Are we ready for polygenic risk scores in the clinical world?

Lavania Sharma², Peter Hulick¹, Brian Helfand¹, Elissa Levin², Alex Bolze², Keith Dunaway², James Lu², Jianfeng Xu¹

¹ NorthShore University HealthSystem, Evanston, Illinois  ² Helix LLC, San Carlos, California

Introduction

- Pathogenic variants explain only a small portion of prostate cancer (PCa). However, polygenic risk scores can explain a higher number of PCa cases.
- The utility of disease risk measured by polygenic risk score has been consistently demonstrated for many common diseases, including PCa.
- Polygenic tests are currently being developed, offered and used in the clinical space. However there is a lack of medical management guidelines and studies showing clinical impact.
- Here we propose best practices for developing a market-first clinical polygenic risk score test in multiple ethnicities (East Asian, African American, and Non-Hispanic White), and counseling patients.

Test Development

- This product was developed by researchers and urologists at NorthShore University HealthSystem in collaboration with Helix.
- We used the odds ratio (OR)-weighted and population-standardized genetic risk score (GRS) method. Each SNP is first standardized against the general population and then multiplied for all SNPs. Thus its expected mean in the general population will always be 1.0, regardless of the number of SNPs used in calculation, and its values can be simply interpreted as relative risk to that of the general population.
- These two important features of population-standardized GRS makes the interpretation and implementation of an individual’s risk comprehensible. We also applied two benchmarks, baseline and calibration, to ensure the reliability of GRS values.
- This test involves a physician sign-off pre-test and a discussion of the result with a genetic counselor, post-test.

Design of Clinical Report

- Based on the GRS, individuals are categorized as average, moderately-high or high risk for developing PCa.
- Medical management recommendations are based on the individuals’ risk category, and generally follow the risk-based PCa screening guidelines of the U.S.Preventive Service Task Force
  
  Medical management recommendations:
  1. **Average risk**: a discussion with physicians about PSA screening for prostate cancer at age 55.
  2. **Moderately-High risk**: may benefit from starting PSA screening 5 years earlier than general recommendations and/or more frequent screening
  3. **High risk**: may benefit from starting PSA screening 10 years earlier than general recommendations and/or more frequent screening.

![Fig: Example of the clinical report](image)

Discussion

- Working with the experts in the field, we have developed a user-friendly report that includes relative and absolute risks, and standardized the method for developing GRS in multiple ethnicities.
- The report was designed to include an in-depth discussion of the risk score for physicians who may be new to this test/concept.
- Our test may help patients and physicians make a personalized decision for PCa screening.

References:
- Inherited risk assessment of prostate cancer: it takes three to do it right. Xu et al. (PMID 31417171)
- Concept and benchmarks for assessing narrow-sense validity of genetic risk score values. Xu et al. (PMID 31037745)