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North Carolina Newborn Exome Sequencing for Universal Screening

An NSIGHT research study jointly funded by NHGRI and NICHD

Project #5U19HD077632-03

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

RTI INTERNATIONAL

Objectives

- Brief background about standard newborn screening (NBS) as a public health program
- Limitations to adding additional conditions to newborn screening
- The potential of using next-generation sequencing in NBS
- Ethical issues raised about using this technology in NBS
- Explain our research study examining the possibility and potential of using next-gen sequencing to improve the sensitivity and specificity of current NBS and to increase the number of conditions screened for in newborns
- Ways in which we are exploring these issues and helping parents make decisions about whether they would like to have their child participate

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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

Newborn Screening Task Force Report, Pediatrics 106: 383-427 (2000)

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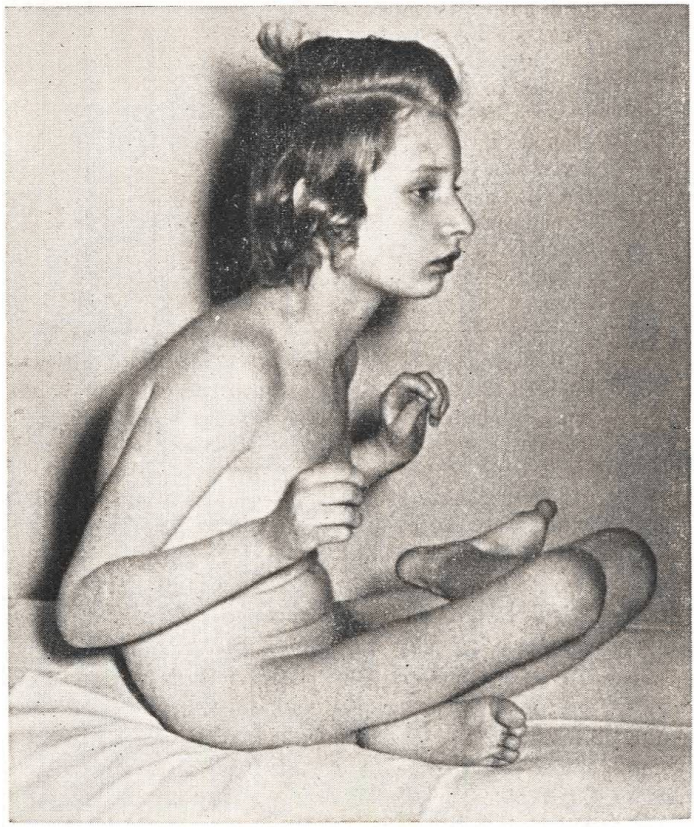


Untreated PKU

Prior to Newborn Screening

The Metabolic Basis of Inherited Disease, Stanbury et al . eds,

McGraw-Hill,1966

Treated PKU

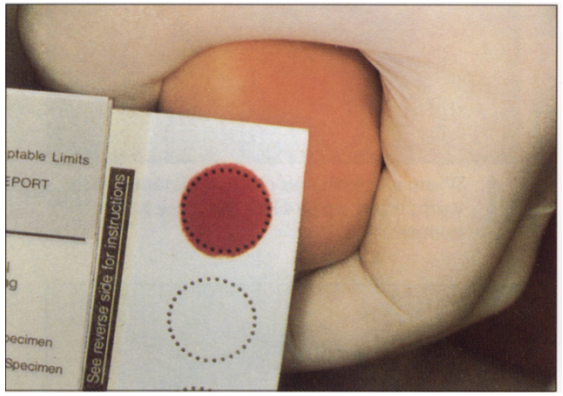
After Newborn Screening

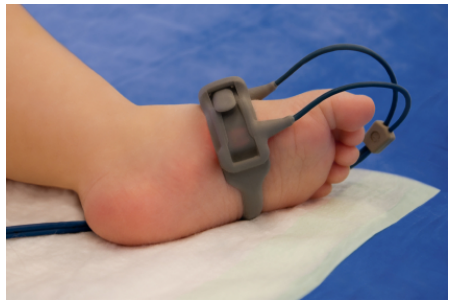
Me, You and PKU
a rare disease, a wonderful life
https://meupku.wordpress.com/

Recommended Uniform Screening Panel (RUSP)

- Effort to standardize conditions screened for by states across the US
- 2005 Task Force funded by HRSA recommended 29 conditions
- *Advisory Committee on Heritable Disorders in Newborns and Children*
  - http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/
- New conditions can be “nominated”
- Limitations to adding new conditions include no screening tool available, screening tool too expensive, no treatment

Newborn Screening





- 32 conditions are now on the Recommended Uniform Screening Panel (RUSP) http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/

- Molecular genetic testing is increasingly being used for second tier screening (e.g. CF, hemoglobinopathies) and to determine the severity or specific condition found on screening (e.g. MCADD, SCID, hearing loss)

Next Generation Sequencing in Newborn Screening

- **Theoretically**, barriers to adding any disorder to NBS panel may be overcome if there is a genetic etiology established for a condition
- **But**, as recognized early on by Wilson and Jungner: "The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement is far from simple though sometimes it may appear deceptively easy"

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Next-Generation Newborn Screening Ethical Issues

- “Incidental” or “secondary” findings

http://newsmomsneed.marchofdimes.org

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“Incidental Findings”

- Testing can identify things that are not related to the original intent of testing (“incidental” or “secondary” findings”)
  - Example: Finding a mass in the brain (?tumor) when doing a CT scan in someone who was in a car accident and hit their head
- 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
- Protecting the autonomy of the child while balancing the rights of parents to have information

http://www.myelin.org

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Child's Autonomy

- Testing for adult onset conditions in infants
- "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
- Carrier status for hemoglobinopathies has been shared for more than 30 years and CF carrier status revealed for some in standard NBS
- Research studies have not shown deleterious effects to children/ adults learning information but there have been few studies

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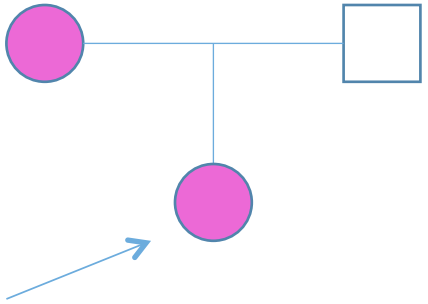
Autosomal Dominant Conditions

- 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?
- Some have argued that children should not have screening to provide genetic information about their parents



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Next-Generation Newborn Screening Ethical Issues

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

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Why screen for conditions that don't fulfill the definition of "treatable" in the traditional sense, such as those associated with intellectual disability?

- Ends the search for a cause (the "diagnostic odyssey")
- Avoids unnecessary and expensive testing
- Decreases the time to interventions (therapy services, etc.)
- Informs family of genetic risk information

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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.

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NC NEXUS Overarching Aims

1. Study how Next Generation Sequencing (NGS)-Newborn Screening (NBS) can extend the utility of current NBS.
2. Devise and evaluate a clinically oriented research framework for analysis of NGS-NBS.
3. Develop best practices for incorporating NGS-NBS into clinical care.

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Three Groups of Children to be Studied

- Cohort 1: children ages 0-5 years with one of four conditions identified by current NBS
  - PKU
  - MCADD
  - CF
  - Hearing loss
- Cohort 2: Children with rare genetic disorders not tested for with current NBS
  - Primary ciliary dyskinesia
  - Mucopolysaccharidoses
  - Wilson disease
  - Adrenoleukodystrophy
- Cohort 3: Well-child group, prenatal recruitment

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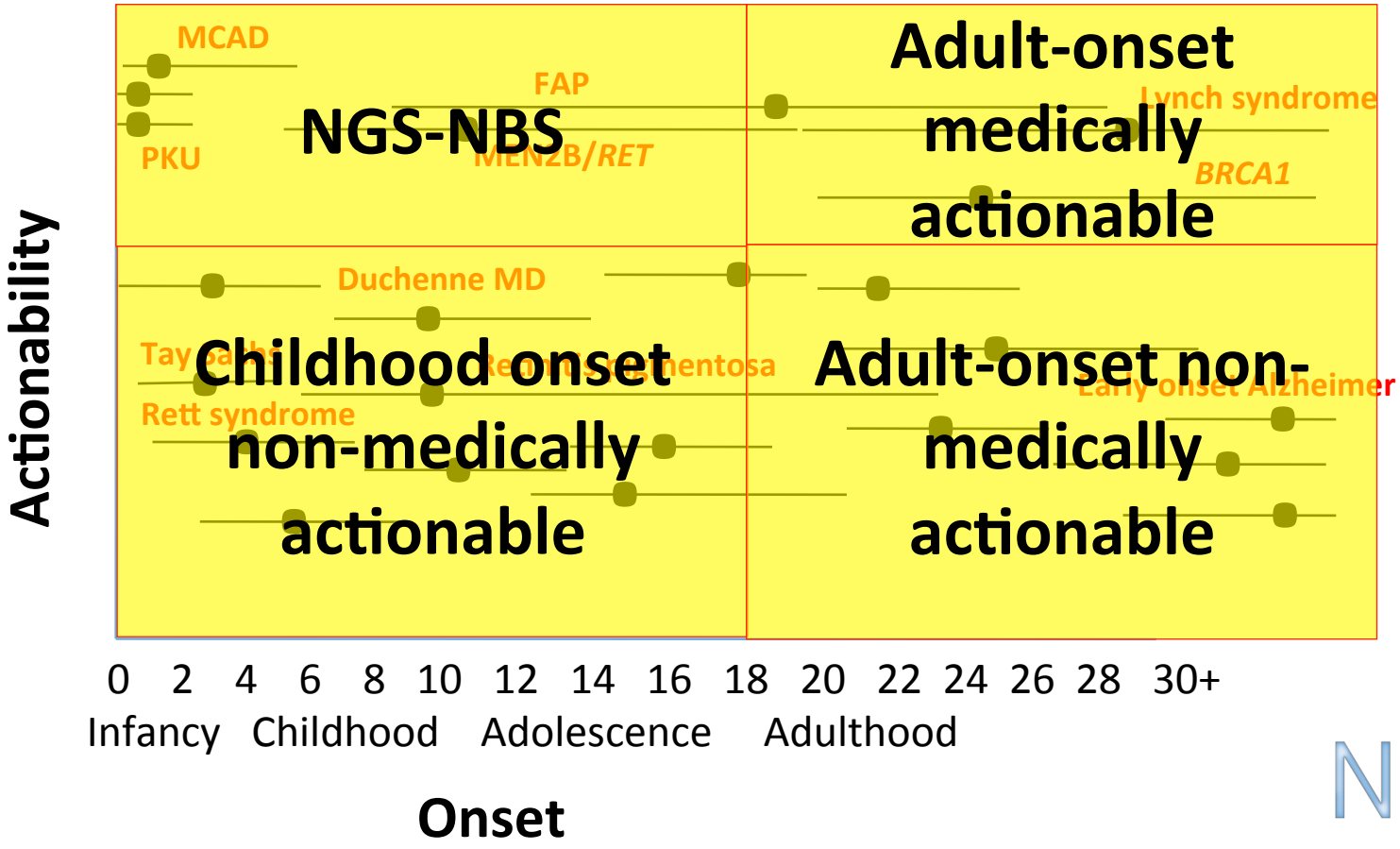
An age-based modified metric system



From Jonathan Berg

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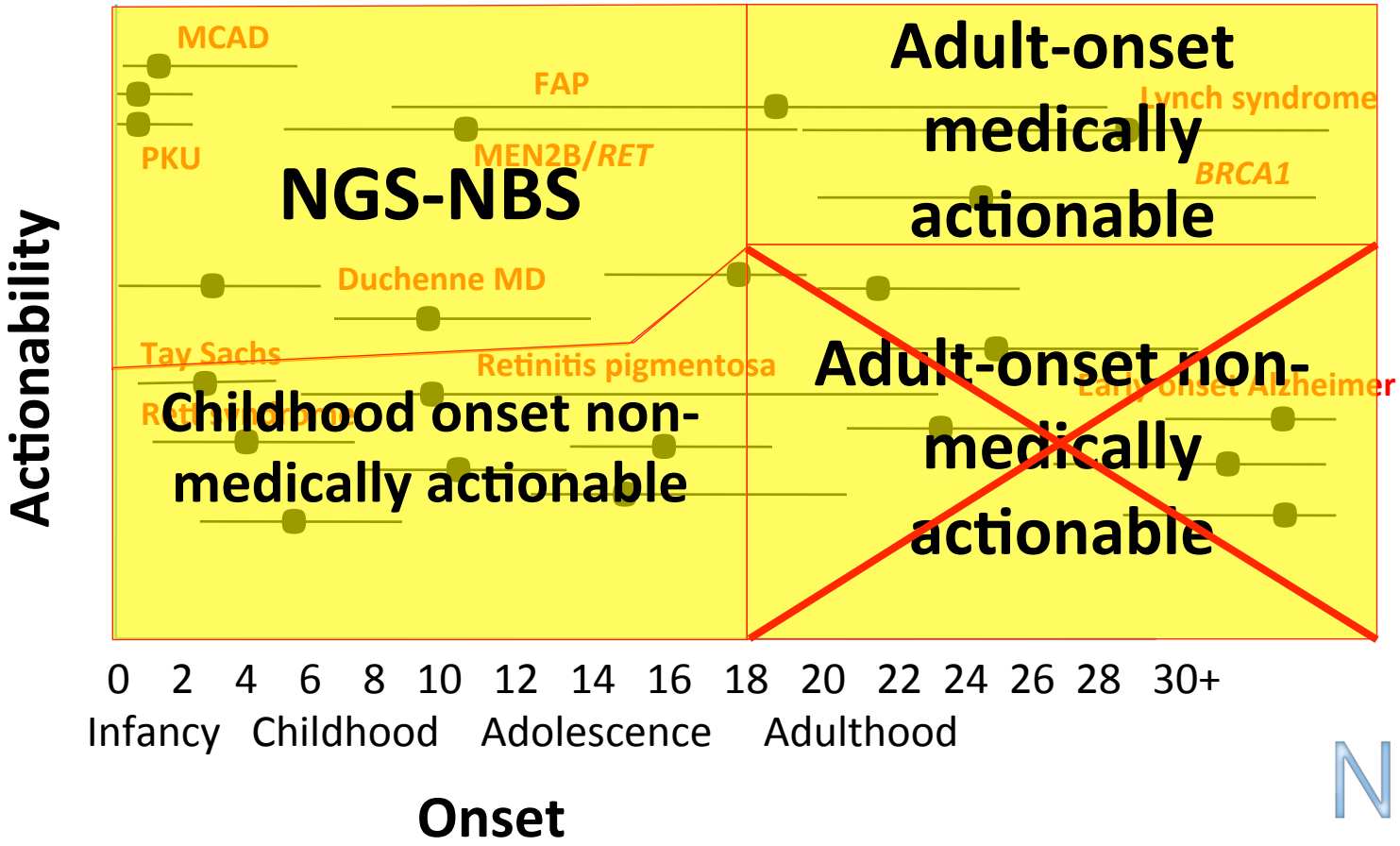
An age-based modified metric system

Age of onset can be variable for many genetic conditions



Actionability may change over time as new treatments become available.

From Jonathan Berg

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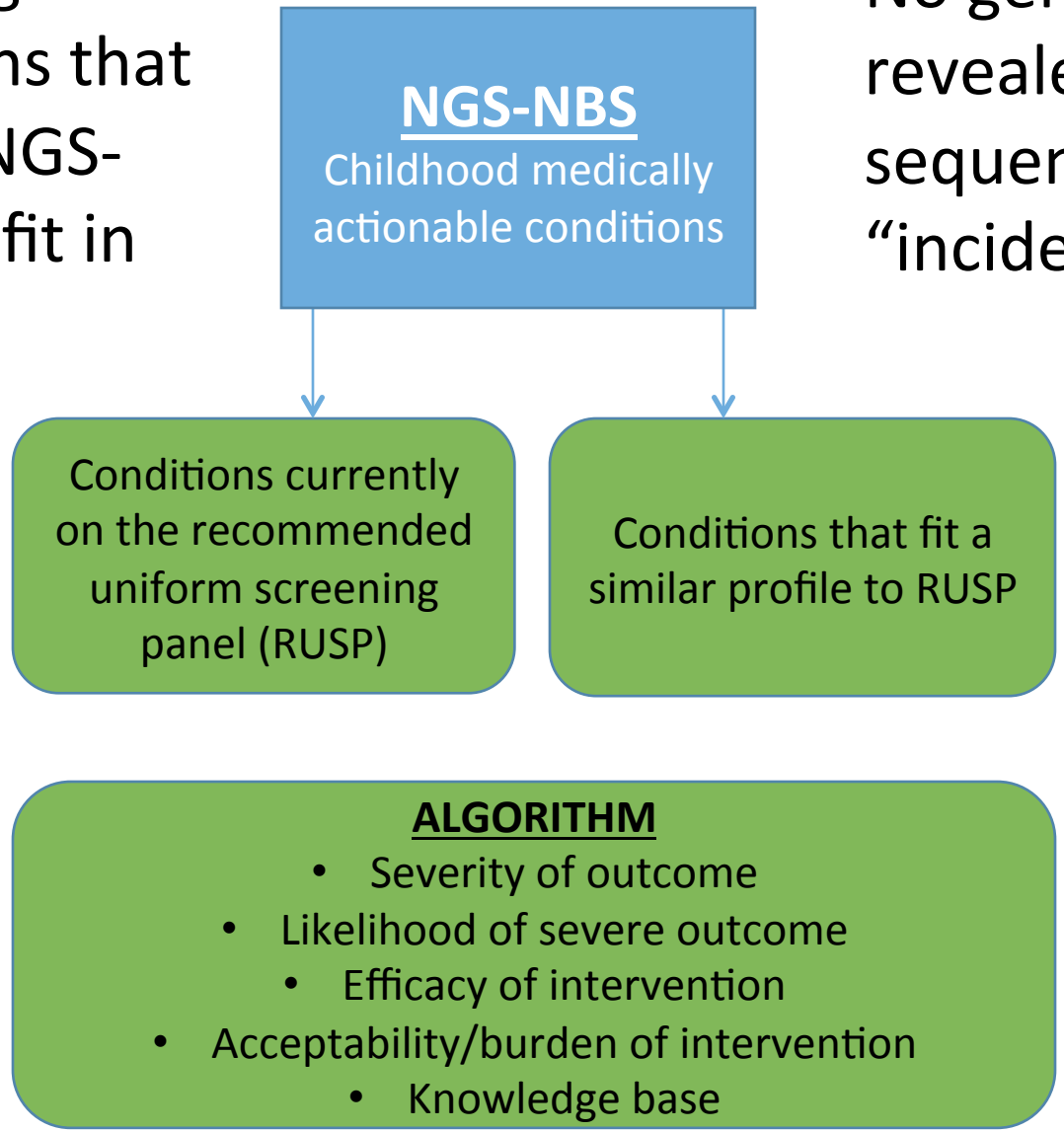
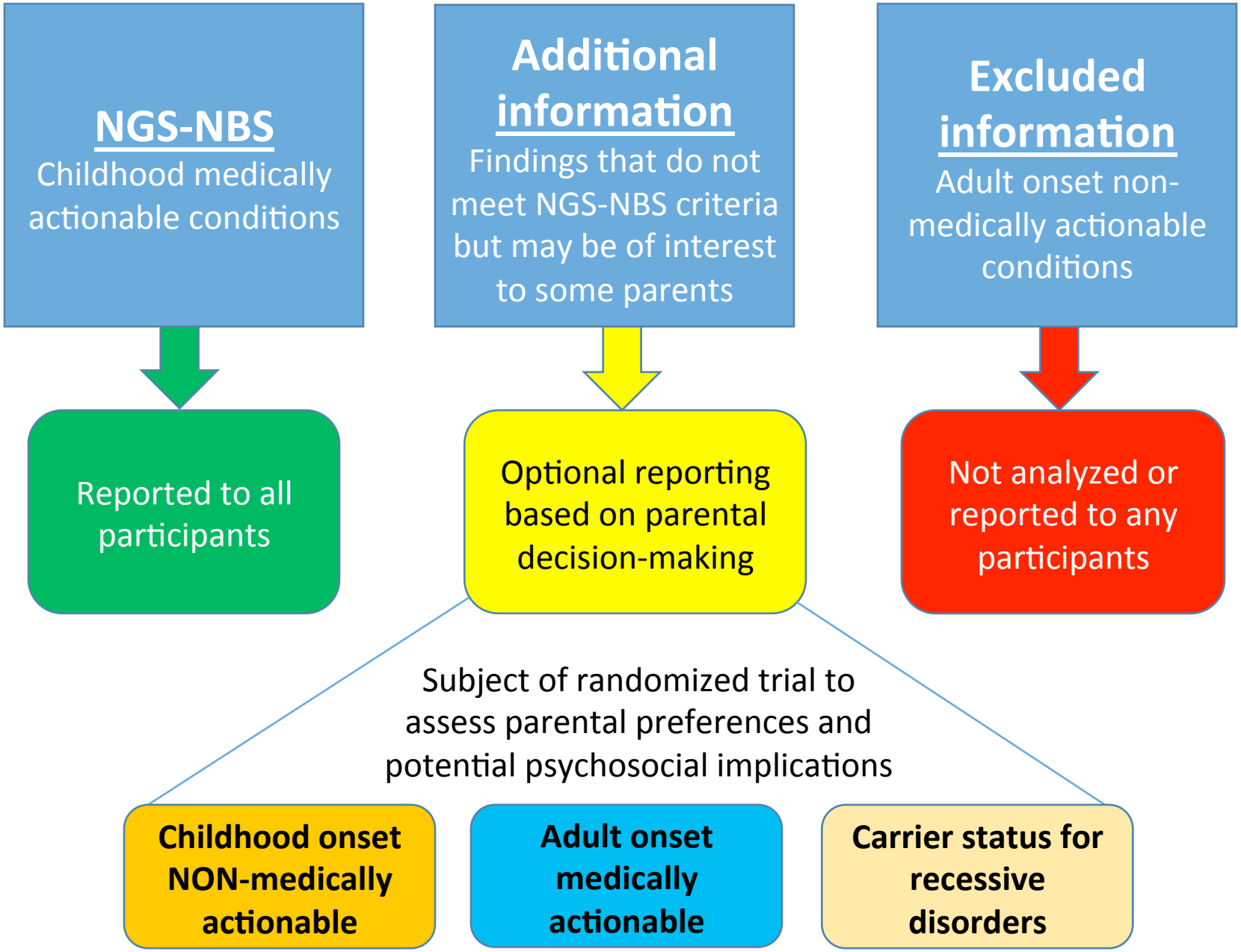
Actionability: scoring genes to determine conditions that are appropriate for a NGS-NBS versus those that fit in other categories



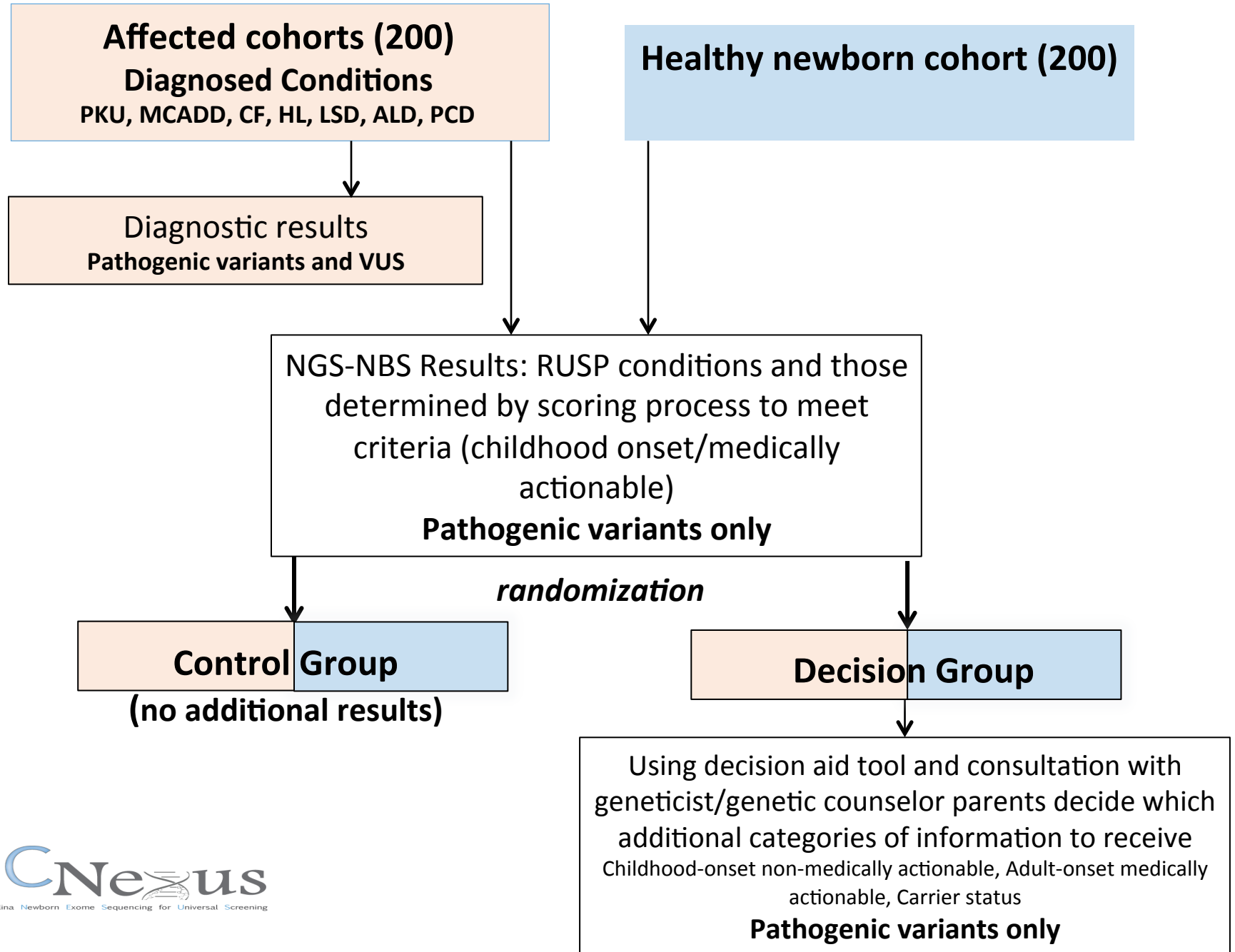
No genetic changes revealed through sequencing will be "incidental"

NGS NBS Candidate Condition

- Multiple Endocrine Neoplasia type 2B
  - Caused by mutations in the *RET* gene
  - 100% develop medullary thyroid cancer in infancy or early childhood
    - High rate of metastases at time of diagnosis
  - 50% develop pheochromocytomas (adrenal tumors)
  - 50% have negative family history
  - Not suspected if there is no family history because it is rare (1/35,000 for all types of MEN type B) and there are no early signs or symptoms in infants
  - Benefit of identifying the genetic mutation:
    - Thyroid cancer can be prevented by removing the thyroid before tumors develop
    - Can monitor the occurrence of pheochromocytomas by biochemical screening of catecholamines
    - Knowing an individual's mutation affects their medical management


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 analyzed or 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
Not analyzed unless parents request it

University of North Carolina (UNC) Project Overview



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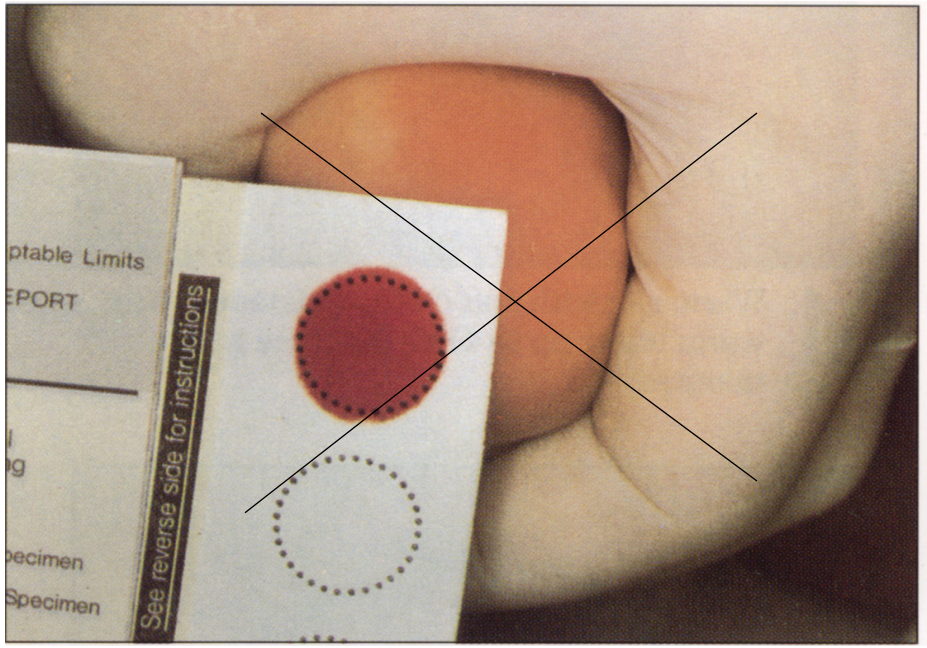
Using DNA from saliva



Scientific Objective for Project 3:

Develop best practices for incorporating next generation newborn screening into clinical care by exploring ethical, legal and social issues involved in informed decision-making and return of results

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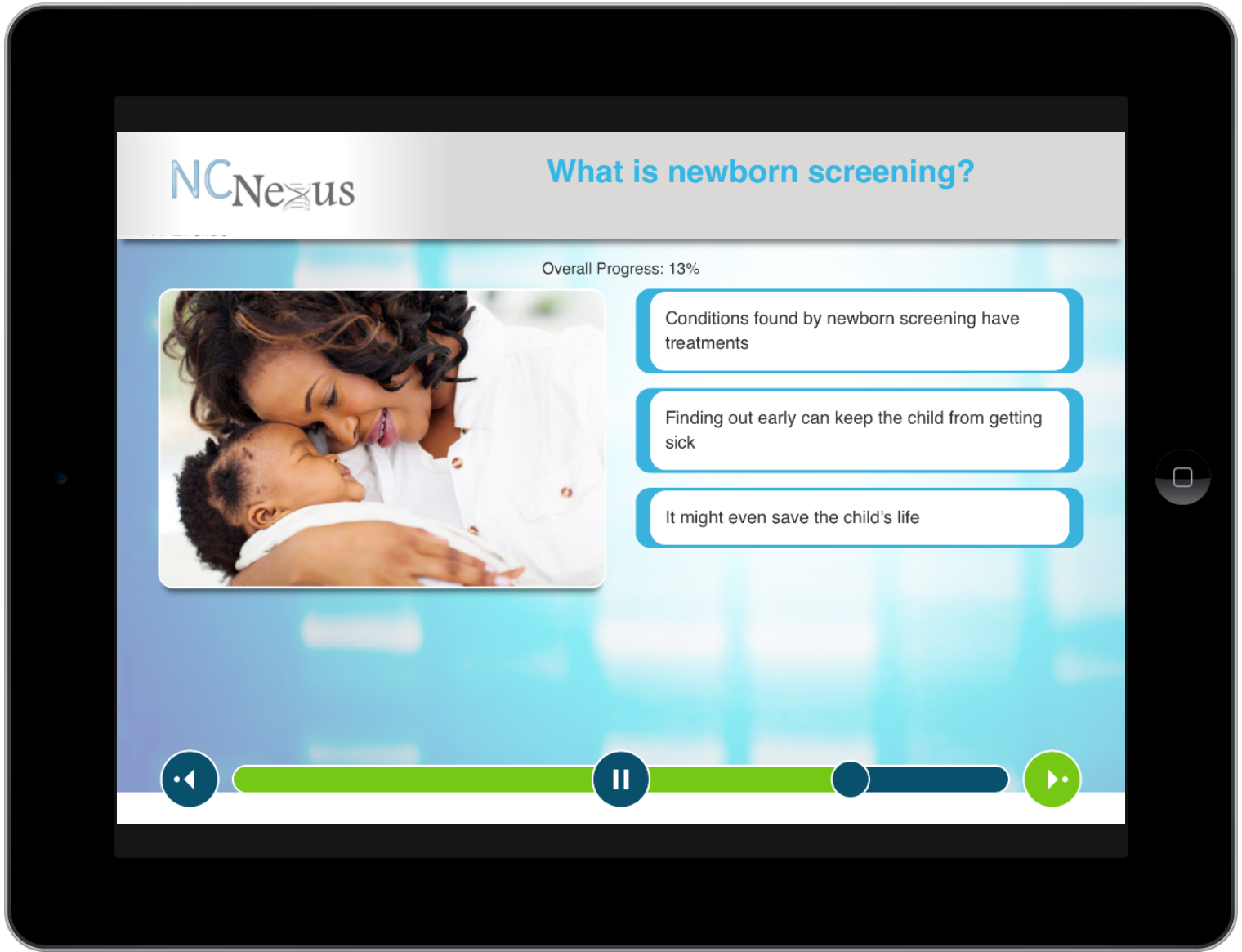
Decision Aid – contains 4 “sections”



Traditional Newborn Screening and Similar Conditions

Non-Medically Actionable Childhood Conditions

Medically Actionable Adult Onset Conditions

Carrier Status

Screenshot – Decision about Genomic Sequencing

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NC NEXUS TEAM

Principal Investigators

- Cynthia Powell – PI and Project 2 PI
- Jonathan Berg – PI and Project 1 PI
- Don Bailey – Project 3 RTI PI
- Chris Rini – Project 3 UNC PI
- Megan Lewis – Project 3 RTI Co-PI

Project Coordinator

- Laura Milko

Co-Investigators

- Myra Roche – Project 3 UNC
- Kirk Wilhelmsen – Project 1

Other Investigators

- Muge Calikoglu – Project 2
- James Evans – Projects 1 and 3
- Piotr Mieczkowski – Project 1 (HTSF)
- Phillips Owen – RENCI/Project 1
- George Retsch-Bogart – Project 2
- Pat Roush – Project 2
- Neeta Vora – Project 2
- Karen Weck-Taylor – Project 1

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