Sequencing in Newborns: Studies of Utility in the Public Health Setting

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Presenter Disclosure

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• **Relationships with commercial interests:**
  – None
Pediatric Genomic Sequencing

Indication-Based

- Critically ill newborn
- Child with physical and/or functional anomalies when standard testing (karyotype, CMA, fragile X) negative
- Uncharacterized genetic disorder in family
- Positive newborn screen
- Research

Screening

- Newborn screening
  - Second or third tier test
    - i.e. CFTR, SCID
    - May decrease number of false positives
- Healthy infant or child
  - “elective” genome
  - expanded newborn screen
- Research
NSIGHT Projects Update
(Newborn Sequencing In Genomic medicine and public HealTh)
Required 3 Components

Genomic Sequencing (C1)
Clinical Research (C2)
Ethical, Legal, and Social Implications (C3)
NC NEXUS Binning

**NGS-NBS Panel**
- Pediatric-onset of symptoms
- Higher actionability: scores of ≥12 AND scores of 9-11 discussed as “In”

**Parental Decision**
- Pediatric-onset of symptoms
- Lower actionability: scores of <9 AND scores of 9-11 discussed as “Out”

**Parental Decision**
- Adult-onset of symptoms
- Higher actionability: scores of ≥11

**Not Returned**
- Adult-onset of symptoms
- Lower actionability: scores of <11
NC NEXUS Binning

NGS-NBS Panel
(450 gene-disease pairs)

- ACADVL: VLCAD deficiency
- PAH: Phenylketonuria
- CFTR: Cystic fibrosis
- APC: Familial adenomatous polyposis
- MEN1: Multiple endocrine neoplasia 1

Parental Decision (240)

- HPD: Tyrosinemia, type III
- HEXA: Tay-Sachs disease
- GALC: Krabbe disease
- MLH1, MSH2, MSH6, PMS2: Mismatch repair cancer syndrome
- CLN3: Neuronal ceroid lipofuscinosis 3

Parental Decision (25)

- BRCA1, BRCA2: Hereditary breast and ovarian cancer
- MLH1, MSH2, MSH6, PMS2: Lynch syndrome
- CDH1: Hereditary diffuse gastric cancer

Not Returned (21)

- AUH: 3-Methylglutaconic aciduria, type I
- SLC25A13: Citrullinemia, type II, adult-onset
- CLN8: Neuronal ceroid lipofuscinosis 8, Northern epilepsy variant
- F12: Factor XII deficiency

SQM Actionability Score

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Age of Onset/Intervention

18 years
Reported to all participants

**NGS-NBS**
Childhood medically actionable conditions

Optional reporting based on parental decision-making

**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

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**
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
160 pregnant women approached in prenatal clinic and asked to join study

121 (76%) agreed to join study

41 (34%) completed first decision aid

27 (66% who completed DA) “yes”
17% of total approached
22% of those who agreed to join study

5 (12%) undecided

9 (22%) “no”
140 parents of children with diagnosed conditions sent letter asking them to join study

65 (46%) agreed to join study

41 (63%) completed first decision aid

35 (85% who completed DA) “yes”
25% of those sent letters
54% of those who agreed to join study

5 (12%) “undecided”
1 (2%) “no”
NC NEXUS Recruitment

• For those who complete the decision aid
  • 66% of parents from well-child cohort agree to have their child’s genome sequenced
  • 85% of parents from diagnosed cohort agree to have their child’s genome sequenced

• Most of those initially approached who do not agree are passive decliners and never complete the on-line survey or decision aid

• Some of the reasons given by active decliners are:
  • concern for child
  • too busy
  • too far to travel
  • not interested
  • do not want additional testing
  • do not want to share information
NC NEXUS TEAM

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NICHD Presolicitation Notice: Newborn Screening Pilot Studies

On May 1st, 2015, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) issued a presolicitation notice requesting proposals for Newborn Screening Pilot Studies.

Purpose: The purpose of this acquisition is to create a pool of high throughput newborn screening laboratories with the capacity to screen a large number of newborns in relatively short periods of time that are representative of various regions of the United States. The selected Contractors will operate under an IDIQ Task Order contract to rapidly develop protocols and initiate testing shortly after the addition of a new condition to the Recommended Uniform Screening Panel (RUSP). See full presolicitation notice for greater detail.

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Links:
NICHD/NIH Presolicitation Notice
Indefinite Delivery-Indefinite Quantity (IDIQ) Contract Task Orders

• NIH contracts with states to carry out newborn screening pilot projects
• IDIQs awarded to Georgia, Massachusetts, North Carolina
• North Carolina: RTI International, NC State Public Health Lab, UNC, Duke
• First Task Order was for MPS-I
Mucopolysaccharidosis I (MPS I)

• Deficiency of lysosomal enzyme $\alpha$-L-iduronidase

• Onset of symptoms before 6 months of age in severe form (Hurler syndrome)

• The severe form has both somatic and CNS involvement

• Early mortality in severe form (3 to 10 yrs of age)

• Rare (est. incidence 1:100,000)

• Autosomal recessive disorder

Age 4

Courtesy of Joseph Muenzer, MD, PhD
MPS I Treatment

• Early hematopoietic stem cell transplant (before 2 years of age)
• Peripheral IV enzyme replacement therapy effective for somatic complications
• Without early detection and treatment estimated cost for surgical procedures alone > $270,000 per patient

http://thethomasfamilytrials.blogspot.com/2012/02/one-year-post-transplant.html
With 3-Plex Reagents

2 other enzymes are in normal range

Inconclusive??

Two of the three enzymes have low activity

Screening Algorithm

Screening test measure IDUA activity

Value below initial cut-off?

Yes

Retest in duplicate

Average 3 values below reporting cut-off?

No

No further testing action

Yes

DNA testing

No further testing action

No mutation

Request repeat NBS specimen

Value below reporting cut-off?

Yes

Positive referral

One or more mutations, VUS or pseudo-deficiency variants

No

No further testing action

No
Work Flow for Positive MPS-I Newborn Screens

1. Abnormal Screen Result
   NC State NBS Lab

2. Communicate by Phone Call or Fax

3. Genetic Counselor UNC Division of Pediatric Genetics and Metabolism

4. Phone Call

5. Infant’s Primary Care Provider

6. PCP contacts family directly or has GC contact family and appointment made to see infant and parents at UNC-CH
Work Flow for Positive MPS-I Newborn Screens

Family comes to UNC for confirmatory testing
urine sample for glycosaminoglycan (GAG) measurement, blood sample for enzyme testing

Negative urine GAG, normal enzyme level = false positive screen
No follow-up needed

Negative urine GAG, decreased enzyme, IDUA pseudo-deficiency mutation
Likely pseudo-deficiency
12 month follow-up at UNC

Positive/borderline/possibly negative urine GAG and decreased or no enzyme with at least 1 known pathogenic variant

Confirmed MPS I

NO
Two IDUA nonsense mutations (associated with severe form)
q 3 month follow-up at UNC to evaluate for somatic and CNS disease and determine need for ERT and/or HSCT

YES
Referral to Duke for hematopoietic stem cell transplant (HSCT)
60,000 infants screened

68 Screen Positive Cases

9 MPS-I +

1 true positive (WM)
Homozygous p.Gln70*
pathogenic variant
Plasma IDUA low
+ all urine GAGs

Clinical exam c/w
severe MPS-1 at 4
months
s/p HSCT 5 months

7 Black 1 White
2 heterozygous
pathogenic variant and
pseudodeficiency allele
6 with 1-3
pseudodeficiency
variants

10 Indeterminate

8 Black 2 White
Normal exams
1-3 pseudodeficiency alleles
1 low plasma IDUA
(9 pending)
2 normal chondroitin sulfate
(8 pending)
Newborn Screening for
MPS I

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We are developing *Early Check*, a voluntary newborn screening research study.

**DBS from infants whose parents consent would undergo additional testing for conditions to be determined**

**Opportunities to**
- Determine population prevalence
- Detect early symptom onset
- Examine genotype-phenotype correlations
- Test pre-symptomatic treatments

**Could reduce the length of time for conditions to be added to the RUSP by providing evidence of accurate high-throughput screening technology, lab capacity, treatment efficacy, and parental acceptance**
Planning and communication

Finalizing conditions and methodology

Public web site
www.earlycheck.org

Advisory group

Developing plan for IT and informatics
IRB
Developed a decision model for conditions to be included

- Types of conditions
- High throughput validated assay on DBS
- Treatment – Proven or Potential
- Incidence
- Expertise
- Not nominated for RUSP yet
Study ethical issues associated with voluntary NBS on a large scale and develop a plan for consent

• Consenting on a mass scale will be our most significant challenge
  • Multi-tiered consent process beginning in prenatal period
  • Electronic

• Other ethical issues related to disclosure of results such as carrier status and family adaptation
Fragile X syndrome

• Most common inherited form of intellectual disability (@1:4500)
• Males and females affected, males more severe
• Many individuals with FXS also meet the diagnostic criteria for autism (35-60%)
FX is now considered a spectrum of conditions

- Female premutation carriers at risk for FX-POI
- Male premutation carriers at risk for FX-TAS
- Other possible effects of premutation
- Premutation carriers are much more common than individuals with FXS
  - 1:209 females
  - 1:430 males
RTI investigators

- Psychology
- Medicine
- Chemistry
- Neuroscience
- Molecular microbiology
- Genetic counseling
- Bioethics
- Early childhood special education
- Family studies
- Public health
- Health behavior
- Communication

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FUNDING

• National Center for Advancing Translational Sciences
  • U-01 CTSA Collaborative Innovation Award
  • Project Title: Early Check: A Collaborative Innovation to Facilitate Pre-Symptomatic Clinical Trials in Newborns
  • UNC/RTI, Duke, Wake Forest

• John Merck Family Foundation
Can Genomic Sequencing Expand the Utility of Newborn Screening?

• Improve specificity and sensitivity of standard screening
  • Cystic fibrosis
  • Hemoglobinopathies
  • Severe combined immunodeficiency
  • PKU
  • Fatty acid oxidation disorders
  • Urea cycle disorders
  • Hearing loss
  • Tyrosinemia
  • Galactosemia
  • Lysosomal storage disorders (MPS I, Pompe disease)
  • Peroxisomal disorders (X-ALD)

• Test for additional conditions for which there are no current screening methods
  • Initiate presymptomatic treatment or surveillance
  • Identify presymptomatic infants for clinical trials
  • Gather data on prevalence, penetrance, clinical utility, cost effectiveness, impact on family, etc.