Session 1: Risk prediction with and without genomics

- Both non-genetic and genetic risk contribute, are independent but correlated

- Challenges in non-EA: different SNPs, betas, absolute risk

- Best predictor of using risk scores is available informatics support

- Scores can evolve over time; variant discovery will continue

- Big hurdle is moving from sophisticated centers to payers and everyday clinicians

- Genomics needs to engage in implementation science

- Critical to define disease subtypes in non-white populations, different mutation signatures

- AfAm more likely to have aggressive tumor types for some

Session 2: Using informatics and electronic health record (EHR) data in risk prediction

- PheRS– another reason not to store genetic data as PDFs
  - Identifies novel pathogenic variants, interpret VUS
  - Potential solutions vary; recommendation- bring them together to share
- Structure-leveraged models improve prediction from both PRS and mammography and both contribute compared to LR
  - Learned models sometimes are improvements over conventional methods, identify novel risk factors
  - Simple models often work well
- Perfectly calibrated, very high (0.95) AUC models can give very different results– 0.1 vs 0.9 risk
- Identifying high/low risk subgroups could be integrated into healthcare delivery system rather than post hoc research
- Need for research on the best way to deliver information to clinicians

Session 3: Choosing the best models—lessons from diverse complex diseases

- Integrated risk prediction models (SNPs + FHx + imaging + OCPs/lifestyle) can identify more women at increased risk

- Most cases still occur outside high-risk groups, still need population-wide strategies

- Current PRS are better at predicting low-risk disease because there's more of it (specifically in breast cancer), need better prediction of aggressive disease

- PRS provide solid foundation for identifying biomarkers and associated risk– badly needed in schizophrenia

- PRS as biomarker for AF patients at high risk of cryptogenic stroke or pts without AF needing long-term monitoring?

- PRS can identify persons at risk (for obesity) at very early ages– other conditions?

Session 4: Other 'omic data

- Distantly acting (>1Mb) eQTLs much more cell type specific than locally acting eQTLs that act across all tissues

- Can examine entire medical phenome for rare diseases like VACTERL, develop PheRS, identify associated genetic variants

- At highest exposure levels, risk likely multiplicative but appears additive at low levels of exposure

- Epigenetic association studies (EWAS) more complicated than GWAS, include temporal variation and direction of causality

- Adult-onset methylation of many CpGs heritable, may explain more variability than SNPs

- EWAS identify new genomic regions influencing complex traits

- "DNAmet age" as potential biomarker of aging, but warrants further research

- Predictors of disease may not be the best predictors of therapy response

Panel– Clinical Trial of Genomic Risk Prediction?

- Do we need a clinical trial of genomic risk prediction?
  - Yes, probably multiple trials depending on purpose
  - Probably a trial of multiple conditions/scores
- If so, what should it test
  - Should have actionable response; response implementation should be feasible
  - Include educational components
  - Collaborate across multiple diseases, multiple NIH Institutes
  - Value for diagnosis (bipolar disease) as well as intervention
- In whom
  - Ancestry-matched scores
  - Include appropriate environmental exposures

Panel– Clinical Trial of Genomic Risk Prediction?

- With what outcomes?
  - Hard outcomes
  - Implementation outcomes: acceptability, costs, sustainability
  - Hybrid designs: clinical as well as implementation outcomes
  - Psychological outcomes: impact on patients
  - Reproductive outcomes
  - Influence physician behavior, uptake of recommendations
- What do we need to know before planning such a trial?
  - Analytic and clinical validity; effect size
  - Potential for worsening outcomes or widening health disparities in under-represented groups
  - Practice guidelines with known interventions

Panel– Clinical Trial of Genomic Risk Prediction?

- Consider PRS for response to therapy such as IBD, employers
- 20 diseases may be enough to capture breadth across them
  - Data in non-EA populations– those where risk estimates are several-fold different
  - Age of onset, when to intervene
  - Strength of environmental component
  - Burden/invasiveness of intervention
  - Genetic architecture
  - Implementation model
  - Availability of hard endpoints
  - Bigger impact of PRS on AUC

Prioritization of Research Directions

- Complexity of disease

  - Lack of environment or other confounders (Prostate cancer)

- Amount of existing data

- Effect size

  - Use of models for assessment of potential impact

  - Prevention vs. therapeutic intervention

  - Differential response to intervention in different populations

- Availability of hard endpoints

- Use of existing longitudinal cohorts, trial data (with genotypes?)

- Find ways to incorporate genetics into existing risk calculators

Prioritization of Research Directions

- Diversity

  - Risk scores for every ethnic group? Different weights across ethnicities? Pan-ethnic scores?

  - Disproportionately increased (benefits) findings of more variants and more causal variants in non-EA groups

- Multiplex approach in populations

  - Increase number in population at high (or low) risk of something

- Amenability to implementation in real-world health systems

- Use 'omic data as way to weight SNPs, how to combine 'omics

- Patient-centered measures

Critical Knowledge Gaps

- Applicability of risk prediction models from 1960s or 1990s to risk prediction now and in future

  - Lowered risk of AD for *APOe4* carriers over time

- Role of other 'omics may be more predictive than genomics

- Studying populations of recent African Ancestry with large variation can help discover new causal variants, and better narrow down causal variants

- Explore serial transcriptomics/epigenomics as indicators of early disease rather than q6mo imaging with burden/harm

- Acceptability of risk estimation to patients

- Converting relative risk to absolute risk differs across populations

Next Steps

- Develop and distribute summary of this meeting

- Consider manuscript on research directions in genomic risk

- Post slides, videos, meeting summaries on website

Future Directions

- Improve PRS to be disease subtype and ancestry-specific

- New risk factors/biomarkers needed to further improve risk stratification

- Double size of current GWAS to find risk variants in diverse populations

- Find ways to incorporate genetics into existing risk calculators

Out-takes

- GRS for CHD adds to risk for hard ASCVD, increasing risk about 2.2 times per unit increase in GRS (vs. 2.4 for PCE)

- Pooled Cohort Equations (PCE) risk does add to genetics, statistically independent but correlated

- Requires adoption of common standards across studies: outcomes, risk score components

- Unanswered questions:
    - When to test?
    - How to test?
    - Whom to test?
    - When to intervene?
    - How to coordinate care providers?

Out-takes

- Relationship inference from EHR enables h2 estimates; some good, some not– why?

- Risk prediction for psychiatric disorders less likely to be applied in population screening

- Engage companies with large employee base to conduct trials? Large healthcare systems?

- Workflow for implementation– but these are local

- Distinguish effect of "gene" vs. "variant"

Did we reach our objectives?

- Review the state of science of polygenic risk scores and how it can be improved

- Examine other information sources that should be integrated with genetic variant information in predicting risk

- Identify research directions in development and implementation of genomic risk prediction