Newborn Genomic Sequencing in the NC NEXUS Project

Jonathan S. Berg, MD, PhD

Department of Genetics

The University of North Carolina at Chapel Hill

“As we learn more about effective interventions for genetic risk factors, and recognize that interventions early in life provide significant advantages, it will become more and more compelling to determine this information at birth.”

— F. S. Collins, The Language of Life: DNA and the Revolution in Personalized Medicine. New York: Harper Perennial (2010)

NC NEXUS

North Carolina Newborn Exome Sequencing for Universal Screening

- Two cohorts
  - Healthy newborns, parents enrolled prenatally
  - Infants and children with conditions identified through NBS
- Categories for disclosure defined by clinical actionability
- Parents completed online decision aid prior to sequencing
- All parents received results for childhood onset, actionable conditions (termed “NGS-NBS”), if any
- Randomized to “decision” or “control” arm for additional genomic findings
- Extensive parental surveys

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North Carolina Newborn Exome Sequencing for Universal Screening

The NC NEXUS team

Cynthia Powell, PI
co-PIs: Jonathan Berg, Don Bailey

- Cindy Powell
- Don Bailey
- Laura Milko
- Myra Roche
- Bradford Powell
- Megan Lewis
- Chris Rini
- Rita Butterfield
- Katie Souris

- Kate Foreman
- Julianne O'Daniel
- Tasha Strande
- Art Aylsworth
- Jessica Booker
- Muge Calikoglu
- Joe Muenzer
- Dianne Frazier
- Neeta Vora
- Lacey Boshe
- Zahra Girnary

- Kirk Wilhelmsen
- Phil Owen
- Dylan Young
- Alicia Brandt
- Christian Tilley
- Kristen Dougherty
- Chelsea Gustafson
- Andy Rivera
- Lonna Mollison

NICHD U19 HD077632

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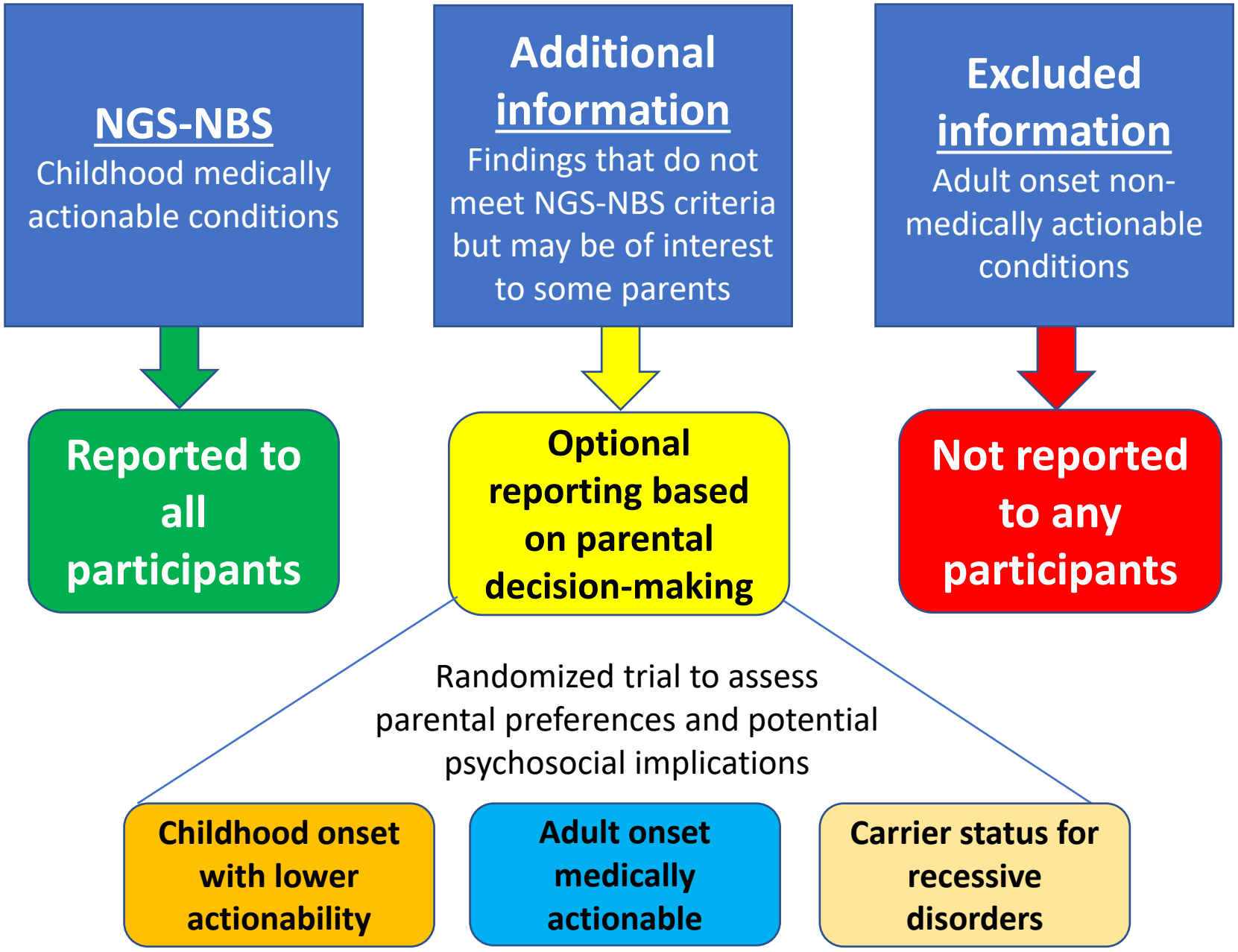

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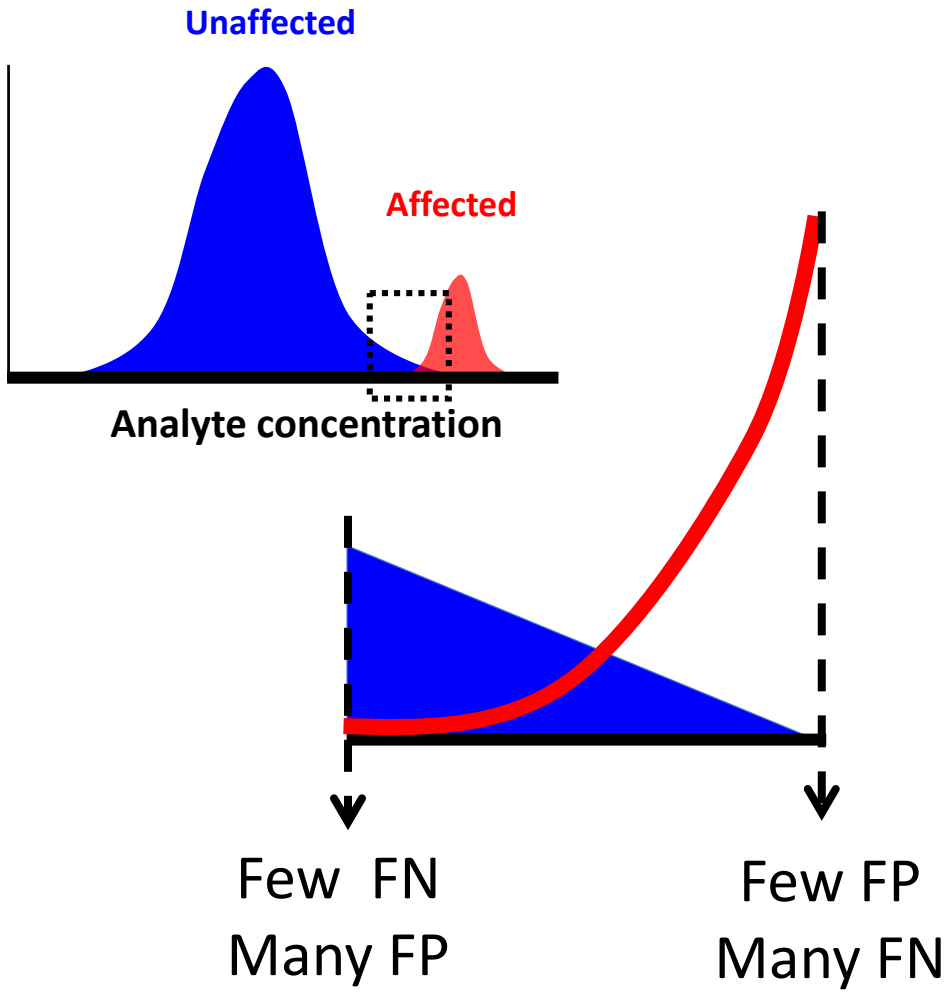
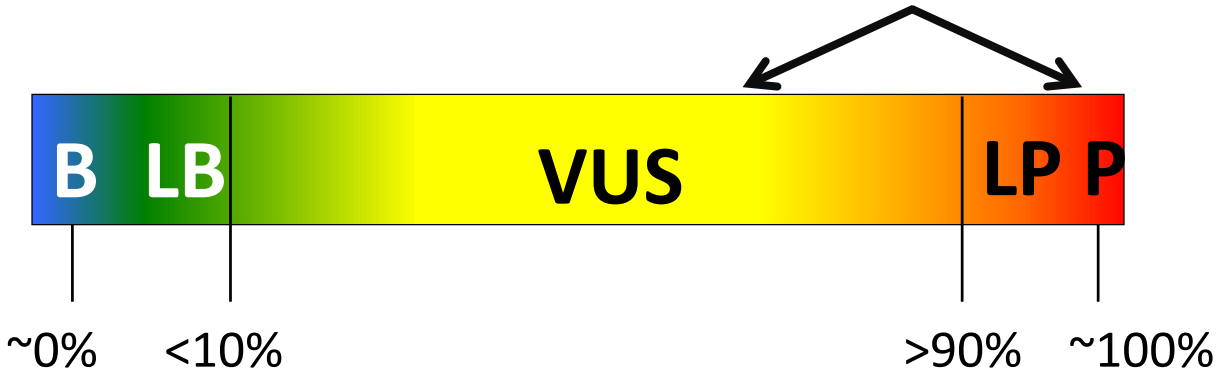
Challenge: unlike quantitative analyte tests, variant classification is qualitative



Sensitivity/Specificity happens here!

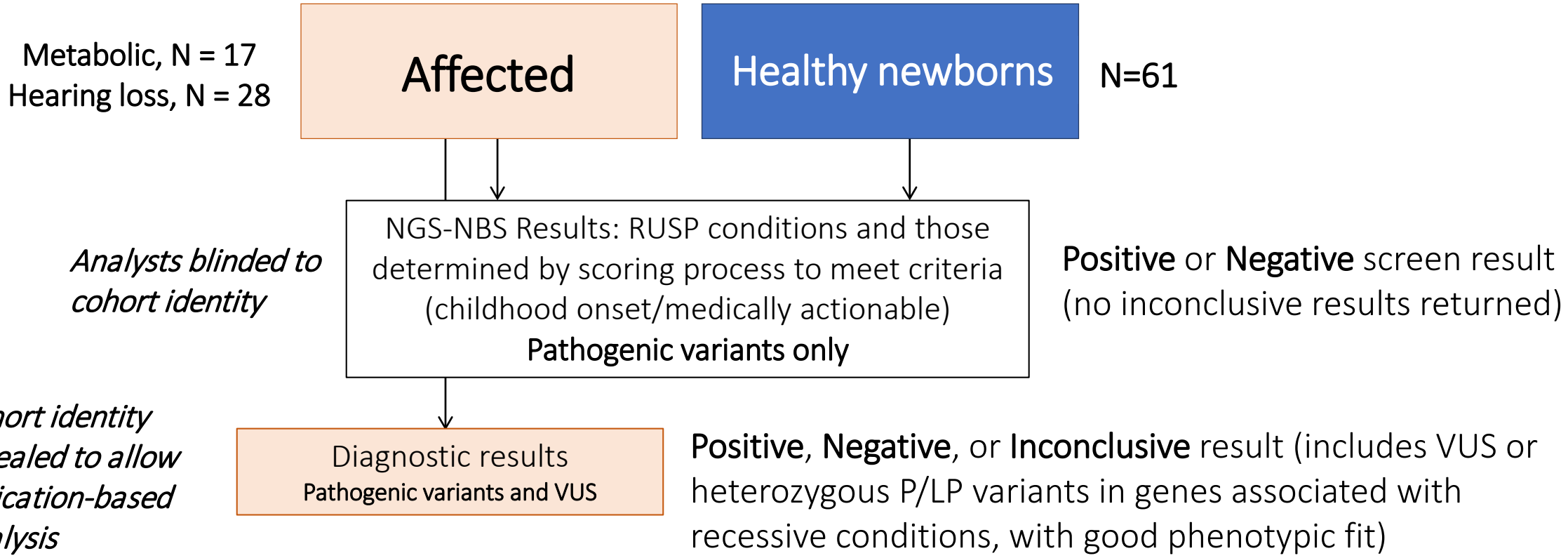


"Probability of pathogenicity"

Genomic sequencing as a “screen”

- Restricting results to “known pathogenic” variants (100% specificity) will sacrifice detection of true positives
  - Especially when many disease-causing variants are rare/private
- Including results with <99.9% specificity means high false positives
  - Resulting in downstream costs and consequences
- For metabolic conditions on the newborn screen (PKU, for instance), secondary testing determines who needs intervention
  - Can we even use “likely pathogenic” results in a population screen for conditions without an available secondary test?

Molecular analysis in NC NEXUS



All returnable findings Sanger confirmed and reported by CLIA lab

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Primary results from “Affected” cohorts

- NGS-NBS was positive for 15/17 metabolic patients (88.2%)
  - False negatives due to single heterozygous pathogenic variant in BCKDHA in a patient with MSUD, and a homozygous missense VUS in MLYCD in a patient with Malonyl-CoA decarboxylase deficiency
  - Both reported as “inconclusive” findings on diagnostic report
  - One female PKU patient was also found to be a carrier for OTC
- NGS-NBS was positive for 5/28 hearing loss patients (17.9%)
  - Five additional inconclusive results on unblinded analysis
  - Two patients had “positive” screen results unrelated to hearing loss

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Primary results from “NGS-NBS”

- Four unexpected positives out of 106 total patients (3.8%)
  - Heterozygous *LDLR* pathogenic variant (not a surprise to family due to a known family history of hypercholesterolemia)
  - Heterozygous *DSC2* novel canonical splice variant
  - Two heterozygous *F11* variants (P, LP)
  - Heterozygous *OTC* pathogenic variant in a female with PKU (variant reported to be hypomorphic in the literature)

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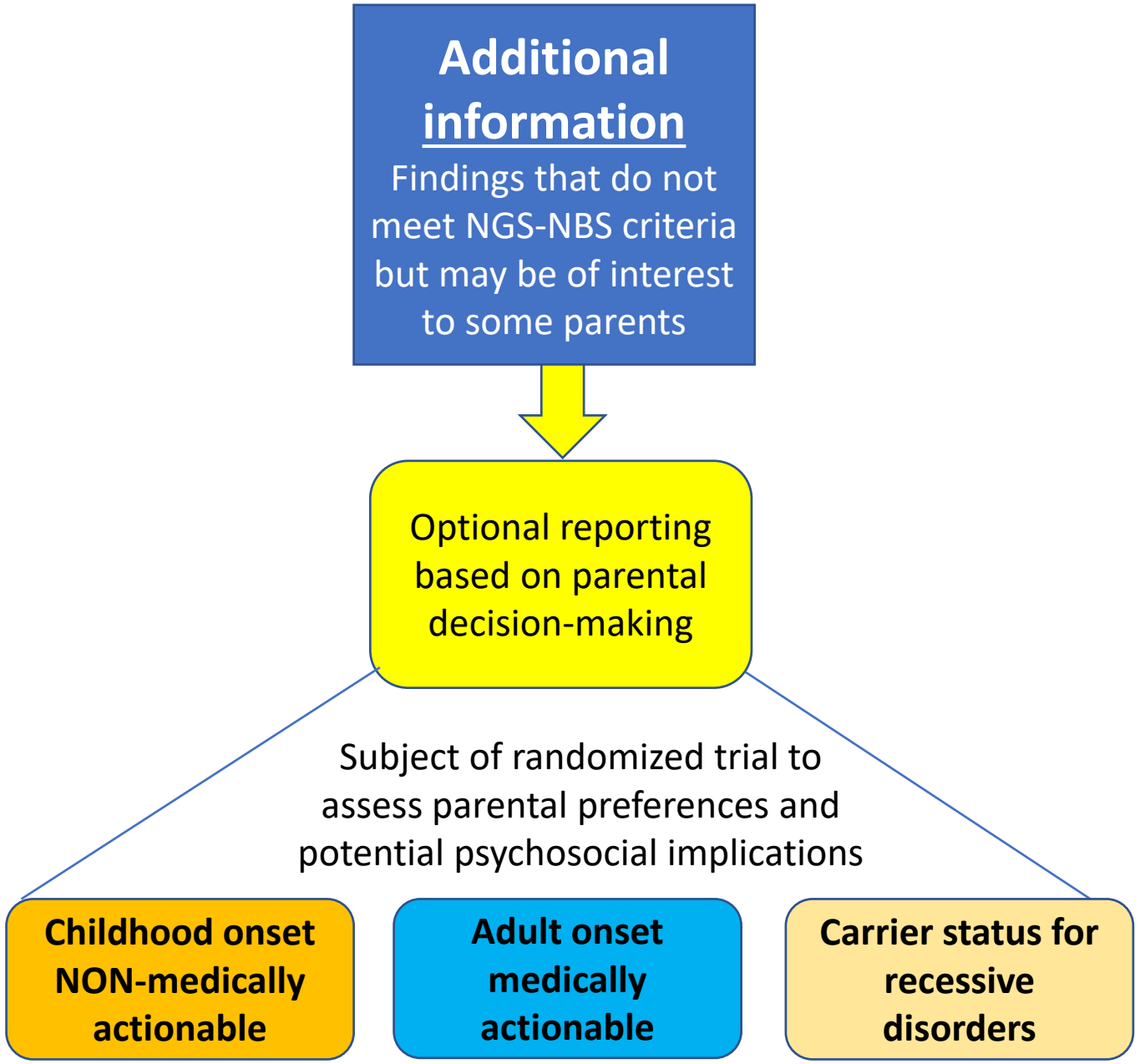

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Additional findings from NC NEXUS

- Of 45 parents randomized to the “decision” arm, 41 (91%) requested at least one other category of information
  - 34 asked for all three categories
- One adult-onset medically actionable finding (*RAD51C* / ovarian cancer)
- One childhood-onset non-medically actionable finding (*OCRL* / Lowe syndrome) that ended up being a diagnostic result for the child’s complex medical condition

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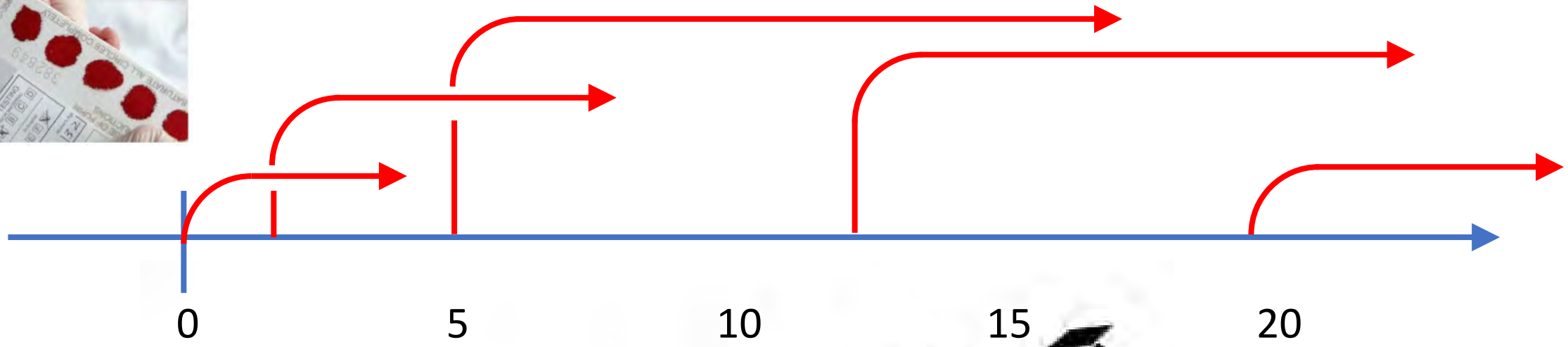
Considering genomic sequencing as a “screen”

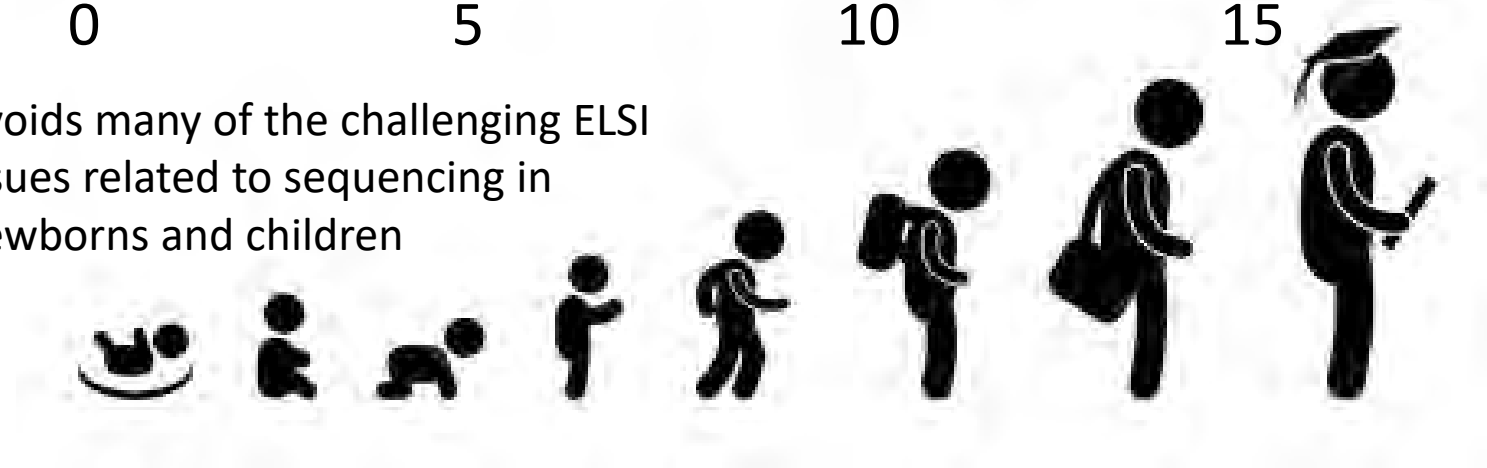
- Perinatal period is a difficult time to conduct informed consent
- Tolerance may vary for false positives and overdiagnosis (incomplete penetrance and variable expressivity):
  - Consequences of “missing” a diagnosis
  - Availability of gold-standard follow-up test
  - Nature of recommended management plan
  - Economic impact, societal consequences
- A strong argument can be made for starting with a subset of the most well understood, highly actionable conditions, rather than exome or genome sequencing

Age-based genomic screening

Integrate population-level targeted genetic screening for highly actionable, age-relevant conditions, into routine wellness visits for newborns and children



Avoids many of the challenging ELSI issues related to sequencing in newborns and children



Gradually introduces genomic screening over time, preparing adolescents to engage in decision-making when they reach adulthood

As we learn more about effective interventions for genetic risk factors, and recognize that interventions early in life provide significant advantages, it will become more and more compelling to determine some of this information at birth and other information throughout the individual's lifespan.

- Clinical diagnostic testing is increasingly available for addressing the diagnostic odyssey
  - Genomic screening would be ill-suited for that purpose
- Parental carrier screening is also widely available
  - We should not need rely on newborn screening for that purpose
- Focusing on age-relevant actionable information would streamline consent, molecular analysis, and disclosure

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Cindy Powell

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UNC SCHOOL OF MEDICINE

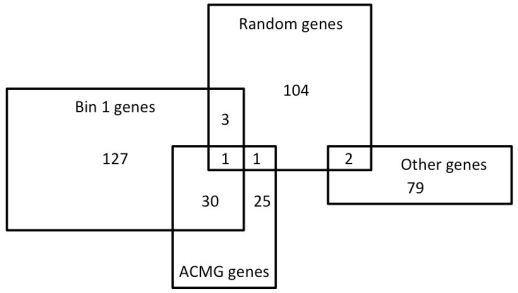
A semi-quantitative metric (SQM) to define "actionability" for secondary findings

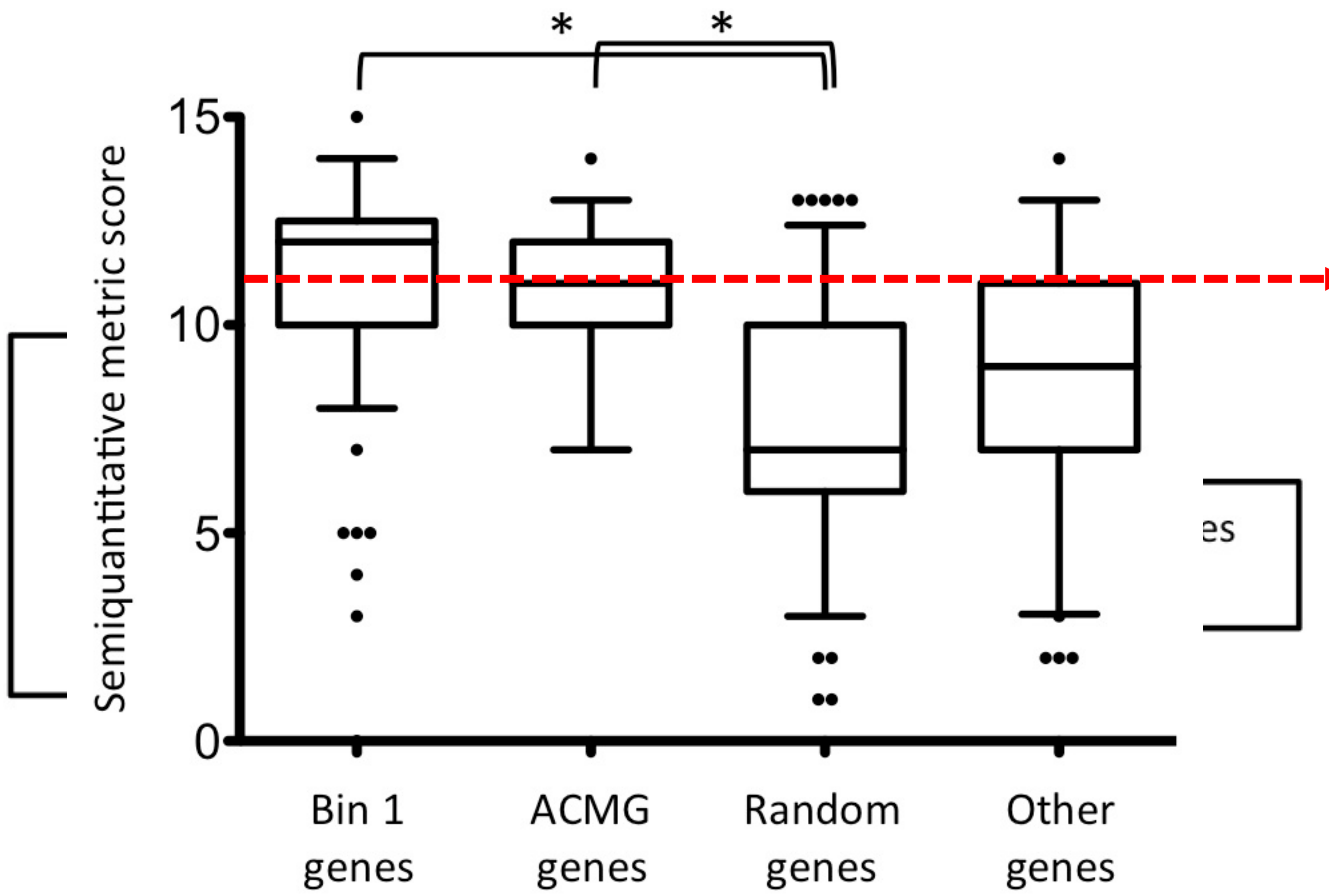
• Severity of disease	(0-3)
• Likelihood of a severe outcome	(0-3)
• Effectiveness of interventions	(0-3)
• Acceptability of interventions	(0-3)
• Knowledge base	(0-3)
	0-15

These elements can be used to generate a semi-quantitative "clinical actionability" score for every gene-disease pair

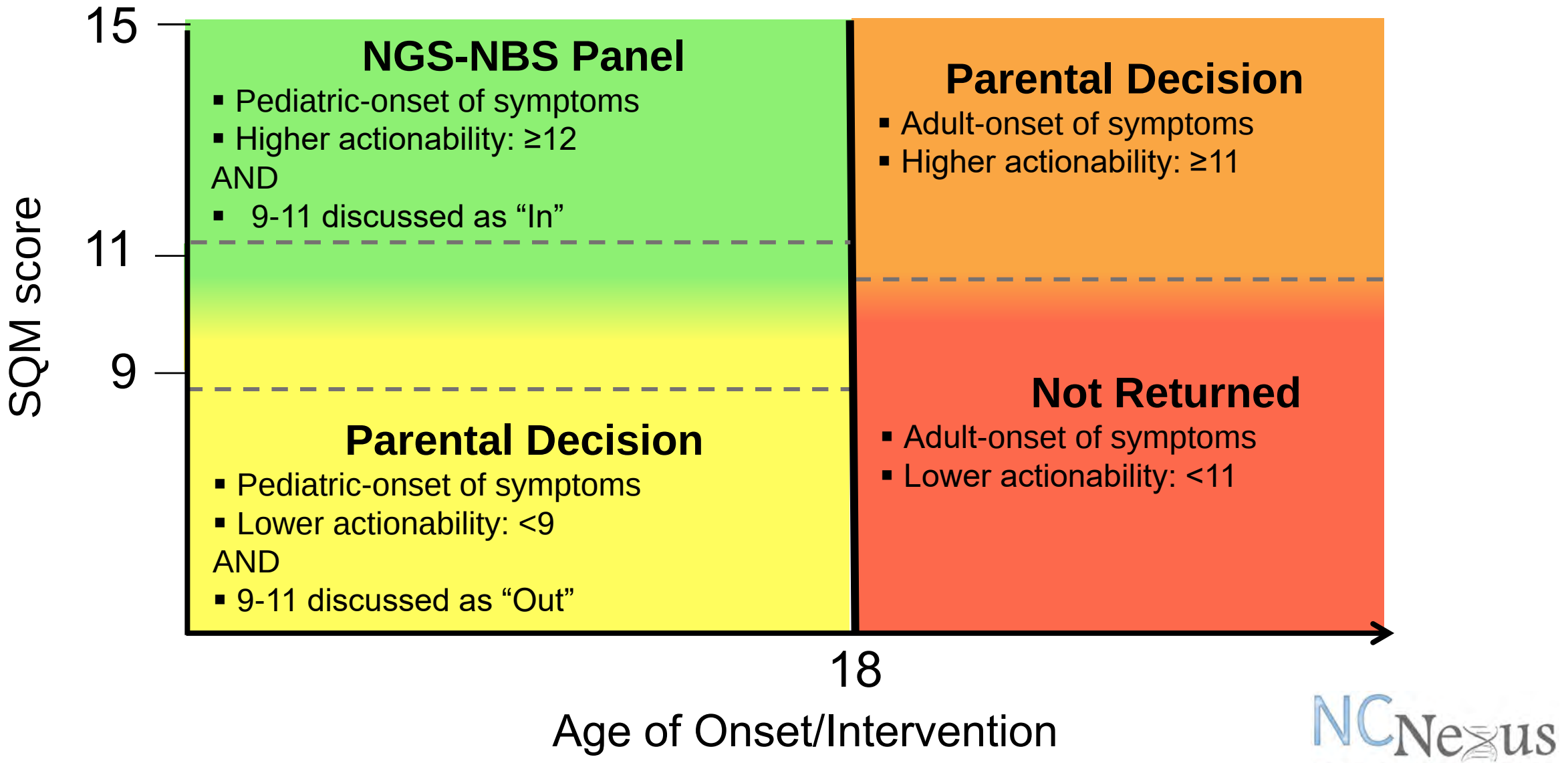
NCGenes

372 gene-disease pairs scored using the SQM





Top quintile of random genes was 11



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What conditions should be included?