

October 24, 2018. Stephen F. Kingsmore

On June 10, 2016, Stephen Kingsmore presented a talk entitled “What is an Investigational Device in the Context of Genomic Medicine Research? The CMH/RCIMG NSIGHT Experience” at a joint NHGRI-FDA Investigational Device Exemptions (IDE) and Genomics Workshop at 5635 Fishers Lane, Conference Center, Rockville, Maryland 20852. This presentation is appended.

Present from the FDA were David Litwack Ph.D., Paula Caposino Ph.D., Jeffrey Seidman, M.D., Haja El Mubarak, Ph.D. and Kellie Kelm, Ph.D. from the FDA.

Dr. Kingsmore’s presentation covered the topic of changes in the NSIGHT Investigational Device which had occurred in the period between the FDA notification of non-significant risk in May 2014 and June 2016. The changes in the Device had been the subject of a manuscript that described the analytic performance of the device (Miller NA, Farrow EG, Gibson M, Willig LK, Twist G, Yoo B, Marrs T, Corder S, Krivohlavek L, Walter A, Petrikin JE, Saunders CJ, Thiffault I, Soden SE, Smith LD, Dinwiddie DL, Herd S, Cakici JA, Catreux S, Ruehle M, Kingsmore SF. A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases. *Genome Med.* 2015 Sep 30;7:100) and had shortened the time to diagnosis to 26 hours, a Guinness World Record that had resulted in considerable publicity, including Newsweek. They included change in laboratory and NICU location from Kansas City to San Diego, addition of rWES, change in sequencer, change in the manner of extracting clinical features of the patient’s disease, change in alignment method, change in variant calling method, and change in variant interpretation and reporting software. Dr. Kingsmore also presented clinical utility data from the first 32 children enrolled in the NSIGHT study (Willig LK, Petrikin JE, Smith LD, Saunders CJ, Thiffault I, Miller NA, Soden SE, Cakici JA, Herd SM, Twist G, Noll A, Creed M, Alba PM, Carpenter SL, Clements MA, Fischer RT, Hays JA, Kilbride H, McDonough RJ, Rosterman JL, Tsai SL, Zellmer L, Farrow EG, Kingsmore SF. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *Lancet Respir Med.* 2015 May;3(5):377-87).

During the workshop, Dr. Kingsmore asked Dr. Litwack and colleagues whether he should submit a second pre-investigational device exemption enquiry to the FDA, given the changes noted above. Dr. Litwack and colleagues responded that this was not necessary. In particular, they noted that the device changes had not altered the risk determination of the NSIGHT study protocol. This related to the fact that rapid whole genome sequencing was being performed in acutely ill infants with diseases of unknown etiology in a regional NICU in whom a genetic disease was suspected and that a verbal provisional result was only being disclosed to a physician before confirmatory testing in cases where testing identified high likelihood, acutely actionable, diagnostic variants for a life-threatening treatable condition in whom the risk of a delay in reporting significantly exceeded the risk of disclosure before confirmatory testing. This advice was consistent with presentations made by David Litwack Ph.D., Paula Caposino Ph.D., Jeffrey Seidman, M.D., Haja El Mubarak, Ph.D. and Kellie Kelm, Ph.D. at the workshop that are available at <https://www.genome.gov/27564792/workshop-investigational-device-exemptions-ide-and-genomics-workshop/>