A categorical framework to aid parental decision-making for next-generation, newborn sequencing results

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Introduction:

Traditionally, newborn screening (NBS) enables early detection and presymptomatic intervention for selected conditions based on population impact and availability of efficacious treatments. Next generation sequencing (NGS) would allow the inclusion of vastly more conditions for which early treatment or surveillance is crucial, but also presents significant ethical complexity for conditions where there is no proven medical intervention, or where avoiding the "diagnostic odyssey" might be the only benefit. NGS can also reveal findings where the initial benefit may not be to the child, such as adult-onset conditions or carrier screening. To explore potential medical benefits and ethical challenges, NC NEXUS (North Carolina Newborn Exome Sequencing for Universal Screening) is developing a framework to characterize categories of conditions about which parents may choose to learn. The framework is built upon determining the "medical actionability" of genomic findings and has been applied to >500 gene/conditions. This semi-quantitative scale incorporates likelihood and severity of disease outcome, efficacy and potential harms of interventions, and knowledge base, while also accounting for age of disease onset.

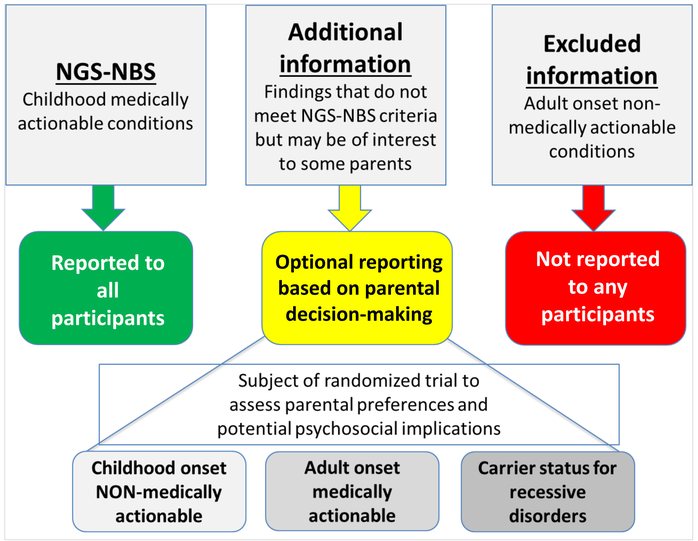
The core panel is composed of medically actionable childhood-onset disorders, including standard NBS conditions. All parents will receive this core "NGS-NBS" panel results about their child. Parents will be further randomized into either a control arm, or an experimental arm in which they may choose to learn additional information from three categories:

1. Adult-onset, medically actionable conditions
2. Childhood-onset, non-medically actionable conditions
3. Carrier status for recessive and x-linked conditions

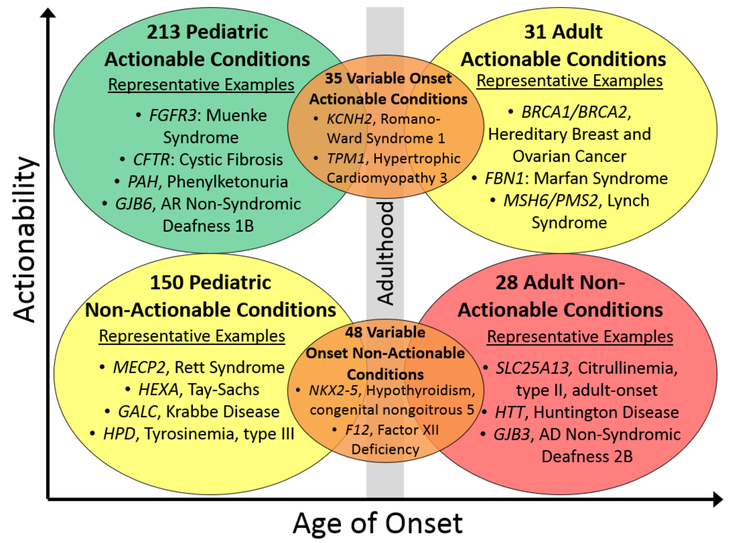
Information about adult onset, non-medically actionable disorders will not be returned.

We hypothesize these distinct categories of conditions will facilitate informed decision-making in the complex setting of genome-scale sequencing for healthy newborns. This study will yield information about how to approach the categorization of gene-condition pairs, how and why parents decide whether to participate, what results they elect to receive, and the impacts of their decisions.

NC NEXUS Classification Scheme for Genomic Information:



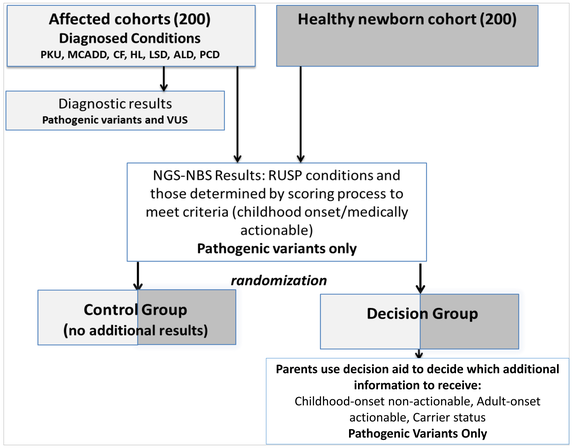
Age-based modification of the semi-quantitative metric:



A semi-quantitative metric is used to score "Medical Actionability" on a 0-3 point scale for 5 criteria:

Category	Description	0	1	2	3
Severity of Disease	"What is the effect on morbidity / mortality to an individual carrying a pathogenic variant in this gene?"	Modest Morbidity	Serious / Chronic Morbidity	Possible Death	Sudden Death or Unavoidable Death in Childhood (<10yo)
Likelihood of Outcome	"What is the chance that a threat will materialize?"	<1%	1-5%	5-49%	>50%
Efficacy of Intervention	"How effective are the interventions for preventing harm in a presymptomatic individual?"	No Effective Intervention	Minimally Effective	Modestly Effective	Highly Effective
Acceptability of Intervention	"How acceptable are the interventions in terms of the burdens or risks placed on the individual?"	No Effective Intervention	Minimally Acceptable	Modestly Acceptable	Highly Acceptable
Knowledge Base	"What is the evidence base for decisions about the natural history of the disease, and interventions used for preventing serious outcomes?"	Poor	Minimal	Modest	Substantial Evidence and / or Practice Guidelines

NC NEXUS Study Design:



Control Group
- Healthy: NGS-NBS
- Affected: NGS-NBS and diagnostic results related to infant's condition

Parental Decision Group
NGS-NBS, plus randomized option of additional findings:
- Adult-onset actionable
- Childhood-onset non-actionable
- Carrier status for AR conditions

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