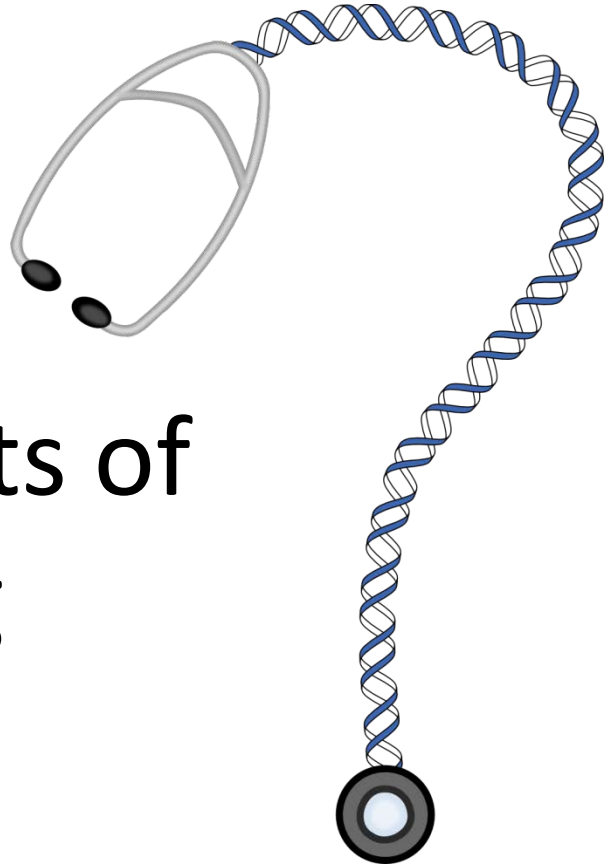

Clinical Costs and Effects of Genomic Screening

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Diagnostic Testing vs. Screening

- Diagnostic Testing
  - Performed in an individual who either has or is suspected of having a particular disorder because of clinical symptoms
- Screening
  - Population-based method for identifying persons with a condition or predisposition to a condition
  - Screening may “inflict” healthcare on apparently-healthy individuals

Learning from secondary findings

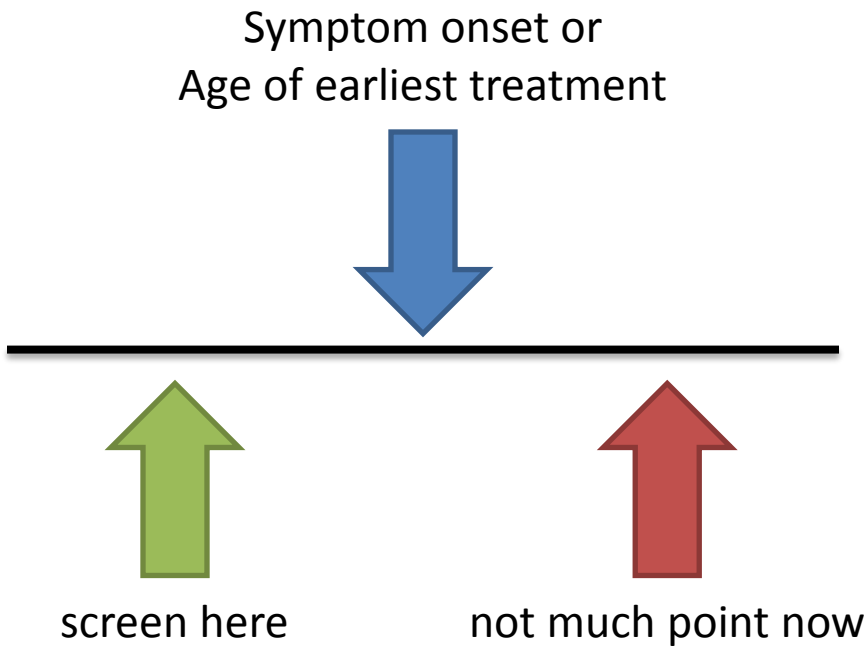
- ACMG 56->59
  - “highly” actionable
  - Selected by expert consensus then semi-quantitative metric
- “opportunistic screening” – low marginal cost (of testing…)
- Can we generalize to population screening?
  - Can we provide the same level of pre-test counseling for population genomic screening?
  - How well do our penetrance estimates hold up against ascertainment bias?

Screening Criteria

(reorganized from Wilson and Jungner 1968)

- Characteristics of the **condition**:
  - An important health problem (reasonable prevalence)
  - Well-understood natural history
  - Recognizable latent or early symptomatic phase in which treatment is more effective
  - Have an accepted treatment for patients with recognized disease
- Characteristics of **case-finding**:
  - Based on a suitable test or examination (acceptable to the population)
  - Economically balanced in terms of other healthcare expenditures
  - A continuing process (not ”once and for all”)
- Characteristics of “**the system**”:
  - Available facilities for diagnosis and treatment
  - Risks (physical and psychological) less than the benefits
  - Costs balanced against the benefits

When should we screen?



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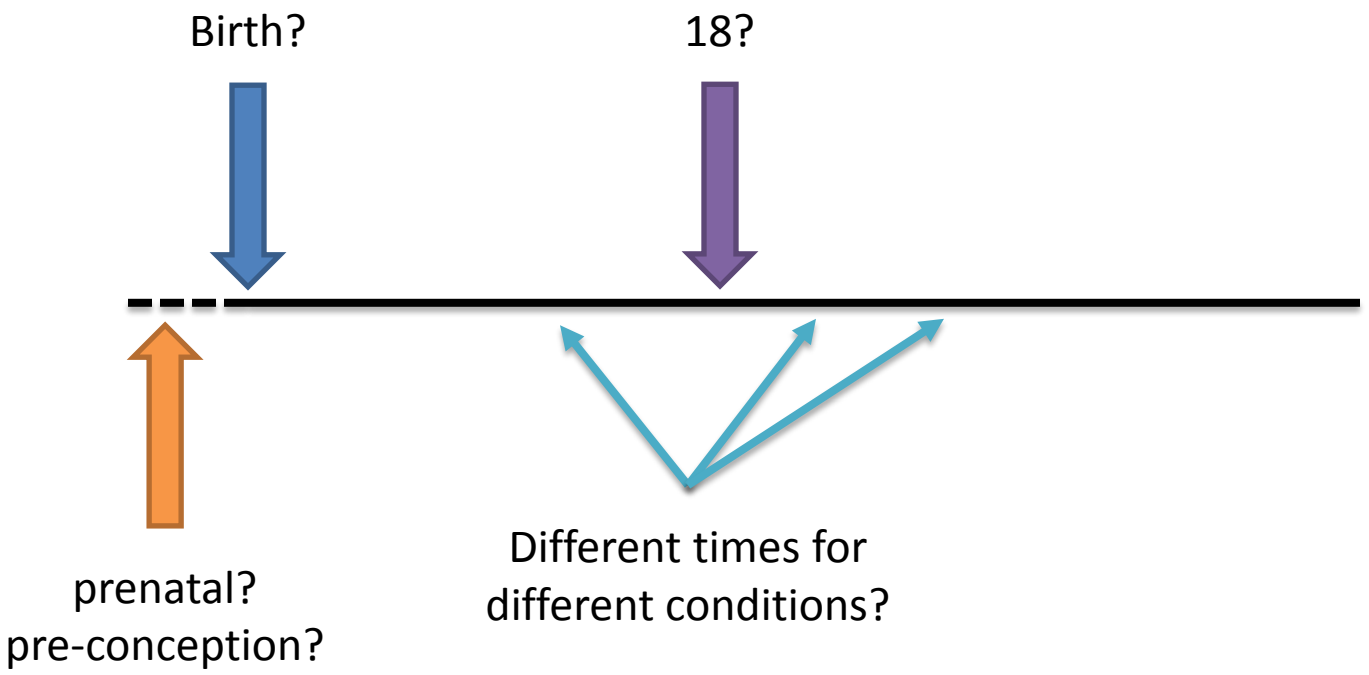


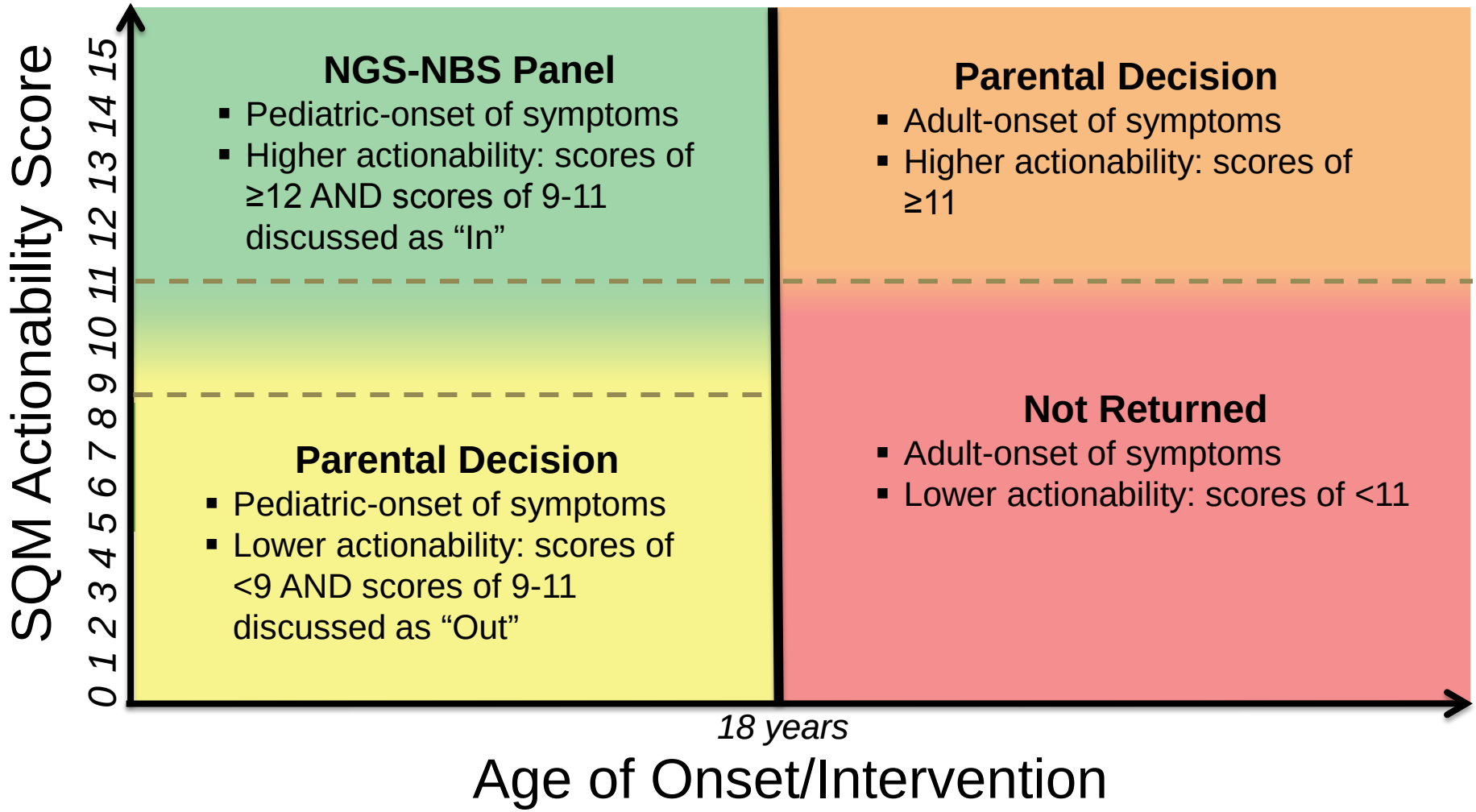
Sequence first and ask questions later?

Genomic screening in children

NCNexus
North Carolina Newborn Exome Sequencing for Universal Screening

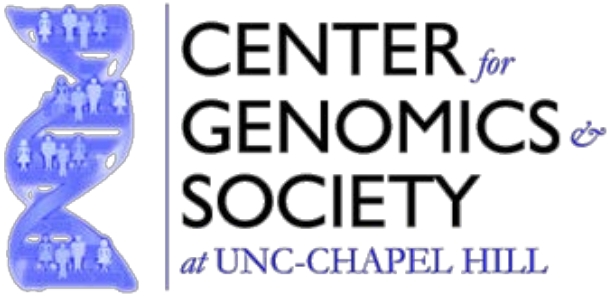
- Proxy decision-making
- Preservation of future autonomy by deferring adult-onset conditions
  - What if this is all the genomic screening the child gets?
  - What if testing would indicate that a parent has a treatable medical condition?

What results should be returned to "apparently" healthy infants?



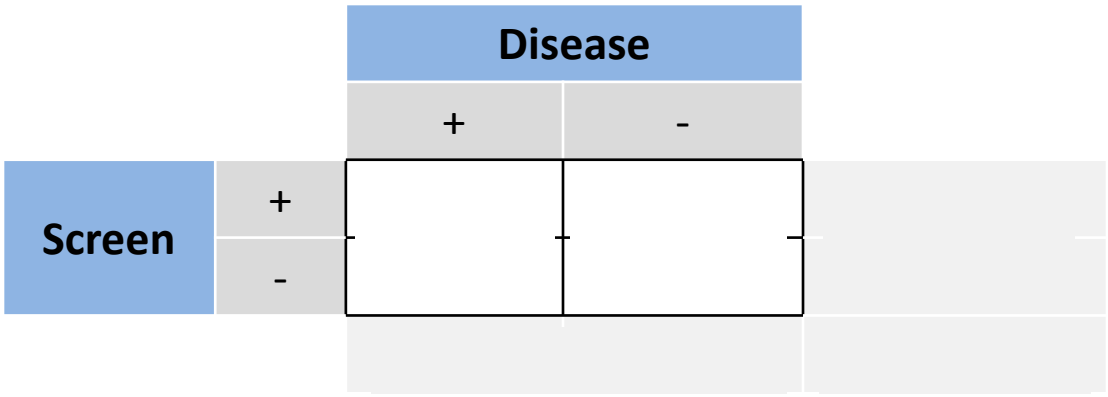
Genomic screening in adults

- A smaller subset of genes will provide the majority of health benefits across the population
- Prevalence for individual conditions is low -> concerns about false discovery rate
- The most common conditions among ACMG59 have incomplete penetrance



When prevalence is low (in general population) false positives > true positives

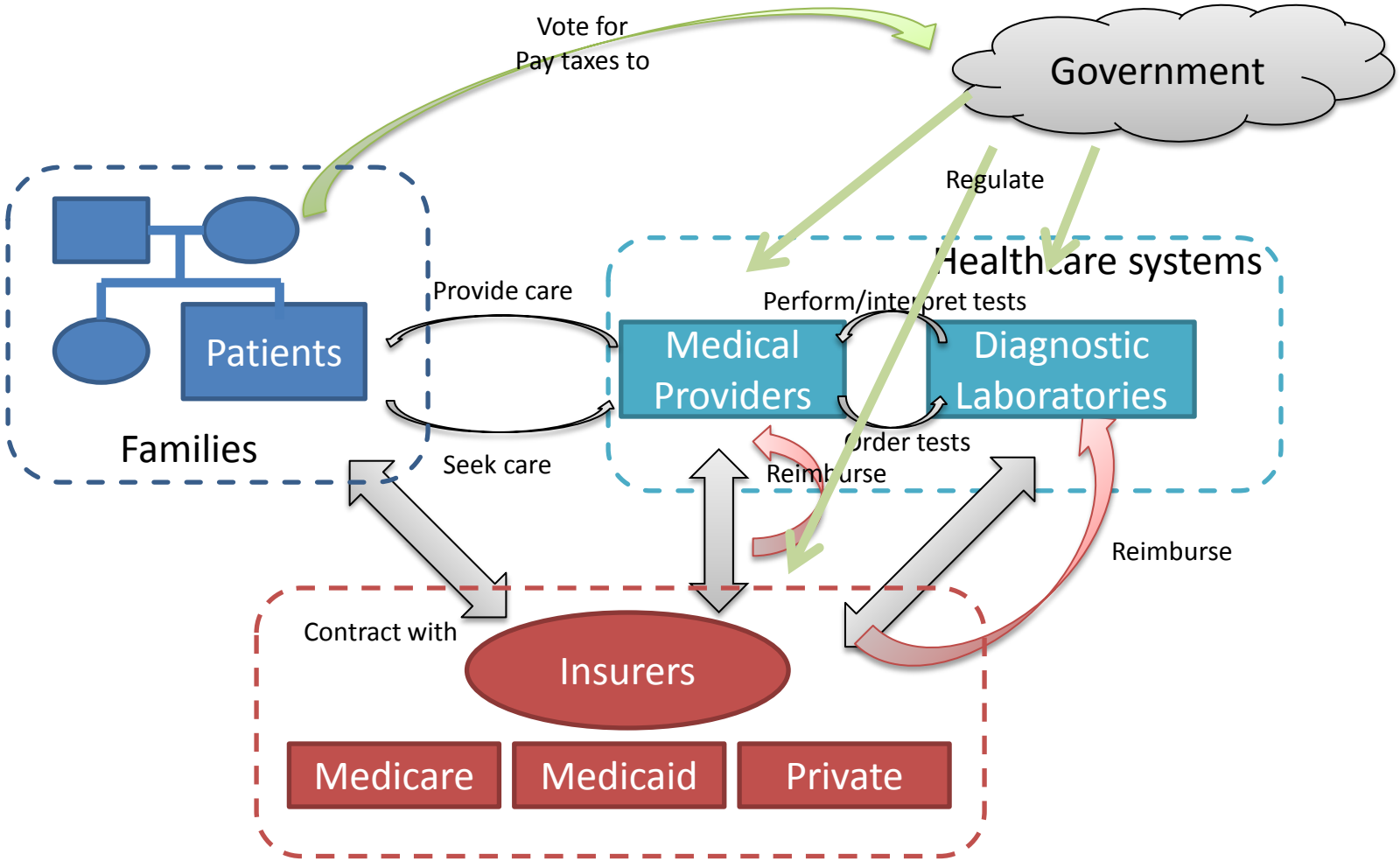
For a condition present in 1 in 10,000 (0.01%) of the population and a screen that is 99% sensitive and 99.94% specific



- The expected number of positive screens is 699/1,000,000, ~0.07%
- Most of these (about 86%) are false positive results!
- Put another way, for each true positive, you would have 6 false positives
- This screen would still miss 1% of cases

- For metabolic conditions on the newborn screen (phenylketonuria, for instance), secondary testing determine who needs intervention
- Can we really use even “likely pathogenic” results in a population screen?

Who pays and who benefits?

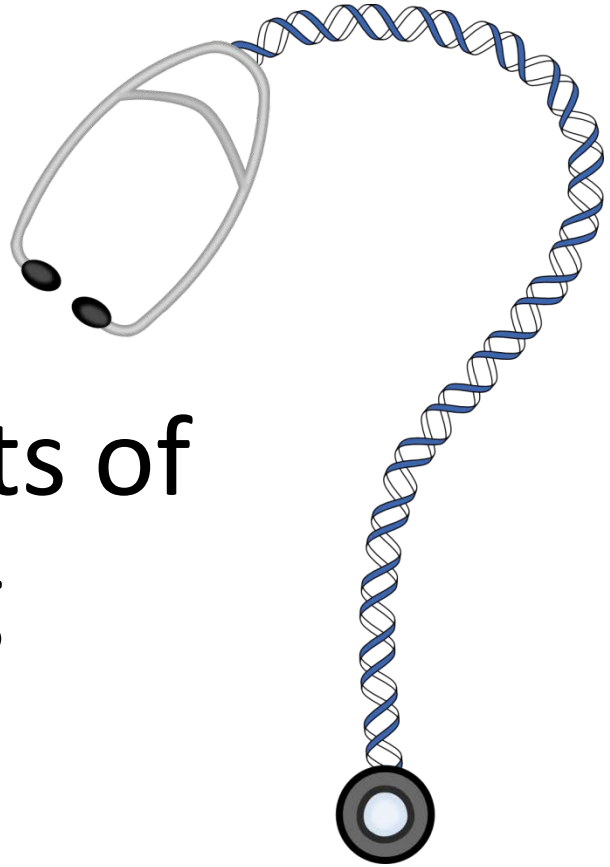


What drives the costs?

- Direct
  - Assay
  - Analysis
  - Return of results
- Downstream
  - Provider education
  - Confirmatory testing
  - Interventions/surveillance
  - Complications of interventions
- Ancillary costs
  - False reassurance (misunderstanding of info)
  - Interventions/surveillance in ”clinical false positives”
  - Patient anxiety/discomfort
  - Effects on insurance/employment

“Unknowns” that will affect the balance of costs and benefits

- Prevalence
  - How many people can possibly be helped?
- Penetrance
  - How many people might not have needed treatment anyway?
- Efficacy of pre-symptomatic intervention
  - How much of a difference will we make even if we identify people at risk?



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