Review

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Prostate cancer genotyping for risk stratification and precision treatment

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Abstract

Prostate cancer (PC) is the most frequently diagnosed cancer and second leading cause of cancer-related deaths in men. It is heterogeneous, as is evident from the wide spectrum of therapeutic approaches. Most patients with PC are initially responsive to androgen deprivation therapy; however, the majority of cases are either hormone-sensitive PC or castration-resistant PC. Current therapeutic protocols follow the evolution of PC, a continuously progressive process involving a combination of widespread genomic alterations. These genomic alterations are either hereditary germline mutations, such as mutations in *BRCA2*, or specific only to tumor cells (somatic). Tumor-specific genomic spectra include genomic structural rearrangements, canonical androgen response genes, and many other specific genes such as *TMPRSS2-ERG* fusion, *SPOP/FOXA1*, *TP53/RB1/PTEN*, and *BRCA2*. New evidence indicates the involvement of signaling pathways including PI3K, WNT/β-catenin, SRC, and IL-6/STAT, which have been shown to promote epithelial-mesenchymal transition cancer stem cell–like features/stemness, and neuroendocrine differentiation in PC. Over the last decade, our understanding of the genotype-phenotype relationships has been enhanced considerably. The genetic background of PC related to canonical genetic alterations and signaling pathway activation genes has shed more insight into the molecular subtype and disease landscape, resulting in a more flexible role of individual therapies targeting diverse genotypes and phenotypes.

Keywords: Prostate cancer; Prostate cancer treatment; Prostate cancer genomics; Hereditary prostate cancer; Androgen deprivation therapy; Hormone sensitive prostate cancer; Kinase signaling

1. Introduction

Prostate cancer (PC) remains the most common cancer in males and the second most common cancer overall in the United Kingdom, accounting for 14% of all new cancer cases.[1] Worldwide, 1.4 million cases of PC are diagnosed each year.[2] Incidence and disease stage distribution patterns follow a combination of biological, genetic, and lifestyle factors but are also influenced by national and international screening and diagnosis recommendations.[3] The Swedish survey on PC provides data on the economic burden thereof.[4] This prevalence-based PC registry study provides data on the societal costs of existing PC testing, diagnosis, management, and treatment of PC and additionally provides reference values for future cost-effectiveness analyses of PC screening and treatment. The analysis methods and data are relevant for cost-effectiveness evaluation of PC screening and treatment.

The epidemiology of PC includes several closely interrelated determinants, namely, geographic location; ethnic origin; sociocultural environment; dietary habits; personal lifestyle; natural aging process; consumption of and/or exposure to toxins, including smoking and alcohol; occupational hazards such as working with hazardous chemicals; and possible risks associated with radiation (Fig. 1).[5] In addition, genetic and genomic factors play a crucial role in the risk and pathogenesis of PC.[6] These might include somatic mutations in genes regulating prostate structure and function or part of the inherited predisposition segregating in either the Mendelian manner or complex polygenic mechanisms.[7]

Prostate cancer diagnosis remains a significant area of focus in clinical and laboratory-based research, with tools constantly evolving. The current tools available to clinicians include prostate-specific antigen (PSA) testing, prostate magnetic resonance imaging (MRI), and prostate biopsies,[3] and PC guidelines are available from the European Consortium.[8] These tools have been subjected to constant refinement, and recently, the PRECISION trial has demonstrated the use of MRI-directed targeted biopsies.[9] Furthermore, use of prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (CT) scans has been suggested to offer further enhancement of imaging modalities.[10–12]

However, the diagnostic conundrum still facing clinicians is genetic counseling and testing in both men with strong family histories and those in the wider population. Specific germline mutations can lead to aggressive PC development, particularly in patients with a family history of PC.[13] Apart from autosomal loci, several Y chromosome–linked genes are relevant for PC predisposition and growth. Y-chromosome PC genotyping may reveal specific genes (*BPY2*, *RPS4Y1*, *NLGN4Y*, *SMAD3*, and others), *DYZ* region mutations (DYS458, allele 12 of DYS393, and others), tumor suppressor genes (*KDM5D* and *MSY*), and several loci.[14]

Evidence supports the implementation of germline testing with concomitant genetic counseling,[15,16] and several commercial genetic screening tools are now available to assess germline mutations in genes that have been identified to increase the risk of PC. These include *BRCA2*, *ATM*, *CHEK2*, *BRCA1*, and *HOXB13*

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Figure 1. Risk factors for prostate cancer.

genes and carriers of *MSH2* mutation in the DNA-MMR genes.[17,18] However, their overall impact is yet to be ascertained, as published data suggest that germline *BRCA1* and *BRCA2* mutations occur in approximately 0.2% to 0.3% of the general population.[19,20] It is argued that most genetic factors are nonspecific and cannot be used on their own to accurately stratify patients with indolent versus more aggressive PC tumors.[21] It is imperative to use more sensitive and specific biomarkers that can predict and allow for the proper selection of patients at high risk of developing life-threatening PC.[22–24] The ultimate aim would be to plan and institute personalized and precision therapy for better outcomes, which may also prevent overtreatment in patients with low-risk PC.

In this article, the role and current clinical status of genomic and molecular biomarkers in PC treatment are reviewed with the aim of developing precision treatment. Although the emphasis is on medical therapy, some elements of personalized surgical management are also included.

2. Prostate cancer diagnosis and treatment

Current PC diagnoses, treatment recommendations, and protocols are available from various sources. The National Institute for Health and Care Excellence (www.nice.org.uk; NICE) produced an updated set of PC guidelines in 2021 (https://www.nice.org.uk/guidance/ng131/chapter/Recommendations).[23] However, there is still insufficient evidence from formalized population screening programs.[25,26]

2.1. Clinical diagnosis of PC

All informed men requesting an early diagnosis are offered a PSA test and undergo digital rectal examination (DRE).[24] Upon fast-track referral to a secondary care facility, multiparametric MRI is the first-line investigation for patients with suspected clinically localized PC, and the results are reported using a 5-point Likert scale. All patients with a Likert score of ≥3 should be offered the MRI-guided prostate biopsy.[27] Those with a multiparametric MRI Likert score of 1 or 2 could consider omitting prostate biopsy after discussing the risks and benefits and reaching a shared decision.[28] Alternatively, a CT scan can be performed in patients with contraindications to MRI. Additional factors to be considered are as follows:

- the patient's PSA level
- their DRE findings (including prostate size estimation)
- any comorbidities, together with their risk factors
- increasing age
- Afro-Caribbean ethnicity
- any history of a previous negative prostate biopsy

Additional tests, including an isotope bone scan, may be requested if aggressive PC is clinically suspected. However, sclerotic metastases can also be identified using plain radiography. All cases are discussed at a urological cancer multidisciplinary team meeting.[29] Even if a prostate biopsy is reported as negative, the NICE advises that a review of the risk factors of all people who have had a negative first prostate biopsy must be discussed. Factors that must be discussed include the following:

- There remains a risk that PC is present.
- The risk is slightly higher if any of the following risk factors are present:
  - the biopsy showed high-grade prostatic intraepithelial neoplasia,
  - the biopsy showed atypical small acinar proliferation, and
  - an abnormal DRE.

2.2. Risk stratification for localized or locally advanced PC

There are different options for risk stratification of local or advanced PC. One such approach is based on the current NICE (www.nice.org.uk) guidance in the context of all urological cancers. This is broadly similar to the National Comprehensive Cancer Network (NCCN)–recommended criteria based on serum PSA level and clinical tumor stage and grade, which define 3 major groups of localized disease based on the probability of biochemical recurrence after local therapy: low, intermediate, and high risk.[8,24] The NCCN risk classification for the high-risk category is further subdivided into favorable high-risk, standard high-risk, and very high-risk disease (Fig. 2).[30] In a later review, high-risk PC is further subdivided into 3 categories based on the Decipher genomic testing. This includes 2 additional categories: standard high risk and very high risk.[30,31]

The NICE guidelines[24] recommend that the urological cancer multidisciplinary teams assign a Cambridge Prognostic Group Criteria risk category to all people with newly diagnosed localized or locally advanced PC:

(1) Gleason score 6 (grade group 1) and PSA <10 μg/L and Stages T1–T2
(2) Gleason score 3 + 4 = 7 (grade group 2) or PSA 10–20 μg/L and Stages T1–T2
(3) Gleason score 3 + 4 = 7 (grade group 2) and PSA 10–20 μg/L and Stages T1–T2 or Gleason 4 + 3 = 7 (grade group 3) and Stages T1–T2
(4) One of Gleason score 8 (grade group 4), PSA >20 μg/L, or Stage T3
(5) Two or more of Gleason score 8 (grade group 4); PSA >20 μg/L; Stage T3 or Gleason score 9 to 10 (grade group 5) or Stage T4

2.3. Treatment options for localized or locally advanced PC

The NICE guidelines recommend evidence-based PC treatment according to the Cambridge Prognostic Group risk category (Table 1).

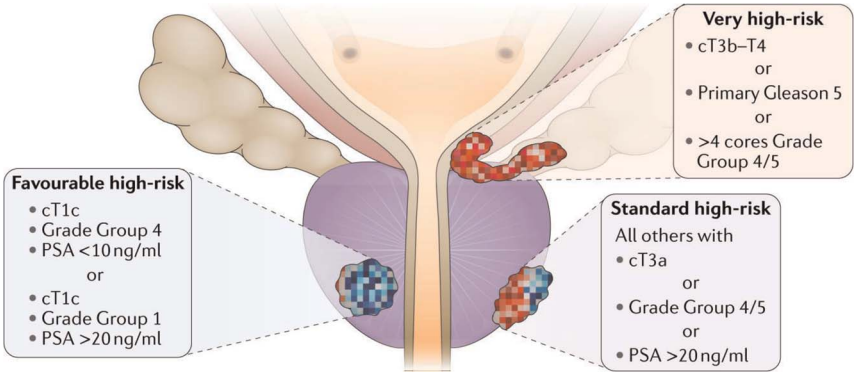

Figure 2. Heterogeneity of prostate cancer risk.[30] PSA = prostate-specific antigen.

The current NICE recommendations for active surveillance protocols in Year 1 include PSA testing at 3- to 4-month intervals and a DRE at 12 months with an MRI. In the second year, the NICE guidance suggests every 6 months serum PSA measurements and yearly DRE assessment. If there is evidence of disease progression in the active surveillance protocols at any stage, patients should receive radical treatment. In all cases, it should be explained to patients and, if they wish, their partner that radical treatment for PC will result in an alteration of sexual experience and may result in loss of sexual function. In addition, patients must be warned that radical treatment for PC could affect their urinary continence.

Important consideration should be given to people with localized CPG 4 and 5 and any man with locally advanced PC; in these situations, active surveillance should not be offered. However, patients with CPG 4 and 5 localized and locally advanced PC can be offered radical prostatectomy or radical radiotherapy with androgen deprivation therapy (ADT) when it is likely that the cancer can be controlled in the long term. The NICE recommends the use of docetaxel chemotherapy in specially selected cases of T3/4 PC that are to be managed long-term with ADT.[32]

2.4. Treatment options for metastatic PC

Evidence-based guidelines are available from leading urology organizations, including the American Urology Association (www.auanet.org), UK National Institute of Clinical Excellence (www.NICE.org.uk), and European Association of Urology (www.uroweb.org). Most recommendations are broadly similar for nonmetastatic, metastatic, hormone-sensitive, and castration-resistant PC. According to all guidelines, all patients should consider commencing ADT. In addition, all guidelines suggest offering docetaxel chemotherapy to patients with newly diagnosed metastatic PC who do not have significant comorbidities:

- start treatment within 12 weeks of starting ADT
- use six thrice weekly cycles at a dose of 75 mg/m^2 (with or without daily prednisolone)

Other options that may be offered include bilateral orchidectomy (as an alternative to continuous luteinizing hormone–releasing hormone agonist therapy). Patients with metastatic PC who are willing to accept the adverse impact on overall survival and gynecomastia, with the aim of retaining sexual function, are offered antiandrogen monotherapy with 150 mg of bicalutamide.

In cases with biochemical evidence of hormone-relapsed disease, an oncologist and/or specialist palliative care opinion is best sought where appropriate. In these situations, docetaxel is recommended if the Karnofsky Performance Status score is 60%.[33] After 10 cycles of docetaxel, if serious adverse effects occur, or if there is disease progression according to any criteria, docetaxel must be discontinued. The next step would be to offer a daily corticosteroid, such as dexamethasone (0.5 mg), as a third-line hormonal therapy after ADT and antiandrogen therapy in patients with hormone-relapsed PC. In men with hormone-relapsed metastatic PC, zoledronic acid should be considered to prevent or reduce skeletal-related events. These treatments can be combined with oral or intravenous bisphosphonates for pain relief in patients with hormone-relapsed metastatic PC when other treatments, including analgesics and palliative radiotherapy, do not provide satisfactory pain relief.[34,35]

Table 1

NICE guidelines for localized or locally advanced PC.[24]

CPG 1 localized PC	Offer active surveillance Consider radical prostatectomy or radiotherapy if active surveillance is not suitable or acceptable to the patient
CPG 2 localized PC, offer a choice between	Active surveillance Radical prostatectomy or radical radiotherapy, if suitable
CPG 3 localized PC	Offer radical prostatectomy or radical radiotherapy Consider active surveillance for patients who choose not to have immediate radical treatment

CPG = Cambridge Prognostic Group; NICE = National Institute for Health and Care Excellence; PC = prostate cancer.

3. Role of genetic and genomic factors in PC

Cancer is fundamentally a genetic condition involving 1 or more genetic factors that interfere with the molecular regulation of different stages of the cell cycle (Fig. 3).

Genetic factors predominantly control DNA synthesis (S phase) and cell growth (G2, mitosis, and G1). In most cases, genetic factors are nonspecific and are similar in many eukaryotes. However, these can be cell- or tissue-specific, with a predilection for a particular organ, such as neural components or endocrine glands. Understanding these complex molecular and cellular changes is the key to cancer diagnosis, progression, metastasis, and treatment.[36,37]

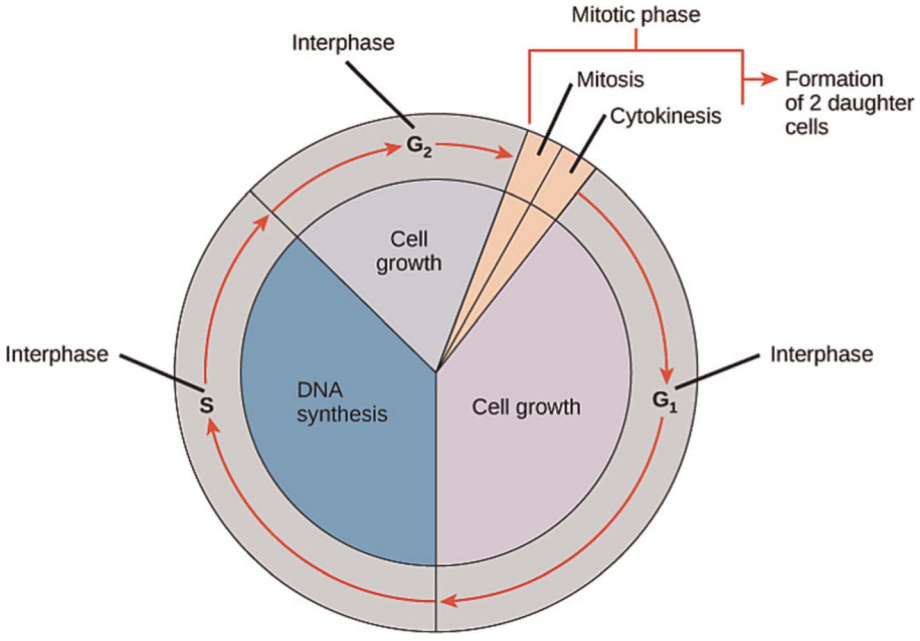

Figure 3. Schematic display of stages of the cell cycle. Source: OpenStax. https://cnx.org/contents/FPtK1zmh@8.25:fEI3C8Ot@10/Preface.

Genetic factors involved in cancer are heterogeneous and may include gross imbalances in genome structure, such as aneuploidy or copy number variations ranging from gain (insertion) to loss (deletion), commonly referred to as indels. Specific DNA sequence changes within an exon may result in chain termination (nonsense mutations) or alter the selection of amino acids for peptide synthesis (missense mutations). Sequence changes at the exon-intron splice site may also interfere with peptide synthesis by blocking transcription. Moreover, there are several RNA molecules that may interfere with the cell cycle.

Morbid genetic factors, or diseases that cause genetic changes, are inherited from one or both parents and are referred to as germline mutations. In contrast, mutations that are confined to a particular tissue are called somatic mutations (Fig. 4). Conceptually, this distinction is important when dealing with a family history of cancer. Most tissue-specific neoplasms carry somatic mutations except for small subsets with de novo or inherited germline mutations. Thus, it is imperative to identify germline mutations in tumors with somatic mutations. Germline mutations in certain genes, such as DNA repair genes, may involve different tissues in multiple organs, including the breasts, ovaries, and prostate.[38,39] Further, presence or absence of germline mutations may influence risk for distant metastasis or poor prognosis.

Several acquired and nongenetic factors are involved in cancer development and progression. These factors are diverse, including geographic location, dietary habits, adverse or extreme environmental habitats, occupational hazards, exposure or use of chemicals or drugs, hormonal changes, aging, and comorbidity (Fig. 1). Family history, although strongly influenced by inherited or genetic traits, may be limited to sharing nongenetic or acquired factors.

Although PC tumor genotyping provides insight into the molecular pathology, it cannot offer reliable predictions for very high-risk metastatic PC, particularly the risk of distant metastasis. Genome-wide studies, specifically genome-wide association studies, have led to the construction of morbid PC genome maps.[40] The karyogram (Fig. 5) provides a graphical display of the PC-associated gene density correlated with lifelong PC risk. Next-generation genome sequencing has enabled the identification of PC-specific genes, most of which are either involved in or regulated by complex molecular mechanisms in DNA repair.[41,42]

There are several molecular targets of PC (Table 2). These include genes, proteins, and other molecules involved in genomic instability or diversity, androgen receptors (ARs), signaling pathways, molecular subtypes, biomarkers, and cancer evolution.[43,44] The International Consortium for Prostate Cancer Genetics has identified a list of genes from PC genome-wide association studies

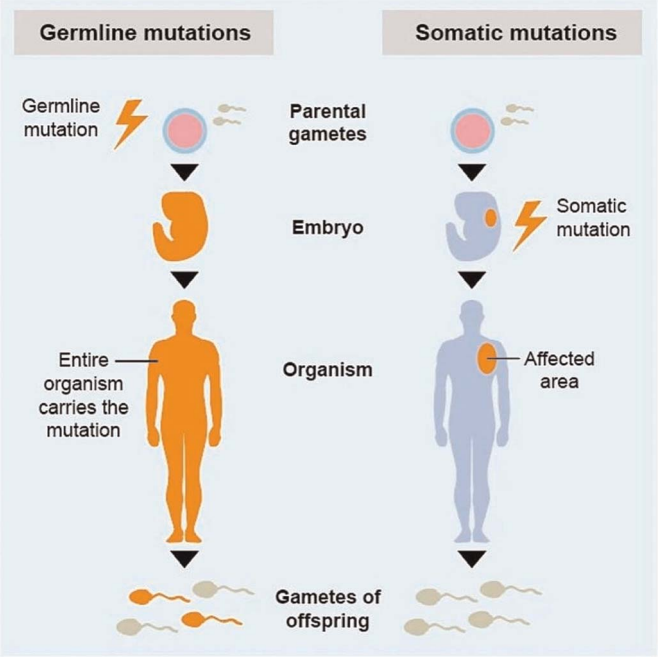

Figure 4. Fundamental difference between germline and somatic mutations (www.learn.colontown.org).

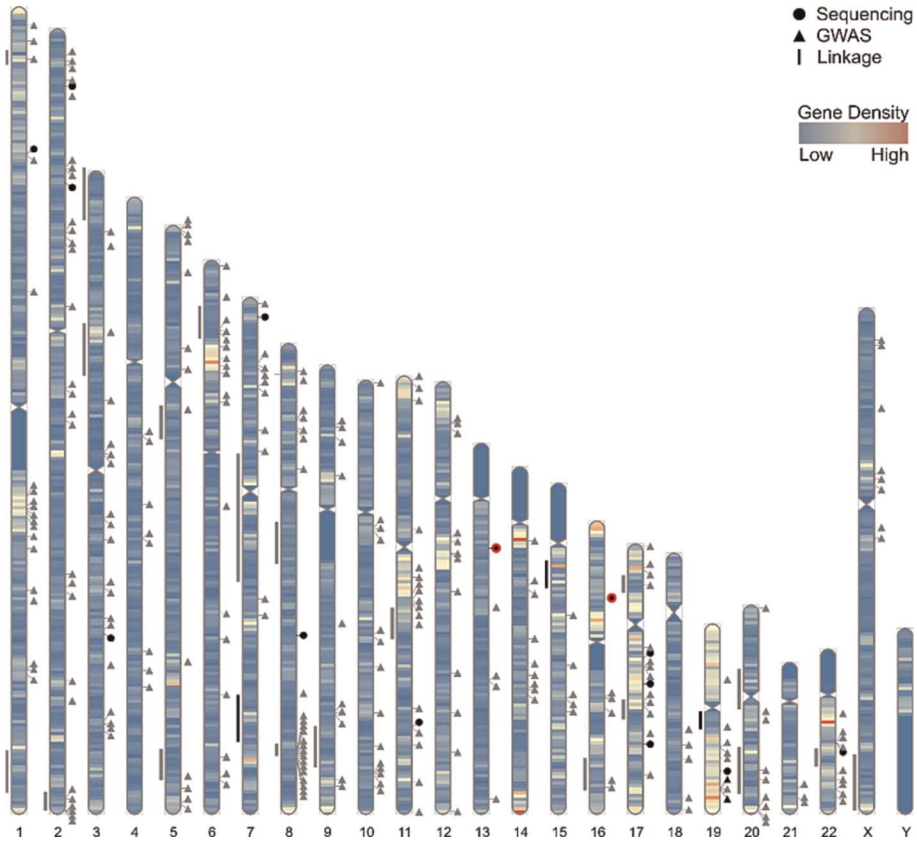

Figure 5. Karyogram showing the approximate genome mapping of candidate prostate cancer risk loci based on linkage, GWAS, and sequencing study analyses.[40] GWAS = genome-wide association studies.

data, some of which confer susceptibility to PC and/or poor prognosis (Table 3).[40]

4. Genotyping for PC risk stratification

Germline genotyping can reveal the level of lifetime PC risk (Table 4). The derived risk estimates thus derived are used for genetic counseling, particularly in the context of family history.[45] It is now recommended that men should be carefully selected for effective PC surveillance and prophylactic intervention.

The majority of moderate to severe PC genetic susceptibilities are correlated with mutations interfering with either DNA damage repair or damage response. In contrast, mutations in the *HOXB13* confer a higher risk of developing PC, probably through an AR repressor mechanism[46–48] (Fig. 6).

Table 2

Different molecular targets and genes in prostate cancer.

Genomic instability	Aberrations of AR, *TP53/PTEN*, *BRCA*
Androgen signaling	AR sensitive, AR mutations, AR independent, AR resistance, AR variants, AR loss
Signal pathways	CYP17, P13K, SRC, JAK/STAT/PGE2
Molecular subtypes	*ERG/SPOP/FOXA1PTEN/TP53/CHD1, AR-V7, DDR* genes
Biomarkers	PSA, DNA methylation, UBE2C, CgA/Syn/CD56
Cancer evolution	HSPC, AIPC, CRPC-Adeno, CRPC-NE

AR = androgen receptor; PSA = prostate-specific antigen.

Approximately 1 in 10 men with PC is likely to harbor mutations in one of the germline PC genes (Table 5; Fig. 7). The bulk of PC risk is associated with *BRCA2* followed by *ATM*, both of which are predominantly involved in DNA damage repair.[52,53] Delineation of genomic and molecular heterogeneity in PC has led to the widespread use of PC germline genotyping, particularly in metastatic PC. Approximately 12% of men with metastatic PC have inherited one of the DNA repair gene mutations compared with less than 5% of men with localized disease. DNA repair genotyping is relevant in the selection of men treated with olaparib for castration-resistant PC.[54]

Table 3

DNA repair genes associated with high-risk/poor-prognosis prostate cancer.

Gene	Chromosome
ATM	11
ATR	3
BRCA1	17
BRCA2	13
BRIP1	17
CHECK2	22
ERCC2	19
GEN1	2
MSH2	2
MUTYH	1
NBN	8
PALB2	16
PMS2	7
RAD51D	17

Table 4

The lifetime PC risk with selected genes associated with cancer family syndromes (www.prostatematters.co.uk).

Mutated gene	Increased lifetime risk of PC
BRCA1	7%–25%
BRCA2	19%–60%
HOXB13	33%–60%
Lynch syndrome	12%–52%
ATM and *CHEK2*	Moderate risk

PC = prostate cancer.

Genome sequencing analysis of the biopsy and blood samples of men with castration-resistant PC generated data supporting genotyping as a reliable tool for predicting distant metastases (Fig. 8).[51,55] The NCCN guidelines explicitly recommend PC germline genotyping as opposed to molecular biopsy (Table 6).

In the context of the genomic analysis of malignant PC, recent advances in molecular diagnosis of PC include the emerging role and clinical application of liquid biopsy.[56,57] This approach is considered most beneficial in the very early stages of PC, particularly in those with an aggressive course, and early diagnosis may allow for early treatment with favorable outcomes. This technique uses peripheral blood and other body fluids, such as urine and cerebrospinal fluid.[58] The peripheral blood analysis includes quantitative assays of circulating tumor cells and extracellular vesicles and nucleic acid sequence analysis (mutations or variants) of cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) (Fig. 9).[59] In addition to the ctDNA or cfDNA analysis, circulating RNAs, particularly microRNAs, are emerging as potential molecular markers in the clinical setting.[60] The liquid biopsy is a complex process performed in a limited number of laboratories. Briefly, various analytical approaches include enumeration and morphometric, protein, DNA, and RNA analyses (Fig. 9).

5. Molecular basis for novel PC therapy

Among the many molecular targets for PC therapy, the PSMA is an excellent target for both PC imaging and therapy.[9] Prostate-specific membrane antigen is involved in the PI3K/Akt pathway (Fig. 10)

Table 5

Summary of different gene mutations and the respective PC risk.

Gene	PC risk	Mechanism
ATM	Elevated	DNA damage response
BRCA1	~20%	DNA damage repair
BRCA2	~20%	DNA damage repair
CHEK2	Elevated	DNA repair through phosphorylation of *BRCA2*
EPCAM	Up to 30%	Upregulate c-myc
HOXB13	Up to 60%	AR repressor
MLH1	Up to 30%	DNA repair
MSH2	Up to 30%	DNA repair
MSH6	Up to 30%	DNA repair
NBN	Elevated	DNA repair
PMS2	Up to 30%	DNA mismatch repair
TP53	Unknown	Tumor suppressor
PALB2	Preliminary	Tumor suppressor
RAD51D	Preliminary	DNA repair

PC = prostate cancer.
Courtesy: American Urological Association.

and is a diagnostic biomarker and a potential therapeutic target, enabling a phenotypic precision medicine approach to guide patient selection for therapy in advanced PC.[12]

Prostate cancer inhibitors targeting PSMA and other kinase molecules are effective in treating both localized and metastatic PC. The use of PSMA inhibitors along with positron emission tomography/CT imaging has been shown to be effective in tailored precision PC therapy (Fig. 9).[61]

Liquid biopsy–based molecular profiling has rapidly modified PC therapy. Quantitative analysis of circulating tumor cells, particularly AR-V7 phenotyping, is helpful for delivering AR surface inhibitor therapy.[12] The cfDNA and ctDNA analyses are powerful tools for detecting AR and DNA damage repair genes. These mutations determine the outcomes of PC therapy using taxanes or poly (ADP-ribose) polymerase inhibitors.[13]

6. Discussion

Diagnosis of PC has been the subject of significant clinical and laboratory-based research, leading to the constant evolution of

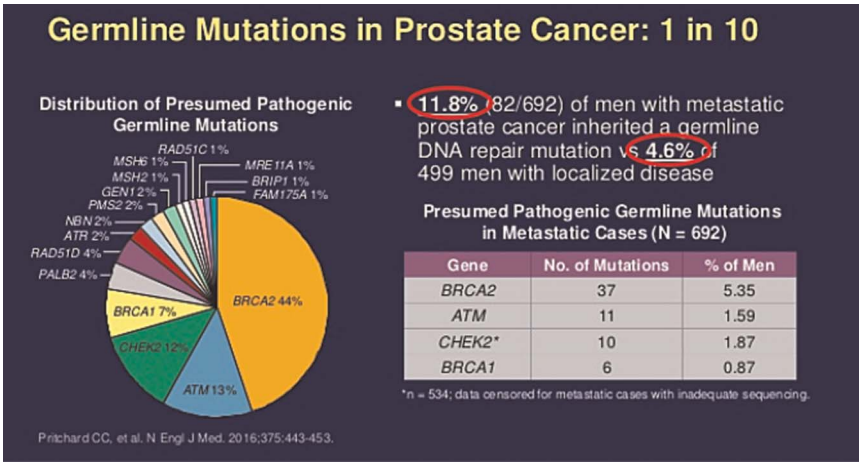

Figure 6. Genomic and molecular heterogeneity in prostate cancer. Reproduced from www.prostatematters.co.uk.[49,50]

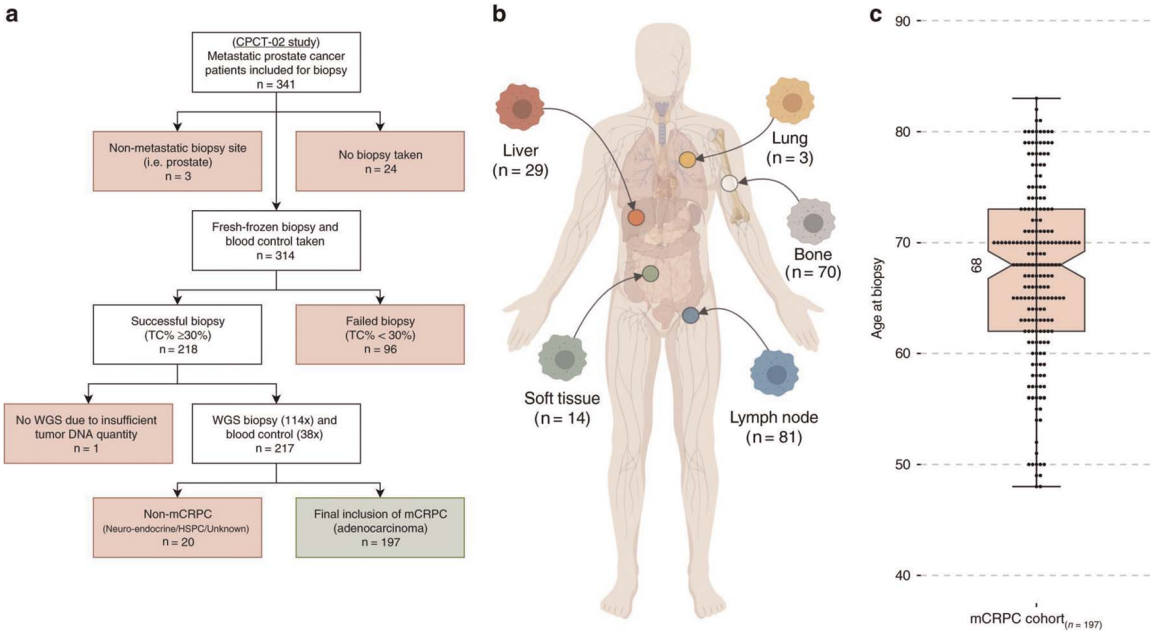

Figure 7. Genotyping in castration-resistant metastatic prostate cancer.[51]

clinical guidelines and evidence-based research. The ideal diagnostic pathway is a streamlined, individual patient-focused protocol that allows busy clinicians to use a validated, reliable, and reproducible method to diagnose and determine the risk of PC.

Over the past few decades, much of the evidence has evolved and stemmed from the use of clinicopathological data, such as those utilized by the PREDICT prostate trial. Cancer-specific and overall survival data from the PREDICT Prostate trial have been endorsed by the NICE, as they provide up to 15 years of data.[62] However, these data typically involve available clinicopathological data (age, PSA level, grade, stage, biopsy involvement, treatment types, and comorbidities).[63] Furthermore, PREDICT does not include the impact of a family history of PC or the role of genetic factors. The NICE recognizes the role of family history as a risk factor for PC.[24] Patients are at a higher risk if they have a close relative, such as a brother or father, with PC. It is estimated that approximately 5% to 10% of PC cases have a substantial inherited component.[14,15]

The NICE therefore acknowledged the significance of a meta-analysis reporting a pooled relative risk (RR) of 2.48 in men with 1 first-degree relative (brother or father) with PC compared with no first-degree family history. The risk was higher if the first-degree relative was a brother (RR, 3.14) rather than a father (RR, 2.35). An RR of 4.39 was reported in men with 2 or more first-degree relatives with a history of PC.[16,17] In addition, strong predisposing genes could be responsible for up to 40% of cases in men up to the age of 55 years.[18,19] For example, a recurrent *HOXB13* G84E germline mutation has recently been shown to be significantly associated with an increased risk of PC and is significantly more common in men with early-onset familial disease.[20,21] It can therefore be hypothesized that the diagnostic conundrum in patients with a strong family history will not be fully evaluated unless genetic counseling and molecular testing are incorporated into future guidelines. In addition, previous reports have shown that patients with hereditary PC are diagnosed 6 to 7 years before spontaneous cases, indicating that younger age at diagnosis plays a role.[15] The underlying genetic mechanisms of hereditary PC have now been established as several PC-specific germline and somatic mutations, particularly in *HOXB13* and *BRCA2* (Table 7). A recurrent *HOXB13* G84E germline mutation is significantly associated with an increased risk of PC and is significantly more common in men with early-onset familial disease.[47] Germline mutations associated with other cancers (such as those in *PTEN* and *BRCA1*) are also associated with an increased risk.[64] The link between PC and a family history of breast cancer, specifically due to the *BRCA1* and *BRCA2* gene mutations, has been established.[22,23] Clinicians need a low threshold to investigate PC risk in men with a family history of breast cancer.

Ultimately, this raises the question of whether there is a role for genetic testing, but how, when, and for whom have yet to be

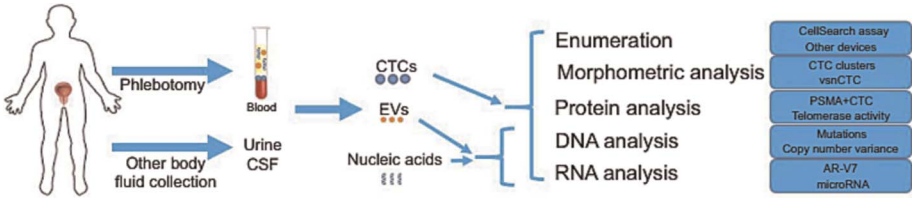

Figure 8. Schematic overview of liquid biopsy molecular profiling in prostate cancer.[5]

Table 6

NCCN definition of both high-risk and very high-risk prostate cancer.

Risk group	Clinical/pathological features	Imaging	Germline testing	Molecular/biochemical analysis of tumor
High	No very high features and 1 high-risk feature: T3a OR Gleason 4 or 5 OR PSA >20 ng/mL	Bone scan Pelvic ± abdominal imaging	Recommended	Consider if life expectancy >10 yr
Very high	At least one of the following: T3b–T4 Primary Gleason 5 2–3 high-risk features >4 cores with grade 4 or 5	Bone scan Pelvic ± abdominal imaging	Recommended	Not routinely recommended

NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.
Courtesy: Christopher J. D. Wallis, University of Toronto Twitter: @WallisCJD during the 2021 American Urological Association Annual Meeting; September 10–13, 2021.

established. Although several commercial genetic screening tools are now available, further work is needed to ascertain which of the germline mutations in genes increasing the risk of PC should be tested. As discussed, germline *BRCA1* and *BRCA2* mutations occur in approximately 0.2% to 0.3% of the general population, and their impact on the diagnosis of blood relatives with PC needs further research. However, these factors are nonspecific and do not accurately distinguish patients with indolent PC tumors from those with more aggressive tumors. Thus, it is imperative to use more sensitive and specific biomarkers that can predict and allow the proper selection of patients at high risk of developing life-threatening PC.

The overriding aim should be to plan and implement personalized and precision therapies to achieve better outcomes. Similar strategies may also prevent overtreatment in patients with low-risk PC. This review suggests that comprehensive PC tumor and blood genotyping should be included in PC stratification for targeted treatment, prognostic prediction, long-term surveillance, and effective prophylaxis. Several commercial panel kits for PC genotyping are available (Table 7). In the future, the scope of whole-genome sequencing will likely increase with the development of annotated cancer genome databases. Prostate cancer remains on the priority list of the International Cancer Genome Consortium, and further work to translate specialized investigation pathways must be incorporated into daily practice.

Prostate cancer is a priority cancer on the agenda of the International Cancer Genetics Consortium (www.icgc.org). Multiple centers worldwide have contributed a large amount of epidemiological and genotyping data. This risk resource is extremely important for planning and delivering the most effective and efficient PC management, including that for males in communities with high PC risk, particularly those with a likely aggressive clinical course. Digital health technologies, specifically artificial intelligence (AI), are now being rapidly used to manage genome- and gene-specific databases. Appropriate and judicious use of AI might further strengthen genotyping-based PC risk assessment, clinical course prediction, selection of optimal therapeutic options, facilitating comprehensive and integrated multidisciplinary management of patients with PC, and risk reduction in close male members of the family. A consortium of leading academic institutions in England

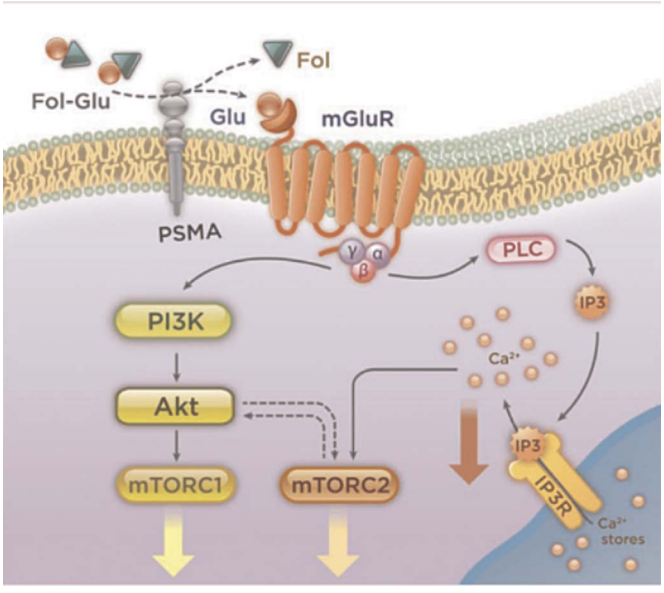

Figure 9. PSMA-P13K/Akt pathway. PSMA = prostate-specific membrane antigen.

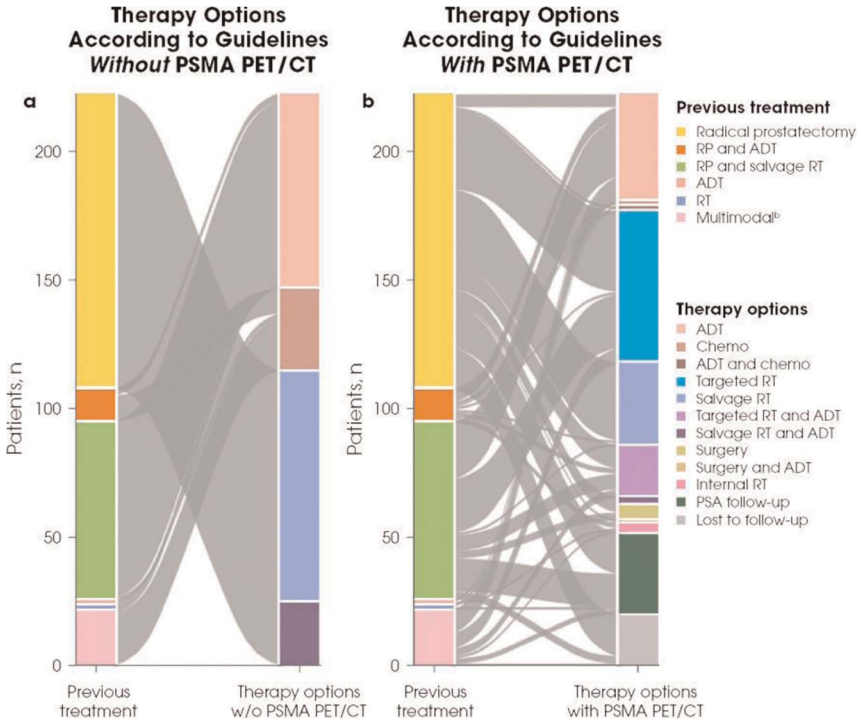

Figure 10. PSMA and targeted prostate cancer therapy.[8] PSMA = prostate-specific membrane antigen.

Table 7

Various commercial multigene prostate cancer genetic testing kits for risk stratification.

Genetic testing kit (no. of genes tested)	Genes tested
Ambry Genetics "ProstateNext" (14)	*ATM, BRCA1, BRCA2, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53*
Fulgent "Prostate Cancer Panel" (12)	*ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53*
GeneDx "Prostate Cancer Panel" (12)	*ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53*
Invitae "Prostate Cancer Panel" (15)	*ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53; ADD ON FANCA, PALB2, RAD51D* NB: *HOXB13* Analysis limited to the NM_006361.5.c.251G > A, p.Gly84Glu variant
NeoGenomics "Hereditary DNA Repair Panel for Prostate Cancer" (20)	*ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, GEN1, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, XRCC2*
Strand Diagnostics "UroSeq" (12)	*BRCA1/2, ATM, CHEK2, RAD51D, HOXB13, PALB2, MLH1, MSH2, MSH6, PMS2, EPCAM*

is engaged in a pioneering study to improve PC diagnoses using AI (www.transform.england.nhs.uk).

7. Conclusions

Comprehensive PC tumor and blood genotyping should be included in PC stratification for risk evaluation, planning and delivery of targeted molecular therapy, predicting prognosis, long-term surveillance, and effective prophylaxis. Currently, several commercial PC genotyping panel kits with enhanced accuracy and predictability are available. Technical advances in laboratory genomics and the refinement of highly sensitive methods, such as PC liquid biopsy, have greatly improved PC diagnosis. Increasingly, the specific prescription of expensive new therapeutic drugs such as taxanes and poly(ADP-ribose) polymerase inhibitors has been based on PC genotyping. In the future, the scope of whole-genome sequencing will likely increase with the development of annotated cancer genome databases. Prostate cancer remains a priority for the International Cancer Genome Consortium. In this context, the rapid expansion and healthcare applications of digital health or AI would further strengthen genotyping-based PC risk assessment, clinical course prediction, selection of optimal therapeutic options, facilitating comprehensive and integrated multidisciplinary management of patients with PC, and risk reduction in close male members of the family.

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Statement of ethics

Not applicable.

Conflict of interest statement

No conflict of interest has been declared by the author.

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Author contributions

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Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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