Letter to the Editor Regarding Coles, Gailey, Mulle, Kable, Lynch, and Jones (2016): A Comparison Among 5 Methods for the Clinical Diagnosis of Fetal Alcohol Spectrum Disorders

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To the Editor:

IN THIS LETTER to the Editor, I discuss a study conducted by Coles and colleagues (2016) that took on the important task of comparing the outcomes of 5 fetal alcohol spectrum disorder (FASD) diagnostic systems when retroactively applied to the records of 1,581 patients. Valid comparisons require valid administration of each diagnostic system. The purpose of this Letter to the Editor is to share with readers the methods used, but not reported, that influenced the outcomes of this study. These additional details will allow readers to more accurately interpret this study.

Coles and colleagues (2016) applied 5 FASD diagnostic systems: Emory, FASD 4-Digit Code, CDC, Canadian, and Hoyme (Astley, 2004, 2013; Bertrand et al., 2004; Blackston et al., 2005; Chudley et al., 2005; Coles et al., 1997; Hoyme et al., 2005) to the records of 1,581 patients. These patients received an evaluation at the Emory clinic for alcohol- and drug-exposed children between 1995 and 2011. Fifty-two percent of the population had a confirmed prenatal alcohol exposure and 46% of the population was African American. Data from records collected at the patient's evaluation were used to retrospectively render FASD diagnoses in accordance with the criteria for each diagnostic system. The purpose of their study was to compare the prevalence of fetal alcohol syndrome (FAS), partial FAS (pFAS), and alcohol-related neurodevelopmental disorder (ARND) across the 5 different diagnostic systems. The authors reported the percent of alcohol-related diagnoses by diagnostic system as follows:

- 4-Digit Code: FAS 0.25%, pFAS 12.97%
- Canada: FAS 1.83%, pFAS 10.31%
- CDC: FAS 4.74%, pFAS N/A
- Hoyme: FAS 12.21%p, FAS 22.83%
- Emory-20: FAS 13.73%p, FAS 16.13%

To derive these outcomes, the authors reported they administered the 4-Digit Code "fully consistent with instruction for clinical coding for this system (Astley, 2004) (Coles et al., 2016, p. 1004)." They went on to report "these 4-digit codes were then translated into diagnostic categories as recommended by this system (Astley, 2004)" (Coles et al., 2016, p. 1004). "In all cases when norms were required (e.g., palpebral fissure length, PFL), we used those recommended by the diagnostic systems themselves (Coles et al., 2016, p. 1001)." The authors offered to provide more detailed information on request.

Two outcomes caught my attention: (i) the strikingly low prevalence of FAS (0.25%) and (ii) the comparatively high prevalence of pFAS (12.97%) reported for the 4-Digit Code. These outcomes were in stark contrast to the diagnostic outcomes we observe in the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (Astley, 2013). In our population of 2,496 patients with prenatal alcohol exposure receiving a FASD diagnostic evaluation using the 4-Digit Code between 1993 and 2016, the prevalence of FAS is 3.5% and the prevalence of pFAS is 5.5%. Our population is 7.4% African American. Their population was 46% African American. But the prevalence of FAS and pFAS is comparable across all races in our clinic population. The prevalence of prenatal alcohol exposure in their population was 52%; ours is 100%. If you recomputed the prevalence of FAS and pFAS among just those with prenatal alcohol exposure (FAS 0.48% and pFAS 24.94%), the prevalence estimates are even more discrepant from what we observe in our clinical population. In an effort to understand why their 4-Digit Code prevalence estimates were so discrepant from ours, I conversed with the authors and they were kind enough to provide me the following additional information regarding how they administered the 4-Digit Code. Below is how they redefined which 4-Digit Code Diagnostic Categories A-V were used to define each diagnosis.

- FAS: Categories A, B
- pFAS: Categories C, E, G

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- ARND: Categories F, H
- Other Diagnosis: Categories D, I to V

It is important to note that the 4-Digit Code case-defines pFAS as Diagnostic Category C only (Astley, 2004). Category C includes 20 different 4-Digit Code combinations that meet the 4-Digit Code's growth, facial, central nervous system (CNS), and alcohol exposure criteria for pFAS. In contrast, Coles and colleagues (2016) redefined the 4-Digit Code's diagnosis of pFAS to include diagnostic Categories C, E, and G. Diagnostic Category E is Sentinel Physical Findings/Static Encephalopathy/Alcohol-Exposed. Diagnostic Category G is Sentinel Physical Findings/Neurobehavioral Disorder/Alcohol-Exposed. Thus, in contrast to their published methods, the authors did not *translate the 4-Digit Codes into diagnostic categories as recommended by the system* (Astley, 2004). They redefined the 4-Digit Code's pFAS diagnosis. This increased the number of 4-Digit Codes that case-defined pFAS from 20 to 60, resulting in a substantially elevated prevalence of pFAS. In addition, although the authors reported they used the physical features and neurobehavioral deficit (defined as per each system), the physical features and neurobehavioral deficit for pFAS (as defined per the 4-Digit Code) were not used. For example, individuals in Diagnostic Category G have moderate CNS dysfunction. But, pFAS (as defined per the 4-Digit Code) requires severe CNS dysfunction. pFAS also requires the FAS facial phenotype be a Rank 3 or Rank 4. But, none of the individuals in Diagnostic Category E met this criterion.

The authors also reported that "In all cases when norms were required (e.g. PFL), we used those recommended by the diagnostic systems themselves" (Coles et al., 2016, p. 1001). This was not true for the 4-Digit Code. The 4-Digit Code requires African American PFL charts be used on African Americans (e.g., Iosub et al., 1985), because African Americans have PFLs that are significantly larger (2 to 3 mm larger) than Caucasians. This is illustrated in a study by Astley (2011). The authors used the Stromland Scandinavian (Caucasian) PFL charts (Stromland et al., 1999) on the 788 African Americans in their study population. In accordance with the 4-Digit Code, an individual must present with PFLs 2 or more standard deviations (SD) below the mean to meet 1 of the 3 required facial features for FAS. As African Americans have significantly larger PFLs than Caucasians, it would be near impossible for an African American to have PFLs 2 SDs below the mean on the Stromland Caucasian PFL chart. Their PFLs would have to be 3 to 4 SDs below the mean on an African American PFL chart to register as 2 SDs below the mean on the Stromland Caucasian PFL chart. As 46% of the authors' study population was African American (n = 788), use of the Stromland Caucasian PFL chart would have a significant impact on the prevalence estimates of FAS and pFAS. The prevalence of FAS would be substantially under estimated and prevalence of pFAS would be substantially over estimated. Upon request, the authors revealed the following FAS and pFAS diagnostic prevalence estimates for the 788 African American subjects who made up 46% of their study population:

- 4-Digit Code as revised by Coles and colleagues (2016): FAS n = 0 (0.0%), pFAS n = 119 (16.0%)
- Canadian: FAS n = 16 (2.2%), pFAS n = 85 (11.4%)
- CDC: FAS n = 39 (5.2%), pFAS N/A
- Hoyme: FAS n = 100 (13.5%), pFAS n = 175 (23.6%)
- Emory: FAS n = 117 (15.7%), pFAS n = 141 (19.0%)

As anticipated, not a single African American received a diagnosis of FAS using the 4-Digit Code. Also as anticipated, the prevalence of pFAS was unusually high (16%). The 4-Digit Code criterion for pFAS allows the PFL to be relaxed to 1 SD below the mean. The 4-Digit Code criteria for FAS requires the PFL to be 2 or more SDs below the mean. Use of the wrong PFL chart on the African Americans prevented them from meeting the −2 SD PFL criterion for FAS, but allowed many to meet the −1 SD PFL criterion for pFAS.

When the 4-Digit Code is administered in accordance with the published instructions, as it has been for patients evaluated in the UW FASDPN clinic over the past 24 years, the prevalence of FAS and pFAS among Caucasian and African American individuals with prenatal alcohol exposure is as follows: Caucasian (4% FAS, 6% pFAS) and African American (6% FAS, 10% pFAS). The prevalence of pFAS is higher than FAS, but <2-fold higher. In stark contrast, the revisions imposed on the 4-Digit Code by Coles and colleagues (2016) resulted in a prevalence of pFAS that was 52-fold higher than FAS (12.97% vs. 0.25%, respectively). The prevalence of pFAS relative to FAS for the other diagnostic systems ranged from <2-fold higher to 5-fold higher.

The Journal published an Erratum (2016) to alert Readers that the authors used a PFL growth chart for the 4-Digit Code that was not consistent with their published methods: "In all cases when norms were required (e.g. PFL), we used those recommended by the diagnostic systems themselves."

In the Erratum (2016), the authors expressed concern about the applicability of the Iosub PFL chart for African Americans. The chart is based on a relatively small sample (n = 170) and binned into age ranges (<1 year, 1 to 2, 3 to 5, and 6 to 15 years of age). Despite these constraints, the Iosub PFL chart is a more accurate reflection of African American PFLs than the Stromland Scandinavian (Caucasian) PFL chart. The 4-Digit Code uses the Iosub PFL chart because, to date, it is the only chart available for African Americans that addresses the full age span and it reports PFLs that are commensurate with other published African American PFL charts for adults, as detailed below. It is confirmed in both the published literature and in our 24-year clinical experience (Astley, 2011) that the PFL for African Americans is significantly larger (by 1.5 to 2.4 mm) than the Caucasian PFL. Starting at birth, Fuchs and colleagues (1980) reported the PFL was 1.5 mm longer among African American term

neonates (20.0 mm, 2.0 SD) compared to Caucasian neonates (18.5 mm, 1.3 SD). Among adults, Barretto and Mathog (1999) reported the PFL was 2.6 mm longer among African Americans (32.0 mm, 2.3 SD) compared to Caucasians (29.4 mm, 2.3 SD). Farkas and colleagues (2005) reported the PFL was 1.6 mm longer among African American adults (32.6 mm, 2.0 SD) compared to Caucasians (31.0 mm, 1.3 SD). Stromland and colleagues (1999) report the PFL for 18-year-old Scandinavians is 29.1 mm (1.6 SD), commensurate with the Caucasian PFL reported by Barretto and Mathog (1999) and Farkas and colleagues (2005). Iosub and colleagues (1985) report the PFL for African Americans 6 to 15 years of age is 33.0 mm (3.0 SD), commensurate with the African American PFL reported by Barretto and Mathog (1999) and Farkas and colleagues (2005). The magnitude of difference between African American and Caucasian PFLs necessitates the use of PFL charts normed to their respective races. African American PFL normal growth charts exist (Barretto and Mathog, 1999; Farkas et al., 2005; Fuchs et al., 1980; Iosub et al., 1985), but as we reported back in 2011 (Astley, 2011), would benefit from an update.

In conclusion, the prevalence of FAS, pFAS, and ARND reported for the 4-Digit Code do not reflect the 4-Digit Code or any published FASD diagnostic system. The 4-Digit Code case-definition for pFAS was substantially revised and the administration of the 4-Digit Code was not *fully consistent with instruction for clinical coding for this system,* as reported by the authors. As a result, the prevalence estimates for FAS, pFAS, and ARND reported for the 4-Digit Code cannot be validly compared to one another and cannot be validly compared to the diagnostic prevalence estimates reported for the other diagnostic systems.

CONFLICT OF INTEREST

The author declares she has no conflict of interest.

REFERENCES

Astley S (2004) Diagnostic Guidelines for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. 3rd ed. University Publication Services, Seattle, WA. Available at: http://depts.washington.edu/fasdpn/pdfs/guide04.pdf. Accessed October 29, 2016.

Astley SJ (2011) Canadian palpebral fissure length growth charts reflect a good fit for two school and FASD clinic-based U.S. populations. J Popul Ther Clin Pharmacol 18:e231–e241. Available at: http://www.jptcp.com/articles/canadian-palpebral-fissure-length-growth-charts-reflect-a-good-fit-for-two-school-and-fasd-clinicbased-us-populations.pdf. Accessed October 29, 2016.

Astley SJ (2013) Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code. J Popul Ther Clin Pharmacol 20:e416–e467. Available at: http://www.jptcp.com/articles/validation-of-the-fetal-alcohol-spectrum-disorder-fasd-4digit-diagnostic-code.pdf. Accessed October 29, 2016.

Barretto RL, Mathog RH (1999) Orbital measurement in black and white populations. Laryngoscope 109:1051–1054.

Bertrand J, Floyd RL, Weber MK, O'Connor M, Riley EP, Johnson KA, NTFO FAS/FAE (2004) Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis. Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA.

Blackston RD, Coles CD, Kable JA (2005) Evidence for Severity of Dysmorphology in Fetal Alcohol Syndrome and Direct Correlation With Developmental, Behavioral, Social and Educational Outcomes and to Psychotropic Medications. David Smith Dysmorphology Meeting, Iowa City, IA.

Chudley AE, Conry J, Cook JL, Loock C, Rosales T, Leblanc N, Public Health Agency Of Canada's National Advisory Committee On Fetal Alcohol Spectrum Disorder (2005) Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ 172: S1–S21.

Coles CD, Gailey AR, Mulle JG, Kable JA, Lynch ME, Jones KL (2016) A comparison among 5 methods for the clinical diagnosis of fetal alcohol spectrum disorders. Alcohol Clin Exp Res 40:1000–1009.

Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE (1997) A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. Alcohol Clin Exp Res 21:150–161.

Erratum (2016) Alcohol Clin Exp Res, 40:1795. Doi:10.1111/acer.13117

Farkas LG, Katic MJ, Forrest CR (2005) International Anthropometric study of facial morphology in various ethnic groups/races. J Craniofac Surg 16:615–646.

Fuchs M, Iosub S, Bingol N, Gromisch DS (1980) Palpebral fissure size revisited. J Pediatrics 96:77–78.

Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, Buckley DG, Miller JH, Aragon AS, Khaole N, Viljoen DL, Jones KL, Robinson LK (2005) A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. Pediatrics 115:39–47.

Iosub S, Fuchs M, Bingol N, Stone R, Gromisch D, Wasserman E (1985) Palpebral fissure length in black and Hispanic children: correlation with head circumference. Pediatrics 75:318–320.

Stromland K, Chen Y, Norberg T, Wennerstrom K, Michael G (1999) Reference values of facial features in Scandinavian children measured with a range-camera technique. Scand J Plast Reconstr Surg Hand Surg 33:59–65.