

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

**Welcome- Dr. Diana Bianchi and Dr. Eric Green**

Dr. Bianchi, Director, *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD), and Dr. Green, Director, National Human Genome Research Institute (NHGRI), welcomed participants and provided overviews of their respective institutes.

Dr. Bianchi noted that NICHD funds 18% of the child health research across the National Institutes of Health (NIH), though that comprises 55% of NICHD's budget. Most of NICHD's remaining budget is focused on reproductive health, including pregnancy. Although NICHD has a significant investment in prenatal genomics, most of the institute's grants are focused on research in epigenomics or the biology of healthy pregnancy, rather than the implementation of genomics in healthcare.

Dr. Green discussed NHGRI's characteristic features as a relatively young Institute, representing 1.5% of the NIH budget with an emphasis on Team Science, rapid dissemination, societal/bioethics research, and a vibrant intramural research program. NHGRI's overarching goal is advancing genomics research and the Institute's role is to define and execute steps toward that goal. NICHD and NHGRI are both entering strategic planning processes and are eager to incorporate feedback from research communities about scientific priorities.

The purpose of this workshop was to explore reproductive, prenatal, and neonatal genomics while discussing technology implementation, ethical, legal, and social implications (ELSI), and the implementation of genomics in healthcare. The questions "Can we do it?"; "Should we do it?"; and "How do we implement it?" were addressed 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 healthcare setting.

**Session 1: Reproductive Genomics- Presentation by David Keefe, Discussion Moderated by Lisa Halvorson**

Preimplantation genetic testing (PGT) is the process by which one or more cells are biopsied from an embryo and screened to aid in the selection of embryos with normal chromosome number (euploid) for transfer into the uterus and to avoid transfer of embryos with an abnormal chromosome number (aneuploid) or other genetic abnormalities that would result in *in vitro* fertilization failure or miscarriage. PGT can be divided into preimplantation genetic diagnosis (PGD), which is used to test for monogenic or single gene defects (now called PGT-M), and preimplantation genetic screening (PGS) which tests for aneuploidy and translocations (now called PGT-A). Preimplantation genetic screening (PGS) has evolved from using Fluorescent *In Situ* Hybridization (FISH) techniques to detect meiotic aneuploidies in polar body biopsies to less invasive comprehensive chromosome screening by array comparative genomic hybridization (aCGH) or next generation sequencing (NGS) in trophoctoderm biopsies. The next generation of screening is moving towards non-invasive screening of early embryos—blastocysts—via analysis of cell-free embryonic DNA obtained from culture medium surrounding embryos.

The Single Embryo Transfer of Euploid Embryo (STAR) Trial was a randomized controlled trial evaluating the effectiveness of PGS using NGS in trophectoderm biopsies to optimize euploid embryo selection for elective single embryo transfer. The primary outcome of this trial was ongoing pregnancy at 20 weeks post embryo transfer by comparing PGS/NGS in the experimental arm versus standard embryo selection through morphological analysis in controls. 650 subjects were randomized in both arms of the trial. The only significant difference in ongoing pregnancy rates between the two arms was seen in 35-40-year old women, and found an improvement in pregnancy rates from 37% to 51% in the control and PGS arms, respectively. The STAR Trial miscarriage rates were surprisingly low. Therefore, PGS in trophectoderm biopsies has the potential to significantly improve successful pregnancies in 35-40-year old women who undergo *in vitro* fertilization.

The urgent clinical questions about PGS include – will studies following intention to treat analysis show benefit? How do we interpret results from multicenter trials given high levels of heterogeneity in patient populations? How do we deal with mosaic embryos? Why do nearly half of euploid embryo transfers still fail to result in viable pregnancies? There are also questions about embryonic mosaicism, where the embryo is composed of both euploid and aneuploid cells, and whether NGS is reliable and accurate in detecting aneuploidy in these embryos. A study found 97% concordance for aneuploidy between the trophectoderm and the embryo, bolstering the confidence that PGS testing in trophectoderm is very reliable. This would support the idea that embryonic mosaicism is partly biological, and not a technological artifact.

Testing for mosaicism in embryos can result in a high false positive rate, potentially resulting in viable embryos not being transferred. However, in many cases, mosaic embryos result in viable, ostensibly normal offspring. This information can be used to counsel on the relative advantage or disadvantage of transferring mosaic embryos, especially when the mosaicism could result in a viable aneuploidy.

In summary, PGS was previously thought to provide a binary output of either euploid or aneuploid, but with increased sensitivity associated with NGS, PGS now detects more subtle abnormalities and mosaicism, including copy number variants, that fall within a continuum that may indicate risk factors for the fetus. More studies are needed to understand the fate and impact of embryonic mosaicism on fetal and neonatal development.

The future development of non-invasive PGS of DNA fragments from embryonic culture medium is an exciting concept, especially as questions still remain about the safety of embryo biopsy. There are still many questions to answer about this approach: how are cell fragments getting through the zona, will this approach exacerbate mosaicism questions, and will it prove to be a more sensitive but less specific test?

Are we misinforming patients by calling current PGS testing ‘embryo biopsies’ since we screen the trophectoderm and not the inner cell mass which becomes the embryo? Does it matter where the biopsy takes place within the 3D structure of the trophectoderm, and in turn are we oversimplifying the trophectoderm? These and other questions remain to be answered.

## **Session 2: Prenatal Genomics- Presentation by Mary Norton, Discussion Moderated by Uma Reddy**

3 million women undergo prenatal genetic testing each year. The rapid uptake of cell-free DNA screening suggests that women will continue to desire the next best prenatal genetic test, which is

genome sequencing as a prenatal screening tool. The question is not *whether* prenatal noninvasive genome sequencing should be performed, but *how* to optimally implement it. To do this, rigorous evidence regarding outcomes needs to be collected, with careful attention paid to avoiding ascertainment bias as best as possible.

Cell-free 'fetal' DNA is a byproduct of trophoblast turnover and apoptosis that is found in maternal blood. Bioinformatics analysis parses out the maternal and fetal genomes and calculates a fetal fraction (the ratio of cell-free fetal DNA to maternal DNA). The fetal fraction is an important quality metric of prenatal screening; with larger fetal fractions leading to more accurate test results. There can also be large variations in fetal fractions. This variation is found over gestational age, in cases with fetal abnormalities, and it varies some with maternal characteristics such as obesity. Fetal fraction is relatively stable during the first and second trimesters and increases afterwards, going up faster in women who deliver preterm. Variation in fetal fraction is not completely understood, and it could potentially reflect placental function/health. Cell-free fetal DNA analysis may also reveal issues when there are maternal secondary findings, such as copy number variations (CNVs) and malignancies in the mother, both of which can affect the outcome of the pregnancy. Although the American College of Medical Genetics and Genomics (ACMG) has recommendations for reporting secondary findings for a specific list of 59 genes that are thought to be actionable, these don't address prenatal sequencing or fetal sequencing, and clinicians are not sure how to manage these cases.

Prenatal diagnosis has largely relied on ultrasound examination and karyotyping to identify congenital anomalies in addition to those associated with Down syndrome. More recently, introduction of fetal magnetic resonance imaging and chromosome microarray technologies have been introduced. Despite its increased resolution to detect microdeletions and microduplications, chromosomal microarray (CMA) testing has had a slow uptake in the clinic. This is mainly due to issues with insurance coverage and concerns about the clinical meaning of variants of uncertain significance.

With regard to carrier screening, ethnicity-based screening has moved to multiplex panel screening and universal screening, which are cheaper and can screen for hundreds of disorders at once. However, there are questions about the criteria by which labs are including variants on a panel: only 27% of commercially available panels include disorders that meet ACMG criteria.

Prenatal exome sequencing appears to be the next major technology to be potentially used for prenatal testing. However, so far there is a wide range of reported diagnostic yields (6.2%-80%). As there are medical therapies that can be better applied antenatally or in the immediate neonatal period if a fetal diagnosis is made, it should be made clear that prenatal testing goes beyond considerations of pregnancy termination. There is a need for further technological development to optimize outcomes in the prenatal period.

The mechanism of where cell-free fetal DNA comes from is becoming increasingly important. It's clear that this DNA comes from trophoblast cells and can be detected as early as 7 weeks after implantation. It is possible for animal models to be used to trace the origin of these cells during this process. Because ascertainment bias is present in prenatal diagnosis, the prognosis for a prenatal diagnosis based on genomic findings cannot be extrapolated from postnatal data.

Studying clinical utility for prenatal tests is very important. This research may benefit from partnerships with industry. It's also important to understand the clinical utility from the patient's perspective. The rapid uptake of cell-free DNA screening indicates that noninvasive exome or genome sequencing will be

highly desired by women, and it is important to understand how to optimally implement this genetic testing when it becomes more widely available.

### **Session 3: Neonatal Genomics- Presentation by Jonathan Berg, Discussion Moderated by Melissa Parisi**

Timing and context are key when discussing neonatal genomics, as diagnosis/prognosis/management imply a disease process is present and that there is a substantial probability of the disease having a genetic etiology, whereas screening/prevention imply an individual is not affected and the probability of disease is the same as in the general population. Based on context, the same technology and molecular tools can be used to provide a diagnosis (e.g., in sick newborns in the neonatal intensive care unit (NICU)), or to predict the likelihood of disease in the future (e.g., in healthy infants). Timing is also important to think about in neonatal genomics: when are some of these conditions likely to manifest during the neonatal period, and when do we need to know about them? Clinical utility can be defined broadly as “any use of test results to inform clinical decision-making” or “any outcomes considered important to individuals and families.” Clinical utility requires both measured outcomes and a net benefit. Early indications of clinical utility may include ending the diagnostic odyssey, stratifying patients by prognosis, and increasing the number of conditions with promising medications or available clinical trials. There is a lot of evidence for the effectiveness of genomic medicine, but we have not organized it and presented it well to evidence reviewers. We need to have better ways of communicating the evidence we have, such as the Population, Intervention, Comparison, Outcomes, Timing, and Setting (PICOTS) Framework, which is essential for evidence generation and communication.

The current practice in medical genetics is reactive (i.e. waiting for a sick individual to present for medical care, then testing family members by cascade), whereas genomic medicine should be proactive by identifying at-risk individuals in the population and managing their healthcare before the disease develops (i.e. screening). The point then becomes: “At what point in time are you identifying these individuals, and at what point in time can you act?” An example would be the current practice of screening newborns for a universally recommended set of genetic diseases. There’s both a major potential and major challenge in using genomic medicine in newborn screening, and this was the key question that drove the Newborn Sequencing In Genomic medicine and public Health (NSIGHT) consortium funded by NHGRI and NICHD.

Challenges to the North Carolina Newborn Exome Sequencing for Universal Screening (NC NEXUS) pilot within the NSIGHT consortium were identified: prediction is much harder than diagnosis, informed decision making is critical, and there is a serious potential to overwhelm patients and physicians with genomic information of uncertain clinical value. Other questions remain about whom should be screened when and for what, who should pay for screening, who should be responsible for follow-up, and how the interpretation and potential re-interpretation should be done. Using genomic sequencing as a screening method also has the potential for over-diagnosis since variant pathogenicity is non-quantitative and is often based on probabilities, which can lead to the overuse of further tests and treatments. Over-diagnosis in genomic medicine can occur, for example, when a person is labeled with a condition that may never cause them harm, because there is a low prior probability of disease in the general population, confirmatory testing may be lacking, and there are issues with incomplete penetrance and variable expressivity. Population screening may require weighing thresholds on a condition-by-condition basis to balance benefits and harms. There are opportunities in neonatal genomic medicine to articulate clear outcomes that are studied systematically, which will minimize bias

and confounding. Diagnostic yield, clinical outcomes, and patient/family outcomes are all outcomes that can be closely studied through neonatal genomics.

Complex diseases affecting newborns can cause providers to make decisions with incomplete evidence. To help avoid this, it would be useful to implement the PICOTS Framework to identify specific research questions for testing.

In addition, those who self-refer for screening tend to have higher disease risk than the general population, since they are often requesting screening due to family history. Considering pharmacogenomics in the newborn period may also be useful in determining the utility of medications used in neonates.

Screening during the prenatal period will inform many aspects of care in the neonatal period. However, lack of communication between prenatal and neonatal providers can hinder early treatment or disease management. Prenatal diagnosis is sometimes seen as a technique to terminate pregnancies, though it is often about providing better care for the child.

When considering returning every variant back to patients, it's important to consider the shift from variants of unknown significance (VUS) and other qualitative measures, to quantitative measures. This will allow for better guidance to patients on risk and level of risk in the future.

Since technology is advancing at such a rapid rate, it will be important to be able to systematically go back to patients as the knowledge base builds. Variants will need to be reviewed and determinations about when to re-approach patients will need to be made. This type of learning healthcare system will help to increase diagnosis and management of disorders identified in the newborn period or earlier.

#### **Session 4: Technology Implementation- Presentation by Stephen Kingsmore, Discussion Moderated by Jyoti Dayal**

'Omic technologies are part of an integrated and evolving data platform that involves implementation science, precision medicine, and the learning health care system. Artificial intelligence (AI) may be the next critical step in precision medicine, and together with implementation of electronic clinical decision support tools, AI will improve health outcomes and decrease healthcare costs. It is anticipated that the cost of a 30X genome sequencing will be \$500 by 2020, not including analytic costs, and by 2020, a 12-hour clinical genome may be possible. We are already approaching these targets of technology efficiency.

There is extreme heterogeneity in studies of the diagnostic rate of exome sequencing, genome sequencing, and CMA in symptomatic infants. However, meta-analyses show that CMA in general has a lower diagnostic rate than exome and genome sequencing, while exome and genome sequencing have comparable rates of diagnosis. As genomic sequencing technologies have improved, the diagnostic rates for these approaches have increased over time. The rate of diagnosis associated with *de novo* (not inherited) variants increases as the rate of consanguinity decreases. Finally, the rate of diagnosis increases with the depth of phenotypic information available for infants. One recent development to improve phenotyping is the use of clinical natural language processing (NLP) to extract phenotypic terms from the unstructured electronic health records (EHR). The use of NLP increases the number of phenotypes over those using standardized approaches, such as manual extraction or Online Mendelian Inheritance in Man (OMIM) terms from the EHR, and thereby improves the likelihood of making a

provisional diagnosis by filtering against all the potential disease-causing genomic variants identified. Thus, using AI as a supplemental analytic tool can help lab directors make an efficient and potentially life-saving diagnosis.

One research question is whether the paradigm for testing of a proband should be singleton or trio. Based on meta-analysis, there is evidence in favor of trio testing, but additional studies are required. Preliminary studies show that rapid genome sequencing decreases infant morbidity and cost of hospitalization for symptomatic newborns.

#### **Session 5: Ethical, Legal, and Social Implications- Presentation by Ruth Farrell, Discussion Moderated by Joy Boyer**

Researchers, clinicians, and patients should think about the promise of genomic medicine, not just the perils, when considering the ELSI of genomics. ELSI issues are complex and interconnected across all life stages, including preconception, preimplantation, prenatal, newborn, and adult. Researchers and clinicians should not think in terms of reproductive, prenatal, and neonatal silos because they are all interconnected, especially over the course of one's life.

Informed decision-making is at the center of implementation and translation. The patient perspective is critically important because it helps identify points of confusion. For rapidly emerging prenatal testing technologies, researchers should consider what ELSI issues have stayed the same and what ELSI issues have changed, such as the volume, nature, and complexity of the information the tests provide. Access issues, including availability of testing and costs to the patient, are critical. The drivers of technology that change ELSI issues, for example, direct-to-consumer testing and the internet, change how patients interact with their genomic information. Law and policy are the external bounds to action because they affect both the administration of healthcare and clinical practice guidelines. In addition, changes in medicine are intertwined with changes in society.

In general, innovative and systematic approaches are needed to tackle the complexity associated with the ELSI of genomics in the reproductive, prenatal, and neonatal timeframe. A lifespan approach is critical given the interconnected relationships between the different time periods of life. Moreover, genomics should consider ways to leverage decision science to help investigate these complex issues. It is important to expand the moral debate beyond embryos, fetuses, and newborns, and consider women and their families. The technology exists today, so the conversation should shift to how society can best adapt.

#### **Session 6: Implementation of Genomics in Healthcare- Presentation by Heidi Rehm, Discussion Moderated by Anastasia Wise**

NHGRI-funded genomic medicine programs around implementation include the Clinical Sequencing Evidence-Generating Research (CSER) Program, the NSIGHT program, and the Electronic MEDical Records and GENomics (eMERGE) Network. The BabySeq Project, part of the NSIGHT program, examines the clinical utility of genomic sequencing in newborns, across dimensions of medical, behavioral, and economic analyses. This project is randomizing both well newborns and infants in the NICU to either standard of care newborn screening plus family history or standard of care/family history in addition to a genomic report with indication-based analysis that is disclosed to parents and pediatricians. Recruitment and enrollment into both arms of the study has been challenging, in part because of initial logistic difficulties in engaging busy and overwhelmed parents of newborn infants. Once families

engaged in an enrollment session with a genetic counselor, reasons to decline participation in the study included concerns about insurance discrimination, loss of privacy, and fear of unfavorable results. As genomics moves into routine practice, there may be fewer logistical barriers to enrollment, but these sorts of ELSI-related concerns should continue to be discussed. Unanticipated findings are a big barrier to introducing genomics into the practice of medicine, and should be tackled as a fundamental challenge. Careful consideration of what is being reported and why will continue to be important to implementation of genomics in practice, as there are implications for at-risk family members or those with similar phenotypes.

Management of carrier status and longitudinal follow-up is an area of interest in these projects. In the BabySeq project, there was an average of 2 recessive variants identified in each infant, with a range of 0-7. In some cases, this information led to parents being identified as carriers and subsequent pursuit of PGD for future pregnancies.

Researchers should also consider the healthcare-associated and family-associated costs of genomic sequencing. If a genomic variant indicates a risk of developing a later-onset condition such as cardiomyopathy, there are medical costs associated with referral to specialists, periodic cardiac assessments such as echocardiogram and electrocardiogram, and treatment with prophylactic medications. The key question is whether incremental costs required for genomic sequencing are justified by the health benefits. Researchers should consider how to keep all clinicians and patients up-to-date with changing variant classifications. One potential solution is an open-source EHR application that links genetic data sources with the ClinVar database and provides alerts to physicians and patients when classification of a variant has changed.

### **Technology Implementation Breakout Report- Presentation by David Ledbetter and Liz Worthey, Discussion Moderated by Jyoti Dayal**

The group created a table summarizing the current genomic technologies ready for implementation. Technologies included: genome sequencing, and single nucleotide variants (SNVs), structural variants (SVs), single-cell genome sequencing, aneuploidy panels, ribonucleic acid sequencing (RNAseq), CMA, karyomapping, methylation, metabolomics, and long-read sequencing. Clinical implementation categories included: embryo, reproductive (mother, father), prenatal (cell-free, amniocentesis), and neonatal. Many genomic sequencing technologies are available and ready for clinical use, but a host of additional technologies are required for data interpretation. In addition, there is a gap in communication among the reproductive, prenatal, and neonatal fields, and there are few mechanisms in EHRs to transfer information between them. The continuum among reproductive, prenatal, and neonatal health should be addressed in any future research efforts.

The group discussed that it is critical to gather and share phenotypic and genomic datasets, but the most important technology to address is around clinical decision support. While AI technologies exist, there is a need to educate people on how to use the data. There was also a call to treat the prenatal and neonatal period as a continuum, eliminating birth as a sharp demarcation between prenatal health and neonatal health. This is important, as early diagnosis prior to birth may optimize health outcomes. In addition, there needs to be a medical record for the future individual that spans the continuum between the fetal and neonatal periods.

Additional thoughts critical to the field include supporting development of novel informatics, data sharing/dissemination for phenotype and genotype data, and developing appropriate clinical decision

support tools for EHR integration. Support for better and more comprehensive phenotyping harvesting was also discussed. It is also important to encourage payers to contribute to the development and implementation of technologies and to improve the translation of knowledge gained among periods of health in the reproductive, prenatal, neonatal, and beyond time frames.

*All of Us* could be a potential research platform for information on long-term outcomes. Additionally, NIH data resources such as GenBank and PubMed could be leveraged. For reproductive health, there is a critical knowledge gap in genomics of fertility and infertility. One solution could be a Working Group for infertility in the Clinical Genome Resource (ClinGen) curation model. For prenatal health, there is a reluctance to undertake testing that is different from that in reproductive and neonatal health. Non-invasive prenatal screening sensitivity is high, but there are gaps in understanding the underlying biology. Cell-free technologies are replacing amniocentesis and chorionic villus sampling (CVS), and patients' consents are changing depending on the test.

There is a gap in decision-making science, and patients are making prenatal healthcare decisions based on screening tests, not diagnostic tests. For neonatal health, genomic sequencing technologies are ready to implement for critically ill infants. Certain newborn screening (NBS) disorders could be screened for prenatally so the appropriate care could be provided in the first 24-48 hours after birth. However, phenotypic and genotypic correlation is more challenging for the prenatal period. Longitudinal studies are needed to best assess health outcomes.

#### **Ethical, Legal, and Social Implications Breakout Report- Presentation by Jeff Botkin and Josephine Johnston, Discussion Moderated by Joy Boyer**

Many issues are cross-cutting, and it is difficult to silo issues into specific domains of healthcare. It is important to understand both the benefits and risks of genetic testing. The positive impact of genomic sequencing should be maximized while recognizing its implications. Patient education and engagement is critical, especially engagement of diverse participants. Researchers should consider how the risks and benefits may vary by population. There is a need to develop innovative tools (e.g., iPad or online apps) for informed consent. Equal access to genomic sequencing technologies and insurance coverage are critical issues. There is a need to develop and validate outcome measures for prenatal and neonatal contexts as adult measures may not be appropriate. Researchers should consider how to bridge the gap between diagnostic and preventative medicine. Partnerships between the broader community, families, the public health enterprise, and educators should be built at the beginning of research projects.

For reproductive health, there are additional issues in evidence-based practice due to limited federal funding and oversight, and implications of potential gene editing in gametes. For prenatal health, the use of trios can reveal familial relationships and implications that have not been anticipated nor thoroughly explored. Detection of later- and adult-onset disorders can also be problematic. For neonatal health, there are consent issues for the parents, child, and potentially the adult child with age. Privacy and stewardship questions should be considered, especially in relation to NBS programs. There are also opportunities for and barriers to behavior change based on genomic results.

Researchers should consider how to approach non-disclosure and reinterpretation of genomic results. Many emerging questions are practical and immediate rather than conceptual because the technology is already in clinical use.

## **Implementation of Genomics in Healthcare Breakout Report- Presentation by Wendy Chung and Brendan Lee, Discussion Moderated by Anastasia Wise**

There are many challenges to implementing genomic medicine. In general, these include: financial considerations, clinical utility, interpretation of testing, point-of-care delivery of information, access to and sharing of genomic information, and limitations of phenotyping and longitudinal follow up.

Some of the challenges to implementing genomic medicine in reproductive health are lack of equitable access to assisted reproductive technologies (ART), the lack of standardization of what is being tested and when, and how it is reported. To overcome some of these challenges, it would be useful to investigate animal models that may inform clinical issues that are difficult to assess currently in humans. Improving the phenotypic information that is provided to the clinical laboratory will allow for discovery of a broader genotypic basis of phenotypic variability. To effectively implement genomic medicine in reproductive health, it may be necessary to pursue models for public-private partnerships.

Challenges in implementing genomic medicine in prenatal health include: limitations in phenotyping, difficulty in interpreting the impact of variants in the prenatal vs. postnatal periods, changing perceptions of the potential outcomes of prenatal testing, and lack of longitudinal follow-up. These challenges could be addressed by improving communication about the impact of clinical management decisions in the prenatal period, improving genotype-phenotype correlations, understanding the impact of prenatal genomic information on postnatal parental-child bonding, addressing the translation of prenatal to postnatal phenotypes, and understanding the potential for cell-based technologies.

Implementing genomic medicine in neonatal health is limited by long turn-around-times and the need for Sanger confirmation. Longitudinal follow-up of clinical outcomes and health economics are also challenges that must be addressed. These obstacles could be mitigated by standardizing the approach to genomic sequencing for newborn screening, ensuring a learning health record over the lifespan (as it relates to genomic information), investigating new technologies to elucidate modifiers and improve interpretation of genomic variants, and applying genomic technologies to diagnostics in the NICU setting.

## **Summary and Next Steps Day 1- Presentation by Jyoti Dayal, Joy Boyer, and Anastasia Wise**

Genomic sequencing technologies exist and are generally ready for implementation in reproductive, prenatal, and neonatal health. The next steps for technology implementation include the use of AI to educate clinicians and patients on how to use data, implementation of clinical decision support tools, transfer of EHR from prenatal to newborn, support for data sharing and dissemination, support for more efficient and comprehensive phenotype harvesting, and standardization of technologies as part of routine clinical care to allow assessment of long-term outcomes. Additionally, there is a lack of standardization in technology workflows, so assessing the impact of pipeline differences is needed.

ELSI issues are complex and cross-cutting. New technologies are rapidly being adopted in reproductive settings—both within the healthcare system and through direct-to-consumer services. Research is needed that focuses on what can be done to ensure these technologies are applied safely and effectively and in ways that benefit all members of society. Education, engagement, and stakeholder partnerships are important. Concerns about equal access must be addressed. Next steps include clarifying the meanings of utility, actionability, and benefit for stakeholders; exploring challenges faced by reproductive healthcare providers; developing new research methods and measures for preconception, prenatal and neonatal populations; examining barriers to behavioral change; and

developing and validating new tools for consent, education, decision-making and engagement. Additionally, longitudinal studies are needed to assess family impact.

There is a pressing need for enhanced genomic literacy and education, but NHGRI and NICHD have educational efforts that are somewhat separate from their research and training objectives. NICHD and NHGRI leadership will look at what other NIH Institutes have done regarding education in the past 5-10 years.

For implementation of genomics in healthcare, researchers should investigate animal models to inform reproductive clinical genomics; investigate new technologies to elucidate modifiers, improve genotype-phenotype correlations, and improve interpretation of genomic variants; ensure a learning health record; integrate data across time periods; understand “true” recurrence risk in families; examine the application of genomics to diagnostic clinical settings; standardize screening options and access; and pursue potential models for public-private partnerships and/or international collaborations. Overall, the technologies exist, but there are access inequalities that need to be addressed. Barriers between medical records before and after birth should be removed. Access and sharing of genomic information inside and outside of the health system is critical. Longitudinal follow-up is needed to examine long-term outcomes.

**Reproductive Genomics Breakout Report- Presentation by Donald Conrad and Linda Giudice, Discussion Moderated by Lisa Halvorson**

There are many gaps in reproductive genomics, and they span areas such as understanding the unexplained causes of male and female infertility, the monogenic causes of infertility and reproductive disorders, the genetic causes of hypothalamic dysfunction, and the genetic basis of reproductive dysfunction that represents complex traits. There is limited use of carrier testing in evaluation of infertility and limited data on the optimal use of carrier screening in the general population, and there is little research on pharmacogenomic responses to reproductive drugs, deep phenotyping for impaired fertility, and computational methods to understand genomic contributions to miscarriage aside from aneuploidy analysis. Additional areas of need include understanding of the genetic basis of pubertal development, common and uncommon female reproductive and gynecologic disorders, the genomics of hypothalamic-pituitary-gonadal axis and pubertal development, and a comprehensive genetic roadmap of reproductive cell types. An interesting area with great potential to understand overall health is the ability to study genetic causes that impact fertility status as a window into co-morbidities in adulthood. The fundamental biology of germ cell mutations is poorly understood, and deep sequencing of gametes and single-cell analysis could reveal some of these mechanisms. Finally, the role of the microbiome and other environmental factors that impact fertility and the success of reproductive technologies remain to be explored.

To address these gaps, the challenge is to take basic science discoveries and apply them in a clinical setting. In the field of reproductive genomics, there is a need to create reference standards for genomics and transcriptomics in reproductive tissues, which can in turn improve the genotypic and phenotypic classification of disease. ELSI gaps include disparities in access to fertility evaluations and treatments, and the psychological contributions to subfertility and infertility are under-explored.

Next steps could include using existing and well-annotated clinical cohorts for sample acquisition, development of interpretive methods to assess predictability of genomic assessments and success of reproductive technologies, phenome-wide association studies (PheWAS) to look at co-morbidities and

sub-phenotyping, and long-term follow-up of ART, including transgenerational studies. A ClinGen expert curation panel for infertility could explore some of the genomic contributions to reproductive function and dysfunction. Generally, there are a lack of non-invasive biomarkers of fertility across the lifespan and their relevance to adult health, and a need for fundamental genomic information related to reproductive health.

**Prenatal Genomics Breakout Report- Presentation by Anthony Gregg and Ronald Wapner, Discussion Moderated by Uma Reddy**

While the technology for exome and genome sequencing exists, there are challenges in the application of genomic sequencing in prenatal genomics, such as establishing a stepwise approach to validate genome sequencing, and comparing exome/genome sequencing results using maternal cell-free DNA, chorionic villus sampling (CVS), and amniocentesis. For the patients, understanding the information and what they can expect from these results is another challenge. Longitudinal studies collecting genotypes, phenotypes and 'omics data across the entire length of pregnancy would also benefit prenatal genomics.

Prenatal studies should be conducted for gene discovery and to determine the 'intolerome', which comprises genes critical for human development, the loss of which is incompatible with life. These are genes or variants that are not seen in healthy populations, as they are either embryonic-lethal or fetal-lethal variants. Studies of genomic testing should include families (trios) and incorporate environmental exposures (e.g., Environmental influences on Child Health Outcomes (ECHO)) if possible.

Further studies of the benefits of prenatal diagnosis in terms of outcomes from *in utero* and early neonatal interventions are needed. Multi-omic studies of maternal health and major obstetric complications such as preeclampsia are needed in order to devise prevention strategies.

There is no infrastructure for sharing prenatal data; thus, it will be important to piggy-back on existing infrastructures, such as ClinGen and PregSource™. There is also the potential to integrate data into the *All of Us* master plan. Engaging in collaborations with industry can allow for improved and more thoughtful implementation. This will also ease resource sharing and funding obstacles. Finally, fostering international collaboration will allow for larger sample sizes and alignment of outcomes.

**Neonatal Genomics Breakout Report- Presentation by Susan Berry and Louis Muglia, Discussion Moderated by Melissa Parisi**

There are many challenges and gaps for effectively implementing neonatal genomics. Turn-around-times and gaps to access these technologies are a barrier for many institutions. It's unclear what the true clinical utility is for many emerging genomic technologies. Gaps in knowledge such as unknown pharmacogenetic contributors, VUS, and microbiome ontogeny are difficult to address without the linkage of maternal and infant data, as well as a proven value of genomic sequencing in healthy children. Over-diagnosis, long-term implications, biobanking, and cultural competency are among the ELSI concerns in neonatal genomics. Since genomics is not already a routine part of clinical care, and there is a limited ability to incorporate genomic data into EHRs, there is a poor integration of maternal and neonatal health records. In addition, there is a need for long-term follow-up of disorders diagnosed pre- and postnatally.

Despite these challenges, there are many opportunities that can be addressed in neonatal genomics. Research in epigenetics, pharmacogenomics, and the microbiome would help to provide missing information to clinicians and help with identification of novel disease genes. Potential use of a late prenatal, urgent care sequencing panel could facilitate prompt interventions for treatable conditions in the prenatal or immediate newborn period. Public education and justification for mandated screening versus voluntary screening could be explored. This would require stakeholder engagement from all sectors. Enhancing registries with longitudinal follow-up information would address the need for data across the lifetime.

Next steps include exploring partnerships with commercial entities and health care systems, evaluating NGS on a much larger scale, developing an expert curation panel for NBS that considers the economic and care benefits, gathering long-term data through consortia, and educating the public on benefits of genetic screening. Implementation requires community buy-in to build the evidence base that will need to be developed through public support.

### **Summary and Next Steps Day 2- Presentation by Lisa Halvorson, Uma Reddy, and Melissa Parisi**

Reproductive genomics is a broad topic that includes developmental aspects, male/female/transgender populations, gametes/embryo/implantation, and the impact of reproductive disorders. There are opportunities to use genomic information to direct new treatment targets, new treatment vectors, and treatment doses. Fertility status may be a marker of overall health and may be useful when considering preventive medicine. The use of reproductive genomic information raises many ELSI issues, including the drive to have genetic children and concerns about germline gene editing. The next steps for reproductive genomics include utilization of current samples, genetic data banks, and Genome-Wide Association Study (GWAS) results, and development of new resources to collect large amounts of genomic information for analysis. In partnerships with pharma and commercial genomics companies, institutions can lower costs and bolster data sharing. Improved interpretation of data could lead to better predictability and actionability. Long-term follow-up of children and parents following ART is important to understand the full trans-generational implications of these technologies. Other technologies such as non-invasive genomic biomarkers and single-cell genetic diagnostics should be explored.

For prenatal genomics, genome sequencing using maternal blood to evaluate the condition of the fetus is one future goal. To accomplish this, direct fetal samples will be needed to learn about genotype/phenotype correlations, as well as to develop a resource to determine feasibility and accuracy of non-invasive prenatal screening (NIPS). Multi-omics approaches across pregnancy will allow for the prediction of fetal outcomes. To serve as a resource for future studies, longitudinal collection of genotypes, phenotypes, and 'omics data should be collected. There is a growing need for environmental exposure data to be combined with genomic testing data and family information. The value of results for patients and the medical community should also be considered. As more information becomes available, it is likely that patients will want control over the information they are receiving. International collaborations will increase sample sizes and help align outcomes. Industry collaborations have similar benefits and can work to ensure important questions are addressed prior to marketing to patients.

Neonatal genomics requires a strong evidence base for the value of 'omics approaches. There needs to be clear evidence that these technologies can increase coverage, improve acceptance, and reduce disparities in neonatal genomic medicine. Cross-collaboration among providers, medical records systems, and healthcare systems will increase the speed in which technologies can be implemented for

neonatal use. The genome as a living document is an important concept requiring reinterpretation at different life stages. Prenatal consent for actionable neonatal conditions can enhance the speed of implementing treatments. Next steps include developing follow-up mechanisms for the current NSIGHT cohorts, linking maternal and neonatal medical records, creating expert curation panels for NBS conditions in ClinGen, and developing an 'urgent' prenatal panel, that includes biochemical and genomic data to efficiently diagnose ill neonates.

As both NICHD and NHGRI are currently working on their respective strategic plans, conference participants are encouraged to continue to send ideas to NIH program officers.