Polygenic risk scores for prostate cancer: testing considerations

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Genome-wide association studies (GWAS) have identified more than 170 single nucleotide variants (SNVs) associated with prostate cancer risk. Each variant is associated with only small increases in risk and is not predictive of an individuals' overall risk of developing prostate cancer.

Polygenic risk scores (PRS) combining these variants are now clinically available and may improve predictive value of other factors such as PSA. This overview reviews the current state of PRS for prostate cancer including testing considerations.

Key Words: polygenic risk score, prostate cancer, risk prediction, genome-wide association study

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Numerous genome-wide association studies (GWAS) have been performed for prostate cancer leading to the discovery of over 170 single nucleotide variants (SNVs) showing modest contributions to prostate cancer risk.[1-3] Currently these variants are estimated to explain 28%-33% of the familial risk of prostate cancer.[1,2] Although these variants are not predictive for risk on their own, polygenic risk scores (PRS) combining risk for many SNVs are showing promise for stratifying individuals well-above average population risk as well as below population risk. One study using a model of 72 SNVs in 1725 cases and 1415 controls found that men in the top decile of PRS have a lifetime risk of prostate cancer of about 30% and men in the top 1% have up to a 42% lifetime risk.[4] Another study of 147 SNVs found that the relative risk for men with the top 1% of the PRS was 5.7-fold higher than men in the middle 25%-75%.[2]

PRS may help to explain prostate cancer diagnoses in men with high-probability of carrying a high to moderately penetrant pathogenic variant who test negative on clinical panels for known prostate cancer genes. PRS may also be useful in decreasing overdiagnosis of prostate cancer, specifically by improving the predictive value of prostate-specific antigen (PSA) testing. A study by the PRACTICAL and UK ProtecT consortia tested a 54 SNV model in discovery and validation sets of over 21,000 prostate cancer cases, 17,500 controls and 8900 men with high PSA levels.[5] This study showed that the positive predictive value for PSA testing for aggressive prostate cancer was ~25% for individuals in the highest 5% of genetic risk, compared to ~16% for individuals in the middle 50% of risk and less than 8% in individuals in the lowest 20% of risk. PRS in this study was more predictive of prostate cancer risk than family history. Inclusion of cancer family history did not improve predictive value, but in this and other studies family history further modifies absolute risk.[5,6] Another population-based study found that among individuals with elevated PSA there was over a two-fold increase in the incidence of prostate cancer for those in the top PRS decile compared to those in the middle deciles.[7] Collectively, these studies suggest the value of PRS in improving predictive value of family history and PSA, known risk factors for prostate cancer.

Although the majority of GWAS and PRS studies for prostate cancer have been done in European populations, a few studies evaluated the utility of PRS in other racial and/or ethnic groups.[3] The majority (68%-83%) of SNVs studied show similar directional effects in East Asians, Latinos, and African Americans relative to Europeans. Although the PRS in these populations showed significant fold differences (e.g. 3-fold) between the top 10% and average risk (25%-75%) groups, the overall p values were lower.[8,9]

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Further research on the predictive value of PRS in non-European populations is critically important in order to provide equal access to predictive genetic testing.

Only one commercial company currently offers clinical PRS for prostate cancer. Criteria for testing includes male sex, European ancestry and being negative for a personal or family history of a pathogenic variant in one of 14 moderate-high risk prostate cancer-associated genes. Clinical testing reports provide an estimated lifetime risk of prostate cancer compared to the general population risk of 10.2%. A limitation of this test is that the PRS model is not combined with family history, PSA or other known risk factors to provide a more comprehensive assessment of risk.

There are multiple ways in which prostate cancer PRS could be used clinically including risk stratification for making personalized screening recommendations (alone or in a model with other risk factors), as part of national screening guidelines, to provide more refined risk estimates for individuals with a pathogenic high-risk variant, and for prognostic information in individuals with elevated PSA. Future clinical applications may include PRS for prediction of radiation side effects after prostate cancer treatment.[1] PRA may also have utility for some patients who are already undergoing genetic testing for high-risk genes in helping them to understand why they developed prostate cancer.

Despite the promise of clinical utility of prostate cancer PRS, there are a significant number of gaps in our knowledge. Most critical are our limited understanding of their predictive value, especially in non-European populations, how much models may change with additional genetic information, what other risk factors should be included, what predictive value is needed for clinical use, the accuracy of PRS across different age groups, whether PRS can be used to predict "when" an individual's risk crosses a screening threshold, if PRS impacts outcomes, how to present the information to patients, and how to train providers to understand and appropriately use this information. On-going clinical trials are determining if PRS are useful biomarkers for screening. As PRS for prostate cancer become more widely available clinically, additional studies are needed before routine use of PRS for prognosis and screening strategies.

Disclosures

Dr. Amanda Toland has no disclosures. □

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