NCNexus

North Carolina Newborn Exome Sequencing for Universal Screening

Cynthia M. Powell, MD, Jonathan S. Berg, MD, PhD, Donald B. Bailey, Jr. PhD
Professor of Pediatrics and Genetics

2014 APHL Newborn Screening and Genetic Testing Symposium

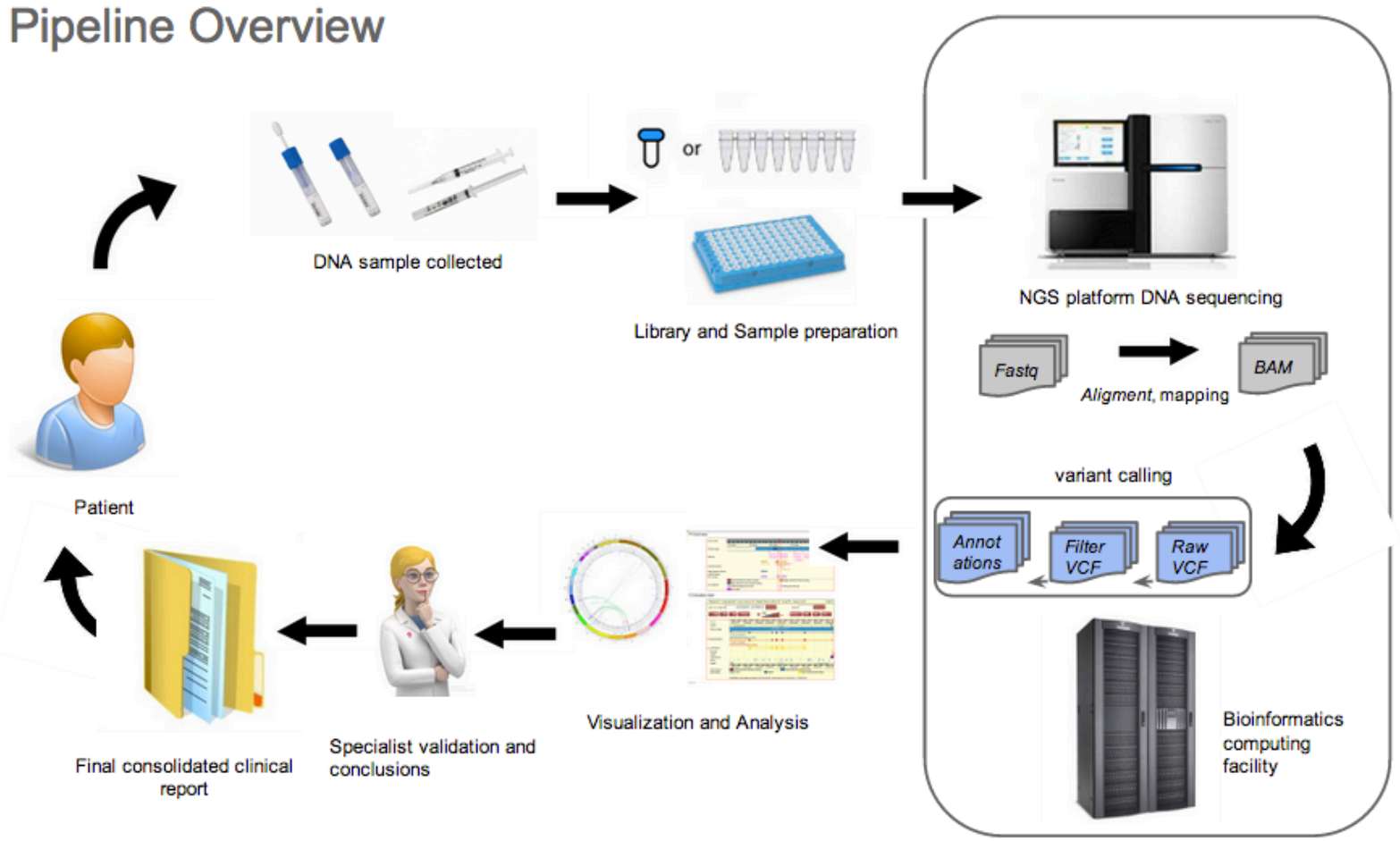
October 27, 2014

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Conflicts of Interest

- None

Next Generation Sequencing



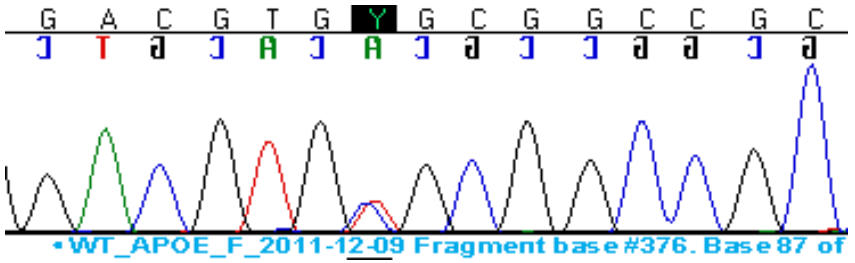
http://aimotion.blogspot.com/2014/08/mip-proposal-high-performance-pipeline-whole-exome-dna-sequencing.html

Next Gen Sequencing

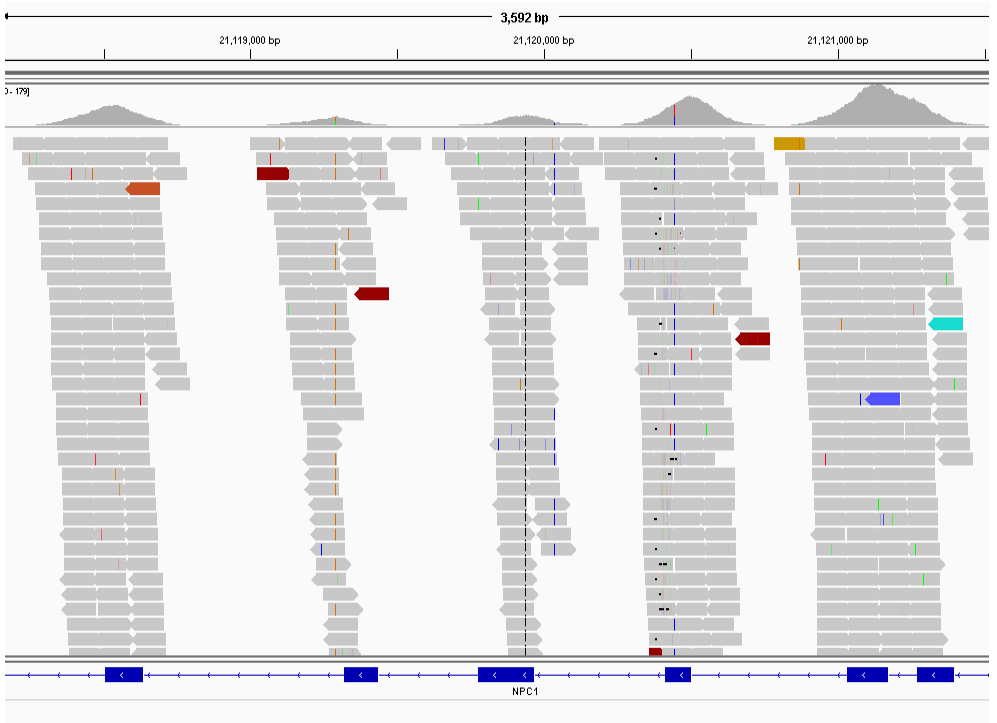
- Can search for mutations in all genes (20,000)
- Whole exome: just coding parts of genes (exons)
- Whole genome: everything (exons and introns)
- Analysis is complex – our understanding of what is a significant mutation and what is a benign polymorphism is incomplete

Sanger vs. Whole-Exome Sequencing: Technical Considerations

- Sanger
  - 100-800+ bp
  - Targeted mutation analysis
  - Complete coverage
  - “Gold standard”



- WES
  - 30 Mb in exome (3 billion in entire genome)
  - Mutation fishing in many targets
  - Interpretation difficulties
  - Not considered reliable enough to use without confirmation



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

August 2012

- **Question A)** For **disorders currently screened for in newborns**, how can genomic sequencing replicate or augment (e.g., make more accurate, comprehensive or inexpensive) known newborn screening results?
- **Question B)** What knowledge about **conditions not currently screened for in newborns** could genomic sequencing of newborns provide?
- **Question C)** What **additional clinical information** could be learned from genomic sequencing **relevant to the clinical care of newborns**?
- In order to be considered responsive to the FOA, each applicant must also propose a research plan that includes **each of the following three component projects**:
- **Research Component 1)** acquisition and analysis of **genomic datasets** that expand considerably the scale of data available for analysis in the newborn period;
- **Research Component 2)** **clinical research** that will advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis; and
- **Research Component 3)** research related to the **ethical, legal and social implications (ELSI)** of the possible implementation of genomic sequencing of newborns.
- The methods and scope of the research in all three of these component projects should be tailored to **focus on the newborn period** and the **research context** in which the sequencing is performed.

Four Centers Funded – U19/NICHD and NHGRI

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

NSIGHT: **N**ewborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h

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
- New conditions can be “nominated”
- Limitations include no screening tool, screening tool too expensive, no treatment
- Currently 31 core disorders and 26 secondary disorders

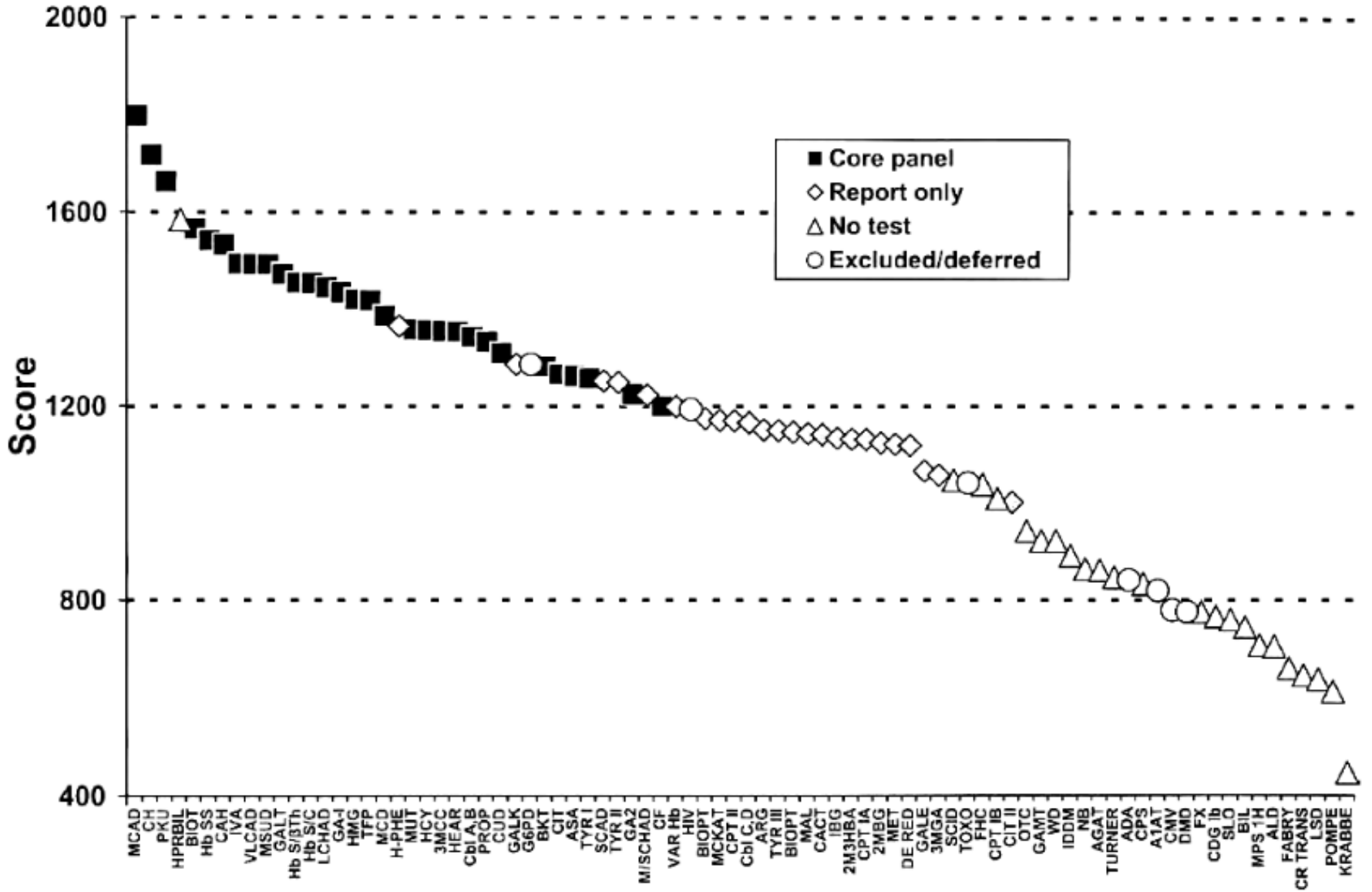


Fig. 7. Scores for all conditions distinguished by screening panel category

Watson et al. Genetics in Medicine May 2006
Vol. 8 No. 5, 12S-252S Supplement

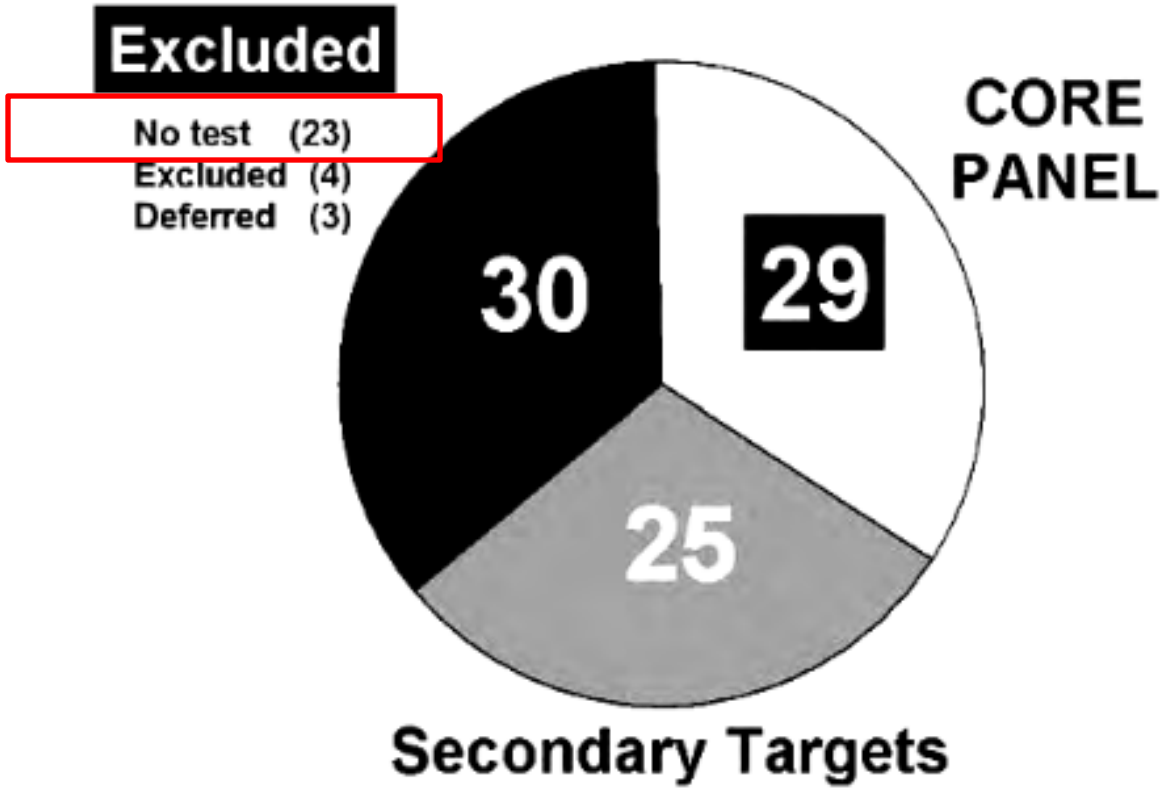


Fig. 8. Distribution of conditions into screening panel categories

Watson et al. Genetics in Medicine
May 2006 Vol. 8 No. 5, 12S-252S
Supplement

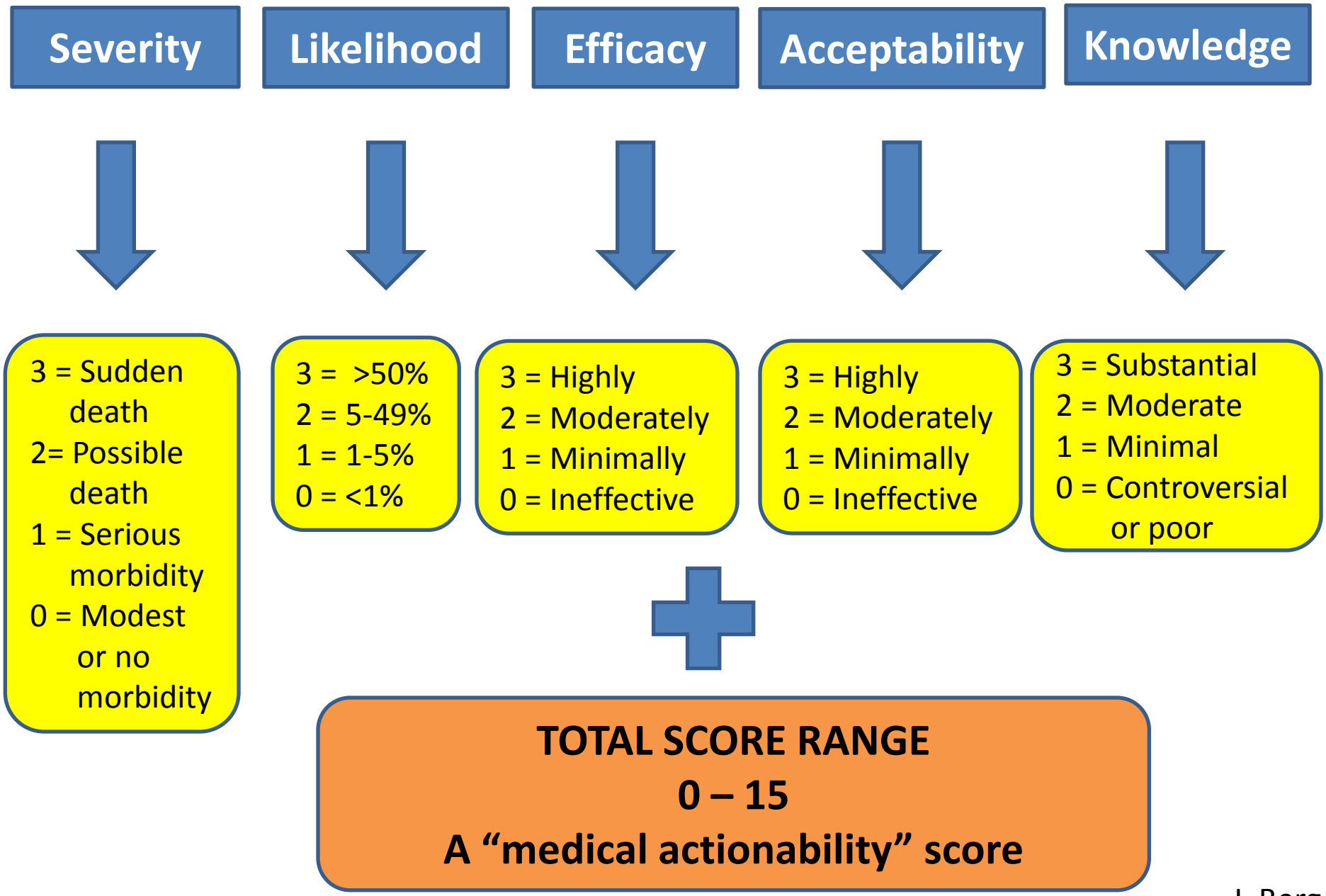
Next Generation Sequencing in Newborn Screening

- Barriers to adding any disorder to NBS panel may now be overcome if there is a genetic etiology established for a condition

NC Newborn **Ex**ome Sequencing for **U**niversal **S**creening (**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.

A Semi-Quantitative Metric Approach to Scoring Genes



J. Berg

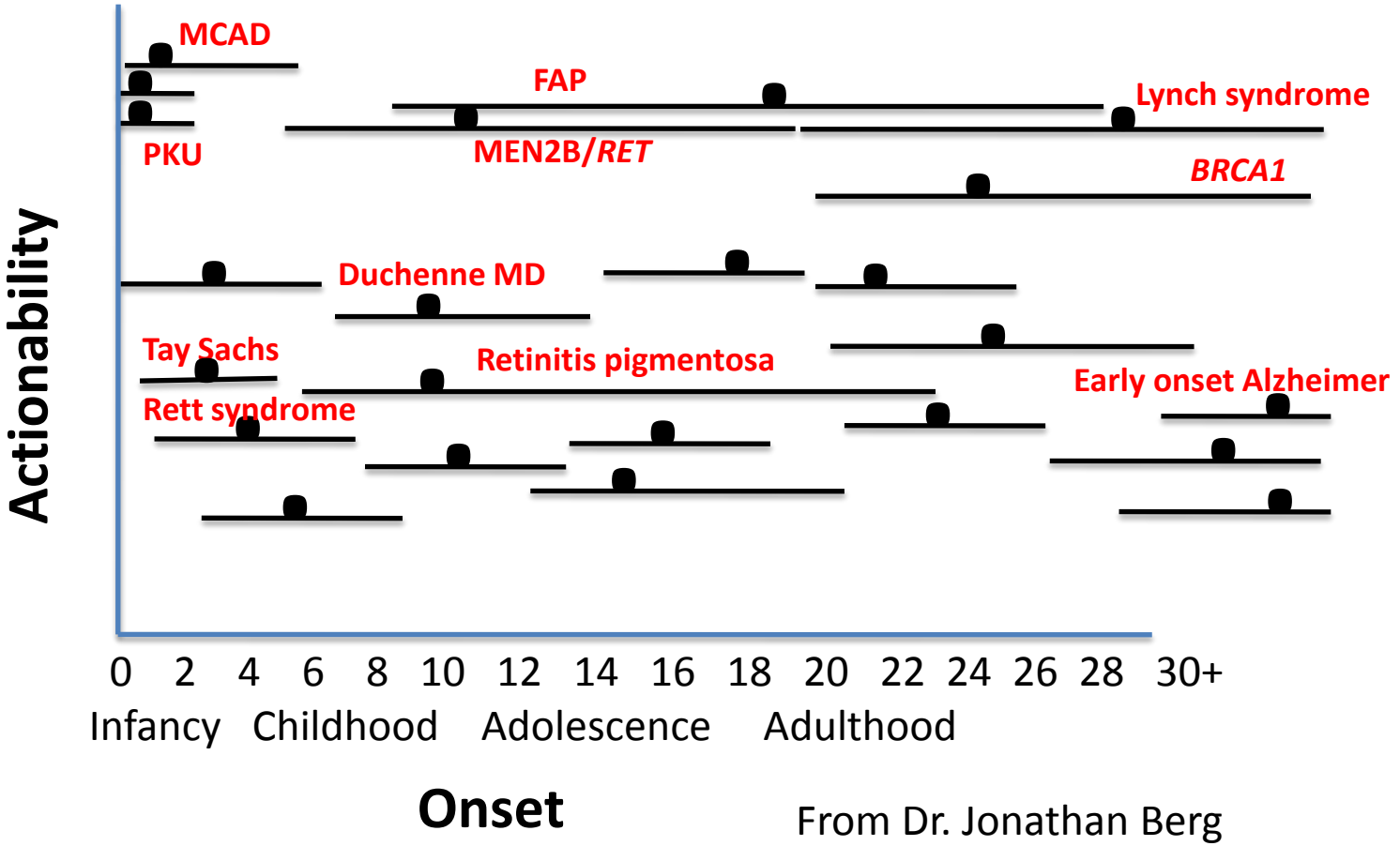
Example: PAH (PKU)

- Severity of disease (ID) = 1
- Likelihood of a severe outcome = 3
- Effectiveness of interventions = 3
- Acceptability of interventions = 2
- Knowledge base = 3
  - TOTAL SCORE = 12

Example: APC (Familial adenomatous polyposis)

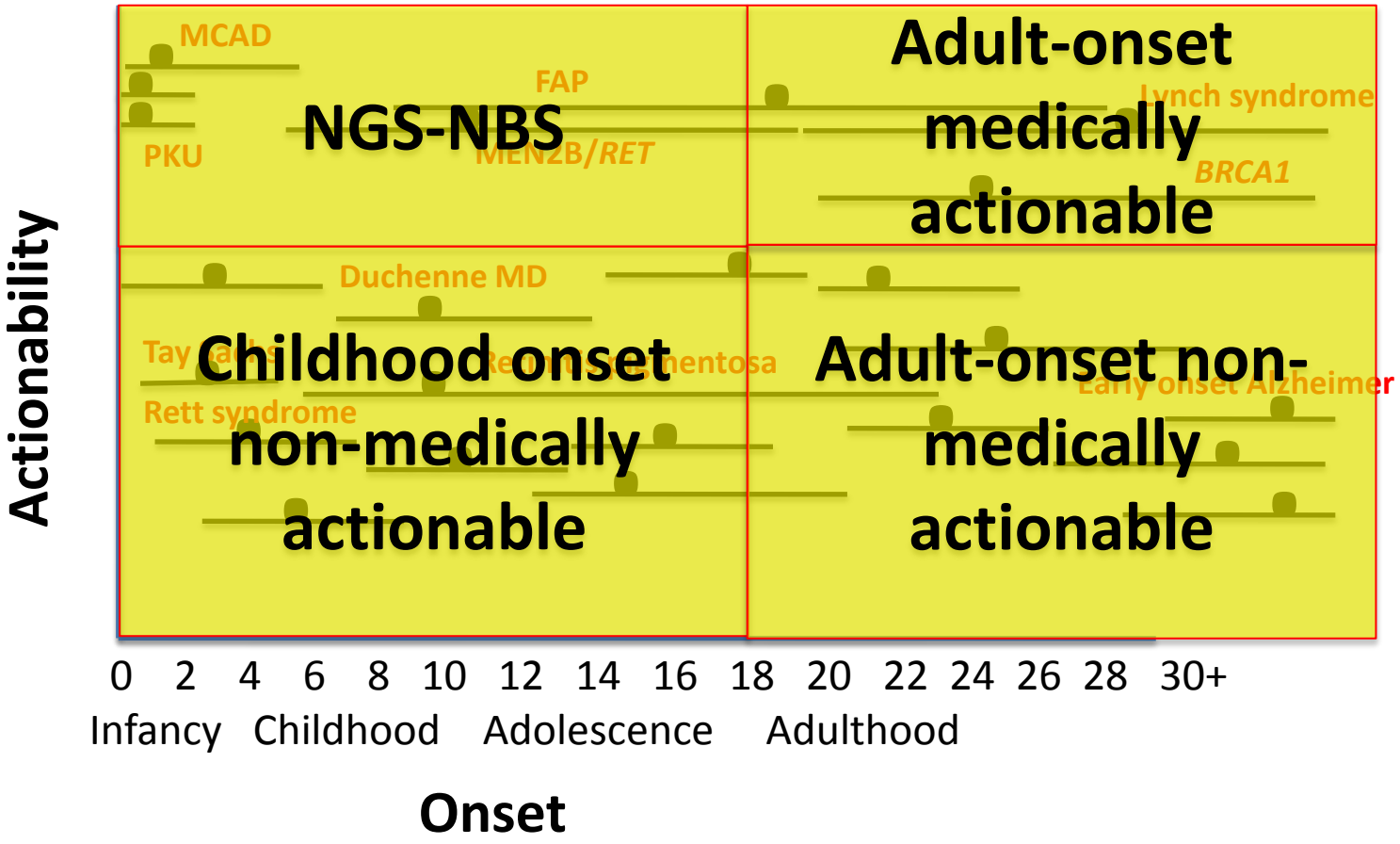
- Severity: possible death due to cancer = 2
- Likelihood: high penetrance = 3
- Effectiveness of intervention: colonoscopy = 3
- Acceptability of intervention: colonoscopy = 2
- Knowledge base: high = 3
  - TOTAL SCORE =13

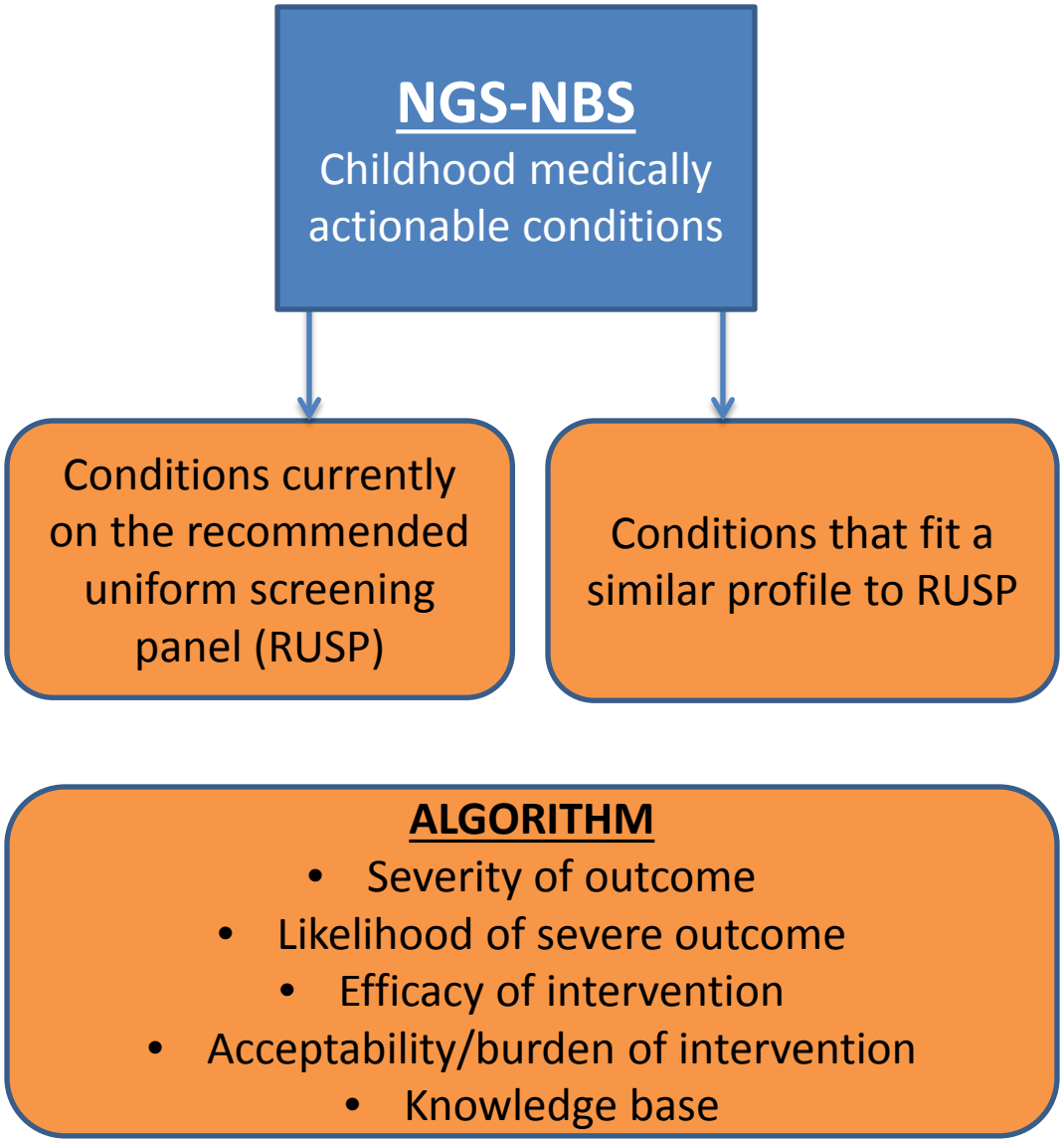
An age-based modified metric system



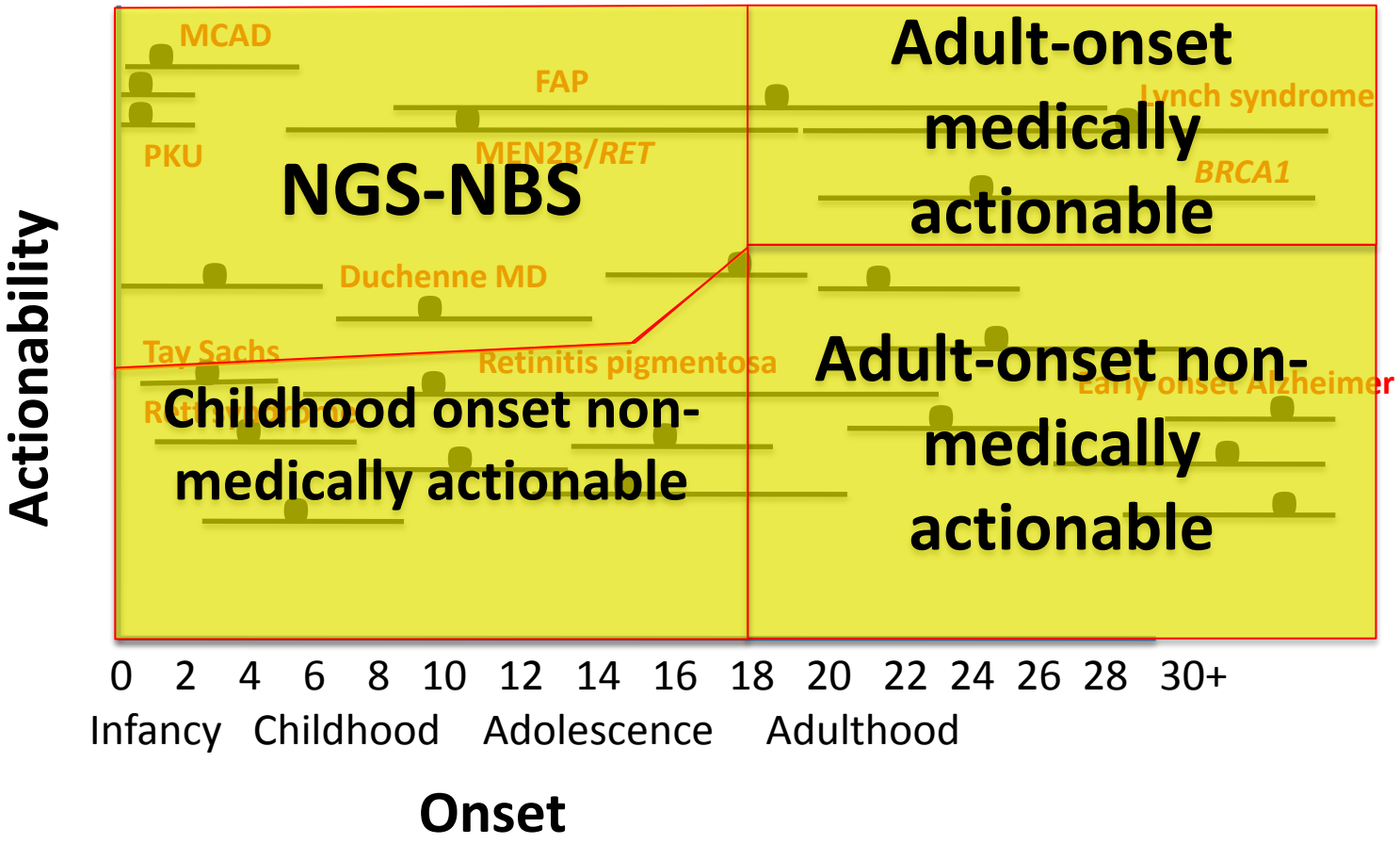
From Dr. Jonathan Berg

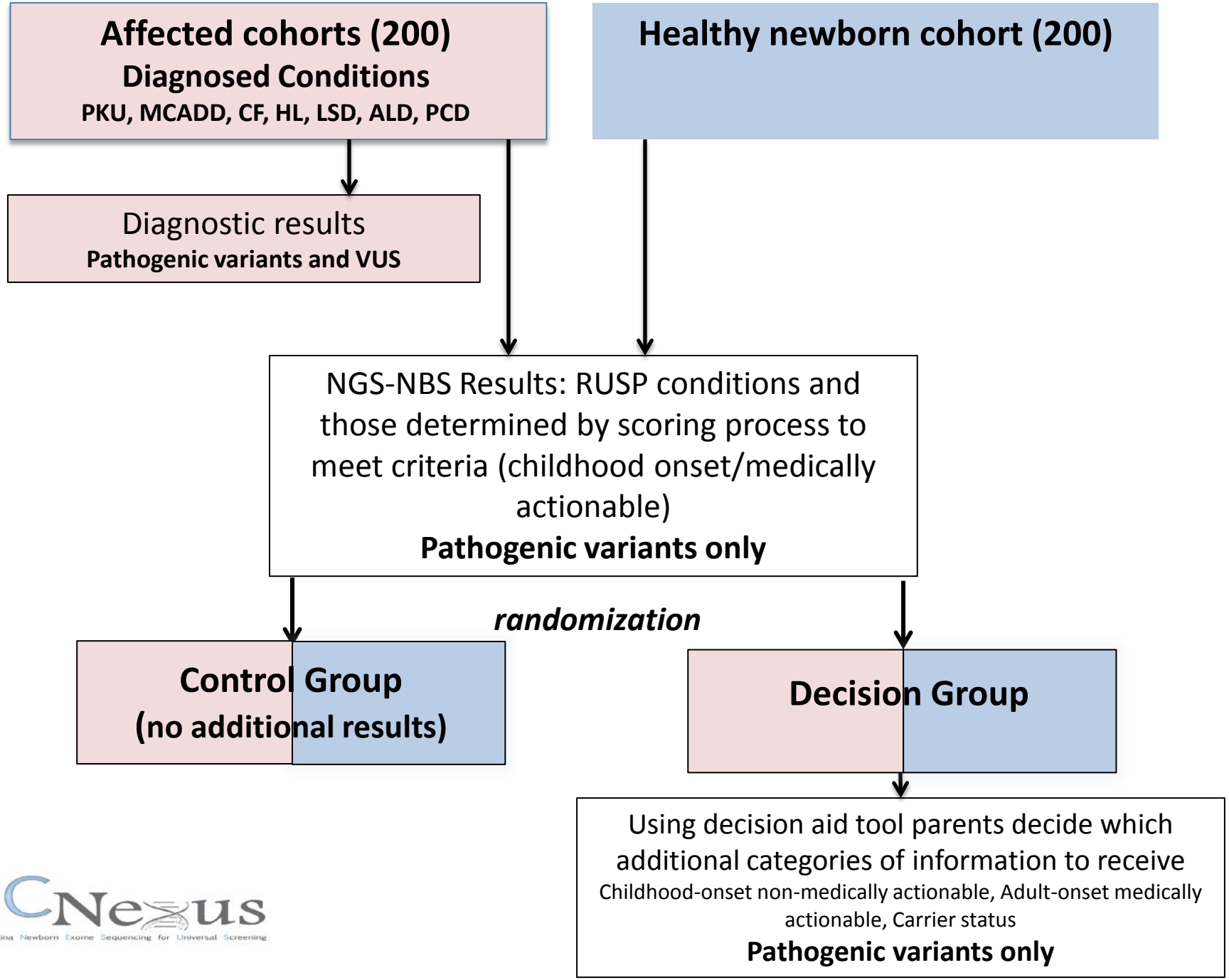
An age-based modified metric system



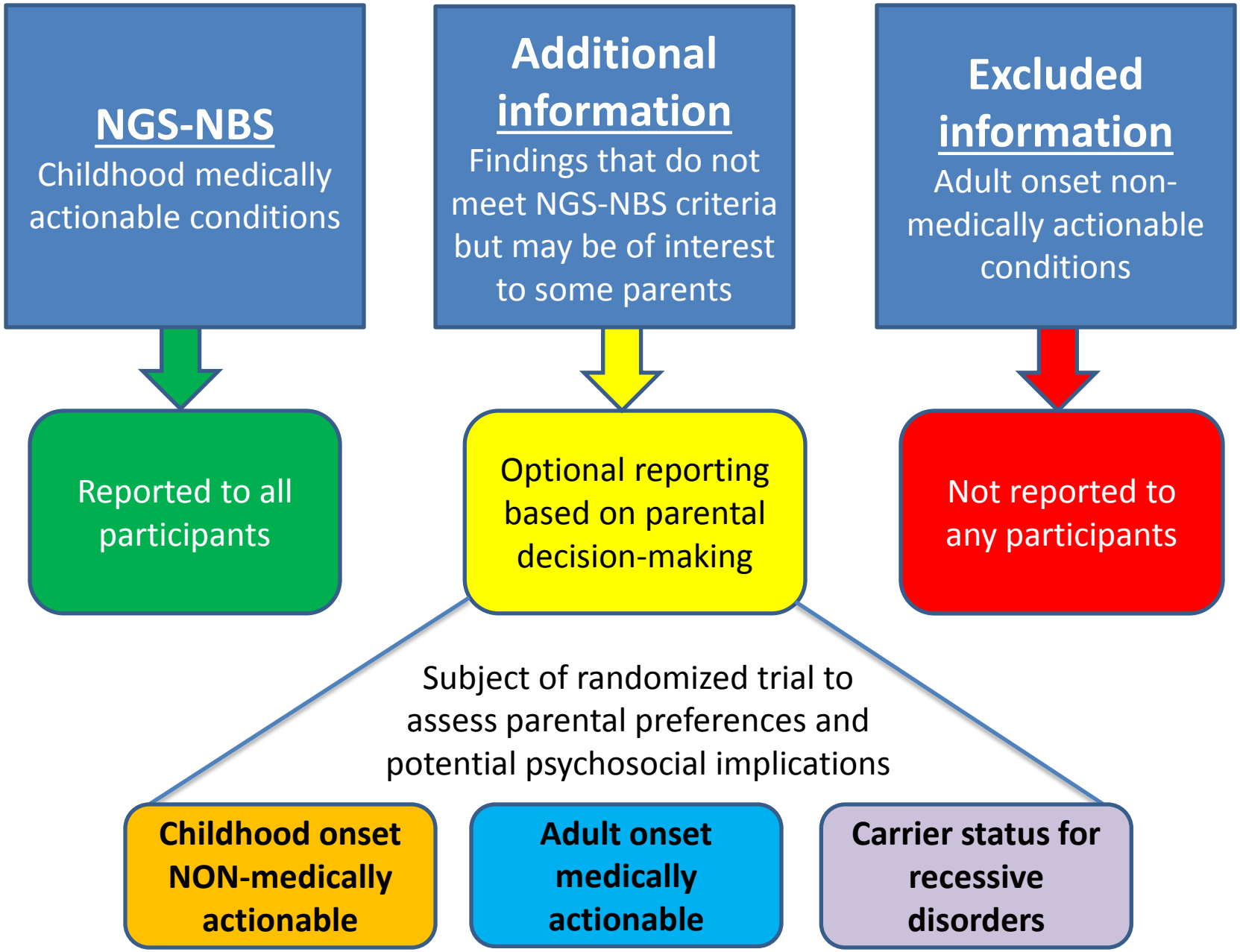

NGS-NBS
Childhood medically actionable conditions
Conditions currently on the recommended uniform screening panel (RUSP)
Conditions that fit a similar profile to RUSP
ALGORITHM
• Severity of outcome
• Likelihood of severe outcome
• Efficacy of intervention
• Acceptability/burden of intervention
• Knowledge base

An age-based modified metric system





NCNexus
North Carolina Newborn Exome Sequencing for Universal Screening


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

Next Gen-Newborn Screening?

Not as a stand-alone test

If genetic sequence information is not returned should it be stored? Where? Whose responsibility is it?

Child's autonomy versus parental rights to child's DNA sequence

How to recontact if conditions become treatable?

New gene/variant discoveries ?

Commercial testing

Mandatory/voluntary? Health disparities

Demands on public health and health care systems

Genetic discrimination (employment, insurance,…)

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

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)
- 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

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
  - Don Bailey
  - Jonathan Berg
  - Cynthia Powell
  - Tess Stohrer
  - Tasha Strande

RTI Project 3 members:

- Don Bailey
- Megan Lewis
- Tania Fitzgerald
- Rebecca Moultrie
- Alex Stine
- Brittany Zulkiewicz
- Carol Mansfield
- Dallas Wood

- Collaborators
  - Oliver Adunka
  - Craig Buchman
  - Zheng Fan
  - Dianne Frazier
  - Robert Greenwood
  - Michael Knowles
  - Margaret Leigh
  - Maimoona Zariwala