



Polygenic risk score for genetic evaluation of prostate cancer risk in Asian populations: A narrative review

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Decreasing costs of genetic testing and interest in disease inheritance has changed the landscape of cancer prediction in prostate cancer (PCa), and guidelines now include genetic testing for high-risk groups. Familial and hereditary PCa comprises approximately 20% and 5% of all PCa, respectively. Multifaceted disorders like PCa are caused by a combinatory effect of rare genes of high penetrance and smaller genetic variants of relatively lower effect size. Polygenic risk score (PRS) is a novel tool utilizing PCa-associated single nucleotide polymorphisms (SNPs) identified from genome-wide association study (GWAS) to generate an additive estimate of an individual's lifetime genetic risk for cancer. However, most PRS are developed based on GWAS collected from mainly European populations and do not address ethnic differences in PCa genetics. This review highlights the attempts to generate a PRS tailored to Asian males including data from Korea, China, and Japan, and discuss the clinical implications for prediction of early onset and aggressive PCa.

Keywords: Multifactorial inheritance; Polygenic traits; Prostatic neoplasms

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INTRODUCTION

Prostate cancer (PCa) is one of the leading types of cancer among males, with increasing prevalence worldwide, currently accounting for 3.8% of all cancer-related deaths in 2018 [1,2]. This trend is more marked in Asian populations, with recent literature suggesting changes to Westernized diets and lifestyles leading to obesity and consumption of dietary fat, as well as broader implementation of early prostate specific antigen (PSA) testing and cancer registration [3]. As such, prediction of individual risk for PCa has risen to prominence, especially as certain mutations such as *BRCA1*

or *BRCA2* may be actionable targets for novel therapy including Olaparib and other PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitors [4,5].

National Comprehensive Cancer Network (NCCN) guideline for PCa now recommends germline testing for any patient with a positive history, as well as in high- to very-high risk regional or metastatic PCa, as well as in any patient with an Ashkenazi Jewish ancestry or known family member with an identified high-risk germline mutation [6]. A pivotal study published in 2016 by Pritchard et al. [7] identified significant increase in homologous DNA repair gene mutations including *BRCA1/2*, *ATM*, and *CHEK2* in

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metastatic PCa, with up to 11.8% harboring germline mutations regardless of family history. Further mutations in mismatch repair genes such as *MSH2*, *MSH6*, *MLH1*, and *PMS2* are known to be associated with Lynch syndrome, which cause hereditary colorectal and gynecological cancers as well as PCa [8,9]. At least two-fold to 5.8-fold PCa risk was found in mismatch repair gene loss and high levels of microsatellite instability carriers [8], who may be eligible for use of pembrolizumab in unresectable metastatic CRPC based on its U.S. Food and Drug Administration (FDA) approval in 2017. The G84E variant of *HOXB13*, a gene encoding homeobox transcription factor B13, increases familial frequency of PCa with an odds ratio of 3.4 (95% confidence interval [CI], 2.2–5.4) [10]. Current guidelines for PCa only recommend Ashkenazi Jews for PCa genetic testing based solely on ethnicity alone due to previous reports of Ashkenazi Jewish males being more likely to harbor *BRCA1/2* mutations and those with mutations almost 3-fold more likely to have PCa on age-matched analysis [11,12]. While no other ethnicities are currently recommended for genetic testing for PCa based on ethnicity alone, numerous literature has pointed out the ethnic differences in Asian males compared to Caucasian populations, with higher susceptibility for aggressive and early-onset PCa, with increased risk of PCa biomarker expression including p53 [13,14]. Genome-wide association study (GWAS) and next-generation sequencing (NGS) analysis have resulted in numerous race and ethnic-specific SNPs with significant predisposition to PCa [15], with new variant and gene-associations identified over time, such as *ENTPD3-AS1*, *LOC102724438*, and *SPATA3* genes in Korean cohorts [16], as well as rs817826 and rs103294 in Chinese males [17].

Previous reports from western populations estimate familial PCa to comprise 10% to 30% of all PCa and hereditary PCa to be around 3% to 5% based on pedigree [18–22]. The Nordic Twin Study of Cancer estimated heritability of PCa to be at a high 57% (95% CI, 0.51–0.63) [23]. A meta-analysis including 13 studies estimated a 2.5 relative risk between first-degree relatives, with risk greatest in males diagnosed earlier than age 60 and with more than two relatives with PCa [24]. It is important to distinguish familial and hereditary PCa. Familial disease is an umbrella term encompassing any disorder with family history without a clear genetic cause or mutation, whereas hereditary disease refers to conditions significantly associated with genetically distinct and detectable mutations [25]. Hence, hereditary PCa is caused by inherited gene mutations with high penetrance, such as *BRCA1* and *BRCA2* mutations reported to increase risk of PCa before age of 65 years by 1.8 and 8.6 fold, respectively. However, while patients with PCa-associated genetic altera-

tions are more susceptible to early onset and aggressive disease [26,27], PCa, like most cancer, is more likely a polygenic condition additionally influenced by a cumulative effect of multiple variants with a smaller effect size, affecting a larger population. Thus, in order to develop a broad and accurate strategy for screening and protection for genetically high-risk PCa males, polygenic models that include multiple single nucleotide polymorphism (SNP) with positive or negative associations are becoming increasingly necessary.

POLYGENIC RISK SCORE

Polygenic risk score (PRS) are also known as polygenic hazard score (PHS), genome-wide polygenic risk score (GPS), or genetic risk score (GRS) depending on literature. First applied for clinical use in the early 2000s [28], PRS was conceptualized as a single value, combinatory estimate for an individual's genetic risk for disease using an additive sum of effect size estimated from GWAS summary statistics. Target case cohorts and controls are compared for rare variants or polymorphisms in their genetic data that hold predictive significance in the form of SNPs. PRS is a weighted sum of risk allele (α_i) or an identified allele of a disease-associated SNP, and its corresponding effect size (β_i) or Cox proportional hazard ratio [29]. The equation is described as follows:

$$\text{Polygenic Risk Score} = \sum_i^n \alpha_i \beta_i$$

As GWAS summary statistics are prone to bias due “overfitting” of effect size estimates to a finite development cohort, validation to an independent population is key to achieve accurate predictive power. Also, pruning or clumping of variants are required to compensate for linkage disequilibrium (LD), or non-independent associative relationship between different alleles, as it may lead to under- or over-estimation of SNP effect size. Genotype imputation is recently being used to better performance of PRS models by detecting SNPs that may be overshadowed or exaggerated by effects from adjacent SNPs [30].

COMMERICAL TESTING

Numerous commercial genetic testing panels from companies such as AmbryGenetics, Color, Invitae, and Myriad ProLaris utilize various combinations of DNA damage repair and mismatch repair genes including - but not limited to - *BRCA1/2*, *CHECK2*, *ATM*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, and *EPCAM*. In contrast to the rapid technological

advances and falling costs of DNA sequencing that has fueled identification of pathogenic SNPs, to date, only one commercial PRS is offered for PCa (Table 1). AmbryScore is available in North America, and eligible patients are limited to 18–84-year-old males of Northern European ancestry with negative personal or family pathogenic mutation in 14 PCa susceptibility genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *EP-CAM*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *RAD51D*, *TP53*). PRS was constructed for 72 PCa associated SNPs, and validation trials including 4,327 patients (1,972 PCa cases and 1,919 control) revealed an area under the receiver operating characteristics curve (AUC) of 0.64 (95% CI, 0.62–0.66), with males in the 4th quartile to be 3.98 times more likely to have PCa compared to those in the 1st quartile of age-adjusted PRS [27]. These findings are in line with previous findings from the PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) multinational consortium, where Amin Al Olama et al. [31] reported a 306-fold and 4.2-fold risk increase in the top 1st percentile compared to the bottom 1% and median risk, respectively, based on 25 SNPs from 40,414 individuals.

Other PCa biomarkers incorporate PRS with other genetic and clinical information to improve detection. Stockholm3 (STHLM3) is a commercially available blood-based biomarker test which combines patient clinical information including age, family history, PSA, and other Kallikrein levels, as well as a PRS of 232 SNPs [32]. STHLM3, currently available in Sweden, Norway, Denmark, and Finland, achieved an AUC of 0.74 (95% CI, 0.72–0.75) in the original trial consisting of 145,905 males, and 0.86 (95% CI, 0.83–0.89) in an independent multi-center validation trial of 533 participants [32,33]. By utilizing more clinical factors other than PRS, STHLM3 is able to report a simple negative or positive result that stratifies males with low PSA into low–normal and high genetic risk. Males with positive results are referred to a urologist for check-up, and prostate volume and digital rectal exam (DRE) is measured to determine whether further biopsy is needed. Negative results recommend follow-up in 2 to 6 years (Table 1).

Direct-to-consumer (DTC) tests, currently offered by numerous companies such as My Heritage, 23andMe, and a23.com, further expand the possibility of individuals to utilize their genetic data for various diseases. DTC tests which initially caught the interest of the general public for information on ethnic ancestry and carrier status for common hereditary diseases can now be utilized and reassessed for personal risk assessment for other multifactorial conditions such as Parkinson's [34] and type 2 diabetes [35]. Fur-

ther third-party programs offer interpretation of polygenic risk [36], but while these diverse platforms have increased accessibility and utilization of personal genetic information, validation with external cohorts are lacking, and clinical confirmation by experienced laboratories have found 40% false positives in DTC raw data or other third-party services [37], cautioning against unconsulted application to clinical practice [38]. However, these services allow the possibility of secondary analysis of individual GWAS data through third-party DTC platforms for PRS of other diseases.

In Korea, where DTC genetic testing has only recently been introduced via amendments to the Bioethics and Safety act in 2017 [39], no single PRS is currently available to the average consumer. However, research has gained momentum by the government granting a regulatory sandbox for predictive genetic tests as well as piloting government programs for expanding DTC tests to 57 phenotypes such as obesity, diabetes, and coronary artery diseases [39]. PCa-Gene Test, a PRS predictive model produced by a Korean company, is currently under development for commercialization utilizing 29 SNPs for PRS and 1 SNP within *HOXB13* (Table 1, Supplementary Table 1). Present age-specific risk and lifetime risk for PCa development is reported.

ASIAN PATHOLOGY AND HERITABILITY

Previous literature has reported that Asian males are at greater risk of harboring advanced and aggressive PCa pathology compared to Caucasian and European counterparts [13,40]. Korean males are especially susceptible to high incidence of adverse pathology on radical prostatectomy (RP) when compared to Caucasian populations, with significant OR of 3.48 for high grade (Gleason score ≥ 8) and 2.40 for pathologic $\geq T3$ stage PCa. Assessment of familial and hereditary PCa based on pedigree on a Korean population matched with males with RP pathology found 8.4% to be familial and 0.9% hereditary [14], whereas GWAS from 2,321 Chinese males (1,401 PCa and 920 control) found approximately 9 to 11 % of PCA to be heritable [41].

Racial disparity is not only caused by socioeconomic factors or lifestyle, but also by genetic polymorphisms more prone to be found in Asian males [2]. Over 100 individual SNPs located in genes including 8q24 [42], *CYP24A1* [43], *FGF23* [44], *VDR* [45], and *COMT* [46] have been identified with significant association for PCa, some specific to Asians and most universal across ancestry. SNPs including rs721048, rs1859962, rs5945572, and rs4430796 share increased risk across different heritage [47], whereas novel mutations in ethnic-specific populations are constantly being identi-

Table 1. Currently available and upcoming commercial PRS incorporating models

Test name	STHLM3	Ambryscore	PCa-Gene Test ^b
Sample	Blood (EDTA)	Blood (EDTA+LiHep)	Blood (EDTA)
SNP count (n)	232	72	30 ^c
Available region	Sweden, Norway, Denmark, Finland	North America	South Korea
Eligible ancestry	None specified ^a	Northern European	Korean/East Asian
Eligible age (y)	50–70	18–84	18–84
Exclusion criteria	Males with known PCa or males outside the eligible age.	No individual or family history of mutation 14 prostate cancer susceptibility genes (<i>ATM</i> , <i>BRCA1</i> , <i>BRCA2</i> , <i>CHEK2</i> , <i>EPCAM</i> , <i>HOXB13</i> , <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>NBN</i> , <i>PALB2</i> , <i>PMS2</i> , <i>RAD51D</i> , <i>TP53</i>)	None
Other blood biomarkers required	Total PSA, free PSA, intact PSA, hK2, M1C1, MSMB	None	None
Clinical information	Age, family history, previous biopsy, use of 5-ARI, DRE, prostate volume	Age, ethnicity	Age, ethnicity
AUC in validation trials	0.86 (95% CI, 0.83–0.89)	0.64 (95% CI, 0.62–0.66)	0.7 (95% CI, 0.667–0.734)
Reported results	- A negative or positive result is given. - Positive results recommend patient for urologist referral and check-up for prostate volume, DRE, and possible biopsy - Negative results identify males with low to normal risk and recommend follow-up in 2–6 years.	- Results report the remaining lifetime risk compared to the general population in percentage - Polygenic Risk Score for genetic contribution for PCa developed is reported in affected (PCa-diagnosed) individuals	- Present (age-specific) risk for PCa development is reported - Lifetime polygenic risk for PCa development is reported

PRS, polygenic risk scores; STHLM3, Stockholm3; PCa, prostate cancer; EDTA, ethylenediaminetetraacetic acid; LiHep, lithium heparin; SNP, single nucleotide polymorphism; PSA, prostate specific antigen; 5-ARI, 5-alpha reductase inhibitor; DRE, digital rectal exam; AUC, area under the receiver operating characteristics curve; CI, confidence interval.

^aA clinical trial to validate performance of STHLM3 in African American, Asian, Hispanic, and non-Hispanic Caucasian populations are currently underway (NCT04583072). ^bPCa-Gene Test is in progress of commercialization. ^cTwenty-nine SNPs were included for PRS and one SNP within HOXB13 was included.

fied over time, such as rs1125927, rs73862213, rs77911174, and rs138708 in Japanese cohorts [48] and additional 19 variants in a Korean population reported in 2019 [16]. SNP variation on 8q24 has been reported to be associated with a 1.6-fold increased risk of PCa, as well as 1.77 to 1.85-fold increase in risk for high Gleason score ≥ 7 and metastatic PCa [49]. In a cohort of 1,417 Chinese PCa males, rs636291 variation at 1q23 was significantly associated with a higher risk for PCa with an OR of 1.123 [50]. A large-scale GWAS meta-analysis utilizing 1,583 Japanese and 1,417 Chinese populations found two susceptible loci rs12791447 and rs58262369 to be associated in PCa risk for Asian males and was not replicated in other males of European descent [51]. These data suggest that while most SNPs are shared across ancestry, ethnic-specific SNPs continue to be identified and have varying significance. Replication of PRS derived from Western populations do not have the same predictive power in Asian cohorts, primary because not all genomic loci are shared, nor do they have same effect size in GWAS summary statistics [52,53]. Hence, it is becoming increasingly important to develop a model tailored to each race and ethnicity to more accurately predict risk.

POLYGENIC RISK SCORE IN ASIANS

While most large-scale GWASs recruited genotypic data from mainly Caucasian and European cohorts, a handful of attempts have been made to generate a PRS for Asian populations (Table 2). A recent article utilizing a multi-ethnic cohort from the PRACTICAL Consortium reported results based on a PRS using 46 SNPs [54]. Asian ancestry composed 3.0% of the entire the 80,491 dataset ($n=2,382$), and self-reported race/ethnicity revealed East and South Asians as 1.5% ($n=1,212$) and 0.2% ($n=167$). Males of Asian genetic ancestry in the 98th percentile of the PRS had a hazard ratio (HR) of 3.77 (95% CI, 2.80–5.13) and 4.14 (95% CI, 2.92–6.03) for any PCa and aggressive PCa compared to the 30th to 70th percentile. This was comparable to performance in the European subgroup, in which the top 2% had a HR of 4.34 (95% CI, 4.09–4.60) and 4.40 (95% CI, 4.15–4.70) for any PCa and aggressive PCa, respectively. However, despite efforts to compare inter-ethnic variations in PRS performance, this study was limited by the grossly small number of non-European cohorts and limited analysis of local ancestry. Also, because the PRS was constructed largely based on European GWASs, SNPs significant in Asians may have been under-represented.

A similar meta-analysis based on multi-ancestry GWAS summary statistics combined results from large-scale ge-

netic studies including the PRACTICAL and ELLIPSE (Elucidating Loci Involved in Prostate Cancer Susceptibility) OncoArray consortium culminated in a total of 107,747 PCa cases and 127,006 control [55]. Total 269 risk variants were identified, of which 86 were novel variants, and captured 33.6% of familial risk for PCa. Subanalyses on East Asian ancestry (1,652 PCa and 1,803 control) conferred similar results of males of European and Hispanic ancestry, placing East Asian males in the 90th percentile of PRS at 4.47-fold risk of PCa compared to males in the 40th–60th percentile (95% CI, 3.52–5.68). High PRS was predictive of early age of diagnosis across populations, explaining almost 26% lifetime absolute risk for PCa in Asian males in the top 10% (95% CI, 22%–30%). The addition of PRS improved prediction of PCa (AUC, 0.836; 95% CI, 0.832–0.840) compared to a conventional model using age and family history (AUC, 0.784; 95% CI, 0.779–0.789).

A series of attempts to isolate individual ethnic populations for PRS have also been reported. Oh et al. (2020) [15] constructed a PRS based on 3,211 Korean patients (1,001 PCa and 2,210 control) with validation performed on an independent cohort composed of 1,062 cases (516 PCa and 546 control), identifying 11 PCa-associated SNPs. The highest predictive PRS comprised of 4 SNPs with the largest effect size after LD pruning conferred an AUC of 0.637 (95% CI, 0.582–0.692) with a sensitivity of 0.543 and specificity of 0.677. Patients in the top 5th and 25th percentile had an OR of 3.71 and 2.61 for developing PCa, respectively.

Whole exome array analysis on a cohort of 7,258 Korean males (985 PCa and 6,273 control) indicated 19 rare SNP variants across 7 genes, which included 3 novel genes (*ENTPD3-AS1*, *LOC102724438*, *SPATA3*), 3 previously known to be associated with PCa (*MST1R*, *GPER1*, *PARD3B*), and 1 breast cancer-related (*CDYL2*) [16]. Oh et al. [56] constructed a similar PRS based on 912 PCa patients to predict biochemical recurrence (BCR) after RP, selecting 16 SNPs with significant p-value of 10^{-3} . Patients with high PRS had a 1.63-fold risk of BCR (95% CI, 1.454–1.826; $p<0.001$), and addition to clinical factors such as age, PSA, Gleason scores, extra-prostatic extension, seminal vesicle invasion, and positive surgical margin improved prediction models with an AUC of 0.844 to 0.888 [56]. An earlier study by the same group utilized 1,001 PCa patients and 2,641 Korean males for development of PRS based on 5 SNP variants [57]. Validation on an independent cohort of 514 PCa and 548 control cases resulted in a AUC of 0.605 (95% CI, 0.573–0.637), with the highest PRS group harboring a 4-fold risk for PCa compared to the median PRS group.

Wei et al. (2015) [58] generated a PRS based on 29 SNPs

Table 2. PRS in Asian populations

Author (year)	No. of case (n)	Ethnicity	No. of SNPs (n)	AUC	95% CI	Findings
Huynh-Le et al. (2021) [54]	2,382	Asian ancestry	46	-	-	Males in the highest 2nd percentile had OR 3.77 (95% CI, 2.80–5.13) for any PCa and HR 4.14 (95% CI, 2.92–6.03) for aggressive PCa. PRS models had better performance of predicting any PCa compared to models based on family history (OR, 4.17 vs. 2.05).
Conti et al. (2021) [55]	3,455	East Asian ancestry	269	0.836 (age+PRS)	0.832–0.840	Males in the highest 10th percentile had OR 4.77 (95% CI, 3.52–5.68) compared to males in the median 40th to 60th percentile.
Oh et al. (2017) [56]	912	Korean	16	0.880 (clinical parameters+PRS)	-	Mean PRS was 0.73 times lower in East Asian males compared to Europeans, with PRS associated with higher lifetime risk of PCa and early diagnosis. PRS improved prediction of PCa BCR compared to a clinical model based on age, PSA, and RP pathology from AUC 0.844 to 0.880. PRS was an independent predictor of BCR on multivariate analysis (HR, 1.630; 95% CI, 1.454–1.826; p<0.001).
Oh et al. (2017) [57]	3,642	Korean	5	0.605	0.573–0.637	Males with PRS greater than 8 (mean GRS=4.23) had an OR of 3.34 (95% CI, 1.05–10.62) for risk of PCa, with a strong positive correlation of PRS with any PCa risk.
Oh et al. (2020) [15]	3,642	Korean	4	0.637	0.582–0.692	Males in the highest 25th percentile had OR 2.61 (95% CI, 1.53–4.72) and OR 3.71 (95% CI, 1.10–23.14) in the highest 5th percentile compared to the remaining group.
Jiang et al. (2013) [61]	308	Chinese	24	-	-	Two-fold higher median PRS was detected in males with PCa, with increasing rate of PCa detected in higher PRS scores.
Ren et al. (2013) [60]	667	Chinese	29	0.60	-	PRS created from 24 previously established SNPs had a AUC of 0.61, and the addition of 5 more SNPs had an AUC of 0.60. More than 50% of males in the highest PRS group was diagnosed with PCa.
Wei et al. (2015) [58]	99	Chinese	29	0.70	-	PRS improved prediction of any PCa from AUC 0.73 in PSA only and AUC 0.84 in PSA+PCA3 models to AUC 0.81 in PSA+PRS and AUC 0.86 in PSA+PCA3+PRS models.
Zhu et al. (2015) [59]	724	Chinese	24	0.561 (for all patients) 0.612 (60–70 yr)	0.514–0.609 0.541–0.684	PRS significantly improved prediction of high risk PCa when added to previous clinical parameter-based models and was an independent predictor of PCa in males between 60 and 70 (OR 1.744; p=0.031).
Akamatsu et al. (2012) [62]	1,438	Japanese	16	0.659	0.649–0.670	High PRS groups had a greater rate of 42.4% positive biopsy vs. 10.7% in low PRS groups.
Takata et al. (2019) [48]	15,575	Japanese	82	-	-	Males in the top 5th percentile had a lower mean age at diagnosis (71.4-year-old) compared to the rest of the group (68.7-year-old), whereas no difference was found in the low PRS group.

PRS, polygenic risk scores; SNP, single nucleotide polymorphism; AUC, area under the receiver operating characteristics curve; CI, confidence interval; OR, odds ratio; PCa, prostate cancer; HR, hazard ratio; BCR, biochemical recurrence; PSA, prostate specific antigen; RP, radical prostatectomy; GRS, genetic risk score; PCA3, prostate cancer antigen 3.

for any PCa in a Chinese population ($n=99$). When added to predictive models based on PSA alone and PSA+PCA3, PRS was able to improve prediction from AUC 0.73 to 0.81 and 0.84 to 0.86, respectively. PRS created by Zhu et al. (2015) [59] based on 724 Chinese males (176 biopsy-proven PCa and 548 control) utilized 24 SNPs. The PRS performed best in 60 to 70 year olds, with an AUC of 0.612 (95% CI, 0.541–0.684) and 0.647 (95% CI, 0.541–0.684) for any PCa and GS ≥ 7 PCa, respectively.

A GWAS study of 649 Chinese males detected 29 PCa-associated SNPs, 24 of which were previously confirmed to be PCa-significant in Han Chinese [60]. PRS calculated from the 29 SNPs showed a discriminatory performance of AUC 0.60, with 50.85% of males with high PRS harboring PCa compared to only 29.52% males in the low PRS group. A similar construct of 24 SNPs in 308 Chinese males (141 PCa) found comparable rate of increasing PCa detection of 26.3%, 43.2%, and 60.0% in low, average, and high PRS groups [61]. However, almost 40% of patients in both studies had PSA over 20 ng/mL, making it difficult to apply to real-world scenarios where patients would be stratified to high-risk regardless of PRS.

Akamatsu et al. (2012) [62] generated a PRS prediction model incorporating 689 Japanese PCa cases and 749 control in the development set. Validation was performed in two independent sets of 3,294 case and 6,281 control, and conferred an AUC of 0.659 (95% CI, 0.649–0.670) when all samples were combined. The authors found that serum PSA levels did not alter the predictive performance of the PRS models, nor was there a correlation between PSA and PRS-based odds-ratio. PRS developed in a Japanese cohort consisting of 4,893 PCa cases and 10,682 control utilized 82 significant SNPs [48]. Patients in the upper 5% of PRS were designated as high-risk and were more susceptible to early age of diagnosis by average 2.7 years (mean 68.7-year-old vs. 71.4-year-old in non-

high risk group). Addition of PRS enriched prediction of PCa in patients with family history. Interestingly, only 8 out of 10 SNPs previously reported to be PCa-associated in Asian males were significant, emphasizing the heterogeneity of inter-ethnic variation of genetic factors within the same Asian ancestry.

CLINICAL UTILITY OF PRS

PRS can augment predictive models based on traditional screening methods such as PSA for PCa and identify individual risk that may be obscured by absence of family history information. While family history is one the most commonly used risk factors that guide clinical decisions for early screening for detection and aggressive intervention [63], large scale studies of PRS on PCa found that family history did not predict onset of aggressive PCa nor improve prediction based on PRS alone [26]. Also, PRS can provide additional stratification within risk estimates of high penetrance genes. A study by Lecarpentier et al. [64] reported that the penetrance of BRCA2 may vary as much as 46% depending on whether the patient was at the top or bottom 5th percentile of PRS. In limited situations, patients with low PRS in a PSA gray zone may escape unnecessary biopsy, whereas males with high genetic risk may be indicated for a more active clinical approach (Fig. 1). In a Japanese cohort where the overall probability of positive biopsy was 20%, patients with high PRS were twice more likely to harbor PCa (42.4%), where males with low PRS only had 10.7% risk [62]. This means that PRS can supplement patient-specific medical practice by identifying individuals of genetic high-risk who may otherwise be missed when profiled by traditional clinical variables alone. Application of PRS is becoming more accessible as GWAS and NGS is becoming less costly, and as PRS utilizes the fixed genetic imprint of an individual, a

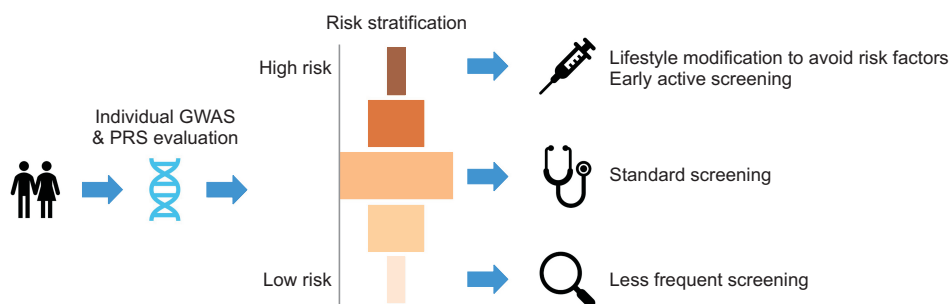


Fig. 1. Genetic risk to clinical practice. The calculated lifetime risk of PCa based on PRS allows for selection of high-risk patients for early intervention such as lower PSA thresholds for prostate biopsy. Patients stratified to low-risk may be able to avoid unnecessary screening procedures and be eligible for more non-invasive treatment options such as active surveillance. GWAS, genome-wide association study; PRS, polygenic risk scores; PCa, prostate cancer; PSA, prostate specific antigen.

single GWAS analysis has the potential to provide prognostic evaluation of lifetime risk trajectory to not only PCa but of all spectrum of diseases from coronary heart disease to obesity [65,66].

PRS, like any clinical tool, is not without its limitations. Despite national guideline changes to include genetic testing for males at high risk for PCa, insurance coverage standards are not universal and costs may vary depending on companies. Such discrepancies between needs of a clinician to provide personalized medicine and the financial burden on the patient must be assessed prior to any type of genetic testing, as well as the potential risk of exposure of personal genetic information. Also, risk models based on GWAS are population-specific by design, as allelic effect sizes can easily be over- or under-estimated depending on the distribution in the development cohort. Hence, thorough validation processes in independent cohorts are pertinent to establish objectivity, and perhaps the most sensible method is to modify and reassess PRS models on both multiethnic and single ancestry populations. This approach necessitates a much larger scale international effort and collection of genetic data than previously reported. Also, PRS is an estimate of fixed genetic risk that is in fact relative and susceptible to variation depending on addition of other non-genetic clinical factors as well as gene-environment interaction. Therefore, unlike Mendelian monogenic causes of certain diseases, PRS based on SNPs of low penetrance and relatively smaller individual effect size may have less of an impact on the actual clinical course of a patient than previously assumed, an aspect which requires more prospective evaluation in time to come.

CONCLUSIONS

PRS allows for personalized assessment for prediction of PCa onset and may guide decisions on when and how to screen and intervene for cancer. Literature presented so far in Asian populations are limited but hold promise for increasing roles of genetics in risk stratification in PCa, both as an independent tool as well in combination with previously established clinical factors such as PSA. The gradual rise in PCa incidence in Asian countries further facilitate the need to identify congenital genetic risk factors that are specific to Asian ancestry. Although there are obvious limitations in current prediction models provided by PRS, further accumulation of genetic data over time will continue to expand PRS application to other diseases and optimize predictive power.

CONFLICTS OF INTEREST

Seok-Soo Byun is concurrently employed by PROCAGEN.

AUTHORS' CONTRIBUTIONS

Research conception and design: Seok-Soo Byun. Data acquisition: Sang Hun Song and Seok-Soo Byun. Data analysis and interpretation: Sang Hun Song. Drafting of manuscript: Sang Hun Song. Critical Revision of the manuscript: Sang Hun Song and Seok-Soo Byun. Administrative, technical, or material support: Seok-Soo Byun. Supervision: Seok-Soo Byun. Approval of the final manuscript: Sang Hun Song and Seok-Soo Byun.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via <https://doi.org/10.4111/icu.20210124>.

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