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Rapporteurs

Genomic Medicine XII: Genomics and Risk Prediction

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Silver Spring, MD

https://www.genome.gov/event-calendar/genomic-medicine-xii-genomics-and-risk-prediction

Executive Summary

NHGRI's twelfth Genomic Medicine meeting convened leaders in genomic medicine, healthcare, and research to discuss the role of genomics in risk prediction. Specifically, the meeting aimed to: 1) Review the state of science of polygenic risk scores (PRS) and how it can be improved, 2) Examine other information sources that could be integrated with genetic variant information in predicting risk, and 3) Identify research directions in development and implementation of genomic risk prediction.

Lessons Learned:

Implementation:

- Available information technology (IT) support is a strong determinant of clinicians' use of PRS
- Physicians are likely to be uncomfortable with decreasing screening for patients at lower risk for a condition; information is needed on whether "downgrading" risk is useful
- PRS must be actionable and there must be clear procedures for interventions based on the PRS before implementation can occur
- Increasing clinician burden through workflow disruption (e.g., alert fatigue) and more complex health interventions in addition to currently recommended population health interventions are significant barriers to clinician use of PRS
- PRS provide another reason not to store genomic data as PDFs, as variants (or risk scores based on variants) need to be computable
- Despite stratification by PRS most cases will continue to occur outside of high-risk groups so population-wide strategies are needed

Risk model construction:

- Genetic and non-genetic risk factors provide independent but correlated information
- PheRS generated from EHR data can be used to identify novel pathogenic variants
- Machine learning models based on EHR data can identify novel risk factors; simple, linear machine learning models are often comparable to complex ones and may be easier to use
- PRS provide a foundation for identifying biomarkers in psychiatric and other difficult-to-diagnose disorders
- PRS are in some cases being constructed from outdated data, which creates challenges with applying PRS in the current healthcare environment
- Risk is likely multiplicative when effect size is high but appears to be additive/linear when effect sizes or exposure levels are low
- Predictors of disease development may differ from predictors of response to therapy

- Epigenome-wide association studies (EWAS) are more complicated than GWAS due to temporal variation and unknown direction of causality, but may identify new genomic regions influencing complex disease risk
- PRS appear to be independent predictors and are useful for further stratifying risk of developing conditions in patients with monogenic disease or high-risk genetic variants
- 'omic measures such as epigenomics and transcriptomics may be useful for calculating gene-environment interactions and developing proxies for unknown environmental contributions

Challenges in non-EA populations:

- PRS results from European Ancestry (EA) populations may not replicate in non-EA populations
- Non-EA populations have different absolute risk for diseases and disease subtypes due to differences in causal variants, disease incidence and pathology, social determinants, and environmental factors
- PRS have the potential to worsen outcomes or widen health disparities in underrepresented groups if these groups are not included in research

Recommendations:

Implementation Research:

- Invest in implementation science that investigates how to accelerate adoption of evidence-based risk prediction from early adopting centers to a diverse range of systems.
- Research the best way to communicate risk to patients and consider whether and how patients will want to receive risk score results, depending on disease
- Continue to investigate the potential benefits of fewer interventions for low risk patients
- Research the best ways to deliver risk information to clinicians

PRS Development Research:

- Investigate the value of using DNA methylation as a biomarker of aging and disease risk
- Prioritize validating existing PRS in diverse populations to determine how causal variants and effect sizes vary based on patient background
- Continue discovery research to identify disease risk variants and associated risk estimates
- Current PRS tend to be better at predicting low-risk and high prevalence disease due to availability of data; there needs to be better prediction of aggressive disease
- Prioritize validating PRS in conditions that are amenable to real-world implementation
- Investigate methods for integrating other 'omic data into risk prediction, potentially using 'omic data as a way to weight SNP-based risk scores
- Explore serial transcriptomics/epigenomics for detection of early disease rather than frequent repeated imaging or other testing that can cause burden/harm
- Prioritize investigation of diseases with existing data, longitudinal cohorts, and availability of hard clinical endpoints
- Investigate how PRS can further stratify risk of developing disease in patients with monogenic disease or high-risk genetic variants

- Measure process outcomes and intermediate phenotypes related to clinical outcomes to increase PRS predictability in cases where hard outcomes are difficult to collect
- Find ways to incorporate PRS into existing risk estimation tools to improve and speed acceptance into professional societies' guidelines

PRS Clinical Trials:

- Create PRS clinical trials that combine several major diseases with similar risk estimation methods based on single genome-wide assay rather than one condition at a time
- Ensure diseases chosen have actionable responses and response implementation is feasible
- Include patient/clinician education and environmental exposures as components of PRS trials
- Evaluate improved diagnosis and response to therapy as outcomes in PRS trials
- Add clinical trials of PRS to existing clinical scenarios (such as breast cancer, fracture risk) where clinical risk stratification is already in use
- Embed clinical trials for PRS into existing research, such as All of Us or the eMERGE network
- PRS trial outcomes should include disease morbidity/mortality, implementation outcomes such as acceptability, uptake, costs and sustainability, and psychological and reproductive outcomes
- Before planning trials, need to know analytic and clinical validity of PRS, effect sizes of interventions, potential for worsening outcomes or widening health disparities, availability of practice guidelines with accepted interventions, and impact of PRS on AUC
- Capture a breadth of conditions in multiple-condition PRS trials, covering a spectrum of:
    - Disease incidence, risk variants, risk magnitudes across different ancestries
    - Age of onset, optimal age of intervention
    - Strength of environmental component and other non-genetic risk contributors
    - Genetic architecture
    - Burden/invasiveness of intervention
    - Implementation model
    - Availability of hard endpoints

PRS Development:

- Determine whether ancestry-specific PRS are needed for every ethnic group or every condition or whether different weightings or pan-ethnic scores may be possible for some conditions
- Develop PRS for specific disease subtypes; a "one size fits all" approach does not always work when predicting disease risk, especially in non-EA populations
- Increase transparency and standardize methods of risk score characterization, development, and validation to facilitate comparison; models such as the GRIPS Statement (PMID: 21502867) may be useful
- Integrate methods to identify high and low risk subgroups within learning healthcare systems rather than through post hoc research
- Include dedicated funding for IT professionals and informaticists to facilitate integration of algorithms and clinical decision support into health systems