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The National Children's Study. Abstracts of the National Children's Study Research Day 2011

Carol H. Kasten*

NCS Program Office, Eunice Kennedy Shriver National Institute for Child Health and Human Development, National Institutes of Health, Bethesda, MD

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FOREWORD

The following are selected abstracts from the National Children's Study (NCS) Research Day at NIH held August 24, 2011on the Bethesda campus of the National Institutes of Health. The goal of the NCS is to improve the health and well-being of children. The study will examine the role of genomics and the environment broadly defined (biological, chemical, physical, and psycho-social cultural), and their impacts on the health and development of children, following 100,000 participants from before birth until age 21 years. It is the largest longitudinal observational study of children ever undertaken in the United States. The purpose of NCS Research Day was to engage the NIH community and the public, display the Study's preliminary data, and stimulate collaboration. Much of the research presented was initiated to evaluate the feasibility, acceptability, and cost of either new "instruments" needed to standardize data collection or real time analysis of selected variables. Subject domains and titles of all the NCS Research Day Posters were distributed and broadcasts of the Plenary Sessions were available via NIH Videocast. The abstracts were selected based on their innovativeness and relevance to the fields of medical genetics and clinical teratology.

Feasibility, Acceptability, and Cost of Alcohol Screening in Dried Blood Spots Collected During Routine Newborn Screening

Bakhireva LN[1] Savich RD[1] Leeman L[1] Raisch D[1] Savage DD[1] Goff CD[1] Cano S[1] Moya D[1] Wafer M[1] and Annett RD[1]

[1]University of New Mexico, Albuquerque, NM

Introduction: The collection of dried blood spot (DBS) cards obtained during newborn screening or routine newborn testing offers numerous advantages compared to liquid blood samples. This pilot study investigated the feasibility, acceptability, and cost of collecting a DBS card for research purposes at the University of New Mexico (UNM) during routine testing on newborns.

Methods: Nurses collected DBS cards from infants who still bled after the routine heel prick. Between February 12 and March 24, 2011 a total of 250 infants were admitted, 95.8% cards were collected and 4.2% infants were missed by the research protocol. From 250 cards collected, 200 (87%) had at least one full blood spot. Cards were analyzed at the U.S. Drug Testing Laboratory for a novel ethanol biomarker—phosphatidylethanol (PEth). PEth is a phospholipid in cell membranes, detectable in blood up to 3 weeks after alcohol exposure.

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Results: Among 200 samples, 6.5% had PEth >20ng/ml—the cutoff concentration indicative of potential prenatal alcohol exposure in late pregnancy, even though we could not determine the validity of this biomarker relative to maternal alcohol use. The use of DBS cards rather than liquid blood decreases the cost per sample for collection and analysis of PEth by $14.2 per sample (sensitivity analysis: $4.6–$23.5). A typical hospital with 3,000–3,500 deliveries per year would save $43,034–$50,205 annually by using DBS for the newborn screening of prenatal alcohol exposure compared to whole blood specimens obtained by phlebotomy.

Conclusions: These results indicate that the collection of DBS cards during routine screening (a) can be incorporated into newborn admission orders; (b) is feasible for the majority of newborns without re-puncture and accepted by families; (c) can be used to assess prenatal exposures, though biomarker validity needs to be established; (d) is cost-efficient compared to liquid specimens.

Building Capacity for Whole Genome Sequencing (WGS) in the National Children's Study (NCS): DNA Sequencing and the 100 Trios Project

Bamshad M[1] Nickerson D[1] Rieder M[1] Yu J[1] Eichler E[1] Shendure J[1] McMillin M[1] Anderson N[1] Hartzler A[1] Tabor H[2] Swanson J[3] Flodman P[3] Lakes K[3] Wadhwa P[3] Faustman E[1] Jarvik G[1] Burke W[4] Gutzman K[4] and Murray J[5]

[1]University of Washington, Seattle, WA

[2]Seattle Children's Hospital, Seattle, WA

*Correspondence to:
Carol H. Kasten, MD, National Children's Study Program Office, NIH, 6100 Executive Boulevard, Suite 3A01, Bethesda, MD 20892-7510 (Courier Delivery Use: Rockville, MD 20852). E-mail: kastenca@mail.nih.gov

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[3]University of California Irvine and Orange County CA Vanguard Center, Irvine, CA

[4]South Dakota State University, BYPL Study Center, Brookings, SD

[5]University of Iowa, Polk County Iowa Study Center, Iowa City, IA

Introduction: Whole genome sequencing (WGS) is a potentially transformative new tool for discovery of genes influencing pediatric health-related traits. To develop a robust model for understanding natural human genetic variation and its impact on disease, sequencing genomes of a larger number of individuals is needed. We proposed to evaluate feasibility, acceptability, and cost of WGS in the National Children's Study (NCS) by using technological advances and low-cost protocols for DNA sequencing and analytic methods that assess genomic variation accurately.

Methods: We engaged a group of experts at the Northwest Genome Center and developed a plan for WSGS and analysis of 300 individuals (from 100 parent-proband trios). We obtained samples from the NCS Biorepository for a pilot study while waiting for OMB approval to implement the "100 Trios" study.

Results: We created additional capacity of 250 genomes/yr (current capacity of 4 Illumina HiSeq 2000 sequencers). For NCS Biorepository samples, we developed and validated DNA extraction from frozen mixed buffy coat and red blood cell samples. We sequenced at average 30-fold coverage across euchromatic genomic regions (~85% of the genome). We catalogued DNA variation in each sample and amongst parent-child trios to assess inheritance, concordance, and de novo mutation rates and to serve as test data for future assessments of genome-wide copy number variation.

Conclusions: Based on this experience, we can provide current empirical estimates and future projections of feasibility, acceptability, and cost of WGS in the NCS. This may provide valuable information for incorporating WGS into other large population-based cohort studies.

Development of a Visit Assessment Tool to Address Birth Defects and Dysmorphology

Carey JC[1] Abdul-Rahman O[2] Hayes L[1] Loyola B[1] Taggart E[1] Gilliland J[1] Firth SD[1] Clark EB[1] and the Dysmorphology Assessment Instrument (DAI) NCS Working Group

[1]University of Utah, Salt Lake City, UT

[2]University of Mississippi Medical Center, Jackson, MS

Introduction: Continuing the observational nature of the National Children's Study (NCS), this formative research project will develop, evaluate, and implement an assessment tool to be used to document and categorize physical features by digital photography and physical assessment. The NCS protocol for the newborn baseline physical assessment currently includes a standardized physical examination and photographs at birth, 6 months and 12 months. The focus of this project is to refine a tool for application to the NCS main study, which can be used to standardize observation and documentation of physical variations and abnormal features in field settings.

Methods: Clinical geneticists and pediatricians from University of Utah (UU), University of Mississippi Medical Center, South Dakota State University, University of California, Irvine (UCI) and San Diego campuses, and Dr Susan Astley, an authority on photographic and training modules at the University of Washington, have joined with NCS collaborators to design the dysmorphology assessment instrument (DAI). In the original planning of the study, the investigators had decided to use the *Elements of Morphology* (http://elementsofmorphology.nih.gov/index.cgi) definitions and illustrations on over 400 phenotypic features as a guide for variations and anomalies needing documentation. Bimonthly conference calls were followed by two in-person meetings, one at UCI to train in photographic assessment, and the other at the UU to decide on the features not captured by photography that needed inclusion in the DAI physical assessment.

Results: The DAI working group developed the two components of the assessment. The first component is the proposed Photographic Protocol made up of 15 photographic images (views of craniofacies and hands and feet), and three 10-sec videos. The second component is the proposed Physical Assessment list, which was the result of narrowing down the *Elements* list to 25 features that are not captured sufficiently on the Photographic Protocol (see attached instrument and examination, which provides an example of instructions for the training module). An online training module that is comprised of detailed instructions for the Photographic Protocol and Physical Assessment is in development and close to completion (Fig. 1, poster).

Conclusions: Our working group has developed the consensus DAI that includes two components: The Photographic Protocol and the Physical Assessment list. The next steps include finalization of the training module for both components of the DAI; local training of field examiners by the individual centers; pilot study; evaluation of the working DAI and modification of it per piloting; validation studies of DAI; and implementation into NCS.

Insights from the NCS Neonatal Stem Cell Lab

Fury B[1] Kennedy G[1] O'Donnell K[1] Szabo S[2] Miller RK[3] Rinderknecht A[3] and Stodgell C[3] Pontow S[1] Walker C[1]

[1]University of California Davis, Sacramento, CA

[2]Medical College of Wisconsin, Milwaukee, WI

[3]University of Rochester, Rochester, NY

Introduction: We tested the influence of elapsed time from delivery and storage temperature on the resilience of neonatal stem cells. As these samples are meant to be included in a large-scale NCS research archive rather than a transplant bank, we began to explore alternative processing strategies aimed at reducing personnel effort and overall cost without compromising specimen integrity.

Methods: Cord blood, placenta, and umbilical cord were obtained from three sites. Paired external specimens were maintained at 4 and 20°C and[Q1] shipped to UCD for processing according to standardized procedures at 48/96 hr. Pre-pilot testing was performed with minimal processing and cryopreservation of heterogeneous cell populations including MSC.

Results: Contamination was common in vaginal birth placental samples, prompting an experiment of effects of antibiotic use on cell function. There were no differences in functional capacities that we tested of MSC grown in media enhanced with penicillin and streptomycin. We also recognized that tissue dissociation and prolonged culturing to obtain a homogenous population of MSC before cryopreservation, which commonly requires 3–4 weeks, might not be necessary. Preliminary results of minimal tissue

processing and cryopreservation at time points prior to passage 3 are promising. Comparisons of feasibility and cost savings for various methods will be presented.

Conclusions: Early experimentation with minimal processing and early cryopreservation suggest that simplified options for cell archiving should be explored in the pilot study. These changes would result in substantial savings to any plan for targeted or broad-scale cell archiving during the main phase of the NCS.

Optimizing blood collection tubes and timing for plasma processing to facilitate multicenter studies focused on cell-free DNA analysis

Hidestrand M[1] Deavers J[1] Goetsch MA[1] Simpson PM[1] Kuhlmann R[1] Sandoval N[2] Leuthner SR[1,2] Mitchell ME[1] and Tomita-Mitchell A[1]

[1]Medical College of Wisconsin, Milwaukee, WI

[2]National Children's Study Wisconsin Study Center, Waukesha, WI

Objective: To investigate the suitability of Streck Blood Collection Tubes (BCT) on cell-free DNA (cf-DNA) levels in plasma and establish a protocol for transporting blood samples prior to plasma processing.

Methods: To test robustness for downstream cf-DNA analysis of samples collected in BCT tubes blood was collected in EDTA and BCT tubes from pregnant women carrying male fetuses (number suppressed per NCS disclosure guidelines). One set of each tube from each subject was processed to plasma immediately (standard cf-DNA protocol) whereas the other set was shipped by air courier and then processed. Total and fetal DNA concentrations were measured by multiplexed quantitative real-time PCR. In addition, samples from National Children's Study (NCS) participants have been collected in BCT tubes and stored at room temperature for up to a week in order to facilitate weekly batch processing. These NCS samples were also analyzed for total cf-DNA. Fetal cf-DNA percentages are currently being evaluated.

Results: Total cf-DNA and fetal percentage determination from collection tube testing showed that BCT tubes can be used for sample collection at remote sites and subsequently shipped at room temperature without immediate need for plasma processing (Hidestrand et al. Fetal Diagnosis and Therapy, 2012). Total cf-DNA in samples collected for the NCS were measured and data are in agreement with previously published data.

Discussion: The ability to batch process would be a tremendous advantage for a multicenter study such as the NCS. BCT tubes are suitable for transporting whole blood prior to plasma processing and are being utilized in this NCS pilot formative project. However, care should be taken to ensure that samples are not exposed to extreme temperatures during transportation.

Reference:

Hidestrand M, Stokowski R, Song K, Oliphant A, Deavers J, Goetsch M, Simpson P, Kuhlmann R, Ames M, Mitchell M, Tomita-Mitchell A: **Influence of Temperature during Transportation on Cell-Free DNA Analysis.** Fetal Diagn Ther 2012;31: 122–128 (DOI: 10.1159/000335020)

Biospecimen Protocol: Lessons Learned from the Initial Phase of the NCS Vanguard Study

Merrill L[1] Layton M[1] Cagnina C[1] Todd D[1] Lawrence C[1] O'Brien B[1] and Moye J[2]

[1]Westat, Rockville, MD

[2] NCS Program Office, *Eunice Kennedy Shriver* National Institute for Child Health and Human Development, National Institutes for Health, Bethesda, MD

For the initial phase (Phase 0) of the NCS Vanguard Study, the Coordinating Center (CC) developed standard operating procedures for collection, processing, storage, and shipping of biospecimens including venous blood, hair, nails, saliva vaginal swabs and slides, urine, cord blood, placenta, meconium, dried blood spots, and breast milk. The CC trained and certified data collectors from seven Screening Centers (SCs) and monitored all biospecimen and related data collection activities. When problems were identified, the CC investigated causes and when appropriate, developed alternative procedures. Operational issues were documented to be evaluated in conjunction with the results of the analysis operational data and biospecimens to assess the acceptability and feasibility of Phase 0 NCS biospecimen measures. Response rates were determined for each biospecimen measure as an indicator of acceptability and feasibility. Laboratory test results were compared to normal reference ranges for selected biomarkers to evaluate quality and suitability of biospecimens and the technical performance of procedures.

A variety of valuable lessons were learned regarding operations at the SCs, the repository and the laboratories. (1) The cord blood collected in a bag with liquid CPD was not suitable for a variety of critical analysis. (2) The P100 tubes separators did not function properly upon centrifugation of the tubes according to manufacturer's instructions. (3) Saliva samples contained excessive amounts of particulate matter necessitating extensive cleaning prior to analysis. (4) The repository procedures for aliquotting breast milk introduced perchlorate contamination. (5) The standard procedure for shipping placentas was not adequate for all geographic locations and seasons.

SCs achieved high success (approximately 80–100%) in completion of sample collection for nearly all specimen types at all visits. Exceptions were 2-day saliva (66%), paternal hair (63%), and breast milk or formula (70%). The early results of laboratory analysis are encouraging. Three biomarkers of diabetes—glucose, hemoglobin A1c (HbA1c) and insulin, and two biomarkers of stress, ACTH and cortisol—were analyzed in pregnant women. A small percentage had elevated levels of serum glucose and HbA1c consistent with development of gestational diabetes in pregnancy. For serum insulin, 27% of NCS subjects had measured values above the reference range. For plasma ACTH, 26% of samples had values above the normal reference range for non-pregnant females, consistent with higher levels of ACTH found in pregnant women. Cortisol measured in saliva is expected to have elevated levels in morning samples, and low levels in evening samples. This was confirmed in the tested NCS subjects. The mean for morning and evening samples was 0.66 and 0.15 ng/ml, respectively. However, for both morning and evening samples, about half of the samples were above the normal reference range for non-pregnant levels consistent with expected higher levels in pregnant women.

Evaluation of Biological Specimen Protocols in the Vanguard Study (VS)

Mortensen ME[1] Caldwell KL[1] and Moye J[2]

[1]Division of Laboratory Sciences (DLS), National Center for Environmental Health, Centers for Disease Control and Prevention (CDC), Atlanta, GA

[2]NCS Program Office, *Eunice Kennedy Shriver* National Institute for Child Health and Human Development, National Institutes for Health, Bethesda, MD

Background: We evaluated biological specimen collection protocols and Repository processing by measuring a panel of environmental and nutritional analytes in samples collected by each VS center. Collection materials had been prescreened or evaluated by lab research staff and determined not to contain interfering substances that would contaminate the specimens. We planned to investigate anomalous results and use these findings to modify protocols, as appropriate. Analyte values were compared with U.S. population reference ranges from the National Health and Nutrition Examination Survey (NHANES).

Methods: Prenatal blood and urine, cord blood, and breast milk specimens collected from mothers and infants at each VS center and then shipped to the central Repository, were sent to the DLS at CDC. Specimens were collected and transported according to VS protocols. Pre-screened collection containers were used for blood and urine metals. Samples were collected using kits prepared by NCS and then shipped to the Repository where aliquots were prepared and frozen at −150°C according to protocols. Blood metals tubes and aliquots for specific analytes were shipped on dry ice to the DLS, where measurements were completed using analytical methods developed and used for the NHANES.

Results: Analytes included persistent and non-persistent chemicals, pesticides, and metals. Environmental chemical results in prenatal urine and serum generally were within reference ranges for U.S. females in NHANES. In breast milk specimens, 9% had detectable bisphenol A levels. Too few infant urine specimens were available for analysis because the timing coincided with an interruption of specimen collection in the VS. The collection method for cord blood rendered specimens unsuitable for analysis, and as a result, the protocol has been modified. Anomalous perchlorate results for several breast milk aliquots were investigated and determined to have resulted from inadvertent contamination by perchloric acid during the milk aliquotting process. Modifications have been made to the Repository's aliquotting procedure. Planned infant urine collection using diaper inserts or diapers was changed to use of adhesive collection bags after it was determined that diaper materials would contaminate urine with various chemicals, including perchlorate and bisphenol A.

Conclusions: Our approach provided actionable results for validating and improving biological specimen protocols, and it was an invaluable step prior to implementing protocols across additional study centers. Failure to conduct a limited feasibility study such as this could risk wasted efforts in specimen collection and unwitting introduction of external contaminants into specimens. Use of pre-screened collection containers for metals, and for other analytes, selecting collection containers that would not be a source of chemical contamination are essential planning activities prior to collecting biological specimens.

Genotype and Gene Expression Correlates in Human Placentas

Murray JC[1] Kim J[1] Busch TD[1] Xing Y[1] Zhao K[1] Rigdon J[1] Stodgell CJ[2] Salamone L[2] Penmetsa A[2] Miller RK[2] Walker CK[3] Pontow SE[3] and Szabo S[4]

[1]University of Iowa, NCS Polk County, Iowa City, IA

[2]University of Rochester, Rochester, NY

[3]University of California Davis, Sacramento, CA

[4]Medical College of Wisconsin, Milwaukee, WI

Introduction: The human placenta plays a critical role in the maintenance and parturition process of pregnancy. Genetic factors are known to play a role in many common diseases associated with pregnancy including preterm birth and preeclampsia. To develop a resource for understanding normal gene expression and its correlates with genotype and to investigate gene expression differences in pathological placenta states we have created a bank of placentas collected both with the NCS and locally.

Methods: We have conducted preliminary gene expression profiling on a global basis for term placentas in labor and no labor deliveries using RNA sequencing of amnion, chorion, and decidua. For NCS samples we did RT-PCR to assay gene expression and TaqMan assays for genotype determination.

Results: We studied eight SNPs in four preterm birth candidate genes (*PGR*, *OXTR*, *PLA2G4A*, *PTGER2*) for genotype and expression using placentas from the NCS prepilot study. Our work shows that gene expression in different placental tissues correlate better with each other than with other tissues and that there are unique tissue specific gene profiles associated with placental tissue.

Conclusions: Based upon the limited prepilot data set, the NCS collection should provide material that is robust for both genetic and gene expression studies. The outcomes of this work from the Pilot and Main Studies will be provided on publically accessible web sites and extended to additional tissue and gestational ages.

"My46," An Innovative Web-Based Tool for Management of Results Returned From Exome and Whole Genome Sequencing Studies

Tabor HK[1,2] Yu J[2] Civan A[2] Crouch J[1] Kuwana E[2] McMillan MJ[2] Stock J[1] Dent KM[3] Anderson N[2] Lakes K[4] Burke W[2] Murray J[5] Swanson J[4] and Bamshad M[2]

[1]Seattle Children's Hospital, Seattle, WA

[2]University of Washington, Seattle, WA

[3]University of Utah, Salt Lake City, UT

[4]University of California, Irvine, CA

[5]University of Iowa, Iowa City, IA

Introduction: Whole genome sequencing (WGS) has the potential to identify all variants that influence health-related traits and challenges existing approaches for return of results.

Methods: As a feasibility study for the NCS, we are developing "My46:" A web-based tool that allows research participants to manage return of results from WGS. We developed four modules: (1) "Learn the basics" about the genome, including an overview of possible results categories and their potential impact, (2) a tool for selecting preferences for return of results, (3) a platform for reporting results, and (4) an instrument for conducting surveys. The preferences tool allows choice of broad return of results categories: Disease(s), carrier status for recessive disorders, complex health-related traits, and medication responses. Participants

receive available results only in selected categories and can modify preferences at any time. Each module can be customized to fit a study's specific needs and population.

Results: We are presenting model pages and database structure for My46. Usability testing will proceed in the fall with non-NCS parents. Upon OMB approval, we will test My46 with parents of births in Orange County CA and Brooking County SD Vanguard Centers in the 100 trios WGS project.

Conclusions: "My46" provides participants secure access to their individual genetic results to review at their convenience and as they become available over time. "My46" also facilitates interaction with a genetic counselor via telephone or live streaming video. These features make "My46" an attractive tool for managing the return of individual research results in WGS studies.

Development of a Simple, Cost Effective Procedure for the Rapid Collection of Placental Tissue for High Throughput Screening Assay Studies

Savage DD[1] Rosenberg MJ[1] Gregory C[1] Bakhireva LN[1] Savich RD[1] and Annett RD[1]

[1]University of New Mexico, Albuquerque, NM

Introduction: Normal placental function is vitally important for fetal development and favorable neonatal outcomes. With proper collection and storage procedures, the placenta offers researchers the opportunity to study RNA, proteins, and other chemical species that could be important for understanding perinatal health and development, as well as pathological mechanisms. Currently, however, there is very limited practical information regarding optimal methods and timing for collecting human placental tissue for biochemical studies.

Methods: In the first study, placentas were collected immediately after a scheduled C-section. Each placenta was divided in half, with one half placed in room temperature buffered saline and the other half placed in ice-cold (4°C) buffered saline. Core biopsies of placental tissue were taken from each half over an 8-hr period, and assays performed to determine RNA integrity at each time point. In the second study, placentas were collected within 30 min after vaginal delivery and a tissue core sample collected and processed for RNA integrity. In addition, data collection forms captured factors that could potentially affect "placental health", including maternal characteristics (age, parity, gravidity), complications during pregnancy (gestational diabetes, preeclampsia, bleeding) and labor (duration of Stage II and Stage III labor, baby presentation, premature rupture of membranes).

Results: Placental RNA from a cesarean section procedure remains stable (defined as RNA Integrity Number (RIN) >8), for at least 1 hr in either room temperature or 4°C buffered saline. The RIN values at each time point over the first hour in the room temperature group were not significantly different than those in the 4°C temperature group. Further, the duration of Stage II and Stage III labor did not significantly affect RNA integrity in placental samples collected within 30 min after vaginal delivery.

Conclusions: We have developed the logistical and technical procedures to rapidly harvest core tissue samples of placenta for biochemical assay procedures. Placentas collected within 30 min of vaginal delivery provide RNA of sufficiently high quality to conduct functional genomic screening studies. We conclude that a variety of high throughput screening procedures can be conducted using placental tissue when samples can be collected and rapidly frozen in the first 30 min after delivery.

Facilitating Transition from Genetic to Genomic Medicine: Applications in Genomics, Epigenomics, and Ancestral Informative Markers (AIMs)

Swanson J[1] Flodman P[1] Lakes K[1] Wadhwa P[1] Baker D[1] Cooper D[1] Tycko B[2] Chambers C[3] Frazer K[3] Luderer U[4] Blackburn E[5] Faustman E[6] Vigoren E[6] Swanson W[6] Bamshad M[6] Burke W[6] Tabor H[7] Aagaard-Tillery K[8] Murray J[9] and Gutzman K[10]

[1]University of California, Irvine, CA
[2]Columbia University, New York, NY
[3]University of California, San Diego
[4]University of California, Irvine
[5]University of California, San Francisco, CA
[6]University of Washington, Seattle, WA
[7]Seattle Children's Hospital, Seattle, WA
[8]Baylor College of Medicine, Houston, TX
[9]University of Iowa, Iowa City, IA
[10]South Dakota State University, Brookings, SD

Introduction: In response to LOI3, five Study Centers developed a proposal to conduct feasibility studies related to RT 02 (Genomics and Epigenomics) and RT 05 (Ancestry and Genomics).

Methods: We studied the earliest phases of the NCS—conception, pregnancy, and birth. For RT-02, we proposed feasibility studies of pregnancy and birth. For RT-05, we proposed to evaluate AIMs as moderators of fecundability and infertility, as well as recruitment before pregnancy.

Results: While waiting for OMB approval, we prepared to implement our feasibility studies in multiple areas: (a) To evaluate placental epigenomes based histone modification using RNA sequencing, (b) allele specific methylation and expression to pinpoint regulatory SNPs and CNVs, and (c) gene expression in placenta and cord blood; (d) to conduct a genome wide association study (GWAS) of preterm birth and (e) a study of stress biology in pregnancy; (f) to develop a set of AIMs for use in EBHR location and (g) techniques to return results from WGS to characterize parent preferences, experiences, and concerns about genomics in the NCS; (h) to evaluate whether mismatch of sperm egg recognition molecules lowers the probability of successful in vitro fertilization and (i) novel genotypic variations modulate susceptibility to PAH reproductive toxicity and are associated with infertility.

Conclusions: Combining infrastructure of the NCS with infrastructure in established research laboratories, feasibility studies were formulated and are poised for implementation that will evaluate feasibility, acceptability, and cost of genomic and epigenomic applications in the NCs.

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