NICHD’s Report to the Advisory Committee to the Director

Diana W. Bianchi, M.D.
Director, NICHD
December 14, 2017
What’s In a Name?

Eunice Kennedy Shriver
National Institute of Child Health and Human Development
The Docent Approach to NICHD Science

- Fertility
- Pregnancy
- Neonatal Health
- Data Sharing
Fertility

- Normal fertility is a biomarker for long-term human health
- Mildest manifestation of single gene disorders is infertility
- NICHD’s portfolio encompasses research in contraception, fertility and infertility, gynecologic health and disease
- New concept: Oncofertility
  - Made possible by funding multidisciplinary team science
Voice of the Patient: Megan Connolly

Improving Fertility Options for Childhood Cancer Survivors

3D printed ovarian scaffold

Woodruff lab, Northwestern
HD076188, HD28934, UH3TR001207

Bioprosthetic ovary restores function in vivo
EVATAR: The “Mother” of Microhumans

- Enables testing of female tissue function in the presence of cycling hormones
- Contains connected 3D organ models of ovary, fallopian tubes, uterus, cervix and liver (metabolizes hormones)
- Ovaries produce cycling levels of hormones; pumps and channels bring hormones to other organs
- Allows pre-clinical testing of drugs and toxicology studies

Woodruff lab, Northwestern UH3TR001207
A healthy placenta is essential for normal human development and fetal metabolic programming

The Human Placenta Project was launched in 2014 to develop novel safe, real-time technologies for assessment of placental development/function

Current investment of more than $51M across 9 FOAs: imaging, ’omics, microbiome, epigenetics, exosome analysis

A global effort: Many PIs from the U.S. but includes researchers in Canada, the UK, and Australia – 32 Awards made since 2015

Initial successes are beginning to emerge
Multidisciplinary Science

4th Annual Human Placenta Project Meeting

July 24-25, 2017
Grantee updates, poster session and demos
Wireless Compact Wearable Device for Continuous Placental Oxygenation Monitoring

- Continuous
- Non-invasive
- High Clinical Impact Potential

Laboratory of Dr. Amir Gandjbakhche

Clinical Collaborations with

Wayne State/Hutzel Hospital and

Walter Reed National Medical Center
Applying Cutting-Edge MRI Technologies to Placental Assessment

Anatomy: Microvascular Imaging

- 15-16 weeks gestation – can visualize both fetal and maternal circulation
- Can count spiral arteries, fetal arterioles, and do quantitation with doppler techniques
- Generate a vascular index – the degree of vascularity for a given region of the placenta

Allows assessment of the overall health of the placenta

Alfred Abuhamad, EVMS - HPP Grantee
Applying Cutting-Edge MRI Technologies to Placental Assessment

Connecting placental function to outcomes

- Monochorionic diamniotic twins
  - Same placenta, separate amniotic sacs
- Unequal placental delivery of oxygen
- Differences in brain formation
- Differences in brain volume and birth weight

Ellen Grant, Harvard Medical School - HPP Grantee
June 23, 2017

Ira Flatow, Host

Getting To Know The Placenta

Researchers look to the mysterious organ for a new way of monitoring fetal health during pregnancy.

https://www.sciencefriday.com/segments/getting-to-know-the-placenta/
Using Crowdsourcing to Define Typical Pregnancy

PregSource™ Home Page

• Pregnant women will provide information about their experiences in real-time:
  - Sleep
  - Nausea
  - Exercise
  - Weight
  - Medications

• Answers to these topics will help researchers build a more complete picture of normal pregnancy and develop strategies for improving maternal care
Specific topics to be addressed:

• Existing Federal efforts and programs to understand the health effects on pregnant and lactating women, and related birth and pediatric outcomes
• Research collaboration potential
• Ethical issues surrounding inclusion of pregnant and lactating women in clinical research
• Effective communication strategies with health care providers and the public
• 2 of 4 meetings have been completed
• Report to HHS due in September 2018
NICHD Pregnancy and Lactation Literature Analysis 2006-2017: Results for Pregnancy

- RCTs rare in almost all areas
- Exceptions:
  - Hypertension
  - Preterm labor
  - Labor pain medication
  - Opioids and tobacco
Status of Industry-Sponsored Interventional Trials in the US

Search terms included:
- Study type: "interventional"
- Study phase: "Early Phase 1; Phase 2; Phase 3; Phase 4"
- Funder type: "industry"

Completed: 135
Suspended; Terminated; Withdrawn: 35
Recruiting; Not yet recruiting; Active, not recruiting; Enrolling by invitation: 67

Lactation: 8
Pregnancy: 67

Source: www.clinicaltrials.gov (Site accessed 09 Aug 2017)

Slide courtesy of Christina Bucci-Rechtweg, MD, Novartis Pharmaceuticals Corporation
Reproductive Genomics: Partnership with NHGRI

Spring 2018 workshop on Genomic Medicine for Reproductive, Prenatal and Neonatal Health


*Cherchez la femme*: maternal incidental findings can explain discordant prenatal cell-free DNA sequencing results

Diana W. Bianchi, MD
Neonatal Health

Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT)
Newborn Sequencing Questions

For disorders currently screened for in newborns, how can genomic sequencing replicate or augment known newborn screening results?

What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?

What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?
N SIGHT Findings to Date

- Exome sequencing currently cannot replicate known newborn biochemical screening results – of 182 exomes, 12.3% false negatives
- However, WES is useful to augment newborn screening – can identify mutated gene(s)
- Recruitment much lower than anticipated based on survey data – 46% reported “very”, or “extremely” interested in newborn genomic testing
- Initially, only 7% enrollment – 24 of 345 sick NICU infants, and 138 of 2062 healthy babies
  - Noted logistical concerns on 1st approach
  - After GC meeting, privacy, unclear results, and insurance discrimination concerns noted
Rapid DNA Sequencing in Critically Ill Newborns

• NICU sequencing leads to diagnoses and changes in clinical management
  • 20 out of 35 (57%) infants diagnosed
  • 13 out of 20 (65%) diagnoses impacted acute clinical management such as: change in medication, palliative care, or reproductive genetic counseling

Willig et al. 

Rapid whole-genome sequencing identifies a novel homozygous NPC1 variant associated with Niemann-Pick type C1 disease in a 7-week-old male with cholestasis

Amber Hildreth,1,2 Kristen Wigby,3 Shimul Chowdhury,1 Shareef Nahas,1 Jaime Barea,3 Paulina Ordonez,2,4 Sergey Batalov,1 David Dimmock,1 Stephen Kingsmore,1 and on behalf of the RCIGM Investigators

1Rady Children's Institute of Genomic Medicine, San Diego, California 92123, USA; 2Department of Pediatrics, Division of Gastroenterology, University of California San Diego, La Jolla, California 92030, USA; 3Department of Pediatrics, Division of Medical Genetics, University of California San Diego, La Jolla, California 92030, USA; 4Sanford Consortium of Regenerative Medicine, La Jolla, California 92037, USA
Centralized resource for researchers to store and access de-identified data from studies supported by NICHD

Can help investigators meet NIH’s data sharing requirements for their own studies and find others’ study data for secondary analyses

Aims to accelerate scientific findings and improve human health

Launched in August 2015 and governed by the NICHD DASH Committee

53 Studies Available 22 Study Topics 11.3K+ Users 68 Data Requests

Questions? Contact supportdash@mail.nih.gov.

For NICHD studies not archived in DASH, visit: https://dash.nichd.nih.gov/Resource/LinksToOtherArchives.
Average 4.5 studies submitted and released in DASH each quarter, up from 2.5 last year

Key Take-away: Obtaining IRB approvals by the PI or the Data Coordinating Center for sharing data in DASH, especially for the 38 multi-site studies, was the single rate limiting factor for timely submission in DASH
DASH Registered Users

Number of Registered Users in DASH: Aug ’15 – Oct ’17

- United States: 9,150
- 10% of users from 105 other countries
• NICHD is at the forefront of multi-disciplinary science in reproduction, pregnancy, and neonatal health
• The Human Placenta Project is already delivering impactful results
• Major gaps in understanding drug effects in pregnancy/lactation
• Too early to tell the analytical validity and clinical utility of newborn DNA sequencing
• Our vision= to improve *lifelong health* by understanding human development
Tara Shafer’s presentation at the 4th Annual Human Placenta Project Meeting, July 2017 (begins at 1:41:00).
Questions?