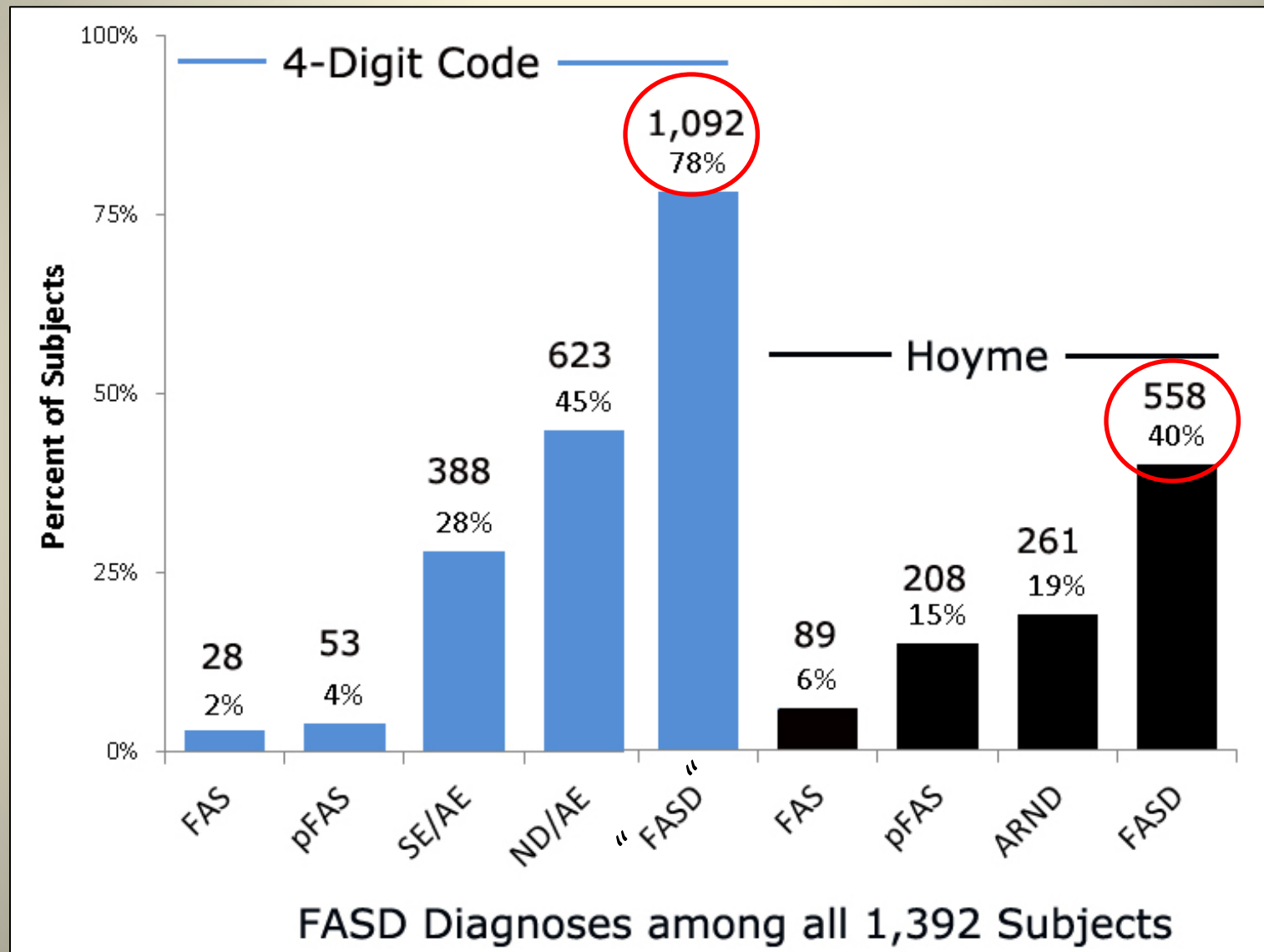
# Study Population

Study Population	1,392
Females	608 (44%)

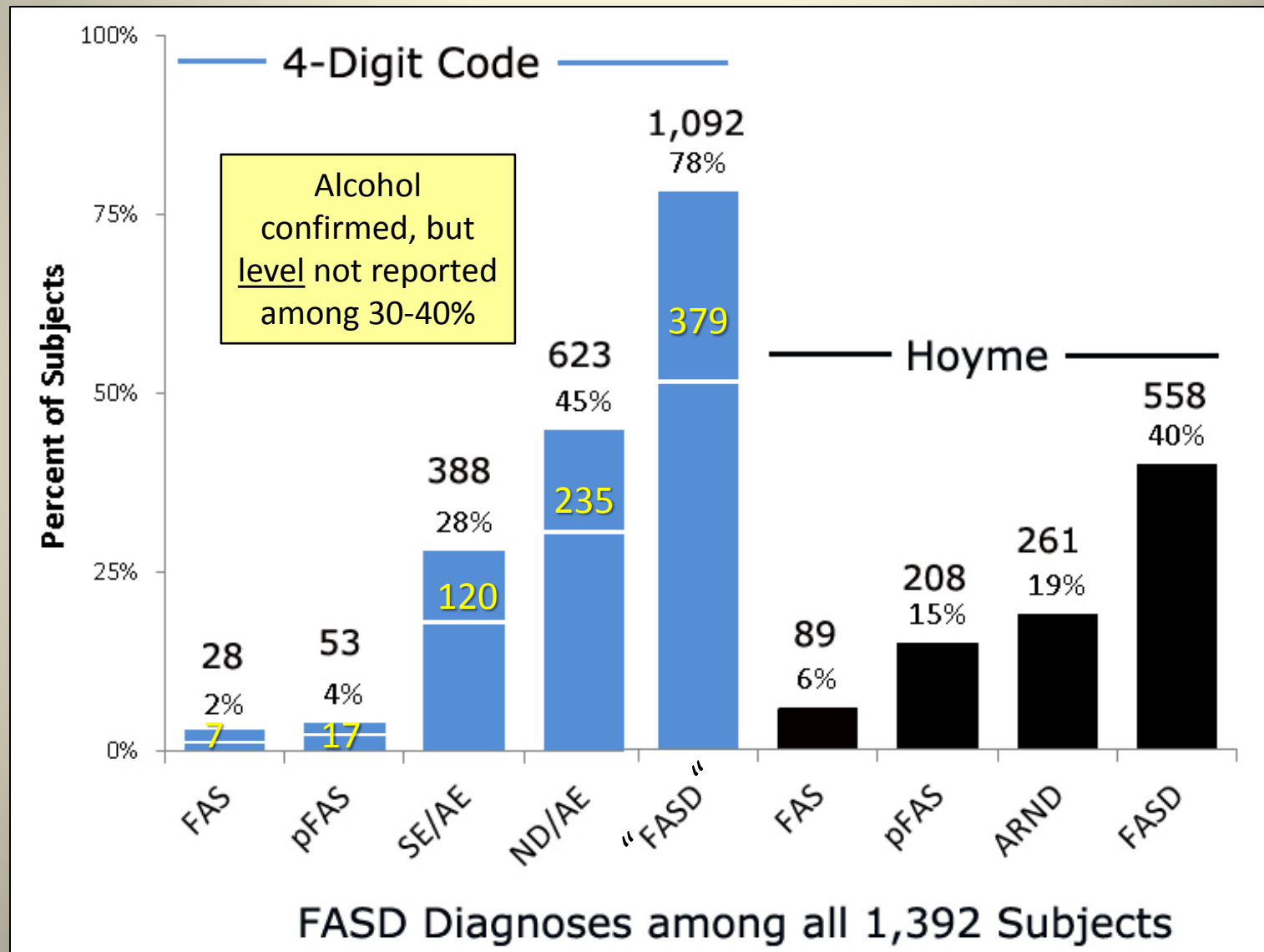




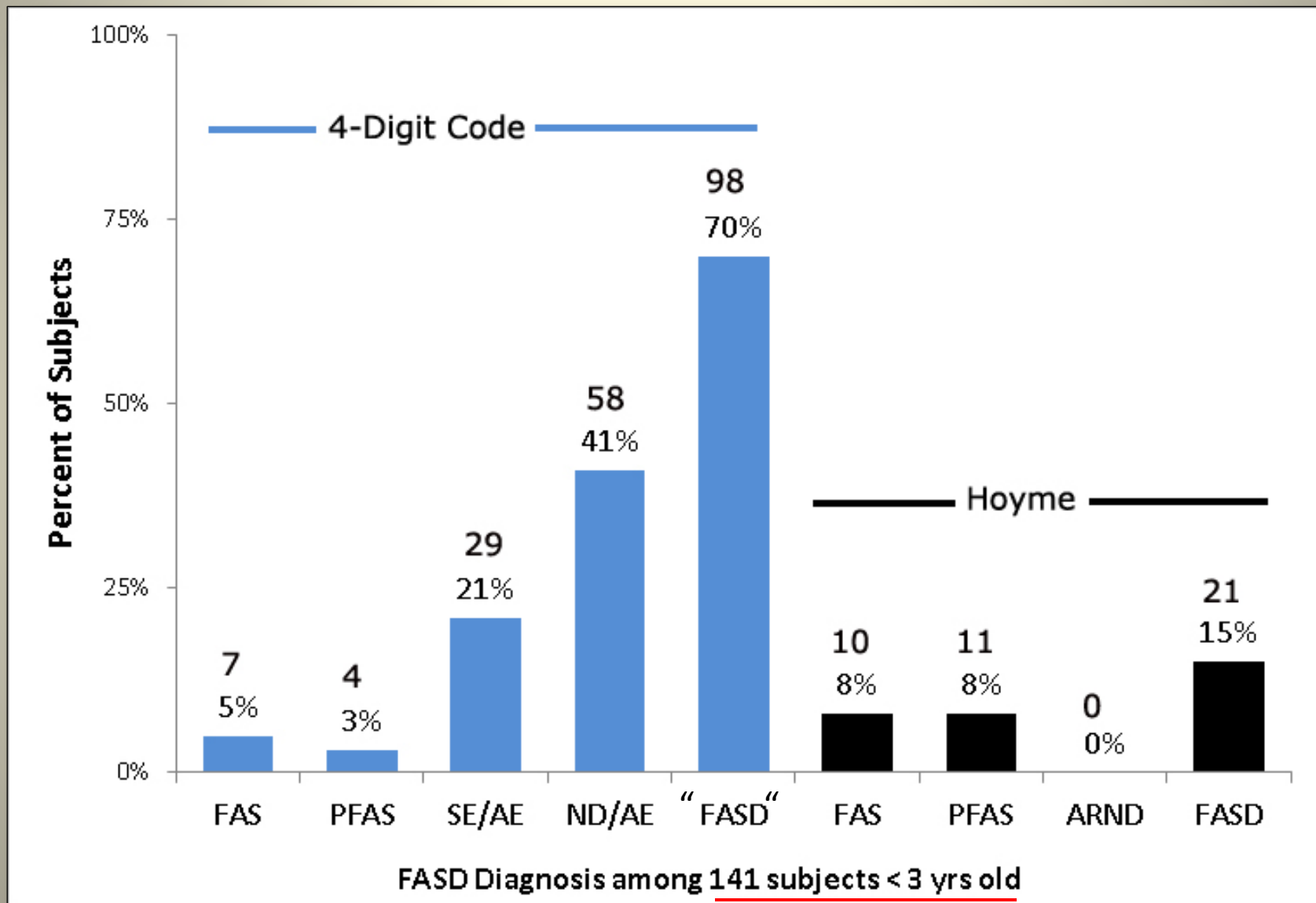
## 4-Digit versus Hoyme 2016 Diagnostic Outcomes



30-40% have confirmed exposure, but level unknown.



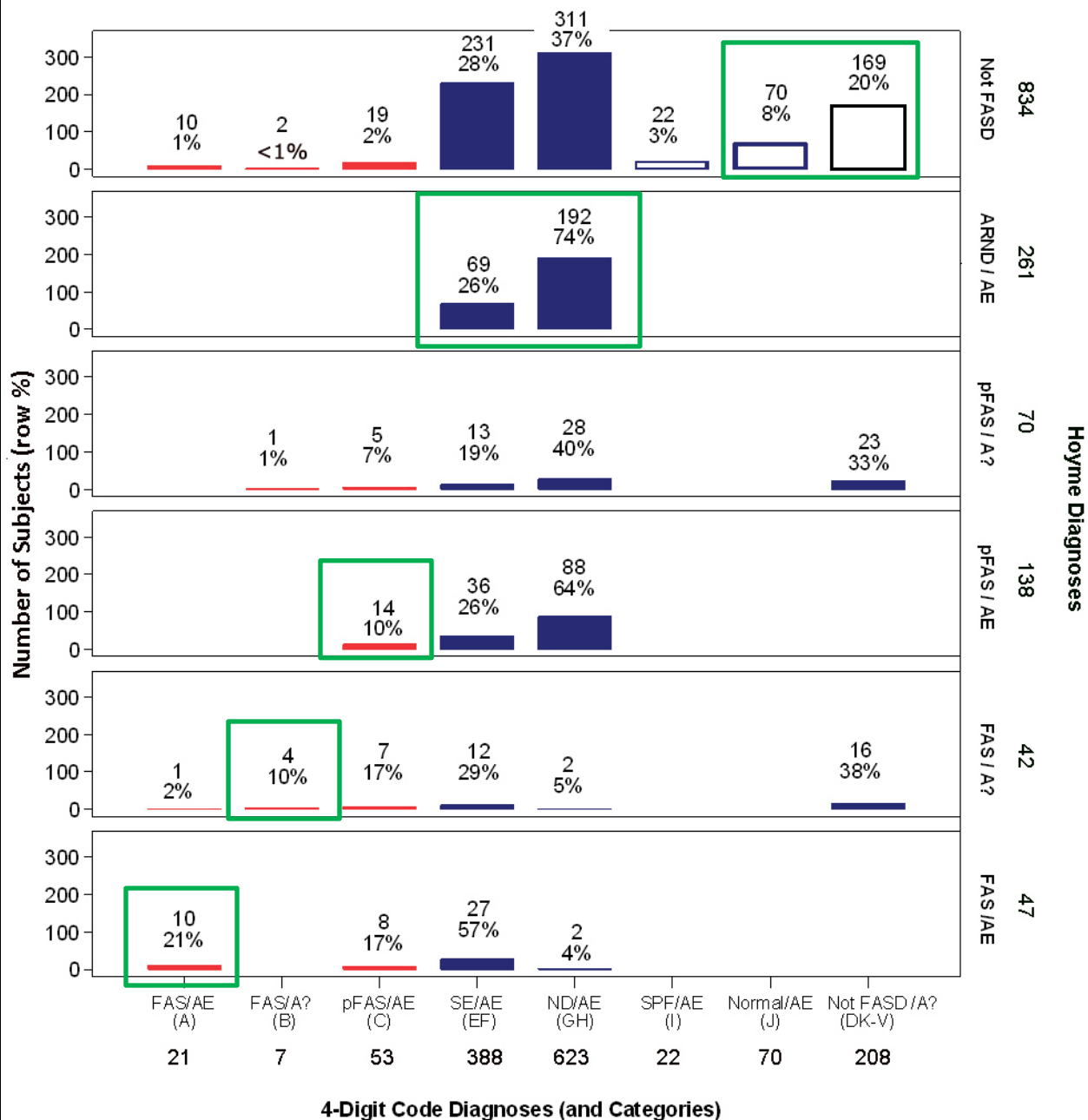
## 4-Digit versus Hoyme 2016 Diagnostic Outcomes among 141 subjects less than 3 years old





## Diagnostic Concordance

528 out of 1,392  
(38%)  
receive the same diagnosis  
from both Guidelines



## Diagnostic **Discordance**

864 out of 1,392  
(62%)  
receive different diagnoses  
from each Guideline.

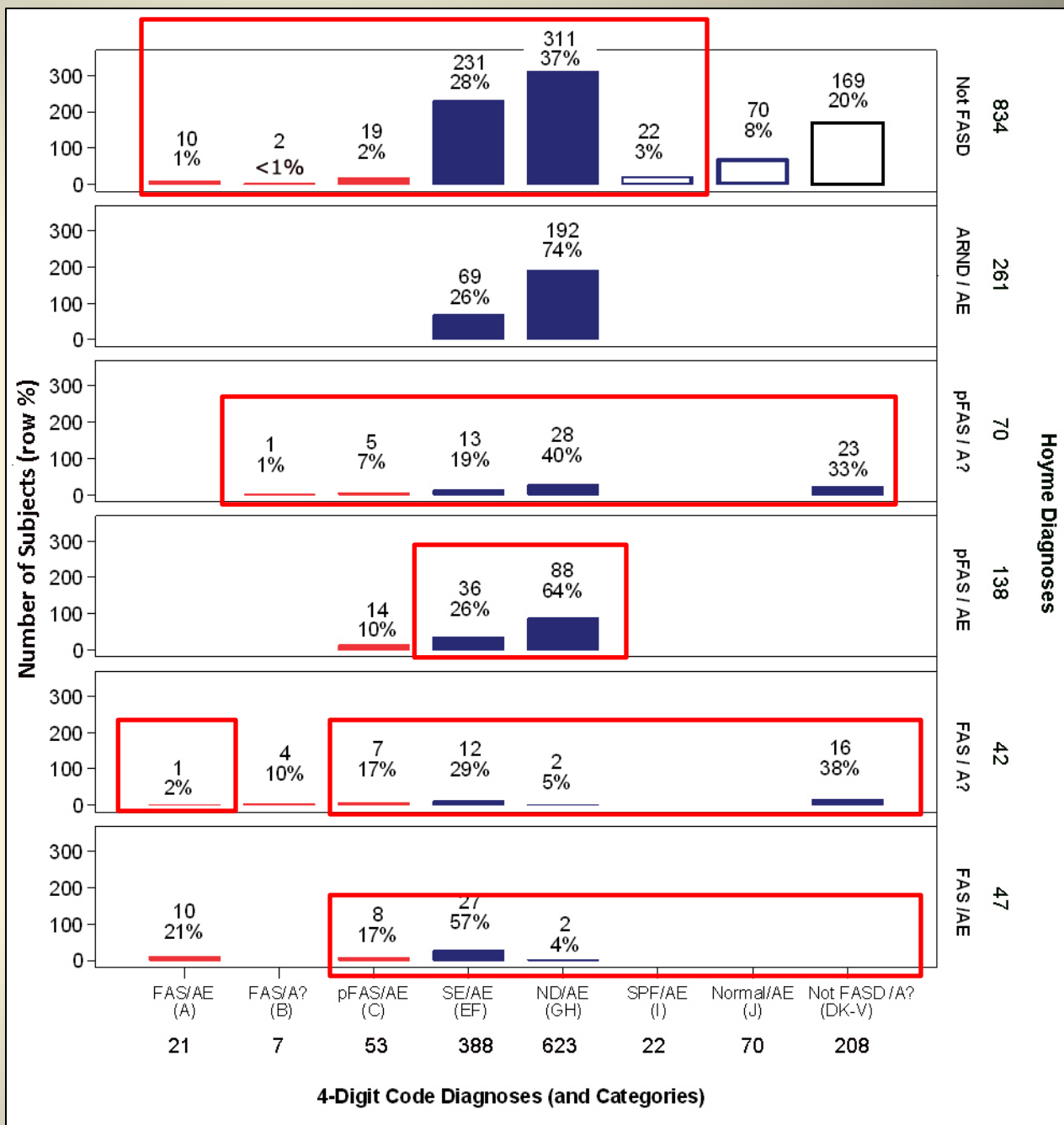
Sometimes the discordance  
between the diagnoses is  
striking.

For example....

There are cases where the 4-  
Digit Code calls it FAS, while the  
Hoyme criteria do not even  
place it under the umbrella of  
FASD.

And vice versa...

The Hoyme criteria call it FAS,  
while the 4-Digit Code says it is  
no where under the umbrella.

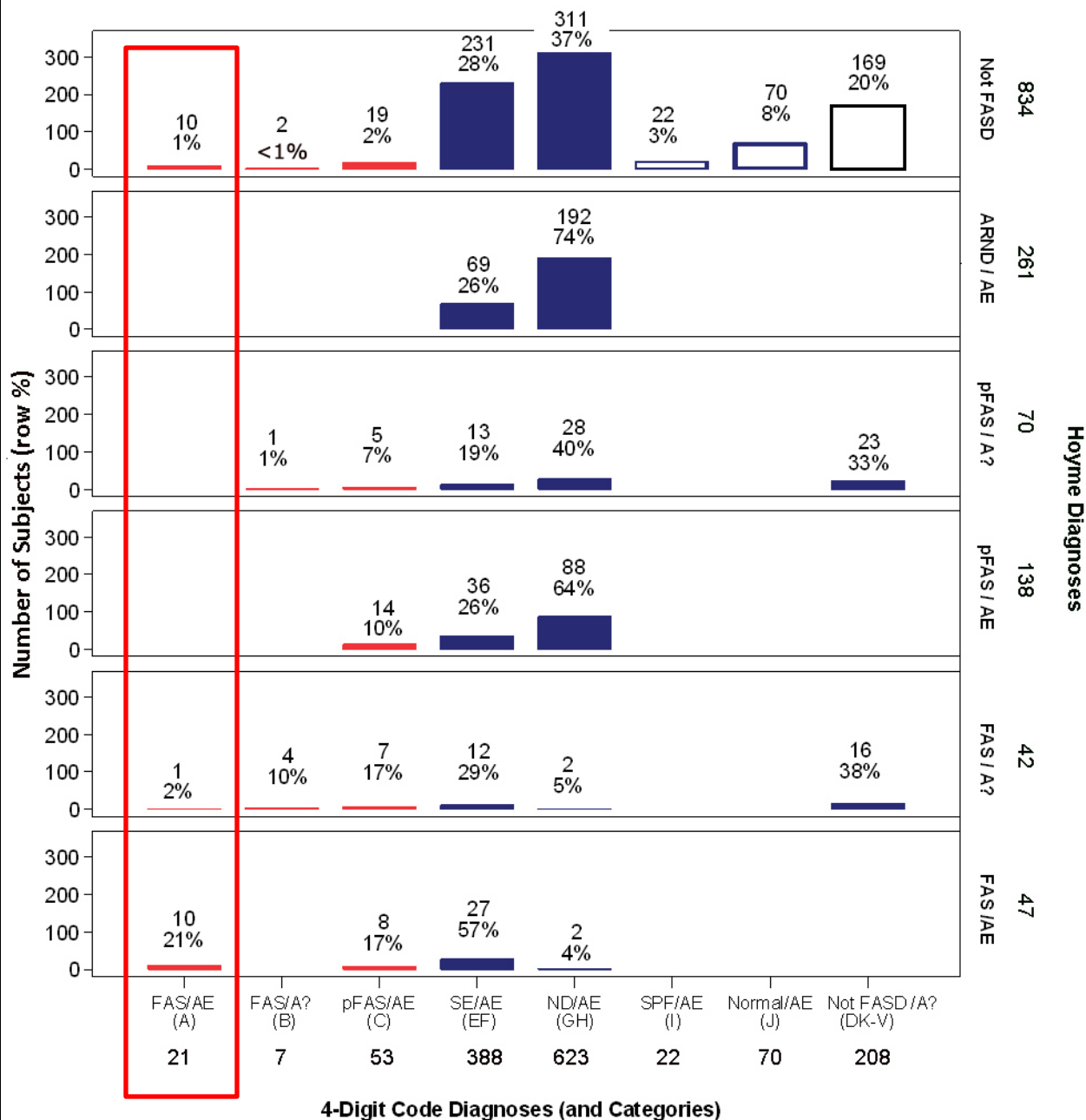


## Diagnostic Discordance

Of the 21 with 4-Digit FAS/AE,

10 (48%) did not receive a FASD diagnosis using the Hoyme Guidelines.

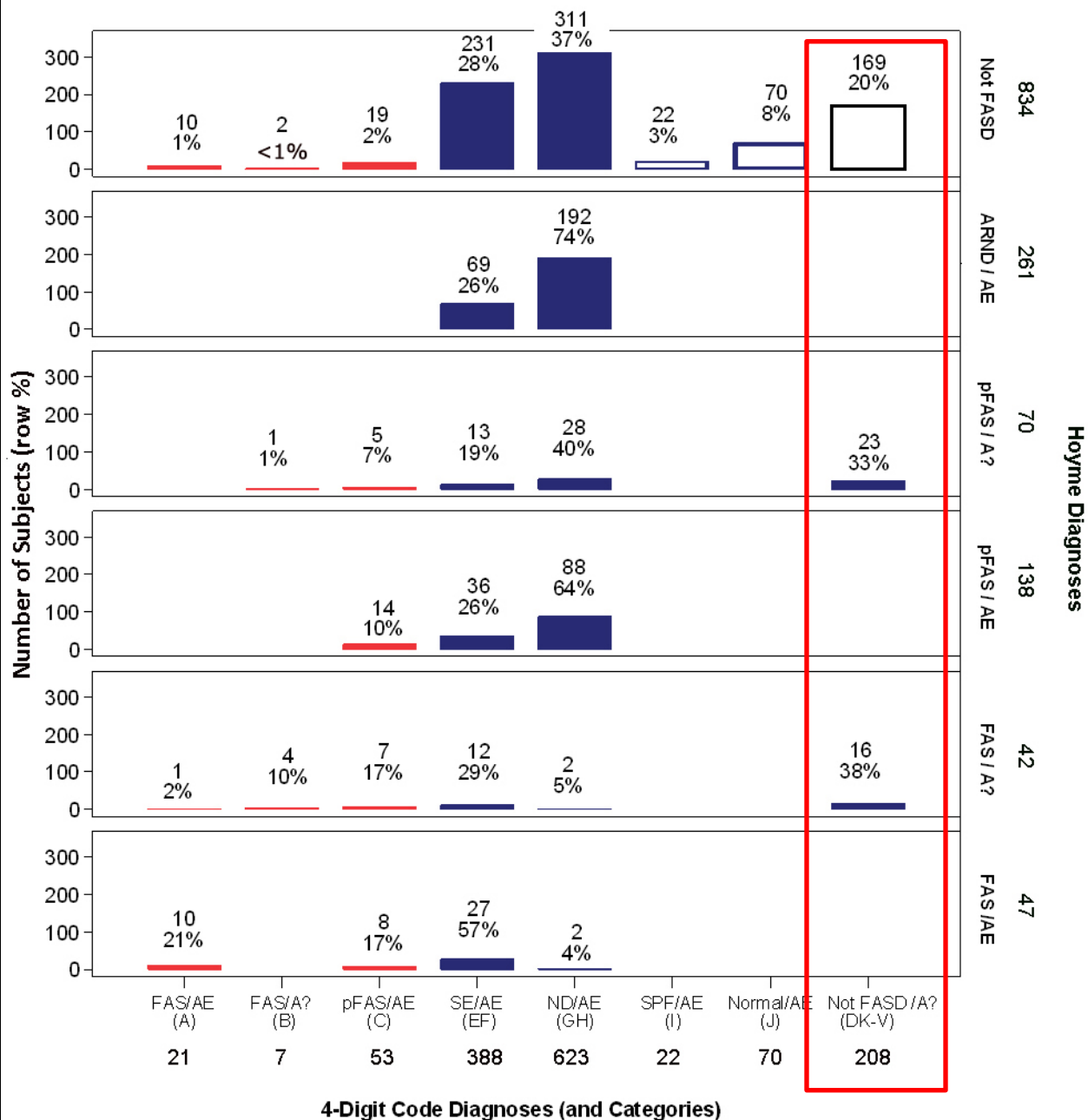
- 8 were microcephalic, but had normal development (all < 5 yrs old)
- 2 had severe CNS dysfunction, but were normocephalic (both were > 11 yrs old)





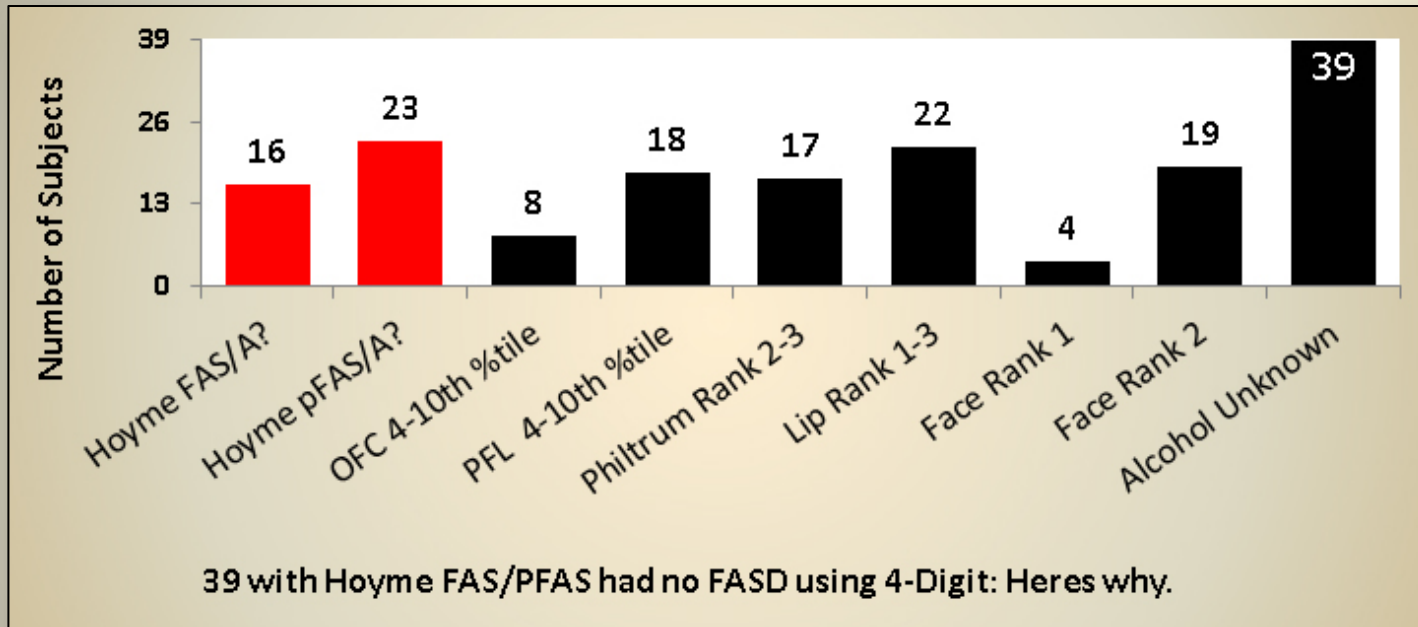
## Diagnostic Discordance

Let's focus on  
this column now



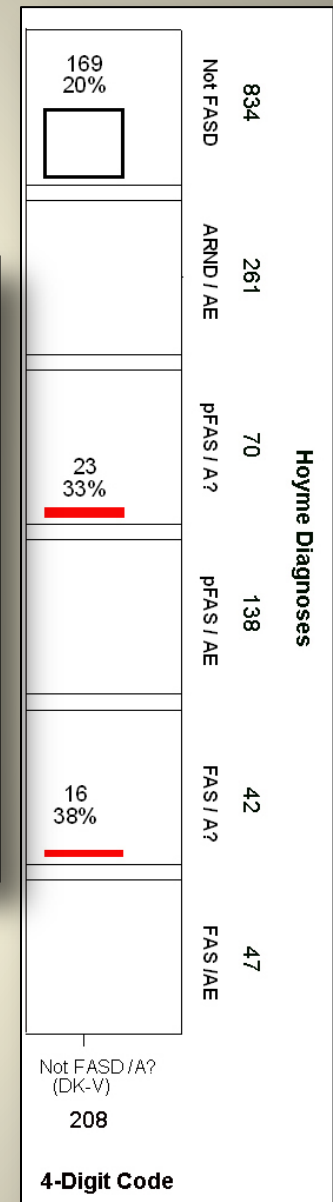
Among the 208 that were Not FASD using the 4-Digit Code;  
39 received a FAS/PFAS diagnosis using the Hoyme Guide.

Here's why....



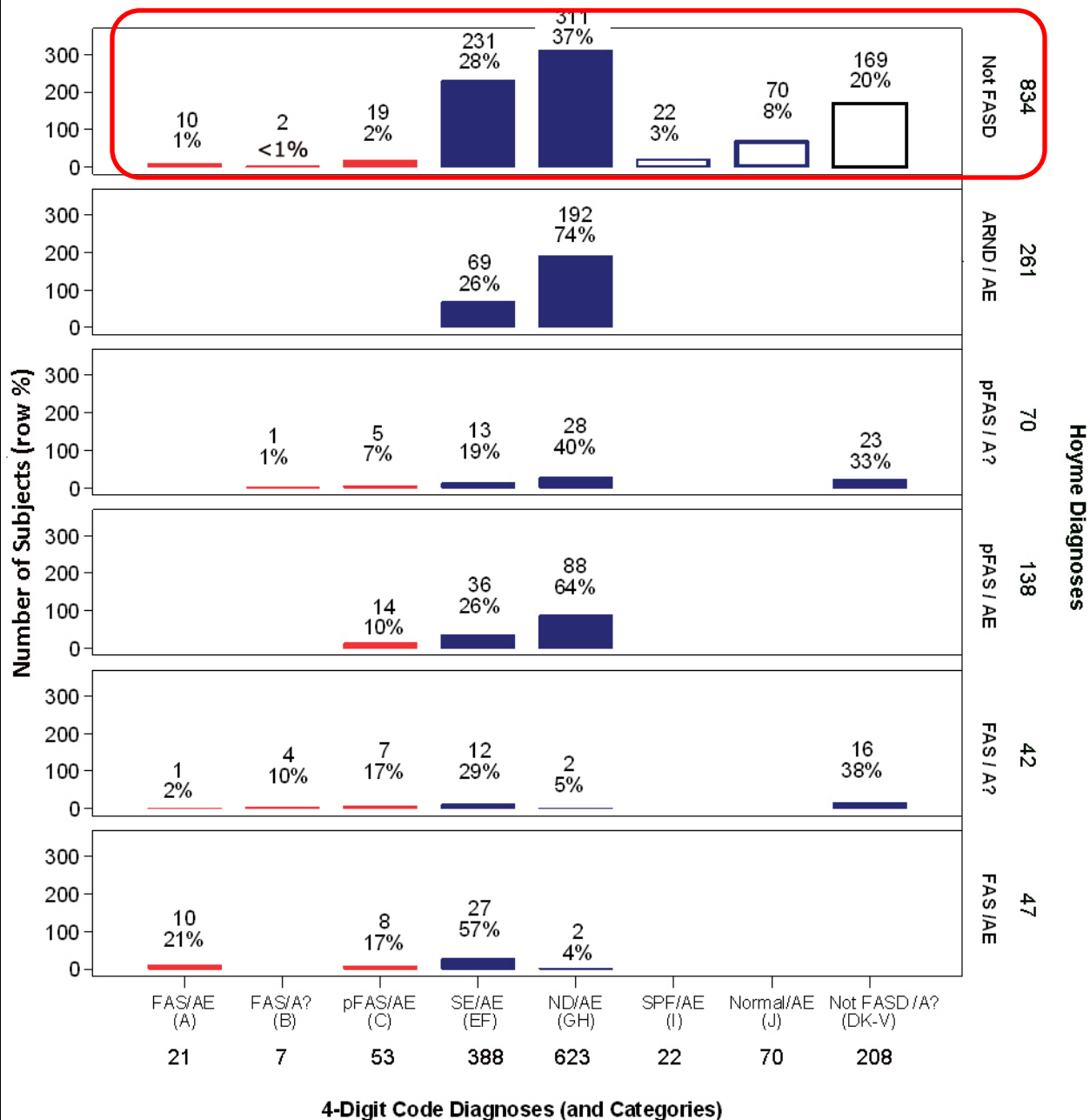
The 4-Digit Code does not render a diagnosis under the umbrella of FASD if:

- alcohol exposure is unknown and
- the Rank 4 FAS face is absent.



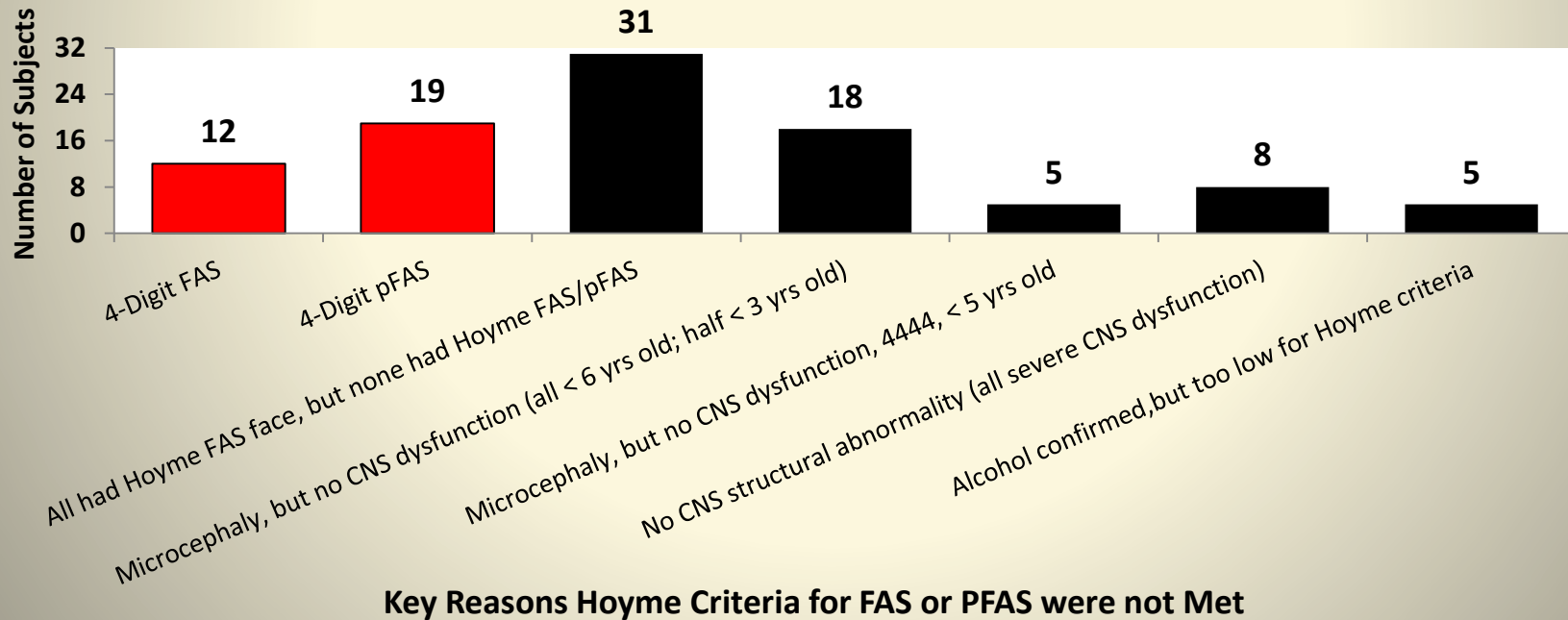
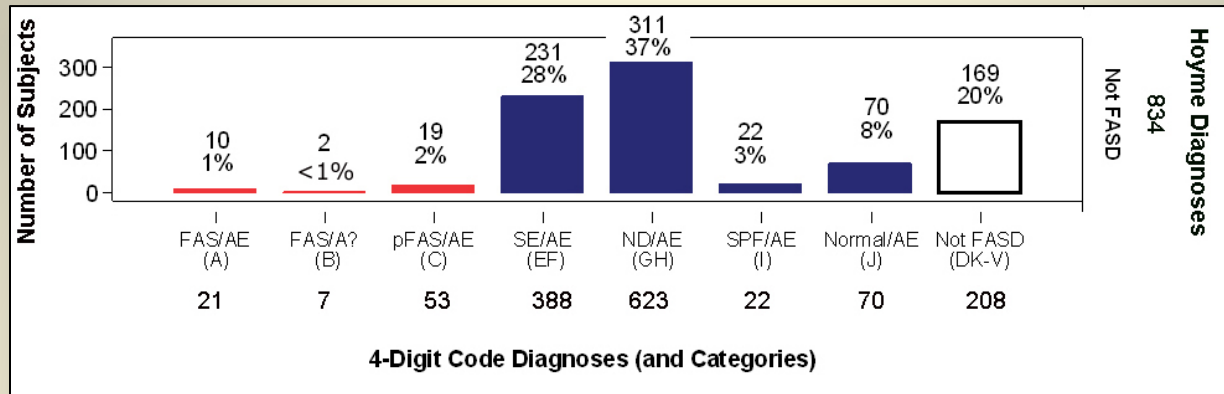
## Diagnostic Discordance

Now let's focus on this row.

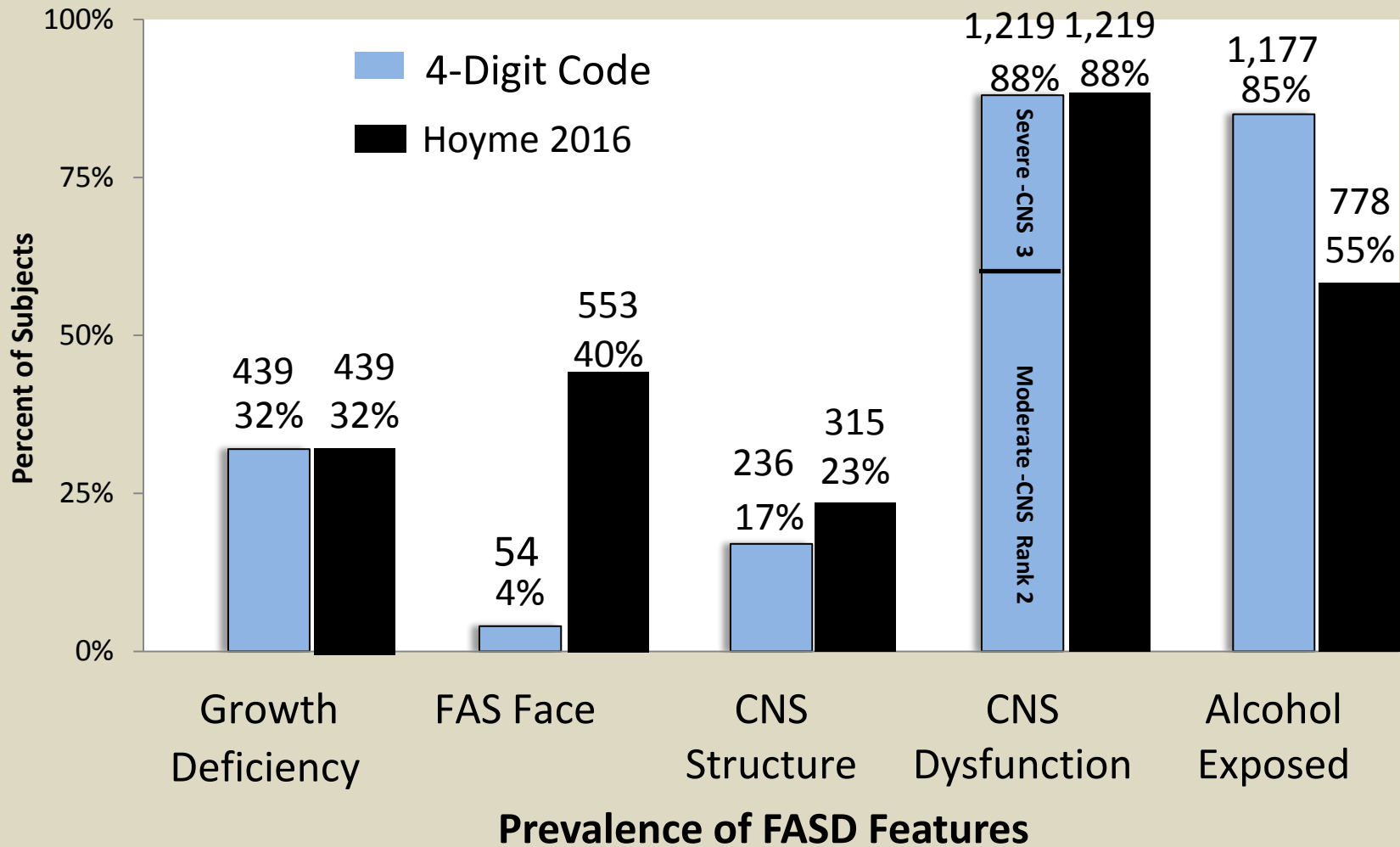




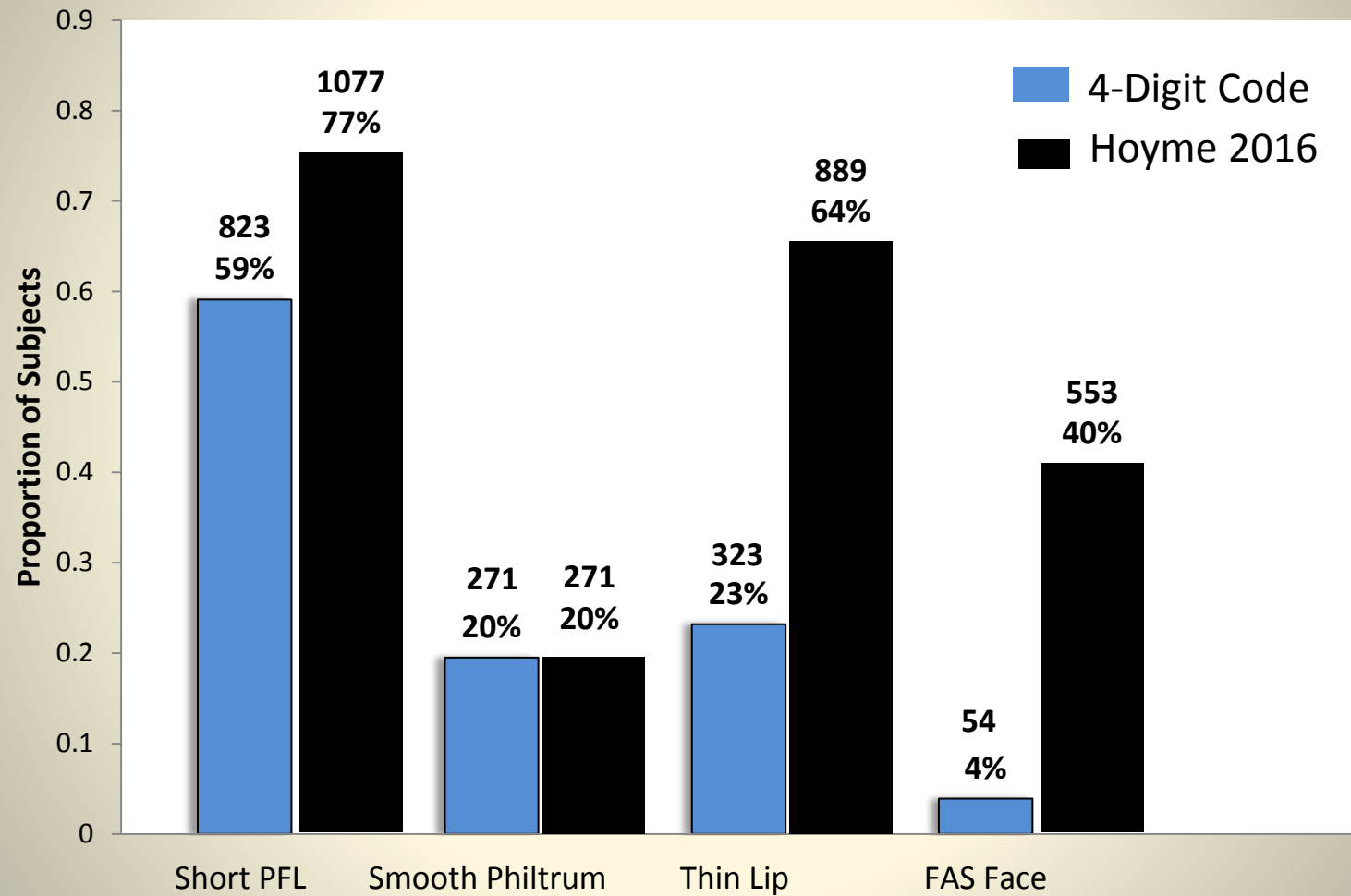
Among the 834 that were Not FASD using the Hoyme Guide;  
31 received a FAS/PFAS diagnosis using the 4-Digit Code.



# Prevalence of FASD Features among 1,392 Subjects



# Prevalence of FAS Facial Features

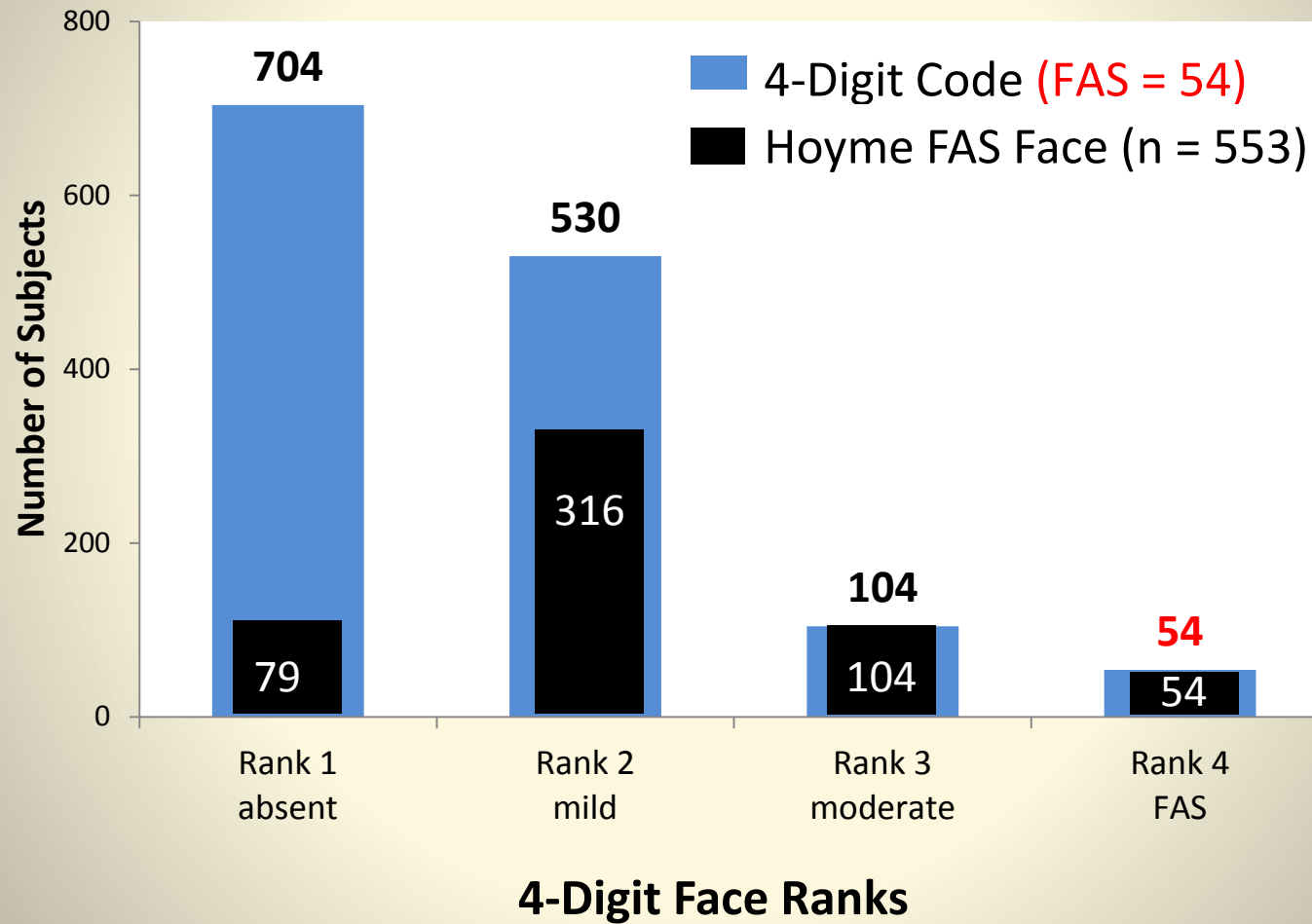


**FAS Face and Facial Features among 1,392 Subjects**



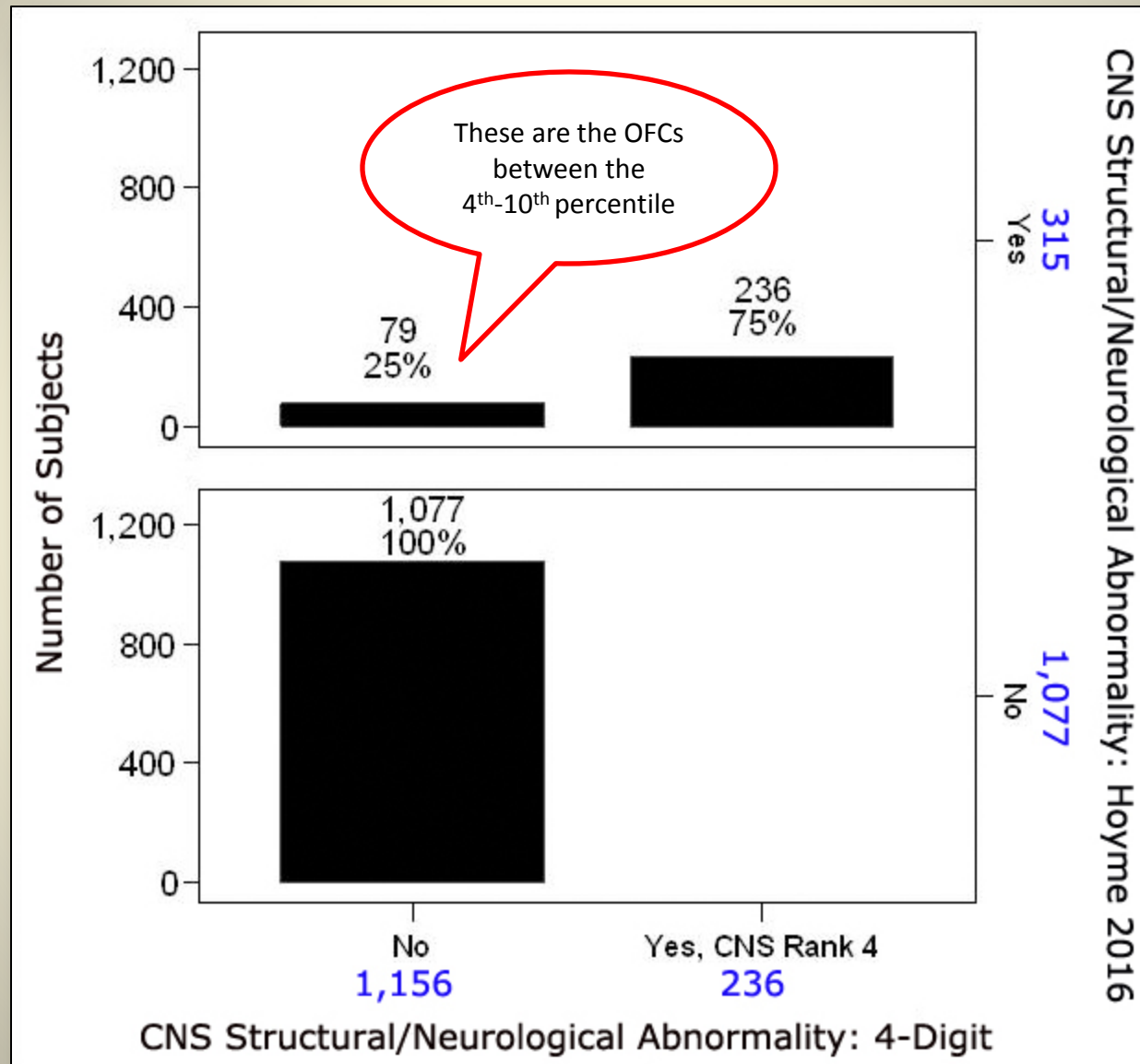
71% of Hoyme FAS faces are in the 4-Digit Normal Range (Face Ranks 1-2)

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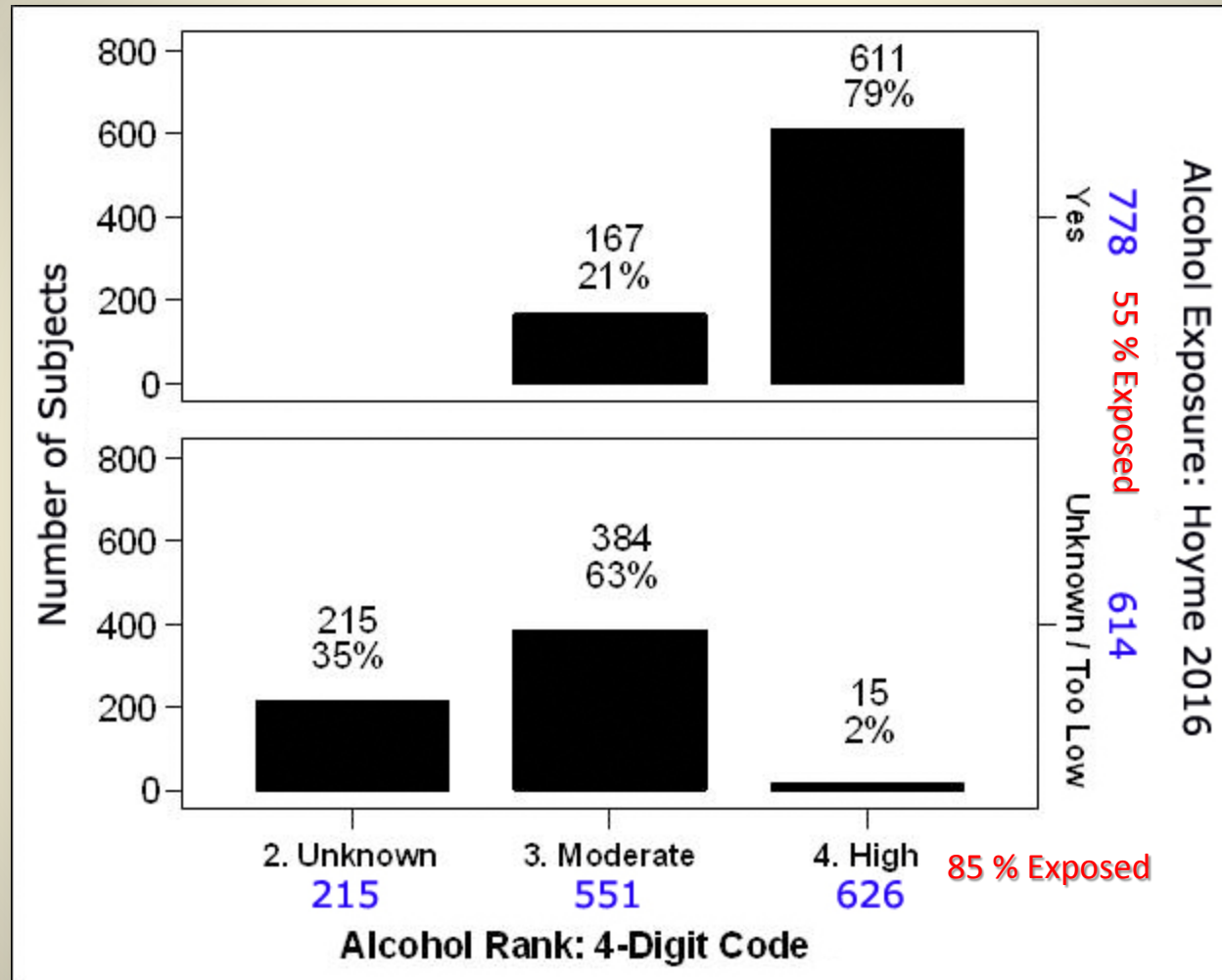


Among 1,392 Subjects

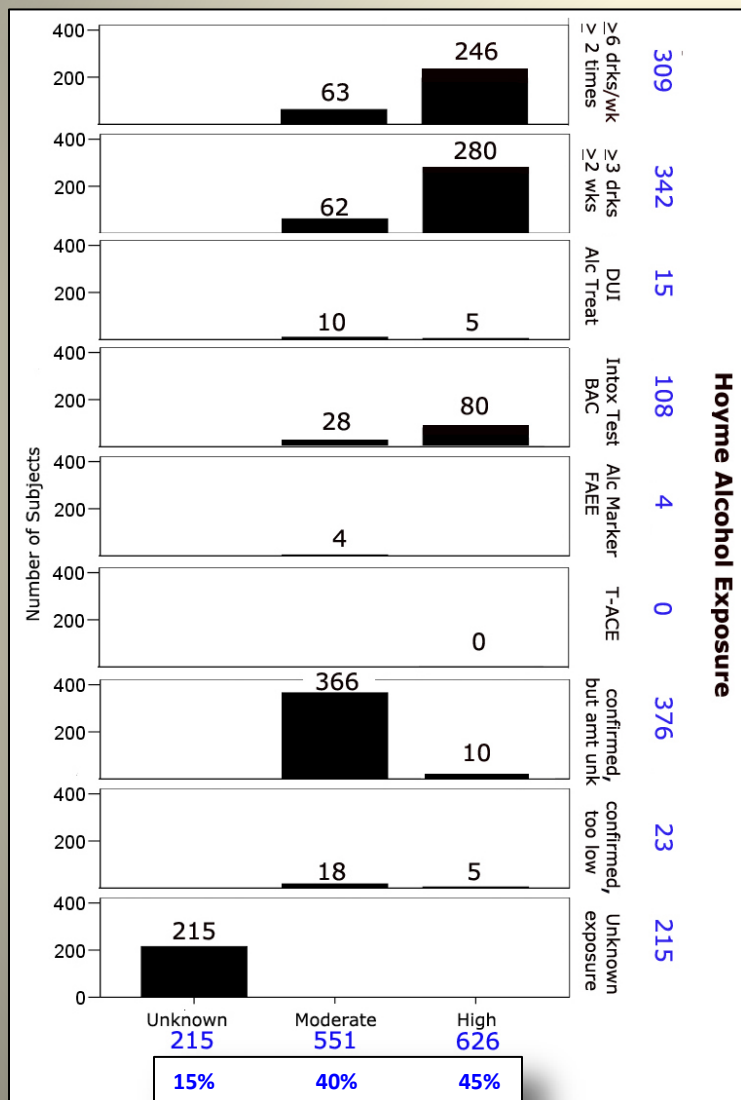
# Contrast in Prevalence of CNS Structural/Neurological Abnormalities



# Contrast in Prevalence of Alcohol Exposure Classification



# Alcohol Exposure Classification: 4-Digit versus Hoyme 2016 (n = 1,392)



**TABLE 2** Definition of Documented Prenatal Alcohol Exposure (as Applied to the Diagnostic Categories Set Forth in Table1)

One or more of the following conditions must be met to constitute documented prenatal alcohol exposure during pregnancy (including drinking levels reported by the mother 3 mo before her report of pregnancy recognition or a positive pregnancy test documented in the medical record). The information must be obtained from the biological mother or a reliable collateral source (eg, family member, social service agency, or medical record):

- (22%) ≥ 6 drinks/wk for ≥ 2 wk during pregnancy
- (25%) ≥ 3 drinks per occasion on ≥ 2 occasions during pregnancy
- (1%) Documentation of alcohol-related social or legal problems in proximity to (before or during) the index pregnancy (eg, history of citation[s] for **driving while intoxicated** or history of **treatment of an alcohol-related condition**)
- (7%) Documentation of **intoxication** during pregnancy by **blood, breath, or urine alcohol content testing**
- (< 1%) Positive testing with established alcohol-exposure biomarker(s) during pregnancy or at birth (eg., analysis of **fatty acid ethyl esters**, phosphatidylethanol, and/or ethyl glucuronide in maternal hair, fingernails, urine, or blood, or placenta, or meconium)
- (0%) Increased prenatal risk associated with drinking during pregnancy as assessed by a validated screening tool of, for example, **T-ACE** (tolerance, annoyance, cut down, eye-opener) or **AUDIT** (alcohol use disorders identification test)

(28%) A Hoyme FASD diagnosis cannot be rendered.

( 2%) A Hoyme FASD diagnosis cannot be rendered

(15%) A Hoyme FAS or PFAS can be rendered

## Alcohol Criteria Met

4-Digit: 85%

Hoyme: 55%



# Specificity of the FAS Facial Phenotype

FASD Guideline	Specificity	What does Specificity Mean?
Hoyme FAS Face 2 features (2013 Vancouver presentation)	71.4 %	Of those with the FAS face, 29 % will be false-positives <ul style="list-style-type: none"> <li>• will NOT have FAS/PFAS</li> <li>• Will NOT have PAE</li> </ul>
4-Digit Rank 4 FAS Face 3 features (Astley et al, 1996, 2003)	> 95 %	Of those with the FAS face, < 5 % will be false-positives <ul style="list-style-type: none"> <li>• Will NOT have FAS</li> <li>• Will NOT have PAE</li> </ul>

Sensitivity and Specificity with Two Facial Features
<ul style="list-style-type: none"> <li>• If the cut off required <i>two cardinal features</i> for a diagnosis of FAS:                             <ul style="list-style-type: none"> <li>– Sensitivity = 0.972</li> <li>– <b>Specificity = 0.714</b></li> <li>– Predictive value (isolated) = 0.287</li> </ul> </li> </ul> <p><i>Sensitive but not as specific.</i> Again, taken alone they are not adequate predictors of FAS.</p>

If the FAS face is specific to FAS (e.g., occurs only among individuals with FAS) and is specific to (caused only by) prenatal alcohol exposure...

One would expect that the vast majority of subjects with the FAS face would have FAS and prenatal alcohol exposure.

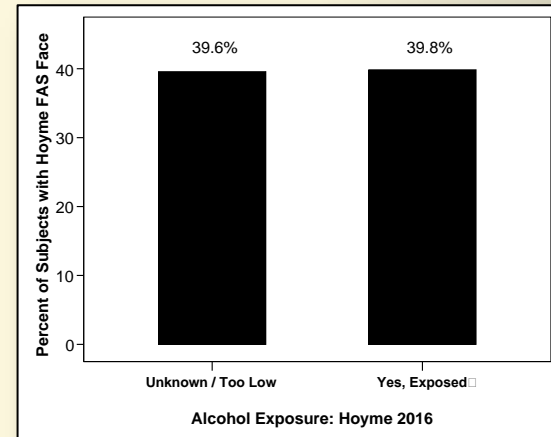
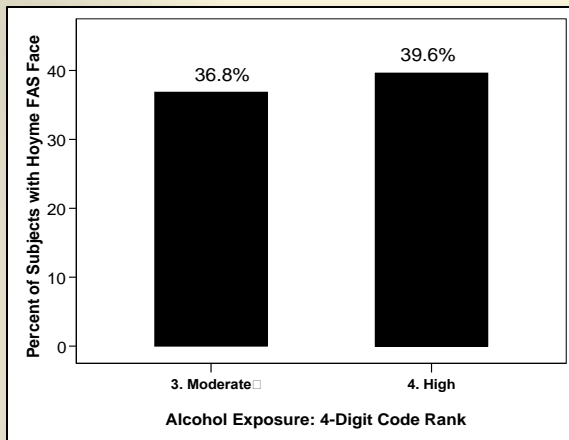
- 40 % (553 of 1,392 subjects) met the criteria for the Hoyme FAS face.
- 46 % with the Hoyme FAS Face did not meet Hoyme criteria for FASD.
- 44 % with the Hoyme FAS Face did not meet Hoyme criteria for documented prenatal alcohol exposure.

No Correlation between Alcohol Exposure and Hoyme FAS Face.  
Strong Correlation between Alcohol Exposure and 4-Digit FAS Face.

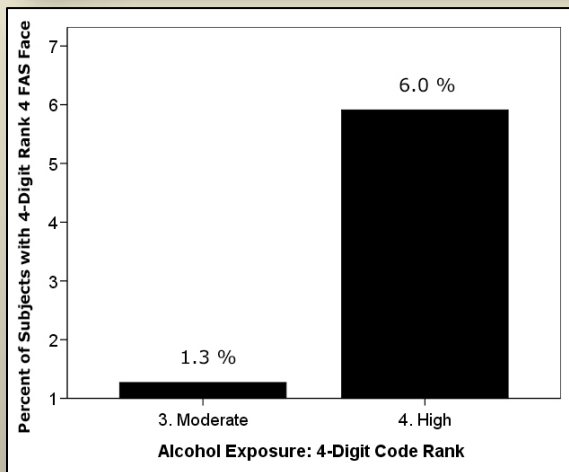
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If the FAS face is specific to (caused only by) prenatal alcohol exposure, it should be more prevalent among those with higher exposures.

Hoyme



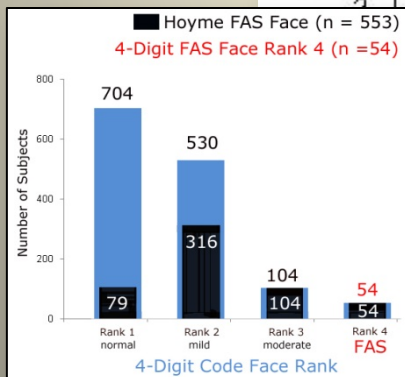
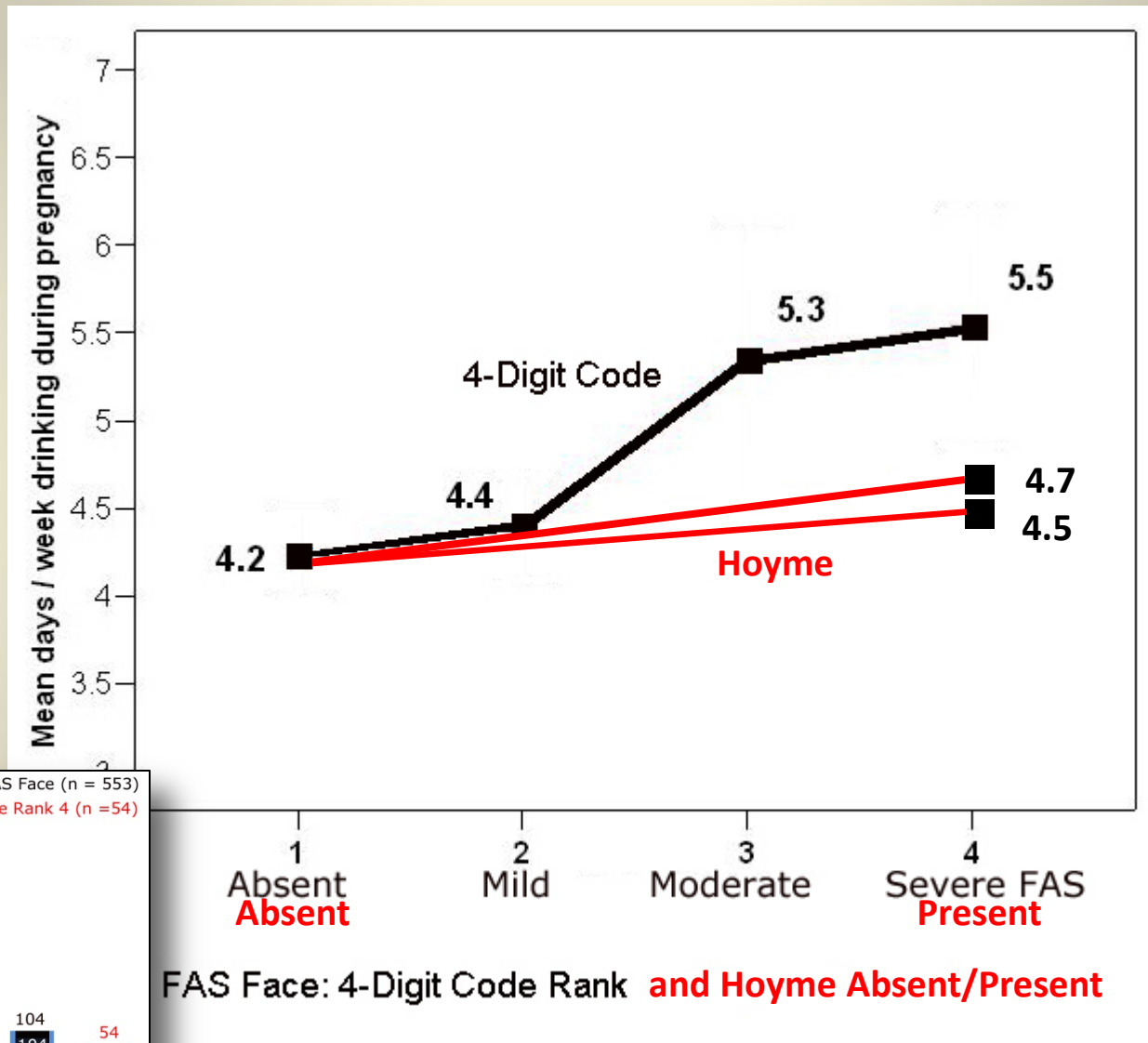
4-Digit Code



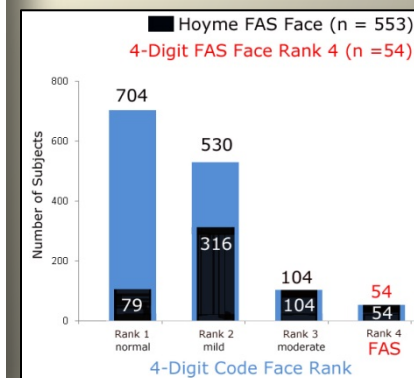
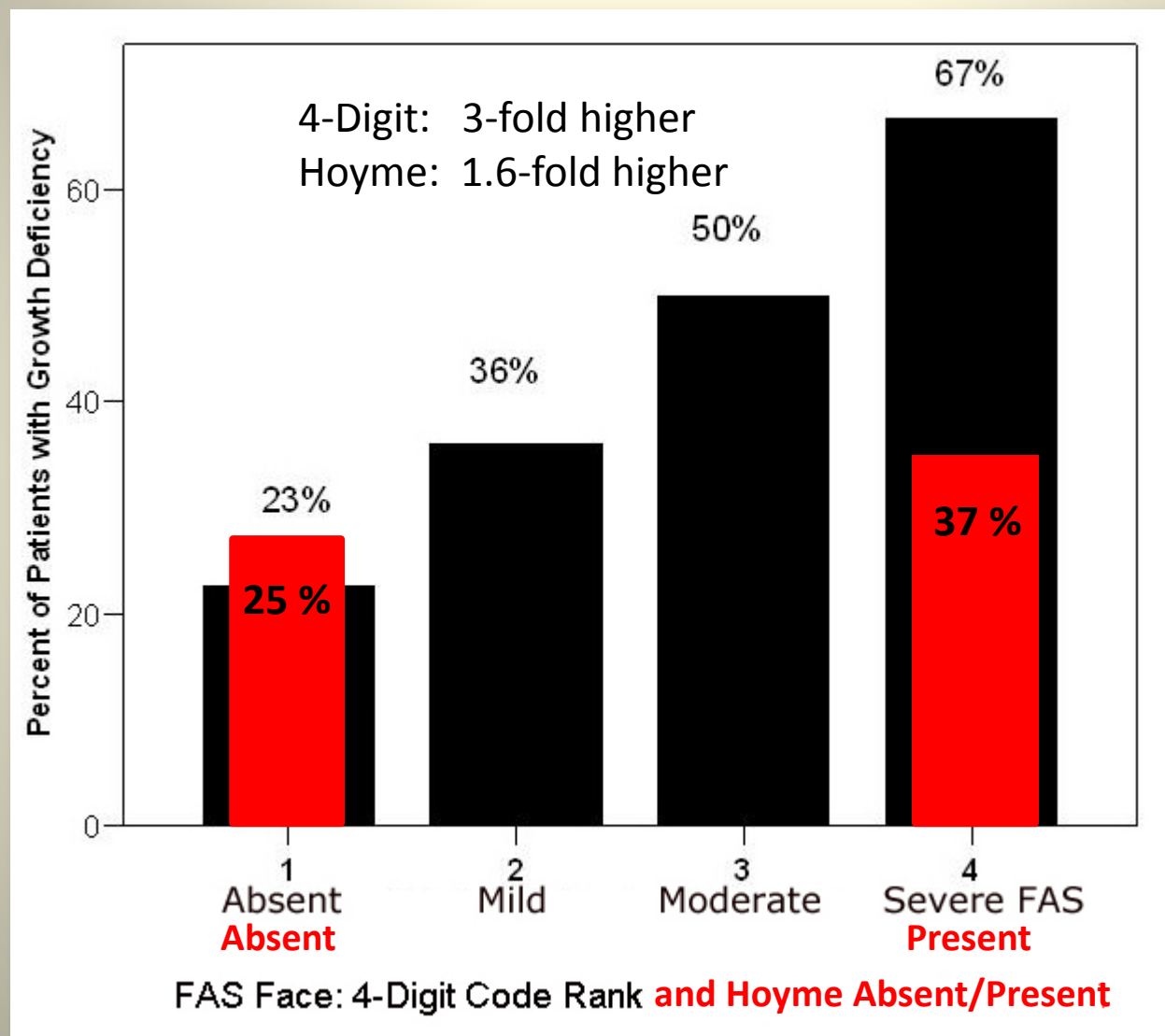
The Hoyme FAS face is **equally prevalent** and **highly prevalent** in the moderate and high exposure groups.

4-Digit FAS face is **5 times more prevalent** in the high exposure group than the moderate exposure group.

# ALCOHOL correlated with 4-Digit FAS Face, not with Hoyme FAS Face

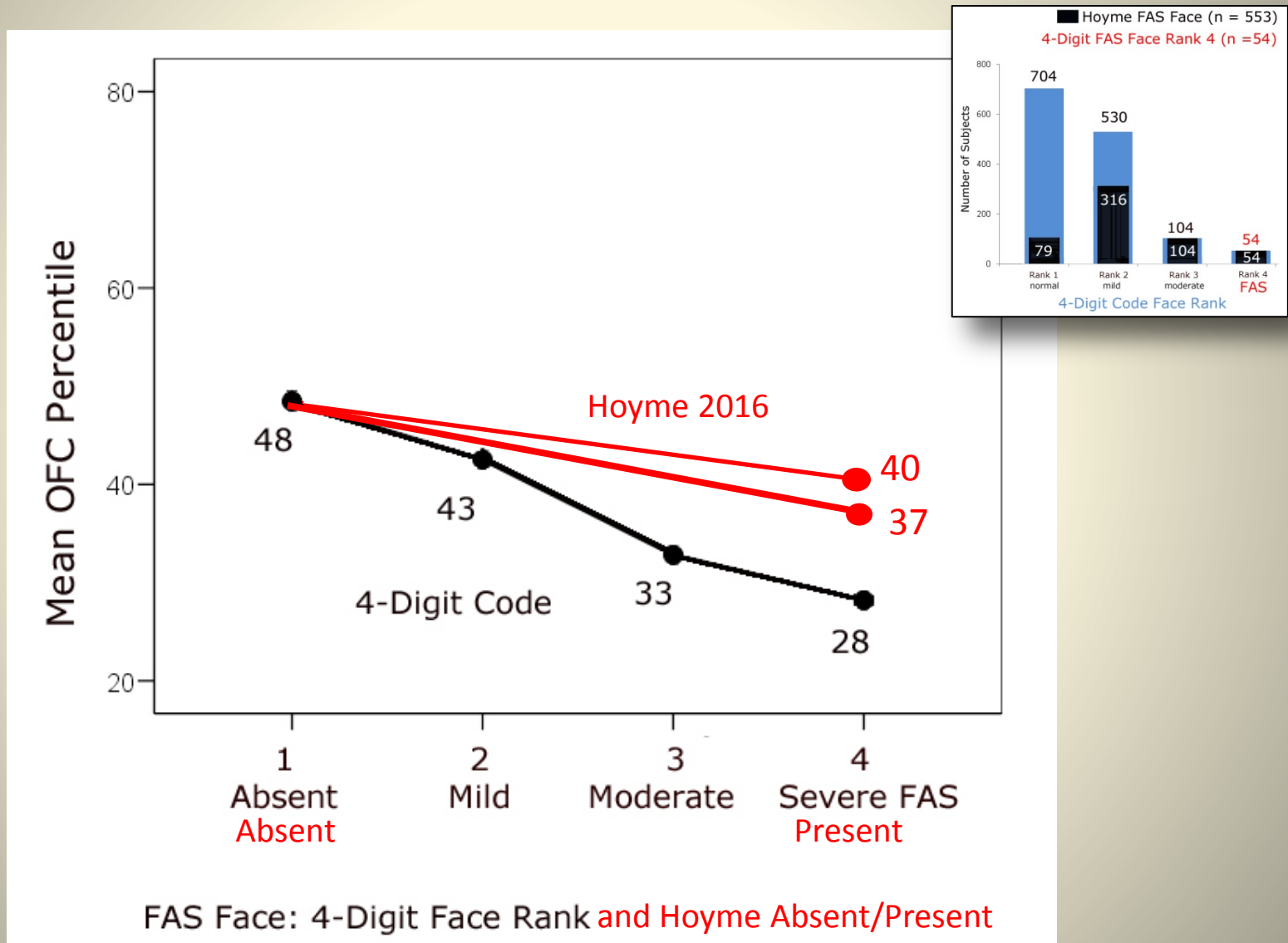


Stronger GROWTH correlation with 4-Digit FAS face than Hoyme FAS face.

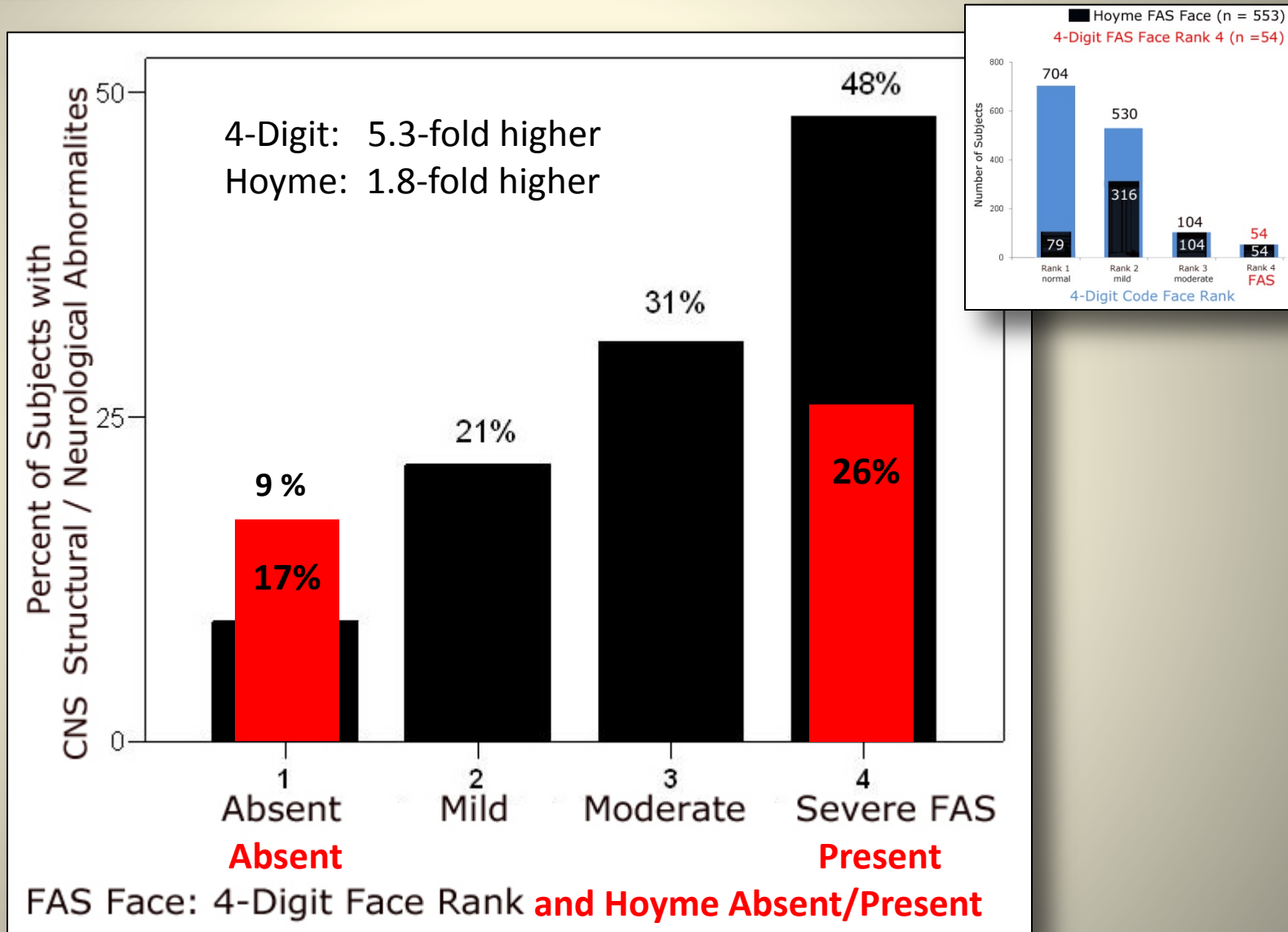




# Stronger OFC Correlation with 4-Digit FAS Face than Hoyme FAS Face



## Stronger CNS Structural/Neurological correlation with 4-Digit FAS Face than Hoyme FAS Face



## 5 Factors Accounted for the Greatest Contrasts in Diagnostic Outcomes between the 2 Systems

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1. The relaxation of the Hoyme FAS facial phenotype greatly increased the prevalence of FAS and PFAS
  - 10 times more FAS faces (553 vs 54)
  - 16 times more FAS/PFAS diagnoses with Unknown Alc (112 vs 7).

This is particularly concerning because 68 of these patients had normal facial phenotypes (Ranks 1 and 2). Rank 1 and 2 faces are not specific at all to prenatal alcohol exposure, thus it is unclear how the facial phenotype could be used to overcome an Unknown alcohol exposure to label the outcome FAS or PFAS.
  - 4 times more FAS/pFAS diagnoses overall (297 versus 81).
  - Only 32 (10%) of the 297 Hoyme FAS/PFAS cases had the 4-Digit Rank 4 FAS face.
  - Only 90 (30%) of the 297 Hoyme FAS/PFAS cases had the 4-Digit Rank 3 or 4 FAS face.
2. The Hoyme requirement for both CNS structural and CNS functional impairment for FAS reduced the prevalence of FAS. 50% of the 4-Digit FAS cases did not meet the Hoyme criteria for FAS because they were microcephalic, but too young to fully assess brain dysfunction.
3. The Hoyme requirement for CNS functional impairment prevented many children < 3 years of age from receiving a FAS or PFAS diagnosis. Eight of the 11 infants with 4-Digit FAS/PFAS did not receive a Hoyme diagnosis under the umbrella of FASD.
4. The Hoyme criteria do not allow children under 3 years to receive a diagnosis of ARND. As a result, 73 of the 87 infants/toddlers that received a 4-Digit diagnosis of ND/AE or SE/AE did not receive a Hoyme FASD diagnosis.
5. Documentation of significant alcohol exposure prevented half of the individuals with confirmed exposure from receiving a FASD diagnosis (558 versus 1,092).
6. Final Outcome: Hoyme criteria rendered half the diagnoses and placed a much higher proportion in the FAS/PFAS categories by relaxing the FAS facial criteria.

# FAS Face: 4-Digit Code (Rank 4) vs Hoyme 2016

## 4-Digit Code (Rank 4) FAS Face

- |                    |                            |
|--------------------|----------------------------|
| 1) Short PFL       | $\leq -2$ SD ( $\leq 3$ %) |
| 2) Smooth Philtrum | Rank 4 or 5                |
| 3) Thin Upper Lip  | Rank 4 or 5                |



F  
A  
S



## Hoyme 2016 FAS Face

When the facial criteria are relaxed:

- PFL  $\leq 10\%$
- And only 2 of 3 features required

The phenotype moves well into the normal range (both in definition and appearance) and is no longer specific to FAS or alcohol.



Example of a healthy, normal child (IQ 105) with confirmed absence of prenatal alcohol exposure who meets the Hoyme 2016 criteria for the FAS face.

PFL 5%, Philtrum Rank 4, Lip Rank 1



# The Quintessential Role of the FAS Facial Phenotype

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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.
- 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 Specific to FAS and Prenatal Alcohol Exposure?

---

The whole FASD  
diagnostic system  
collapses like a house  
of cards.

Here is why!



# The Quintessential Role of the FAS Facial Phenotype

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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.

If the face is NOT specific to (caused only by) alcohol, you can no longer call 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.

2. The diagnosis (FAS/alcohol exposure unknown) is also rendered invalid.

The FAS face can no longer serve as the confirmation 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 FAS face, there is no distinction between FAS and ARND. Thus, one can no longer justify classifying FAS and ARND separately.

4. The term “ARND” remains problematic.

Since ARND has no feature specific to prenatal alcohol, one is in no position to declare the Neurodevelopmental Disorder is “Alcohol-Related” (ARND) in an individual patient.

# The Ethical Consequences of the FASD Diagnostic Nomenclature

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When one uses a term like ARND, one finds oneself needing to require a significant exposure to alcohol to increase the odds that the individual's impairments may be caused, at least in part, by their alcohol exposure. This is a dangerous road to go down.

- 1) Setting a threshold of significant 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.
- 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 limited ability to make/defend such a claim. These claims have medical, ethical and even legal consequences.

The 4-Digit Code introduced the terms ND/AE and SE/AE back in 1997. In 2013, the DSM5 chose the term ND/PAE over ARND.



# When is it a FASD?

Fetal Alcohol Spectrum Disorders are adverse outcomes **CAUSED** by prenatal alcohol exposure.

In the absence of a outcome that is specific to (caused only by) prenatal alcohol exposure (like the Rank 4 FAS facial phenotype), one cannot CONFIRM or RULE-OUT the role prenatal alcohol exposure played in an individual's CNS dysfunction.

So....

**Do all individuals with SE/AE, ND/AE and ARND have FASD?**

Not necessarily. Only the subset of individuals whose CNS dysfunction was caused (in whole or in part) by their alcohol exposure.

**Which subset is that?**

We currently have no way of knowing.

**But if they are exposed to HIGH alcohol levels, can't we just assume alcohol caused their disability?**

No!

Not everyone exposed to high levels of alcohol presents with adverse outcomes.

Among 2,576 individuals evaluated for FASD,

- 40 (1.6%) were 1114 (NORMAL growth, face, and brain, but HIGH exposure).
- 26 (1.0%) were 4444 (full FAS, with HIGH exposure)
- Among 20 twin pairs with identical HIGH exposures, 5 had normal CNS function while their twin had moderate to severe CNS dysfunction.

When an individual presents with HIGH alcohol exposure and severe CNS dysfunction (SE/AE, 2134)

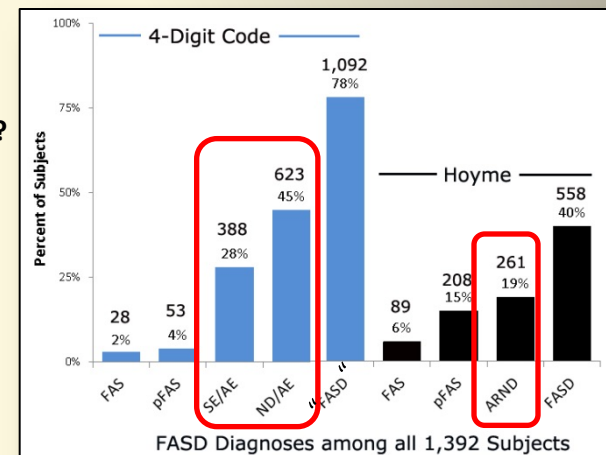
- If their **CNS dysfunction** is caused by their alcohol exposure, then their SE/AE is an FASD.
- If their **CNS dysfunction** was caused by other risk factors, not their alcohol exposure, then their SE/AE is NOT an FASD.
- The only way we can link alcohol to an individual's CNS dysfunction is if they present with a highly specific FAS face (FAS 2434).

**If we cannot confirm alcohol caused their disabilities, does this impact our ability to provide them intervention?**

Absolutely not. Our intervention recommendations and a patient's access to services and supports are based on their disabilities, not on what caused their disabilities. Twenty years of published patient surveys (Astley, 2014) confirm patients with a diagnosis of ND/AE and SE/AE were as likely to access and benefit from interventions as patients with FAS/PFAS. We did not have to call it FAS/PFAS to qualify them for services.

**Does this impact our ability to prevent FASDs?**

Again, absolutely not. To prevent FASD you must prevent prenatal alcohol exposure. To know if you are preventing PAE, you need to document all occurrences of PAE in the patient's medical record (regardless of outcome) and track the prevalence of PAE by birth cohort annually. If you are reducing the prevalence of PAE, you are reducing the prevalence of FASD. That is the approach the 4-Digit Code takes.



# Sensitivity versus Specificity

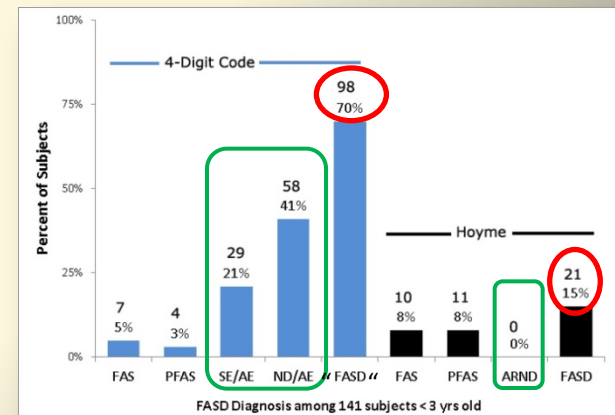
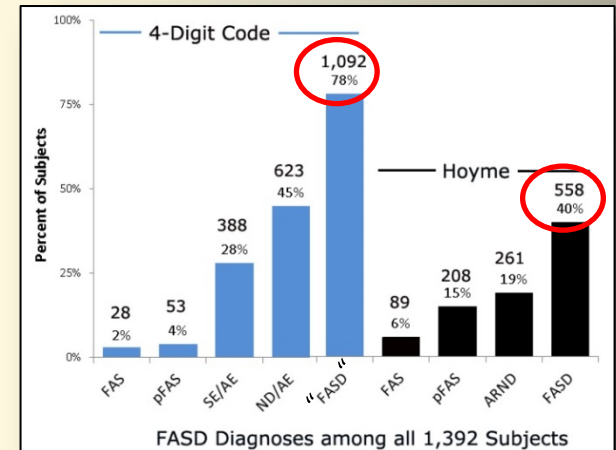
Hoyme et al (2016)

## Sensitivity Versus Specificity in Clinical Diagnosis

Similar to others, our goals in the formulation of FASD diagnostic guidelines have been improved sensitivity and greater inclusion of children in the complete continuum of FASD<sup>4,8</sup>; thus, we have set cutoff levels for growth deficiency, head circumference, and palpebral fissure length at  $\leq 10$ th centile and required 2, rather than 3, cardinal facial features for a diagnosis of FAS and PFAS. Because we advocate for a structured expert-led multidisciplinary diagnostic approach to the diagnosis of FASD, casting a broad net early in the diagnostic process and later using the case conference to carefully assign diagnoses has been our standard. Other diagnostic systems advocate for more stringent cutoffs: growth deficiency, head circumference, and palpebral fissure length less than or equal to the third centile and requiring all 3 of the cardinal facial features for alcohol-related diagnoses.<sup>5,9,10</sup> Sensitivity and specificity are 2 sides of a diagnostic coin. Theoretically, the guidelines

presented here demonstrating increased sensitivity could lead to overdiagnosis; thus, our advocacy for a structured expert multidisciplinary approach. On the other hand, strict diagnostic cutoffs associated with increased specificity could lead to underdiagnosis of affected children. Children with FASD are subject to a host of societal, educational, health, and judicial problems, all of which are affected by the time of diagnosis.<sup>84,85</sup> Because early diagnosis and initiation of intervention should be of paramount importance, the authors assert that improved, sensitive, and inclusive diagnostic criteria for FASD should continue to be imperatives in the diagnostic process.

But just the opposite occurred.



# Sensitivity versus Specificity

Strict diagnostic cutoffs associated with increased specificity do NOT lead to under-diagnosis when using the 4-Digit Code.

The 4-Digit Code uses stringent cutoffs for the FAS face to achieve diagnostic [accuracy/validity](#). If the face is not specific to (caused only by) alcohol, you cannot validly label the condition FAS because you cannot link the patient's outcomes to their alcohol exposure.

High specificity does not prevent individuals at risk for FASD from being identified and diagnosed. The 4-Digit Code is able to document the full continuum of outcomes and exposures (from 1113 to 4444) across the entire age span because it is not constrained by the implication of causation that comes with the term ARND.

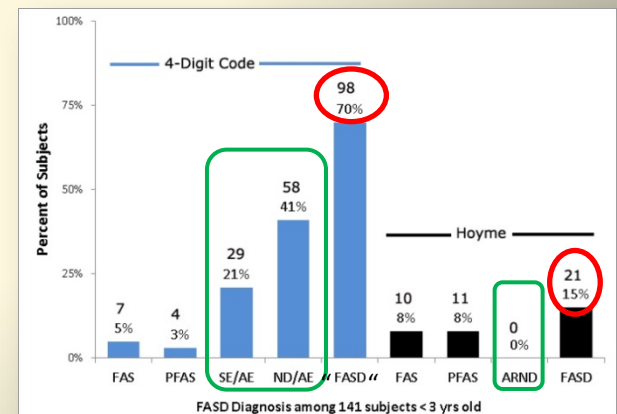
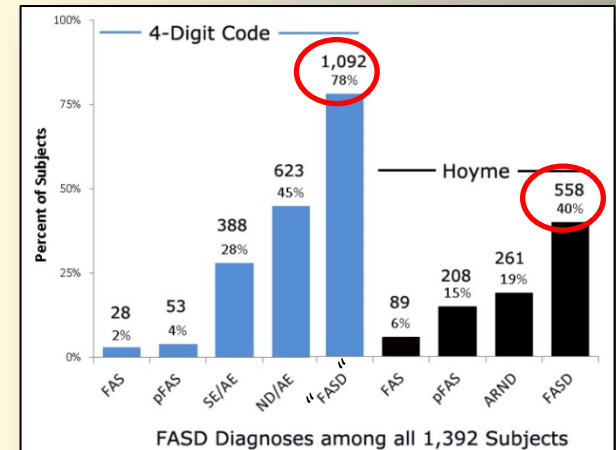
Aase and colleagues (1995) urged *“simple recording of the verifiable conclusions. . . . If prenatal alcohol exposure has taken place, but FAS cannot be substantiated, the exposure still should be indicated, and any nonspecific abnormalities or problems noted.”*

Aase JM, Jones KL, Clarren SK. Do we need the term “FAE”? Pediatrics. 1995; 95: 428-30

This is exactly the approach taken by the 4-Digit Code. This approach ensures no one is missed and no one is misdiagnosed.

Early diagnosis and intervention are paramount for the child and maximize the success of primary prevention efforts with the mother.

Most importantly, the 4-Digit Code captured ALL 128 infants at risk because those with and without adverse outcomes had their high-risk prenatal alcohol exposure documented in their medical record.



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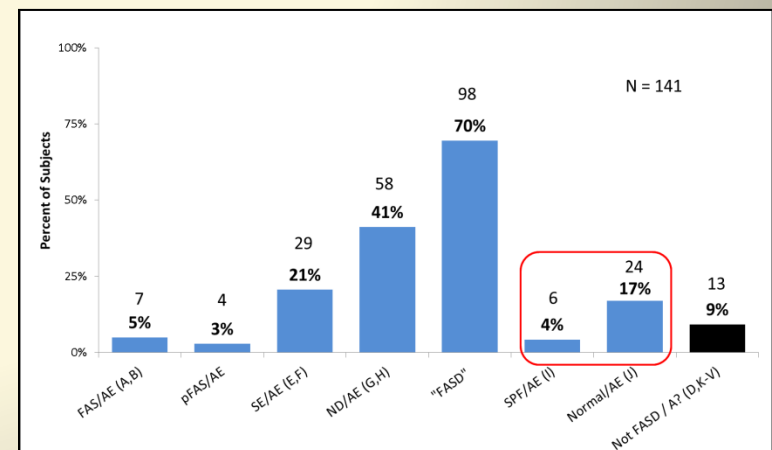
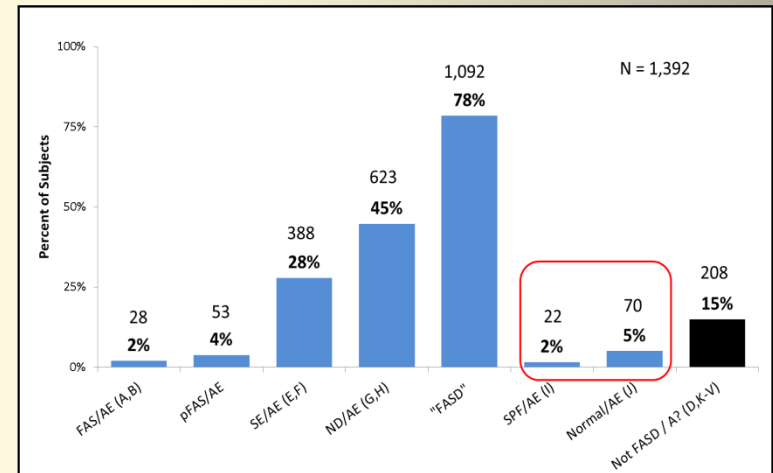
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Most importantly, the 4-Digit Code captured ALL 128 infants at risk because those with and without adverse outcomes had their high-risk prenatal alcohol exposure documented in their medical record.





## FASDPN Recommendation for Children < 6 Years Old with Prenatal Alcohol Exposure

---

Lets say Justin is 18 months old and received a 4-Digit Code of 1114 (normal outcomes, but high exposure). This is the recommendation we place in the child's medical summary report.

Justin is still quite young (18 months) and remains at high risk for additional learning and developmental challenges because of his prenatal alcohol exposure.

It is important to note that the majority of children who have cognitive or other developmental challenges caused by prenatal alcohol exposure do not exhibit these challenges fully until school-age. All those working with and caring for Justin are advised to keep monitoring him closely. If difficulties arise, interventions should be implemented right away.

This team would very much like to see Justin in clinic again to update assessment of CNS functioning and overall diagnosis when he is old enough to allow for a broader range and depth of assessment. We invite Justin to return to our clinic after his 8<sup>th</sup> birthday.

In the meantime, development should be closely monitored. Even with scores now indicating adequate developmental progress, his prenatal alcohol exposure risk status should be a factor in decision-making in educational settings. A "wait and watch" strategy is not recommended.

If his 4-Digit Code was 4414 (growth deficient, FAS face, high alcohol, but normal development), we would include his growth and facial outcomes as additional risk factors (predictors) of learning challenges he will likely face later in childhood.

# Prenatal Alcohol Exposure is Never the Only Risk Factor

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Prenatal and Postnatal Risks are formally ranked on a 4-point scale.

This text is included in every FASDPN diagnostic medical report, including those with full FAS

## **Co-Morbidities**

When assessing the potential impact of prenatal alcohol exposure on an individual, it is important to document all other significant prenatal and postnatal exposures and events, for they too serve as potential risk factors for cognitive/behavioral dysfunction.

Prenatal risk factors may include, but are not limited to, poor prenatal care, genetic conditions that may run in the family, and other potential teratogenic exposures.

Postnatal risk factors may include, but are not limited to, perinatal difficulties, adverse home environments, multiple home placements, neglect, abuse and other events that could explain brain dysfunction like head injuries or a patient's own chronic substance abuse.

While it is not possible with today's medical technology to determine which risk factor(s) may be responsible for each adverse outcome, it remains important to document all exposures and events and take them into consideration when deriving a diagnosis and intervention plan.

Potential risk factors reported to the clinic to date include:

### **Prenatal:**

Reported in utero exposure to cocaine, marijuana, and tobacco

### **Postnatal:**

Severe neglect for first two years of life.

Multiple out-of-home placements.

# Summary

1. Twice as many patients received a “FASD” diagnosis with the 4-Digit Code than with the Hoyme-2016 system (1,092 vs 558).
2. Five times as many patients (< 3 yrs old) received a “FASD” diagnosis with the 4-Digit Code than with the Hoyme system (98 vs 21).
3. The prevalence of the Hoyme FAS face was 10-fold higher (40% vs 4%) than the 4-Digit FAS face.
4. The Hoyme FAS face was not specific to or correlated with PAE. It was equally prevalent among those with moderate and high alcohol exposure and was present in high-functioning individuals with confirmed absence of PAE. The 4-Digit FAS face is highly specific to PAE, was 6-fold higher among patients with high exposure than those with moderate exposure, and does not occur among patients with confirmed absence of PAE.
5. The relaxed Hoyme facial criteria produced 3-times more FAS diagnoses (6% vs 2%) and 4-times more PFAS diagnoses (15% vs 4%) than the 4-Digit Code.
6. It is unclear what outcome defined by the Hoyme criteria has sufficient specificity to PAE to allow a diagnosis of FAS or PFAS to be made when alcohol exposure is unknown.
7. 71% of the Hoyme FAS facial phenotypes were in the 4-Digit Code normal range (Rank 1 and Rank 2 faces).
8. The Hoyme North American Rank 4 lip is equivalent to the 4-Digit Code Rank 2 normal lip.
9. The more stringent Hoyme alcohol criteria prevented 379 patients with confirmed PAE from receiving a FASD diagnosis.
10. Only 38% of patients received the same diagnosis from both systems.

