

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

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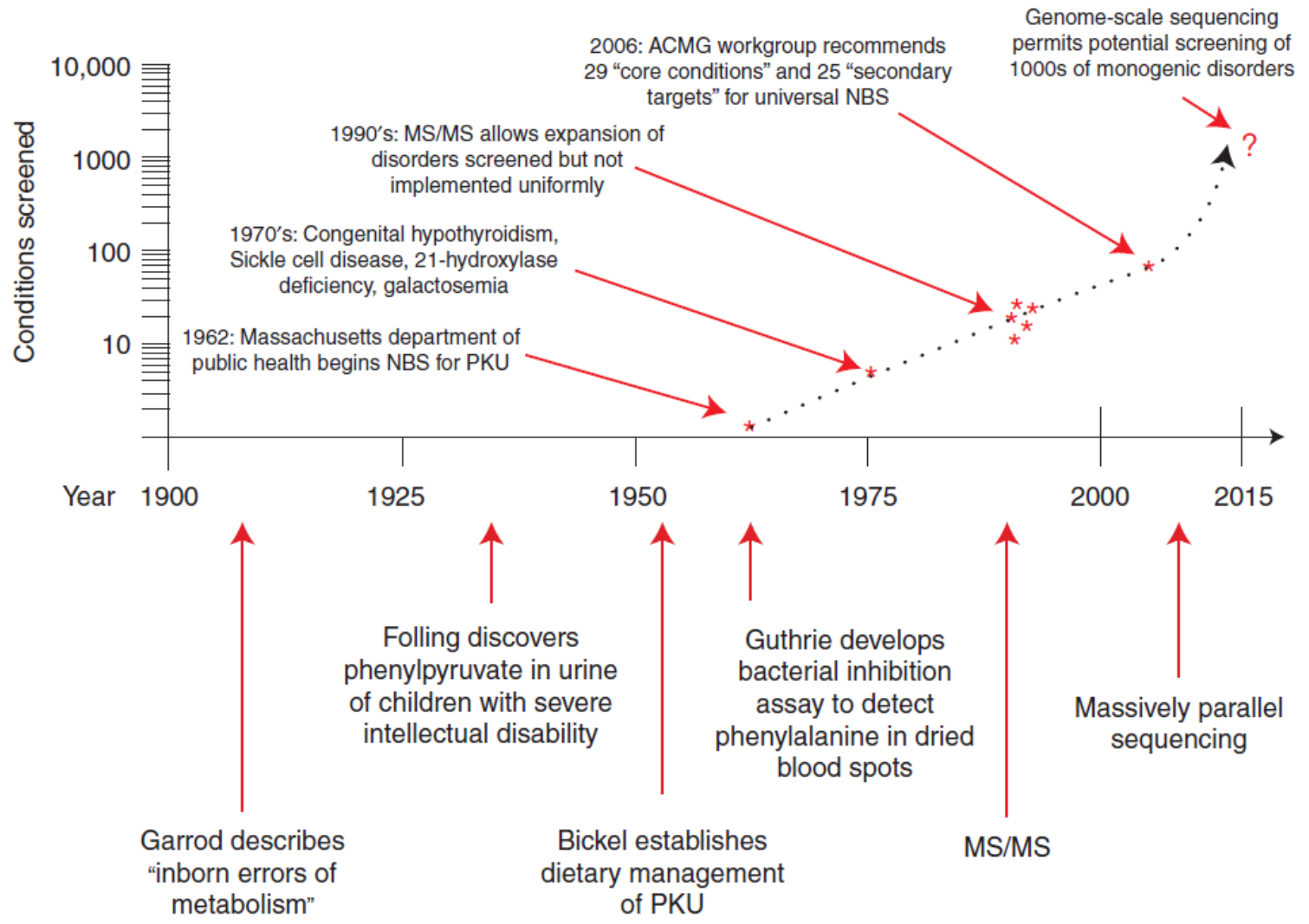
The University of North Carolina at Chapel Hill

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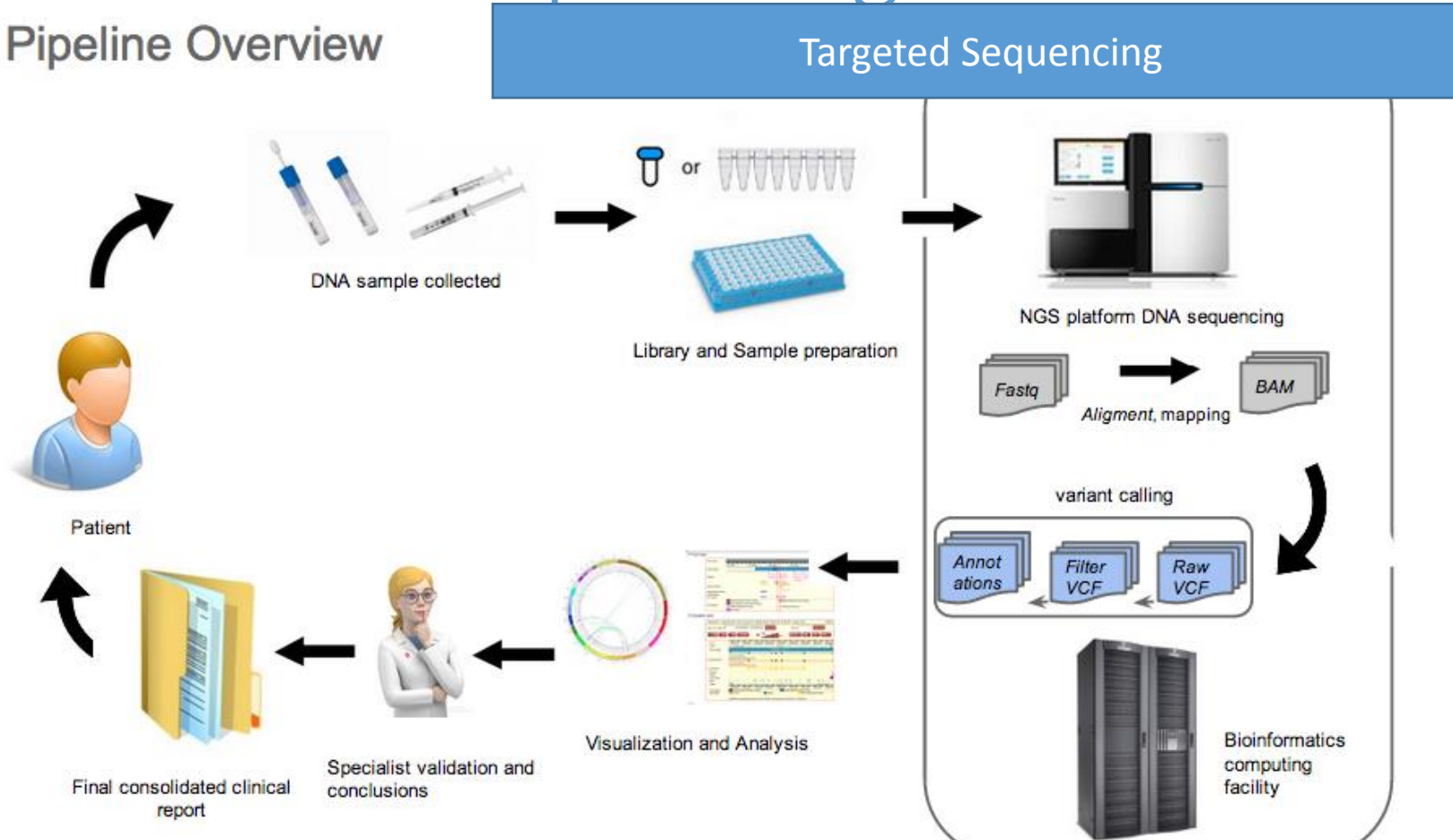
THE UNIVERSITY  
*of* NORTH CAROLINA  
*at* CHAPEL HILL





# Next Generation Sequencing

## Pipeline Overview



Targeted Sequencing

NGS platform DNA sequencing

Fastq → BAM  
Alignment, mapping

variant calling

Annotations ← Filter VCF ← Raw VCF

Bioinformatics computing facility

Visualization and Analysis

Specialist validation and conclusions

Final consolidated clinical report

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
<b>Severity</b> 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)
<b>Likelihood</b> of Outcome	"What is the chance that a problem will materialize?"	<1%	1-5%	5-49%	>50%
<b>Efficacy</b> of Intervention	"How effective are the interventions for preventing harm in a presymptomatic individual?"	No Effective Intervention	Minimally Effective	Modestly Effective	Highly Effective
<b>Acceptability</b> 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
<b>Knowledge</b> 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**



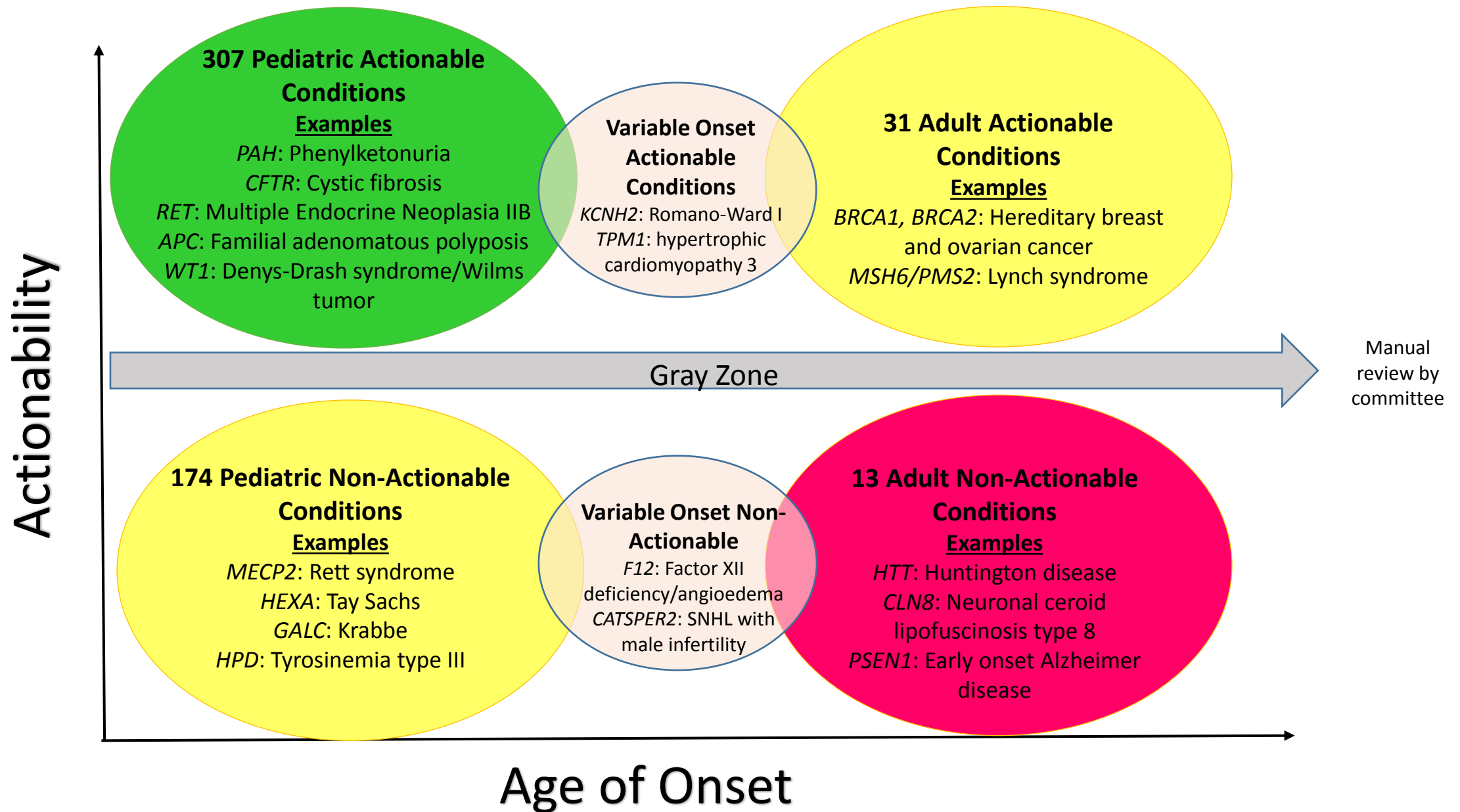
## *Example: KCNH2 (Long QT syndrome)*

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

- **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

## Project Coordinator

- Laura Milko

## Project Manager

- Myra Roche

## Research Associates

- Rita Butterfield
- Andy Rivera
- Dylan Young

## Investigators

- Muge Calikoglu – Project 2
- 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

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Project #5U19HD077632



# NC NEXUS TEAM

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