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A report on the Fetal Alcohol Spectrum Disorders Study Group meeting of 2012, theme title, "*Biomarkers for FASD*"

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ABSTRACT

The 2012 meeting of the Fetal Alcohol Spectrum Disorders Study Group (FASDSG) focused on the development and ethics of biomarkers for fetal alcohol exposure. This one-day international conference brought students and trainees together with clinicians and researchers to discuss the latest research on FASD. One keynote speaker discussed the value of profiling epigenetic modifications in readily available fetal tissues to diagnose fetal exposure to environmental agents, while the second speaker discussed the ethics of biomarker development within the context of core principles of justice, autonomy, beneficence and non-maleficence. Three sessions of short data talks informed the audience of research advances with particular emphasis on the diagnosis of FASD. Other activities included updates on FASD-related activities by representatives of government agencies, a report on the implementation FASD-related diagnostic criteria in the fifth edition of the Diagnostic and Statistical Manual (DSM-5) of the American Psychiatric Association and a networking lunch, and the presentation of the "Merit Award" to Dr. Nathan Muraski for his work on behavioral outcomes of fetal alcohol exposure. The capstone of the meeting was the presentation of the "Henri Rosett" award to Dr. Denis Viljoen, in recognition of his role in raising awareness about the incidence of FASD in South Africa and in promoting FASD prevention and treatment programs as chairperson and chief executive officer of the Foundation for Alcohol Related Research (FARR).

The 2012 meeting of the Fetal Alcohol Spectrum Disorders Study Group (FASDSG), held in San Francisco, CA included a total of 190 attendees. Of these, 42 were students/trainees. Twelve students received travel awards to present their research at FASDSG and to attend the subsequent Research Society on Alcoholism meeting. Countries represented included Argentina, Canada, France, Japan, New Zealand, Norway, South Africa, Turkey, and the USA. During the course of the meeting, attendees learned about new directions in research on FASD from two keynote speakers as well as fourteen short research presentations by the membership. Eleven of the short presentations were made by students or post-doctoral fellows. A timely update on the newest revision of the Diagnostic and Statistical Manual, Fifth Edition (DSM-5) of the American Psychiatric Association was also presented. Aside from research presentations, attendees received updates on FASD-related activities from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Centers for Disease Control and Prevention (CDC), the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD) and from the Substance Abuse and Mental Health Services Administration (SAMHSA) FASD Center of Excellence. Attendees also participated in a networking lunch, which gave student attendees the opportunity to interact with more senior researchers and clinicians. The capstone of the meeting was the presentation of the Merit award to recognize an outstanding young researcher, and the Rosett Award, to recognize the lifetime achievement and service toward eradication of FASD.

Keynote presentations

The theme of the 2012 meeting of the FASDSG, "Biomarkers for FASD," focused on identifying promising approaches for, as well as the ethics of developing biomarkers for FASD. The rationale behind the focus on biomarkers for FASD is that fetal exposure to ethanol does not result in characteristic craniofacial dysmorphology or growth deficiency in all cases. Indeed, the presence of craniofacial dysmorphology detects only the severest instances of fetal alcohol exposure. Moreover, a confirmed history of prenatal

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ethanol exposure is frequently absent, making a definitive diagnosis difficult in many cases. Therefore, there is a significant need to identify alternate biomarkers of ethanol exposure at stages of both fetal and child development that will aid in the identification of children at risk. The meeting also addressed the issue that the need for good biomarkers has to be balanced with the significant ethical, biomedical and legal implications associated with the use of biomarkers to make a medical diagnosis of fetal alcohol exposure. There is a very real possibility that such a diagnosis will generate unintended legal and economic consequences for the birth mother as well as for the child. The keynote presentations contrasted the future promise and risks associated with biomarker development.

The first keynote presentation by Dr. Robert Wright, Harvard Medical School and School of Public Health, was entitled, "*Epigenetics and Reproductive Health*." Dr. Wright presented data from two human studies, the Early Life Exposures in Mexico and Environmental Toxicology (ELEMENT) longitudinal birth cohort in Mexico City, and the Metals Assessment Targeting Community Health (MATCH) study in Tar Creek, Oklahoma, assessing the role of environmental chemicals on child health and development. This presentation touched on the fact that a variety of agents including maternal tobacco smoke exposure, social stress, lead exposure, air pollution as well as ethanol are risk factors for impaired fetal growth. In recent years, a growing body of literature has demonstrated that all of the risk factors for impaired fetal growth can also alter DNA methylation, suggesting a common pathway by which environmental factors impair fetal growth. Vascular system tissues including blood cells, blood vessels like umbilical arteries and veins, as well as the placenta are important for fetal growth and are logical target tissues for environmental agents. Furthermore, these tissues are readily accessible at birth and can therefore be harvested to assess the presence of 'biomarkers' for environmental exposures. In assessing DNA methylation patterns in vascular tissues, Dr. Wright's presentation focused on the use of "methylomics" in umbilical cord vessels as a biomarker for fetal growth restriction associated with multiple environmental agents. He presented data showing that environmental agents can influence tissue methylation patterns, but that the effect of the environment on methylation patterns of many genes is tissue-specific. When comparing low to normal birth-weight children, DNA methylation responses in blood, umbilical artery and umbilical vein differ from each other. Therefore, while gene methylation patterns in each of these tissues may be used as a marker for exposure, they may have limited value in terms of assessing the effects of exposure on other target tissues like the brain. However, other genomic elements including repetitive elements, retro-transposons and imprinted genes (wherein one parent-of-origin allele is silenced while the allele derived from the other parental genome is transcribed), are expected to exhibit similar methylation patterns across tissue and their assessment may permit inferences about the effects of environmental agents on other tissues including the brain. Loss of imprinting in particular is associated with fetal growth retardation or overgrowth syndromes, and therefore assessment of the imprinted status of these gene loci is likely to be particularly informative about child development and health (Fleisch, Wright, & Baccarelli, 2012).

The development of biomarkers for maternal drug exposure is fraught with significant ethical and legal issues that merit analysis and discussion before these biomarkers are broadly adopted. Therefore, the second keynote presentation, entitled, "*Ethical considerations in screening for biomarkers related to prenatal exposure to alcohol*," was delivered by Dr. Nina Di Pietro, National Core for Neuroethics, The University of British Columbia, Canada. Although current biomarkers of prenatal alcohol exposure remain limited in their predictive and diagnostic power, progressive technological advancements in alcohol research will continue to improve their accuracy and clinical utility. While screening may offer opportunities for early intervention, many complicated ethical issues must be considered, including the potentially stigmatizing effects of targeted vs. population screening, the legal and personal ramifications of a positive test result, understanding the limitations of screening with regard to diagnosis of FASD, and the implications for maternal rights and decision-making. Dr. Di Pietro introduced the topic with a Canadian case report that served as an example of the intersection between medical and legal decisions about childcare associated with the diagnosis of drug exposure. In a follow-up, she used perinatal meconium screening as an example of a source of a variety of biomarkers. An important point that was raised is that biomarker tests may result in both false-positive or false-negative outcomes, each of which could result in important negative consequences such as failure to provide services, or emotional distress and the inappropriate referral to child protective services. Dr. Di Pietro also discussed the core principles of bioethics, i.e., justice, autonomy, beneficence and non-maleficence. The bioethical principle of justice, i.e. the obligation to be fair in the distribution of risks and benefits, may be served by implementing universal screening. The principle of autonomy would be served by strong protections for the rights to informed consent and refusal to participate in testing. The principle of beneficence would be served if testing were a gateway to social and medical services, while the principle of non-maleficence would be served by limiting harm (e.g., punitive legal consequences). Evidence indicates support for universal screening under the above principles, and in the Canadian health care system, projected savings per quality-adjusted life year would justify the additional costs of routine testing. Finally, the limitations to the practice of bio-ethical principles were discussed, including practical limitations of 'opt-in' vs. 'opt-out' screening protocols, the inadequacy of counseling and disclosure practices in the medical system, limited access to services and tension in the medical–legal profession between punitive and non-punitive approaches subsequent to diagnosis (Zizzo et al., 2013).

These keynote presentations were followed by a spirited and open discussion moderated by Dr. Cynthia Bearer, University of Maryland School of Medicine. The discussion reinforced the need for careful ethical consideration of the adoption of biomarkers for screening for fetal alcohol exposure, before such screening becomes more sophisticated (such as the approaches outlined by Dr. Wright) and universal.

Update on DSM-5

Dr. Julie Kable (Emory University School of Medicine) provided an update to the membership regarding efforts by the Alcohol Related Neurodevelopmental Disorder (ARND) workgroup from the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD), to include a disorder, titled Neurobehavioral Disorder Associated with Prenatal Alcohol exposure (ND-PAE) in DSM-5. In addition to Dr. Kable, membership on the ARND workgroup included (in alphabetical order), Dr. Sally Anderson (NIAAA, NIH), Dr. Heather Carmichael Olson (University of Washington), Dr. Sarah Mattson (San Diego State University), Dr. Mary O'Connor (University of California at Los Angeles), Dr. Blair Paley (University of California at Los Angeles), Dr. Edward Riley (San Diego State University), and Dr. Kenneth R. Warren (NIAAA, NIH). The ARND workgroup proposed including the ND-PAE category in DSM-5 to address three identified problems: (1) there is no specific mental health code that adequately documents the cognitive and mental health impact of PAE, (2) children with FASD may not respond to treatment regimens developed using the existing codes, which may lead to inappropriate treatments, and (3) when seeking mental