Panel Discussion

Moderator: Rex Chisholm

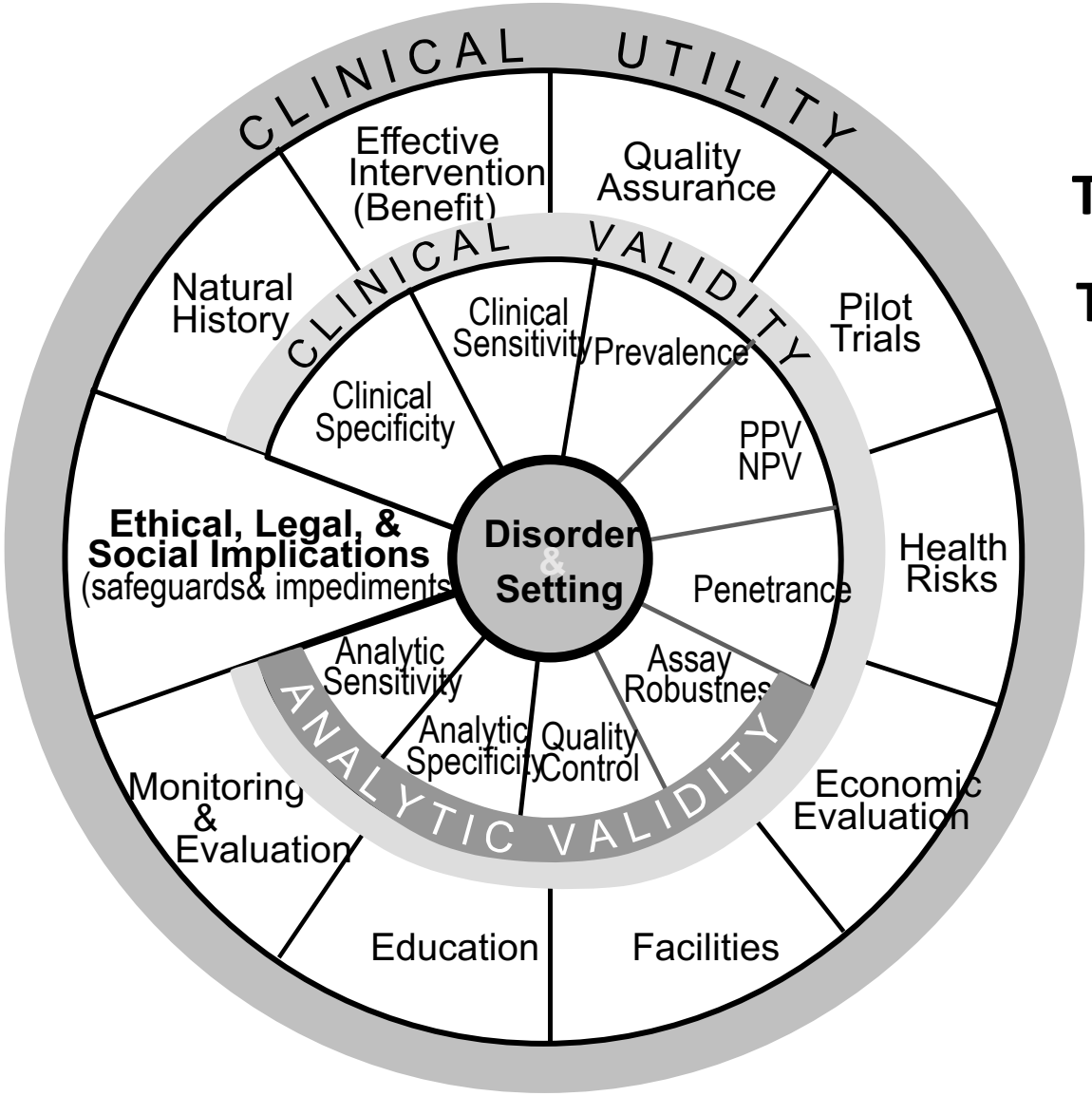
Panel Members: Muin Khoury, Alicia Martin, George Mensah, Gina Peloso, David Valle

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?

Evaluation Framework for Genetic Tests, Including Polygenic Risk Scores, Using ACCE and Tier System



Tier 1

Tier 2

Tier 3

Green	• 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
Yellow	• 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
Red	• 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 availble 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!

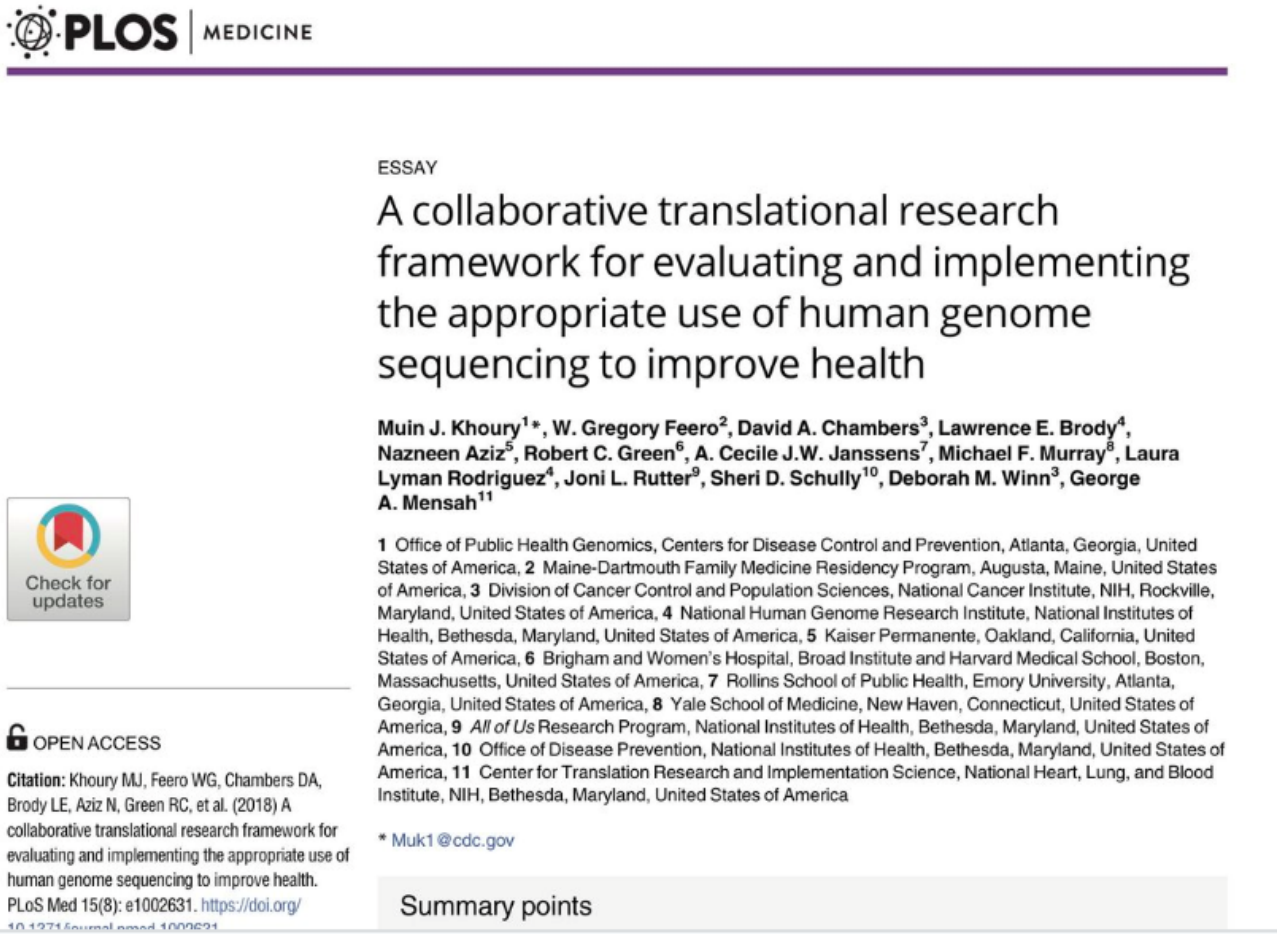
An Evaluation Framework for Polygenic Risk Scores

- 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



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ESSAY

A collaborative translational research framework for evaluating and implementing the appropriate use of human genome sequencing to improve health

Muin J. Khoury[1]*, W. Gregory Feero[2], David A. Chambers[3], Lawrence E. Brody[4], Nazneen Aziz[5], Robert C. Green[6], A. Cecile J.W. Janssens[7], Michael F. Murray[8], Laura Lyman Rodriguez[4], Joni L. Rutter[9], Sheri D. Schully[10], Deborah M. Winn[3], George A. Mensah[11]

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Check for updates

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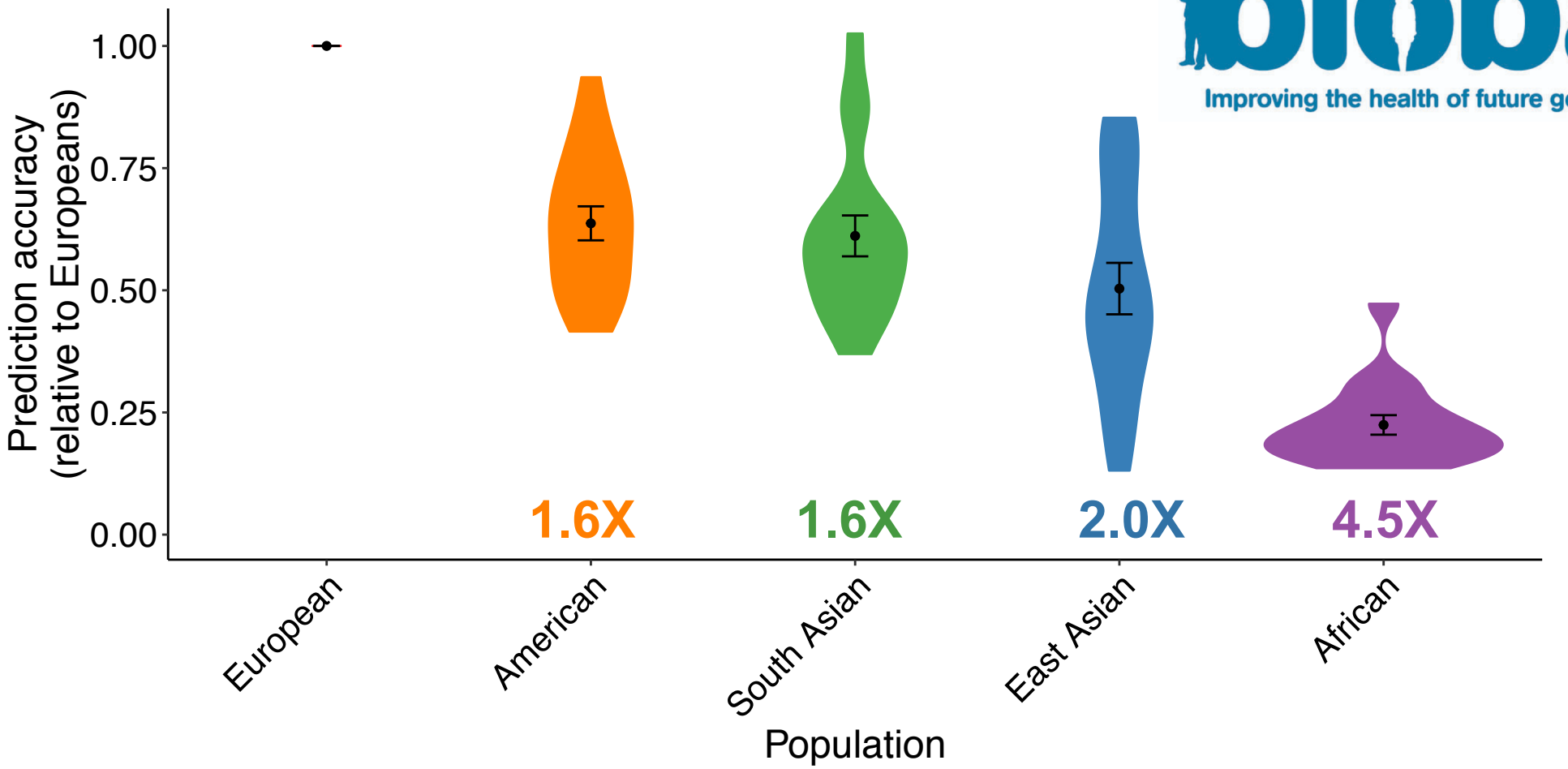
Summary points

Staggering disparities in accuracy warn of translational challenges



biobank uk
Improving the health of future generations

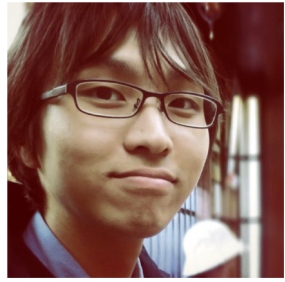
Genetic basis:

Correlated variants, not causal effects

Differences in allele frequency, LD

Martin, A. R. *et al.* Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* (2019).

Consistent promise from diversifying efforts

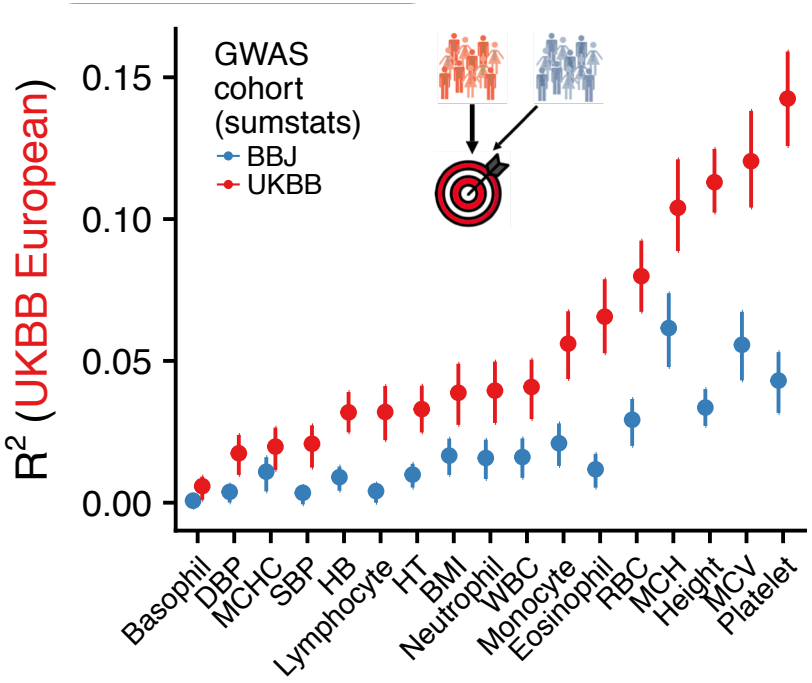


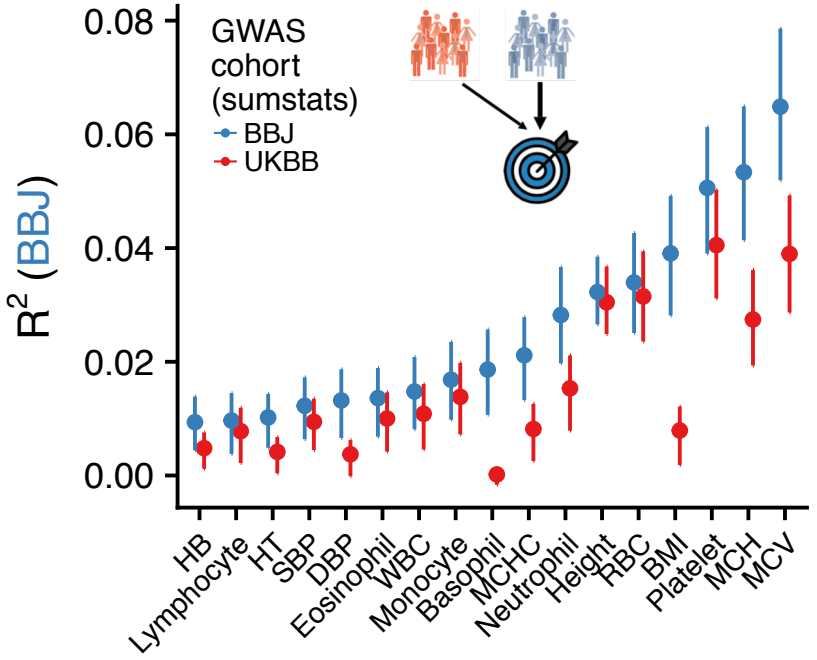
Masahiro Kanai

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

Martin, A. R. *et al.* Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* (2019).

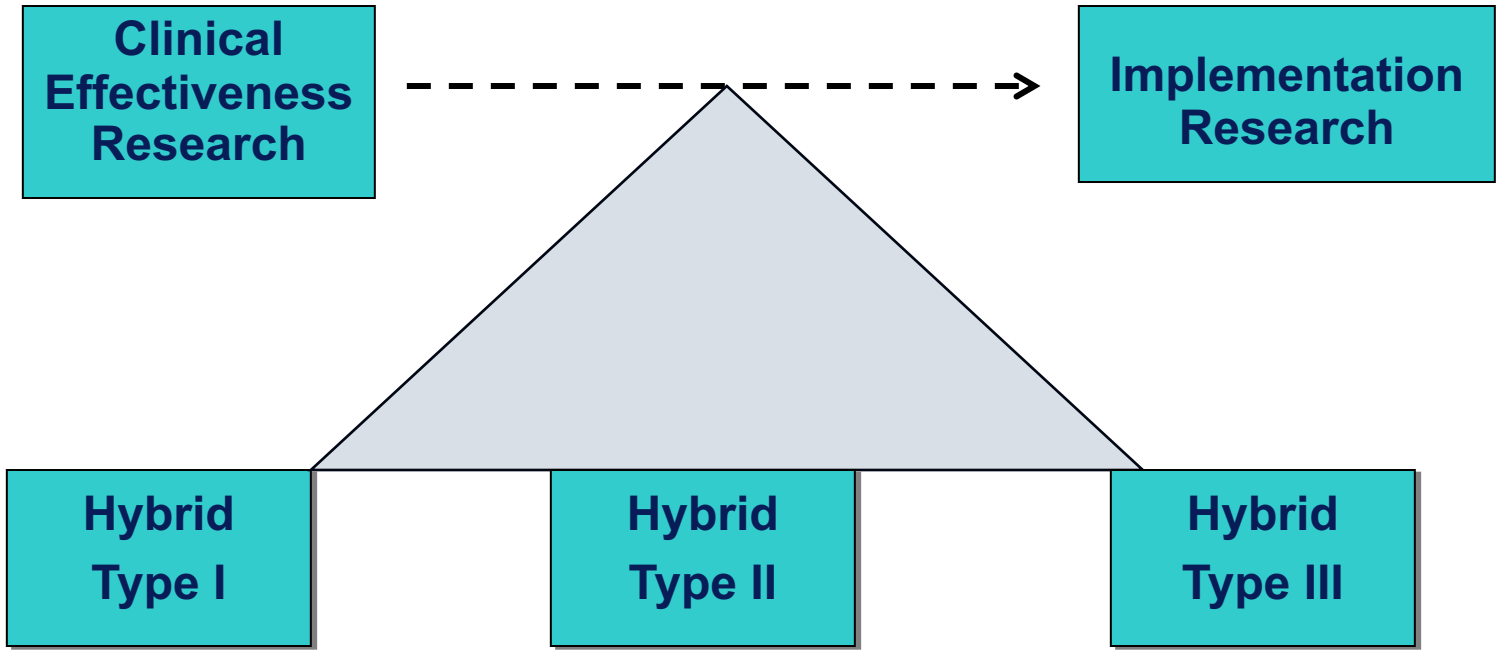
Clinical Trials of Genetic Risk Prediction Should Emphasize

Three Types of Outcomes

Modified from Proctor et al. *Adm Policy Ment Health* (2011) 38:65–76

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

Center for Translation Research and Implementation Science
Modified from C. Hendricks Brown

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

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Clinical Trial(s) for Genomic Risk Prediction - 2

- 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

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