DIAGNOSING THE FULL SPECTRUM OF FETAL ALCOHOL EXPOSED INDIVIDUALS: INTRODUCING THE 4-DIGIT DIAGNOSTIC CODE

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Abstract-The medical/research records of 1,014 patients diagnosed at the Washington State FAS Diagnostic and Prevention Network of clinics were used to develop a new, comprehensive, reproducible method for diagnosing the full spectrum of outcomes among patients with prenatal alcohol exposure. This new diagnostic method, called the 4-Digit Diagnostic Code, was compared to the standard gestalt method of diagnosis on the first 454 patients who had received a gestalt diagnosis of FAS, atypical FAS (AFAS) or possible fetal alcohol effect (PFAE) prior to the development of the 4-Digit Diagnostic Code. The outcomes of the patients were more accurately and comprehensively documented by the 4-Digit Diagnostic Code because of it's use of quantitative, objective measurement scales and specific case-definitions. The four digits in the Code reflect the magnitude of expression of the four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) central nervous system damage/dysfunction, and (4) gestational alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong 'classic' presence of the FAS feature**.** The 4-Digit Diagnostic Code is being used effectively for diagnosis, screening and surveillance efforts in all Washington State FAS DPN clinics.

INTRODUCTION

The fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of the FAS has changed little since the 1970's when the condition was first described and refined (Jones and Smith, 1973; Rosett, 1980; Clarren and Smith, 1978; Sokol and Clarren, 1989; Stratton *et al*., 1996). The syndrome has been broadly characterized by pre- and/or postnatal growth deficiency, a characteristic set of minor facial anomalies, central nervous system (CNS) dysfunction and prenatal alcohol exposure. The presentation of each individual feature of the syndrome may be variably expressed with age.

For trained clinicians, dysmorphologists, or clinical geneticists, there is likely to be full agreement on a diagnosis of FAS only when the anomalies in growth, face, and brain are all very extreme and the alcohol exposure is conclusive and substantial. But the features are not dichotomous, that is either normal or clearly abnormal. Rather, the features, and indeed the history of alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive.

In the absence of accurate, precise, and unbiased methods for measuring and recording the severity of exposure and outcome in individual patients, diagnoses will continue to vary widely from clinic to clinic (Chavez *et al*., 1988; Aase, 1994; Stratton *et al*., 1996). From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities (Streissguth and Kanton, 1997) and missed opportunities for primary prevention. From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence (Stratton *et al*., 1996). Inaccurate estimates thwart efforts to allocate sufficient social, educational and health care services to this high-risk population and preclude accurate assessment of primary prevention intervention efforts. From a clinical research perspective, diagnostic misclassification reduces the power to identify clinically meaningful contrasts between groups. Non-standardized diagnostic methods prevent valid comparisons between studies.

The primary limitations in the current practice of diagnosing individuals with prenatal alcohol exposure include:

1. While there are diagnostic guidelines that physicians and medical researchers are encouraged to follow, the guidelines are not sufficiently specific to assure diagnostic accuracy or precision. While the diagnostic guidelines published by Sokol and Clarren (1989), which were a minor modification of the definition by the Fetal Alcohol Study Group of the Research Society for Alcoholism (Rosett, 1980) which, in turn, were derived from the work of Clarren and Smith (1978), do provide guidance, they are not sufficiently specific to assure diagnostic accuracy and precision. They reflect a more gestalt approach to diagnosis. The guidelines for CNS dysfunction do not address how many areas of deficit must be present, how severe the deficits must be or what level of documentation must exist to substantiate the presence of the deficit (i.e., parental history, psychometric testing or structural imaging). The guidelines for the facial phenotype are equally nonspecific. How many facial features must be present, how severe must the features be and what scale of measurement should be used to judge their severity? One need only read the clinical literature or review medical records, birth certificates, birth defect registries or ICD-9 codes to see how variably these criteria are interpreted, applied and reported (Cordero *et al*., 1994; CDC, 1995, 1995a; Ernhart *et al*., 1995; Stratton *et al*., 1996). Although the most recent guidelines published by the Institute of Medicine (Stratton *et al*., 1996) have not been out long enough to judge their impact on diagnostic accuracy and precision, the Institute guidelines present with the same limitations as previous guidelines.

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2. There is a lack of objective, quantitative scales to measure and report the magnitude of expression of key diagnostic features. For example, although a thin upper lip and smooth philtrum are key diagnostic features (Jones and Smith, 1973; Clarren and Smith, 1978; Astley and Clarren, 1996, Stratton *et al*., 1996), quantitative measurement scales have never been used to measure thinness or smoothness and guidelines have never been established for how thin or smooth the features must be. Objective quantitative scales would not only improve accuracy and precision, they would also greatly increase the statistical power to detect clinically important exposure-outcome patterns (Polit and Hungler, 1995) by increasing the level of measurement from the current nominal scales (e.g., upper lip thin/not thin) to ordinal scales (e.g., 5-point Likert pictorial scale for lip thinness) or continuous scales (e.g., upper lip circularity: perimeter^2/area). Ordinal and continuous scales better reflect the true continuum of outcome and exposure in FAS. Objective, quantitative scales also establish a common descriptive language for communicating outcomes in medical records and in the medical literature (Polit and Hungler, 1995).

3. The term fetal alcohol effects (FAE) is broadly used and poorly defined. The term 'suspected fetal alcohol effects' was first introduced into the medical literature in 1978 and was defined as 'less complete partial expressions' of FAS in individuals with prenatal alcohol exposure (Clarren and Smith, 1978). Based on this definition, an individual whose mother drank a few glasses of wine intermittently throughout pregnancy and presented with attention deficit hyperactivity disorder would meet the criteria for FAE. So would an individual whose mother drank a fifth of vodka (757ml) daily throughout pregnancy and presented with microcephaly, severe mental retardation, growth deficiency and no facial anomalies. The broad use of this term and the reluctance to abandon it points to the clear need to develop diagnostic terms for individuals with prenatal alcohol exposure who present with physical anomalies and/or cognitive/behavioral disabilities, but do not meet the criteria for FAS.

4. Clinical terms like FAE, alcohol related birth defects (ARBD) and alcohol related neurodevelopmental disorder (ARND) (Stratton et al. 1996) inappropriately imply a causal link between exposure and outcome in a given individual. With the likely exception of the full facial phenotype, no other physical anomalies or cognitive/behavioral disabilities observed in an individual with prenatal alcohol exposure are necessarily specific to (caused only by) their prenatal alcohol exposure (Stratton *et al*., 1996). There have already been formal appeals by noted dysmorphologists in the field to discontinue the use of the term FAE (Aase *et al*., 1995; Sokol and Clarren, 1989). The diagnostic terms ARBD and ARND introduce the same limitations as FAE, namely, implying alcohol exposure caused the birth defect or neurodevelopmental disorder in an *individual* patient.

5. The terms FAS and FAE fail to convey the diversity of disability present in these individuals. No two individuals with FAS present with precisely the same constellation of anomalies and disabilities. Growth, facial phenotype, CNS dysfunction and alcohol exposure all vary along separate continua. The term FAS only conveys that the condition is permanent and was caused by prenatal alcohol exposure. The term does not convey what the individual's disabilities are. A nomenclature that not only conveys the diversity of outcomes among individuals with prenatal exposure, but also separates outcome from exposure would benefit both the patient and their medical/social/educational care network.

Each of these limitations have been largely overcome with the development of a comprehensive manual for the diagnosis of FAS entitled '*Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions*' (Astley and Clarren 1999) introducing a new quantitative approach to diagnosis, the '4-Digit Diagnostic Code'. The diagnostic method was developed through the combined expertise of the University of Washington FAS Diagnostic and Prevention Network (FAS DPN) multidisciplinary, clinical team and the comprehensive records of 1,014 FAS DPN patients (birth to 51 years of age) with reported prenatal alcohol exposure.

The creation of the 4-Digit Diagnostic Code was developed to assure accurate and precise diagnosis of individuals with prenatal alcohol exposure across all seven FAS Clinics in the Washington State FAS DPN (Clarren and Astley 1997). The FAS DPN (expanded from the CDC-sponsored FAS Clinic at the University of Washington) was mandated by the 1995 Washington State Legislature in response to the high, statewide demand for diagnostic services. The guide was developed to meet the needs of a broad range of professionals in an equally broad range of settings. A core team that includes a physician, a psychologist, a language pathologist, an occupational therapist staffs each clinic and a family advocate. Each core team has community-based links to alcohol treatment centers, genetics clinics, schools, and social and legal service agencies. The seven clinics have been established in the following settings: a children's hospital neurodevelopmental clinic, two public health clinics, an alcohol treatment clinic, a private psychological services clinic paired with an academic institution and a comprehensive children's medical/social services center. These six clinics are led by the FAS DPN core center at the Center for Human Development and Disability at the University of Washington.

The need to standardize the criteria for FAS was recognized early on by the Fetal Alcohol Study Group of the Research Society of Alcoholism, resulting in a published guidelines by Rosett (1980) followed by several efforts to hone, clarify and express concern about the guidelines (Sokol and Clarren, 1989; Aase e. al., 1995; Stratton *et al*., 1996). In the absence of specific case-definitions, the FAS DPN has responded to both a mandate by its State legislature and recommendations by the Institute of Medicine (Statton *et al*., 1996) to establish a diagnostic method which could be administered accurately and reproducibly.

Below are a brief description of the 4-Digit Diagnostic Code and a comparison of the gestalt (Sokol and Clarren, 1989) and 4-Digit Diagnostic code outcomes for 454 patients seen in the FAS DPN who received both diagnostic approaches. A more detailed description of the 4-Digit Code can be found in a 111 page manual distributed by the University of Washington in Seattle. The diagnostic guide includes a standardized FAS Diagnostic and Evaluation Form accompanied by instructions, case definitions, normal anthropometric charts, pictorial Likert scales for ranking lip thinness and philtrum smoothness, and a New Patient Information Form which is completed by the patient's family to document the patient's exposure and developmental history. The guide is accompanied by an instructional CD-ROM entitled 'Fetal Alcohol Syndrome Tutor

Medical Training Software' (Astley *et al*., 1999). We have used the 4-Digit Code to diagnose over 1,000 patients and have found the system to be very helpful in clinical and research areas. We describe it here and present preliminary assessments of its accuracy, precision and power so that others can consider and evaluate its use.

METHODS

The 4-Digit Diagnostic Code was developed through the expertise of the multidisciplinary FAS DPN clinical staff and use of the medical research records of 1,014 patients diagnosed in the FAS DPN. The purpose was not to redefine, but rather, more specifically case define the key diagnostic components of FAS as presented across several published FAS diagnostic guidelines (Clarren and Smith, 1978; Rosett, 1980; Sokol and Clarren, 1989; Stratton *et al*., 1996). The first working draft of the method completed in 1997 (Astley and Clarren, 1997), was pilot tested on all patients seen in the FAS DPN from 1997 – 1999 ($n \approx 400$) and was refined to its current form. Prior to the development of the 4-Digit Code, all 598 patients seen in the University of Washington FAS DPN Clinic (1993-97) were diagnosed using the 'gestalt' (Sokol and Clarren, 1989) method. In 1997, the FAS DPN clinics stopped using the gestalt method and started using the 4-Digit Diagnostic Code method. The charts of all patients who had previously been diagnosed with the gestalt method were retrofitted to the 4-Digit Diagnostic Code system for research purposes. The gestalt and 4-Digit Diagnostic Code outcomes are compared among the 454 patients who had received gestalt diagnoses of FAS, atypical FAS (AFAS) or possible fetal alcohol effect (PFAE). The University of Washington Human Subjects Review Board approved use of this data.

Preliminary assessments of precision, accuracy and power are presented to assist the reader in their evaluation of this new diagnostic method. The diagnostic evaluation forms of 20 patients were randomly selected from the 736 patients who received a 4-Digit Diagnostic Code one to four years ago at the University of Washington FAS DPN Clinic by SKC and SJA. The standardized diagnostic forms document the clinical and psychometric data that was available on the patient at the time of their diagnosis. The 4-Digit Codes were deleted from the forms by the research assistant and re-derived by SKC and SJA independently. Inter-rater reliability between SKC and SJA was assessed by comparing their re-derived 4-Digit Codes. Intra-rater reliability was assessed by comparing the re-derived codes to the original 4-Digit Codes. An additional assessment of inter-rater reliability was conducted on all 16 patients who had received 4-Digit Diagnostic Codes from one of the six FAS DPN clinics without consult by the FAS DPN Core team at the University of Washington. The level of agreement between the 4-Digit Diagnostic Codes derived by the Network and University of Washington clinical teams was assessed. The Kappa statistic was computed to test intra-and inter-rater agreement. Accuracy (the degree to which a measurement represents the true value of the attribute that is being measured) was assessed by comparing the 4-Digit Diagnostic outcomes to the gestalt diagnostic outcomes of the 454 patients who were diagnosed by both methods. Each of the diagnostic outcomes were also compared to the published diagnostic guidelines (Sokol and Clarren, 1989) available when the gestalt diagnoses were made. Power, the probability of detecting an effect in a study sample if an effect of a specified size or greater truly exists in the population was computed using SamplePower (SPSS Inc., 1997).

RESULTS

The 4-Digit Diagnostic Code

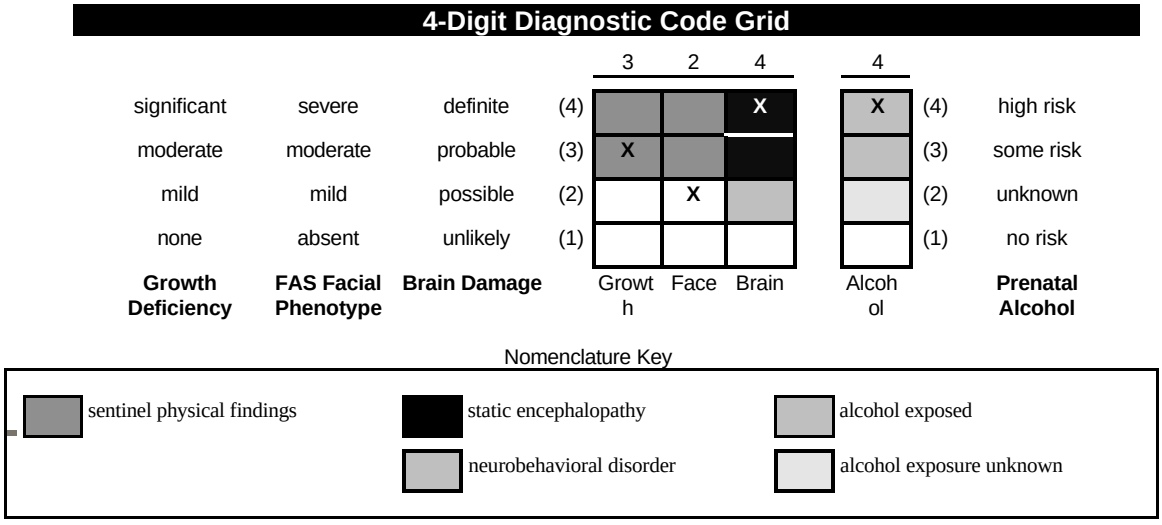
The four digits of the diagnostic code reflect the magnitude of expression of four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain damage/dysfunction, and (4) gestational alcohol exposure (Fig. 1). The 4-Digit Diagnostic Code is generated by first recording key clinical data on the standardized FAS Diagnostic Evaluation Form and following specific case-definitions to generate each digit.

The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong 'classic' presence of the FAS feature. Each Likert rank is specifically case-defined. The 4-Digit Diagnostic Code can be used to diagnose individuals of all ages.

Clinical Nomenclature

There are 256 possible 4-Digit Diagnostic Codes ranging from 1111 to 4444. Each 4-Digit Diagnostic Code falls into one of 22 unique Clinical Diagnostic Categories (labeled A through V) (Table 1). The 22 Diagnostic Categories are named to reflect the Likert ranking of each digit in the 4-Digit Diagnostic Code. The names are constructed sequentially from four terms: 'sentinel physical findings', 'neurobehavioral disorder', 'static encephalopathy' and 'alcohol exposure status' as presented in Figure 1 and Table 1. Note that the names for Diagnostic Categories E-J, K-P and Q-V only differ by alcohol exposure, thus there are essentially only nine unique diagnostic *outcome* categories ranging from 'no cognitive/behavioral or sentinel physical findings detected' to 'FAS'. This is in contrast to the five diagnostic outcome categories (FAS, Partial FAS, ARBD, ARND and FAE) currently in use across the various gestalt guidelines (Clarren and Smith, 1978; Sokol and Clarren, 1999; Stratton *et al*., 1996).

The first two diagnostic categories (A and B) meet the criteria for a clinical diagnosis of FAS and are named as such (Table 1). The term Atypical FAS (category C) is introduced for use with a relatively small group of patients who present with static encephalopathy, most, but not all of the sentinel physical findings of FAS, and were alcohol exposed. The term FAS Phenocopy (category D) applies to the patient who presents with all of the features of FAS, but has a confirmed *absence* of gestational ethanol exposure. We have not yet observed such a patient. The remaining 19 categories (E - V) do not meet the minimum criteria for FAS and are subsequently named to reflect the Likert ranking of each digit in the 4-Digit Diagnostic Code. For example, a code of 4342 is the Diagnostic Category called '*sentinel physical findings / static encephalopathy (alcohol exposure unknown)*'. Many of these patients might have previously been referred to variably as having possible ARBD), or alcohol related neurodevelopmental disorder ((ARND) (Stratton *et al*., 1996).



4-Digit Diagnostic Code Grid and Nomenclature

This grid is used to record the 4-Digit Diagnostic Code following the guidelines presented in the text. A code of 3 or 4 in the Growth or Face column is referred to as a 'sentinel physical finding'. A code of 2 in the Brain column is a 'neurobehavioral disorder'; a code of 3 or 4 is 'static encephalopathy'. A code of 3 or 4 in the alcohol column is 'alcohol exposed'. The code 3244 would receive the name 'sentinel physical findings, static encephalopathy, alcohol exposed'. A subset of 4-Digit Diagnostic Codes that fall within the category 'sentinel physical findings, static encephalopathy, alcohol exposed' are referred to as FAS when the four digits are sufficiently high to meet the criteria for FAS (see Table 1).

This new nomenclature replaces all of these terms. These terms are not used here because the inclusion of 'alcohol-related' or 'alcohol-effect' in the diagnostic name inappropriately implies a confirmed causal link between exposure and outcome in an individual. Diagnostic Categories E - I would have previously been referred to as 'fetal alcohol effects', 'alcohol related birth defects' or 'alcohol related neurobehavioral disorder'. Categories J - V are new categories that describe a large number of patient groups who have never been adequately classified or described in the past. The Likert ranks for the four digits of the code are case defined for consistent application. The case definitions are briefly presented below and are more fully presented in the Diagnostic Guide for FAS (Astley and Clarren, 1999).

Case Defining the Growth Component of the 4-Digit Diagnostic Code

Age- and gender- adjusted height- and weight-centiles are ranked by circling A, B or C in the ABC-Score table (Table 2A). The Height-Weight ABC Score recorded in Table 2A is converted to a 4-Digit Diagnostic Code Rank using Table 2B. The 4-Digit Code Rank is transferred to the 4-Digit Diagnostic Code Grid (Figure 1). Detailed instructions are provided in the Diagnostic Guide for FAS (Astley and Clarren, 1999) for ranking growth when growth measures are available at more than one time point.

Case Defining the Facial Phenotype Component of the 4-Digit Diagnostic Code

Three key diagnostic features characterize the FAS facial phenotype: small palpebral fissures, a smooth philtrum and thin upper lip (Clarren and Smith, 1978; Astley and Clarren, 1996). Palpebral fissure length z-scores are computed with adjustment for age and when possible, race (Hall *et al*., 1989). The thinness of the vermilion border of the upper lip and the smoothness of the philtrum are coded independently on 5-point pictorial Likert scales using Figure 2. Lips must be gently closed with no smile. The magnitude of palpebral fissure length deficiency, philtrum smoothness and upper lip thinness are ranked by circling A, B, or C in each column in the ABC-Score table (Table 3A). The ABC-Score is converted to the 4-Digit Diagnostic Code Rank for face using Table 3B.

Facial phenotype can be assessed directly or from digitized facial photographs (Astley and Clarren, 1996; Astley *et al*., 1999). It has been our experience that palpebral fissure length and upper lip thinness can be more accurately measured from digitized photographs using image analysis software (SigmaScan, 1996). A standardized, digital, facial photograph is taken of the patient with an internal measure of scale (2 cm sticker) placed on the forehead. The image is displayed on a computer monitor and PFL is measured by clicking the mouse on the endocanthion and exocanthion landmarks and comparing the distance between the landmarks relative to the size of the internal measure of scale. Upper lip thinness is measured by tracing the outline of the vermilion border with the mouse and computing circularity ($perimeter^2/area$). The thinner the lip the smaller the circularity. Circularity is used to guide the 5-point ranking of upper lip thinness as demonstrated in Figure 2. All patients seen in the FAS DPN clinic have their digital facial photographs analyzed during their diagnostic evaluation. The process takes approximately ten minutes and is described in detail in the FAS Tutor™ CD-ROM (Astley *et al*., 1999).

Table 1. Diagnostic Categories.

Category	Diagnostic Category Name and 4-Digit Codes within each Category
A	Fetal alcohol syndrome (alcohol exposed)
	3433 4433 3434 4434 3443 4443 3444 4444
B	Fetal alcohol syndrome (alcohol exposure unknown)
	3432 4432 3442 4442
C	Atypical fetal alcohol syndrome (alcohol exposed)
	1443 1434 2434 3334 4334 2443 1444 2444 3344 4344 4343
D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
	3431 4341 4441 3441 4431
E	Sentinel physical findings / static encephalopathy (alcohol exposed)
	1333 1433 2344 3143 3243 4133 4233 4333 1334 2333 2433
	3144 3244 4134 4234 1343 2334 3133 3233 3333 4143
	4243 1344 2343 3134 3234 3343 4144 4244
F	Static encephalopathy (alcohol exposed)
	1133 1144 1243 2134 2233 2244 1134 1233 1244 2143 2234
	1143 1234 2133 2144 2243
G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
	1323 2323 3123 3323 4123 4323 1324 2324 3124 3324 4124
	4324 1423 2423 3223 3423 4223 4423 1424 2424 3224 3424
	4224 4424
H	Neurobehavioral disorder (alcohol exposed)
	1123 2123 1124 2124 1223 2223 1224 2224
I	Sentinel physical findings (alcohol exposed)
	1313 2313 3113 3313 4113 4313 1314 2314 3114 3314 4114
	4314 1413 2413 3213 3413 4213 4413 1414 2414 3214 3414
	4214 4414
J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
	1113 2113 1114 2114 1213 2213 1214 2214
K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
	1332 2332 3132 3332 4232 1342 2342 3142 3342 4242 1432
	2432 3232 4132 4332 1442 2442 3242 4142 4342
L	Static encephalopathy (alcohol exposure unknown)
	1132 1232 2132 2232 1142 1242 2142 2242
M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
	1322 2322 3122 3322 4122 4322 1422 2422 3222 3422 4222
	4422
N	Neurobehavioral disorder (alcohol exposure unknown)
	1122 1222 2122 2222
O	Sentinel physical findings (alcohol exposure unknown)
	1312 2312 3112 3312 4112 4312 1412 2412 3212 3412 4212
	4412
P	No cogn./behavioral or sentinel physical findings detected (alcohol exposure unknown)
	1112 2112 1212 2212
Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
	1331 2341 3231 4141 1341 2431 3241 4231 1431 2441 3331
	4241 1441 3131 3341 4331 2331 3141 4131
R	Static encephalopathy (no alcohol exposure)
	1131 2131 1141 2141 1231 2231 1241 2241
S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
	1321 3121 4121 1421 3221 4221 2321 3321 4321 2421 3421
	4421
T	Neurobehavioral disorder (no alcohol exposure)
	1121 2121 2221 1221
U	Sentinel physical findings (no alcohol exposure)
	1311 3111 4111 1411 3211 4211 2311 3311 4311 2411 3411
	4411
V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
	1111 2111 1211 2211

The 4-Digit Diagnostic Code reflects the magnitude of expression of four key diagnostic components of FAS in the order growth, facial phenotype, CNS damage/dysfunction and alcohol exposure. Each component is measured on a 4-point Likert scale, thus producing 256 possible combinations of 4-Digit Diagnostic Codes. These codes are collapsed into 22 Diagnostic Categories as presented above

Case-Defining the Brain Damage/Dysfunction Component of the 4-Digit Diagnostic Code

Brain damage/dysfunction is the most significant disability for individuals damaged by prenatal alcohol exposure. Ethanol alters the developing brain in a variety of ways from structural to gross anomalies of gray and/or white matter and/or to subtle alterations in neurochemical levels (West, 1986). Accurately quantifying and qualifying brain damage/dysfunction

Table 2. ABC score and case definitions for growth deficiency

A)

ABC Rank	Centile Range	Circle the ABC-Score for: Height	Weight
C	≤ 3rd	C	**C**
B	>3rd and ≤ 10th	**B**	B
A	>10th	A	A

B)

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

A) The first step in deriving the Likert rank for growth is to derive the ABC-Score for growth. If a patient's height centile was 8% and weight centile was 2%, an ABC-Score of **BC** would be assigned. B) The final step in deriving the Likert rank for growth is to convert the ABC-Score for Growth into a 4-Digit Diagnostic Code rank. A score of **BC** translates into a 4-Digit Diagnostic Code rank of **3.** This rank would serve as the first digit in the 4-Digit Diagnostic Code (Figure 1).

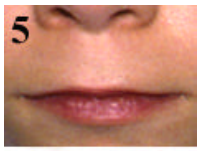
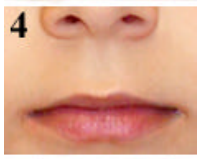
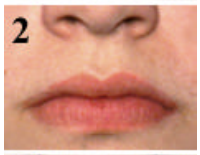
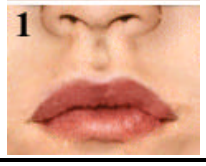
Lip-Philtrum Guide Likert Ranks	ABC-Score	Upper Lip Circularity
	C	178
	C	80
	B	65
	A	50
	A	35

Figure 2. Lip-Philtrum Guide

Pictorial examples of the 5-point Likert scale, upper lip circularity scale and the ABC-scale used to rank upper lip thinness and philtrum smoothness. Circularity (perimeter^2/area) is a continuous measure of upper lip thinness that can be used to facilitate the ranking of the upper lip. Circularity ranges from 12.8 for a circle to infinity as the circle is squashed into a line (or becomes thinner). Circularity is measured by outlining the vermilion border of the upper lip using image analysis software such as SigmaScan Pro (1996) (Astley and Clarren, 1996; Astley *et al*., 1999). It is important that the individual's lips are gently closed with no smile.

is important for both diagnosis and treatment planning. Brain damage can be defined in a large number of ways that are each associated with a broad spectrum of disability. The 4-point Brain Damage Likert Scale (Table 4) allows the clinician to separate patients with clear evidence of brain damage (Likert Rank 4) from patients with no evidence of brain damage (Likert Rank 1). The 4-Digit Rank for brain does not rank the severity of structural, neurologic or functional problems faced by the patient. Rather it ranks the strength of evidence supporting the presence of an organic cause for cerebral/cerebellar dysfunction.

A rank of 4 is reserved for patients who present with 'medical' evidence of structural or neurologic brain damage. Examples include any one of the following: microcephaly, structural alterations on brain imaging studies, hard neurologic findings like a primary seizure disorder or cerebral palsy or an intelligence quotient that is clearly below the normal distribution (FSIQ<60).

A rank of 3 is reserved for patients who present with 'psychometric' evidence of brain damage. Clearly, there are patients who have organic brain damage at a level not detectable by the current technology that allows us to derive a Rank 4. In the absence of advanced technology, we feel it is important to identify patients who present with cognitive/behavioral dysfunction as measured on standardized psychometric tests. At this time we case define Rank 3 to mean that a patient has had an age appropriate battery of tests in the areas of intelligence, adaptation, academic achievement, language and neuropsychology. The pattern of abnormality on the test battery, when taken as a whole, must be clinically interpreted by the assessing team to strongly support abnormal brain function. Patients who do not meet the

Table 3. ABC score and case definitions for facial phenotype

A)

5-Point Likert Scale for Philtrum & Lip	Z-score for largest Palpebral Fissure Length	Palpebral Fissure	Circle the ABC-Scores for: Philtrum	Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

B)

4-Digit Diagnostic Code Rank*	Level of Expression of FAS Facial Phenotype	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	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

A) The first step in deriving the Likert rank for facial phenotype is to derive the ABC-Score for facial phenotype. If a patient's palpebral fissure lengths were > 2 SD below the norm and their philtrum and upper lip received Likert scores of 2 and 3 respectively (Figure 2), the facial phenotype would receive an ABC-Score of **CAB**. B) The final step in deriving the Likert rank for facial phenotype is to convert the ABC-Score for Facial Phenotype to a 4-Digit Diagnostic Code Rank. A **CAB** score translates into a 4-Digit Diagnostic Code rank of **2**. This rank would serve as the second digit in the 4-Digit Code (Figure 1).

Table 4. Case Definitions for Brain Damage.

4-Digit Diagnostic Code Rank	Brain Damage Scale	Confirmatory Findings
4	**Definite** *referred to as static encephalopathy*	● **Microcephaly, OFC ≤ -2 S. D.** *and / or* ● Abnormalities on brain images diagnostic of prenatal alteration *and / or* ● Evidence of persistent neurologic findings likely to be of prenatal origin *and / or* ● I.Q. score ≤ 60
3	**Probable** *referred to as static encephalopathy*	● Substantial deficiencies or discrepancies across multiple areas of brain performance such as cognition, achievement, adaptation, neurologic 'soft' signs, and language. Three or more areas should be found aberrant.
2	**Possible** *referred to as neurobehavioral disorder*	● Historical information / personal observations strongly suggest that the possibility of brain damage, but data to this point does not permit a Rank 3 or 4 classification.
1	**Absent**	● No problems likely to reflect brain damage are presented.

A patient presenting with a head circumference below the second centile would receive a 4-Digit Diagnostic Code rank of **4**. This rank would serve as the third digit in the 4-Digit Code (Figure 1).

criteria for a Rank 4, yet have psychometric test outcomes that document abnormal brain function (greater than 2 standard deviations below the mean) across three or more areas listed above receive a Rank 3. Although there are no scientific data to support that a criterion of three or more failures is more reflective of brain damage than a criterion of one or two failures, our experience with over 1,000 patients has demonstrated that the criteria we have selected have good face validity (e.g., the team is more likely to clinically interpret the battery as a whole as strongly supporting abnormal brain function when there are three or more failures). We anticipate that further clinical research coupled with rapidly advancing technology will likely provide more objective scientific data from which to judge the validity of these criteria. It is important to note that it is possible for a patient to meet the criteria for both a Rank 3 and Rank 4 since these are not mutually exclusive categories. If this occurs, the higher rank (Rank 4) is inserted into the 4-Digit Code because, for diagnostic purposes, it reflects the strongest clinical evidence of brain damage. The psychometric outcomes, whether normal or abnormal, facilitate the development of the treatment plan for all patients.

Likert Rank 2 is given to two subgroups of patients. All patients in Rank 2 should have histories of behavioral and/or cognitive problems that strongly suggest underlying brain dysfunction. One group of patients has not yet had the types of testing that would move them into Ranks 3 or 4, if positive. The reason for

Table 5. Case Definitions for Prenatal Alcohol Exposure.

4-Digit Diagnostic Code Rank	Prenatal Alcohol Exposure Category	Description
4	**High Risk**	● Alcohol use during pregnancy CONFIRMED *and* ● Exposure pattern is consistent with the medical literature placing the fetus at 'high risk' (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy).
3	Some Risk	● Alcohol use during pregnancy CONFIRMED *and* ● Drinking occurred in gestation in frequencies and volumes less than in Rank 4 or exact amounts unknown.
2	Unknown Risk	● Gestational exposure is simply not known or information is of questionable reliability.
1	No Risk	● Alcohol use during pregnancy is CONFIRMED to be completely ABSENT.

The case-definitions used to derive the 4-Digit Diagnostic Code rank for alcohol exposure. If a birth mother reported drinking a fifth of liquor several times a week throughout pregnancy, alcohol exposure would receive a 4-Digit Diagnostic Code rank of **4**. This rank would serve as the fourth digit in the 4-Digit Code (Figure 1).

this lack of testing is usually because the patients are too young to be reliably or conclusively tested (i.e., less than six years of age). The other group of patients is those who have had testing that did not reveal compelling evidence for Rank 3 or 4 classification, and yet, in the clinician's judgment, a strong possibility of brain damage can not be wholly dismissed. Alternative testing and/or follow-up testing should usually be considered. If adequately sensitive and appropriate testing has been carried out without clear evidence of brain dysfunction, it is unlikely a Rank 2 classification would be given.

Patients are classified as Rank 1 when no structural, neurological or cognitive/behavioral problems measured by clinical/psychometric assessment or caregiver interview are discerned.

Case Defining the Gestational Alcohol Exposure Component of the 4-Digit Diagnostic Code

Alcohol exposure is ranked according to the quantity, timing, frequency and certainty of exposure during pregnancy (Table 5). The case-definitions address the facts that exposure information is often unavailable and/or inaccurate and a clear consensus is not available concerning the amount of alcohol that can actually be toxic to each individual fetus (Stratton *et al.*, 1996). The case-definitions differentiate four clinically meaningful exposure groups (4. confirmed high exposure, 3. confirmed exposure, but level is low or unknown, 2. unknown exposure, and 1. confirmed absence of exposure).

High exposure is defined generally to be a blood alcohol concentration of greater than 100 mg/dL (a level that typically can be reached by a 55-kg woman consuming six to eight beers) weekly, early in pregnancy. In the absence of a clear consensus on the amount of alcohol that can actually be toxic to the fetus, this general definition should only serve as a guide, not a threshold. One example of a 'rank 4' exposure is birth mother reported drinking to intoxication weekly throughout pregnancy. Two examples of 'rank 3' exposures include: a) birth mother was observed to be drinking during pregnancy, but the amount is unknown, b) birth mother reported drinking one glass of wine once a week, but stopped drinking as soon as she learned she was pregnant. A few examples of when alcohol exposure is ultimately unknown and thus coded as a 'rank 2' include: a) the child is adopted and the records are closed, b) birth father reports birth mother drank while pregnant, but birth mother

Table 6. Cross-tabulation of Gestalt and 4-Digit Diagnostic Outcomes.

4-Digit Diagnostic Categories		Gestalt Diagnostic Categories FAS n = 69	AFAS n = 41	PFAE n = 344	Total n = 454
A	FAS (AE)	8	2	0	10
B	FAS (AE Unknown)	1	0	0	1
C	Atypical FAS (AE)	12	2	2	16
E	Sentinel physical findings/static encephalopathy (AE)	10	10	17	37
F	Static encephalopathy (AE)	8	8	69	73
G	Sentinel physical findings/neurobehavioral disorder (AE)	15	11	15	41
H	Neurobehavioral disorder (AE)	11	7	179	197
I	Sentinel physical findings (AE)	0	1	6	7
J	No cognitive/behavioral or sentinel physical findings (AE)	0	1	18	19
K	Sentinel physical findings /static encephalopathy (AE unknown)	1	0	2	3
L	Static encephalopathy (AE unknown)	0	1	5	6
M	Sentinel physical findings /neurobehavioral disorder (AE unknown)	2	0	5	7
N	Neurobehavioral disorder (AE unknown)	1	0	25	26
P	No cognitive/behavioral or sentinel physical findings (AE unknown)	0	0	1	1

Cross-tabulation of the Gestalt and 4-Digit diagnostic outcomes for 454 patients diagnosed by both methods in the Washington State FAS DPN clinics.
AE, alcohol exposure during gestation confirmed; AE unknown, alcohol exposure during gestation unknown; FAS, fetal alcohol syndrome; AFAS, atypical fetal alcohol syndrome; PFAE, possible fetal alcohol effects.

Table 7. Comparison of Gestalt and 4-Digit Diagnostic Outcomes.

4-Digit Ranks for Key	Diagnostic Outcomes						
	FAS		AFAS		PFAE		All Other
Diagnostic Features	Gestalt	4-Digit[1]	Gestalt	4-Digit[2]	Gestalt	4-Digit[3]	4-Digit[4]
	n = 69	n = 11	n = 41	n = 16	n = 344	n = 365	n = 62
Growth Deficiency[5] (n)							
1. None	37	0	28	8	295	295	57
2. Mild	10	0	1	2	24	31	2
3. Moderate	8	3	5	2	11	17	2
4. Significant	14	8	7	4	14	22	62
FAS Facial Phenotype[6] (n)							
1. Absent	0	0	1	0	71	60	12
2. Mild	27	0	21	0	247	253	43
3. Moderate	15	0	11	6	20	36	4
4. Severe	27	11	8	10	6	17	3
Brain Damage[7] (n)							
1. Unlikely	0	0	2	0	25	7	20
2. Possible	29	0	18	0	224	238	33
3. Probable	13	2	9	7	44	53	4
4. Definite	27	9	12	9	51	67	5
Prenatal Alcohol Exposure[8] (n)							
1. No0	0	0	0	0	0	0	
2. Unknown	5	1	1	0	38	0	43
3. Some risk	26	5	17	2	160	188	8
4. High risk	38	5	23	14	146	177	11

Magnitude of expression of key FAS diagnostic features compared between the gestalt (Sokol and Clarren, 1989) and 4-Digit (Astley and Clarren 1999) diagnostic outcomes of 454 patients diagnosed by both methods in the Washington State FAS DPN clinics

FAS: fetal alcohol syndrome; AFAS: atypical fetal alcohol syndrome; PFAE: possible fetal alcohol effects; (1) 4-Digit Diagnostic categories A and B; (2) 4-Digit Diagnostic Category C; (3) 4-Digit Diagnostic Categories E-I; (4) All other 4-Digit Diagnostic Categories D, J-V; (5) Defined in Tables 2A, 2B; (6) Defined in Tables 3A and 3B; (7) Defined in Table 4; (8) Defined in Table 5.

reports she did not drink, c) birth mother started drinking at the age of 13 yrs, was never known to have a prolonged period of sobriety, thus the family assumed she drank during pregnancy.

Other Prenatal and Postnatal Exposures/Experiences

A comprehensive diagnostic process must take into consideration the risks associated with prenatal and postnatal exposures and experiences other than prenatal alcohol exposure. Most of the features associated with FAS are not specific to prenatal alcohol exposure. A variety of prenatal (poor prenatal care, prenatal complications, familial genetics and exposure to other potentially teratogenic agents, etc.) and/or postnatal (physical/sexual abuse, disrupted placement histories, head injuries, chronic substance abuse by the patient, etc.) events could explain all or some of the symptoms presented by the patient. The 4-Digit Diagnostic method requires the clinician to record pertinent prenatal and postnatal exposures and events on the standardized FAS Diagnostic Evaluation Form, rank their severity using case-defined 4-point Likert scales and report them in the standardized medical summary template provided in the Diagnostic Guide for FAS (Astley and Clarren, 1999).

Comparison of the Gestalt and 4-Digit Diagnostic Methods

The gestalt (Sokol and Clarren, 1989) and 4-Digit Diagnostic Code outcomes for 454 patients who initially received gestalt diagnostic evaluations at the University of Washington FAS DPN clinic are compared in Tables 6 and 7. Table 6 presents a cross-tabulation of the gestalt and 4-Digit diagnostic outcomes. Table 7 illustrates the variable magnitude of expression of the key diagnostic features of FAS (growth, face, brain and alcohol) for the three gestalt diagnostic outcomes (FAS, PFAS and PFAE) and for the equivalent 4-Digit diagnostic categories (Categories A and B are equivalent to the gestalt FAS; Category C is equivalent to the gestalt PFAS; and Categories E - I would be equivalent to the gestalt category of PFAE). The study population was 57.7% male, ranged in age from birth to 51 years old with a mean of 10.1 ± 7.0 years and had the following racial distribution: Caucasian (57.5%), African American (9.0%), Native American/Alaskan (14.1%), other (19.4%). Race, age and gender were equally distributed across the 4-Digit and gestalt diagnostic categories.

Of the 69 patients who received a gestalt diagnosis of FAS, only nine met the 4-Digit criteria for FAS (Categories A and B) (Table 6). In the absence of specific case-definitions, quantitative measurement scales and only three diagnostic choices (FAS, PFAS, or PFAE), the gestalt method for diagnosing FAS produced a very heterogeneous population, more heterogeneous than would be supported by the gestalt guidelines (Sokol and Clarren, 1989). For example, 37 of the 69 patients had no evidence of growth deficiency, 27 had only one of the three facial features, 29 had no psychometric or structural evidence of brain damage and five had unknown exposure to
alcohol (Table 7). Of the 344 patients who received a gestalt diagnosis of PFAE, the outcomes of these patients are also remarkably variable. These patients fall into 13 different 4-Digit

Diagnostic Categories (Table 6) and present with every combination of diagnostic features (Table 7). The term PFAE clearly fails to convey the diversity of outcomes within this group. Some patients received a diagnosis of PFAE based solely on alcohol exposure (n = 18) while other patients received a diagnosis of PFAE based on outcomes that fell just short of the full syndrome (n = 2). Research studies that treat this diverse group of patients as one 'homogeneous' group are at great risk of failing to identify clinically meaningful outcomes.

Precision: Inter- and Intra-rater Reliability

The 4-Digit Diagnostic Codes of 20 randomly selected patient files were rederived by SKC and SJA independently while masked to the original 4-Digit code that had been derived one to four years ago by the University of Washington Clinical team. The codes re-derived by SKC and SJA matched the original 4-Digit Codes across all four digits for all 20 subjects (inter- and intra-rater reliability was 100%, (Kappa = 1.0, p = 0.000). The 4-Digit Codes for the 20 randomly selected patients spanned the entire spectrum of normal to AFAS (1124 to 1444). Inter-rater reliability between the six FAS DPN regional clinics and the University of Washington FAS DPN Core clinic resulted in an exact match across all four digits on 15 of 16 (94%) patients (Kappa = 0.93, p = 0.000) and an exact match on Diagnostic Category on all 16 (100%) of the patients (Kappa = 1.0, p = 0.000). The one 4-Digit code that did not match was coded by the regional FAS DPN clinic as 1223 and the University FAS DPN clinic as 1123. The mismatch in the facial score was due to the network physician not pulling the epicanthal fold back before measuring the palpebral fissure length resulting in an underestimate of the length.

POWER

To demonstrate the statistical power of the 4-Digit Code over the gestalt method of diagnosis, the hypothesis that the full-scale intelligence quotient (FSIQ) decreases with increasing magnitude of expression of the FAS facial phenotype was tested among 216 patients who had been diagnosed by both the gestalt and 4-Digit diagnostic systems. Of the 216 patients, 31 received a gestalt diagnosis of FAS. The difference in the mean FSIQ between the patients with and without the gestalt FAS facial phenotype (82.3 and 85.0 respectively) was not statistically significant (t = -1.56, p = 0.13). In contrast, when the same 216 patients were classified by their 4-point Likert rank reflecting the magnitude of expression of the FAS facial phenotype, a statistically significant, inverse, linear association was revealed. The mean FSIQ among the patients with Likert facial ranks of 4, 3, 2, and 1 were 78.5, 83.8, 84.8 and 87.7 respectively (f = 4.1, p = 0.04). The power of the t-test to detect a contrast in facial phenotype between the two gestalt groups was only 23%, whereas the power of the ANOVA to detect the linear trend was 85%. By convention, the minimum power of a clinical research study is set at 80% (Hulley and Cummings, 1988). Thus, a clinically important linear association between face and brain that was detected by the 4-Digit Code failed to be detected by the gestalt method of diagnosis.

DISCUSSION

The 4-Digit Diagnostic Code method has been used in all seven FAS DPN clinics in Washington State for over three years, demonstrating that it can be taught to a broad array of social and health care professionals in an equally broad array of clinical settings. Some of our FAS DPN colleagues were hesitant to make diagnoses in patients with prenatal alcohol exposure prior to using this system precisely because the old nomenclature was too simplistic and did not offer consistent or helpful diagnostic outcomes. After three years of field testing this method, both prospectively and retrospectively on over 1,000 patients, it continues to uniformly reflect clinical judgement (a measure of face validity) and provide tremendous power to identify clinically meaningful patterns of outcome.

The 4-Digit Diagnostic Code presents with many strengths. It offers an intuitively logical digital approach to reporting outcomes and exposure that reflects the true diversity and continuum of disability associated with prenatal alcohol exposure. Preliminary assessments of precision, accuracy and power appear to be greatly increased over the 'gestalt' method of diagnosis. This can be attributed, in large part, to the use of objective, ordinal and continuous measurement scales, specific, comprehensive case-definitions (Polit and Hungler, 1995) and the use of a multidisciplinary clinical team approach. This study as well as others (Abel, 1990; Hannigan *et al*., 1992) have demonstrated that the current gestalt approach to diagnosis can often lead to diagnoses of FAS made solely on exposure, made in the absence of CNS dysfunction or made when only a single facial anomaly is present. The 4-Digit Code prevents this from occurring. Outcomes and exposures are reported independently so as not to imply that an *individual's* disabilities and/or anomalies are confirmed to be caused by their prenatal alcohol exposure. The 4-Digit Code serves as a standardized, descriptive language that will allow clinicians and researchers to clearly and objectively communicate the exposures and outcomes of their patients. Although the FAS DPN has gone one step further and clinically categorized and labeled the codes, use of the 4-Digit code is independent of this step, much like measuring and reporting birth weight in grams and centiles is independent of defining the cut-off for 'low birth weight'. Failure to reach consensus on the categorization and labeling of the codes need not prevent the use of the 4-Digit Codes. The 4-Digit diagnostic method is fully comprehensive. It can be used to diagnose individuals of all ages and races who present across the full spectrum of exposure and outcomes. This is achieved by directing the clinician to age-, gender- and race - adjusted anthropometric and psychometric measures when available and appropriate. The availability and reliability of outcome and exposure information varies across patients. The derivation of the 4-Digit Code addresses this reality by encoding both the presence and absence of outcome and exposure information. This method can be taught to a wide array of health care and social service providers, thus greatly expanding the availability of diagnostic services. Multidisciplinary clinical teams from six States in the U.S. and three Canadian Provinces have been trained to use the 4-Digit Code to date.

Although the 4-Digit diagnostic method was developed for prospective use in a fully staffed, multidisciplinary clinic, it can also be used in active and passive screening and surveillance efforts. Surveillance generally uses methods distinguished by their practicality, uniformity, and frequently their rapidity, rather

than by complete accuracy (Last, 1988). A key feature of the 4-Digit Diagnostic Code is that it not only documents exposure and outcome, but also documents how much data was available (or not available) to support the diagnostic outcome. The standardized FAS Diagnostic Evaluation Form served as an efficient tool for conducting the retrospective chart review on the 736 patients whose gestalt diagnoses were upgraded to 4-Digit Diagnostic Codes. The method provides an efficient and reproducible method for conducting retrospective chart reviews, a process that is the very essence of passive surveillance. The computerized facial analysis component of the 4-Digit Code also serves as an efficient and highly effective photographic method for screening for FAS (Astley *et al*., 1999). This method is currently being used to screen all children entering foster care in one county in WA State.

Meaningful progress in the areas of screening, diagnosis, intervention, surveillance and primary prevention all hinge on development of an accurate, precise, valid and efficient method for identification of individuals damaged by prenatal alcohol exposure. The 4-Digit Diagnostic Code was developed to achieve that goal in Washington State.

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