Newborn Screening and Genomics: Fast Forward Into the Future

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Presenter Disclosure

• **Faculty:** Cynthia M. Powell, MD

• **Relationships with commercial interests:**
  – None
Objectives

• Describe current pilot studies of genome sequencing in newborns
• Describe appropriate counseling of families whose infants have had genome sequencing
• List three ethical issues associated with genome sequencing of all newborns
Newborn Screening
Newborn Screening

• Newborn screening ... is a public health program aimed at the early identification of conditions for which early and timely intervention can prevent or reduce associated mortality and morbidity

Criteria for Effective Newborn Screening Programs adapted from Wilson and Jungner 1968

• Treatment is available.
• Early institution of treatment before symptoms manifest reduces or eliminates severity of illness.
• Routine observation or exam will not reveal disorder in newborn (a test is required).
• A rapid and economical laboratory test is available that is highly sensitive (no false negatives) and reasonably specific (few false positives).
Recommended Uniform Screening Panel

• 2005 Task Force funded by HRSA through contract to ACMG recommended core panel of 29 conditions that all states should screen for and 29 additional secondary conditions that would be detected as part of screening for core conditions

• Now the *Discretionary Advisory Committee on Heritable Disorders in Newborns and Children*

• New conditions can be “nominated”

• Limitations include no screening tool, screening tool too expensive, no treatment
Fig. 7. Scores for all conditions distinguished by screening panel category
Of the 23 conditions, 21 are detectable in some or all cases with molecular genetic analysis.
Next Generation Sequencing in Newborn Screening

• Barriers to adding any disorder to NBS panel may now be overcome if there is a genetic etiology established for a condition
What is next generation sequencing?

• Aka massively parallel sequencing
Sanger sequencing
Next Generation Sequencing
aka Massively Parallel 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 polymorphism has a long way to go
ATGCCCTTTAGTTACCTTTAGCCCTTAGCCCATCGGGTTACCCTTCCCCCTTACGGGCTCTTT
TTATATATCCGGGCACGCGGTTTTAATATACCCTTTATATCGGACGTTTTACTACCTACGGATAC
TGGGCTAGGATACTAGACTTAAACGATTAATCGGCCCTTACGCAGGTTACTACTTAGCAGTT
AATCGGGCGTTATACGGCCCTAC........
GENE VARIANT

ATGCCCTTTAGGTACCCTTACGCCCTTAGCTCGGGGTACCCTTCCTCCCCCTTACGGGCTCTTTTAT
ATATCCGGGCGCGCGTAAAATATACCCCATTTATATCGGACGTTTACTACCTACGGGATACTGG
GCTAGGATACTAGACTTTAAACGATTAATCGGCCCTTACGCAGGTTACTACTTAGCAGTTAAT
CGGGCGTTATACGGCCTAC.........
Genetic Variation
~ 3.8 million per person

• Not all variations in a sequence are deleterious
• Most (3.1 million) are polymorphisms (present in 1% or more of the population)
• Most are benign
• Some are not benign and are pathogenic
  – Because they adversely affect gene function
    • Protein product
    • Regulatory
Challenges with Whole Exome Sequencing

• As with microarrays and Sanger sequencing you find changes that have unknown clinical significance
  – Variant calling software
  – Use of databases of known population variants (1000 genome, ClinVar, dbSNP, ExAC, etc) and effect of amino acid substitution on protein structure (PolyPhen, SIFT)
  – Zebrafish and other model organisms
Limitations of Whole Exome Sequencing

- Repetitive DNA (trinucleotide repeats)
  - Fragile X syndrome, Huntington disease
- GC rich areas of exons are difficult to analyze
- Not all pathogenic mutations are contained in exons
- Copy number variants (*ability to detect improving*)
  - Williams syndrome, DiGeorge syndrome
- Structural variants (*ability to detect improving*)
  - Balanced chromosome translocations
- Epigenetic alterations
  - e.g. some forms of Angelman syndrome and Prader-Willi syndrome
- Pseudogenes causing false positive results
- Turnaround time
- Cost
- Cannot distinguish cis versus trans for compound variants in AR genes
Next-Generation Newborn Screening
Ethical Issues

• “Incidental” or “secondary” findings
INCIDENTAL FINDINGS

• Testing can identify variants that are not related to the original intent of testing ("incidental" or "secondary" findings)

• With next gen sequencing these can include mutations in genes such as those for breast or colon cancer, cardiac arrhythmias, intellectual disability, etc.

• What should be reported back to patients/families?
Next-Generation Newborn Screening

Ethical Issues

• “Incidental” or “secondary” findings

• Broadening the definition of “treatable”
Conditions that don’t fulfill definition of “treatable” in traditional sense

• e.g. those associated with intellectual disability
• Search for a cause: the “diagnostic odyssey”
• Avoiding unnecessary and expensive testing
• Delayed interventions (therapy services, etc.)
• Genetic risk information
Next-Generation Newborn Screening
Ethical Issues

• “Incidental” or “secondary” findings
• Broadening the definition of “treatable”
• Expanding the concept of “benefit” of screening to the family in addition to the child
Autosomal Dominant Conditions

• e.g. *BRCA* gene mutations
• Associated with increased risk of breast and ovarian cancer
• If identified in a child, likely inherited from a parent
• Is saving the life of a parent a “benefit” to the child?
Next-Generation Newborn Screening
Ethical Issues

- “Incidental” or “secondary” findings
- Broadening the definition of “treatable”
- Expanding the concept of “benefit” of screening to the family in addition to the child
- Protecting the autonomy of the child while balancing the rights of parents to have information
Child’s Autonomy

• Testing for adult onset conditions in infants
• Testing a child for carrier status
• “Pre-symptomatic genetic testing”
• The right of the child not to know this information
  – Genetic discrimination
• Versus the rights of parents to have information about their child
Privacy and Discrimination

• GINA: Genetic Information Non-Discrimination Act
• Passed and signed into law in 2008
• Will take effect in 2009
• To prevent discrimination in health insurance and employment based on genetic information
Federal Legislation
GINA

- What it does not include
  - Members of the military
  - Life insurance, disability insurance, long-term care insurance
...invite applications that propose to explore the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period.
Four Centers Funded: U-19 “NSIGHT”

- University of North Carolina at Chapel Hill
- Brigham and Women’s Boston
- Children’s Mercy Hospital in Kansas City, MO
- University of California San Francisco
Brigham & Women’s Hospital–Boston Children’s Hospital (BWH-BCH) 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

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

Optional:
- Indication-Based Report

Consultation and Results Disclosure with Genetic Counselor and Study Physician. Consultation Note and Reports (NBS Report, Family History, Genome Report) 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.
Children’s Mercy-KC Project Overview

Prescreen of Neonates
- **Inclusion criteria**
  - Genetic test order
  - Congenital anomaly
  - Poor response to routine care
- **Exclusion criteria**
  - >4 months of age
  - Pathognomonic for known chromosomal rearrangement or previous genetic diagnosis

Consent and Blinded Randomization
- Control group (n=500 trios)
- Acuity guided trio WGS group (n=500 trios)
- Refusal Assessment

Pretest Questionnaires
- Clinician questionnaire on clinical impact

Return of Results
- Phone conference or care conference between

72 hours Post test results
- Parent Questionnaires

12 months post results
- Patient questionnaires and medical follow up

Unblinding/Potential crossover to WGS.
Examination of variants in selected immunodeficiency and pharmacogenetic 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. To be done in conjunction with Project 3.
NC NEXUS 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.
Project 1 Specific Aims
Generation and Analysis of Whole Exome Sequence Datasets

• **Aim 1:** Generate a high quality whole exome sequence dataset for next-generation newborn

• **Aim 2:** Implement an analytic strategy for NGS-NBS and incidental findings

• **Aim 3:** Develop and evaluate novel bioinformatics approaches for utilization in NGS-NBS
Informatics – variant selection

• In NGS, informatics filters play a critical role in selecting which variants will undergo detailed review by a human
  – 100,000 variants per exome
  – 20,000 coding variants
  – 1000’s of missense variants
  – 100’s of truncating variants

• The vast majority of variants are benign or have uncertain clinical significance

• There is no gold standard method for selecting variants for confirmation in a diagnostic setting
  – Although some groups have started to explore different strategies or establish routine internal practices
Results of Diagnostic Sorting

### Analysis results

**For participant: NCG_00014**  
**Diagnostic type: Cardiomyopathy**

#### Donor selection
- NCG_00014

#### Dx filter selection
- No filter

#### Gene filter selection
- No filter

Please select an analysis result type:
- Diagnostic

---

| Class | Calculated Class | Homogender | Type | Homogene | Variant Effect | Max Alt Allele | Tag | Acc num | Depth | qval | Read pass | Read failure | Strand score | dfr | Abs depth | Gene name | rsid | Ter | Inheritance | Sex | Note(s) |
|-------|------------------|------------|------|----------|---------------|----------------|-----|----------|-------|------|-----------|--------------|-------------|------------|-----|-----------|-----------|------|-------|-------------|------|---------|
| VUS 3 | A                | NCG0014    | 80   | 0.050057 | 10.23792996   | 0.0120392     | DM | CMRF00187 | 58    | 53.34| 1         | 0             | 0           | 0          | 58  | 50        | NCG0014   | 0.120020   | 0.68692    | AR        | Cardiomyopathy |
|       |                  |            |      |          |               |                |     | CMRF00187 | 58    | 53.34| 1         | 0             | 0           | 0          | 58  | 50        | NCG0014   | 0.120020   | 0.68692    | AR        | Cardiomyopathy |
|       |                  |            |      |          |               |                |     | CMRF00187 | 58    | 53.34| 1         | 0             | 0           | 0          | 58  | 50        | NCG0014   | 0.120020   | 0.68692    | AR        | Cardiomyopathy |

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*Note: The table contains detailed analysis results for a participant with the identifier NCG_00014, categorized under Cardiomyopathy, showing variant effects, max alt allele, tag, acc num, depth, qval, read pass, read failure, strand score, dfr, abs depth, gene name, rsid, ter, inheritance, and sex. The results are tabulated for various classes and include notes for each entry.*
Project 2 Specific Aims
Clinical Utility of Whole Exome Sequencing in Newborns

• **Aim 1:** Evaluate the use and performance of WES as a diagnostic tool in NBS
  – **Subaim 1A** - Determine the *sensitivity* of WES in detecting three of the most common genetic conditions currently identified in newborns
  – **Subaim 1B** – Determine the *impact of WES on the specificity* of NBS

• **Aim 2:** Determine the *diagnostic capacity* and utility of WES to extend the range of current NBS techniques.
  – **Subaim 2A** – Assess the use of WES in screening for conditions not identifiable by current NBS testing methods
  – **Subaim 2B** – Assess the ability of WES to illuminate genotype-phenotype correlations and identify novel causes of phenotypic variability.

• **Aim 3:** Develop practical, ethical, and clinically-oriented mechanisms to facilitate interpretation, return of results, and informed decision making about WES data in NBS.
Project 3 Specific Aims
Ethical and Social Implications of Applying Whole Exome Sequencing in Newborn Screening

• **Aim 1:** Refine and describe, in lay terms, meaningful “bins” or categories of genes to enable parents to make informed decisions about which types of incidental findings they wish to learn. External advisory committee will review process.

• **Aim 2:** Develop and evaluate the effectiveness of a decision aid to help parents make an informed decision about study participation and their preference for return of results.

• **Aim 3:** Apply the decision aid and recruitment procedures in a prospective study designed to determine parents’ willingness to accept WES for their child; the choices they make regarding the spectrum of results they wish to learn; factors associated with their choices; and the consequences of return of results for both children and families.
What is the nature of the threat to health for an individual carrying a deleterious allele in this gene?  

Severity:  
3 = Sudden death or inevitable death in childhood  
2 = Possible death due to disease or severe intellectual impairment  
1 = Serious morbidity or moderate intellectual impairment  
0 = Modest or no morbidity  

Likelihood:  
Penetrance  
3 = >50%  
2 = 5-49%  
1 = 1-5%  
0 = <1%  

Efficacy:  
How effective are interventions?  
3 = Highly  
2 = Moderately  
1 = Minimally  
0 = Ineffective  

Acceptability:  
How acceptable are the interventions in terms of the burdens or risks placed on the individual?  
3 = Highly  
2 = Moderately  
1 = Minimally  
0 = Ineffective  

Knowledge:  
Evidence to score other categories  
3 = Substantial  
2 = Moderate  
1 = Minimal  
0 = Controversial or poor  

TOTAL SCORE RANGE  
0 – 15  
A “medical actionability” score  

J. Berg
Example: PAH (PKU)

- Severity of disease (severe ID) = 2
- Likelihood of a severe outcome = 3
- Effectiveness of interventions (diet) = 3
- Acceptability of interventions = 2
- Knowledge base = 3

• TOTAL SCORE of 13
NGS NBS Candidate Condition

- Multiple Endocrine Neoplasia type 2B
  - Medullary thyroid carcinoma in early childhood with high rate of metastases
    - 100% penetrance
  - Pheochromocytoma
    - 50% penetrance
  - Mucosal neuromas
  - Marfanoid body habitus
NGS NBS Candidate Condition

- Multiple Endocrine Neoplasia type 2B
  - Medullary thyroid carcinoma in early childhood with high rate of metastases
    - 100% penetrance
  - Pheochromocytoma
    - 50% penetrance
  - Mucosal neuromas
  - Marfanoid body habitus
  - Prevention: prophylactic thyroidectomy
  - Surveillance: biochemical screening of catecholamines
  - 50% of cases are de novo
  - Prevalence (all MEN 2) 1:35,000
  - Gene: RET
    - Genotype/phenotype correlation


http://www.ijponline.net/content/38/1/9/figure/F1
<table>
<thead>
<tr>
<th>ATA Risk Level</th>
<th>Mutations</th>
<th>Age of Prophylactic Surgery</th>
<th>Age to Begin Screening For PHEO</th>
<th>For HPT</th>
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</thead>
<tbody>
<tr>
<td>Level C</td>
<td>p.Cys634Arg/Gly/Phe/Ser/Trp/Tyr</td>
<td>&lt;5 yrs</td>
<td>8 yrs</td>
<td>8 yrs</td>
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GeneReviews
http://www.ncbi.nlm.nih.gov/books/NBK1257/

Adapted from American Thyroid Association Guidelines Task Force [2009]
NGS NBS Candidate Condition

• Multiple Endocrine Neoplasia type 2B
  – Medullary thyroid carcinoma in early childhood with high rate of metastases
    • 100% penetrance
  – Pheochromocytoma
    • 50% penetrance
  – Mucosal neuromas
  – Marfanoid body habitus
  – Prevention: prophylactic thyroidectomy
  – Surveillance: biochemical screening of catecholamines
  – 50% of cases are de novo
  – Prevalence (all MEN 2) 1:35,000
  – Gene: RET
    • Genotype/phenotype correlation
  – No population screening method currently available
What is the nature of the threat to health for an individual carrying a deleterious allele in this gene?

Severity

Likelihood

Penetrance

3 = >50%
2 = 5-49%
1 = 1-5%
0 = <1%

Efficacy

How effective are interventions?

3 = Highly
2 = Moderately
1 = Minimally
0 = Ineffective

Acceptability

How acceptable are the interventions in terms of the burdens or risks placed on the individual?

3 = Highly
2 = Moderately
1 = Minimally
0 = Ineffective

Knowledge

Evidence to score other categories

3 = Substantial
2 = Moderate
1 = Minimal
0 = Controversial or poor

TOTAL SCORE RANGE
0 – 15
A “medical actionability” score
Example: RET (MEN2B)

- Severity of disease (possible death) = 2
- Likelihood of a severe outcome = 3
- Effectiveness of interventions = 3
- Acceptability of interventions = 2
- Knowledge base = 3

- TOTAL SCORE = 13
Example: APC (Familial adenomatous polyposis)

- Severity: possible death due to cancer = 2
- Likelihood: high penetrance = 3
- Effectiveness of intervention: colonoscopy = 3
- Acceptability of intervention: colonoscopy = 2
- Knowledge base: high = 3

• Total score = 13
Example: Tay Sachs Disease (HEXA)

- Severity: inevitable death in childhood = 3
- Likelihood: high penetrance = 3
- Effectiveness of intervention: none = 0
- Acceptability of intervention: N/A = 0
- Knowledge base: high = 3

- Total score = 9
An age-based modified metric system

From Dr. Jonathan Berg
An age-based modified metric system

<table>
<thead>
<tr>
<th>Onset</th>
<th>Actionability</th>
</tr>
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<tbody>
<tr>
<td>Infancy</td>
<td>Childhood onset non-medically actionable</td>
</tr>
<tr>
<td>Childhood</td>
<td>Childhood onset medically actionable</td>
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<tr>
<td>Adolescence</td>
<td>Adult-onset medically actionable</td>
</tr>
<tr>
<td>Adulthood</td>
<td>Adult-onset non-medically actionable</td>
</tr>
<tr>
<td>30+</td>
<td></td>
</tr>
</tbody>
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Conditions:
- NGS-NBS
- PKU
- FAP
- MEN2B/RET
- Lynch syndrome
- BRCA1
- Rett syndrome
- Duchenne MD
- Early onset Alzheimer
- Retinitis pigmentosa
- Early onset Alzheimer
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- Early onset Alzheimer
- Early on
NGS-NBS
Childhood medically actionable conditions

- Conditions currently on the recommended uniform screening panel (RUSP)
- Conditions that fit a similar profile to RUSP

ALGORITHM
- Severity of outcome
- Likelihood of severe outcome
- Efficacy of intervention
- Acceptability/burden of intervention
- Knowledge base
University of North Carolina (UNC) Project Overview

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

Diagnostic results
Pathogenic variants and VUS

**Healthy newborn cohort (200)**

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
NGS-NBS
Childhood medically actionable conditions

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

Excluded information
Adult onset non-medically actionable conditions

Reported to all participants

Optional reporting based on parental decision-making

Not reported to any participants

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
What are patient decision aids for informed decision making (IDM)?

- Tools to help people participate in their health decisions in ways they prefer
- Used when there is more than one medically reasonable option to diagnose or treat a health condition
- Decision aids aim to:
  - Provide facts about a condition, options, and features
  - Help people clarify their values
  - Help people plan a course of action
- Decision aids do not advise people to choose one option over another
Discrete Choice Experiment Methods

• 1289 participants included in analysis
  – 6 participants did not complete the conjoint survey

• Statistical analysis estimates the implicit decision weights (preference weights) consistent with observed patterns of choices

• Conditional logit regression run in Sawtooth version 6.6
<table>
<thead>
<tr>
<th>Condition Feature</th>
<th>Profile A</th>
<th>Profile B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance that the Condition Will Develop</td>
<td><img src="image" alt="Grid" /></td>
<td><img src="image" alt="Grid" /></td>
</tr>
<tr>
<td>Gray Will not develop the health condition</td>
<td>50 children out of 100 (50%) with the change in their gene will develop the health condition</td>
<td>10 children out of 100 (10%) with the change in their gene will develop the health condition</td>
</tr>
<tr>
<td>Red Will develop the health condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of Onset</td>
<td>1 to 5 years old</td>
<td>5 to 12 years old</td>
</tr>
<tr>
<td>Level of Mental Disabilities</td>
<td>Severe</td>
<td>Mild to Moderate</td>
</tr>
<tr>
<td>Level of Physical Disabilities</td>
<td>Mild to Moderate</td>
<td>None</td>
</tr>
<tr>
<td>Speed that the Condition May Get Worse</td>
<td>Moderate</td>
<td>Slow</td>
</tr>
<tr>
<td>Options to Improve Quality of Life</td>
<td>Limited options available</td>
<td>Effective options available</td>
</tr>
<tr>
<td>Lifespan</td>
<td>Shortened</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Dependent variables

• Which profile would be more important for you?
  - Profile A
  - Profile B

• If Profile _____ was in your child’s genetic test results, would you want to know this information?
  - Yes, I would want to know
  - No, I would not want to know
<table>
<thead>
<tr>
<th>Condition Feature</th>
<th>Profile A Leber Heriditary Optic Neuropathy</th>
<th>Profile B Rett Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance that the Condition Will Develop</td>
<td><img src="image" alt="Gray = Will not develop the health condition" /></td>
<td><img src="image" alt="Red = Will develop the health condition" /></td>
</tr>
<tr>
<td>Age of Onset</td>
<td>13 to 18 years old</td>
<td>Less than 1 year old</td>
</tr>
<tr>
<td>Level of Mental Disabilities</td>
<td>None</td>
<td>Mild to Moderate</td>
</tr>
<tr>
<td>Level of Physical Disabilities</td>
<td>Mild to Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Speed that the Condition May Get Worse</td>
<td>Rapid</td>
<td>Moderate</td>
</tr>
<tr>
<td>Options to Improve Quality of Life</td>
<td>Limited options available</td>
<td>Effective options available</td>
</tr>
<tr>
<td>Lifespan</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Which profile would be more important for you to know?

- □ 23.38% would choose Profile A
- □ 76.62% would choose Profile B
**Figure 1:**
Summary of Longitudinal Study for Healthy Newborn Cohort

- **Initial recruitment--Prenatal clinic**
  - **Agree to hear about study?**
    - **NO**
      - Count as approached but do not gather data
    - **YES**
      - Describe study, give study brochure, study consent form, intake form; get contact information.
      - Staff calls to ascertain interest in joining the study
      - **Agree to join?**
        - **NO**
          - Gather basic demographic data and reason for declining
        - **YES**
          - Perform informed consent procedures by phone, document consent, and schedule study visit

- **In-person study visit**
  - **Collect intake form; assess health literacy/numeracy; sequencing decision/consent**
  - **Consent for NGS-NBS?**
    - **NO**
      - Provide link to complete T2 questionnaire
    - **YES**
      - Provide link to complete T2 questionnaire

  - **Study arm instructions**
    - **DECISION**
      - Call study when ready
    - **CONTROL**
      - Call study when ready

- **Randomization (2:1)**
  - Use online decision aid onsite or at home to make decision about additional information
  - **Consent to at least some additional info?**
    - **NOT SURE**
      - Call study when ready
    - **YES**
      - Swab from newborn
      - Return NGS-NBS/add'l results; T3 survey
      - 3 months later, T4 survey
    - **NO**
      - Swab from newborn
      - Return NGS-NBS results; T3 survey
      - 3 months later, T4 survey
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
<table>
<thead>
<tr>
<th>Recommended Uniform Screening Panel Core Conditions</th>
<th>GENE(S)</th>
<th>Metabolic Disorder</th>
<th>Endocrine Disorder</th>
<th>Hemoglobin Disorder</th>
<th>Other Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Organic acid disorder</td>
<td>Fatty acid oxidation disorder</td>
<td>Amino acid disorder</td>
<td></td>
</tr>
<tr>
<td>Proionic acidemia</td>
<td>PCCB, PCCA</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylmalonic academia (methylmalonyl-CoA mutase)</td>
<td>MUT</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylmalonic academia (cobalamin disorders)</td>
<td>MMAA, MMAB</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Isovaleric acidemia</td>
<td>IVD</td>
<td>x</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3-Methylcrotonyl-CoA carboxylase deficiency</td>
<td>MCCCI1, MCCCI2</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Hydroxy-3-methylglutaricaciduria</td>
<td>HMGCL</td>
<td>x</td>
<td></td>
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<tr>
<td>Holocarboxylase synthase deficiency</td>
<td>HLC5</td>
<td>x</td>
<td></td>
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<tr>
<td>β-Ketothiolase deficiency</td>
<td>ACAT1</td>
<td>x</td>
<td></td>
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<tr>
<td>Glutaric acidemia type 1</td>
<td>GCDH</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Carnitine uptake defect/carnitine transport defect</td>
<td>SLC22A5</td>
<td>x</td>
<td></td>
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<tr>
<td>Medium-chain acyl-CoA dehydrogenase deficiency</td>
<td>ACADM</td>
<td>x</td>
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<tr>
<td>Very long-chain acyl-CoA dehydrogenase deficiency</td>
<td>ACADVL</td>
<td>x</td>
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<tr>
<td>Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency</td>
<td>HADHA</td>
<td>x</td>
<td></td>
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</tr>
<tr>
<td>Trifunctional protein deficiency</td>
<td>HADHA, HADHB</td>
<td>x</td>
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<tr>
<td>Argininosuccinic aciduria</td>
<td>ASL</td>
<td>x</td>
<td></td>
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<tr>
<td>Citrullinemia, type I</td>
<td>ASS1, SLC25A13</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Maple syrup urine disease</td>
<td>BCKDHA, BCKDHB, DBT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Homocystinuria</td>
<td>CBS, MTHFR, MTR, MTRR, MMDHC</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Classic phenylketonuria</td>
<td>PAH</td>
<td>x</td>
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<tr>
<td>Tyrosinemia, type I</td>
<td>FAH</td>
<td>x</td>
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<tr>
<td>Primary congenital hypothyroidism</td>
<td>1</td>
<td>x</td>
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<tr>
<td>Congenital adrenal hyperplasia</td>
<td>CYP21A2</td>
<td>x</td>
<td></td>
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<tr>
<td>Sickle cell anemia</td>
<td>HBB</td>
<td>x</td>
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<tr>
<td>B-thalassemia</td>
<td>HBB</td>
<td>x</td>
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<tr>
<td>S.C disease</td>
<td>HBB</td>
<td>x</td>
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<tr>
<td>Biotinidase deficiency</td>
<td>BTD</td>
<td>x</td>
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<tr>
<td>Critical congenital heart disease</td>
<td>2</td>
<td>x</td>
<td></td>
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<tr>
<td>Cystic fibrosis</td>
<td>CFTR</td>
<td>x</td>
<td></td>
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<td></td>
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<tr>
<td>Classic galactosemia</td>
<td>GALT</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>3</td>
<td>x</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Severe combined immunodeficiencies</td>
<td>4</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pompe disease</td>
<td>GAA</td>
<td>x</td>
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</table>

Table adapted from www.hrsa.gov/advisorycommittees/mchadvisory/heritable/sorders/recommendedpanel

1. Most cases are sporadic but 15-20% are genetic with DUOX2, PAX8, SLCSA5, TG, TPO, TSHB, or TSHR gene mutations
2. Multifactorial; most genetic causes unknown
3. Multiple etiologies including genetic and environmental; multiple genes associated with non-syndromic and syndromic forms
4. 15 known genes associated; 14% of cases of unknown cause
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 testing (Parabase Genomics)
Mandatory/voluntary? Health disparities
Demands on public health and health care systems
Genetic discrimination (employment, insurance,...)
For One Baby, Life Begins with Genome Revealed

How a California father made an end run around medicine to decode his son's DNA.

Razib Khan, a graduate student at the University of California, Davis, and blogger at Unz, sequenced his son's genome before he was born.

Khan, who had no real medical reason to learn his son’s DNA code, says sequencing his son in utero “was more cool than practical.” He did it to show where technology is headed and because he likes “pushing the envelope.”

When Khan got the DNA earlier this year, he could have ordered simple tests for specific genes he was curious about. But why not get all the data? “At that point, I realized it was just easier to do the whole genome,” “I popped him through Promethease and got 7,000 results,” says Khan. “Our attitude is that you make a lot of decisions for your kids, including ones that may seem sketchy in hindsight.”
NC NEXUS TEAM

Cynthia Powell  Jonathan Berg  Don Bailey  Megan Lewis

Myra Roche  Chris Rini  Laura Milko  Kirk Wilhelmsen
# 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

## Investigators
- Muge Calikoglu – Project 2
- James Evans – Projects 1 and 3
- Megan Lewis – Project 3
- Piotr Mieczkowski – Project 1 (HTSF)
- Phillips Owen - RENCI
- 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
NC NEXUS TEAM

• Binning Committee
  Joe Muenzer
  Muge Calikoglu
  Art Aylsworth
  Carl Seashore
  Christie Turcott
  Dianne Frazier
  Dan Nelson
  Bradford Powell
  Neeta Vora
  Debra Skinner
  Jessica Booker
  Myra Roche
  Kate Foreman
  Julianne O’Daniel
  Megan Lewis
  Kristy Crooks
  Chris Rini

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  Jonathan Berg
  Cynthia Powell
  Tess Stohrer
  Lacey Boshe
  Rebecca Moultrie
  Tasha Strande
  Tania Fitzgerald
  Zahra Saadat Girnary
  Oliver Adunka
  Craig Buchman
  Zheng Fan
  Dianne Frazier
  Robert Greenwood
  Michael Knowles
  Margaret Leigh
  Maimoona Zariwala
I just got my 23andme data! More than 500,000 genotypes!

Cool beans! What does it all mean?

SO MANY GENES, SO LITTLE TIME