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# The Role of Family History and Germline Genetics in Prostate Cancer Disease Profile and Screening

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**Abstract:** Established risk factors for prostate cancer include age, ethnicity, a family history of prostate cancer or carrying a pathogenic germline variation in a prostate cancer predisposition gene. Approximately 10–15% of men with advanced prostate cancer have a germline genetic predisposition to the disease (i.e., *BRCA2*). Whilst the largest, and most well-known prostate cancer screening studies (i.e., ERSPC) have focused on the use of prostate-specific antigen as a screening tool, the incorporation of tissue and liquid genomic biomarkers alongside modern imaging modalities are being designed to individualize and improve the accuracy of both the screening and diagnostic pathway. The use of a polygenic risk scoring can now also offer a man his personalized prostate cancer risk based on a number of low-risk, common genetic variants and is currently the subject of ongoing research. The mainstreaming of genomics into the prostate cancer

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screening, diagnostic and treatment pathway will soon become embedded into routine clinical practice. This chapter aims to summarize current knowledge on the topic of men who harbor a genetic predisposition to prostate cancer, how this predisposition arises, its stratification into low-risk common variants vs. high-risk, rare variants, and its impact and incorporation into screening and diagnostic algorithms. The importance of germline genetics beyond screening and diagnostics, its role in the identification of lethal prostate cancer, and in the selection of targeted treatments for advanced disease is also discussed.

**Keywords:** familial prostate cancer; family history and prostate cancer; genetics of prostate cancer; hereditary prostate cancer; prostate cancer disease profile and screening

## INTRODUCTION

Men with a family history of prostate cancer present a challenge in early prostate cancer detection whilst considering in parallel the well-known harms of PSA screening. The strength of a man's family history (i.e., first degree or second-degree relative) as well as the age of prostate cancer onset of his affected family members are also of importance. The literature is conflicting regarding treatment outcomes, survival, and grade/stage of disease in men with a family history, compared to those without.

Men with a family history of prostate cancer constitute an important population of men with a higher incidence of prostate cancer compared to men from the general population. Evidence suggests a spectrum of risk, with at least a two-fold increase (1) and worsening risk with the number and closeness (i.e., first degree) of relatives affected. A Swedish study reporting from a family-database of over nine million people reported a standardized incidence ratio (SIR) of 23 for men whose father and brother were affected (2). Hereditary prostate cancer (HPC) is a unique and specially defined circumstance based on a man's pedigree, with three categories described: (i) prostate cancer in three successive generations; (ii) at least two cases of prostate cancer in the family, both with an age of onset of <55 years old; and (iii) three or more first-degree relatives with prostate cancer at any age. This type of prostate cancer was first described by Carter et al in 1993 (3). It remains unclear if the biology of HPC is different to those with 'sporadic' (i.e., those with no family history of prostate cancer) disease but men with HPC do develop prostate cancer at an earlier age. In men with prostate cancer diagnosed at ≤-55 years, HPC (as defined above) was found in up to 43% of cases. Genes implicated in HPC include *BRCA1/2* and *HOXB13*.

## DOES PROSTATE CANCER IN MEN WITH A FAMILY HISTORY BEHAVE DIFFERENTLY COMPARED TO THOSE WITHOUT?

Evidence for differences in disease biology between sporadic, familial, and hereditary prostate cancer is varied. Gronberg analyzed American families with familial and

HPC compared to men with sporadic prostate cancer. They showed that men with HPC were diagnosed with more aggressive prostate cancer and had an earlier age of onset (by 2 years) and had worse TNM stage (4). Poorer biochemical-free relapse rates at five-years following radical prostatectomy in men with familial prostate cancer (one first-degree relative affected with prostate cancer) compared to those without have been shown by Kupelian et al in a retrospective review of over 1,000 men. This work described family history as an independent predictor of biochemical recurrence after adjusting for age, histology, stage, and surgical pathology such as positive margins (5, 6). However in a similar analysis of 708 men undergoing radical prostatectomy published by Bova with longer follow-up (7), no differences in biochemical recurrences were seen between men with familial prostate cancer/HPC compared with men without a family history who were disease and age-matched.

In an analysis of 481,000 men in the Cancer Prevention Study II (CPS-II), men who had any family history of prostate cancer were 60% more likely to die from prostate cancer compared to those without, with a pronounced effect if the affected relative was diagnosed with prostate cancer before 65 years old (8). In an analysis of 5,519 men in the placebo arm of the Prostate Cancer Prevention Trial (PCPT), men with a family history (16% of the cohort) of prostate cancer had an odds ratio of 1.31 for harboring prostate cancer on any form of prostate biopsy undertaken during study follow-up. In the family history group, 24% who had a prostate biopsy had prostate cancer diagnosed compared with 17% of men without a family history; importantly, the investigators did not report that family history was associated with high-grade disease (9). Interrogating the Prostate, Lung, Colorectal and Ovary (PLCO) data, Liss et al found that when men with a family history underwent PSA screening, there was a significantly higher incidence of prostate cancer and prostate cancer cancer-specific mortality in those with a family history compared to those without (10).

Westerman et al. reviewed the impact of family history in a first-degree relative on clinical and mortality outcomes in a surgical population of approximately 16,000 men at the Mayo clinic undergoing radical prostatectomy from 1987–2010. Their cohort had a large incidence of family history (32.3%). They found men with a family history were significantly more likely to have organ-confined and low-risk disease and higher 10-year cancer-specific (99% vs 97%) and overall survival (92% vs 85%) compared to men without a family history (11). Overall survival has been reported as superior in men with a family history of prostate cancer in an Australian analysis of 9459 men by Ang et al (12) after adjusting for NCCN disease-risk category, age, and year of treatment. In this analysis, family history definition was a binary yes or no response relating to grandfather, father, uncle child or grandchild. Recently, Urabe et al published a meta-analysis of 8 studies with 33,027 patients reporting no impact of family history on cancer specific mortality or the risk of biochemical recurrence in patients with localized prostate cancer (13).

## HOW DOES PSA SCREENING PERFORM IN MEN WITH A FAMILY HISTORY OF PROSTATE CANCER?

A subset analysis of European Randomised Screening Study of Prostate Cancer (ERSPC) (n=4,932) analyzed the effect of family history. The incidence of

prostate cancer differed significantly over an 11-year period between men with and without a family history (18% vs 12% respectively, HR 1.6). Family history status along with age and baseline PSA were significant predictors of prostate cancer incidence, but family history status was not an independent predictor for clinically significant prostate cancer. When men were stratified by family history status, 5.1% of men with a family history of prostate cancer were found to have clinically significant cancer compared to 4% of men without a family history (14).

When analyzing by screening arm vs non-screening arm in the PLCO screening trial, men with a family history of prostate cancer in a first-degree relative and the number of first degree relatives with a diagnosis of prostate cancer was significantly associated with prostate cancer mortality (HR 1.89) in the non-screening arm compared to the screening arm (15) suggesting a benefit to screening this group. Across both study arms, 10.5% of men without a family history were found to have prostate cancer compared with 16.5% of men with a family history. There was no difference in cancer stage, age, or PSA at diagnosis between the groups. It must be remembered however that the PLCO study was in essence (due to contamination of the trials' screening arm), a trial of routine PSA screening vs opportunistic screening.

## SPECIFIC GERMLINE GENETIC MUTATIONS INVOLVED IN PROSTATE CANCER

Specific prostate cancer risk genes exist, occurring rarely in the general population (0.2–0.3%) but with evidence for enrichment in cases of metastatic prostate cancer. Pritchard et al (16) highlighted the important role of DNA repair gene mutations in the biology of men presenting with advanced prostate cancer, demonstrating a relative risk (RR) of 18.6 for men with germline *BRCA2* mutations and 3.1 for men with *CHEK2* mutations. In their analysis of 692 men with metastatic prostate cancer, they found 11.8% of men carried a germline mutation in a DNA repair gene with 44% of all mutations found in the *BRCA2* gene. These men were unselected for age at diagnosis or family history status. This differed to men with localized prostate cancer, in whom a frequency of germline mutations of 4.6% was described (17).

Pathogenic germline mutations were also found in approximately 17% of men in a cross-sectional study of 3607 men with prostate cancer, unselected for family history, age or disease stage, of which 30.7% were *BRCA1/2* variants, 4.5% were due to *HOXB13*, 14.1% *CHEK2* and 9.6% due to *ATM* (18). The United Kingdom Genetics Prostate Cancer Study (UKGPCS) (19) reported 7.3% of 191 prostate cancer patients with a family history of prostate cancer (with three or more cases in their family) were found to carry a pathogenic germline variant, the most commonly detected being in *BRCA2* (28.57% of all pathogenic variants). Importantly, there was a significant association seen between carrying a pathogenic variant and a diagnosis of nodal or metastatic disease.

## BRCA

Mutations in *BRCA1/2* are rare in the general population and enriched in the Ashkenazi Jews (with a frequency of approximately 2–2.5% of Ashkenazi women carrying a mutation in *BRCA1/2* and 3.2–4% of Ashkenazi men with prostate cancer) (20). *BRCA2* mutations confer the highest risk of prostate cancer (8.6-fold in men aged ≤65 years) (21, 22), with the effect of mutations in *BRCA1* being significant (23). In an Icelandic study, *BRCA1/2* mutation carriers were younger at diagnosis, (69 vs. 74 years) and presented with more advanced tumor (T) stage (T3–4: 79% vs. 36%) and histologically aggressive tumors (84% vs. 52.7%). Median cancer-specific survival (CSS) for carriers was 2.1 years compared with 12.4 years for non-carriers (24).

Poorer outcomes in carriers have also been reported. Edwards et al (13) compared overall survival (OS) after prostate cancer diagnosis in a series of *BRCA2* mutation carriers and controls. *BRCA2* mutation carriers had a median OS of 4.8 years vs with 8.5 years for non-carriers. Castro et al (25) reported a more aggressive prostate cancer phenotype more frequently associated with lymph node involvement and distant metastasis compared to non-carriers. An Icelandic study by Tryggvadottir et al showed a mean overall survival of approximately 2 years in men with prostate cancer who carried the specific 999del5 *BRCA2* pathogenic variant compared with non-carriers (26).

The most optimal treatment strategy for men with prostate cancer who carry a high-risk genetic mutation such as *BRCA2* is yet to be established, with no randomized clinical trials or large-volume series demonstrating a clear advantage of one radical treatment strategy over another. Such a trial would prove difficult due to the relative rarity of the mutation in the general population and in men with organ-confined disease undergoing radical treatment with surgery or radiotherapy. A retrospective series by Castro et al reviewed 1302 men (67 *BRCA1/2* mutation carriers) with prostate cancer and found poorer metastasis-free survival and cancer specific survival after radiotherapy (27) although this was not statistically significant. The PROREPAIR-B study was a multi-center study enrolling men presenting with metastatic castrate resistant prostate cancer for germline testing for defects in 107 DNA damage repair genes. 16.2% of their population (419 men) were found to carry a germline mutation, of which *BRCA2* was the most common. The investigators reported worse outcomes in men with a *BRCA2* mutation receiving taxane chemotherapy as first line treatment compared to those without a *BRCA2* mutation, along with a reduced median cancer-specific survival (28). Active surveillance (AS) is now an acceptable and recommended treatment option for localized prostate cancer of favorable risk so men may avoid the risks and morbidity of radical treatment until the disease profile requires it. Carter et al (29) have demonstrated an association between the incidence of disease upgrade in men on AS with germline mutations in *BRCA1/2/ATM* compared with non-carriers (five-fold greater risk; adjusted HR 2.40, p=0.046).

## CHEK2, NBN, ATM

*CHEK2* mutations have been implicated in familial and hereditary prostate cancer, in particular in Slavic populations (30, 31). In a UK study of 191 men with 3 or

more cases of prostate cancer in their family, Leongamornlert et al reported *CHEK2* germline mutations accounted for 14% of all germline loss of function mutations and was associated with more aggressive prostate cancer (19).

In Polish men with disease onset less than 60 years and in men with a family history of prostate cancer, frequencies of mutations in *BRCA1*, *CHEK2* and *NBN* were higher than in those without. A founder mutation (675del5) in *NBN* has also been associated with a three-fold increase in prostate cancer incidence amongst carriers and a significant effect on overall survival after adjusting for age, stage, and tumor grade (32–34). In a UK study of aggressive prostate cancer cases, Mijuskovic et al found a protein-truncating variants in *NBN* was present in 5.8% of aggressive cases of prostate cancer (35). Men carrying a pathogenic variant in the ATM gene have been reported as having upwards of a four-fold increase in prostate cancer risk and were more likely to have earlier onset disease in a large case-control, European analysis by Karlsson et al (36), along with shorter survival times and younger age at death from prostate cancer (37).

## HOXB13

Carriers of a pathogenic germline missense variant of the *HOXB13* gene had a 33% risk of developing prostate cancer, compared to a 12% risk of non-carriers in a Scandinavian population of over 5,000 cases (38). An analysis of approximately 2,400 Prostate cancer families found a *HOXB13* mutation in 5%, suggesting a potential role of targeted screening in men known to carry this germline variant (38, 39). A further large-scale Finnish analysis of 4,000 prostate cancer cases revealed a significantly higher carrier-rate of the specific G84E mutation amongst men with prostate cancer (3.5%) and those with a family history (8.4%) compared to controls (40). In a separate study, Ewing et al found the carrier rate of the G84E mutation was more commonly encountered in men with a diagnosis of prostate cancer at an early age and in those with a positive family history (1.4%), than those without (0.1%) (41). There was no difference in Gleason grade between carriers and non-carriers (41). Nyberg et al described age-specific risks for carriers of the pathogenic G84E variant for developing prostate cancer and stratified men by varying pedigrees. The average predicted risk of prostate cancer by age 85 was 62% for those carrying the mutation, compared with 15% for those without. In a mutation carrier with a history of prostate cancer in his father, the risk estimate ranged from 69% to 92% depending on the father's age at prostate cancer diagnosis, and for a man with two affected first-degree relatives, the risk estimate ranged from 70% to 98% (42).

## LYNCH SYNDROME

Lynch syndrome is a rare, inherited cancer predisposition syndrome caused by germline mutations in the miss-match repair genes; *MLH1*, *MSH2* or *MSH6*. It has been estimated in a study investigating 106 men with miss-match repair mutations that the cumulative risk of prostate cancer by the age of 70 in

mutation carriers is 30%, compared with 9–12% in the general population. Of the cancers diagnosed with available histology, 5 cases (62.5%) were poorly differentiated, with a Gleason score ≥8 (42). Recent results from the first screening round of the IMPACT study described higher prostate cancer incidence in *MSH2* and *MSH6* mutation carriers (compared to age-matched, non-carrier controls), with results suggesting a possible benefit in targeted PSA screening in these high-risk groups (43).

## THE IMPACT OF GERMLINE GENETICS ON TREATMENT AND OUTCOMES

Targeted therapy for men with pathogenic variants in DNA damage repair genes has been the subject of recent research. In men with metastatic castration-resistant prostate cancer with germline or somatic pathogenic variants in *BRCA1/2*, Olaparib has been evaluated in the UK based, Phase 2 TOPARP study (44) which recruited 92 patients with known mutations in DNA damage repair genes to receive either 300mg or 400mg of olaparib. Results showed greater radiological, PSA or circulating tumor cell response in the 400mg group, and this was greatest in those with a *BRCA1/2* mutation. PARP inhibitors are now licensed in the US and Europe for men with germline mutations in DNA repair genes (*BRCA1*, *BRCA2* and *ATM)* (45–47). In addition, men with advanced prostate cancer pathogenic variants in *BRCA1*, *BRCA2* and other DNA repair genes have also demonstrated encouraging sensitivity to platinum chemotherapy (48–50).

## GERMLINE SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS)

Large scale genome-wide-association-studies (GWAS) have led to the discovery of approximately 269 SNPs specifically associated with Prostate cancer risk (51–54) across multiple chromosomal loci. At present, 34–43% of the familial risk in prostate cancer can be explained based on these SNPs, with men in the top 1% of the risk profile having a 5.7-fold increase in risk of developing prostate cancer compared with the average risk of men in the general population (55–57).

By measuring the genetic burden for a specific disease, a polygenic risk score (PRS) provides a novel tool in identifying those at greatest or the lowest risk. A PRS is calculated by summing all detected (and weighted) risk alleles, with the effect of each allele described from published GWAS. Using PRS in addition to clinical information (i.e., age, PSA, and family history) has been shown to predict prostate cancer and also reduce the need for prostate biopsies (58, 59). Limitations include extensive underrepresentation of non-Caucasian populations in the studies have resulted in prostate cancer risk SNP discovery, though multi-ethnic analyses have now been reported by Conti et al in a recent GWAS and meta-analysis of over 107,000 cases and controls across different ethnic populations reporting 269 risk SNPs. They reported men of African ancestry having a genetic risk score (GRS) that was 2.18 times higher than that of Caucasians (57).

In a meta-analysis by Schumacher et al, men in the top 1% of the risk profile according to a 147 prostate cancer-risk SNP profile had a 5.7-fold increased risk of prostate cancer compared to men of average risk (defined as those in the 25–75$^{th}$ centiles of risk) (60, 61). Of note, the PRS effect increased with the presence of positive family history and in those with a prostate cancer diagnosis under the age of 55 years.

Pashayan et al. assessed the implications of using a PRS in reducing the prostate cancer over-diagnosis associated with PSA-based prostate cancer screening. They built a PRS-based on 17,000 prostate cancer cases using 66 prostate cancer risk SNPs, separating men into risk quartiles. They found that PRS-based risk stratification had the ability to lead to a 56% reduction in over-diagnosis between the lowest PRS quartile and the highest (62). The PRS described by MacInnis et al (based on 26 risk SNPs) in men specifically with familial prostate cancer (53), demonstrated the parallel effects of family history status and known prostate cancer susceptibility variants. Seibert et al reported a polygenic hazard score (PHS) using 54 prostate cancer risk SNPs. This showed the ability to predict age at prostate cancer diagnosis of any prostate cancer and aggressive prostate cancer. In this study, the positive predictive value (PPV) of PSA also increased with increasing PHS (63).

Apart from predicting risk in the general population, prostate cancer SNPs are known to modify the risk associated with *BRCA1/2* mutations. Recently, the utility of a 147-prostate cancer SNP assay was investigated in approximately 1,800 Caucasian men of European ancestry from the CIMBA consortium. They reported a wide range of absolute prostate cancer risks in men with *BRCA1/2* mutations, depending on where one falls on the spectrum of polygenic risk (Figure 1). These results indicate that a PRS could be clinically informative in assigning men an

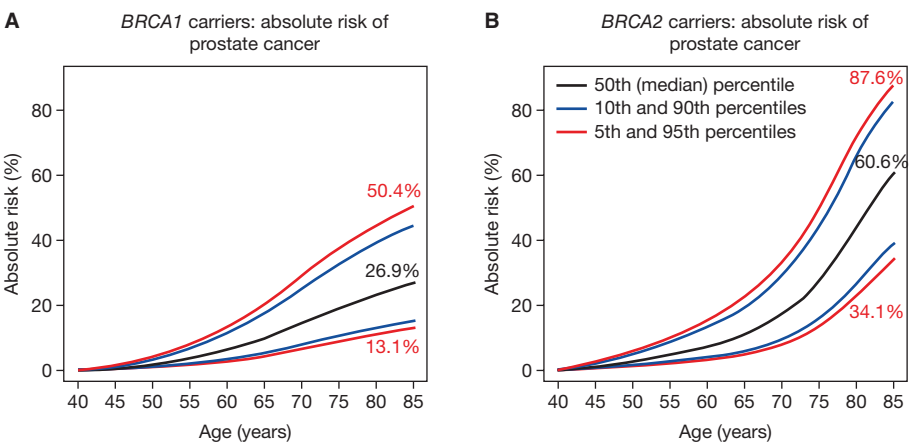


**Figure 1. Risk of prostate cancer in *BRCA1/2* mutation carriers according to age and polygenic risk.** Reproduced from Barnes et al (64). The predicted absolute risks of developing breast cancer and prostate cancer by PRS percentile. Risks were calculated assuming the per standard deviation ratio estimates in the combined sample of *BRCA1* and *BRCA2* carriers. (B) absolute risk of prostate cancer in male BRCA1 carriers (C) absolute risk of Prostate cancer in male BRCA2 carriers. 

individualized cancer risk for those carrying pathogenic *BRCA1/2* variants, a small but important group of men could form part of a novel, future enhanced screening strategies for *BRCA1/2* mutation carriers (64).

## INCORPORATING GENETICS INTO SCREENING AND DIAGNOSTIC PATHWAYS

The STOCKHOLM3 study (STHLM3) (65) was the first population-based prostate cancer screening study prospectively assessing a prostate cancer screening strategy incorporating genetic information. The study's screening model combined serum biomarkers (including PSA and its isomers), 232 risk SNPs and known clinical variables (e.g., age, a family history of prostate cancer, previous prostate biopsy) and compared this with a PSA alone (using a threshold of ≥3.0ng/ml) screening strategy. The sensitivity of the STHLM3 model for the detection of clinically significant Prostate cancer was superior (AUC 0.74 vs 0.56) when compared to PSA. The STHLME3 model also reduced the number of prostate biopsies by 32% and avoided 44% of negative biopsies. Given the Caucasian ethnicity of the majority of participants in the original STHLM3 screening study, the evaluation and validation of the STHLM3 model in non-Caucasian populations will be important and this is being investigated prospectively in a multi-ethnic cohort (SEPTA trial) in Chicago (NCT04583072). The STHLM3MRI study incorporated the use of prostate MRI, which combines a paired and randomized study design, the results of which have recently been published (66). When Nordstrom et al compared a strategy of PSA screening combined systematic biopsies with that of a 'positive' STHLM3 test combined with MRI-targeted biopsies, they found 69% fewer low-grade cancers were diagnosed (95% CI 52–80; 45 vs 142 per 10,000 tested men) and 52 percent fewer biopsies (95% CI 43–58; 409 vs 853 per 10,000 tested men) were performed in the STHLM3/MRI cohort. This test combination therefore shows great promise for minimizing prostate cancer over-detection whilst maintaining the detection of clinically significant disease.

BARCODE1 (NCT03857477) will be the first prospective study to utilize a prostate cancer risk SNP profile to evaluate targeted prostate cancer screening in the general population. The investigators recruited patients via their general practitioners and offered intervention with MRI and prostate biopsy to men only falling in the top 10% of polygenic risk. In the BARCODE1 pilot study, uptake following invitation was 26% with 25/303 participants being identified for MRI/Biopsy invitation based on their PRS falling in the top 10% (67). The pilot study is now complete, with the full study having completed recruitment and is ongoing.

A risk-stratified approach to refining breast cancer screening was modelled by Pashayan et al (68) in a hypothetical UK cohort of over 300,000 women comparing no screening, age-based screening and a PRS-based model where only women in the highest PRS were offered screening mammography. Reduced rates of breast cancer overdiagnosis and improved cost-effectiveness were found when women with low risk were not offered screening. The WISDOM study is an RCT comparing personalized, risk-based screening with routine annual breast cancer screening in 100,000 women aged 40–74 in the USA. The personalized screening,

experimental arm is based on a woman's breast density, a PRS based on over 200 breast cancer risk SNPs, 9 gene-panel and ethnicity (69). A similar approach could be utilized in prostate cancer in the future.

## TARGETED PROSTATE CANCER SCREENING

PSA is not a diagnostic test for prostate cancer and is unlikely to ever be deemed a satisfactory tool on its own for population screening. Given that advanced and aggressive prostate cancer can significantly affect a man's survival (70), targeting men at a high risk of cancer and a high risk of lethal prostate cancer would be the better target of a screening program. It is in this scenario where clinical and genetic risk modelling may play a large part in future targeted screening strategies.

In a prospective screening study of Israeli males with known *BRCA1/2* mutations for 5 different cancers including prostate cancer, the rate of prostate cancer detection in *BRCA1/2* mutation carriers was 3.8–8.6% using annual PSA screening and digital rectal examination (71). Das et al have also reported their intention to prospectively study a cohort of men with known pathogenic germline variants (*BRCA1/2*, *HOXB13*, *ATM*, Lynch syndrome genes), managed in a high-risk clinic which will include a PSA, DRE, SelectMDx™ and MRI based algorithm (72).

The IMPACT study (NCT00261456) is a targeted screening study enrolling over 3,000 men (*BRCA1/2*, *MSH2, MSH6, MLH1* mutation carriers and controls) investigating the outcomes of targeted PSA screening; the screening intervention being annual PSA and a biopsy triggered with a PSA threshold of 3.0 ng/ml. Preliminary and interim results in the *BRCA1/2* cohort suggested targeted screening using PSA in this population is beneficial in those with a *BRCA2* mutation, with mutation carriers having with a higher rate of prostate cancer diagnosis, at a younger age and having more significant disease than non-carriers. In 2020, Segal et al reported their first round of screening combining age-stratified PSA and MRI in *BRCA1/2* mutation carriers. This approach detected cancer in 8.6% of the 188 men recruited, with a significant net benefit of screening using MRI compared to PSA found in men aged 40–55 years (PSA had the highest benefit in those aged >55) (73). The early screening results of Das et al (72), the Lynch cohort of the IMPACT study (43) and interim results of the IMPACT BRCA cohort (74) have been published and the full results are awaited. Dahut et al have described a screening protocol for men with pathogenic variants in known or suspected high-penetrance cancer predisposition genes where they intend on screening 500 men with prostate MRI, PSA and DRE with repeat screening interventions every two years (75).

It is yet unclear exactly what role PRS can play as a screening tool in detecting prostate cancer in asymptomatic men selected for a family history as most who will have low PSAs. The PROFILE pilot study evaluated the feasibility of recruiting men with a family history of prostate cancer to undergo up front prostate biopsy and germline SNP testing for prostate cancer risk SNPs to assign all men a PRS. No significant association between the PRS and prostate cancer diagnosis was found in 100 healthy men with a family history of prostate cancer undergoing screening prostate biopsy irrespective of PSA. However, the number of cancers

diagnosed in this group of men (mean age 53) with a low median PSA (1.3) was sizeable; 25% had prostate cancer found on screening biopsy of whom 48% had clinically significant disease. Twelve men with prostate cancer had a PSA <3 (52%). No adverse psychosocial variables were noted (76).

## CONCLUSION

Germline mutations in a prostate cancer predisposition gene have emerged as important in all aspects of the prostate cancer pathway, from screening and diagnosis through to patient counselling regarding prognosis and targeted treatments. Germline analysis for prostate cancer risk SNPs is also likely to play a role in the future of prostate cancer screening and diagnostic risk-stratification pathways; identifying men who may benefit more from further diagnostic tests or reassuring those at low risk.



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