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?

Symptom onset or
Age of earliest treatment

screen here  not much point now
When should we screen?

Birth? 18? Different times for different conditions?

Sequence first and ask questions later?

prenatal? pre-conception?
Genomic screening in children

- Proxy decision-making
- Preservation of future autonomy by deflecting 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?

**NGS-NBS Panel**
- Pediatric-onset of symptoms
- Higher actionability: scores of \( \geq 12 \) AND scores of 9-11 discussed as “In”

**Parental Decision**
- Pediatric-onset of symptoms
- Lower actionability: scores of <9 AND scores of 9-11 discussed as “Out”

**Parental Decision**
- Adult-onset of symptoms
- Higher actionability: scores of \( \geq 11 \)

**Not Returned**
- Adult-onset of symptoms
- Lower actionability: scores of <11
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?

Patients

Medical Providers
- Perform/interpret tests

Diagnostic Laboratories
- Order tests

Insurers
- Medicare
- Medicaid
- Private

Families

Government
- Vote for
- Pay taxes to
- Regulate

Healthcare systems

Medicare
- Contract with

Medicaid

Private
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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