Genetics of prostate cancer: a review of latest evidence

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ABSTRACT

Prostate cancer (PrCa) is a largely heritable and polygenic disease. It is the most common cancer in people with prostates (PwPs) in Europe and the USA, including in PwPs of African descent. In the UK in 2020, 52% of all cancers were diagnosed at stage I or II. The National Health Service (NHS) long-term plan is to increase this to 75% by 2028, to reduce absolute incidence of late-stage disease. In the absence of a UK PrCa screening programme, we should explore how to identify those at increased risk of clinically significant PrCa.

Incorporating genomics into the PrCa screening, diagnostic and treatment pathway has huge potential for transforming patient care. Genomics can increase efficiency of PrCa screening by focusing on those with genetic predisposition to cancer—which when combined with risk factors such as age and ethnicity, can be used for risk stratification in risk-based screening (RBS) programmes. The goal of RBS is to facilitate early diagnosis of clinically significant PrCa and reduce overdiagnosis/overtreatment in those unlikely to experience PrCa-related symptoms in their lifetime. Genetic testing can guide PrCa management, by identifying those at risk of lethal PrCa and enabling access to novel targeted therapies.

PrCa is curable if diagnosed below stage III when most people do not experience symptoms. RBS using genetic profiling could be key here if we could show better survival outcomes (or reduction in cancer-specific mortality accounting for lead-time bias), in addition to more cost efficiency than age-based screening alone. Furthermore, PrCa outcomes in underserved communities could be optimised if genetic testing was accessible, minimising health disparities.

INTRODUCTION

Prostate cancer (PrCa) is the most common cancer in people with prostates (PwPs) and is a heterogeneous disease which can be slow growing and indolent, or a fatal diagnosis.[1] In the UK 52 000 PwPs are diagnosed with PrCa every year on average (144 per day) and there are 490 000 PwPs living with/having had PrCa.[2] There were 1.4 million new cases and 375 000 deaths worldwide in 2020, and the incidence is rising.[2] There is no established NHS screening programme, and the existing method of testing in primary care is a prostate-specific antigen (PSA) blood test which generally has a poor predictive value and does not distinguish between indolent or clinically significant disease.[1] This generates debate around overdiagnosis and overtreatment, with consequent patient harm and low cost efficiency. Detecting disease in the early stages, without inducing harm from overdiagnosis of indolent disease, requires more precise screening methods, as discussed in this review.

Prognosis

For those diagnosed with stage I and stage II PrCa (localised and low grade), the 5-year survival rate is almost 100%. However, those with stage IV PrCa (metastatic) at diagnosis have a 5-year survival of 50%.[3]

Risk factors

The only established risk factors for PrCa are age, ethnicity and having a family history of PrCa.[4]

Age

Incidence of PrCa increases from age 50 years, although two-thirds of cases are diagnosed at age 70 years and above.[2] The number of people diagnosed below age 55 years is increasing each year,[2 4] with higher morbidity and mortality associated with disease in this group. These PwPs are more likely to carry constitutional (germline) genetic variants that caused their PrCa.[4]

Family history

PrCa is the most heritable of all common cancers, with 58% heritability observed in monozygotic twins in the Norwegian Twin Cancer Study.[5] An individual's risk of developing PrCa rises with the number of affected relatives and the younger their age of diagnosis.[1] A person's lifetime risk is 2.5 times that of the general population if they have a first-degree relative with PrCa.[4] Aggressive PrCa has been seen to cluster in certain families, indicating that aggressiveness of PrCa is linked to constitutional genetic variation.[6 7] Furthermore, in some studies familial PrCa is more likely to relapse and have poorer outcomes after radical prostatectomy (RP).[8] Some papers suggest such families experience higher rates of other cancers, particularly breast cancer.[9] A Swedish study showed that sons and fathers who both had PrCa had similar overall survival times.[10] Interestingly, a 2023 paper investigating the all-cause PrCa-associated mortality in those with a strong family history of PrCa, compared with those with no family history, found a reduction in mortality among those with a strong family history—which is likely due to increased awareness of the disease.[11]

Ethnicity

Black PwPs are twice as likely to be diagnosed with PrCa than white PwPs (1 in 4 compared with 1 in 8).

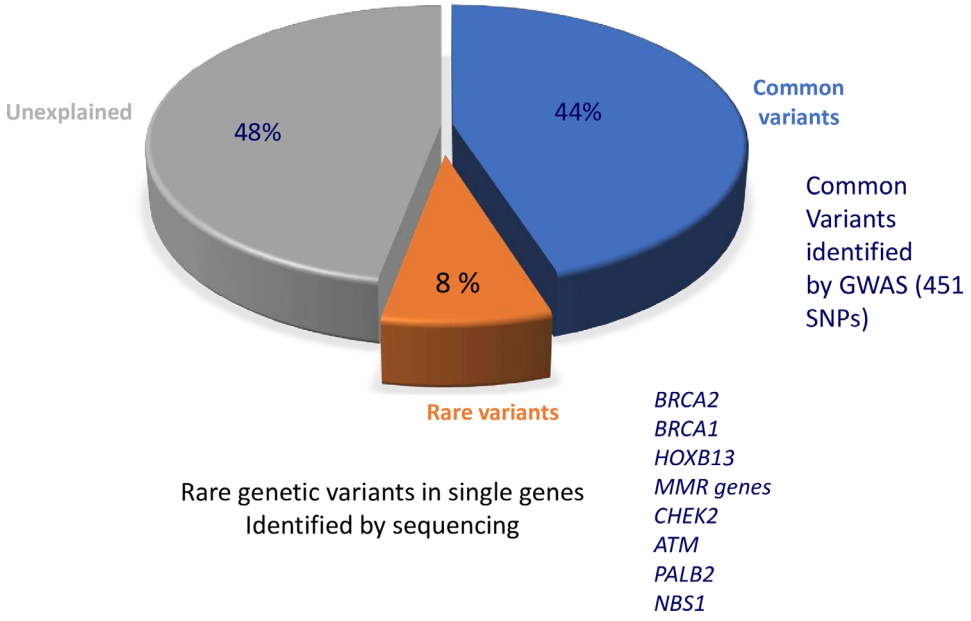

Figure 1 Proportion of prostate cancer familial risk due to common and rare constitutional variants. GWAS, genome-wide association studies.

They are also more likely to be diagnosed at a younger age. Due to scarce genetic data from black African and black Caribbean populations, we cannot adequately determine whether genetic variants could explain this higher incidence and mortality.

Multiethnic genome-wide association studies (GWAS) have discovered more SNPs linked to PrCa than previously reported from European GWAS, indicating constitutional variation for PrCa risk varies across ethnicities, with those of African ancestry having a Polygenic Risk Score (PRS) 2.18 times higher than those of East Asian ancestry.[12] Those of East Asian ancestry had 0.73 times lower risk than those of European ancestry.[12] One multiethnic study identified that SNPs associated with PrCa found those with African ancestry carried higher per-allele ORs than most SNPs found in European populations.[12]

Carter *et al*, investigating the reclassification of PrCa under 'Active Surveillance' (AS) (low grade PrCa evolving to a higher grade, found on repeat biopsy), demonstrated that Americans of African descent were three times more likely to reclassify PrCa grade on serial biopsy than Americans of European descent.[13] Interestingly, those with a high-risk family history did not have an increased rate of reclassification.[14]

Genetic predisposition to PrCa

Genetic predisposition to PrCa is determined by the combination of common and rare constitutional genetic variants.[4] Rarer variants are more likely to present in clusters in families, whereas common variants (SNPs) have a larger contribution to risk in the general population.[1] Figure 1 details the variants associated with PrCa risk as a proportion of PrCa cases.

Risk from common variants

Common variants are SNPs found in more than 1% of the population and individually cause a small increased risk of PrCa. However, in combination they can increase PrCa risk to a clinically significant level.[4] The cumulative effect of the 451 risk-elevating SNPs known to be associated with PrCa are used to generate a PRS.

Until recently the most extensive SNP profile associated with PrCa consisted of 269 SNPs; these are predominantly in Europeans.[12] A multiethnic GWAS has just been published and a further 187 novel SNPs have been identified—bringing the total to 451 SNPs associated with development of PrCa.[15] Some of these are unique to individuals of African ancestry and are also associated with aggressive disease. These act multiplicatively (log additive), conferring up to a 5.7-fold to 11-fold increase in PrCa risk[12] (see table 1 taken from the Conti *et al* data[12]) for those in the top 1%–10% of the risk profile compared with the general population of European ancestry.[4] Online supplemental figure 1 illustrates PrCa absolute risk with age in those with European ancestry against those with African ancestry. This suggests that some SNP combinations can confer a risk comparable to moderate-risk genes (such as *BRCA1*/*BRCA2*/*MSH2*)[16] and people can be stratified into risk groups and given an individualised PRS.

Polygenic Risk Scores

A PRS predicts a person's lifetime risk of cancer, based on their genotype. A PRS can be generated for any disease with genetic aetiology, however it is most commonly used for cancer and cardiovascular disease. The cancer risk represented by PRS is derived from disease-associated SNPs only and does not include

Table 1 Relative risk of prostate cancer in each polygenic risk percentile range (Conti *et al*)[12]

Risk Category percentiles	Relative risk (95% CI)
99%–100%	11.65 (10.56 to 12.85)
90%–100%	5.06 (4.84 to 5.29)
80%–90%	2.45 (2.34 to 2.56)
70%–80%	1.73 (1.65 to 1.82)
60%–70%	1.36 (1.29 to 1.42)
40%–60%	1.00 (ref)
30%–40%	0.73 (0.69 to 0.77)
20%–30%	0.57 (0.54 to 0.60)
10%–20%	0.42 (0.40 to 0.45)
0%–10%	0.24 (0.23 to 0.26)

the risk from single gene variants like in *BRCA1/2*, although they can interact. The score is the sum of the alleles across SNPs, where each allele is weighted by their probability of the SNP affecting disease risk (which is estimated by log-ORs[9]). Identifying which SNPs are present, and in what combination, identifies a PRS which predicts an individual's risk of developing PrCa compared with the general population of the same ancestry. In practice, this score is used with other risk factors (such as age and family history) to provide personalised risk prediction and to enable risk-based screening (RBS).[17]

Most GWAS data are from European populations. Therefore, using them to calculate a PRS in non-European ethnicities requires further data from such populations. Multiethnic GWAS have discovered that many PrCa-associated SNPs are shared across varying ethnicities, though individual SNP-associated level of risk may vary according to ethnicity.[4] Conti *et al* identified 86 new PrCa-associated SNPs from multiethnic GWASs,[12] with European populations having a PrCa relative risk (RR) of 11.65 in the top 1% of PRS (demonstrated in table 1). Chen *et al* identify specifically nine novel variants in those with African ancestry and describe a 3.19-fold risk of PrCa for those of African ancestry in the top decile PRS, and a 5.75-fold increased risk for those in the top 1% PRS.[18] This study highlighted S860X in *ANO7* (which is a prostate-specific gene) as a PrCa risk-associated variation that is unique to African ancestry PwPs. Chen *et al* also demonstrate that PRS association with PrCa risk was stronger in younger PwPs of African ancestry for those in the top PRS decile compared with middle PRS deciles (40%–60%), with ORs 4.13 in those <55 years compared with ORs 2.69 in those >55 years.[18] They also report that PRS showed stronger association with aggressive disease (ORs 3.95) than non-aggressive disease (ORs 3.08) for PwPs in the top PRS decile compared with middle deciles (40%–60%).[18] Furthermore, subgroup analyses of these multiancestry PRS were positively associated with high-grade (Gleason Score >8), advanced (stage III or IV), metastatic or fatal disease.[18]

Risk from rare variants

Rare susceptibility variants are found in fewer than 1%–2% of PwPs and are autosomal-dominant DNA-repair gene variants or mismatch repair (MMR) variants. Although they contribute to a smaller proportion of the genetic predisposition, they are now numerous and important for considerations for prognosis and treatment. We have therefore summarised this in a summary table (table 2). It is known that 10%–15% of advanced PrCas have a constitutional pathogenic variant that is likely to be causative,[4 19] with up to 25% in somatic samples from metastatic castration resistant PrCa (mCRPC).[4 19–21] Some variants in DNA-repair genes in PrCa are associated with a more aggressive phenotype with higher risk of metastatic progression[21 22] and an earlier age of death from PrCa.[23]

Nicolosi *et al*[24] studied 3607 men with PrCa and 17.2% had a pathogenic germline variant when tested with a 14 gene panel. Berchuck *et al* identified that 9.5% of 201 PwPs with high-risk localised PrCa had DNA-repair gene variants, with the most common being *BRCA2* (3%) and *ATM* (2%).[25] Lee *et al* investigated prevalence of pathogenic variants in DNA-repair genes in 1588 patients with localised PrCa,[26] revealing 3.5% of cases had a constitutional DNA-repair gene variant and these were associated with node-positive disease and Gleason Scores 9–10.[26] When the probands were stratified by European (n=1174) or African (n=351) ancestry, pathogenic variants in DNA-repair genes were found in 4% and 1.4%, respectively.[26] The most frequently seen variants were in *BRCA2* in the European ancestry cohort and *FANCA* in the African ancestry cohort.[26] The authors concluded that germline variants are not the cause of worse outcomes for PrCa in those with African ancestry. Giri *et al* convened a consensus conference which recommended germline testing in men with metastatic PrCa or a family history of PrCa.[27]

Studies show PRS can be used to quantify risk in conjunction with rare DNA-repair gene variants. Lecarpentier *et al* described PrCa risk by age 80 years at the 5th and 95th percentiles of PRS, with risks of 7% to 26%, respectively in *BRCA1* variant carriers and 19%–61% in carriers of the *BRCA2* variant.[9] This was replicated in 2022 by Barnes *et al* with corresponding figures of 34.1% and 87.6% risk by age 80 years in 5th and 95th percentiles for *BRCA2* variant carriers.[28]

In 2023, Darst *et al*[29] published further data to support evidence that in European populations deleterious variants in *BRCA2* and *ATM* are associated with more aggressive PrCa. *BRCA2* variant carriers had a 7.5-fold risk of aggressive PrCa compared with non-aggressive PrCa, and PwPs carrying deleterious alleles in any of the DNA-repair genes analysed had a twofold risk of their PrCa progressing to lethal disease. Castro *et al* demonstrated patients with *BRCA1/2* variants were more likely to have metastatic PrCa at diagnosis and reduced survival compared with PrCa in non-carriers (8.6 years vs 15.7 years).[30]

Darst *et al* in 2021 looked at 3568 PrCa cases from 81 094 PwPs in the UK Biobank, finding that absolute risk of PrCa for *HOXB13, BRCA2, ATM, CHEK2* carriers of rare/likely pathogenic and deleterious variants ranged from 9% to 56% compared with non-carriers (2% to 31%) by age 85 years in the lowest and highest PRS deciles, respectively.[31]

A review of 150 biopsies from patients with metastatic PrCa found rare variants in 23%, of which 8% were constitutional.[32] Pritchard *et al* recruited 692 patients with metastatic PrCa, 11.8% of which had constitutional DNA-repair gene variants with frequencies of 5.3% *BRCA2*, 1.9% *CHEK2*, 1.6% *ATM*, 0.9% *BRCA1*, 0.4% *RAD51D* and 0.4% *PALPB2*[33]. There was reduced constitutional prevalence of these variants in localised PrCa, 4.6% in 499 patients.[33] Of those with tumour tissue available for somatic testing, 67% of tumours had second allele inactivation, indicating the constitutional variants contributed to their PrCa.[33]

DNA-repair genes

The DNA-repair genes detailed in table 2 have been associated with an increased risk of PrCa. It is notable that the risk estimates are broad; pathogenic variants in these genes are rare and the data detailing risk have been gathered from various studies in different cohorts of people with different risk profiles. There appears to be a cohort effect, given the general population born after 1960 in the UK have a PrCa lifetime risk of 18%.[2] The strongest link with inheritable PrCa is seen with *BRCA2* variants.

GENETIC TESTING AVAILABILITY ON THE NHS

The UK Cancer Genomic National Test Directory outlines eligibility for genomic testing funded by the NHS. The directory was updated in June 2023 to include two new testing panels, R444 and R430. R444 is prostate tumour testing for *BRCA1/2* only to determine eligibility for poly ADP ribose polymerase (PARP) inhibitor (PARPi) treatment. R430 is a constitutional panel where a germline variant is suspected—the details of both panels are detailed in table 3.[34] There is some overlap between R430 and other hereditary cancer testing panels, for example, R208 and R210 which are used to test for homologous

Table 2 DNA repair and DNA damage response genes associated with increased risk of prostate cancer (PrCa)

Gene	Function of gene	RR/OR/disease evolution	Research notes
BRCA2	Tumour suppressor, involved in homologous recombination, G2 checkpoint control and resistance to DNA damage[81]	Risk by age 65 years 2.5-fold to 8.6-fold (constitutional variant)[21] Earlier age of diagnosis[82 83] More aggressive disease[82 84] Lifetime risk of PrCa with this variant is 40%[9]	Most common DNA-repair variant seen in PrCa.[21] The results from the first round of the IMPACT Study (https://clinicaltrials.gov/ct2/show/NCT00261456) (prospective study looking at PSA testing in PwPs aged 40–69 years with *BRCA1/2* variants vs non-variant carrier controls) found that the positive predictive value of biopsy in *BRCA2* variant carriers with PSA >3 ng/mL was 48%—twice that reported in population screening studies.[73 85 86] Of the tumours detected, 66% were intermediate or high-risk with a significant difference in tumour detection rates in the *BRCA2* cohort compared with controls.[85] This supports targeted screening for *BRCA2* variant carriers which is now a European Association of Urology (EAU) guideline.
BRCA1	Tumour-suppressor gene essential to chromosome stability with similar function to that of the *BRCA2* gene[87]	RR 1.8-fold to 3.5-fold that of the general population[22 84 88] Lifetime risk of PrCa is 20%[9] Standardised incidence ratio (SIR) at age <65 years is 3.57 in the paper by Nyberg *et al*[16]	Interim results from the IMPACT Study found no significant difference in disease stage or age of diagnosis in *BRCA1* carriers versus controls and further follow-up is ongoing.[73] Nyberg *et al*[16] conducted a prospective analysis of PrCa risk in *BRCA1* carriers which along with *BRCA2* data will be included in the CanRisk Score for PrCa (Antoniou *personal communication*).
ATM	Tumour-suppressor gene involved in DNA repair and inducing apoptosis[89]	OR for PrCa 2.18 has been seen in an Icelandic study[90] PRACTICAL consortium found an OR of 4.4 [86]	The age of onset has been reported to be younger at below 65 years.[86] Variants in this gene have also been linked to more aggressive disease.[91] *ATM* is the second most commonly mutated DNA damage response gene seen in PrCa.[21]
CHEK2	Tumour-suppressor gene that encodes CHK2 serine-threonine kinase protein, inducing cell cycle arrest in the case of DNA damage[92]	OR 1.8–8.2[91]. Cybulski *et al*,[93] Leongamornlert *et al*,[83] Wu *et al*[94] and Shi *et al*[95] detail variants in this gene and their PrCa associations	Most of these risk data relate to the 1100delC[96] variant and originate from Poland,[21] though other variants in *CHEK2* have also been implicated in aggressive disease and found in higher frequency than 1100delC.[83] Brandão *et al* reported a significantly higher prevalence of constitutional variants in the *CHEK2* gene in metastatic than in localised PrCa, interestingly with no association with age at diagnosis or family history.[91]
PALB2	Codes for a binding protein involved in the *BRCA* complex essential for DNA homologous recombination repair[97]	OR 3.5[91 98] Associated with more aggressive disease[33]	Deleterious *PALB2* variants have been linked to PrCa and seen frequently in Polish cohorts.[99] Biallelic loss of function leads to Fanconi anaemia, though heterozygosity is linked to increased risk of pancreatic and breast cancer.[100] Studies looking at breast cancer identified this gene as being linked to their relatives developing prostate cancer, but the evidence was poor.[101] Only recently have *PALB2* variants been associated with aggressive disease, and PARP inhibitor sensitivity has been noted in *PALB2* mutated cancers.[102 103]
MSH2, MSH6	MMR genes repair errors in DNA replication. Failure of MMR results in point deletions or microsatellite instability[104]	2-fold to 10-fold PrCa RR and aggressive disease linked to younger age of diagnosis associated with tumours containing a variant in *MSH2*[105–109]	The IMPACT Study provided the first prospective screening study for PwPs with pathogenic variants in the MMR genes, which published initial findings in 2021.[85] The IMPACT Study results demonstrated a larger positive predictive value for prostate cancer detection on biopsy in those with PSA >3 ng/mL in the high-risk cohort than the control cohort; 51.4% vs 32.1%, respectively.[85] The IMPACT Study found incidence of PrCa is higher among carriers of *MSH2* and *MSH6*, but not *MLH1*[85]. There were no data on *PMS2*.
NBS1/NBN	The Nijmegen Breakage Syndrome 1 (*NBS1*) gene is involved in the double-strand DNA break repair complex[110 111]	A founder variant in this gene (c.657del5) has been associated with a threefold increased risk of prostate cancer below the age of 60 years, and a fourfold increased risk for PwP carriers with a positive family history[91]	The gene is associated with more aggressive and lethal disease and is commonly found in Slavic populations.[93] Cybulski *et al* found significantly increased mortality with 5-year survival reducing to 49%, compared with 72% in controls. They also found that heterozygous carriers were associated with increased PrCa risk.[93]
Other genes associated with prostate cancer:			
HOXB13 G84E	This gene encodes for the transcription factor homeobox B13, important in prostate development.[112] Expression of HOXB13 is restricted to the prostate, where it functions as an androgen receptor repressor and potent transcriptional regulator to modulate androgen receptor signals[113]	Kote-Jarai *et al* in UK data[114] — 2.93-fold increase in PrCa risk, up to 4.53-fold with family history. Nyberg *et al* — Carriers of the G84E variant have an RR of 5.96 (born after 1930) lifetime risk of PrCa by age 85%–60% (no positive family history) and 98% (two relatives diagnosed at a young age), compared with 15% in the general population. Darst *et al*[31] X285K deletion — OR 2.4-fold and observed more aggressive and advanced disease. OR 5.1 in those with metastatic PrCa	The G84E variant in *HOXB13* has been observed to be 20 times more prevalent in people with PrCa than controls and significantly more common in those with a family history of early onset PrCa.[115] G84E is a missense and founder mutation found more commonly in Nordic populations and has almost exclusively been found in European people. Kote-Jarai *et al* calculated PRS for PrCa using the 71 SNPs associated with the disease and the *HOXB13* G84E variant, which act multiplicatively on risk. According to these estimations, this rare variant explains ~1% of the familial risk of PrCa in the UK population. Recently, a rare African ancestry–specific constitutional deletion variant in HOXB13 (rs77179853) which removes the stop codon (X285K) and elongates the HOXB13 protein, was observed.[116] Allele frequencies ranged from 0% to 0.26% in Black African ancestry controls from North America, the UK and France, likely due to the high degree of European admixture in these populations. The *HOXB13X285K* variant was found to be significantly associated with a 2.4-fold increased PrCa risk.

IMPACT, Identification of Men With a Genetic Predisposition to Prostate Cancer Study; MMR, mismatch repair; PARP, poly ADP ribose polymerase; PRACTICAL consortium, The Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; PSA, prostate-specific antigen; PwP, people with prostates; RR, relative risk.

recombination repair (HRR) variants in those with a strong family history of breast and ovarian cancer (*BRCA1/2*, *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D*) and inherited MMR deficiency (Lynch syndrome) (*EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*), respectively.[34]

Panel testing for somatic variants in *TMPRSS2-ERG*, *NTRK1*, *NTRK2*, *NTRK3* is available on the NHS for PrCa but is only required if there is a doubt over the aetiology of a tumour.[34]

For people without a diagnosis of PrCa, genomic testing is still advocated by the NHS Genomic Medicine Service in cases where people are deemed to be at high risk of developing PrCa (see online supplemental table for eligibility criteria in the UK and USA).[35 36] Based on Nyberg *et al*[37]—currently the Manchester Score is used in the absence of PrCa data in CanRisk for determining if people are eligible for testing based on the likelihood of identifying a pathogenic variant in *BRCA1/2*. CanRisk is being

Table 3 Genetic testing panels available on NHS England—R444 and R430

Panel	R444	R430
Eligibility criteria on the NHS	Metastatic castration resistant PrCa	► Proband diagnosed with PrCa below the age of 50 years ► Ashkenazi Jewish Heritage with PrCa at any age ► Proband diagnosed with metastatic PrCa below the age of 60 years ► Proband diagnosed with PrCa with a family history of cancer where estimated likelihood of identifying a pathogenic variant in the relevant target genes is at least 10% (using the CanRisk tool[18]) ► Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist multidisciplinary team (MDT) meeting with a cancer geneticist present
Somatic (tumour tissue)	Yes	No
Constitutional	Only if somatic testing failed/ insufficient tumour sample	Yes
Genes tested	*BRCA1, BRCA2*	*BRCA1, BRCA2, MLH1, MSH2, MSH6, ATM, PALB2, CHEK2*
Purpose	Primarily eligibility for olaparib	Risk stratification

PrCa, prostate cancer.

adapted to incorporate PrCa into its risk prediction, using the Nyberg calculations for PrCa from the 2020 paper (Antoniou *personal communication*) based on UK data.

General management of PrCa

There is a range of management options for PrCa extending from AS to local radical treatment with surgery/radiotherapy/other focal therapies through to an increasingly longer list of options for those with metastatic disease.

As testosterone encourages prostate growth, by blocking testosterone production (in testes, adrenal glands and prostate tissue) and blocking testosterone receptors (in tissues around the body), prostate growth and symptoms from PrCa can be reduced. People diagnosed with PrCa are given androgen deprivation therapy (ADT), antiandrogen therapy or androgen synthesis inhibitors. The tumour cells initially respond to this type of therapy, but over time they can evolve to be 'castration resistant' and the disease progresses despite suppressed testosterone levels.

Individuals diagnosed with low risk, localised (disease confined to the prostate), unilateral PrCa of Gleason Score <3+4 (with small % pattern 4) and clinical stage T1–T2a, are monitored under AS without giving interventional treatment. For the first year postdiagnosis they receive 4-monthly PSA blood tests and repeat magnetic resonance imaging (MRI) in 1 year; if there has been no progression of disease, they receive 6-monthly PSA follow-ups thereafter. A consistent rise in PSA will trigger a repeat MRI and/or biopsy.

In localised, low-risk to intermediate-risk PrCa, with Gleason Score <7 and stage <T2b, standard treatment is radical radiotherapy or prostatectomy. Focal therapy is a treatment option; The National Institute for Health and Care Excellence (NICE) have approved high-intensity focused ultrasound.[38] Irreversible electroporation (known as NanoKnife), laser and cryotherapy are other options which have lower side effect profiles than radical therapies and are better tolerated by patients,[39] but they have higher recurrence rates and are not available with the NHS unless they are part of clinical trials in specialised centres.[40]

Radical prostatectomy (RP) (surgical removal of the whole prostate) is a curative treatment option for localised PrCa. External beam radiotherapy is also a treatment option for localised PrCa. The 'Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy' (STAMPEDE) trial found that radiotherapy to newly diagnosed PrCa improves overall survival compared with no radiotherapy, without detriment to quality of life compared with ADT and docetaxel (if indicated) alone.[41]

In the context of metastatic disease, we use terms metastatic hormone sensitive PrCa (mHSPC) or mCRPC in the case of hormone resistance. Approximately a third of PrCa cases treated with curative surgery or radiotherapy will experience recurrence and once PrCa is metastatic it is incurable.[42]

Locally advanced PrCa or PrCa at high risk of metastasis (disease spread to outside the pelvis) is often treated with taxane chemotherapy, such as docetaxel first line and cabazitaxel second line. Platinum chemotherapy (carboplatin) has been licensed for use in the NHS for palliative PrCa—shown to extend progression-free survival (PFS) when disease has progressed through all other treatment lines.[20] Radiotherapy or surgery is reserved for localised disease only, though metastatic lesions may receive radiotherapy/CyberKnife, such as those impinging the spinal cord. Radium-223 dichloride and lutetium 177 prostate specific membrane antigen (PSMA) are radioactive treatment options for bone metastases and tissue metastases, respectively. Increasingly, targeted agents are being considered in PrCa treatment as later lines of systemic treatment. The only one licensed at present on the NHS is olaparib for PrCa with *BRCA1/2* mutation.

Role of genetic predisposition in PrCa management

Genetic predisposition is increasingly being incorporated into oncological care and in PrCa management. The evidence detailing the interplay between genetic constitution and PrCa treatment options is summarised in figure 2.

Castro *et al*[22] found that in 1302 people with PrCa, 67 were carriers of constitutional *BRCA1/2* pathogenic variants, had higher T Scores, higher Gleason Scores, more frequent nodal involvement and developed metastasis sooner, with a shorter 10-year survival (50% *BRCA* carriers alive at 10 years vs 84% in non-carriers). Constitutional pathogenic variant status is starting to be used to guide treatment of PrCa but is still based on small data sets.

In *BRCA1/2* or *ATM* pathogenic variant carriers, radical treatment is preferred over AS, as there is a higher chance of tumour upgrading on re-biopsy when on the AS pathway.[4] Carter *et al* investigated the rate of reclassification (those on AS whose disease progresses) in *BRCA1/2* and *ATM* carriers, revealing a hazard ratio (HR) of 1.96 for carriers to reclassify under AS.[14]

Castro *et al* demonstrated that *BRCA1/2* pathogenic variant carriers have an HR of 2.36 for metastatic recurrence in the 10-year post-RP or external beam radiation therapy.[22] However, Castro *et al* also showed that there was no difference in recurrence after RP between *BRCA1/2* variant carriers and non-carriers, but after radiotherapy for localised disease, all the pathogenic-variant carriers had relapsed by 5 years.[22] Ahmed *et al* looked at those receiving radiotherapy and used data from GWAS, finding no association between individual SNPs and 2-year postradiation toxicity.[43] The 'Analysing Outcomes After Prostate Cancer

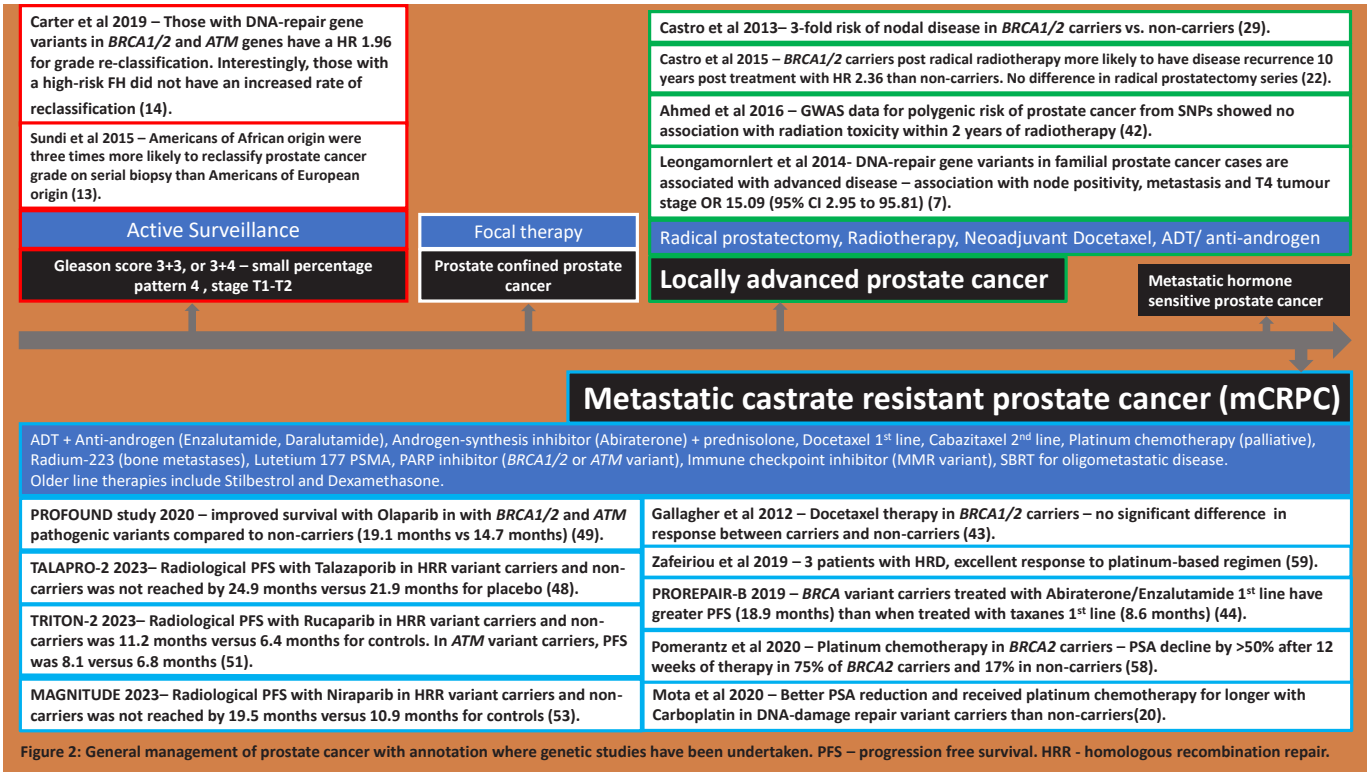

Figure 2 General management of prostate cancer with annotation where genetic studies have been undertaken. ADT, androgen deprivation therapy; FH, family history; GWAS, genome-wide association studies; SBRT, stereotactic body radiation therapy; HRR, homologous recombination repair; HRD. homologous recombination deficiency; MMR, mismatch repair; PARP, poly ADP ribose polymerase; PFS, progression-free survival. PROFOUND study, Study of Olaparib versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer; TALAPRO-2, Phase 3 study of talazoparib and enzalutamide versus placebo and enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer; TRITON-2, Study of Rucaparib in Patients with Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency; MAGNITUDE, Phase 3 study of niraparib with abiraterone acetate and prednisone as first-line therapy in patients with metastatic castration-resistant prostate cancer with and without homologous recombination repair gene alterations; PROREPAIR-B, Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients with Metastatic Castration-Resistant Prostate Cancer.

Diagnosis and Treatment in Carriers of Rare Germline Mutations' (GENPROS) study (https://clinicaltrials.gov/ct2/show/NCT02705846) will further evaluate treatment outcomes in pathogenic variant carriers with PrCa post-radiotherapy.

Gallagher *et al* found no significant difference in response to docetaxel in *BRCA* pathogenic-variant carriers versus non-carriers.[44] The 'Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients with Metastatic Castration-Resistant Prostate Cancer' (PROREPAIR-B) study suggested that PFS is longer in patients with mCRPC with pathogenic variants in *BRCA2* in first-line treatment with abiraterone/enzalutamide (18.9 months) than with taxanes (8.6 months).[45]

In the context of mCRPC, targeted therapies such as PARPi (olaparib) and immune checkpoint inhibitors (pembroliuzumab) are important emerging treatment strategies, in the context of pathogenic constitutional and/or somatic *BRCA1/2* variants, *ATM* variants[46] and MMR variants, respectively.

PARP inhibitors

PARPis inhibit the DNA-repair pathways of tumour cells, leading to apoptosis—especially in homologous recombination deficient cells due to synthetic lethality. Olaparib, a PARPi, has been approved by NICE in 2023 for the treatment of mCRPC in those with *BRCA1/2* variants, where the disease has already progressed on newer hormonal treatments (such as enzalutamide or abiraterone), docetaxel/cabazitaxel and radium-223 dichloride.[47] Trials have shown extended time until progressive disease and longer life expectancy overall compared with retreatment with abiraterone in combination with prednisolone (AAP) and enzalutamide.

Talazoparib, olaparib, rucaparib and niraparib have now been approved by The Food and Drug Administration (FDA) (USA) for patients with mCRPC who have pathogenic variants in HRR genes.[48]

The 'Phase 3 study of talazoparib and enzalutamide versus placebo and enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer' (TALAPRO-2) showed significant benefit in PFS in mCRPC with talazoparib. Median radiological PFS was not reached by 24.9 months in the talazoparib group versus 21.9 months for the placebo group,[49] even in non-carriers of HRR variants.[49]

The 'Study of Olaparib versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer' (PROFOUND) showed improved survival with olaparib in mCRPC with *BRCA1/2* or *ATM* variants—median overall survival 19.1 months versus controls 14.7 months.[50] These findings were consistent with those described by Mateo *et al* in phase III of the PROFOUND Study.[51]

Fizazi *et al*, in the 'Study of Rucaparib in Patients with Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency' (TRITON-2) study, analysed rucaparib

(PARPi) versus controls (docetaxel/abiraterone/enzalutamide) in patients with mCRPC and pathogenic variants in *BRCA1/2*.[52] At 62 months, median imaging-based PFS was 11.2 months in the rucaparib group versus 6.4 months in controls, with an HR of 0.50 (95% CI 0.36 to 0.69).[52] These findings were supported by Abida *et al* who assessed rucaparib in mCRPC. The objective response rates were similar for patients with a germline or somatic pathogenic variant in *BRCA1* or *BRCA2*, while a higher PSA response rate was observed in patients with a *BRCA2* variant.[53]

The 'Phase 3 study of niraparib with abiraterone acetate and prednisone as first-line therapy in patients with metastatic castration-resistant prostate cancer with and without homologous recombination repair gene alterations' (MAGNITUDE) assessed niraparib (a PARPi) and AAP in mCRPC with *BRCA1/2* pathogenic variants versus controls receiving AAP alone. Niraparib prolonged imaging-based PFS to a median of 19.5 months versus 10.9 months in controls.[54] Improvements in time to symptomatic progression and time to initiation of cytotoxic chemotherapy were observed with niraparib plus AAP.[54]

Some studies have looked at treatment outcomes with PARPis in people with variants in other HRR genes aside from *BRCA1/2*, with mixed results. A follow-on analysis in TRITON-2 looked at *ATM* variant subgroups, which showed median imaging-based PFS was 8.1 months in the rucaparib group versus 6.8 months in the controls (HR 0.95; 95% CI 0.59 to 1.52).[52] The improved survival with olaparib in people with *BRCA1/2* pathogenic variants seen in the PROFOUND study was also seen in people with *ATM* pathogenic variants.[50] The 'Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer' (TOPARP-B) showed that not all advanced PrCas with DNA-repair defects derive similar benefit from PARP inhibition.[55] Most benefit was seen among patients with biallelic *BRCA2* deletions, biallelic loss of *PALB2* and loss of *ATM* protein.[55] Loss of *RAD51* foci, evaluating HRR function, was found primarily in tumours with biallelic *BRCA1/2* and *PALB2* variants.[55]

Treatment with PARPi can also provide benefit to those with mCRPC without variants in HRR genes. TALAPRO-2 demonstrated prolonged survival in carriers of pathogenic variants in HRR genes and non-carriers alike with talazoparib. This benefit in non-carriers was also seen in the Phase 3 trial 'Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer' (PROpel) study by Saad *et al*, where overall survival was not significantly different between treatment groups in patients with mCRPC unselected for HRR status treated with olaparib with AAP versus controls receiving AAP alone.[56]

Immunotherapy

Immunotherapy such as immune checkpoint inhibitors (eg, pembroluzimab) can treat MMR-deficient PrCa. They do so by blocking the checkpoint proteins (programmed cell death ligand 1 (PD-L1) on tumour cell, programmed cell death protein 1 (PD-1) on T cell) from binding with partner proteins, preventing the tumour cell from evading the immune system by turning the T cell off, which allows T cells to kill cancer cells.[57] Immune checkpoint inhibitors are not approved yet by NICE for PrCa, however it has been considered previously by NICE—pembroluzimab treatment with enzalutamide and ADT for mHSPC[58] and also with olaparib for mCRPC. In the USA the FDA has approved immune checkpoint inhibitors for 'any solid tumour that is not able to repair errors in its DNA that occur when DNA is copied'.[57]

Platinum chemotherapy

Those with PrCa and pathogenic variants in *BRCA1/2* and other DNA-repair genes have shown increased sensitivity to platinum chemotherapy (carboplatin). The disease response is less significant in those without pathogenic variants in *BRCA2*.[59] Carboplatin has also extended PFS in palliative patients with PrCa[20] and is only licensed on the NHS for palliative PrCa. Pomerantz *et al*, in the largest study to date to assess the benefit of platinum chemotherapy in *BRCA2* carriers with mCRPC, found that PSA decline of >50% within 12 weeks of starting platinum chemotherapy for patients with mCRPC was 75% in *BRCA2* carriers versus 17% in non-carriers ($p<0.001$).[59] Mota *et al*[20] demonstrated how establishing genetic status regarding tumour/constitutional deleterious variants in DNA-repair genes was used as a biomarker for patients with mCRPC to receive carboplatin after disease progression with PARPi, which showed good disease response. Zafeiriou *et al* describe three case reports where mCRPC had excellent response to platinum-based regimens maintaining high quality of life—one patient with a mutational signature of HRR deficiency, one patient with *a BRCA* variant and one with an *ATM* variant.[60] The 'Use of Genetic Profiling to Guide Prostate Cancer Treatment' (BARCODE2) study (https://clinicaltrials.gov/ct2/show/NCT02955082) is investigating the PrCa response to carboplatin in those with mCRPC who have a constitutional pathogenic variant in a panel of 115 DNA-repair genes, and who have progressed through all lines of standard treatment, to provide data to support which specific DNA aberrations are linked to platinum sensitivity.[4]

Given up to 25% of PwPs with mCRPC have a constitutional genetic predisposition,[20] this approach to targeted treatment will be important as genetic testing becomes more widespread and the agents are licensed for this purpose.

Screening

There is no national PrCa screening programme in the UK or internationally, with two exceptions being Lithuania (since 2006) and Kazakhstan (since 2013). Although in PrCa with high Gleason Scores, PSA sensitivity is 80%–90%, it does not differentiate between indolent or progressive PrCa.[61] The success of screening depends on factors such as disease incidence, natural history and harms from overinvestigation and overdiagnosis.[62] There is great variation in overdiagnosis estimates in PrCa screening, which depend on the screening strategy (age range, frequency, modality of testing), investigation type and uptake, duration of follow-up, and methods of estimating overdiagnosis.[63]

In population screening, a test is provided to the whole population to identify the few who could have asymptomatic cancer. With risk-stratified screening, a subgroup of the population would be given the screening test—therefore fewer people would be screened while identifying the majority of the cancers present.

Screening with a PSA test alone cannot distinguish between clinically significant or indolent PrCa, which can result in unnecessary prostate biopsies, overtreatment (with potentially life-changing side effects of incontinence and erectile dysfunction) and psychological burden.[4] Some argue these harms outweigh the benefit of mortality reduction. There are now large data sets which report that PSA screening reduces mortality by about 20%. The European Randomised study of Screening for Prostate Cancer looking at 182 160 PwPs in eight European countries found that a PrCa RR of mortality at 16 years follow-up was reduced by 20% in those receiving PSA screening compared with controls.[64]

PRS use in risk-based screening

The limitations of PSA testing are reduced when it is targeted to higher-risk groups—such as in RBS. Usage in these cohorts awards PSA a higher positive predictive value.[65] PRS is an effective stratification tool to be used with factors such as age to identify those at increased PrCa risk in RBS, and we wish to highlight that PRS itself is not a screening but a stratification tool.

RBS has been demonstrated to be more cost-effective than age-based screening and leads to fewer cases of PrCa overdiagnosis and greater quality-adjusted life years (QALYs)[62 66 67] (see online supplemental figure 2). Callender *et al* examined the benefit-harm trade-offs and cost-effectiveness of RBS versus age-based screening and no screening—in a model of 4.48 million PwPs in the UK aged between 55 years and 69 years. Age-based screening was the least cost-effective strategy (even compared with no screening at all) but prevented the most PrCa deaths and resulted in 94 831 overdiagnosed PrCa cases. RBS (using a threshold of 4% 10-year absolute PrCa risk) demonstrated the greatest number of QALYs and led to a third fewer overdiagnoses (64 384) than age-based screening.[66 67] Though RBS averted 6.3% fewer deaths than age-based screening, RBS was considerably more cost-effective than age-based screening and this improved as the risk threshold increased.[66 67] Huntley *et al* modelled cancer detection rates for multiple tumour types in those in the corresponding top 20% PRS, including PrCa. Their modelled data echoed Callender *et al* with regards to cost-effectiveness and deaths averted of RBS compared with age-based screening.[62] However, their predicted rates of overdiagnosis were high, though we attribute this to the short follow-up time used in their modelling—as is the case with US Preventative Services Task Force and American Academy of Family Physicians, whose PrCa screening risk-benefit calculations are hampered with a 13-year follow-up, which assumes that additional benefit will not accrue over the person's lifetime.[63 68] Indeed, Shoag *et al* demonstrated that the number needed to screen and number of excess diagnoses falls with 25-year follow-up compared with 16-year follow-up.[63]

Pashayan *et al* showed that overdiagnosis in PrCa screening decreases with increasing polygenic risk, therefore overdiagnosis is reduced in targeted screening[69] (see online supplemental figure 3). [69]They calculated PRS for 17 012 PwPs aged 50–69 years in the UK, using 66 PrCa-associated SNPs. Of the 17 012 PwPs, 9404 had received a diagnosis of PrCa. Of those with PrCa, 48% were in the top risk PRS quartile. With a mean sojourn time of nine years, these individuals with PrCa in the top PRS quartile contained the smallest proportion of overdiagnosed cancers compared with the lower quartiles (19% top quartile, then 25%, then 30%, to 40% in the lowest quartile)[69]. Similarly, in a Finnish cohort Pashayan *et al* found 74% of PrCa cases occurred in those with a PRS above the population median, where overdiagnosis rates were 37% above and 58% below the PRS population median.[70] This supports screening for PrCa in those with higher polygenic risk.

For those in the top 5% of PRS for PrCa, Sud *et al* quote an absolute PrCa lifetime risk of 22.2% compared with 12.7% in the general population.[71] The BARCODE1 Study (https://www.clinicaltrials.gov/ct2/show/NCT03857477) is the first prospective study to examine PRS genetic profiling in primary care for PrCa RBS. Aiming to recruit 5000 PwPs of European ancestry from general practitioners in the UK, each participant provides a saliva-based DNA sample, from which the PRS is calculated using a panel of 130 PrCa risk SNPs. PRSs in the top 10% of the genetic risk distribution are invited to have an MRI and prostate biopsy. Those with negative screening tests continue annual PSA for 5 years.[72] This study is likely to report initial findings next year. Nyberg *et al*[37] predicted PrCa risk according to pathogenic variant status, PRS and family history (see online supplemental figure 4).

The Stockholm 3 (STHLM3) Study illustrates that using MRI and genetic risk in screening improves outcomes and screening efficiency, which is supported by Callender *et al*[67] (see online supplemental figure 5). It created a model for screening Swedish PwPs aged 50–69 years using plasma protein biomarkers such as PSA, free PSA and intact PSA. It also includes testing of 232 SNPs and clinical variables such as age, family history, previous prostate biopsy and prostate examination. They used this screening model on one cohort and PSA >3 ng/mL only on the comparison cohort. The results were that the STHLM3 screening model decreased overdiagnosis by averting 32% of prostate biopsies compared with the PSA-only arm and did not significantly decrease sensitivity of detecting high-grade disease (Gleason Score >7). It also detected 17% fewer clinically non-significant (Gleason Score <6) PrCa. Furthermore, when only performing a biopsy on those with both positive STHLM3 and MRI, a further 38% of biopsies were avoided with missing 8% of clinically significant PrCa compared with MRI alone. This indicates the accuracy of genetic screening for PrCa is improved when combined with other variables.

The 'Germline genetic profiling: correlation with targeted prostate cancer screening and treatment' (PROFILE) study (https://clinicaltrials.gov/ct2/show/NCT02543905) evaluates the use of PSA screening and prostate MRI in high-risk groups aged 40–69 years (family history and Black African or Black Caribbean ancestry). It has two arms, one has MRI and biopsy irrespective of PSA and one is a PSA-only arm with a threshold for biopsy of PSA >2 ng/mL in PwPs above age 50 years or PSA >1 ng/mL in the age bracket 40–49 years. The participants also have genetic testing and are assigned a PRS. Specific effort is made in recruiting PwPs of Black African and Black Caribbean ancestry to broaden our genetic data and understanding of PrCa in these ethnicities. The results will be published in the next couple of years.

Screening in carriers of rare constitutional genetic variants

Since 2014 the 'Identification of Men With a Genetic Predisposition to Prostate Cancer' (IMPACT) study has analysed targeted PSA screening in constitutional *BRCA1/2* pathogenic variant carriers. This was the first prospective study to use constitutional genetic markers for identifying PwPs with high risk of PrCa. The IMPACT Study extended in 2020 to include the MMR genes *MSH2, MSH6* and *MLH1*. Of note it was established in the pre-MRI era. A new suite of studies (the PROFILE studies) are now including MRI and are yet to report. The IMPACT study interim results published in 2019 show that targeted screening in *BRCA2* variant carriers from age 40 years detects more clinically significant intermediate or high-risk PrCa than age-based PSA screening alone.[73] The recommendation to screen all *BRCA2* variant carriers with annual PSA from age 40 years has subsequently been adopted by the European Association of Urologists[74] and is under consideration by the UK National Screening Committee (Eeles R and Bancroft E *personal communication*).

PRS can guide cancer screening in otherwise high-risk populations. Lecarpentier *et al* examined the effect of PrCa-associated SNPs in those with pathogenic variants in cancer predisposition genes (such as *BRCA1* and *BRCA2*).[9] Each *BRCA1/2* variant carrier was assigned a PRS to quantify their risk. The most notable difference in cancer risk was observed at the extremes

of PRS distribution—for example, *BRCA1* pathogenic variant carriers in the top 5% and bottom 5% of PRS had a 26% chance and a 7% chance, respectively, of PrCa by 80 years. Those with *BRCA2* pathogenic variants in the top 5% and bottom 5% of PRS had a 62% chance and a 19% chance, respectively, of PrCa by age 80 years.[9] Therefore, adding PRS into a genetic screen for people with high-risk variants could assist with counselling about cancer risks.

PRS and RBS may reduce health disparities in underserved populations compared with current screening programmes across the world. A risk-based approach ensures all PwPs at high risk are invited to screening, rather than relying on PwPs approaching their doctors themselves. Those who initiate a discussion around PSA screening for 'shared decision making' about the risks and benefits of PSA testing tend to be more educated and in a higher social demographic.[75] Ethnic minorities of African origin are at increased risk of PrCa but are less likely to seek PrCa screening due to barriers.[75 76]

Other benefits of PRS include predicting age of diagnosis;[77] for example, in the recent multiethnic paper by Wang *et al*, a PwP of Black African ancestry reaches the same level of PrCa risk at age 66 years as a PwP of European ancestry at age 80 years.[15] It is unknown whether this will result in behavioural change and is subject to research.

Where should we place the cut-off for screening in those with high PRS?

This is societal decision on risk threshold depending on the acceptable trade-off of benefit and harm of screening and cost-effectiveness, capacity and feasibility.

Sud *et al* present a figure to demonstrate the trade-off between cancer detection (multiple tumour types) and overdiagnosis.[71] They suggest overdiagnosis in PrCa screening is amplified by incorporating PRS, because the current variants identified are associated with PrCa incidence, not mortality.[71] However, other studies do not support this claim;[69] RBS screens fewer individuals than whole-population or age-based screening,[66] so RBS would generate fewer cases of overdiagnosis even if rates of overdiagnosis where equal in the top and bottom PRS quartiles. Furthermore, as aforementioned, predictions of overdiagnosis are made inaccurate with short follow-up time. Sud *et al* quote the sensitivity of PRS across a range of diseases as 10%–15%, but this is not reflective of PRS sensitivity in predicting PrCa risk. These figures were quoted from a preprint paper looking into 926 PRS across 310 diseases, of which only 25% are cancer and even fewer are PrCa. Nonetheless, this warrants the question, at what score do we set the cut-off to capture more disease cases (improve sensitivity) but screen fewer people without disease? In PrCa, it is a fine balance between capturing cancer cases and overdiagnosis.

Given the samples used to isolate cancer-associated SNPs from GWASs (which are used to generate PRSs) were mostly from European ancestry, PRS is a less accurate tool in people with non-European ancestry, most pertinent in PwPs of Black African ancestry. The science community is working hard to address this disparity and there are studies recruiting those from black African and Caribbean ancestries to genetic testing, as well as involvement projects to widen participation in genetic testing from underserved communities to reduce health disparities.

It has been suggested that PRSs could cause psychological distress for people awaiting their genetic results, or once they receive results if the meaning is not well explained. There is also concern that those who have a low PRS will disengage from future screening or ignore disease symptoms. Peck *et al* found that with poorer understanding of how to interpret individual genetic risk, psychological distress caused is increased when individuals are informed of their own genetic risk.[78] However, a study by Bancroft *et al* providing PRS to men with a strong family history of PrCa as part of a screening study did not find any indication of poor psychological outcomes or increased distress.[79] Therefore, effective communication from clinicians to patients and the media is vital and must be done well to avoid confusion and misinformation—notably referring to absolute risk in the context of general population risk.

The above limitations are all to be considered but should not discredit PRS use as a tool for risk stratification. And of course, the statistics for sensitivity and specificity are all derived from statistical modelling across a range of diseases—we need UK-specific randomised trials to quantify real world impact, costs and harms.[62] Overdiagnosis and subsequent harm can be reduced with risk assessment to tailor screening frequency and age range. Disease capture for high PRS is highest in more heritable diseases[62] like PrCa compared with other cancers.

DISCUSSION

The UK is a global leader in genetics and genomics.[80] The cost of sequencing is falling, making genomics quicker and more efficient to be incorporated into the clinician's arsenal.[80] The government initiative 'Genome UK -Future of healthcare' aims to create the most advanced genomic healthcare system in the world to deliver better outcomes at reduced cost. With this government support, clinicians in the UK have access to genetic testing as a clinical tool to aid early diagnosis and manage a range of diseases, notably cancer. Therefore, we should use this to our advantage—which requires awareness among healthcare providers and patients alike.

Identifying those who have a genetic predisposition to PrCa allows for those at higher risk to receive targeted screening. This achieves earlier diagnosis and enables targeted therapy in those diagnosed with locally advanced or metastatic PrCa. It also facilitates cascade testing for family members enabling targeted screening for other cancers associated with these genes.[4] Genomics also gives us the ability to reduce health inequalities, by improving health outcomes in underserved communities. However, to do this, we need to dissemble the barriers to genetic testing among these communities.

PRS has limitations as discussed, but so do many medical tools and this does not exclude PRS as a useful component to screening. Screening programmes are expensive and PRS may help stratify screening in the future. To optimise RBS we need to improve the benefit-harm trade-off, cost-effectiveness and equity of access.[17] The only data available on sensitivity and specificity of PRS-based screening is predicted from modelling analysis—therefore the results from prospective studies such as PROFILE and BARCODE will be important for healthcare policy.

In the future, cancer screening may become more accessible and efficient with the development of multicancer early detection tests, however these are as yet of low sensitivity, particularly for PrCa.

With treatments becoming licensed or under consideration by NICE which require genetic analysis prior to commencement, such as PARPis, immune checkpoint inhibitors and possibly also platinum chemotherapy—genetic testing is essential in the oncologist's toolkit for the treatment of PrCa.

Over the next few years studies will report if RBS incorporating genetic profiling will enable early detection of clinically

significant PrCa in PwPs from all backgrounds and ethnicities. This could reduce health disparities and harms from overdiagnosis, and ultimately improve quality of life and survival.

Contributors All authors contributed to this review and the original text, and reviewed the final manuscript. Figure 1 was made by coauthor ZK-J. Figure 2 and tables 1–3 as well as the supplementary table were made by RH. Supplemental figure 1 was created by Wang *et al*. Supplemental figures 2 and 5 were created by Callender *et al*. Supplemental figure 3 was created by coauthor NP and supplemental figure 4 was created by Tommy Nyberg *et al*. Permissions have been granted for use of the above figures.

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