An Introduction to Genomic Sequencing in Newborn Screening: Ethical, Legal, and Social Implications

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children
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The University of North Carolina at Chapel Hill
Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT)

• What is genomic sequencing?
• Background of NSIGHT program
• Overview of the four NSIGHT projects
• Introduction of speakers

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Genes contain instructions for making proteins.

Proteins act alone or in complexes to perform many cellular functions.

U.S. DEPARTMENT OF ENERGY
DNA is made up of molecules called nucleotides

A: Adenine  
T: Thymine  
C: Cytosine  
G: Guanine

Each nucleotide has a corresponding partner making up a “base pair”
GENE

Made up of thousands of nucleotides (base pairs)

Range in size from 250 base pairs to 2,500,000 base pairs
ATGCCCTTTAGGTACCTTTAGCCCTTAGCCCATCGGGTTACCCTTCCCCCTTACGGGCTCTTT
TTATATATCCGGCGCGCGCGTTAAAATATACCCATTTATATCGGACGTTTACTACCTACGGATAC
TGGGCTAGGATACTAGACTTTAACAACGATTAATCGGCCCTTACGCAGGTTACTACTTAGCAGTT
AATCGGGCGTTATACGGCCTAC........
GENE VARIANT

Pathogenic “mutation” or Benign?

ATGCCCTTTAGTTACCTTTAGCCCTTAGCTCATCGGGTTACCCTTCCCTCCCTTACGGGCTCTTT
TATATATCCGGGGCGCGCGTTAAATATACCCCATTTTATATCGGACGTTTTACTACCTACGGGATACT
GGGCTAGGATACTAGACTAAACGATTAATCGGGCCCTTACGCAGGTTACTACTTAGCAGTTA
ATCGGGCGTTATACGGCCTAC...
TYPES OF VARIANTS

POINT

INSERTION

DELETION
# TYPES OF VARIANTS

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
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<tbody>
<tr>
<td>NORMAL:</td>
<td>THE CAT SAW THE DOG</td>
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<td>POINT:</td>
<td>THE BAT SAW THE DOG</td>
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<td>DELETION:</td>
<td>THE CAT THE DOG</td>
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<td>INSERTION:</td>
<td>THE CART SAW THE DOG</td>
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<td>TRIPLET EXPANSION:</td>
<td>THE CAT SAW SAW SAW SAW SAW THE DOG</td>
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How can we look at the genome?
Each chromosome contains from 50 – 250 million nucleotides and from 200 – 800 protein coding genes.
What is sequencing?

- Each peak on chromatogram corresponds to one base pair. Typically can read 1000 bases (1 kb) per read
- This is known as Sanger sequencing after its inventor
- Also known as 1st Generation sequencing
Sanger vs. Whole-Exome Sequencing: Technical Considerations

• Sanger
  – 100-800+ bp
  – Targeted mutation analysis
  – Complete coverage
  – “Gold standard”

• WES
  – 30 Mb in exome (3 billion in entire genome)
  – Mutation fishing in many targets
  – Interpretation difficulties
Next Generation Sequencing
Next Gen Sequencing

• Can search for mutations in all genes (~20,000)
• Whole exome: just coding parts of genes (exons)
• Whole genome: everything (exons and introns)
• Analysis is complex – our understanding of what is a significant mutation and what is a benign polymorphism has a long way to go
• Ethical issues about what genes should be analyzed and what information should be returned to patients
• New, sophisticated and increasingly cost-effective techniques for DNA-based sequencing and analysis may make it possible to expand newborn screening in the future and substantially expand its clinical and public health value.

• To identify elements of a trans-NIH research agenda that could inform the possible application of new genomic concepts and technologies to newborn screening and child health.

• https://www.genome.gov/pages/policyethics/staffarticles/newborn_screening_meeting_summary.pdf
• Question A) For disorders currently screened for in newborns, how can genomic sequencing replicate or augment (e.g., make more accurate, comprehensive or inexpensive) known newborn screening results?

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

• Question C) What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

In order to be considered responsive to the FOA, each applicant must also propose a research plan that includes each of the following three component projects:

• Research Component 1) acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period;

• Research Component 2) clinical research that will advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis; and

• Research Component 3) research related to the ethical, legal and social implications (ELSI) of the possible implementation of genomic sequencing of newborns.

The methods and scope of the research in all three of these component projects should be tailored to focus on the newborn period and the research context in which the sequencing is performed.
3 Components Required

- Genomic Sequencing
- Clinical Research
- Ethical, Legal, and Social Implications
<table>
<thead>
<tr>
<th>Principal Investigators</th>
<th>Institutions</th>
<th>Title</th>
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<tbody>
<tr>
<td>Robert Green</td>
<td>Brigham and Women’s Hospital</td>
<td>BabySeq: Genome Sequence-Based Screening for Childhood Risk and Newborn Illness</td>
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<tr>
<td>Alan Beggs</td>
<td>Boston Children’s Hospital</td>
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<tr>
<td>Stephen Kingsmore</td>
<td>Rady Children’s Hospital, San Diego</td>
<td>Clinical and Social Implications of 2-day Genome Results in Acutely Ill Newborns</td>
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<td>Jennifer Puck</td>
<td>University of California</td>
<td>NBSeq: Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening</td>
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<tr>
<td>Barbara Koenig</td>
<td>San Francisco</td>
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<td>Pui-Yan Kwok</td>
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<tr>
<td>Cynthia Powell</td>
<td>University of North Carolina at Chapel Hill</td>
<td>NC NEXUS: North Carolina Newborn Exome Sequencing for Universal Screening</td>
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<tr>
<td>Jonathan Berg</td>
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<td>Prescreen of Neonates Acutely-Ill Neonates</td>
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<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>• Genetic test order</td>
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<td>• Congenital anomaly</td>
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<td>• Poor response to routine care</td>
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<td><strong>Exclusion criteria</strong></td>
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<tr>
<td>• &gt;4 months of age</td>
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<td>• Pathognomonic for known chromosomal rearrangement or previous genetic diagnosis</td>
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<th>Consent and Blinded Randomization</th>
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<tr>
<td><strong>Control group</strong> (n=500 trios)</td>
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<tr>
<td><strong>Acuity-guided trio WGS group</strong> (n=500 trios)</td>
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<td><strong>Refusal Assessment</strong></td>
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<th>Pretest Questionnaires</th>
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<td>Clinician questionnaire on clinical impact</td>
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<th>Return of Results</th>
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<td>Phone conference or care conference between</td>
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<th>72 hours Post test results</th>
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<td>Parent Questionnaires</td>
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<th>12 months post results</th>
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<td>Patient questionnaires and medical follow up</td>
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Unblinding/Potential crossover to WGS.
University of California- San Francisco (UCSF) Project Overview

• Whole exome sequencing of dried blood spots from CDPH biobank from infants with known conditions identified through standard newborn screening
  • Annotate variants in a set of ~90 primary metabolic genes and additional genes identified through pathway analysis

• Examination of variants in selected immunodeficiency genes obtained by Whole Exome Sequencing of newborn blood spots from patients who are suspected of having primary immunodeficiencies not identified by TREC newborn screening.

• How will next-generation sequencing enhance, challenge, or transform traditional state-mandated NBS?
University of North Carolina (UNC) Project Overview

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

Diagnostic results
Pathogenic variants and VUS

Healthy newborn cohort

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

Control Group
(no additional results)

Decision Group

randomization

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
Wall Street Journal July 7, 2014: “Over the course of the next few decades, the availability of cheap, efficient DNA sequencing technology will lead to a medical landscape in which each baby’s genome is sequenced, and that information is used to shape a lifetime of personalized strategies for disease prevention, detection and treatment.”

Francis Collins, M.D., Ph.D
Director, National Institutes of Health
Volume 48, Issue S2

The Ethics of Sequencing Newborns: Reflections and Recommendations

Pages: S2–outside back cover
July/August 2018

Special Report

Article

Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies

Josephine Johnston, John D. Lantos, Aaron Goldenberg, Flavia Chen, Erik Parens, Barbara A. Koenig, members of the NSIGHT Ethics and Policy Advisory Board

Pages: S2-S6 | First Published: 14 August 2018

Abstract | Full text | PDF | References | Request permissions | Find at UNC
JOSEPHINE JOHNSTON is the director of research and a research scholar at The Hastings Center. She works on a range of ethical, legal, and policy issues in science and medicine, including issues in reproduction and parenting, genetics and gene editing, psychiatry and neuroscience, and the conduct of biomedical research. She is co-leading projects on the ethics of next-generation prenatal testing and the use of gene-editing technologies in humans.

JOHN D. LANTOS is a professor of pediatrics at University of Missouri at Kansas City and the director of the Children’s Mercy Hospital Bioethics Center. His most recent book, Preterm Babies, Fetal Patients, and Childbearing Choices, explores the changing nature of prenatal care and fetal medicine.

BARBARA A. KOENIG is a professor of bioethics and medical anthropology at UCSF. She is the director of the UCSF Program in Bioethics, which spans ethics research, clinical ethics, and education across the university’s four professional schools. Her current research interests include emerging genomic technologies and the use of deliberative democracy to engage communities about research governance.