Fetal Alcohol Spectrum Disorder Primary Prevention through FASD Diagnosis: Identification of High-Risk Birth Mothers through the Diagnosis of their Children. Follow-up Study.

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Abstract

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Epidemiology

Introduction:

Prenatal alcohol exposure is the leading known cause of preventable lifelong cognitive or behavioral disability. The spectrum of adverse outcomes observed among individuals with prenatal alcohol exposure is termed Fetal Alcohol Spectrum Disorders (FASDs) and can range from very mild to the most severe form, Fetal Alcohol Syndrome (FAS). From 1993 to 1998 the FASD Diagnostic and Prevention Network (FAS DPN) conducted a study to assess the feasibility of using the University of Washington interdisciplinary FAS DPN clinic as a center for identifying and targeting primary prevention intervention to high-risk women (women who had given birth to a child with FAS, were still fertile, and still drinking regularly). The pilot project demonstrated that 46% of the patient's birth mothers were still fertile and 49% were still

drinking at the time of the patient's FASD diagnosis. Of those birth mothers who were still fertile, 21% reported that they were still drinking, although all fertile birth mothers (46%) are at risk of having a child with prenatal alcohol exposure. The primary aim of this study was to assess the risk status of all birth mothers whose children received an FASD diagnosis between 1993-2012 to identify changes in annual trends among birth mothers whose children are evaluated at the FAS DPN with the goal of learning how best to target prevention measures to these high-risk women.

Methods:

Two datasets were used to conduct this retrospective study: 1) the FAS DPN clinical research dataset that contains information on all patients evaluated for FASD between 1993-2012, including information on their birth mothers; and 2) the "First Bridges" dataset documenting additional information on the subset of birth mothers whose children were evaluated between 2001 and 2012 to evaluate changes in their risk status with respect to continued alcohol use and fertility. Descriptive statistics were used to assess annual trends in maternal risk and accessibility.

Results:

Annual trends from 1993 through 2012 demonstrate the clinic is evaluating children at a significantly younger age (on average 5 years of age rather than 10 years of age), but an increasing proportion of them are born later in the birth order (parity >2). As a result, the mean age of birth mothers at the time of the index child's birth (25 years old) has remained relatively constant while the mean age of the birth mother at the time of her child's FASD diagnosis has

decreased from 35 years old to 30 years old. Birth mothers who accompany their child to clinic or have recent contact with their child at the time of the diagnosis are more likely to have achieved higher levels of education, are less likely to be cognitively impaired or have learning problems and are reported to be consuming lower levels of alcohol. The birth mother's risk status for bearing additional children with prenatal alcohol exposure has remained high across the 20 years. In 2012, 86% of birth mothers were of reproductive age (18-44 years old) at the time of their child's FASD diagnosis. Seventy-five percent were reportedly still fertile and 66% were reportedly still drinking at the time of their child's FASD diagnosis. Thirty-nine % were reportedly both still fertile and drinking at the time of their child's FASD diagnosis, although 75% are still at risk for having a child with prenatal alcohol exposure, an increase from the pilot study.

Conclusion:

This work confirms and extends the findings of the 1993-1998 pilot FASD prevention study by demonstrating the clinic's continued ability to locate and attract high risk women by assessing their children for FASDs. More recently, children with prenatal alcohol exposure are being identified and diagnosed at younger ages, allowing them to be enrolled in early intervention programs earlier, maximizing their behavioral, physical, and intellectual potential.

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CHAPTER 1: FETAL ALCOHOL SPECTRUM DISORDER PRIMARY PREVENTION THROUGH FASD DIAGNOSIS: IDENTIFICATION OF HIGH-RISK BIRTH MOTHERS THROUGH THE DIAGNOSIS OF THEIR CHILDREN. FOLLOW-UP STUDY.

1.1 INTRODUCTION:

The Centers for Disease Control and Prevention (CDC) estimates the risk of prenatal alcohol exposure at any point during pregnancy at around 7.3%, derived from self- reports of alcohol consumption and contraception use among women aged 15-44 years[1]. These estimates place the number of potentially exposed pregnancies at approximately 3.3 million during a one month period[1]. Further, a 2010 economic estimate of the costs associated with excessive drinking placed the cost of drinking while pregnant at around 5.5 billion dollars annually in the United States[2]. Therefore prevention of alcohol-exposed pregnancies is of critical public health and economic importance.

Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal alcohol consumption during pregnancy. FAS is defined by growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) structural and/or functional abnormalities[3]. Not all individuals exposed to or damaged by prenatal alcohol exposure have FAS. The term fetal alcohol spectrum disorders (FASD) was coined to depict the spectrum of outcomes observed among individuals damaged by prenatal alcohol exposure. FASDs range from mild cognitive impairment to full FAS. The amount, duration, and timing of alcohol consumption during pregnancy that results in FASD is variable among women, therefore abstinence during pregnancy is key to prevention of FASDs.

Public health campaigns aimed at reducing the incidence of FASD have taken many forms since the discovery of the damaging effects of prenatal alcohol consumption, varying from mild awareness campaigns to active intervention. Wide-scale awareness campaigns directed toward the general public including women of childbearing age who drink alcohol, their partners, and families often take the form of educational campaigns including billboards, warning labels on alcoholic beverage containers, pamphlets, and media advertisements[4]. A second type of prevention approach occurs through screening methods in which medical providers routinely ask women of childbearing age to describe their alcohol consumption and birth control methods in order to identify women at greater risk of having a child with a prenatal alcohol exposure[5]. These screening methods may be passive surveillance and simply collect information, or they may be more active, including referrals to specialized treatment programs aimed at prevention through treatment of problematic alcohol use regardless of whether the woman is pregnant. The third prevention approach is directed at high-risk women, those who have confirmed alcohol consumption while pregnant, or who have already given birth to a child affected by a FASD[6]. This method aims to prevent further affected pregnancies by referring pregnant women or women at risk of having an alcohol exposed pregnancy to prevention programs like the Parent Child Assessment Program (PCAP)[4,6–8]

The Fetal Alcohol Spectrum Diagnostic and Prevention Network (FAS DPN)[9] at the University of Washington started in 1993 with two primary goals: to provide individuals with prenatal alcohol exposure an FASD diagnostic evaluation including suggestions and referrals to programs that optimize their educational, physical, and social development, and to identify and intervene with women who are at high risk for having a subsequent affected pregnancies after diagnosis of

a first affected child. In order for this system to work most effectively, children must be evaluated early and women at high risk should be identified as young as possible before the progression of alcoholism worsens and as early in their reproductive years as possible when family planning interventions can be more effective.

To achieve the first goal of the FAS DPN clinic, individuals with prenatal alcohol exposure who are referred to the FAS DPN receive a FASD diagnostic evaluation by an interdisciplinary team of clinicians who specialize in diagnosing and treating patients with prenatal alcohol exposure using the FASD 4-Digit Diagnostic Code system developed by the FAS DPN clinicians at the University of Washington[10]. The 4-digit code reflects the severity of the hallmark features of FAS: growth deficiency, FAS facial phenotype, CNS structural/functional abnormalities, and prenatal alcohol exposure by verbal report of the patient, parent, or caregiver. The FASD Diagnostic team conducts a series of tests and interviews with each patient and their caregiver, assigns a 4-Digit code and creates a unique report for each patient. This report can be used in a patient's medical and court records, and guides caretakers toward appropriate educational materials, therapies, and relevant interventions specific to each patient.

To achieve the second goal of the clinic, a prevention study was designed and performed by the FAS DPN during the first five years of the clinic, from 1993 to 1998[11]. The purpose of the study was to establish an initial comprehensive profile the birth mothers of children with FASD who were evaluated at the FAS DPN in order to understand commonalities among their backgrounds and risk behaviors. Once profiles of these women were established, clinicians could use the information to develop targeted interventions tailored to the specific needs of these high-risk

birth mothers. The researchers enrolled 80 birth mothers who had given birth to a child diagnosed with FASD[12]. These interviews documented the women's reproductive and family planning history, the social and economic conditions in which they lived, educational achievement, healthcare utilization status, alcohol use and treatment history, other substance abuse, mental health, and the extent and type of social support that birth mothers experienced. The results of the study revealed that these women were often victims of abuse, had lower income, had lower educational achievement, a history of substance abuse, and suffered from a variety of learning and mental health disorders. This study also investigated commonalities among women who had achieved sobriety in order to understand the methods and support networks that worked best for them to achieve sobriety. The women who successfully achieved sobriety were more likely to have strong support networks, have higher educational achievement, higher income, more often reported strong religious affiliation, and were more often receiving mental health treatment[11,12]. These data are included in and are supported by other studies investigating common risk factors for having a child with a FASD among women in other countries and ethnic groups[13].

This initial prevention study demonstrated that the clinic was able to successfully reach birth mothers either when the birth mothers attended clinic with their children or through information given by their children's caregivers at the time of their diagnostic evaluation[11,12]. The present study seeks to build upon the initial 1993 to 1998 prevention study by continuing to track the risk status of patient's birth mothers annually through 2012 to assess the on-going feasibility of using the FAS DPN as a critical access point to high-risk birth mothers.

1.2 SPECIFIC AIMS:

Primary prevention of FASD requires early access to the high-risk group of women who have a confirmed history of drinking during pregnancy or have already given birth to a child damaged by prenatal alcohol exposure. Identification of birth mothers earlier in their reproductive years is particularly important, as there is greater potential to provide interventions aimed at decreasing alcohol exposure during subsequent pregnancies and positively influence the health and wellbeing of the mother. To characterize the group of women whose children are evaluated by the FAS DPN we described general trends among them and determined whether they have retained contact with their children since most (80%) of children evaluated in the FAS DPN clinic are in foster or adoptive care. By analyzing trends among birth mothers across the first 20 years of the clinics existence, we can understand how best to tailor interventions aimed at lowering the incidence of FASDs.

The following questions were addressed:

1. Is the mean age of the patient, the parity of the patient, the mean age of their birth mother at the time of the patient's birth and at the time of their FASD diagnostic evaluation increasing, decreasing, or staying the same annually between 1993 and 2012?
2. Is the proportion of birth mothers attending their child's FASD diagnostic evaluation increasing, decreasing, or staying the same annually between 1993 and 2012?
3. What factors (e.g., education, learning disabilities, mental health disorders, level of alcohol use) are associated with the birth mother attending their child's FASD diagnostic evaluation?

4. Is the proportion of birth mothers that have recent contact with their child at the time of the child's FASD diagnostic evaluation increasing, decreasing, or staying the same between 1993 and 2012?
5. What factors (e.g., education, learning disabilities, mental health disorders, level of alcohol use) are associated with a patient having or not having contact with their birth mother 6 months prior to their FASD diagnostic evaluation?
6. Is the proportion of birth mothers who are of reproductive age (between the ages of 18-44 years) , fertile, and drinking at the time of their child's FASD diagnostic evaluation increasing, decreasing, or staying the same across clinic years 2001 through 2012?
7. Is the proportion of birth mothers that are still fertile, still drinking, and have current contact with their child increasing, decreasing, or staying the same across clinic years 2001 to 2012?

1.3 METHODS:

1.3.1 *Establishment of the FAS DPN clinic*

The FAS DPN clinic was established in 1993 with the objective of identifying and diagnosing children with prenatal alcohol exposure to influence their emotional, physical, and educational growth, and identifying and characterizing commonalities among their birth mothers with the goal of introducing prevention mechanisms aimed at reducing the number of children born with prenatal alcohol exposure. The FAS DPN clinic was the first to establish an interdisciplinary model to diagnose children with prenatal alcohol exposure by developing a case definition for FAS[14], and serves as a resource for establishing a common diagnostic procedure and evaluation rubric to identify and categorize the severity of damage from prenatal alcohol exposure[6,15] in

response to the Institute of Medicine's and the Washington State Senate's mandate for diagnostic reproducibility among all clinics who render an FASD diagnosis and all Washington State FAS DPN clinics[12,16]. The clinic assesses the patients emotional, behavioral, educational, and physical development, and supports both patients and caregivers by acting as a diagnostic center and a resource supplying recommendations and referrals to services targeted to optimize life outcomes of children damaged by prenatal alcohol exposure. Establishment of the clinic has been described in detail in previous publications[17,18].

1.3.2 *Interdisciplinary FASD diagnostic model.*

All patients that are referred to the FAS DPN clinic for an evaluation are seen by a clinical team including a pediatrician, a psychologist, a speech-language pathologist, an occupational therapist, a social worker and a family advocate. Patients are assessed for evidence of growth deficiency, the unique facial features of FAS, and structural and/or functional central nervous system abnormalities that may include microcephaly, seizure disorders, and impairments in language, sensory and motor function, cognition, executive function, memory, and attention.[19]. A detailed description of the steps clinicians undertake to evaluate each patient and selection of the appropriate cognitive, behavioral, and physical assessment(s) is published in Astley[20].

1.3.3 *Source of data*

This retrospective study was conducted using data from an existing dataset, the Washington State FAS DPN clinical/research database. The database was established with the FAS DPN in 1993 and data collection is ongoing[20]. Briefly, demographic, social, and medical information is collected for each patient that is assessed at one of seven Washington State FAS DPN clinics.

The dataset reflects over 2000 fields of information that is collected from every patient and entered into an ACCESS database. Assessments derived prior to 2004 were upgraded to the most current 2004 version of the FASD 4-Digit Code[10].

1.3.4 *The FASD 4-Digit code*

The 4-Digit Code was developed by the UW FAS DPN in 1997[17]. Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: 1) height/weight deficiency, 2) FAS facial phenotype in accordance with the FAS case definition[14], 3) central nervous system structural/functional abnormalities, and 4) prenatal alcohol exposure. The magnitude of expression of each feature is ranked on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined[10]. There are a total of 102 4-Digit Codes that reflect the full spectrum of FASDs. These codes cluster under four clinically meaningful FASD diagnostic subcategories from most to least severe: Fetal Alcohol Syndrome (FAS); Partial FAS (PFAS): Static Encephalopathy/Alcohol-Exposed (SE/AE); and Neurobehavioral Disorder/Alcohol-Exposed (ND/AE)[20].

1.3.5 *Patient referral criteria*

The only requirement for an evaluation with the FAS DPN clinic is a confirmed prenatal alcohol exposure. The UW FAS DPN clinic sees patients ranging in age from newborn to adult, while other network clinics located within the state focus on pediatric patients[21]. Referrals primarily come from community professionals (physicians, social workers, psychologists) who suspect prenatal alcohol exposure.

1.3.6 *Data collection*

Data are collected from every patient that is evaluated by the FASD diagnostic interdisciplinary team and reflects all evaluations performed by the FAS DPN clinical staff between 1993 and the present at one of seven FAS DPN clinics located in Washington State. Briefly, information is collected on two standardized forms, 1) the New Patient Information Form[10] and 2) the FASD Diagnostic Form[10]. (These forms can be found at **www.fasdpn.org**). The New Patient Information Form is completed by all families or caregivers requesting a patient evaluation by the FAS DPN. This form collects information regarding the patients medical history including growth, development, lifetime adverse event history including prenatal alcohol exposure, and psychological, medical, social, intellectual, and educational history. The FASD Diagnostic Form is completed by clinicians during a patient's FASD evaluation, and captures all information required to derive and support the FASD 4-Digit Diagnostic Code (growth, facial features, CNS structural, neurological, functional measures, prenatal alcohol exposure, and conditions including all other physical anomalies and/or syndromes). All data that is utilized for analysis in this study has been previously entered into the FAS DPN clinical/research database with patient consent and the University of Washington Human Subjects Review Board approval[22].

1.3.7 *Study population*

This study was conducted on all patients in the FAS DPN dataset that had a FASD diagnosis conducted from 1993 through 2012. There were no exclusion criteria.

1.3.8 *Data extraction from the FAS DPN clinical/research database*

The following data fields were extracted from the Washington State FAS DPN clinical/research database: the patient's birth date, date of FASD diagnosis, race, and 4-digit code diagnosis; the birth mother's birth date, age at their child's FASD diagnosis, educational achievement, educational and developmental characteristics, intellectual problems, psychiatric health, level of contact with their child, and drinking habits before and during pregnancy. The data was imported to SPSS for statistical analysis..

1.3.9 *Creation of the First Bridges dataset*

A second database was created to capture information necessary to determine ongoing changes in the risk status of a subset of birth mothers, the "First Bridges" dataset. This dataset was derived from information collected on a third form, the FAS DPN Clinic Contact Form (Appendix I). This form collects information on the birth mother's fertility, age, and drinking status at the time of the patient's FASD assessment to derive a risk status for subsequent pregnancies. The form also collects information regarding the ongoing contact between the patient and their birth mother in order to determine the number of women who may be accessible to clinicians for primary prevention intervention. The FAS DPN Clinic Contact Form is completed by the family advocate or social worker. The First Bridges dataset contains information collected only at the University of Washington's FAS DPN clinic between 2001 and 2012. FAS DPN Clinic Contact Forms were available on 526 birth mothers. All data that is utilized for creation and analysis of the First Bridges dataset is collected and entered with patient consent and the University of Washington Human Subjects Review Board approval[22].

1.3.10 *Data analysis*

Descriptive statistics (means, standard deviations (SD), valid percents) were used to summarize the demographic and clinical profiles of the study population. T-tests and one-way ANOVAs were used to compare contrasts between groups measured on continuous scales. Chi square and Fisher exact tests were used to compare proportions between groups measured on nominal scales.

1.4 RESULTS:

1.4.1 *Study population*

The demographic and clinical profiles of 2,230 patients who received an FASD diagnostic evaluation from 1993 through 2012 are presented in Table 1. Evaluated cases were predominantly Caucasian, on average 9.1 years of age at the time of their diagnosis, and had a parity of 1 or 2 among their mother's total number of live births. Birth mothers were on average 25.7 years of age at the time of the index cases birth, and 35.0 years of age at the time of their child's FASD diagnosis. FASD diagnoses spanned the full spectrum of FASDs (Table 1).

Table 1. Study population: Sociodemographic and clinical characteristics	
Patient or Birth Mother Characteristic	Outcome
Patients diagnosed between 1993-2012	
N	2,230
Patient's age in years at diagnosis	
N: mean (SD) range	2,225: 9.1 (6.2) 0.2-50.4
Patient's race: N (valid %)	
Caucasian	1,060 (49.6)
Black	151 (7.1)
Native American or Alaska Native	177 (8.3)
Other	748 (34.0)
Patient's FASD Diagnosis, N (valid %)	
FAS	84 (3.8)
PFAS	126 (9.4)
SE/AE	537 (24.1)
ND/AE	976 (43.8)
Sentinel Physical Findings/AE	43 (1.9)
No abnormal findings/AE	133 (6.0)
All others	331 (14.8)
Patient's parity, N (valid%)	
1 or 2	968 (55.9)
3 or more	765 (44.1)
Age of patient's birth mother	
At patient's birth (N: mean (SD) range)	1,700: 25.7 (6.4) 14.0-45.0
At patient's diagnosis (N: mean (SD) range)	1,564: 35.0 (8.6) 16.1-82.5

1.4.2 *Study Questions*

The outcomes to each question posed in the Specific Aims section are presented below.

1. Is the mean age of the patient, the parity of the patient, the mean age of their birth mother at the time of the patient's birth, and at the time of their FASD diagnostic evaluation, increasing, decreasing, or staying the same annually between 1993 and 2012?

Age of the index case at the time of their FASD assessment

Figure 1a (x) documents the mean age of 2,225 patients at the time of their FASD diagnostic evaluation has been decreasing annually between 1993-2012 (oneway ANOVA: Linear term F = 54.4 (p = .000). The mean age in years of all 2,225 patients at the time of their FASD diagnostic evaluation is 9.1 years (6.2 SD). The age of the patient at the time of their FASD diagnostic evaluation has decreased by 5 years between 1993 (average = 10 years) and 2012 (average = 5 years).

Parity of the index case at the time of the FASD assessment

Although the majority of patients are parity 1 or 2, the proportion of patients with parity 1 or 2 has decreased over the years from roughly 60% to 50% (chi-square linear-by-linear 8.0, p = 0.005) (Fig 1B).

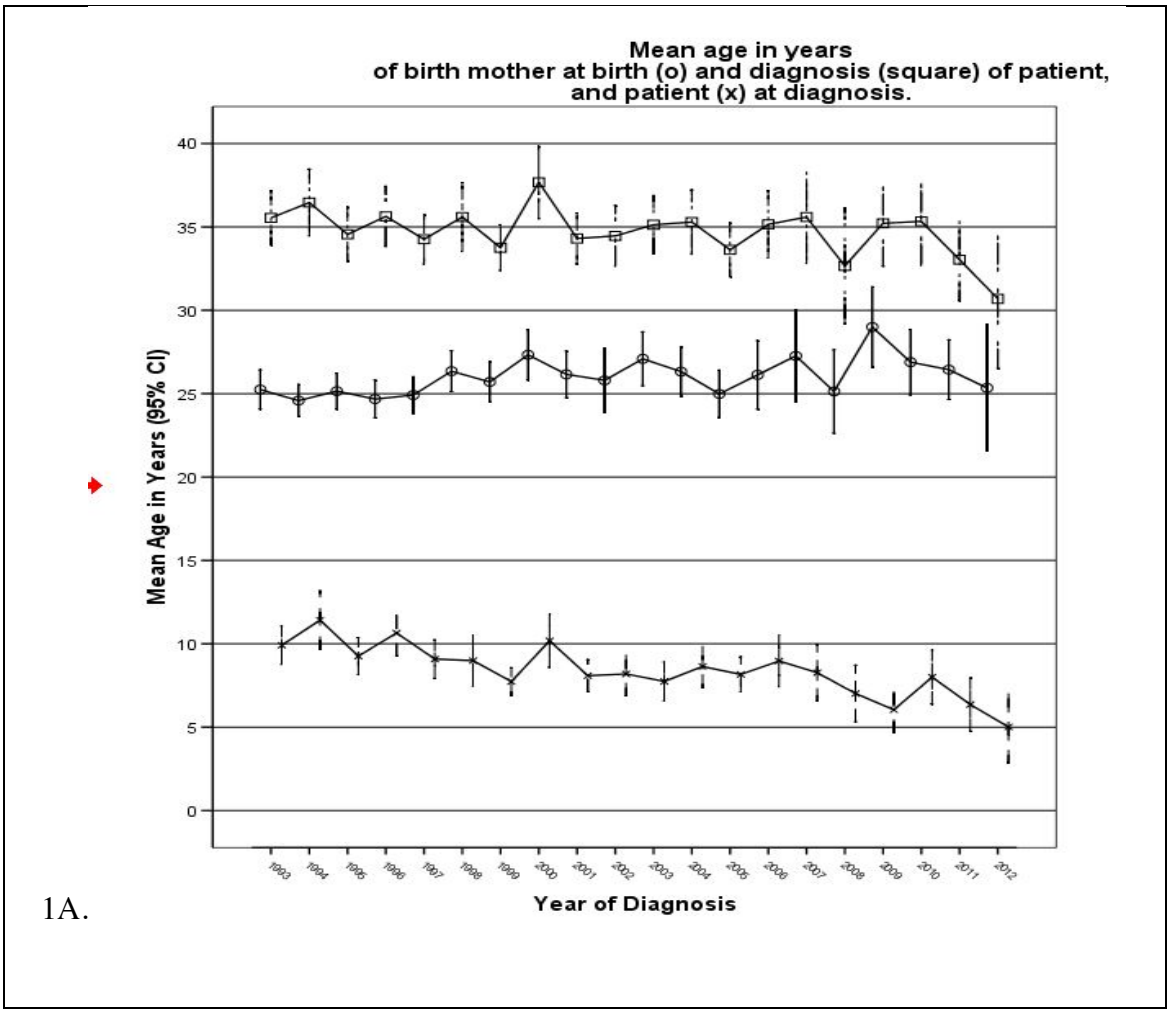
Age of birth mother at birth of index child

The birth mother's birthdate was available for 1,564 subjects. Figure 1a (o) documents the mean age of birth mothers at the birth of the index child is increasing slightly but significantly over the 20 year span from 1993 through 2012 (oneway ANOVA: Linear term F 9.2 (p =.002)).

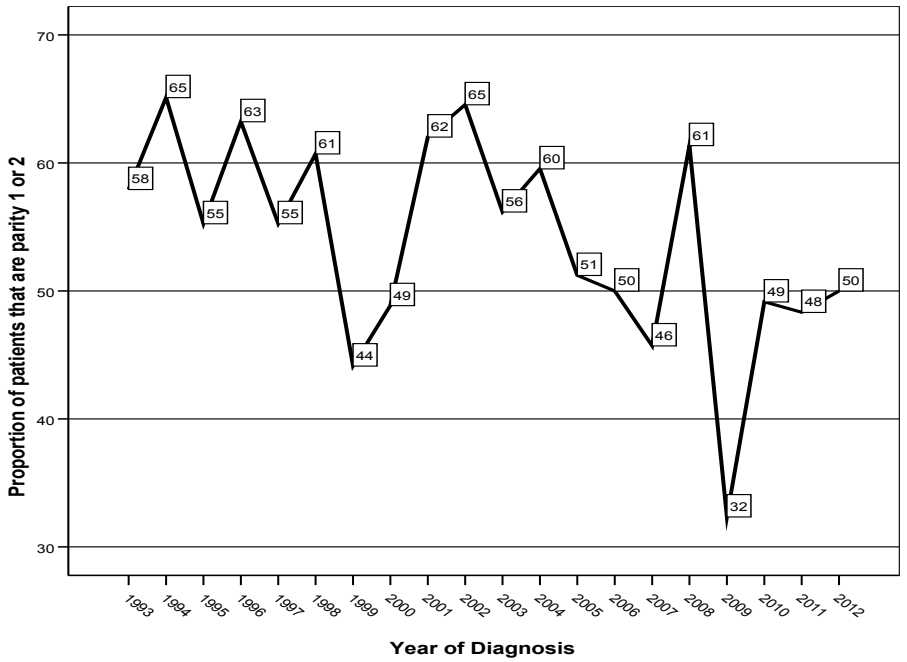
Age of birth mother at the time of their child's FASD diagnosis

The mean age of 1,564 birth mothers at the time of their child's FASD diagnostic evaluation has been decreasing primarily since 2010, (oneway ANOVA: Linear term F 5.8 (p = .016). Figure 1a (squares). The mean age of all 1,564 birth mothers at the time of their child's diagnosis was 35.0 (SD = 8.5). However the mean age of the birth mothers at the time of their child's diagnosis

decreased significantly between 1993 (average = 35 years) and 2012 (average = 30 years) for a 5 year reduction in age at the time of the child's diagnosis.



1A.



1B.

Figure 1: Annual trends in maternal age, patient age and patient parity from 1993 to 2012. 1A) Annual mean age (95% CI) in years of (o) the birth mother on the date of her child's FASD diagnosis, (square) at the date of her child's birth, and (x) the mean age of the child at the time of diagnosis (n = 1,564). Figure 1B) The proportion of patients evaluated each year who were first or second live born (parity 1 or 2) (chi-square linear-by-linear 8.0, p = 0.005)

2. Is the proportion of birth mothers attending their child's FASD diagnostic evaluation increasing, decreasing, or staying the same annually between 1993 and 2012?

Overall, 17.4% (366/2106) of patients were accompanied to the clinic by their birth mothers between 1993 and 2012. Over the years, the prevalence of birth mothers who accompany their child to clinic has decreased from 23% to 15% (Chi square Linear-by-Linear Association 19.7 p = 0.03) (Fig 2).

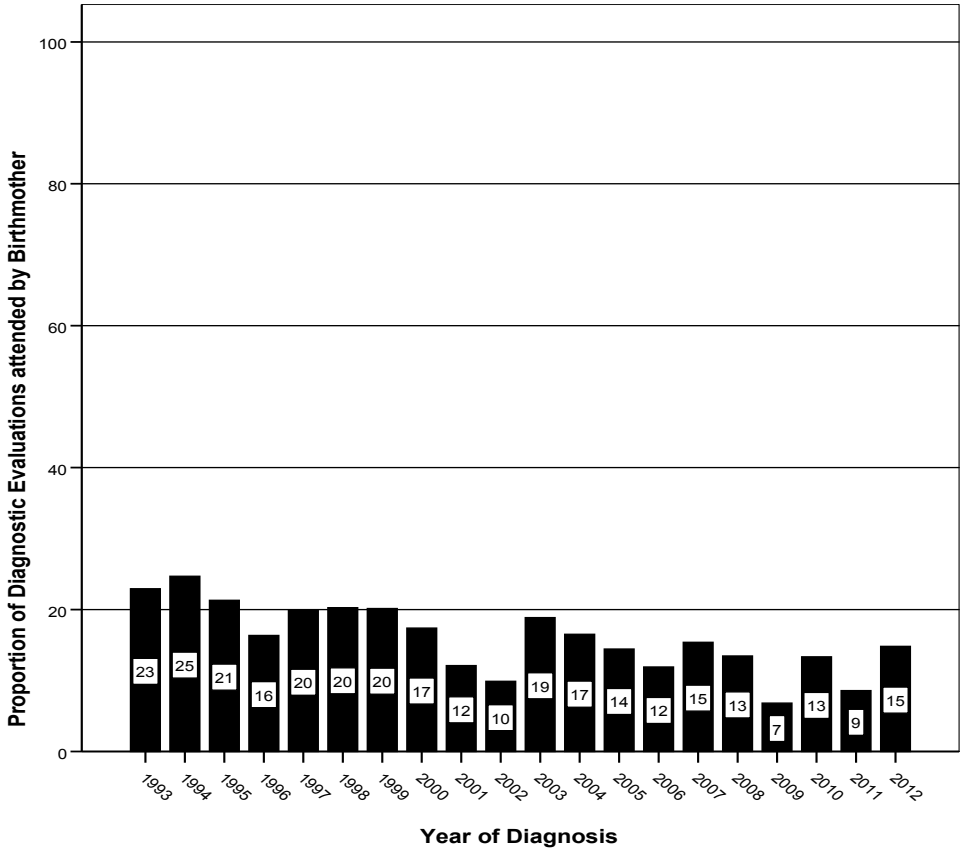


Figure 2: Proportion of patients who were accompanied to their FASD diagnostic evaluation by their birth mother annually from 1993-2012.

3. What factors (e.g., education, learning disabilities, mental health disorders, level of alcohol use) are associated with the birth mother attending their child's FASD diagnostic evaluation?

Birth mothers who attended clinic had higher levels of educational attainment and were less likely to have a learning disability, mental health disorder, or intellectual disability, and were less likely to drink heavily before and during pregnancy (Table 2).

Table 2: Sociodemographic contrasts: Birth mothers who did or did not attend clinic			
Maternal characteristic	Birth mother attended clinic		Chi square (p-value)
	No	Yes	
Education level: N (valid %)			20.4 (.000)
< 12th grade	677 (84)	132 (16)	
High school graduate	344 (76)	107 (24)	
Some college	67 (45)	83 (55)	
College degree	14 (41)	20 (59)	
Learning problems: N (valid %)			20.4 (.000)
Yes	326 (82)	72 (18)	
No	199 (67)	98 (33)	
Learning disability: N (valid %)			34.8 (.000)
Yes	677 (80)	167 (20)	
Suspected	73 (81)	17 (19)	
No	279 (65)	147 (35)	
Developmental Disorder: N (valid %)			9.1 (.011)
Yes	216 (86.4)	34 (13.6)	
Suspected	9 (100)	0 (0)	
No	1195 (79.3)	312 (20.7)	
Intellectual Disabilities: N (valid %)			13.2 (.001)
Yes	104 (94)	7 (6)	
Suspected	12 (80)	3 (20)	
No	1299 (79)	337 (21)	
Mental Illness: N (valid %)			9.7 (.008)
Yes	382 (83)	76 (17)	
Suspected	22 (100)	0 (0)	
No	1016 (79)	271 (21)	
Depression: N (valid %)			22.9 (.000)
Yes	705 (76)	219 (24)	
No	726 (85)	128 (15)	
Suicidal tendencies: N (valid %)			1.9 (.394)
Yes	279 (78)	77 (22)	
Suspected	3 (100)	0 (0)	
No	1146 (81)	271 (19)	
No. of days/week of drinking: mean (SD)			
Before pregnancy	4.8 (2.3)	4.5 (2.2)	T=1.9 (.059)
During pregnancy	4.6 (2.4)	4.1 (2.3)	T = 3.1 (.002)

4. Is the proportion of birth mothers that have recent contact with their child at the time of the child's FASD diagnostic evaluation increasing, decreasing, or staying the same between 1993 and 2012?

Approximately 50%-60% of children and their caregivers have had contact with their birth mothers within 6 months of their evaluation, an outcome that remained relatively unchanged between 1993 and 2012 (Figure 3).

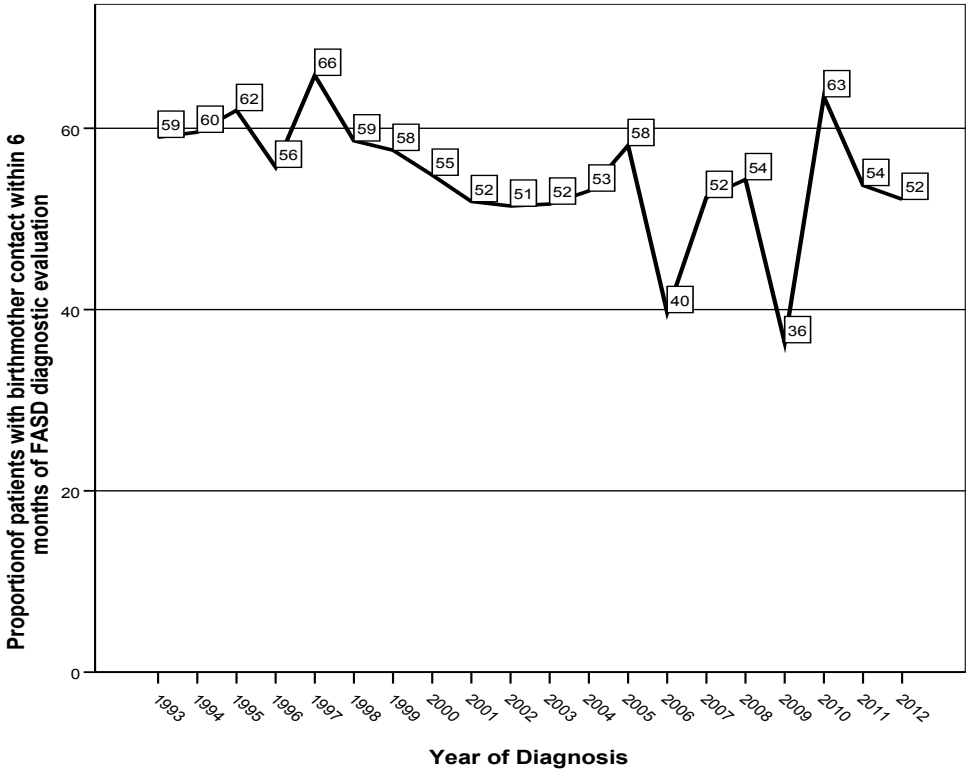


Figure 3: The proportion of children and their caregivers who were in contact with the child's birth mother within 6 months prior to their FASD diagnostic evaluation. These proportions fluctuate over the years, but remain relatively the same.

5. What factors (e.g., education, learning disabilities, mental health disorders, level of alcohol use) are associated with a patient having versus not having contact with their birth mother 6 months prior to their FASD diagnostic evaluation?

Much like the results from Question 3, birth mothers with current or recent contact with their children are more likely to have achieved higher educational status and less likely to present with learning disabilities, mental health disorders and have lower alcohol use during pregnancy.

Table 3: Sociodemographic contrasts: birth mothers who do or do not have recent contact with their children.			
	Current or recent contact (within 6 months) with birth mother		Test Statistic (p-value)
	No	Yes	
Education level: N (valid %)			Chi^2 =39.3 (.000)
< 12th grade	423 (60)	287 (40)	
High school graduate	256 (67)	127 (33)	
Some college	113 (84)	22 (16)	
College degree	28 (90)	3 (10)	
Learning problems: N (%)			Chi^2 = 25.8 (.000)
Yes	149 (42)	210 (58)	
No	60 (22)	210 (78)	
Learning disability: N (%)			Chi^2 = 32.3 (.000)
Yes	283 (39)	44 (61)	
Suspected	38 (49)	39 (51)	
No	90 (24)	285 (76)	
Intellectual Disabilities: N (%)			Chi^2 = 9.9 (.007)
Yes	51 (53)	46 (47)	
Suspected	9 (64)	5 (36)	
No	554 (39)	853 (61)	
Mental Illness: N (%)			Chi^2 = 3.4 (.185)
Yes	185 (54)	231 (56)	
Suspected	9 (45)	11 (55)	
No	428 (39)	659 (61)	
Depression: N (%)			Chi^2 = 27.6 (.000)
Yes	274 (34)	553 (66)	
No	340 (47)	381 (53)	
Suicidal tendencies: N (%)			
Yes	121 (38)	194 (62)	Chi^2 = 3.6 (.17)
Suspected	1 (100)	0 (0)	
No	495 (41)	718 (59)	
No. of days/week of drinking: mean (SD)			
Before pregnancy	5.39 (2.1)	4.47 (2.2)	T = 5.1 (.000)
During pregnancy	4.95 (2.4)	4.24 (2.3)	T = 4.0 (.000)

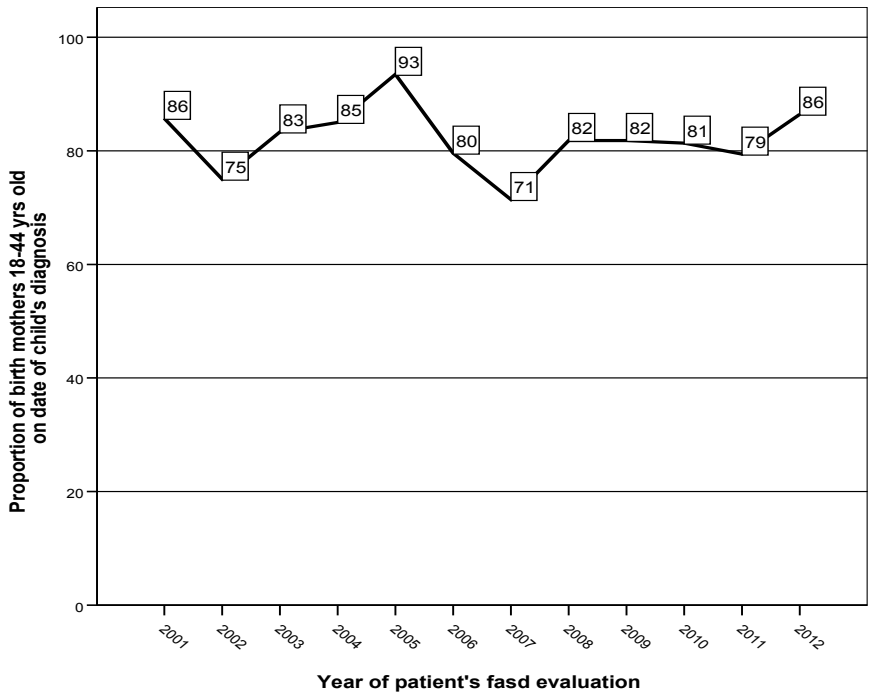
6. Is the proportion of birth mothers who are of reproductive age (between the ages of 18-44 years) , fertile, and drinking at the time of their child's FASD diagnostic evaluation increasing, decreasing, or staying the same across clinic years 2001 through 2012?

Changes in birth mother fertility between 2001 and 2012

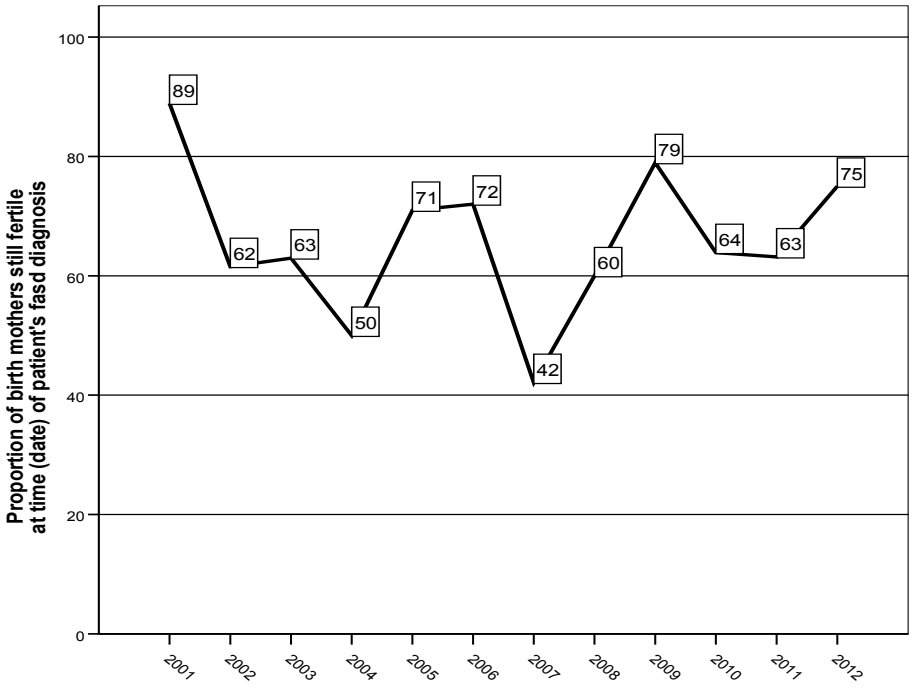
Of the 526 birth mothers with a First Bridges data form completed, the majority s (n = 433; 82%) were between the ages of 18 and 44 (Figure 4A), and were still reportedly fertile (199/305; 65%) at the time of their child's FASD evaluation. The proportion of birth mothers who were still fertile at the time of their child's FASD diagnostic evaluation fluctuated between 2001 and 2012 but did not increase or decrease annually (Figure 4B).

Changes in drinking status of birth mothers between 2001 and 2012

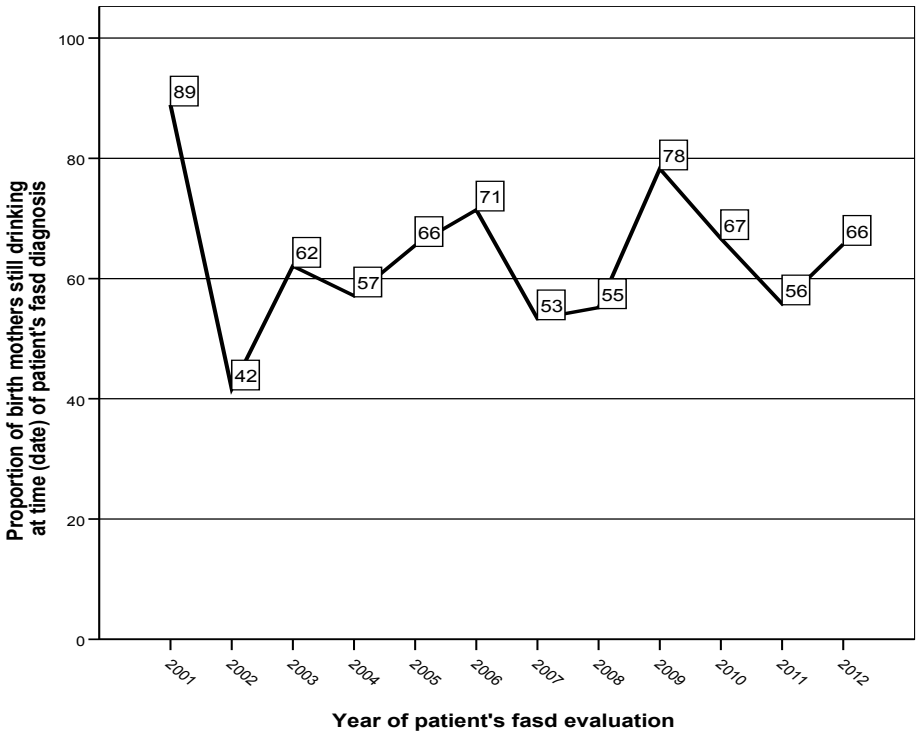
Women who are still drinking while they are fertile are at the highest risk for having a pregnancy exposed to alcohol, placing the fetus at risk for FASDs. Of the 536 birth mothers with a completed First Bridges DPN Clinic Contact Form the majority (197/312; 63%) were reportedly still drinking at the time of their child's FASD diagnostic evaluation. These data indicate mothers who were reportedly still drinking at the time of their child's FASD diagnostic evaluation fluctuated, but did not increase or decrease annually between 2001 and 2012 (Figure 4C).


Proportion of birth mothers 18-44 yrs old on date of child's diagnosis
100
80
60
40
20
0
86
75
83
85
93
80
71
82
82
81
79
86
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Year of patient's fasd evaluation

A


Proportion of birth mothers still fertile at time (date) of patient's fasd diagnosis
100
80
60
40
20
0
89
62
63
50
71
72
42
60
79
64
63
75
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Year of patient's fasd evaluation

B



C

Figure 4: Characterization of birth mother's risk status at the time of their child's FASD assessment. A) Proportion of birth mothers reportedly still in their reproductive years (18-44 years old), B) Proportion of birth mothers who are still fertile, and C) The proportion of mothers with a completed First Bridges DPN Clinic Contact Form who are still drinking at the time of their child's FASD assessment.

7. Is the proportion of birth mothers that are still fertile, still drinking, and have current contact with their child increasing, decreasing, or staying the same across clinic years 2001 to 2012?

Of the 526 records available for this analysis, 217 (47.0%) of the children still had current or recent contact with their birth mother within six months of their FASD assessment. Of these, 114 (72 %) were reportedly still fertile and 89 (51 %) were still drinking. Of the 131 cases with documented fertility and drinking status, 39% (51/131) were both fertile and drinking at the time of their child's FASD assessment, and were at the highest risk for having more children potentially affected by a FASD.

1.5 DISCUSSION:

Fetal Alcohol Syndrome is an avoidable condition, caused by women drinking while pregnant. Since the discovery of FASDs in 1973[3], tremendous efforts have been undertaken to educate women of childbearing age worldwide about the importance of not drinking alcohol during pregnancy, nevertheless, FASDs remain a public health problem.

The FAS DPN clinic started in 1993 with two goals: first, to identify patients with prenatal alcohol exposure, render a complete and comprehensive diagnosis including referrals to resources that encourage the best emotional, social, physical, and neurological development among patients; and second, to identify women at risk of having more children that could be damaged by prenatal alcohol exposures. By identifying at-risk birth mothers, clinicians hoped to provide referrals to appropriate family planning, mental health, and addiction treatment services. Achieving the clinic's second goal is contingent upon diagnosis of patients by FAS DPN clinicians when contact between the patient and their mother can be ascertained, and their willingness to receive necessary family planning, addiction treatment, or mental health services, or to "bridge the gap" to preventive services can be determined.

1.5.1 *Birth mother-child contact*

The initial 1995 to 1998 pilot study revealed that the clinic was able to contact 56% (144/257) of high-risk birth mothers to determine their willingness to participate in the pilot study [12]. This follow-up study documents that over the years, the proportion of birth mothers that are in recent contact with their child has remained roughly the same 50% to 60% (Fig 3). This is encouraging

since on average only 17% of children were accompanied to the FAS DPN clinic by their birth mother.

1.5.2 *Age trends among birth mothers and their children*

The current study revealed several trends that are encouraging for primary prevention efforts: 1). the birth mother's age at the time of their child's FASD evaluation decreased from an average of 35 in 1993 to an average of 30 years of age in 2012, 2). the age of the child at their diagnostic evaluation decreased from approximately 10 years of age in 1993 to 5 years of age in 2012, 3). the age of the birth mother at the time of the child's birth remained relatively the same from 1993 to 2012, 3). the birth mother's age increased slightly but significantly at the time of their child's birth, and 4). the child's parity increased slightly but significantly between 1993 and 2012. The reduction in age of both the children and the birth mothers allows earlier intervention that enhances the physical, educational, emotional, and behavioral outcomes for children[23], and allows clinicians to intervene with birth mothers when they are younger, earlier in the progression of alcoholism[24].

1.5.3 *Characteristics of birth mothers who have current or recent contact with their child*

Birth mothers that attend clinic with their child have an investment in their child's development and success. The current study documented that birth mothers that attended their child's FASD evaluation were more likely to have a college education, less likely to suffer from developmental or educational disabilities, were less likely to suffer from mental health problems, and were more likely to reduce their alcohol intake after learning of pregnancy. While outside of the scope of this project, investigating a correlation between the child's FASD diagnostic code and the

characteristics of the birth mother may indicate whether a more severe diagnosis correlates with a population of women who may be more difficult to access. Understanding these trends may help interventionists identify women more likely to have subsequent children more severely damaged by prenatal alcohol exposure and tailor intervention efforts accordingly.

1.5.4 *Assessing birth mothers' risk status at her child's FASD evaluation*

The First Bridges Program was designed to identify women at risk of having more children affected by FASD after diagnosis of an index case by collecting information on their drinking status, age, and fertility status at the time of their child's FASD evaluation between clinic years 2001 and 2012. To identify women at the highest risk and greatest need for public health intervention, information was also collected on current or recent contact with the child to assess the ease at which these birth mothers may be accessible to clinicians.

The initial pilot study demonstrated that 20% of women enrolled in the study were still drinking and fertile, while 46% were still fertile and had previously had a child with FASD and were therefore at risk for having another affected child. These numbers differ from the current study which revealed that approximately 39% of the women who have current or recent contact with their child are both fertile and drinking, while 75% are still fertile regardless of their current drinking status and are therefore at-risk of having a child who may be affected by FASD. This difference is likely attributable to the type of study. While the initial pilot study was prospective and all women were invited to enroll, only selected women chose to enroll. This retrospective study investigates all of the women whose children have been seen at the FASD clinic, and may be more representative of population as a whole. However, both studies demonstrate that the

clinic can identify women who are both fertile and drinking, a proportion of women who are at a critical junction in their lives with respect to fertility and drinking status, placing them at higher risk for having more children affected by FASD. These outcomes highlight the importance of intervening with this group of women at the highest risk for having more children damaged by prenatal alcohol exposure in a highly targeted fashion.

1.6 CONCLUSION:

This work confirms and extends the findings of the 1993-1998 pilot FASD prevention study by demonstrating the clinic's continued ability to locate and attract high risk women by assessing their children for FASDs. More recently, children with prenatal alcohol exposure are being identified and diagnosed at younger ages, allowing them to be enrolled in early intervention programs earlier, maximizing their behavioral, physical, and intellectual potential.

CHAPTER 2: THE ROLE OF ALCOHOL METABOLISM GENETICS IN ETHICAL PREVENTION FUNDING ALLOCATION

2.1 INTRODUCTION

Alcohol use and misuse are persistent public health problems that can lead to increased rates of disease transmission, automobile accidents, cardiovascular disease, liver disease, injuries and other preventable conditions[25]. Women who drink alcohol during pregnancy are at risk of having a child with Fetal Alcohol Syndrome (FAS), the extreme end of a continuum of Fetal Alcohol Spectrum Disorders (FASDs). Since the discovery of FAS in 1973[3], many types of public health interventions have been undertaken with the goal of reducing the incidence of FASDs. These interventions fall broadly into three categories: large-scale education and awareness programs designed to target all women of child bearing age, their partners, and family members, passive surveillance through interviews by clinicians asking about alcohol use and abuse events, and active surveillance and referral programs targeted to women who have a child with FASD or have confirmed that they are drinking during pregnancy[26]. Eliminating prenatal alcohol exposure is crucial for ending the incidence of FASDs.

Studies investigating the timing, duration, and amount of alcohol consumption that lead to prenatal damage among children has yielded mixed results. Early animal model experiments of alcohol ingestion during pregnancy have concluded that alcohol consumption during pregnancy is damaging to a fetus, however they are inconclusive with respect to duration, timing, and amount of alcohol consumption with a corresponding FASD diagnosis[16,27–31] likely due to complex genetic and environmental conditions that contribute to FASD[32]. Mouse models of

alcohol teratogenesis have demonstrated that certain mouse strains are more susceptible to teratogenic effects with respect to blood alcohol concentrations (BAC)[33]. Three different strains of pregnant mice were given the same amount of alcohol during the same gestational periods with differing fetal results corresponding to BAC. The mother's BAC is likely a function of the her genetic makeup and ability or inability to quickly metabolize alcohol[34]. Interestingly, embryo transfer experiments between certain mouse strains that have differing intoxication susceptibility have demonstrated that the uterine environment may not influence alcohol teratogenesis among neonates[35], therefore confounding easy interpretation of genetic and epigenetic susceptibility to FASD.

Studies of human monozygotic and dizygotic twins demonstrate that monozygotic twins with prenatal alcohol exposure most often have concordant diagnoses, while dizygotic twins can show discordant diagnoses[36–38]. Despite identical age, in utero environment, and amount and timing of alcohol exposure, the incidence of discordant diagnoses indicates that a genetic component may play a role in the severity of FASD diagnoses among dizygotic twins that is not shared among monozygotic twins. The Washington State FAS DPN has demonstrated that in singlet pregnancies, some birth mothers report significant alcohol consumption during pregnancy while their children appear to be unaffected during the FAS DPN evaluations, while others report little consumption and can have children with significant damage, lending more credibility to a genetic predisposition for FASD severity from prenatal alcohol exposure[21].

As the science regarding the incidence and severity of FASD has progressed since its initial discovery, so has genetic and genomic testing for susceptibility genes, starting first with the

discovery of genes that influence alcohol metabolism. As with many existing and newly emerging genetic tests, a complex array of ethical implications has surfaced with respect to a future where women and children can be assessed for susceptibility loci. While no genetic susceptibility test currently exists, the biological framework for one has been developed through basic science research, and bringing such a test to market is theoretically possible. Whether or not to offer such a test relies on the potential harms and benefits to those who may receive one. For public health practitioners, the limited funding dedicated to eliminating FASD through preventative measures may provide justification for offering such a test, while clinicians approach this possibility with respect to individual autonomy by considering possible outcomes a test may offer.

2.2 THE ALCOHOL METABOLISM PATHWAY

In adults, the majority of alcohol metabolism occurs through multiple pathways, principally involving two enzymes. After alcohol ingestion, ethanol is broken down by the enzyme alcohol dehydrogenase (ADH) into acetaldehyde, a highly toxic byproduct and carcinogen. The second enzyme, acetaldehyde dehydrogenase (ALDH) breaks acetaldehyde into acetic acid which can then be cleared from the body. Depending on the amount of alcohol ingested and rate of activity of the ALDH enzyme, toxic intermediates may be present in the tissues for extended lengths of time. The activity of ADH and ALDH is regulated by specific alleles of each gene. For instance, an allele of ADH1, ADH1B*2 is common among people of Asian decent, and is associated with very efficient metabolism of alcohol into acetaldehyde making drinking unpleasant. Similarly, alleles of ALDH, ALDH1A1*2 and ALDH1A1*3 are associated with slow metabolism of acetaldehyde, prolonging tissue exposure to the toxic acetaldehyde intermediate of alcohol

metabolism[39]. A third enzyme, the cytochrome p450 enzyme CYP2E1, is also associated with alcohol metabolism but is induced by chronic alcohol exposure and is responsible for a small amount of alcohol metabolism in the brain and in the liver[40].

The occurrence of specific alleles of alcohol metabolizing enzymes is distributed among different racial and ethnic groups. For instance, alleles of ADH are found in varying amounts; ADH1B*2 is found in the majority of Far East Asians and in some Caucasian populations, individuals of Ashkenazi Jewish descent, and African Americans, while ADH1B*3 is found in people of African descent and some Native American tribes[41,42]. These alleles are associated with flushing while drinking and feelings of nausea, creating a less pleasant experience from drinking and are considered likely protective alleles. Several studies have demonstrated that individuals with this allele are less likely to have children with impairments consistent with FASD[43]. Similarly, the acetaldehyde dehydrogenase enzyme ALDH2*2 is associated primarily with individuals of Asian descent and provides a similar protective effect. This ALDH2*2 allele has not been traced to particular other ethnic and racial populations[44]. While the presence of these alleles does not prevent an individual from becoming an alcoholic, they do create an unpleasant feeling from alcohol consumption.

During pregnancy, alcohol metabolism of both the mother and the fetus must be considered, as alcohol crosses the placental barrier to affect fetal development. In controlled studies elucidating the metabolic differences between alcoholic birth mothers who did or did not have a child with FAS, those women who metabolized alcohol more quickly were less likely to have a child with FAS[45]. Early genetic studies of women who had a child with FASD revealed that the ADH2*3

allele played a protective role in prevention of FASD[43]. Therefore, maternal metabolism of alcohol plays a role in the FASD outcome of their children.

The genetics of fetal alcohol metabolism are considerably more complex. Fetuses do not express the ADH genes in the brain, however they do in the placenta, and they are variably expressed in the fetal liver depending on trimester. Fetal brain tissue relies on CYP2E1 to metabolize alcohol in utero[46]. Reactive oxygen species that arise from CYP2E1 metabolism may cause oxidative stress that contributes to fetal damage from maternal alcohol consumption during pregnancy[46]. Several alleles of CYP2E1 have suspected associations with diseases associated with alcohol metabolism: c1 and c2 alleles of CYP2E1C have been associated with alcoholic liver disease in some populations, and CYP2E1*D is associated with alcohol and nicotine dependency. There have been no conclusive studies of CYP2E1 genotype concordance with the severity of FASDs although several groups have suggested that the association of different alleles with drugs of addiction may contribute to the severity of FASDs in children[46]. It is clear from these studies that the genetic underpinnings of FASD is quite complicated, nevertheless the ability of a person to metabolize alcohol due to their genetic complement influences their likelihood of developing alcohol dependency and results in increasing risk of developing FASD among some fetuses.

2.3 ETHICS AND GENETIC SCREENING

Many medical professions rely on the use of genetics and genetic screening or testing to influence healthcare decisions, especially pediatrics and perinatal services. Choosing to use genetic screening and testing creates many ethical considerations for healthcare workers who use genetics in their practice. The extent to which genetic background influences development of

disease or disorder relies on penetration which directs the likelihood of expression of a particular trait. In many cases penetration relies on the presence of certain environmental exposures to create certain outcomes. In this case the rate of alcohol metabolism relies not only on genetic makeup, but also the amount, duration, and timing of alcohol exposure. In this way genetic testing does not account for the presence of a gene or trait entirely, and is thus different from biomarker screening which helps clinicians determine whether the severity of a condition – for instance, cholesterol screening is used to determine the progress of atherosclerotic disease using an assumption that a person is at risk, not whether a person will eventually have atherosclerotic disease. This is the principle of genetic exceptionalism, which states that genetic information is different – predictive – and can be used in ways that may cause greater harm not only to an individual, but also to their family members through possible discrimination in employment and insurance among other issues[47].

Genetic testing among children creates more ethical concerns. In 2008, the American College of Obstetricians and Gynecologists presented arguments concerning the appropriate timing for using genetic information to direct healthcare among youth. These guidelines state that a physician should consider both the rights of the parents to know information that can help optimize the health of the child against the rights of the child for privacy and for protection of their best interests. The guidelines set forth criteria for using genetic information: 1. genetic information should only be used after an assessment of benefits and harms has been completed, 2. after they have considered the decision-making capacity of the child, and 3. for cases in which they must advocate on the child's behalf. These include instances where genetic information can

be used for a timely medical benefit or to prevent the onset of disease[48]. These considerations lay the foundation for the appropriate use of genetic information in testing and treatment.

2. 4 THE INTERSECTION OF GENETICS OF ALCHOL METABOLISM AND PUBLIC HEALTH ETHICS

The FAS DPN works to eliminate FASDs using a simple concept: the only safe amount of alcohol during pregnancy is none at all[49], a concept that has come under recent scrutiny from numerous publications that demonstrate a small amount of alcohol during pregnancy harbors no ill effects[50–52] boosted by op-eds published in young women's popular magazines that enjoy widespread readership[53]. These approaches reflect attitudes and beliefs from opposite sides of a spectrum, from alcohol consumers who embody autonomy, and medical practitioners who practice prevention by cautioning against the worst possible outcomes through the avoidance of any risk taking behavior.

Medical science has the ability to demonstrate which alleles of ADH, ALDH, and CYP2E1 may create differing abilities to metabolize alcohol and subsequently result in greater or lesser harm to a fetus. Genetic information including someone's complement of ADH, ALDH, and CYP2E1 alleles may consequently identify individuals at higher risk for having children affected by FASDs prior to pregnancy. Through a series of animal model and human studies, scientists have discovered a basic framework through which genetics and epigenetics can modulate the severity of the FASD[54]. The question then becomes, what are the consequences of this knowledge, and how can it be best applied to prevention and treatment of affected individuals?

Much attention has been paid to how clinicians direct care to women with substance abuse problems and changes in service utilization from implicit bias among caretakers. Genetic information may reinforce implicit bias and result in differential treatment based on race or ethnicity. Similarly, policy makers have the unique ability to both positively and negatively affect pregnant women with alcohol use disorders. For instance, Washington law RCW 70.83C.010 directs the Washington Secretary of Health to create and promote statewide strategies designed to increase the use of alcohol and drug treatment before, during, and after pregnancy[55]. Conversely, several states have passed fetal protection laws that direct clinicians who deliver or care for a child suspected of having FASD to inform law enforcement[56]. Genetic information with respect to race and ethnicity may influence how these laws are enforced, as we see disparate arrest and prosecution rates among people of color[57].

Public health is tasked with reducing disease burden across the entire population with very limited resources. Evaluation of public health interventions takes into consideration the reach, efficacy, adoption, implementation, and maintenance (RE-AIM model) of public health interventions during the course of evaluation[58]. Cost-effectiveness analysis is an integral part in determining the effectiveness of particular interventions, and is limited by the amount of federal and state funding that is allocated for specific types of intervention and research. It is well within the bounds of ethical practice to allocate funding to identify women at high-risk of having a second child affected by FASD, particularly in terms of acting in the best interest of the child (and as a consequence locating their mother for preventative purposes) and for the societal reasons of curtailing the excessive cost of drinking during pregnancy. However, with new information in the form of a further identification of women at the highest risk by accident of

their genetic information, we ask: **should genetic information play a role in directing limited government funding toward FASD prevention measures?**

2.5 GENETIC INFORMATION AS A GUIDE TO THE FAIR ALLOCATION OF FASD RESOURCES

The cornerstone of public health is the principle of social justice. It requires fair distribution based on what is owed to individuals or groups, and considers the poor and disabled at much higher risk in any circumstance, and therefore the consequences of decisions that impact the poor and disabled, whether negative or positive, should have greater influence during decision making than those of the wealthy and abled, with the goal of allowing all individuals to live a self-responsible life free of paternalism and stigmatization[59]. Public health genetics is defined as "the application of advances in genetics and molecular biotechnology to improve public health and prevent disease"[60]. There are many considerations important for the application of public health genetics to an entire population, however here we are considering only two principles of social justice, *recognition*, and *redistribution*.

It has been suggested that FASD is the perfect case study for the intersection of biology, society and environment[61]. Scientists now know the kinds of genetic information that could be used to identify women who may be at higher risk for having a child with FASD. How do we use this information to determine whether or not we should use it in the course of finding women at highest risk and dedicating excess public health dollars to prevention? Dr. Nancy Fraser discusses two frameworks within social justice theory that can be applied to public health genetics. *Recognition* details the understanding that a structural hierarchy exists within society

that places some at a disadvantage to others. The social hierarchy as it currently exists can lead to stigmatization and discrimination. A second principle of social justice that Fraser describes is *redistribution*, the distribution of information, resources, or other goods in a manner that does not widen health disparities.

The first principle of *recognition* requires anyone who might apply genetic information in this context to consider who is at greatest risk of being harmed or helped with it. Many studies[11,13] including the above study demonstrate overwhelmingly that people at highest risk of having a child with FASD occupy the lowest educational ranks, are generally at lower income levels, and often suffer from mental health issues and learning disorders or problems. Considering the additional information that genetics applies to this group, that susceptibility alleles have a higher prevalence among African Americans, recognition of a social hierarchy demonstrate that genetic information can be used to further identify and isolate at-risk populations.

The second principle, *redistribution*, considered in the case of not widening health disparities is important in the context of alcoholism and alcohol use disorders, as they are socially stigmatizing conditions. For instance, studies have demonstrated that in clinical settings, when women feel as though they are not being treated with respect due to substance abuse issues, they may abandon prenatal care, thus worsening the chances of a positive outcome for their child. Taken to the extreme, in fetal protection laws, women can be criminalized for using alcohol while pregnant. Tennessee is the only state to attempt such a law, and it has had the effect of women seeking prenatal treatment out-of-state or refusing it entirely for fear of being arrested. In the worst case scenario, women who are extremely poor and may not have the resources to seek

out-of-state care will not seek it at all. In this case, genetic information can be used to widen health disparities among certain groups.

Finally, the likelihood of a mother who is fertile and drinking alcohol during pregnancy is complicated – the development of alcoholism is dependent not only on a person's genetic makeup and their rate of alcohol metabolism, but also the environment in which they grew up, access to the drug, and behavioral choice[62], therefore it is impossible to entirely attribute genetics to whether a woman who is fertile and drinking would give birth to a child with FASD. Given the complex nature of alcoholism, scientists evolving understanding of the complexity of the role of genetic in alcohol metabolism, the apparent distribution of susceptibility alleles among communities of color, and the opportunity to stigmatize others during the allocation of resources among people at the highest risk of having a child with FASD, genetics should not factor into the decision to allocate limited public health resources to further identifying high-risk women from the epidemiological paradigm that is currently used.

2.6 CONCLUSION

In the context of the timeliness in genetic discovery and limited available funding directed for public health interventions for FASD, it is tempting to consider those at highest risk as those who should receive the majority of interventions. However, current understanding of the genetics of alcohol metabolism and the social context in which we live clincians and public health practitioners should not use limited and shrinking resources as a justification for identifying women and children at the highest risk for FASD. Further, in considering the principles of recognition and redistribution as described by Fraser, using genetic information to identify and

direct treatment to the highest risk individuals creates substantially greater risk of harm than benefit.

REFERENCES

1. Vital Signs: Alcohol-Exposed Pregnancies — United States, 2011–2013 | MMWR. http://www.cdc.gov/mmwr/volumes/65/wr/mm6504a6.htm. Accessed February 21, 2016.

2. Sacks JJ, Gonzales KR, Bouchery EE, Tomedi LE, Brewer RD. 2010 National and State Costs of Excessive Alcohol Consumption. *Am J Prev Med*. 2015;49(5):e73-e79. doi:10.1016/j.amepre.2015.05.031.

3. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet Lond Engl*. 1973;302(7836):999-1001.

4. Hankin JR. Fetal alcohol syndrome prevention research. *Alcohol Res Health J Natl Inst Alcohol Abuse Alcohol*. 2002;26(1):58-65.

5. Nilsen P. Brief alcohol intervention to prevent drinking during pregnancy: an overview of research findings. *Curr Opin Obstet Gynecol*. 2009;21(6):496-500. doi:10.1097/GCO.0b013e328332a74c.

6. Centers for Disease Control and Prevention (CDC). Identification of children with fetal alcohol syndrome and opportunity for referral of their mothers for primary prevention--Washington, 1993-1997. *MMWR Morb Mortal Wkly Rep*. 1998;47(40):861-864.

7. Grant TM, Ernst CC, Streissguth A, Stark K. Preventing alcohol and drug exposed births in Washington state: intervention findings from three parent-child assistance program sites. *Am J Drug Alcohol Abuse*. 2005;31(3):471-490.

8. Grant T, Christopher Graham J, Ernst CC, Michelle Peavy K, Brown NN. Improving pregnancy outcomes among high-risk mothers who abuse alcohol and drugs: Factors associated with subsequent exposed births. *Child Youth Serv Rev*. 2014;46:11-18. doi:10.1016/j.childyouth.2014.07.014.

9. FAS Diagnostic & Prevention Network: WA State. http://depts.washington.edu/fasdpn/. Accessed November 30, 2014.

10. Astley SJ. Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. 2004. https://depts.washington.edu/fasdpn/pdfs/guide2004.pdf.

11. Astley SJ, Bailey D, Talbot C, Clarren SK. Fetal alcohol syndrome (FAS) primary prevention through fas diagnosis: II. A comprehensive profile of 80 birth mothers of children with FAS. *Alcohol Alcohol Oxf Oxfs*. 2000;35(5):509-519.

12. Astley SJ, Bailey D, Talbot C, Clarren SK. Fetal alcohol syndrome (FAS) primary prevention through FAS diagnosis: I. Identification of high-risk birth mothers through the diagnosis of their children. *Alcohol Alcohol Oxf Oxfs*. 2000;35(5):499-508.

13. Esper LH, Furtado EF. Identifying maternal risk factors associated with Fetal Alcohol Spectrum Disorders: a systematic review. *Eur Child Adolesc Psychiatry*. 2014;23(10):877-889. doi:10.1007/s00787-014-0603-2.

14. Astley SJ, Clarren SK. A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrome. *J Pediatr*. 1996;129(1):33-41.

15. Guralnick MJ, ed. *Interdisciplinary Clinical Assessment of Young Children with Developmental Disabilities*. Baltimore: Paul H. Brookes Pub. Co; 2000.

16. Stratton KR, Howe CJ, Battaglia FC, Institute of Medicine (U.S.), National Institute on Alcohol Abuse and Alcoholism (U.S.), eds. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. Washington, D.C: National Academy Press; 1996.

17. Astley S, Clarren S. Diagnostic Guide to FAS and Related Condtions: The 4-Digit Diagnostic Code 1st ed. Seattle: University of Washington Publication Services. 1997.

18. Streissguth AP, Kanter J, eds. *The Challenge of Fetal Alcohol Syndrome: Overcoming Secondary Disabilities*. Seattle: University of Washington Press; 1997.

19. De Onis M. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85(09):660-667. doi:10.2471/BLT.07.043497.

20. Astley SJ. Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code. *J Popul Ther Clin Pharmacol J Thérapeutique Popul Pharamcologie Clin*. 2013;20(3):e416-e467.

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

22. Astley SJ, Clarren SK. A fetal alcohol syndrome screening tool. *Alcohol Clin Exp Res*. 1995;19(6):1565-1571.

23. Kodituwakku PW, Kodituwakku EL. From research to practice: an integrative framework for the development of interventions for children with fetal alcohol spectrum disorders. *Neuropsychol Rev*. 2011;21(2):204-223. doi:10.1007/s11065-011-9170-1.

24. Morse RM. The Definition of Alcoholism. *JAMA*. 1992;268(8):1012. doi:10.1001/jama.1992.03490080086030.

25. WHO | Is harmful use of alcohol a public health problem? http://www.who.int/features/qa/66/en/. Accessed June 5, 2016.

26. Barry K, Caetano R, Chang G, et al. *Reducing Alcohol-Exposed Pregnancies: A Report of the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect*. US Department of Health and Human Services; 2009.

27. Clarren SK, Astley SJ, Bowden DM, et al. Neuroanatomic and neurochemical abnormalities in nonhuman primate infants exposed to weekly doses of ethanol during gestation. *Alcohol Clin Exp Res*. 1990;14(5):674-683.

28. Sheller B, Clarren SK, Astley SJ, Sampson PD. Morphometric analysis of Macaca nemestrina exposed to ethanol during gestation. *Teratology*. 1988;38(5):411-417. doi:10.1002/tera.1420380503.

29. Clarren SK, Astley SJ, Bowden DM. Physical anomalies and developmental delays in nonhuman primate infants exposed to weekly doses of ethanol during gestation. *Teratology*. 1988;37(6):561-569. doi:10.1002/tera.1420370605.

30. Sulik KK, Johnston MC, Daft PA, Russell WE, Dehart DB. Fetal alcohol syndrome and DiGeorge anomaly: critical ethanol exposure periods for craniofacial malformations as illustrated in an animal model. *Am J Med Genet Suppl*. 1986;2:97-112.

31. Lindsley TA, Comstock LL, Rising LJ. Morphologic and neurotoxic effects of ethanol vary with timing of exposure in vitro. *Alcohol Fayettev N*. 2002;28(3):197-203.

32. Ramsay M. Genetic and epigenetic insights into fetal alcohol spectrum disorders. *Genome Med*. 2010;2(4):27. doi:10.1186/gm148.

33. Warren KR, Li T-K. Genetic polymorphisms: Impact on the risk of fetal alcohol spectrum disorders. *Birt Defects Res A Clin Mol Teratol*. 2005;73(4):195-203. doi:10.1002/bdra.20125.

34. Chernoff GF. The fetal alcohol syndrome in mice: maternal variables. *Teratology*. 1980;22(1):71-75. doi:10.1002/tera.1420220110.

35. Gilliam D. Embryo transfers between C57BL/6J and DBA/2J mice: Examination of a maternal effect on ethanol teratogenesis. *Front Genet*. 2014;5:436. doi:10.3389/fgene.2014.00436.

36. Christoffel KK, Salafsky I. Fetal alcohol syndrome in dizygotic twins. *J Pediatr*. 1975;87(6 Pt 1):963-967.

37. Fraga MF, Ballestar E, Paz MF, et al. From The Cover: Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci*. 2005;102(30):10604-10609. doi:10.1073/pnas.0500398102.

38. Streissguth AP, Dehaene P. Fetal alcohol syndrome in twins of alcoholic mothers: concordance of diagnosis and IQ. *Am J Med Genet*. 1993;47(6):857-861. doi:10.1002/ajmg.1320470612.

39. *US Department of Health and Human Services - Alcohol Alert*. National Institute on Alcohol Abuse and Alcoholism; 2007. http://pubs.niaaa.nih.gov/publications/AA72/AA72.htm.

40. Gupta KK, Gupta VK, Shirasaka T. An Update on Fetal Alcohol Syndrome-Pathogenesis, Risks, and Treatment. *Alcohol Clin Exp Res*. July 2016. doi:10.1111/acer.13135.

41. Cederbaum AI. Alcohol Metabolism. *Clin Liver Dis*. 2012;16(4):667-685. doi:10.1016/j.cld.2012.08.002.

42. Scott DM, Taylor RE. Health-related effects of genetic variations of alcohol-metabolizing enzymes in African Americans. *Alcohol Res Health J Natl Inst Alcohol Abuse Alcohol*. 2007;30(1):18-21.

43. McCarver DG, Thomasson HR, Martier SS, Sokol RJ, Li T. Alcohol dehydrogenase-2*3 allele protects against alcohol-related birth defects among African Americans. *J Pharmacol Exp Ther*. 1997;283(3):1095-1101.

44. Goedde HW, Agarwal DP, Fritze G, et al. Distribution of ADH2 and ALDH2 genotypes in different populations. *Hum Genet*. 1992;88(3):344-346.

45. Khaole NCO. A PILOT STUDY OF ALCOHOL EXPOSURE AND PHARMACOKINETICS IN WOMEN WITH OR WITHOUT CHILDREN WITH FETAL ALCOHOL SYNDROME. *Alcohol Alcohol*. 2004;39(6):503-508. doi:10.1093/alcalc/agh089.

46. Gemma S, Vichi S, Testai E. Metabolic and genetic factors contributing to alcohol induced effects and fetal alcohol syndrome. *Neurosci Biobehav Rev*. 2007;31(2):221-229. doi:10.1016/j.neubiorev.2006.06.018.

47. Evans JP, Burke W. Genetic exceptionalism. Too much of a good thing? *Genet Med*. 2008;10(7):500-501. doi:10.1097/GIM.0b013e31817f280a.

48. ACOG Committee Opinion No. 410: Ethical Issues in Genetic Testing: *Obstet Gynecol*. 2008;111(6):1495-1502. doi:10.1097/AOG.0b013e31817d252f.

49. New UW research advises against drinking while pregnant. http://www.dailyrecord.com/story/news/health/2015/10/26/new-uw-research-advises-against-drinking-while-pregnant/74619454/. Accessed July 17, 2016.

50. Kesmodel U, Bertrand J, Støvring H, et al. The effect of different alcohol drinking patterns in early to mid pregnancy on the child's intelligence, attention, and executive function: The effects of early prenatal alcohol consumption. *BJOG Int J Obstet Gynaecol*. 2012;119(10):1180-1190. doi:10.1111/j.1471-0528.2012.03393.x.

51. Falgreen Eriksen H-L, Mortensen E, Kilburn T, et al. The effects of low to moderate prenatal alcohol exposure in early pregnancy on IQ in 5-year-old children: The effects of early prenatal alcohol consumption. *BJOG Int J Obstet Gynaecol*. 2012;119(10):1191-1200. doi:10.1111/j.1471-0528.2012.03394.x.

52. Underbjerg M, Kesmodel U, Landrø N, et al. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on selective and sustained attention in

5-year-old children: The effects of early prenatal alcohol consumption. *BJOG Int J Obstet Gynaecol*. 2012;119(10):1211-1221. doi:10.1111/j.1471-0528.2012.03396.x.

53. Ruiz M. Why I Drank While I Was Pregnant. Cosmopolitan. http://www.cosmopolitan.com/sex-love/news/a32292/why-i-drank-while-i-was-pregnant/. Accessed November 30, 2014.

54. Hackler C. Ethical, legal and policy issues in management of fetal alcohol spectrum disorder. *J Ark Med Soc*. 2011;108(6):123-124.

55. RCW 70.83C.020: Prevention strategies. http://app.leg.wa.gov/RCW/default.aspx?cite=70.83C.020. Accessed July 24, 2016.

56. Goodwin, Michele. Fetal Protection Laws: Moral Panic and the New Constitutional Battlefront. 2014. doi:10.15779/Z38BJ8V.

57. Bureau of Justice Statistics (BJS) - Correctional Populations in the United States, 2014. http://www.bjs.gov/index.cfm?ty=pbdetail&iid=5519. Accessed August 3, 2016.

58. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health*. 1999;89(9):1322-1327. doi:10.2105/AJPH.89.9.1322.

59. Bayer R, Beauchamp DE, eds. *Public Health Ethics: Theory, Policy, and Practice*. Oxford ; New York: Oxford University Press; 2007.

60. Khoury MJ, Burke W, Thomson EJ, eds. *Genetics and Public Health in the 21st Century: Using Genetic Information to Improve Health and Prevent Disease*. Oxford ; New York: Oxford University Press; 2000.

61. Meurk C, Lucke J, Hall W. A Bio-Social and Ethical Framework for Understanding Fetal Alcohol Spectrum Disorders. *Neuroethics*. 2014;7(3):337-344. doi:10.1007/s12152-014-9207-2.

62. Rothenberg K, Wang A. The Scarlet Gene: Behavioral Genetics, Criminal Law, and Racial and Ethnic Stigma. In: Farahany NA, ed. *The Impact of Behavioral Sciences on Criminal Law*. Oxford University Press; 2009:439-463. http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195340525.001.0001/acprof-9780195340525-chapter-13. Accessed March 16, 2015.

VITA

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