NSIGHT Projects

(Newborn Sequencing In Genomic medicine and public HealTh)

Cynthia M. Powell, MD

2016 APHL Newborn Screening and Genetic Testing Symposium

February 29, 2016

1:30 PM Keynote Session

Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) National Human Genome Research Institute (NHGRI)
Funding Opportunity Title	**Genomic Sequencing and Newborn Screening Disorders (U19)**
Activity Code	U19 Research Program – Cooperative Agreements
Announcement Type	New
Related Notices	• August 15, 2012 - Informational/Technical Assistance Pre-application Meeting for RFA-HD-13-010. See Notice NOT-HD-12-027.
Funding Opportunity Announcement (FOA) Number	**RFA-HD-13-010**

NSIGHT Research Questions

Must address one or more of the following:

A

- For disorders currently screened for in newborns, how can genomic sequencing replicate or augment known newborn screening results?

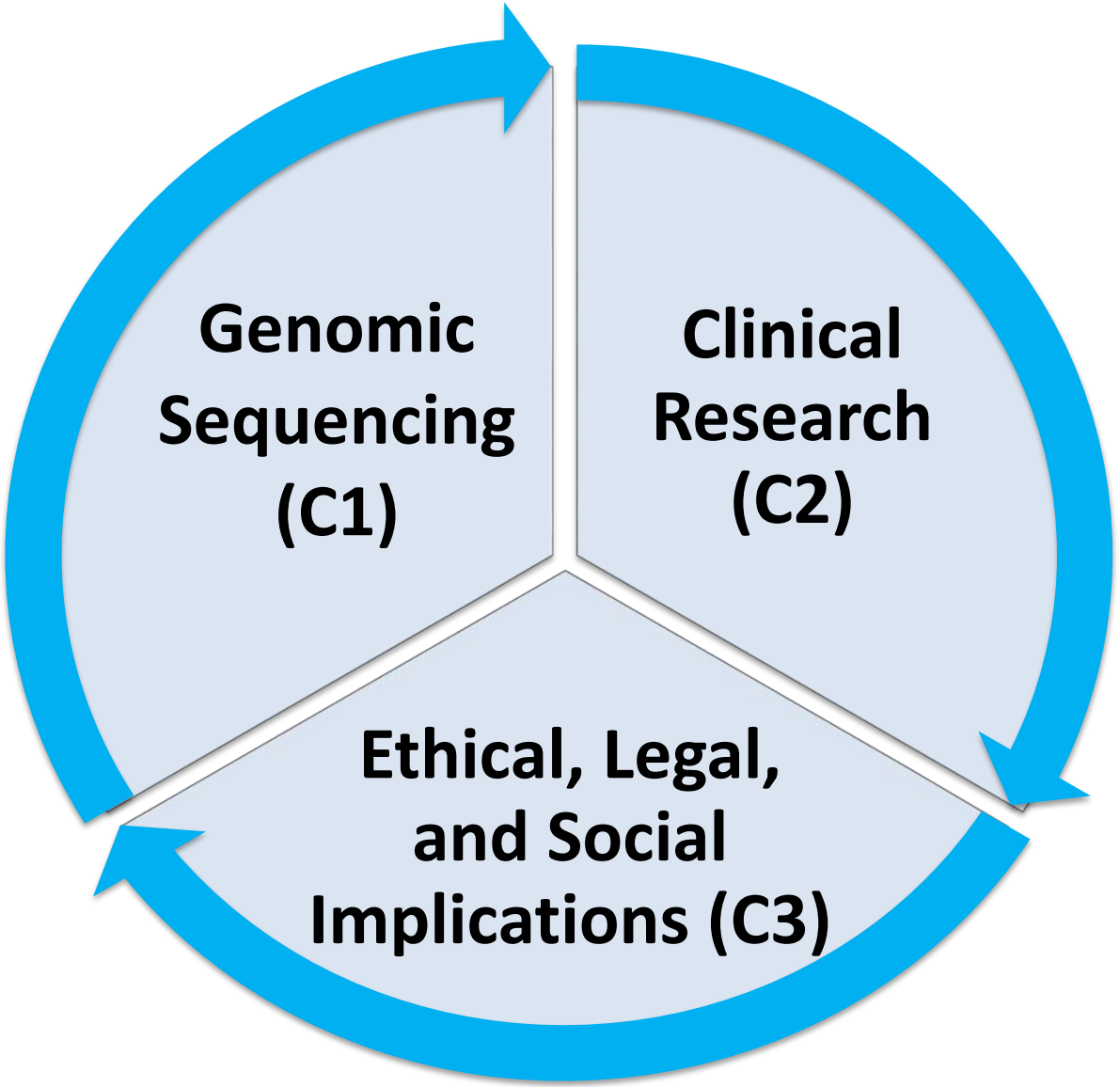
B

- What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?

C

- What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

Required 3 Components



Four Centers Funded: U-19 "NSIGHT"

- Brigham and Women's/Boston Children's Hospital
- Children's Mercy Hospital in Kansas City, MO/San Diego, CA
- University of California San Francisco
- University of North Carolina at Chapel Hill

Boston Children's Hospital
Until every child is well™

BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

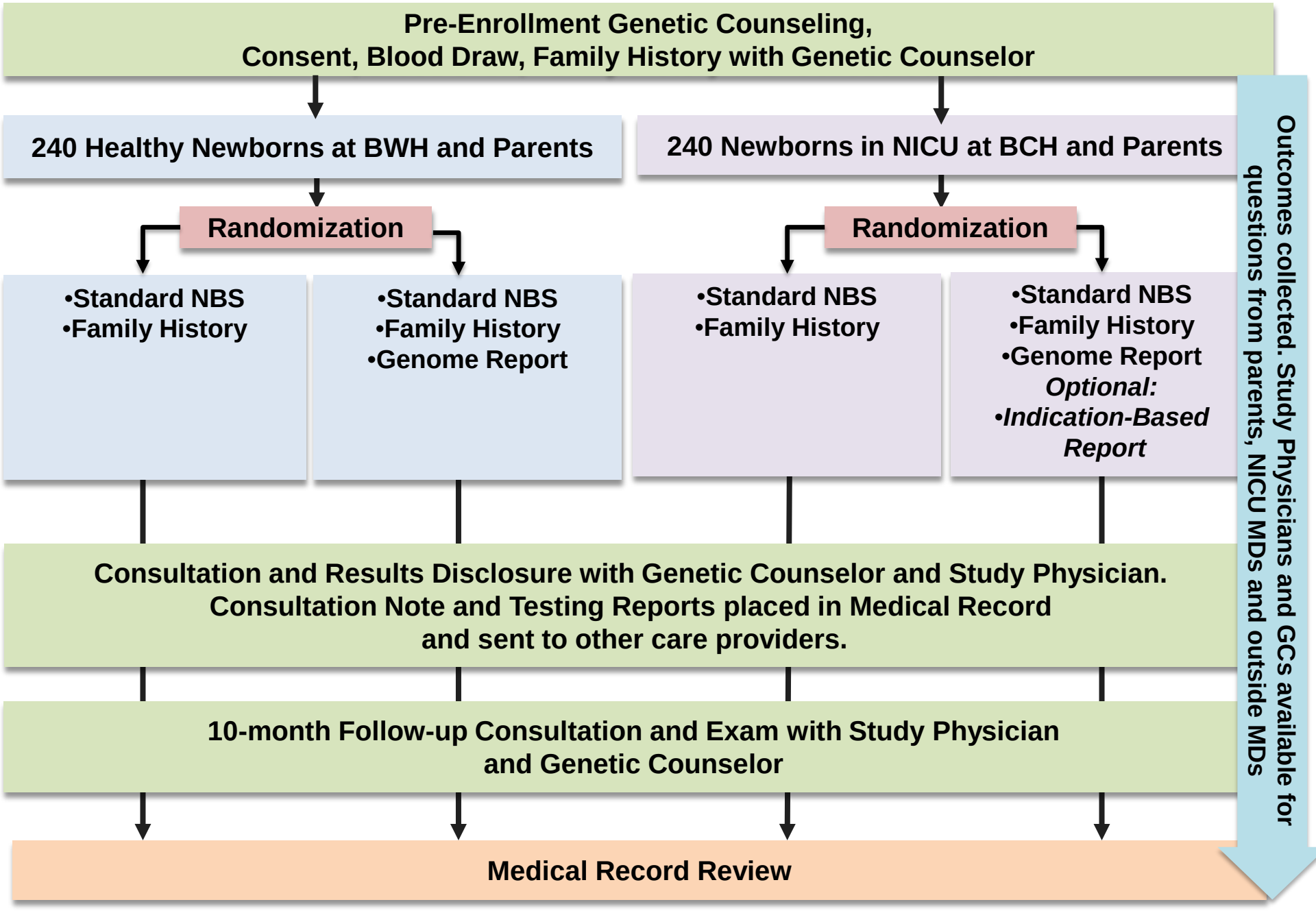
BCM
Baylor College of Medicine

The BabySeq Project

Boston Children's Hospital, Alan Beggs, PI
Brigham and Women's Hospital, Robert Green, PI

Co-PIs: Peter Park (HMS), Heidi Rehm and Richard Parad (BWH), Pankaj Agrawal and Ingrid Holm (BCH), Amy McGuire (BCM)

Project Overview



STAT-Seq: Clinical Utility and Ethical Implications of 2-day diagnostic genomes in Level IV NICUs

Center for Pediatric Genomic Medicine,
Children's Mercy Hospitals and Clinics,
Kansas City, MO

Rady Children's Hospital, San Diego, CA

Stephen Kingsmore, PI

STAT-Seq: Clinical Utility and Ethical Implications of 2-day diagnostic genomes in Level IV NICUs

Study Aims

- Develop routine 1-day clinical genome sequencing methods for NICU diagnosis of genetic diseases
- Prospective, randomized study of risks and benefits of STAT-seq in Level IV NICU
- Test hypotheses about utility of NICU genomes relative to standard care
  - Diagnostic rate
  - Time to diagnosis
  - Rate of change in care attendant to diagnosis
  - Impact on infant morbidity and mortality
  - Identify NICU subpopulations where genome sequencing shows clinical utility and cost effectiveness
  - Determine optimal times-to-result in NICU subpopulations
  - Ethnographic assessment of social, spiritual, psychological, emotional implications for families of whole genome sequencing (WGS) for acutely ill neonates, a population that may stand to benefit largely from WGS given the severity of illness.
- Develop an initial evidence base for physician adoption and provider reimbursement of WGS in Level 4 NICUs

Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening

University of California, San Francisco
Jennifer Puck, Pui-Yan Kwok, Barbara Koenig

UCSF and California Newborn Screening Program Projects

Whole exome sequencing and analysis of variants in newborn blood spots relevant to metabolic disorders and primary immunodeficiencies

ELSI How will “next generation sequencing” enhance, challenge, or transform traditional state-mandated NBS programs?

NCNexus

North Carolina Newborn Exome Sequencing for Universal Screening

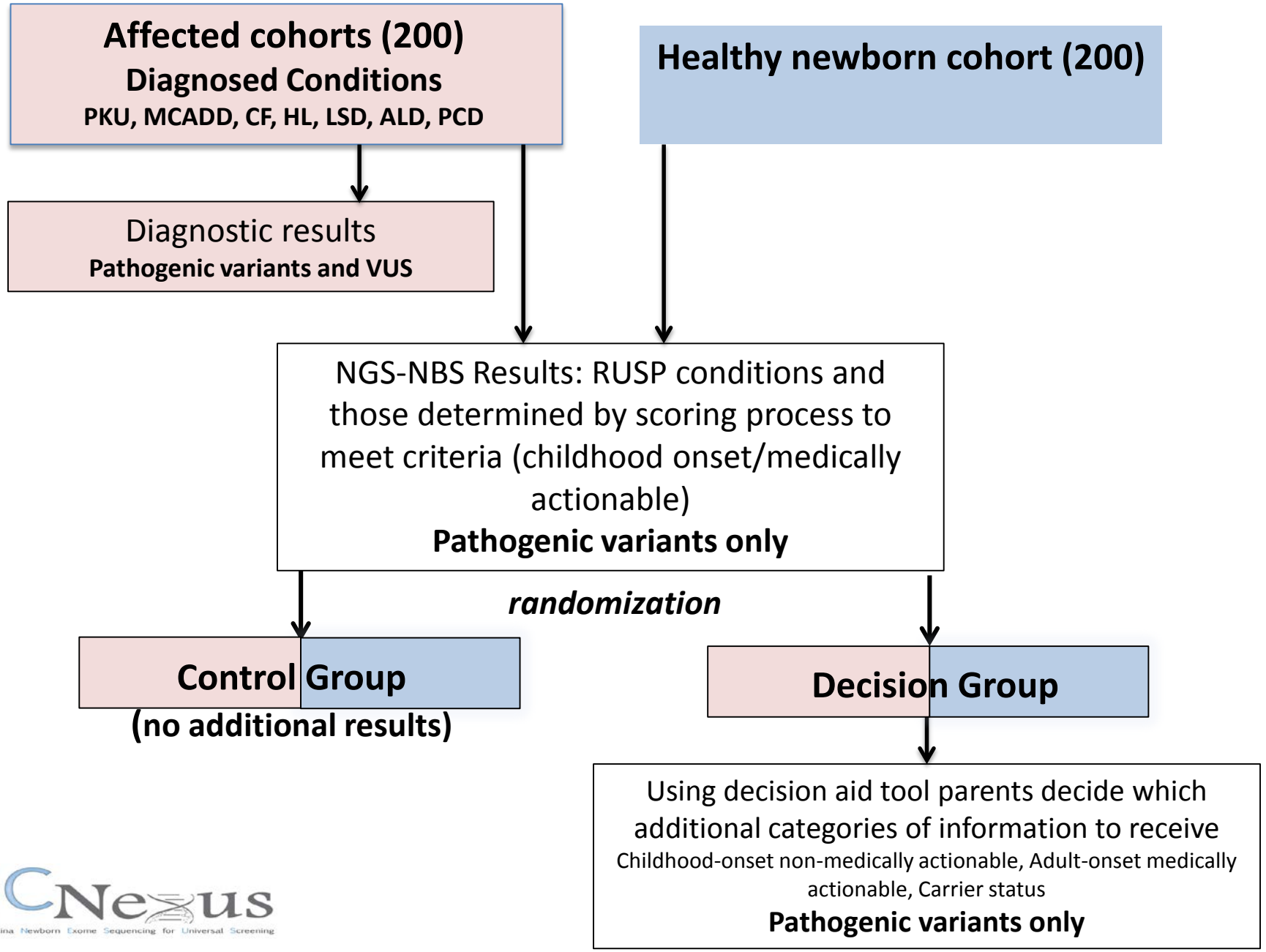
Overarching Aims

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.

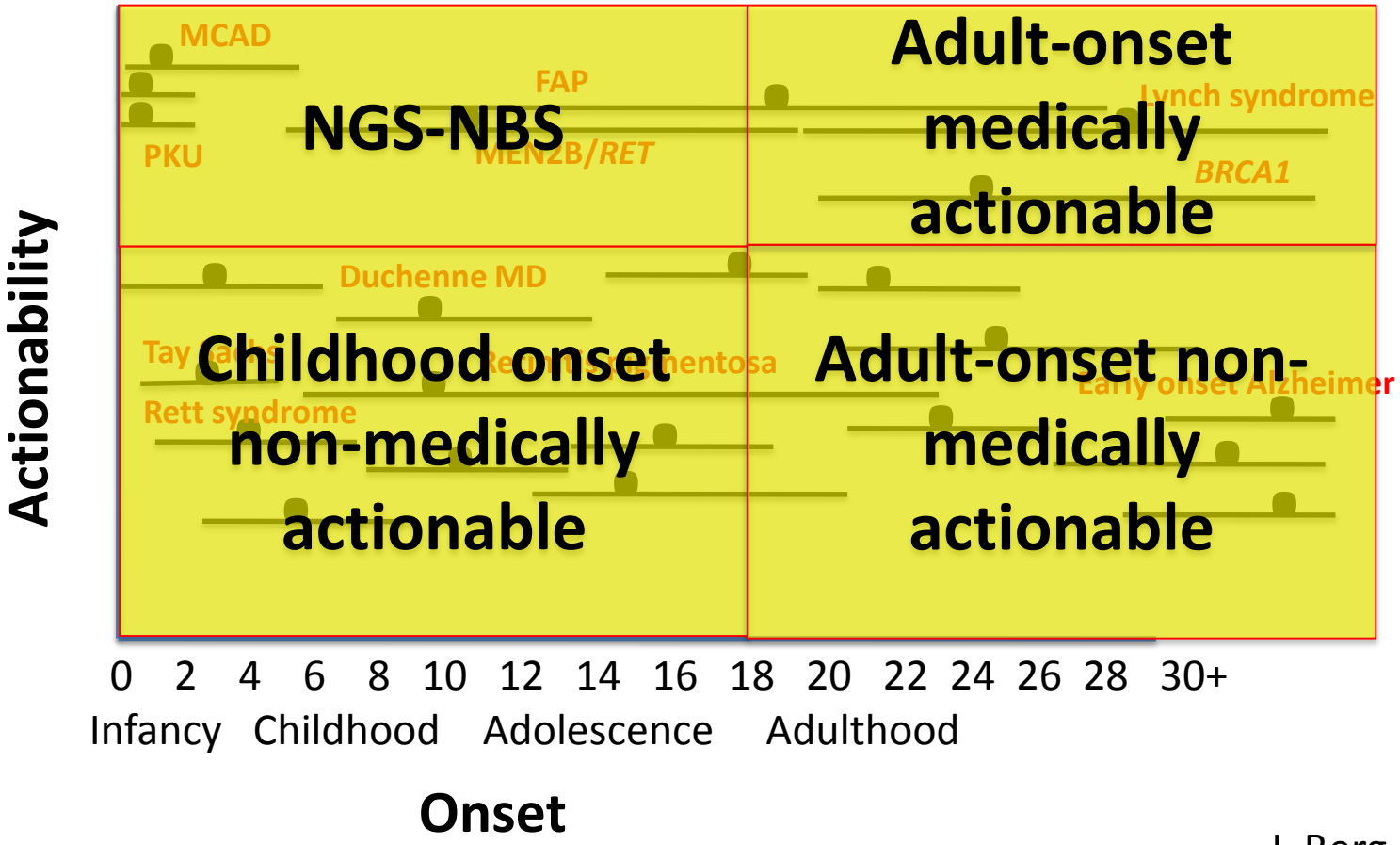
3. Develop best practices for incorporating NGS-NBS into clinical care.

University of North Carolina (UNC) Project Overview

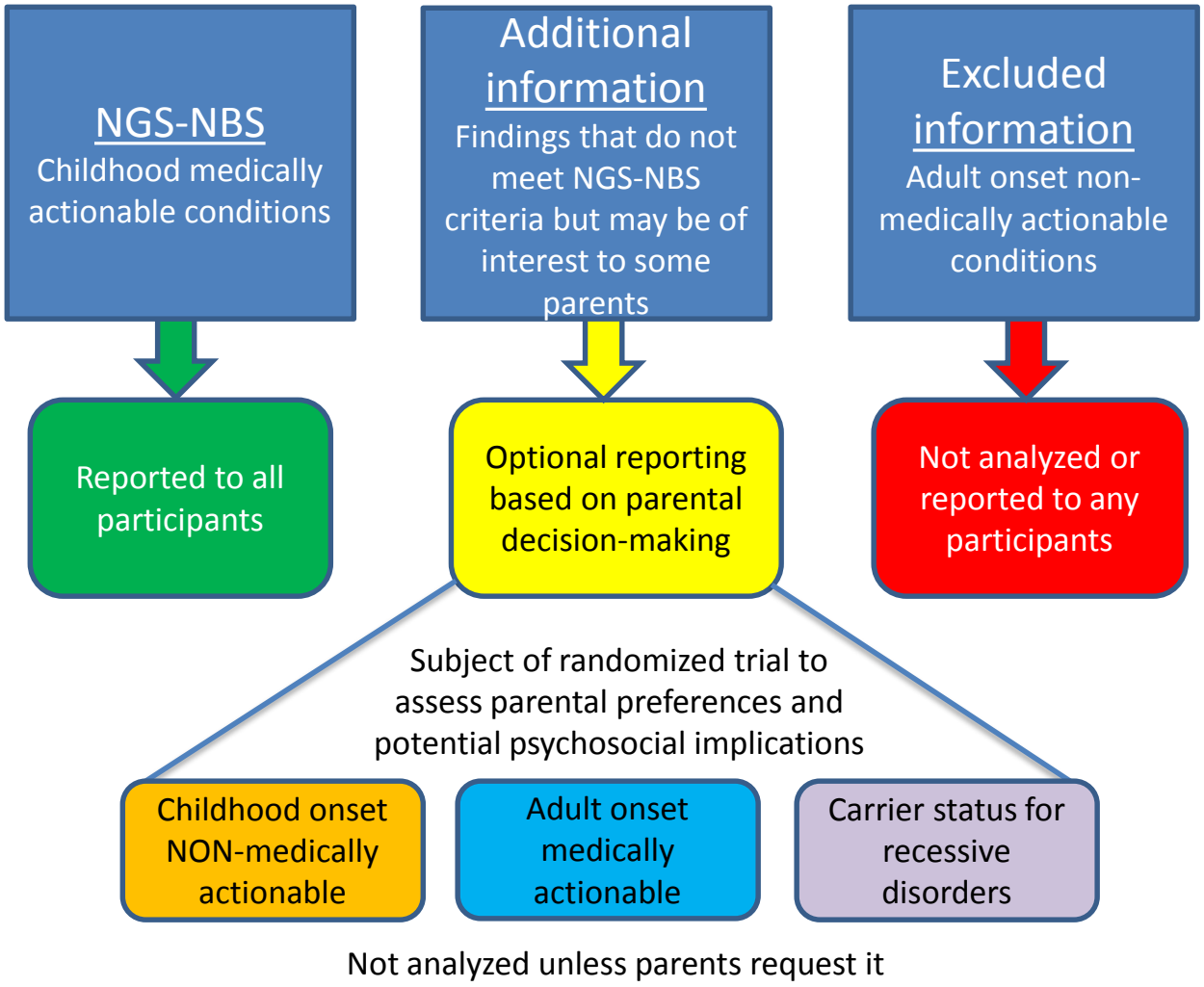


NCNexus
North Carolina Newborn Exome Sequencing for Universal Screening

An age-based modified metric system



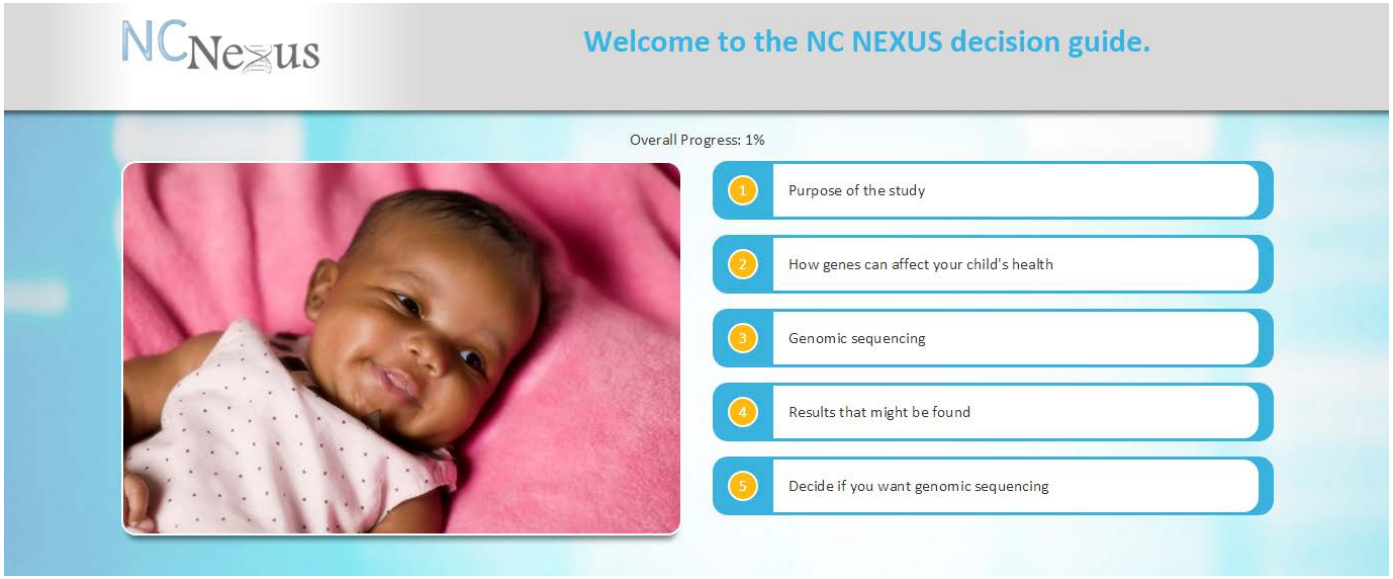
J. Berg


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

NC NEXUS Decision Aid

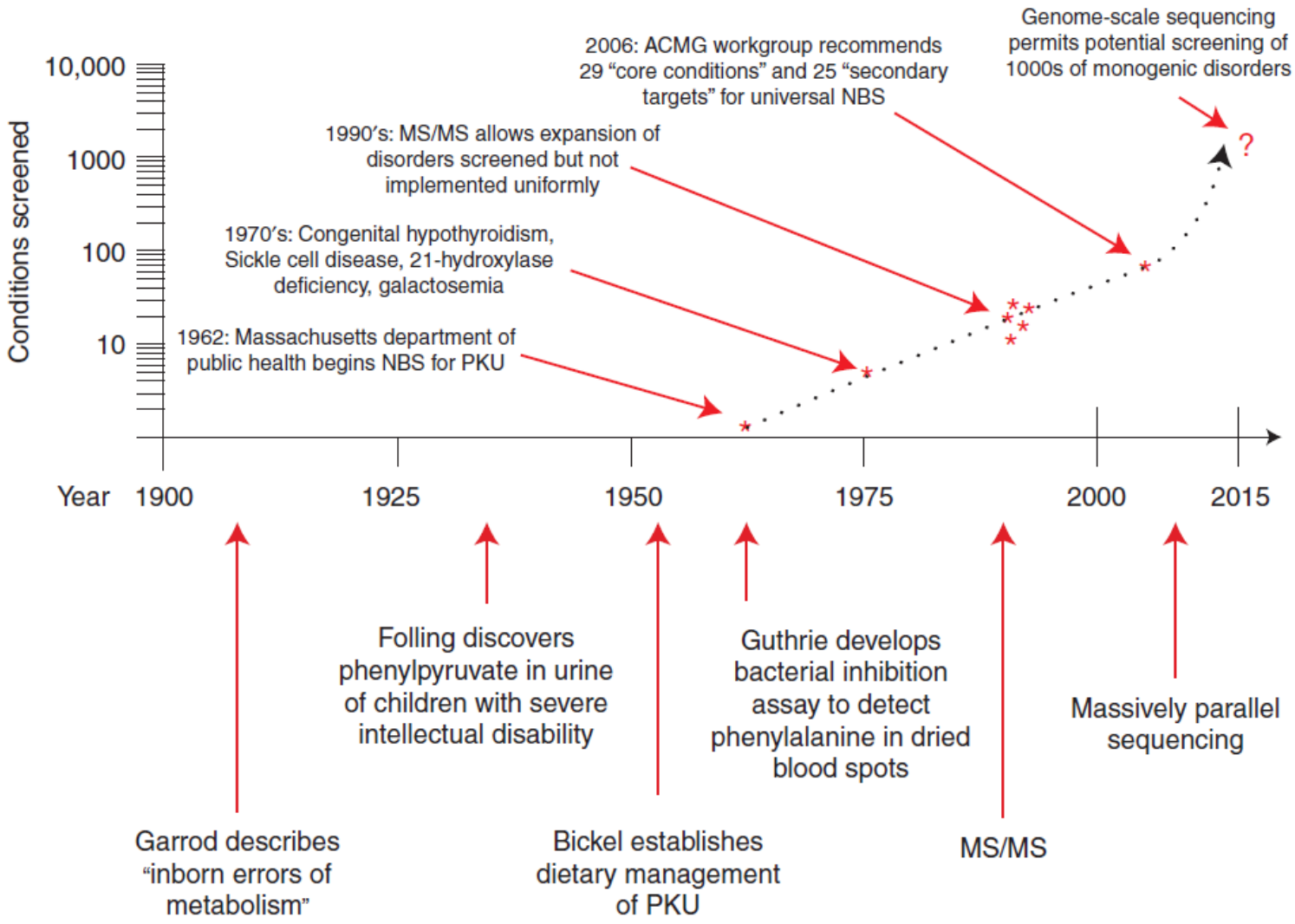
Combined areas of expertise

- Health communication
- Health literacy
- Informatics and computing technology
- Human computer interaction
- Graphical design
- Pediatrics
- Genomics



NSIGHT Projects and FDA Oversight

- Projects contacted by the FDA shortly after awards announced
- Informed that pre-submission to determine need for IDE was required
- FDA determined that UNC project posed significant risk and required full IDE submission and oversite



Berg JS and Powell CM, Cold Spring Harb Perspect Med 2015;5:a023150

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

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 and privately funded screening in progress
- Mandatory/voluntary? Health disparities
- Demands on public health and health care systems
- Genetic discrimination (employment, insurance,…)

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

RTI INTERNATIONAL

NC NEXUS TEAM

Cynthia Powell

Jonathan Berg

Don Bailey

Megan Lewis

Myra Roche

Chris Rini

Laura Milko

Kirk Wilhelmsen

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

RTI INTERNATIONAL

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
- (Andy Rivera)

Investigators

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

An NSIGHT research study jointly funded by NHGRI and NICHD
Project #5U19HD077632-03

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NC NEXUS TEAM

- Binning Committee
  - Joe Muenzer
  - Muge Calikoglu
  - Art Aylsworth
  - 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
  - Don Bailey
  - Jonathan Berg
  - Cynthia Powell
  - Tess Stohrer
  - Lacey Boshe
  - Rebecca Moultrie
  - Tasha Strande
  - Tania Fitzgerald
  - Zahra Saadat Girnary
- Collaborators
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  - Craig Buchman
  - Zheng Fan
  - Dianne Frazier
  - Robert Greenwood
  - Michael Knowles
  - Margaret Leigh
  - Maimoona Zariwala
- Decision Aid
  - Ryan Paquin
  - Tania Fitzgerald
  - Rebecca Moultrie
  - Brittany Zulkiewicz
  - Ben Gil
  - Joe Hakooz (Innova)