NC NEXUS

National Academies: NEXT-GENERATION SCREENING- THE PROMISE AND PERILS OF DNA SEQUENCING OF NEWBORNS AT BIRTH
SESSION II: LESSONS LEARNED FROM NEWBORN GENOMIC TESTING AND SCREENING
June 7, 2023

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UNC HEALTH Children's

Disclosures

- I have no disclosures

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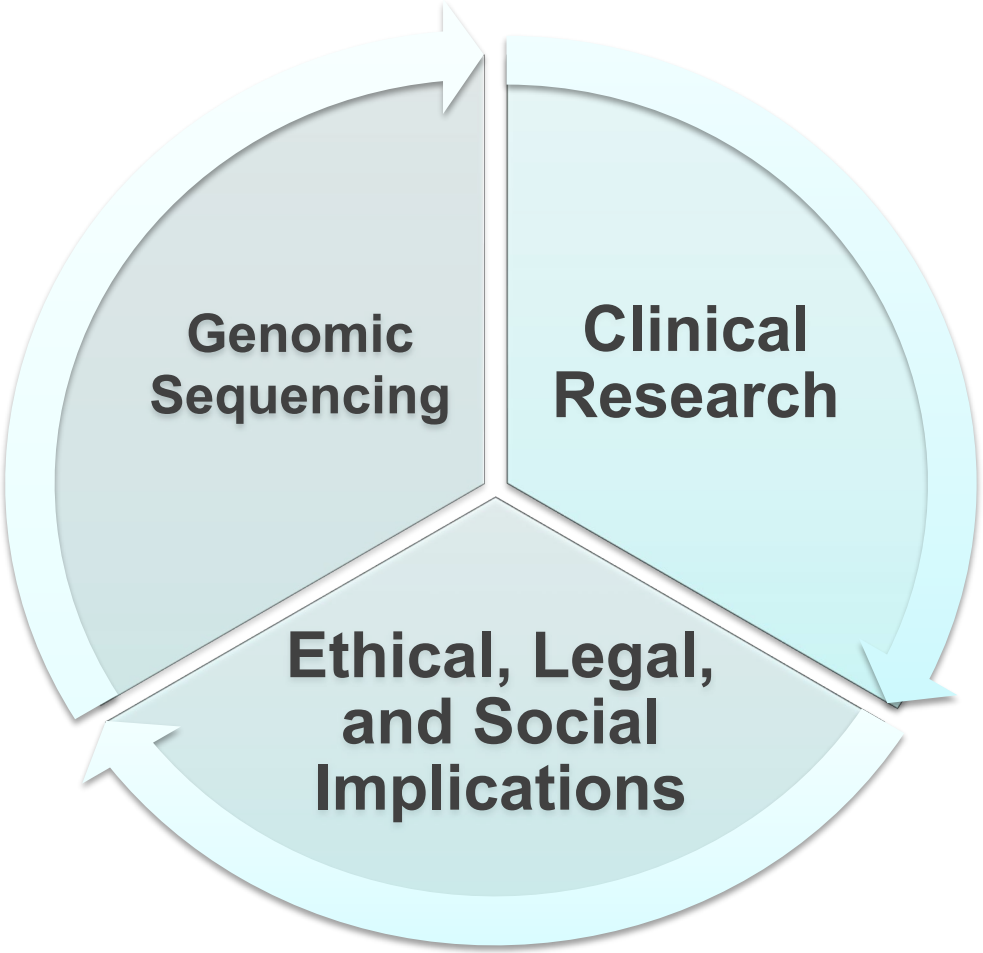
U-19 RFA NIH: Genomic Sequencing and Newborn Screening Disorders NHGRI and NICHD 2012

- …invite applications that propose to explore the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period.

3 Components Required



NCNexus
North Carolina Newborn Exome Sequencing for Universal Screening

Boston Children's Hospital
Until every child is well

BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

BCM
Baylor College of Medicine

UCSF
University of California San Francisco

UC San Diego
HEALTH SCIENCES

Rady Children's Hospital San Diego

Children's Mercy
KANSAS CITY

NSIGHT Projects

Newborn Sequencing in Genomic Medicine and Public Health

Berg et al. Pediatrics. 2017 Feb; 139(2): e20162252.
PMID: 28096516

ADVOCACY
CARE
RESEARCH
EDUCATION

UNC HEALTH
Children's

NCNexus

North Carolina Newborn Exome Sequencing for Universal Screening

jointly funded by NHGRI and NICHD U19 HD077632-03

Advocacy Research Education Care

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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.

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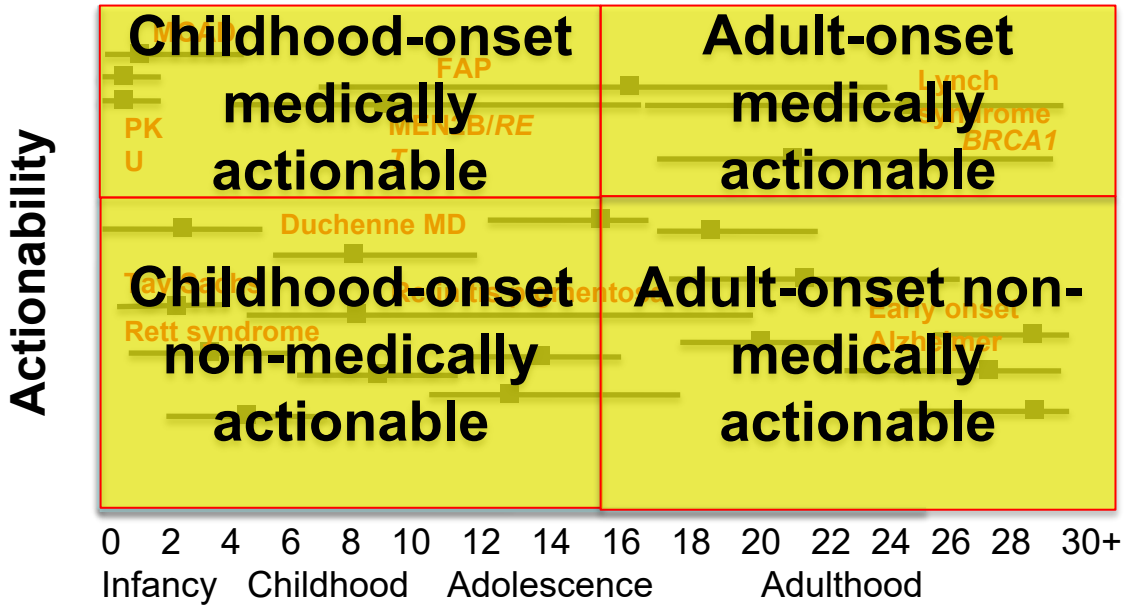
An age-based semi-quantitative scoring system

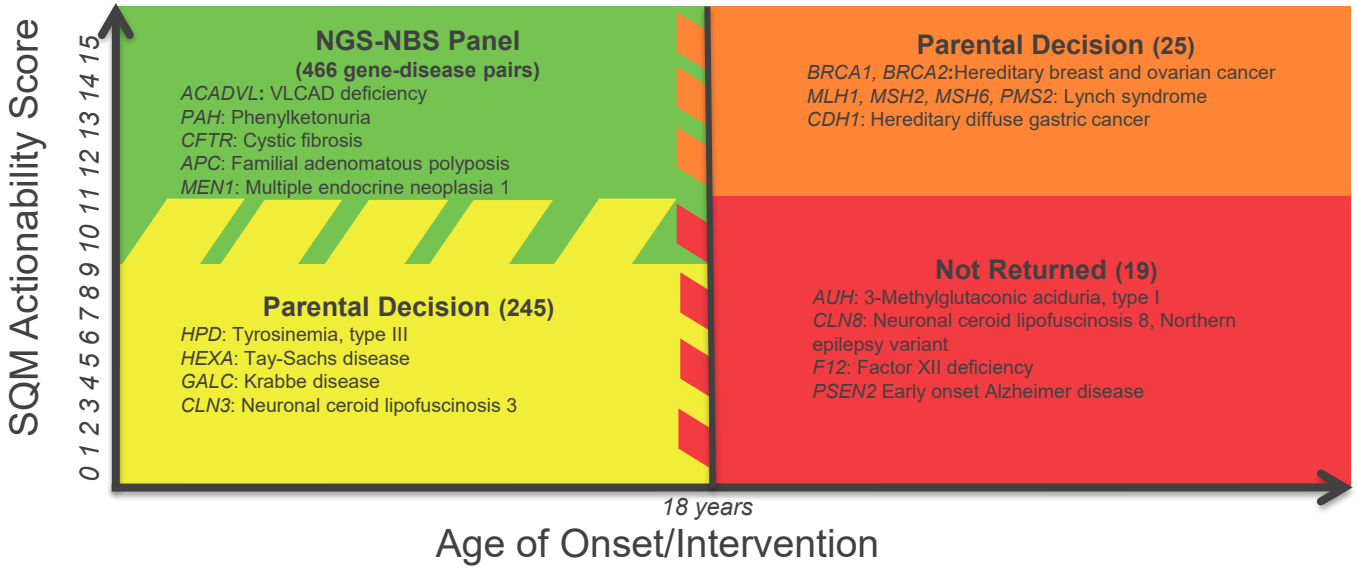


From Jonathan Berg

NC NEXUS BINNING COMMITTEE

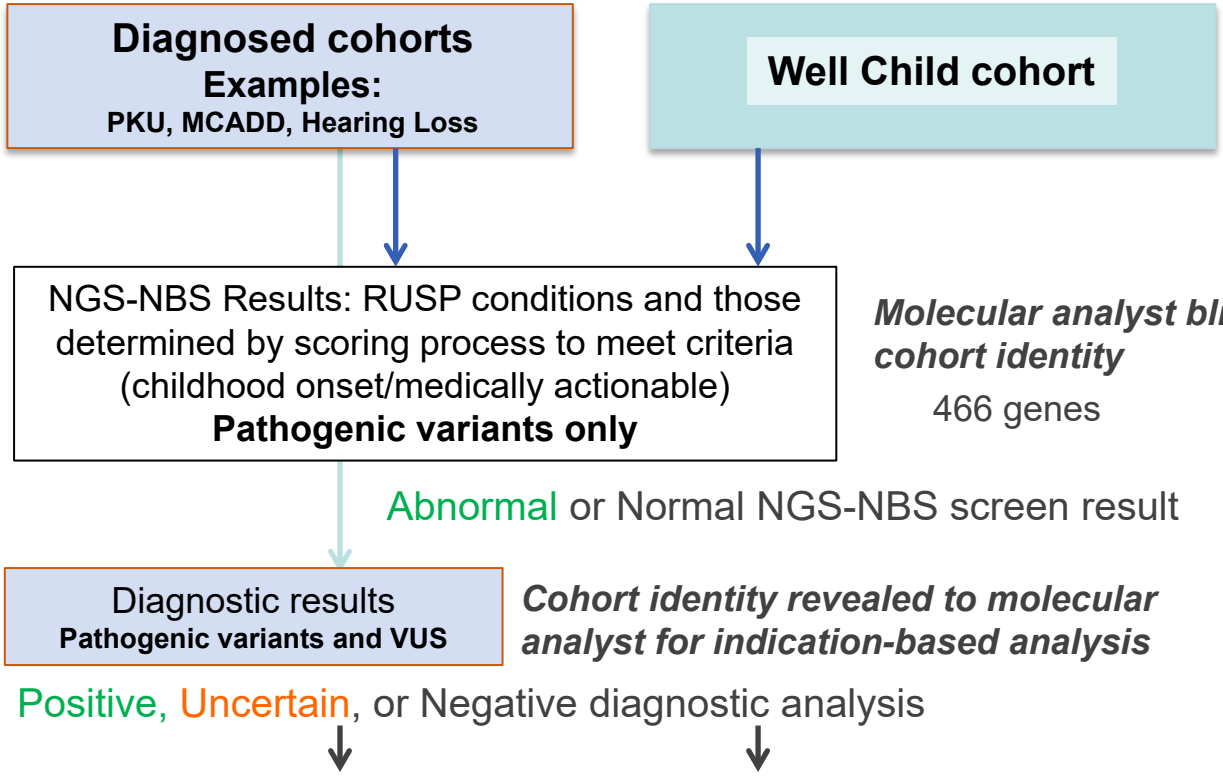
- Clinical geneticists
- Biochemical geneticists
- Genetic counselors
- Metabolic dietitians
- Molecular geneticists
- Medical genetics resident, fellows, post-docs, graduate students

NC NEXUS Binning 822 Gene-Disease Pairs



67 excluded due to insufficient evidence or prenatal onset

Milko et al. An age-based framework for evaluating genome-scale sequencing results in newborn screening. J Pediatr. 2019 Mar 6



2/3 are randomly assigned to a decision group and eligible to request additional information (AI) from 3 categories: 1) adult-onset actionable, 2) childhood-onset nonactionable, 3) carrier status

All returnable findings were Sanger-confirmed in the UNC Molecular Genetics CLIA lab

How do parents decide…

- whether or not to participate
- what information they want

Decision Aid – Categories of information

NGS-NBS

- Medically Actionable Childhood Conditions

Additional Information

- Non-medically Actionable Childhood Conditions
- Medically Actionable Adult Onset Conditions
- Carrier Status

RECRUITMENT

Total Approached 601
(386 WC, 216 DX)

Completed Pre-Enrollment 204
(145 WC, 59 DX)

Yes or Undecided on Decision Aid 172
(120 WC, 52 DX)

Consent Visit 111
(66 WC, 45 DX)

Consented to Sequencing 106
(61 WC, 45 DX)

Am J Hum Genet. 2020 Oct 1;107(4):596-611. doi: 10.1016/j.ajhg.2020.08.001. Epub 2020 Aug 26.

Genomic Sequencing for Newborn Screening: Results of the NC NEXUS Project

Tamara S Roman [1], Stephanie B Crowley [1], Myra I Roche [2], Ann Katherine M Foreman [1], Julianne M O'Daniel [1], Bryce A Seifert [1], Kristy Lee [1], Alicia Brandt [1], Chelsea Gustafson [1], Daniela M DeCristo [1], Natasha T Strande [3], Lori Ramkissoon [3], Laura V Milko [1], Phillips Owen [4], Sayanty Roy [3], Mai Xiong [3], Ryan S Paquin [5], Rita M Butterfield [6], Megan A Lewis [5], Katherine J Souris [7], Donald B Bailey Jr [8], Christine Rini [9], Jessica K Booker [10], Bradford C Powell [1], Karen E Weck [10], Cynthia M Powell [2], Jonathan S Berg [11]

WES revealed diagnostic results for 15 of 17 participants (88%) with inborn errors of metabolism

- 7 PKU, 7 MCAD, 1 Systemic primary carnitine deficiency
- 6 homozygotes, 7 compound heterozygotes (not all confirmed in trans)
- 2 NGS-NBS false negatives due to VUS (*MLYCD*) or heterozygosity (*BCKDHA*)
  - » Reported as “uncertain” findings on diagnostic report

Four of 106 participants (3.8%) had positive NGS-NBS results

- *LDLR* variant (autosomal dominant familial hypercholesterolemia)
- Female with *OTC* (ornithine transcarbamylase deficiency) variant
- *DSC2* splice acceptor variant (autosomal dominant arrhythmogenic right ventricular cardiomyopathy)
- *F11 (*autosomal recessive factor XI deficiency)

How did parents perceive the decision aids?

Decision Aid Perceptions	NGS-NBS DA		Additional Info DA	
	Mothers (*n* = 144)	Fathers (*n* = 131)	Mothers (*n* = 62)	Fathers (*n* = 53)
Clear and understandable	5.28 (0.75)	5.16 (0.61)	5.10 (0.80)	5.04 (0.76)
Gave me all the information I needed	5.15 (0.91)	5.04 (0.66)	5.10 (0.67)	5.17 (0.61)
I trusted the information	5.32 (0.56)	5.10 (0.68)	5.24 (0.56)	5.25 (0.62)
Prepared me to talk with the genetic counselor	4.84 (1.04)	4.69 (1.02)	5.02 (0.88)	4.87 (0.90)
Helped me decide	4.72 (0.94)	4.63 (0.94)	4.60 (0.94)	4.70 (0.93)
Information applied to me	4.33 (1.00)	4.05 (1.04)	4.48 (0.90)	4.23 (0.87)
Easy to log in	5.17 (0.86)	5.05 (0.75)	5.35 (0.55)	5.25 (0.65)
Easy to get from one screen to another	5.37 (0.66)	5.22 (0.60)	5.24 (0.87)	5.23 (0.85)
I had no problems using it	5.26 (0.76)	5.08 (0.84)	5.06 (0.50)	5.34 (0.55)
Overall	**5.05 (0.49)**	**4.92 (0.46)**	**5.06 (0.50)**	**4.93 (0.50)**

Note. M (SD). Response scales ranged from 1 to 6, where larger numbers equaled more favorable perceptions. Feedback on the Decision Aid 2 is from participants who were randomized to make decisions about additional sequencing results.

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How did parents in the control and randomized arms react to their decisions?

Decision Outcomes	Control Arm		Decision Arm	
	Mothers (*n* = 27)	Fathers (*n* = 25)	Mothers (*n* = 58)	Fathers (*n* = 49)
Decision regret[a]	1.44	1.64	1.56	1.55
Satisfaction with partner decision making[a,b]	5.55	5.54	5.43	5.54
Test-related distress[c]	1.37	1.50	1.45	1.48
Concerns about child's future health[c]	2.18	2.24	2.51	2.54

Note. Results from Time 3 survey. Means are reported.

[a]Response scale ranged from 1 to 6.

[b]Only asked of couples

[c]Response scale ranged from 1 to 4.

Conclusions

- 88% sensitivity for detecting a molecular diagnosis in the metabolic cohort. ES is not as sensitive as traditional biochemical screening.
- Almost 4% had an NGS-NBS pathogenic or likely pathogenic variant.
- Participants made up their minds about NGS-NBS early on, largely by the end of the educational section of the decision aid.
- Parents tended to think the decision aid was helpful.
- Control and randomized parent groups did not differ from one another on decision outcomes, like regret, satisfaction with partner decision making, distress, or concerns about child's health.

The NC NEXUS Team

- Jonathan Berg
- Cynthia Powell
- Don Bailey- RTI
- Laura Milko
- Myra Roche
- Bradford Powell
- Megan Lewis - RTI
- Chris Rini - Northwestern
- Rita Butterfield
- Katie Souris
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- Rebecca Moultrie – RTI
- Susana Peinado – RTI
- Tania Fitzgerald - RTI
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- Kate Foreman
- Julianne O'Daniel
- Tasha Strande
- Art Aylsworth
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- Muge Calikoglu
- Joe Muenzer
- Dianne Frazier
- Neeta Vora
- Lacey Boshe
- Zahra Girnary
- Daniela DeCristo
- Kirk Wilhelmsen
- Phil Owen
- Dylan Young
- Alicia Brandt
- Christian Tilley
- Kristen Dougherty
- Chelsea Gustafson
- Andy Rivera
- Lonna Mollison
- Tamara Roman
- Stephanie Bellendir Crowley

NICHD U19 HD077632

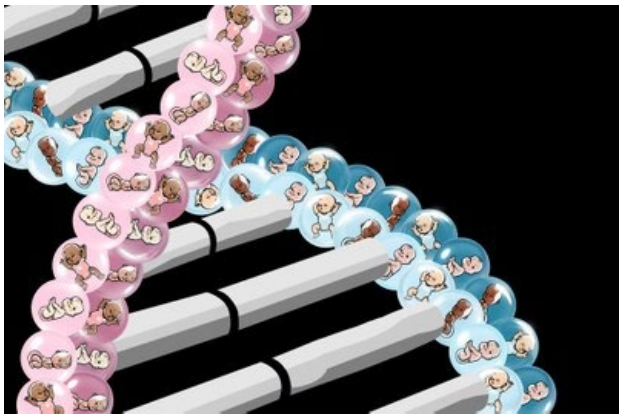
Benefits and Challenges of NGS NBS

BENEFITS

- Detection of conditions undetectable with current technologies
- Decrease number of false positive results
- Universal availability
- Precise delineation of the specific condition (SCID, hearing loss, etc.)

CHALLENGES

- Unknown clinical validity and clinical utility
- Variant interpretation
- Workforce – NBS labs, NBS system
- Cost
- Privacy
- Discrimination



Newborn screening in the U.S.

APHL.org