Panel Discussion
Moderator: Rex Chisholm
Panel Members: Muin Khoury, Alicia Martin, George Mensah, Gina Peloso, David Valle

Do we need a clinical trial of genomic risk prediction?
If so, what should it test, in whom, and with what outcome?
What do we need to know before planning such a trial?

- **Tier 1**
  - FDA label requires use of test to inform choice or dose of a drug
  - CMS covers testing
  - Clinical practice guideline based on systematic review supports testing

- **Tier 2**
  - FDA label mentions biomarker
  - CMS coverage with evidence development
  - Clinical practice guideline, not based on systematic review, supports use of test
  - Clinical practice guideline finds insufficient evidence but does not discourage use of test
  - Systematic review, without clinical practice guideline, supports use of test
  - Systematic review finds insufficient evidence but does not discourage use of test
  - Clinical practice guideline recommends dosage adjustment, but does not address testing

- **Tier 3**
  - FDA label cautions against use
  - CMS decision against coverage
  - Clinical practice guideline recommends against use of test
  - Clinical practice guideline finds insufficient evidence and discourages use of test
  - Systematic review recommends against use
  - Systematic review finds insufficient evidence and discourages use
  - Evidence available only from published studies without systematic reviews, clinical practice guidelines, FDA label or CMS labels coverage decision

*Can be reassigned to Green or Red if one or more conditions in these categories apply

Genetic Risk Scores are Tier 3!
An Evaluation Framework for Polygenic Risk Scores

• Do we need a clinical trial of genomic risk prediction?
  • Yes, probably multiple trials depending on purpose

• If so, what should it test, in whom, and with what outcomes?
  • Based on intended use (ACCE disorder/setting)

• What do we need to know before planning such a trial?
  • Know Analytic and Clinical Validity

• Options for Trials
  • Test/Not Test
  • ROR/Not ROR
  • Hybrid studies
Staggering disparities in accuracy warn of translational challenges

Genetic basis:
Correlated variants, not causal effects

Differences in allele frequency, LD

Consistent promise from diversifying efforts

**Goal:** Compare genetic prediction accuracy in UKBB and BBJ

1. Run equal-sized GWAS for 17 traits (N ~ 80k - 150k)
2. Compute within- and cross-population prediction accuracy

Do we see symmetric, comparable prediction accuracy?

Ancestry-matched results are best

Cohorts, phenotype precision matter

Clinical Trials of Genetic Risk Prediction Should Emphasize Three Types of Outcomes

Clinical Trials of Genetic Risk Prediction Should Embrace Hybrid Effectiveness-Implementation Designs

Hybrid Type I
- Test clinical/public health effectiveness
- Observe and gather information on implementation

Hybrid Type II
- Test clinical/public health effectiveness
- Study implementation strategy & outcomes

Hybrid Type III
- Test implementation strategy.
- Observe and gather information on clinical/public health outcomes
Considerations for designing a clinical trial of genetic risk prediction

• Provides a concrete example of the usefulness of genetic risk for clinical practice
• Considerations
  • Predictions are accurate
    • Correct population is targeted
    • Environmental exposures
  • There is an actionable response
  • Response implementation is feasible
  • Ethical issues
• Outcomes: both clinical/testing and psychological
Clinical Trial(s) for Genomic Risk Prediction

- What has been done before?
  - E.g. NBS (PKU); Prenatal; Tay-Sachs

- What is in progress?

- What are the question(s) --

- Design issues
  - Who
  - Risk for what
  - Controls
  - Numbers
  - Delivery of risk method(s) and follow up
  - Educational add-ons
  - Time frame +/- intermediate points

dvalle@jhmi.edu
Some outcomes measures to consider

- Health outcomes
  - Phenotypic measures; medical encounters; medications, quality of life etc.
  - Reproduction
  - Prevention!
- Economic – fully loaded
  - More or less $
- Medical behavior
  - Physician uptake