Polygenic Risk Scores in Prostate Cancer Risk Assessment and Screening

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KEYWORDS

• Polygenic risk score • Prostate cancer • Risk prediction • Genome-wide association study
• Cancer screening

KEY POINTS

- Polygenic risk scores improve the predictive value of prostate-specific antigen screening.
- Polygenic risk scores may have utility in determining age at which prostate cancer screening should begin and identification of highest and lowest risk individuals.
- Clinical trials to evaluate the utility of polygenic risk scores for screening decision-making and risk prediction are needed.

INTRODUCTION

Prostate cancer (PCa) is the most common cancer among men with a lifetime risk of 12% and median age of diagnosis of 66.[1] In 2020, 191,930 new cases are expected to be diagnosed in the United States.[1] Established risk factors for PCa include genetic factors, African ancestry, older age, and family history of PCa (discussed in Yasin Bhanji and colleagues' article, "Prostate Cancer Predisposition," elsewhere in this issue).[2] African American (AA) men are 1.8 times more likely to be diagnosed with PCa than men of European ancestry, with one in six AA men diagnosed in their lifetime.[1] The cause of increased PCa risk for AA men is unclear; differences in biology, socioeconomic environment, exposures, lifestyle and behavior, or a combination of all these factors may contribute. Age is also strongly associated with PCa because there is a substantial increase in the rate of diagnosis after age 55.[2] There is about an 8.5% chance to be diagnosed with PCa younger than age 55, which increases to 32.4% in ages 55 to 64 and 39.9% in ages 65 to 74.[1] A family history of PCa, especially a first-degree relative (brother or father), has been associated with two-fold to three-fold increased risk of PCa.[3] PCa risk furthermore increases with the number of affected family members and the degree of relatedness (affected brothers compared with a father and son).[3] Importantly, about 10% to 15% of families with two to three PCa diagnoses who do not have a pathogenic variant (PV) in a known high-risk gene, and the cause of the familial clustering is unknown, are called familial PCa.[4]

Of all the common cancers, PCa has the highest heritability, or genetic contribution to risk, with up to 57% of PCa risk because of genetic risk factors.[5] Approximately 5% to 10% of PCa are caused by highly penetrant PVs in genes, such as *BRCA1* and *BRCA2*, which significantly increase lifetime risk of PCa (Matthew J. Schiewer and Karen E.

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Knudsen's article, "Basic Science and Molecular Genetics of Prostate Cancer Aggressiveness," in this issue).[4] One in 400 individuals in the general population carry a *BRCA1* or *BRCA2* PV.[6,7] Men with a *BRCA1* PV have a 7% to 26% lifetime risk of PCa by age 80. This risk increases to 19% to 61% for men with a *BRCA2* PV.[8,9]

PVs in additional genes, such as *CHEK2* and *ATM*, increase PCa risk by 1.9- to 3.3-fold and 6.3-fold, respectively.[10–14] A rare missense founder variant in *HOXB13*, G84E, has a carrier frequency of 0.2% to 1.4% in Nordic populations, which confers up to a 60% lifetime risk of PCa.[15–17] Hereditary PCa is a highly active area of research currently. Further studies are needed to define cancer risk associated with genes to improve clinical management and treatment of patients with PCa and their families.

GENOME-WIDE ASSOCIATION STUDIES AND RISK VARIANTS

In addition to variants that confer moderate to high risk of PCa, some genetic variants are associated with low, but measurable risk. Genome-wide association studies (GWAS) have been used as an agnostic means to identify low-effect common genetic variants associated with disease, most of which are single-nucleotide variants (SNV). Many risk variants associated with cancer susceptibility have low effect sizes, often with odds ratios of less than 1.10 for risk. To reach the low *P* values ($<1 \times 10^{-8}$) required for statistical significance when testing millions of variants, extremely large groups of cancer cases and control subjects are required.

PCa was one of the first disorders for which GWAS were performed. In 2007, three back-to-back PCa GWAS were published leading to the identification of multiple risk variants at 8q24.[18–20] Since that time more than 40 PCa GWAS have been performed with more than 170 variants identified that associate with disease.[21] Collectively, these variants are estimated to explain approximately 28% to 38% of the familial relative risk of PCa.[21,22] Unlike high-penetrant genetic variants associated with hereditary PCa, most GWAS variants are in noncoding regions and exert an effect through gene regulation. As a result, complementary approaches to identify risk variants associated with gene expression levels are being integrated with GWAS.[23–25]

Early GWAS were primarily conducted in populations of European descent. More recently, PCa GWAS in non-European populations have been published including those in AA,[26] Chinese,[27] Japanese,[28] Latino,[29] Ugandan,[30] and multiethnic populations.[31,32] In general GWAS in non-European populations were not as well powered to detect low-risk variants because they had fewer cases and control subjects studies. However, they revealed important insights including that different ethnic and racial populations have unique PCa risk variants that are not present, or present in low frequencies, in European populations. They also uncovered variants that are associated with risk in Europeans but no other groups.[28,33] Despite these findings, there are shared risk alleles across multiple populations. For example, Du and colleagues[29] found that the shared overlap of PCa risk variants is high between men of European Latino and European non-Latino men; 83% of risk variants identified in European populations showed a similar direction of risk in Latino men. These results are not surprising because it is expected that some risk variants will occur in multiple populations.

POLYGENIC RISK SCORES

When disease-associated variants identified using GWAS are considered individually, they each have little to no impact on risk prediction. Complex disease risk prediction in a given individual depends on a combination of associated genetic, environmental, and lifestyle factors. GWAS and genetic modeling analyses indicate that many common diseases, including PCa, are likely to have hundreds to thousands of common variants associated with disease risk.[34] Furthermore, these variants may influence disease risk differentially depending on environmental or lifestyle factors.[35]

Risk prediction models for PCa and other diseases are being developed that include hundreds to thousands of independent risk-associated variants. Additive effects of the variants are generated by summing the number of risk alleles an individual carries and weighting each by their estimated effect size from GWAS data to create a polygenic risk score (PRS), also known as a genetic risk score. Potential clinical use of PRS for cancer and other diseases have been described and range from risk prediction, informing screening decision-making, informing prevention strategies, and personal understanding of risk.[36–39]

Like GWAS, large numbers of samples are needed to generate and validate PRS. For PCa, one study estimated requiring a population of 20,000 men to develop well-calibrated PRS and 10,000 men to test the models.[40] A second study evaluating 14 different cancer types predicted that there are 4530 PCa risk variants in European populations, which collectively explain 77% of the heritability for PCa.[41] The same authors estimated that greater than 750,000 cases and control subjects may be needed to definitely identify all of

these risk alleles, which is about five times the current largest studies. This highlights the issue that most risk variants are not likely to be identifiable for most populations using current methodologies and available populations for study. An unanswered question is how accurate PRS using only a subset of risk variants will be. One argument in favor of using PRS with the current numbers of variants is that these variants are likely to be the ones with the highest effect sizes and that adding in variants with extremely low effects sizes is going to have exceedingly low impact on overall risk models. Because of statistical and population differences, it is important that PRS is calibrated and validated before clinical use. In comparing approaches for calibration and validation, one study suggested that downward adjustments to odds ratio used may need to be made to decrease the likelihood of providing falsely high estimates of risk.[42]

PRS scores are converted to a population distribution with lifetime risks so that scores are more easily interpreted.[37] For example, PRSs are lumped into percentiles of risk to identify the individuals at the top 1% of risk or the bottom 10% of risk with the bulk of individuals at 26% to 74% of the population mean of disease risk. This type of scaling may enable better screening recommendations for PCa. Some individuals may have a low enough PRS that they never cross a median 10-year risk of PCa of a 50-year-old man, the age at which screening for PCa begins in the United States. Conversely, men with a PRS estimating a high lifetime risk may cross this threshold at age 34.

POLYGENIC RISK SCORES FOR PROSTATE CANCER RISK PREDICTIONS

Early PCa PRSs were those for PCa risk (**Table 1**). The first PCa PRS, published in 2008, included only five SNVs and was evaluated in approximately 3000 cases and 2000 control studies.[43] A model of risk that included these variants plus family history, age, and region had an area under the curve (AUC) of 63.3 compared with 60.8 for the same risk factors without PRS. Subsequent studies increased the number of SNVs included in the models (see **Table 1**). A PRS study of 147 SNVs found that men in the top 1% of PRS had 5.71-fold increased risk compared with men in the middle 50% of risk.[22] Just 2 years later, a 2020 study of more than 48,000 men, more than 3700 with PCa, showed that those who are at the top 2.5% of risk of a 6,606,785 SNV risk score had approximately four-fold increased risks[54] compared with individuals in the middle of the distribution of risk. This translates to an approximate 50% lifetime risk of developing PCa compared with the average in the population of 16.3%.

POLYGENIC RISK SCORES IN NON-EUROPEAN POPULATIONS

Using GWAS hits from European and non-European populations, PRS in individuals of Latino, Asian, and African ancestry have been tested and validated (see **Table 1**). Importantly, the odds ratios used in PRS developed in individuals of European ancestry may not be as predictive as odds ratios from the population for which the PRS is being applied. As an example, a 135 SNV PRS tested in 2820 Latino PCa cases and 5293 control subjects showed that men in the top 10% and 1% of PRS had more than threefold and four-fold increased risk compared with those in the middle 26% to 74%. However, when a Latino-weighted PRS, using odds ratios derived from Latino populations was used in the model, those risks increased to nearly four- and seven-fold.[29] Similar findings were observed in Japanese populations. A PRS for PCa of 82 variants was developed specifically for men of Japanese ancestry. It included 12 SNVs that were uniquely identified as showing risk in Japanese populations and 68 variants that had been previously identified in GWAS from other populations but that also were associated with PCa risk in Japanese men. Evaluation of this PRS in 4893 PCa cases and 10,682 male control subjects showed that the age of diagnosis in men at the top 5% of risk was 2 years earlier than the men at the bottom 5% of risk.[28] The highest risk group was also more likely to have a family history of PCa. This model of 82 SNVs was more predictive of risk than a PRS of 150 SNVs that was based on findings from European populations. Helfand and colleagues[55] specifically addressed how a 105 SNV PRS would perform across multiple racial and ethnic groups. The PRS was statistically significant as predictive for risk in European, Latino, East Asian, and AA populations but performed the best in European and Latino groups. Collectively these studies suggest that racial- and ethnic-specific PRS may be more predictive than a "one size fits all" PRS but that European-developed PRS may have some utility for all racial and ethnic groups.[28,55]

POLYGENIC RISK SCORES AND PROSTATE CANCER SCREENING

In addition to lifetime risk prediction, PRS may aid in decisions on when to begin PCa screening. A United Kingdom study found that men at the top

Table 1
Polygenic risk score models for prostate cancer risk

Study	#SNV	Cases/Control Subjects (n)	Phenotype	Population	Main Finding	Ref
Genetic risk factors for PCa	32	779/1643	PCa risk	Norwegian	Top 10% of PRS had 5-fold greater risk compared with men in the bottom 10%	Chen et al,[44] 2018
Improving PPV of low PSA	49	2696 47/125	PCa in low PSA (1–3 ng/mL) patients	Swedish	37% of men in high genetic risk had PCa compared with 18% and 28% in low and intermediate	Nordström et al,[45] 2014
PracticaL	54	1583/4828	Aggressive PCa screening	Europe	HR of top 2% for aggressive PCa = 2.9 (2.2–4.0) High PPV for PSA	Seibert et al,[46] 2018
ProtecT	54	6411/8054	PRS informed screening by age	European	Age of diagnosis varies by 19 y between top 1% and bottom 1% of PRS	Huynh-Le et al,[47] 2020
Predictive value of PRS for prostate cancer	72	1579/1280	Men undergoing testing for hereditary cancer without germline pathogenic variants	European	Men in the top 10% of PRS have a lifetime risk of PCa of 30% and men in the top 1% as high as 42% Men in the bottom 1% had lifetime risks of 2.4% AUC for prostate cancer diagnosis = 0.65 (95% CI, 0.63–0.67)	Black et al,[48] 2020
Race-Specific PRS	7/76	1338 patients with a biopsy	Comparison of race-specific PRS for PCa and high-grade disease	East Asians	An East Asian–specific PRS had higher AUC (0.602 vs 0.573) than non-Asian-specific	Na et al,[49] 2016
Risk	82	4893/10,682	PCa risk	Japan	Mean diagnosis in top 5% of PRS 2.7 y younger than bottom 5% of risk	Takata et al,[28] 2019
Michigan Genomics Initiative	93	1425/9793	Risk	European	23.4% of men in the top decile of risk had PCa compared with 5.4% in the lowest risk decile	Fritsche et al,[50] 2018

Ugandan men	97	571/485	PrCa risk	Uganda	Men in the top 10% had 4.86-fold risk (95% CI, 2.70–8.76) compared with average-risk men	Du et al,[30] 2018
BRCA carriers	103	1313/212	Does PRS for general population modify risk in BRCA carriers?	European	Odds ratio per SD of PRS 1.57 (95% CI, 1.35–1.81; *P* value 3.2 × 10–9; risk by age 80 of 61% for 95% and 19% for 5%)	Lecarpentier et al,[8] 2017
PRACTICAL	65/133	1370/1239	Validation study of PRS for risk	European	AUC 0.67 for 64 SNVs (95% CI, 0.65–0.69) AUC 0.68 (95% CI, 0.66–0.70) for 133 SNVs	Szulkin et al,[51] 2015
Multi-Consortium GWAS	147	46,939/27,910	Risk	European	Men in the top 1% had 5.71-fold increased risk (95% CI, 5.04–6.48) over those in the middle 50% of risk	Schumacher et al,[22] 2018
UK Biobank	147	4430/186,376	Risk	European	HR top 5% 3.20 (2.88–3.56) HR of 2.22 (95% CI, 52.04–2.41) for highest quintile PRS compared with middle HR 0.39 (95% CI, 0.35–0.45) for those in lowest quintile	Jia et al,[52] 2020
Latino	162	2820/5293	PCa risk	Latino	Men in the top 10% had 3.19-fold (95% CI, 2.65–3.84) increased risk and those in the top 1% a 4.02-fold (95% CI, 2.46–6.55) risk relative to average-risk (25%–75%) men	Du et al,[29] 2020
UK biobank	448	379/24,722	Risk	European	AUC 0.6399 (*P* value 3 × 10–6); top 1% has 4.6-fold increase over those in middle 26%–49%	Lello et al,[53] 2019
FINNRISK	6,606,785	1172/47,679	Risk	Finnish	HR 4.07 for PCa in top 2.5% of PRS	Mars et al,[54] 2020

Abbreviations: #SNV, number of SNVs in PRS model; AUC, area under the receiver operating curve; CI, confidence interval; HR, hazard ratio; PPV, positive predictive value; PSA, prostate-specific antigen; SD, standard deviation.

1% of polygenic risk were expected to reach the 50-year-old standard risk level at age 41 and men in the bottom 1% of polygenic risk did not meet this level of risk until age 60. This translates to a 19-year difference in the risk-equivalent age to begin PCa screening in men at the two extremes of risk (**Table 2**).

Although PCa screening using prostate-specific antigen (PSA) results in decreased mortality, it leads to increased numbers of biopsies and a high rate of PCa overdiagnoses that are less likely to result in mortality.[60] Thus, approaches to improve predictive value of PSA, identify men who would benefit most from screening or further diagnostic testing, and decrease biopsies in men with reduced likelihood of being diagnosed with aggressive PCa are needed. Emerging studies suggest that the PRS may improve the positive predictive value of PSA tests (see **Table 2**). A 2015 study of Finnish men showed that combining a 66-SNV PRS with PSA screening may improve sensitivity of the PSA test. In that study of approximately 1100 cases and approximately 3900 control subjects undergoing regular PSA screening, 18% of men who were higher than the median PRS had PSA of 4 ng/mL compared with 7% in the group lower than the median ($P<.001$). PCa overdiagnosis was estimated at 58% (95% confidence interval [CI], 54–65) in the lower PRS group compared with 37% (95% CI, 31–47) in the upper risk group.[58] Other studies have shown similar findings of PRS improving predictive value of PSA screening.[47] PRS for PCa is also associated with other prostate phenotypes. Evaluation of a 93 SNV PRS for PCa risk found that PRS was also associated with increased PSA levels (P value 9.33×10^{-27}) and other phenotypes including erectile dysfunction, urinary incontinence, and prostate hyperplasia, suggesting common biologic pathways between these or the result of a PCa diagnosis of these phenotypes.[50]

Not only are the risks higher for individuals at the top end of the PRS spectrum, but many studies have shown that the age of disease onset is earlier, which could impact screening using PSA. One study found that the individuals at the top 2.5% of risk had a disease onset 5.53 years earlier compared with individuals with average PRS.[54] Another study found that men at the top 1% of risk had an average age of PCa diagnosis of 41 years compared with 60 years in men in the bottom 1% of risk.[47] Additional studies are needed, but developing individual-specific recommendations for beginning PCa screening based on PRS could result in fewer men being overdiagnosed and/or overtreated for PCa.

POLYGENIC RISK SCORES AND CLINICAL OUTCOMES

Because PRS shows promise for predicting overall risk and for improving predictive value for PSA, multiple groups have tested whether PRS is informative for aggressive disease. This would be an immensely valuable clinical tool because it could potentially lead to fewer biopsies or less overtreatment of PCa that would result in less harm to the patient. There are now consistent data that higher PRS is associated with an increased risk of aggressive or high-grade PCa.[46,49,56]

PRS may also be informative for identifying men who would benefit from biopsy. A study of 105 SNVs found that 36% and 40.4% of men with the top PRS without and with a family history of PCa in the placebo arm of the Prostate Cancer Prevention Trial had a positive biopsy compared with 24.6% and 33.3% of men with an average PRS.[55] This study also suggests that men who are considered generally to be a lower risk because of a lack of a family history might benefit from PRS information.[55]

Despite the promise of PRS for risk prediction and screening decision-making, PCa PRS has not been associated with outcomes in chemoprevention trials. A 98-SNV PRS study of men in the PCPT (finasteride or placebo) or SELECT (selenium, vitamin E, or combination) chemoprevention trials, found no association of those with higher PRS and effect of chemopreventative agent[61] despite association of a higher PRS with increased cancer risk. Additionally, GWAS to date have not led to the identification of variants predictive of PCa survival following therapy.[62,63]

POLYGENIC RISK SCORES IN COMBINATION WITH OTHER PROSTATE CANCER PREDICTION TOOLS

Several models to predict PCa and aggressive PCa risk that incorporate age, sex, race, family history, PSA, and other clinical and demographic factors have been developed.[64] PRS is starting to be incorporated into existing models to determine if adding genetic information improves the predictive value of the models (**Table 3**). Although modest, PRS does improve the AUC for prediction of PCa diagnosis. One clinical predictive model that included age, family history, and benign prostate hyperplasia showed an AUC for a PCa diagnosis of 0.840 (95% CI, 0.837–0.842).[54] Adding an approximately 6 million SNV PRS to this model improved the predictive value to 0.866 (95% CI, 0.863–0.868). Adding PRS to other predictive biomarkers, such as a four-kallikrein panel, also

Table 2
Use of PRS for informing screening and treatment decisions

#SNV	Participant Characteristics	Phenotype	Population	Main Finding	Ref
29	7-y follow-up study: 1104 men of 4528 developed PCa	Identifying high-risk men for screening using family history and/or PRS	Prostate Cancer Prevention Trial	29% of men with a high PRS risk and positive family history were diagnosed compared with 23% of men with family history and PRS for risk (P = .001) PCa was diagnosed in 31% of men of high risk (PRS or FH) compared with 21% of men at lower risk	Chen et al,[56] 2016
35	2135 cases 3108 control subjects	Predicting need for biopsy in men with PSA >3–4 ng/mL	Swedish	PRS could result in 12% fewer biopsies	Aly et al,[57] 2011
49	172 men randomly selected from 860 genotyped with PSA 1–3 ng/mL underwent biopsy	PRS for detecting biopsy-positive PCa with PSA 1–3 ng/mL	Swedish STHLM2 cohort	37% of men in high-risk cohort had PCa compared with 28% in the intermediate and 18% in the low genetic groups	Nordström et al,[45] 2014
54	6411 men from Protect study	Effect of PRS on risk-equivalent age (PCa risk equivalent to a 50-y-old man)	ProtecT study (UK)	Age at which risk is equivalent to a 50-y-old (screening age) differs by 19 y between men at the bottom and top 1% of risk	Huynh-Le et al,[47] 2020
54	1583 men with any PCa, 632 with aggressive PCa, with 220 very aggressive PCa, 4828 control subjects all with PSA >3 ng/mL	Using PRS to improve predictive value of PSA test for aggressive PCa	ProtecT study (UK)	The PSA test had a PPV of ~0.24 for men in top 5% of the PRS and ~0.7 for men in the bottom 5% of PRS Men in the top 20% of PRS accounted for 42% of aggressive PCa cases	Seibert et al,[46] 2018

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Table 2 (*continued*)

#SNV	Participant Characteristics	Phenotype	Population	Main Finding	Ref
66	1089 cases 3878 control subjects	Using PRS to help interpret PSA and reduce overdiagnosis	Finnish	18% of men in higher risk group had PSA $\geq$4 ng/mL compared with 7% in lower risk group Overdiagnosis was 58% in lower risk group and 37% in upper risk group	Pashayan et al,[58] 2015
110	3225 cancer-free men at enrollment with 714 diagnoses after enrollment	Age of diagnosis for family history vs PRS	REDUCE trial	Higher GRS had worse PCa-free survival (P_{trend} <0.001); combining family history further stratified genetic risk No association between GRS and age	Na et al,[59] 2019

Abbreviations: #SNV, number of SNVs in PRS model; Dx, diagnosis; GRS, genetic risk score; PPV, positive predictive value.

Table 3
Predictive value of adding PRS to clinical models

#SNV	Population	AUC/C-Index for Clinical Factors	AUC PRS Alone	AUC Clinical Factors + PRS	Ref
66/7	2310 PrCa cases 518/2441 screened	0.71 (0.696–0.707) for PSA		7 SNV PRS + PSA AUC = 0.888 (0.886–0.891); 66 SNVs + PSA AUC = 0.967 (0.965–0.969)	Li-Sheng Chen et al,[65] 2019
135	Multiethnic cohort 1776 men (1254 cases) with PSA >2 ng/mL	4K panel AUC = 0.756 (0.731–0.78) for PCa and 0.790 (0.76–0.82) for aggressive PCa		PRS + 4K panel 0.766 (0.742–0.790) for PCa; 0.801 (0.772–0.83) for aggressive PCa	Darst et al,[66] 2020
147	4430 cases 186, 376 control subjects	Family Hx 0.529 (0.522–0.535)	0.662 (0.655–0.67)	PRS + Fam Hx 0.669 (0.661–0.676)	Jia et al,[52] 2020
6,606, 785	1172 PCa cases 47,679 control subjects	Age, Fam Hx, BPH 0.840 (0.837–0.842)	0.8416	Age, Fam Hx, BPH PRS 0.866 (0.863–0.868)	Mars et al,[54] 2020

Abbreviations: 4K, four-kallikrein; #SNV, number of SNVs in PRS model; AUC, area under the receiver operating curve; BPH, benign prostate hyperplasia; Fam Hx, family history.

improves predictive values (see **Table 3**).[67] Because PRSs on their own do not have as high a predictive value as PRS in combination with other risk factors, it is likely that PRS will not be used in isolation.

RESIDUAL RISK IN INDIVIDUALS WITH HIGH- AND MODERATE-RISK PATHOGENIC VARIANTS

Predicted lifetime PCa risk with inherited PVs varies widely because there are factors that modify risk beyond the PV, such as low-penetrance risk variants. A PRS of 104 SNVs found that additional genetic modifiers impact risk in men with BRCA PVs. For *BRCA2* PV carriers, men in the top 95% of the PRS had a lifetime risk by age 80 of PCa of 61%, whereas men in the bottom 5% had a lifetime risk of 19%. For *BRCA1* men in the top 95% had a lifetime risk of 26% compared with those in the bottom 5% with a lifetime risk of 7%.[8] The AUC for PCa in this group was 0.62 (95% CI, 0.58–0.66).

Although not yet specifically studied, PRS may help to determine lifetime risks of men with PVs in moderate-risk PCa genes. *CHEK2*, a moderate-risk gene for breast cancer, confers an estimated 25% to 39% lifetime risk.[67,68] Studies using an 86-SNV PRS for breast cancer showed that women with the lowest PRS and a pathogenic risk variant in *CHEK2* had similar lifetime risks of breast cancer as the general population, whereas women at the top quintile had 29% lifetime risks.[69] Using PRS in men with PVs in moderate- and high-risk genes may inform timing of screening and prevention decisions.

CURRENT CLINICAL USE OF PROSTATE CANCER POLYGENIC RISK SCORES

Based on the studies to date, PRS may have clinical utility including: (1) identification of individuals at increased disease risk who would benefit from more intensive screening or in the interpretation of screening results; (2) identification of people at higher risk who may benefit from therapeutic-based prevention strategies; and (3) personal understanding of risk, by helping individuals understand their risk of developing a disease for making life-decisions (**Box 1**).[39] In 2018, Ambry Genetics created the only commercially available PRS for PCa to date based 72 SNVs associated with PCa, age, and ethnicity.[48] In non–peer reviewed studies, they found that the predictive performance of the model outperformed that of family history alone for White men who tested negative for a pathogenic or likely PV in a PCa-associated gene.[48,64] There is a lack of data on using PRS in men who have a PCa diagnosis. Thus, research is needed to understand if there is any value in a score after diagnosis. Additionally, the National Comprehensive Cancer

Box 1
Potential future clinical uses of prostate cancer PRS

- Aid in prostate cancer screening decision-making
- Assist in interpretation of prostate cancer screening results
- Predict prostate cancer risk, age of diagnosis, and aggressiveness
- Improve predictive value when combined with prostate cancer biologic markers and pathologic features
- Provide refined risk estimates to individuals with pathogenic variants in high- and moderate-risk prostate cancer susceptibility genes

Network guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic does not recommend PRS usage for clinical management because of significant limitations in interpretation.[70] PRS for genetic/familial assessments is currently only recommended in the setting of a clinical trial.[70]

CLINICAL TRIALS

There are few clinical trials evaluating PRS in a PCa context. One ongoing clinical trial, PLCO-574, aims to develop and validate a model of 50 SNVs with risk factors, such as PSA, digital rectal examination, family history, and demographics, to determine high-grade PCa risk.[71] To better understand risk in AA, a $90 "Smith Polygenic Risk test" for PCa based on more than 250 SNVs, is being developed and tested in this population.[72,73]

DISCUSSION

The addition of PRS with germline genetic testing in the genetic counseling session is the next step in clinical use and PCa risk assessment. This is currently not being done routinely, although one company offers a PRS option for men undergoing germline genetic testing for PCa risk. This may improve PCa risk prediction for men and may help to explain some of the familial PCa families without known pathogenic variations. PRS incorporation is likely to become the next step added into the standard genetic risk assessment of PCa risk in unaffected men for adjustment of risk, and affected men to gather future data.

SUMMARY

Emerging data from research studies suggest that PRS for PCa is predictive for risk; may inform timing for screening; and may improve predictive value for other risk factors, such as family history and PSA.[55,74,75] Studies are warranted to determine if PCa PRS has utility for screening decision-making and/or improving outcomes in a clinical setting.

CLINICS CARE POINTS

- The clinical value of PRS for PCa is emerging; potential benefits include lifetime risk assessments, determining timing of screening, and improving predictive value of PSA tests for aggressive cancer and other PCa models.
- PCa PRS for non-European populations is less well studied and validated.
- PCa PRS is currently only available through a limited number of clinical genetic testing laboratories.

DISCLOSURES

The authors have nothing to disclose.

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