

Determining Medical Actionability of Gene/Disease Pairs and Relevance to Newborn Screening

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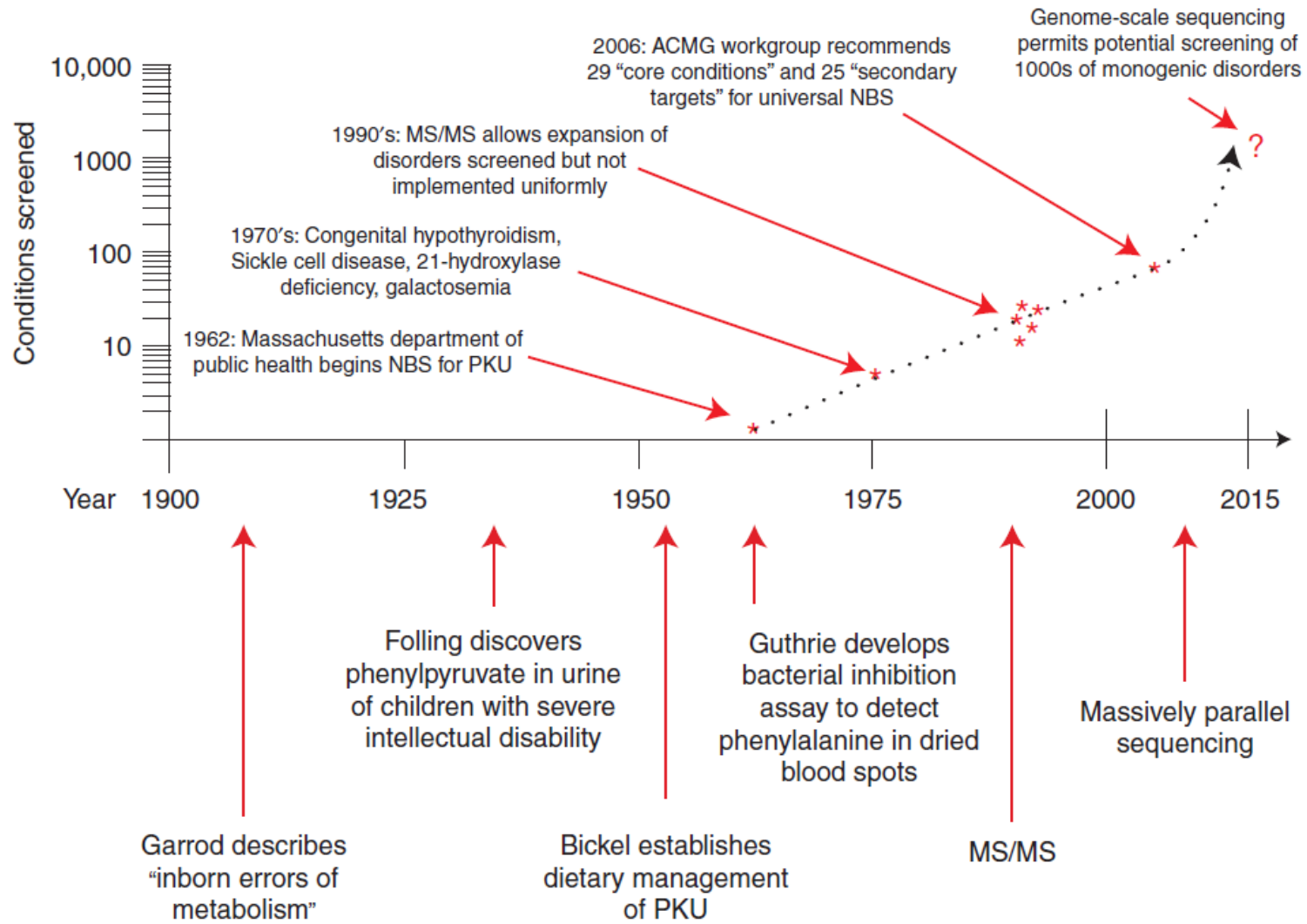
The University of North Carolina at Chapel Hill

ACHDNC Meeting August 25th, 2016



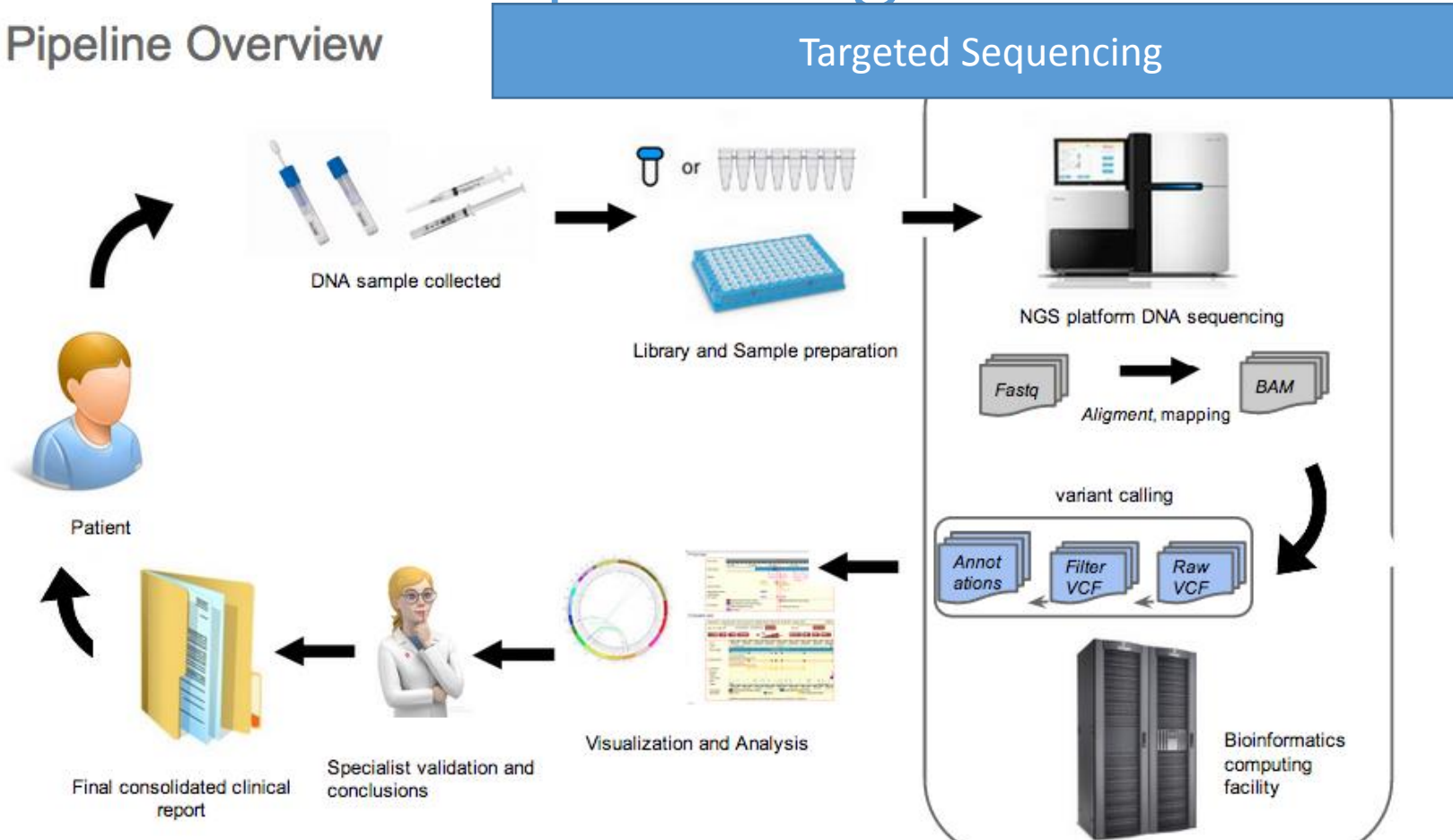
THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL





Next Generation Sequencing

Pipeline Overview



Targeted Sequencing

Targeted Analysis

<http://sequencing.html>

NC NEXUS BINNING COMMITTEE



- Clinical geneticists
- Biochemical geneticists
- Genetic counselors
- Metabolic dietitians
- Molecular geneticists
- Medical genetics resident, fellows, post-docs, graduate students

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 or No Morbidity	Serious/Chronic Morbidity or Moderate Intellectual Impairment	Possible Death/Severe Intellectual Impairment	Sudden Death or Unavoidable Death in Childhood (<10yo)
Likelihood of Outcome	"What is the chance that a problem 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

Example: PAH (PKU)

- Severity of disease (severe ID) = 2
- Likelihood of disease = 3
- Effectiveness of interventions (diet) = 3
- Acceptability of interventions = 2
- Knowledge base = 3

• **TOTAL SCORE of 13**

NGS NBS Candidate Condition

- Multiple Endocrine Neoplasia type 2B
 - Medullary thyroid carcinoma in early childhood with high rate of metastases
 - 100% penetrance
 - Pheochromocytoma
 - 50% penetrance
 - Mucosal neuromas
 - Marfanoid body habitus

Example: RET (MEN2B)

- Severity of disease (possible death) = 2
- Likelihood of a severe outcome = 3
- Effectiveness of interventions = 3
- Acceptability of interventions = 2
- Knowledge base = 3

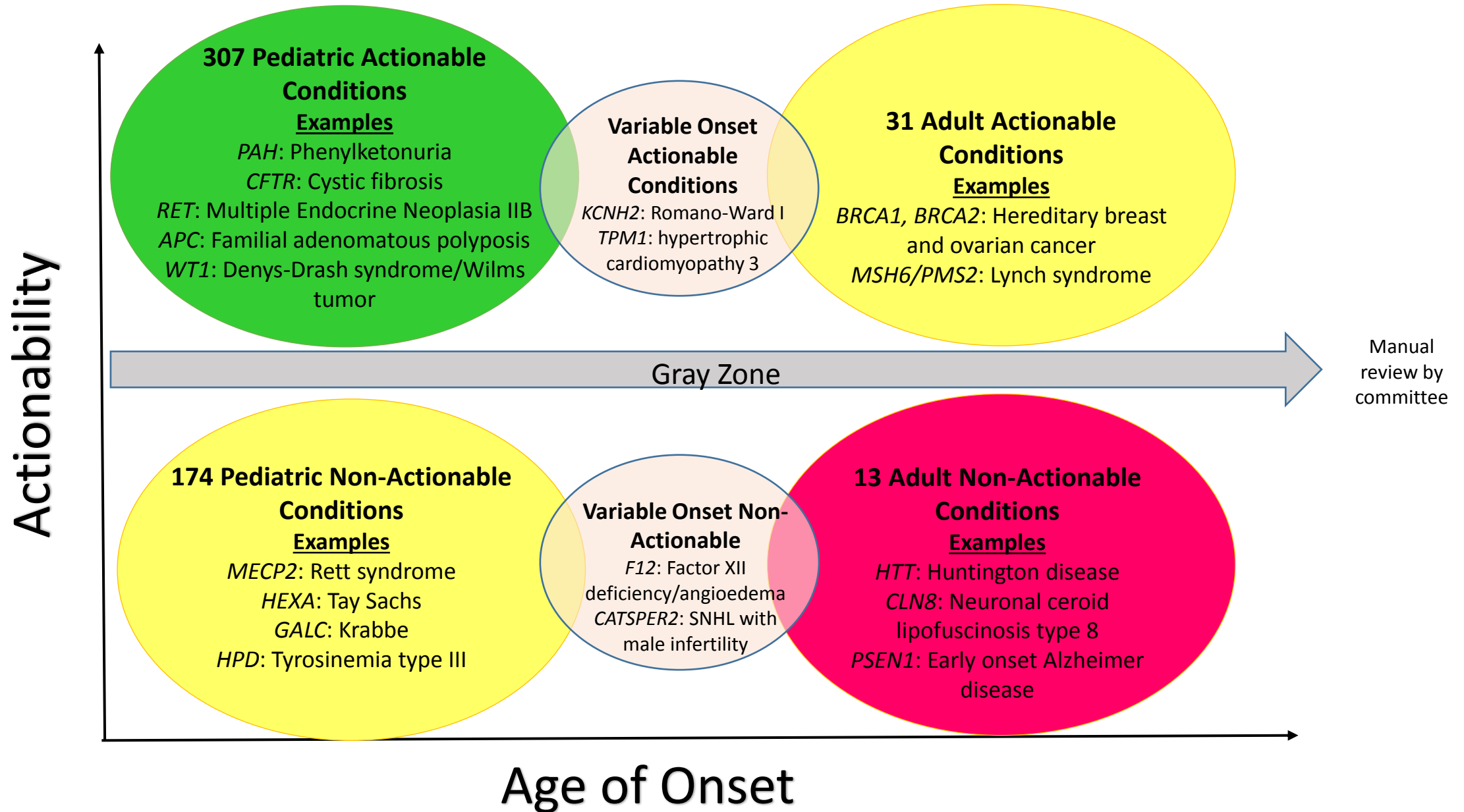
- **TOTAL SCORE of 13**

Example: KCNH2 (Long QT syndrome)

- Severity of disease (sudden death) = 3
 - Likelihood of a severe outcome = 2
 - Effectiveness of interventions = 2
 - Acceptability of interventions = 3
 - Knowledge base = 3
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- **TOTAL SCORE of 13**

Results

- 15,350 human genes in OMIM database (as of 8/18/2016)
- ~4800 OMIM genes with phenotypic description and molecular basis known
- 790 Gene/Condition pairs scored in NC NEXUS
 - 499 finalized
 - 291 pending further review/binning



NC NEXUS TEAM



Jonathan Berg



Cynthia Powell



Don Bailey



Megan Lewis



Myra Roche



Chris Rini



Laura Milko



Kirk Wilhelmsen

NC NEXUS TEAM

Principal Investigators

- Cynthia Powell – PI and Project 2 PI
- Jonathan Berg – PI and Project 1 PI
- Don Bailey – Project 3 PI

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- Rita Butterfield
- Andy Rivera
- Dylan Young

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- James Evans – Projects 1 and 3
- Megan Lewis – Project 3
- Bradford Powell
- 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



NC NEXUS TEAM

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