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

Cynthia M. Powell, MD
2016 APHL Newborn Screening and Genetic Testing Symposium
February 29, 2016
1:30 PM Keynote Session
## Part 1. Overview Information

<table>
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<tr>
<th>Participating Organization(s)</th>
<th>National Institutes of Health (NIH)</th>
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| Components of Participating Organizations | *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)  
National Human Genome Research Institute (NHGRI) |
| Funding Opportunity Title | Genomic Sequencing and Newborn Screening Disorders (U19) |
| Activity Code | U19 Research Program – Cooperative Agreements |
| Announcement Type | New |
| Funding Opportunity Announcement (FOA) Number | RFA-HD-13-010 |
NSIGHT Research Questions

Must address one or more of the following:

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

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

C • What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?
Required 3 Components

Genomic Sequencing (C1)

Clinical Research (C2)

Ethical, Legal, and Social Implications (C3)
Four Centers Funded: U-19 “NSIGHT”

- Brigham and Women’s/Boston Children’s Hospital
- Children’s Mercy Hospital in Kansas City, MO/San Diego, CA
- University of California San Francisco
- University of North Carolina at Chapel Hill
The BabySeq Project

Boston Children’s Hospital, Alan Beggs, PI
Brigham and Women’s Hospital, Robert Green, PI

Co-PIs: Peter Park (HMS), Heidi Rehm and Richard Parad (BWH), Pankaj Agrawal and Ingrid Holm (BCH), Amy McGuire (BCM)
Project Overview

Pre-Enrollment Genetic Counseling, Consent, Blood Draw, Family History with Genetic Counselor

240 Healthy Newborns at BWH and Parents
- Standard NBS
- Family History

Randomization

240 Newborns in NICU at BCH and Parents
- Standard NBS
- Family History
- Genome Report

Randomization

Consultation and Results Disclosure with Genetic Counselor and Study Physician. Consultation Note and Testing Reports placed in Medical Record and sent to other care providers.

10-month Follow-up Consultation and Exam with Study Physician and Genetic Counselor

Medical Record Review

Outcomes collected. Study Physicians and GCs available for questions from parents, NICU MDs and outside MDs
STAT-Seq: Clinical Utility and Ethical Implications of 2-day diagnostic genomes in Level IV NICUs

Center for Pediatric Genomic Medicine, Children’s Mercy Hospitals and Clinics, Kansas City, MO
Rady Children’s Hospital, San Diego, CA
Stephen Kingsmore, PI
STAT-Seq: Clinical Utility and Ethical Implications of 2-day diagnostic genomes in Level IV NICUs

Study Aims

• Develop routine 1-day clinical genome sequencing methods for NICU diagnosis of genetic diseases
• Prospective, randomized study of risks and benefits of STAT-seq in Level IV NICU
• Test hypotheses about utility of NICU genomes relative to standard care
  – Diagnostic rate
  – Time to diagnosis
  – Rate of change in care attendant to diagnosis
  – Impact on infant morbidity and mortality
  – Identify NICU subpopulations where genome sequencing shows clinical utility and cost effectiveness
  – Determine optimal times-to-result in NICU subpopulations
  – Ethnographic assessment of social, spiritual, psychological, emotional implications for families of whole genome sequencing (WGS) for acutely ill neonates, a population that may stand to benefit largely from WGS given the severity of illness.
• Develop an initial evidence base for physician adoption and provider reimbursement of WGS in Level 4 NICUs
Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening

University of California, San Francisco
Jennifer Puck, Pui-Yan Kwok, Barbara Koenig
UCSF and California Newborn Screening Program Projects

Whole exome sequencing and analysis of variants in newborn blood spots relevant to metabolic disorders and primary immunodeficiencies

ELSI How will “next generation sequencing” enhance, challenge, or transform traditional state-mandated NBS programs?
Overarching Aims

1. Evaluate how Next Generation Sequencing (NGS)-Newborn Screening (NBS) can extend the utility of current NBS.

2. Devise and evaluate a clinically oriented framework for analysis of NGS-NBS.

3. Develop best practices for incorporating NGS-NBS into clinical care.
University of North Carolina (UNC) Project Overview

Affected cohorts (200)
Diagnosed Conditions
PKU, MCADD, CF, HL, LSD, ALD, PCD

Healthy newborn cohort (200)

Diagnostic results
Pathogenic variants and VUS

NGS-NBS Results: RUSP conditions and those determined by scoring process to meet criteria (childhood onset/medically actionable)
Pathogenic variants only

randomization

Control Group
(no additional results)

Decision Group

Using decision aid tool parents decide which additional categories of information to receive
Childhood-onset non-medically actionable, Adult-onset medically actionable, Carrier status
Pathogenic variants only
An age-based modified metric system

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<th>Infancy</th>
<th>Childhood</th>
<th>Adolescence</th>
<th>Adulthood</th>
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NGS-NBS
- MCAD
- PKU
- MEN2B/RET
- Lynch syndrome
- BRCA1

Childhood onset non-medically actionable
- NGS-NBS
- Duchenne MD
- Tay Sach's
- Retinitis pigmentosa
- Rett syndrome

Adult-onset medically actionable
- FAP
- MEN2B/RET
- Adult-onset medically actionable
- Adult-onset non-medically actionable
- Early onset Alzheimer
- Adult-onset non-medically actionable

J. Berg
**NGS-NBS**
Childhood medically actionable conditions

- Reported to all participants

**Additional information**
Findings that do not meet NGS-NBS criteria but may be of interest to some parents

- Optional reporting based on parental decision-making

**Excluded information**
Adult onset non-medically actionable conditions

- Not analyzed or reported to any participants

**Findings that do not meet NGS-NBS criteria but may be of interest to some parents**

- Subject of randomized trial to assess parental preferences and potential psychosocial implications

- Childhood onset NON-medically actionable
- Adult onset medically actionable
- Carrier status for recessive disorders

*Not analyzed unless parents request it*
NC NEXUS Decision Aid

Combined areas of expertise

- Health communication
- Health literacy
- Informatics and computing technology
- Human computer interaction
- Graphical design
- Pediatrics
- Genomics
NSIGHT Projects and FDA Oversight

• Projects contacted by the FDA shortly after awards announced
• Informed that pre-submission to determine need for IDE was required
• FDA determined that UNC project posed significant risk and required full IDE submission and oversee
1962: Massachusetts department of public health begins NBS for PKU

1970’s: Congenital hypothyroidism, Sickle cell disease, 21-hydroxylase deficiency, galactosemia

1990’s: MS/MS allows expansion of disorders screened but not implemented uniformly

2006: ACMG workgroup recommends 29 “core conditions” and 25 “secondary targets” for universal NBS

Genome-scale sequencing permits potential screening of 1,000s of monogenic disorders

1900

1925

1950

1975

2000

2015

Year

Conditions screened

Folling discovers phenylpyruvate in urine of children with severe intellectual disability

Guthrie develops bacterial inhibition assay to detect phenylalanine in dried blood spots

Massively parallel sequencing

Garrod describes “inborn errors of metabolism”

Bickel establishes dietary management of PKU

MS/MS
Can Next-Gen Sequencing Expand the Utility of Newborn Screening?

- Test for additional conditions
- Improve specificity and sensitivity of standard screening
  - Cystic fibrosis
  - Hemoglobinopathies
  - Severe combined immunodeficiency
  - PKU
  - Fatty acid oxidation disorders
  - Urea cycle disorders
  - Hearing loss
Next Gen Newborn Screening?

- Not as a stand-alone test
- Targeted NGS panel
- Integrated screening models
- If genetic sequence information is not returned should it be stored? Where? Whose responsibility is it?
- Parental rights to child’s DNA sequence?
- How to recontact if conditions become treatable?
- New gene/variant discoveries?
- Commercial and privately funded screening in progress
- Mandatory/voluntary? Health disparities
- Demands on public health and health care systems
- Genetic discrimination (employment, insurance,...)
NC NEXUS TEAM

Principal Investigators
• Cynthia Powell – PI and Project 2 PI
• Jonathan Berg – PI and Project 1 PI
• Don Bailey – Project 3 PI

Project Coordinator
• Laura Milko
• (Andy Rivera)

Investigators
• Muge Calikoglu – Project 2
• James Evans – Projects 1 and 3
• Megan Lewis – Project 3
• Piotr Mieczkowski – Project 1 (HTSF)
• George Retsch-Bogart – Project 2
• Christine Rini – Project 3/Aim 3
• Myra Roche – Projects 2 and 3
• Pat Roush – Project 2
• Neeta Vora – Project 2
• Karen Weck-Taylor – Project 1
• Kirk Wilhelmsen – Project 1
• Phillips Owen - RENCI

An NSIGHT research study jointly funded by NHGRI and NICHD
Project #5U19HD077632-03
NC NEXUS TEAM

• Binning Committee
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  Muge Calikoglu
  Art Aylsworth
  Christie Turcott
  Dianne Frazier
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  Bradford Powell
  Neeta Vora
  Debra Skinner
  Jessica Booker
  Myra Roche
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  Julianne O’Daniel
  Megan Lewis
  Kristy Crooks
  Chris Rini
  Don Bailey

  Jonathan Berg
  Cynthia Powell
  Tess Stohrer
  Lacey Boshe
  Rebecca Moultrie
  Tasha Strande
  Tania Fitzgerald
  Zahra Saadat Girnary

• Decision Aid
  – Ryan Paquin
  – Tania Fitzgerald
  – Rebecca Moultrie
  – Brittany Zulkiewicz
  – Ben Gil
  – Joe Hakooz
  (Innova)

• Collaborators
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  Dianne Frazier
  Robert Greenwood
  Michael Knowles
  Margaret Leigh
  Maimoona Zariwala