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Genomic Medicine for Reproductive, Prenatal, & Neonatal Health Workshop
April 16-17, 2018, Rockville, MD
Executive Summary

The purpose of this workshop was to explore genomic technology implementation; the ethical, legal, and social implications (ELSI) of genomics; and the implementation of medical genomics in the context of reproductive, prenatal, and neonatal health and disease. Leaders from diverse fields of study, including researchers, medical providers, bioinformaticians, ethicists, industry representatives, insurance providers, representatives from professional organizations, government stakeholders, and others attended. A series of keynote presentations on each of six topics were followed by two breakout sessions and a general discussion on the gaps, opportunities, challenges, and next steps in implementing genomics in these healthcare settings. These sessions sought to answer the questions, "Can we do it?", "Should we do it?", and "How do we implement it?" by exploring the current genomic technologies that are ready for implementation, the ELSI issues that arise with the implementation of genomic medicine, and the challenges to implementing genomic medicine in the reproductive, prenatal, and neonatal periods.

Next steps, recommendations, and future research opportunities for the implementation of reproductive, prenatal, and neonatal genomics include:

Technology Implementation:

- Consider artificial intelligence (AI) approaches for variant calling and classification, deep phenotyping, and clinical decision support
- Address knowledge gaps by developing specific curation groups for the reproductive, prenatal, and neonatal time periods in the Clinical Genome Resource (ClinGen)
- Reconsider a genotype-tissue expression project (GTEx) for neonates, children, and prenatal stages of gestation, including the placenta
- Include longitudinal studies across the lifespan to best assess health outcomes
    - Standardize technologies as part of routine clinical care to allow assessment of long-term health outcomes
- Consider parent-associated ELSI issues when addressing electronic health record (EHR) technology implementation
- Facilitate transfer of EHR information from prenatal to newborn, including parents
- Support data sharing and dissemination
- Support more efficient and comprehensive phenotype harvesting using AI

Ethical, Legal, and Social Implications:

- Examine possible barriers and develop strategies to ensure equal access to sequencing technologies, genomic medicine, and insurance coverage for reproductive health care
- Address privacy and stewardship questions, especially in relation to newborn screening programs
- Develop research and healthcare approaches that recognize and address the interconnected reproductive continuum from preconception through the neonatal period to adulthood
- Examine and develop strategies to address the challenges faced by healthcare professionals providing genomic-based reproductive services

- Partner with the broader community, families, the public health enterprise, and healthcare providers in the design and implementation of research projects
- Engage with and develop culturally appropriate education materials and decision aids for patients, especially those from diverse populations.
- Develop and validate outcome measures for preconception, prenatal and neonatal contexts and examine barriers to behavioral change
- Develop new or refine existing psycho-social, conceptual and analytical research methods and measures for preconception, prenatal and neonatal populations
- Develop and validate new and innovative tools for engagement, consent, education, and health decision making (e.g., iPad or online apps)
- Assess individual, family and population impact through longitudinal studies
- Examine consequences of maternal or paternal incidental findings discovered through prenatal testing
- Clarify the meanings of utility, actionability, and benefit

Implementation of Genomics in Healthcare:

- Investigate and develop animal models that may inform clinical issues
- Improve the quality and value of phenotypic information that is provided, especially as the phenotypes may evolve over time from the prenatal to neonatal, childhood and adulthood periods
- Pursue potential models for public-private partnerships and/or international collaborations that would allow for cost-effective and equitable, standardized approaches for integration of genomics into healthcare
- Improve genotype-phenotype correlations in prenatal health
- Standardize the approach to sequencing in the newborn screening context to allow for longitudinal follow-ups of clinical outcomes
- Ensure a learning health record over the lifespan (as it relates to genomic information)
- Integrate electronic health data across time periods and facilitate linkages of maternal, prenatal, and neonatal health records
- Develop cost-effective implementation strategies for the use of genomic technologies as diagnostics in the neonatal intensive care unit setting
- Understand “true” recurrence risk
- Standardize screening options and access to implement genomics in healthcare

Reproductive Genomics:

- Use existing and well-annotated clinical cohorts for sample acquisition to expand opportunities for research
- Use phenome-wide association studies (PheWAS) to look at co-morbidities and sub-phenotyping
- Collect long-term follow-up data of assistive reproductive technologies (ART), including transgenerational studies
- Increase amount and value of baseline data on reproductive populations, including data that will predict fertility
- Assess impact of aging as well as time and associated environmental impacts on reproduction
- Investigate the origin of *de novo* mutations and gonadal mosaicism in germ cells
- Develop non-invasive genetic biomarkers
- Improve single cell genetic diagnostic capability

- Explore the genomics of reproductive health as a predicter of adult health
- Create ClinGen expert curation panels for infertility, fetal loss, and other reproductive issues

Prenatal Genomics:

- Validate the role of genomic sequencing approaches for fetal DNA by comparing exome and genome sequencing in samples obtained from maternal blood, chorionic villus sampling (CVS), and amniotic fluid.
- Consider public engagement to explore the value of prenatal genomics testing and return of results to patients and the medical community
- Establish longitudinal collection of genotypes and phenotypes across pregnancy
- Explore the "intolerome"—genes that are critical to human development and in which mutations are not compatible with survival to birth—as a source of gene discovery
- Include comprehensive, longitudinal multi-omics approaches of maternal and fetal health during pregnancy
- Utilize existing infrastructures, such as ClinGen, the Environmental influences on Child Health Outcomes (ECHO) program, and the PregSource™ pregnancy registry
- Consider potential to integrate data into and from the *All of Us* master plan
- Consider the lifespan perspective and Barker hypothesis: reproductive, prenatal and neonatal 'omics as predictors of later health and disease
- Engage with industry for improved and more thoughtful implementation of genomics during the prenatal period.

Neonatal Genomics:

- Expand research in RNA-sequencing, epigenomics, pharmacogenomics, and the microbiome to enhance currently available genomics technologies
- Educate the public on the benefits of genetic screening and genomics technologies while engaging stakeholders from all sectors: industry, advocacy groups, insurers, healthcare providers
- Enhance registries with long-term follow-up data on outcomes for ill and healthy newborns identified with genomic variants that impact immediate health or may have long-term health implications
- Explore partnerships with commercial entities and health care systems to leverage available information on genomic health from birth throughout the lifespan
- Evaluate the role of next-generation sequencing (NGS) on health outcomes at the level analogous to the UK 100K population size
- Characterize the evolution of phenotypes that may change and develop from the prenatal to the neonatal period, and beyond
- Develop a process for prenatal consent and rapid prenatal testing (biochemical and/or genomic) or immediate neonatal NGS testing for prenatally-identified anomalies with implications for the health of the newborn
- Develop an expert curation panel for newborn screening that characterizes the clinical utility of genomic variants for newborn screening conditions
- Develop a pipeline for implementation of genomics in the neonatal intensive care setting that considers the economic and health benefits of these technologies