Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT)

Genomic Sequencing and Newborn Screening Disorders U19 Projects

Ingrid A. Holm, MD, MPH
Representing NSIGHT
September 22, 2014
NBSTRN Network Meeting
<table>
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<tr>
<th><strong>Participating Organization(s)</strong></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 |
| **Related Notices** |  
| **Funding Opportunity Announcement (FOA) Number** | RFA-HD-13-010 |
NSIGHT Program Purpose

To explore, in a limited but deliberate manner, opportunities to use genomic information for broadening our understanding of diseases identified in the newborn period.
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)
Members of the NSIGHT Program

- Robert Green, M.D., M.P.H., and Alan Beggs, Ph.D., Brigham and Women’s Hospital, Boston
  - NICU and healthy newborns, 240 exomes, data sharing, return of results

- Stephen Kingsmore, M.D., Children’s Mercy Hospital, Kansas City
  - NICU, 1000 genomes, data sharing optional, return of results

- Robert Nussbaum, M.D., University of California, San Francisco
  - NBS, 1357 exomes, limited data sharing, return of results

- Cynthia Powell, M.D., M.S. and Jonathan Berg, M.D., Ph.D., University of North Carolina, Chapel Hill
  - NBS, 400 exomes, data sharing optional, return of result options

- NIH
  - Program officer: Tiina Urv – NICHD
  - Project Scientist: Anastasia Wise – NHGRI
The BabySeq Project

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

Project PIs: 1 – Peter Park (HMS) and Heidi Rehm (BWH), 2 – Richard Parad (BWH) and Pankaj Agrawal (BCH), 3 – Ingrid Holm (BCH), Amy McGuire (BCM)
BabySeq Goals

• To determine if parents who receive genomic results struggle with the information in a way that could produce anxiety or distress.

• To critically evaluate the positioning of genome sequencing as a resource that can positively impact the care of children early on in life. Sick babies in the NICU are most likely to benefit from this resource as they are most likely to have conditions with a genetic component.
BabySeq Aims

- **Aim 1: Generate genomic data and reports**
  - Standardized "Genomic Newborn Screening Report" (GNSR) that identifies pathogenic and likely pathogenic variants for highly actionable genetic conditions
  - "Indication-Based Genomic Report" (IBGR) for a potentially genetic phenotype

- **Aim 2: Enrollment**
  - 2 cohorts:
    - 240 healthy neonates in the BWH Well Baby Nursery
    - 240 sick neonates in the BCH NICU neonates
  - Randomize within each cohort to either:
    - Conventional newborn screening (cNBS)
    - cNBS plus genomic newborn sequencing (gNBS)

- **Aim 3: Study the impact on families and caretakers**
  - Compare the psychological impact, personal utility, and behavioral response of parents of receiving a GNSR vs standard NBS
  - Evaluate the actions of pediatricians who receive the GNSR and IBGR.
The BabySeq Project

240 NICU infants at BCH
Randomize each patient to receive

240 Healthy Newborns at BWH
Randomize each patient to receive

Standard of Care NBS + Family History

Standard of Care NBS + Family History + Genome Report

Standard of Care NBS + Family History

Standard of Care NBS + Family History + Genome Report + Indication-based Genome Results

Study MDs/GCs disclose results from Genome Report to pediatricians and parents
*Infant’s electronic medical record*

Pediatricians discuss results from Family History and Genome Report with parents

Medical Record Review

Physician & patient outcomes
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
Stephen Kingsmore, PI

Co PIs: Laurel Willig, Steve Leeder, John Lantos
STAT-Seq: Clinical Utility and Ethical Implications of 2-day diagnostic genomes in Level IV NICUs
Stephen Kingsmore, Laurel Willig, Steve Leeder, John Lantos PIs
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
STAT-Seq: Clinical Utility and Ethical Implications of 2-day diagnostic genomes in Level IV NICUs

Study Design

Acutely Ill Neonates and Parents

Group 1: Expanded newborn screen and standard of care
Patients (n=500) + families (n=1250)

Group 2: Group 1 testing + WGS
Patients (n=500) + families (n=1250)

Table 1. Summary of primary outcomes

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<thead>
<tr>
<th>Research Component 2:</th>
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<tbody>
<tr>
<td>28-day definitive diagnostic yield of singleton STAT-seq vs familial triads vs standard tests</td>
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<tr>
<td>Time to definitive diagnosis of STAT-seq vs conventional tests</td>
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<tr>
<td>Physician perception of change in clinical management in STAT-seq vs standard tests</td>
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<tr>
<td>Surrogate measures of objective change in clinical management in STAT-seq vs standard tests</td>
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<th>Research Component 3:</th>
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<tr>
<td>Parental perception of STAT-seq as beneficial (inc. quality of life), harmful or irrelevant</td>
</tr>
<tr>
<td>Clinician perception of STAT-seq as beneficial (inc. quality of life), harmful or irrelevant</td>
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Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening

University of California, San Francisco
Robert Nussbaum, PI

Project PIs: 1 – Pui-Yan Kwok, 2 – Jennifer Puck, 3 – Barbara Koenig
UCSF Study Aims

• Asks whether whole genome analysis (WGA) might serve as a method of cost-effective newborn screening for any and every condition.

• Whole Exome Sequencing (WES) in
  – 1357 deidentified newborn blood spots that are linked to clinical data of the newborns
  – Test WES as a NBS Tool for metabolic and immunological disorders

• These data will be used to
  – Compare the sensitivity and specificity of mutation data with biochemical testing
  – Identify gene variants that predict which children with certain metabolic disorders are at greater risk for metabolic decompensation
  – Identify mutations in genes responsible for those primary immunodeficiencies that are not detected by the current T-Cell receptor excision circle assay used for severe combined immunodeficiency screening
  – Scan a select set of genes for variants that are clinically important for drug metabolism and would be typical "secondary findings" if WES were to be used as a NBS method

• ELSI component
  – ELSI implications of research related to DNA based analysis associated with newborn screening
Project 1

WES and analysis of variants in newborn blood spots relevant to metabolic disorders and primary immunodeficiency

Obtain 1357 de-identified dried blood spots from the CA Department of Public Health previously screened with tandem mass spectrometry and identified as having one of the disorders screened for:
- 13 spots confirmed false negative
- 100 confirmed false positive
- 100 confirmed true negative

Extract DNA from the dried blood spots

Sequence DNA from blood spots

Annotate Variants found in a set of 44 primary metabolic disorder genes and ~200 additional genes associated to the primary genes by pathway analysis

Secure storage of all sequencing, variant and phenotypic data
Project 1 (cont.)

1. Identify variants in genes that underlie metabolic disorders
2. Examine the false negative, false positive and true negative blood spots for variants in the same genes
3. Test sensitivity and specificity of whole exome sequencing of newborn blood spots
4. Examine Variants and Correlate to Clinical Outcomes

Obtain De-Identified 5 year Follow-up Data on All Individuals whose Blood Spots are Sequenced

Secure storage of all sequencing, variant and phenotypic data
Project 2

Examination of variants in selected immunodeficiency, pharmacogenetic genes and other “ACMG Incidental Findings Genes” obtained by WES of newborn blood spots from patients suspected of having primary immunodeficiencies not identified by newborn screening.

Obtain consent from parents for exome sequencing and analysis
Provide Opt-Out for pharmacogenetic and other genes relevant to their disease, and
Provide Opt-Out for other “Incidental Findings” not directly relevant to the immunodeficiency disease but of medical/clinical significance to the patient or parents

All DNA Sequencing will be Performed in the Institute of Human Genetics Sequencing Lab on HiSeq 2500 machines. The lab and analytic pipeline are slated to be CLIA Certified July 1, 2014

Return results for which consent was obtained
ELSI component

- Develop a participant protection framework for conducting WGA during the neonatal period
- Determine the views, perspectives, and value preferences of key stakeholders about using WGA for NBS through focus groups
- Collaborate with the UC Hastings Consortium on Law, Science and Health Policy, to identify the legal and constitutional issues for using WGA, and for incorporating PGx into NBS programs
- Develop and disseminate policy recommendations for expanded NBS programs based on WGA created via a national policy board consisting of experts in a variety of fields
University of North Carolina
Cynthia Powell and Jonathan Berg,
PIs
NC NEXUS Aims

- **Aim 1:** Evaluate the utility of WES as a diagnostic tool to extend the utility of current NBS
  - Examine the sensitivity and specificity of WES in cohorts of infants and young children with known conditions identified through NBS
  - Utilize WES in cohorts of children with known conditions not currently screened for as potential candidates for NBS in the future

- **Aim 2:** Develop and assess a framework for analyzing WES in a clinically oriented framework based on principles of ethics and evidence-based medicine
  - Develop strategies to guide clinicians, clinical laboratories and patients/families in their decisions regarding the inevitable incidental findings that will be detected in ways that respect the child and protect his/her future autonomy, while also respecting parental interests and rights

- **Aim 3:** Explore ethical, legal and social issues (ELSI) involved in informed decision-making and develop best practices regarding return of results after testing
  - Develop novel decision support tools and evaluate their usefulness in parental decision making
  - Examine the burdens placed on clinicians as this new technology is deployed in the vulnerable and special population that are newborns and their families
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
- Steering committee – monthly calls
- ELSI work group
- Common data elements work group
- Variant Interpretation group
- Independent Data Monitoring Committee (IDMC)
- Face-to-face meetings