Cancer Genetics and Epigenetics 2024, Vol.12, No.2, 97-105
http://medscipublisher.com/index.php/cge

Feature Review Open Access

The Role of Genetic Markers in Early Screening of Prostate Cancer

Liting Wang
Hainan Institute of Biotechnology, Haikou, 570206, Hainan, China
Corresponding email: liting.wang@hibio.org

Cancer Genetics and Epigenetics, 2024, Vol.12, No.2 doi: 10.5376/cge.2024.12.0012
Received: 28 Feb., 2024
Accepted: 05 Apr., 2024
Published: 18 Apr., 2024

Preferred citation for this article:
Wang L.T., 2024, The role of genetic markers in early screening of prostate cancer, Cancer Genetics and Epigenetics, 12(2): 97-105 (doi: 10.5376/cge.2024.12.0012)

Abstract Prostate cancer is one of the most common cancers among men worldwide, and early screening and diagnosis are essential for improving treatment outcomes. This study emphasizes genetic susceptibility and key genetic markers such as BRCA1, BRCA2, and HOXB13, analyzing their variability across different ethnic groups and exploring advanced genetic screening technologies such as Next-Generation Sequencing (NGS), Genome-Wide Association Studies (GWAS), and liquid biopsies. These technologies have improved the precision of screening and helped reduce overdiagnosis and overtreatment. However, the application of these technologies also faces challenges such as genetic heterogeneity, ethical issues, and the accessibility and cost-effectiveness of screening. This research deeply investigates the critical role of genetic markers in the early screening of prostate cancer, particularly in predicting the disease's genetic susceptibility, with the goal of further optimizing early screening and management strategies for prostate cancer through genetics.

Keywords Prostate cancer; Genetic susceptibility; Genetic markers; Next-generation sequencing (NGS); Genome-wide association studies (GWAS)

1 Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy among men in the Western world and remains the second leading cause of cancer-related deaths in this population. Despite widespread screening efforts, including the use of prostate-specific antigen (PSA) testing, the disease continues to pose significant clinical challenges. PSA testing, while useful for early detection, has limited specificity and often leads to the diagnosis of indolent cancers that may not require aggressive treatment, resulting in unnecessary morbidity. The genetic basis of prostate cancer is well-established, with familial and hereditary patterns observed, suggesting a strong genetic component to the disease (Lynch et al., 2016).

Recent advances in genomic research have identified several genetic markers associated with the initiation and progression of prostate cancer. These markers include inherited genetic variants, single nucleotide polymorphisms (SNPs), and gene expression signatures that can potentially improve the accuracy of screening and prognostication (Hughes et al., 2012; Choudhury et al., 2012). For instance, genome-wide association studies have pinpointed multiple SNPs linked to increased PCa susceptibility, while urine-based assays and gene expression profiles have shown promise in distinguishing between indolent and aggressive forms of the disease (Downes et al., 2007; Cucchiara et al., 2018). Additionally, specific genetic mutations, such as those in the BRCA2 gene, have been associated with poorer prognosis and may guide therapeutic decisions (Cui et al., 2017).

This study provides a comprehensive overview of the potential applications of genetic markers in identifying high-risk individuals, improving screening techniques, and guiding clinical decisions. It includes assessments of genetic gene variants, SNPs, gene expression profiles, and other emerging biomarkers, with a focus on their clinical utility and validation in large-scale studies. The study also discusses the challenges and future directions of integrating genetic markers into routine clinical practice for the early detection and management of prostate cancer. By synthesizing current research findings, this study aims to provide insights for future research and clinical strategies in early prostate cancer screening using genetic markers.

2 Genetic Markers in Prostate Cancer

2.1 Genetic predisposition and prostate cancer

Prostate cancer (PCa) exhibits a significant genetic component, with familial and hereditary patterns observed in many cases. Studies have shown that prostate cancer has the highest degree of genetic transmission among malignancies, with some families displaying patterns akin to autosomal dominant traits (Lynch et al., 2016). Genome-wide association studies (GWAS) have identified numerous genetic polymorphisms and inherited variants associated with increased PCa risk. These genetic markers can help identify men at higher risk, particularly those with a family history of the disease (Figure 1) (Ni Raghallaigh and Eeles, 2022). For instance, a locus on chromosome 1q42.2-43 has been identified as carrying a putative predisposing gene for early-onset prostate cancer. The identification of such genetic predispositions is crucial for developing targeted screening strategies for high-risk individuals.

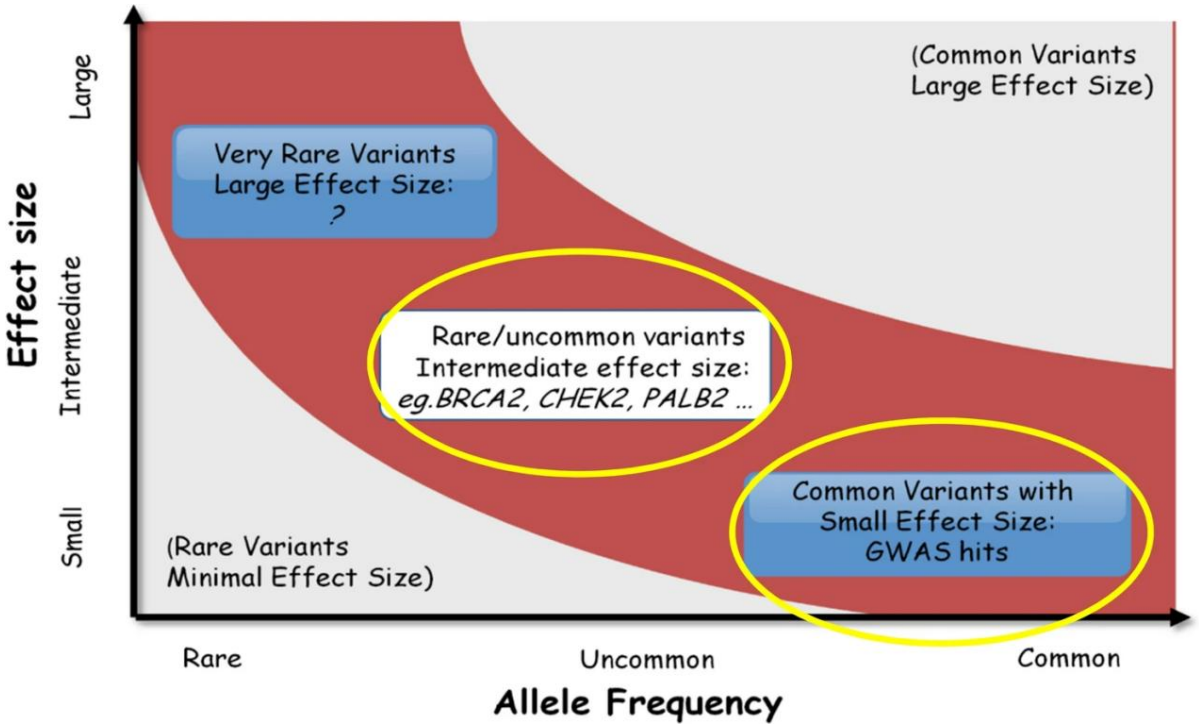

Figure 1 The spectrum of genetic variants in polygenic disease (i.e. PrCa) (Adopted from Ni Raghallaigh and Eeles, 2022)
Image caption: The x-axis plots the risk allele frequency and effect size along the y-axis. The top right corner represents common variants with large effect sizes (none known). The bottom left corner represents rare variants with small effect size (Adopted from Ni Raghallaigh and Eeles, 2022)

Prostate cancer is a polygenic disease, where genetic factors play a significant role in the risk of developing the condition. Men with a family history, especially those with brothers or fathers who have the disease, have a significantly increased risk. Ni Raghallaigh and Eeles (2022) emphasized the importance of genetic screening and early detection in high-risk populations to enable timely intervention and treatment, thereby reducing morbidity and mortality. Genome-Wide Association Studies (GWAS) have provided valuable genetic information, helping to identify numerous gene polymorphisms and variants associated with prostate cancer (PrCa).

2.2 Key genetic markers

Several genetic markers have been identified as significant in the context of prostate cancer. Single nucleotide polymorphisms (SNPs) such as rs6983561 (8q24), rs10993994 (10q11), and rs4430796 (17q12) have been associated with early-onset prostate cancer. These markers, when combined with traditional screening methods like prostate-specific antigen (PSA) testing, can improve the predictive accuracy for prostate cancer diagnosis (Nam et al., 2009; Hughes et al., 2012). Additionally, genomic biomarkers such as PCA3 RNA and TMPRSS2-ERG gene fusion have shown promise in aiding screening and improving prognostic discrimination (Choudhury et al., 2012). The integration of these genetic markers into clinical practice can enhance the early

detection and management of prostate cancer, potentially reducing unnecessary biopsies and overtreatment (Cucchiara et al., 2018; Nevo et al., 2020).

2.3 Ethnic variability in genetic markers

Ethnic variability plays a significant role in the prevalence and impact of genetic markers for prostate cancer. African American men, for instance, are at a higher risk of developing prostate cancer at younger ages compared to other ethnic groups. The rs6983561 genotype has been found to be significantly associated with earlier time to prostate cancer diagnosis among African American men, highlighting the importance of considering ethnic differences in genetic screening (Hughes et al., 2012). Furthermore, studies have shown that the frequency of certain genetic markers and their associated risks can vary among different ethnic groups, necessitating tailored screening and risk assessment strategies (Costa et al., 2007). Understanding these ethnic variations is crucial for developing personalized approaches to prostate cancer screening and treatment.

3 Advances in Genetic Screening Technologies

3.1 Next-generation sequencing (NGS)

Next-Generation Sequencing (NGS) has revolutionized the field of genetic screening by enabling the rapid and cost-effective sequencing of large amounts of DNA. This technology has significantly improved the accuracy and depth of genetic analysis, making it a powerful tool in the early screening of prostate cancer. NGS can be applied to both tissue biopsies and liquid biopsies, allowing for comprehensive genomic profiling of prostate cancer. For instance, NGS has been successfully used to detect mutations in formalin-fixed prostate cancer biopsies, identifying alterations in multiple cancer-related genes, which can inform clinical decision-making and treatment strategies (Beltran et al., 2013; Manson-Bahr et al., 2015). Additionally, the European Society for Medical Oncology (ESMO) recommends the routine use of NGS in advanced prostate cancers to identify actionable genetic alterations that can guide personalized therapy (Mosele et al., 2020).

3.2 Genome-wide association studies (GWAS)

Genome-Wide Association Studies (GWAS) have identified numerous genetic polymorphisms and inherited variants associated with prostate cancer susceptibility. These studies have enhanced our understanding of the genetic basis of prostate cancer and have led to the development of new genomic tools for risk assessment and disease management. For example, GWAS have identified specific genetic markers that can discriminate between clinically insignificant and aggressive tumors, aiding in the stratification of patients and the selection of appropriate therapies (Choudhury et al., 2012). Moreover, commercial tools such as Decipher, Oncotype DX, and Prolaris, which are based on GWAS findings, have improved risk stratification and prognostication in prostate cancer (Cucchiara et al., 2018).

3.3 Liquid biopsy techniques

Liquid biopsy techniques have emerged as a minimally invasive alternative to traditional tissue biopsies, offering a practical approach to monitor tumor dynamics over time. These techniques involve the analysis of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and extracellular vesicles (EVs) in blood samples. Liquid biopsies can provide real-time insights into tumor progression, treatment response, and resistance mechanisms. For instance, NGS applied to ctDNA can detect low-frequency mutations at early stages of cancer, facilitating early diagnosis and monitoring (Chen and Zhao, 2019). Additionally, liquid biopsies have shown promise in identifying prognostic and predictive biomarkers in advanced prostate cancer, such as androgen receptor (AR) variants and DNA repair gene mutations, which can guide targeted therapies (Oellerich et al., 2017; Morrison and Goldkorn, 2018). However, the implementation of liquid biopsy techniques in clinical practice requires standardization and validation to ensure their reliability and clinical utility (Casanova-Salas et al., 2021).

Advances in genetic screening technologies, including NGS, GWAS, and liquid biopsy techniques, have significantly enhanced the early detection and management of prostate cancer. These technologies offer new opportunities for personalized medicine, enabling more accurate risk assessment, early diagnosis, and tailored treatment strategies. However, further research and validation are needed to fully integrate these tools into routine clinical practice.

4 Key Genetic Markers in Prostate Cancer Screening

4.1 BRCA1 and BRCA2

BRCA1 and BRCA2 are well-established genetic markers associated with an increased risk of prostate cancer (PCa). Mutations in these genes are linked to a higher incidence of aggressive and early-onset PCa. Studies have shown that BRCA2 mutation carriers have a significantly higher risk of developing prostate cancer compared to non-carriers, with a higher likelihood of poor prognosis and reduced overall survival (Cui et al., 2017; Brönimann et al., 2020). BRCA1 mutations, while less common, also contribute to increased PCa risk and are associated with more aggressive disease phenotypes (Na et al., 2017). The detection of BRCA1/2 mutations is crucial for identifying individuals at high risk and can inform targeted screening and therapeutic strategies, such as the use of PARP inhibitors in BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC) (Figure 2) (Tukachinsky et al., 2021; Chi et al., 2023).

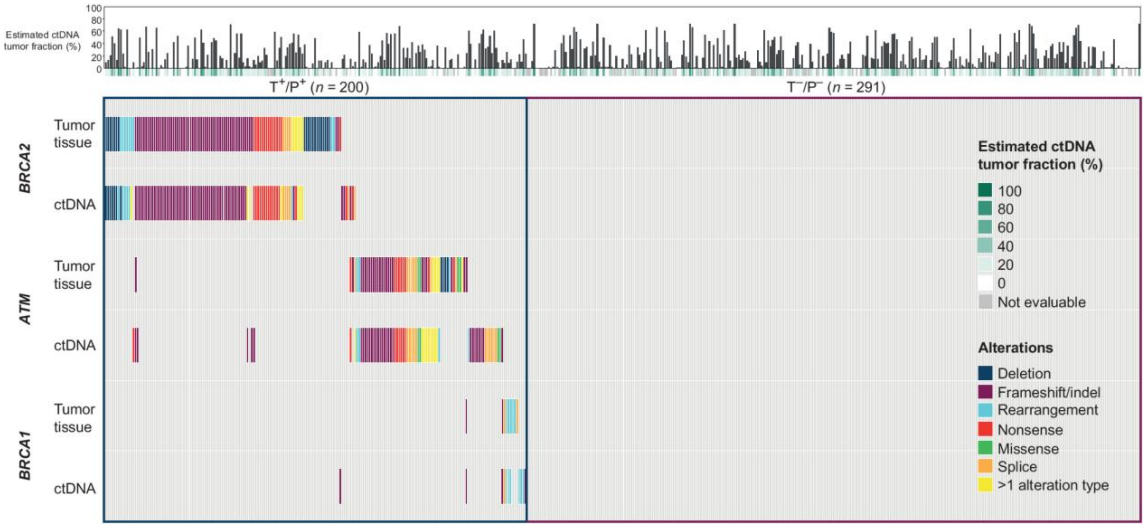

Figure 2 491 patient matched samples (Adopted from Chi et al., 2023)

Chi et al. (2023) demonstrated a high concordance between tumor tissues and circulating tumor DNA (ctDNA) in a study involving 491 patient samples, particularly in terms of the presence or absence of BRCA1, BRCA2, and ATM genes. ctDNA serves as a valuable complement in identifying patients with metastatic castration-resistant prostate cancer (mCRPC) harboring BRCA or ATM gene mutations, especially in cases where there is insufficient or no tissue available for genetic analysis. The detection of BRCA1/2 mutations not only helps in identifying high-risk individuals but also guides the targeted treatment strategies using PARP inhibitors. The application of PARP inhibitors in patients with BRCA-mutated mCRPC has shown potential in personalized treatment, offering new therapeutic options and hope for these patients.

4.2 HOXB13

HOXB13 is another significant genetic marker in prostate cancer screening. Mutations in the HOXB13 gene, particularly the G84E variant, have been associated with an increased risk of hereditary prostate cancer. This gene plays a role in prostate development and function, and its mutations are linked to early-onset and familial forms of the disease (Dias et al., 2018). The Philadelphia Prostate Cancer Consensus Conference 2017 highlighted the importance of testing for HOXB13 mutations in individuals with a family history of prostate cancer to better stratify risk and guide screening protocols.

4.3 Other significant markers

In addition to BRCA1/2 and HOXB13, other genetic markers such as CHEK2 and ATM have been identified as significant in prostate cancer screening. CHEK2 mutations, although less prevalent, are associated with moderate increases in prostate cancer risk and can contribute to familial cancer syndromes (Zhen et al., 2018; Woodward et al., 2024). ATM mutations are particularly noteworthy as they are linked to both increased risk and aggressive disease phenotypes. Studies have shown that ATM mutations are associated with grade reclassification in men

undergoing active surveillance for prostate cancer, indicating a higher likelihood of disease progression (Na et al., 2017; Carter et al., 2019). The detection of these mutations can aid in the identification of high-risk individuals and inform decisions regarding surveillance and treatment strategies.

The identification of genetic markers such as BRCA1, BRCA2, HOXB13, CHEK2, and ATM plays a crucial role in the early screening and management of prostate cancer. These markers help stratify risk, guide screening protocols, and inform targeted therapeutic approaches, ultimately contributing to improved patient outcomes.

5 Clinical Implications and Benefits

5.1 Improved screening accuracy

The integration of genetic markers into prostate cancer screening protocols has shown significant promise in enhancing the accuracy of early detection. For instance, the inclusion of the rs6983561 marker has been demonstrated to improve the predictive accuracy of prostate-specific antigen (PSA) tests among African American men, increasing the concordance index from 0.57 to 0.75 when combined with PSA (Hughes et al., 2012). Additionally, genome-wide association studies have identified several genetic polymorphisms that can help recognize men at high risk of developing prostate cancer, thereby refining screening techniques and reducing unnecessary biopsies (Cucchiara et al., 2018).

5.2 Reduction in overdiagnosis and overtreatment

One of the major challenges in prostate cancer management is the overdiagnosis and overtreatment of indolent cancers. Genetic markers can help address this issue by distinguishing between aggressive and non-aggressive forms of the disease. For example, the use of gene expression signatures and commercially available tools like Decipher, Oncotype DX, and Prolaris has improved risk stratification, allowing for better identification of men at the highest risk of adverse outcomes (Boström et al., 2015; Cózar et al., 2018). This stratification helps in making more informed decisions about the necessity and extent of treatment, thereby reducing the rates of overtreatment (Choudhury et al., 2012; Nevo et al., 2020).

5.3 Personalized risk assessment

Genetic markers offer a pathway to personalized risk assessment, which is crucial for tailoring screening and treatment strategies to individual patients. Studies have shown that genetic markers such as BRCA1, BRCA2, and other DNA damage repair genes can drive the development of prostate cancer and are associated with more aggressive disease (Meng et al., 2019). Personalized risk assessment using these markers can guide early detection and treatment decisions, improving patient outcomes. Moreover, the use of genetic scores based on multiple SNPs has been shown to improve the prediction of prostate cancer risk, even after adjusting for known clinical variables (Kader et al., 2012).

5.4 Case study

A notable case study involves the use of the rs6983561 marker in a cohort of high-risk African American men. In this study, the marker was significantly associated with an earlier time to prostate cancer diagnosis and improved the predictive accuracy of PSA tests. This finding underscores the potential of genetic markers to refine and personalize prostate cancer early detection for high-risk populations (Hughes et al., 2012). Another example is the IMPACT study, which highlighted the elevated cancer detection rate in BRCA1 and BRCA2 carriers, emphasizing the importance of close PSA screening in these men (Das et al., 2019).

6 Challenges and Limitations

6.1 Genetic heterogeneity

Genetic heterogeneity poses a significant challenge in the early screening of prostate cancer using genetic markers. The variability in genetic alterations among different patients can lead to inconsistent results in the identification and prognostication of prostate cancer. For instance, extensive heterogeneity has been observed in Gleason Scores, DNA ploidy, and PTEN expression among prostate cancer patients, which complicates the evaluation of prognostic markers (Cyll et al., 2017). This heterogeneity necessitates multi-sample analyses to support clinical treatment decisions, as single-sample analyses may not provide a comprehensive understanding of the tumor's

genetic landscape. Additionally, the genetic diversity in prostate cancer underscores the need for personalized approaches to screening and treatment, as a one-size-fits-all strategy may not be effective (Cózar et al., 2018).

6.2 Ethical considerations

The use of genetic markers in early screening for prostate cancer raises several ethical concerns. One major issue is the potential for genetic discrimination, where individuals may face discrimination based on their genetic predisposition to prostate cancer. This could affect their employment, insurance, and social standing. Furthermore, the psychological impact of genetic testing cannot be overlooked. The knowledge of carrying a genetic risk for prostate cancer can cause significant anxiety and stress for patients and their families. There is also the ethical dilemma of informed consent, where patients must fully understand the implications of genetic testing, including the potential for false positives or negatives, and the limitations of current genetic markers in providing definitive prognostic information (Aly et al., 2011). Ensuring that patients are adequately informed and supported throughout the genetic testing process is crucial to addressing these ethical challenges.

6.3 Accessibility and cost-effectiveness

The accessibility and cost-effectiveness of genetic testing for prostate cancer screening are significant barriers to its widespread adoption. Genetic tests can be expensive, and their costs may not be covered by insurance, making them inaccessible to many patients, particularly those from lower socioeconomic backgrounds (Boström et al., 2015). Additionally, the implementation of genetic testing in clinical practice requires substantial investment in infrastructure, training, and resources, which may not be feasible for all healthcare settings (Cucchiara et al., 2018). The cost utility of these tests is still under evaluation, and large-scale, multi-institutional studies are needed to validate their efficacy and cost-effectiveness. Moreover, the availability of genetic testing may be limited in certain regions, further exacerbating disparities in access to early screening and personalized treatment options (Nevo et al., 2020). Addressing these issues is essential to ensure that the benefits of genetic markers in prostate cancer screening are equitably distributed across all patient populations.

7 Future Directions

7.1 Emerging genetic markers

The landscape of genetic markers for prostate cancer (PCa) is rapidly evolving, with several promising candidates on the horizon. Recent studies have identified numerous single nucleotide polymorphisms (SNPs) associated with PCa risk, with 35 SNPs already validated and an additional 50~75 expected to be identified soon (Aly et al., 2011). These markers, although modest in their individual effect, collectively explain a significant portion of familial risk. Moreover, emerging markers such as the rs6983561 genotype have shown potential in improving predictive accuracy for early-onset PCa, particularly among high-risk groups like African American men (Hughes et al., 2012). The integration of these new genetic markers into clinical practice could significantly enhance early detection and risk stratification.

7.2 Integration with other diagnostic modalities

The future of PCa diagnosis lies in the integration of genetic markers with other diagnostic modalities. Combining genetic information with traditional biomarkers such as prostate-specific antigen (PSA) and advanced imaging techniques could provide a more comprehensive assessment of PCa risk. For instance, the combination of serum PSA, urinary PCA3, and TMPRSS2-ERG fusion has demonstrated superior sensitivity and specificity compared to traditional diagnostic approaches (McGrath et al., 2016). Additionally, urine-based assays like SelectMDx and Mi-Prostate Score are emerging as valuable tools for identifying patients who may benefit from prostate biopsy (Cucchiara et al., 2018). This multimodal approach could reduce unnecessary biopsies and improve the accuracy of PCa diagnosis.

7.3 Personalized medicine approaches

Personalized medicine is poised to revolutionize the management of PCa by tailoring treatment strategies based on individual genetic profiles. Genomic biomarkers such as AR-V7 expression and mutations in DNA mismatch repair genes are already being used to guide treatment decisions in castration-resistant PCa 3. Furthermore, commercially available gene panels like Prolaris, Oncotype DX, and Decipher are being utilized to estimate

disease outcomes and inform therapeutic choices (Boström et al., 2015; Cucchiara et al., 2018). The integration of these genomic tools into clinical practice represents a significant step towards personalized treatment, potentially improving patient outcomes and reducing overtreatment. Future research should focus on validating these biomarkers in large, diverse populations to ensure their efficacy and cost-effectiveness in routine clinical use.

In conclusion, the future of PCa screening and management will likely be shaped by the continued discovery and validation of genetic markers, their integration with other diagnostic modalities, and the advancement of personalized medicine approaches. These developments hold the promise of more accurate, individualized, and effective strategies for the early detection and treatment of prostate cancer.

8 Concluding Remarks

Recent advancements in genetic research have significantly enhanced our understanding of prostate cancer (PCa) and its early detection. Genetic markers, including single nucleotide polymorphisms (SNPs) and other genomic biomarkers, have shown promise in identifying individuals at high risk for developing PCa, distinguishing between indolent and aggressive forms of the disease, and guiding therapeutic decisions. For instance, SNPs such as rs6983561 have been associated with early-onset PCa, particularly among high-risk groups like African American men, improving the predictive accuracy of prostate-specific antigen (PSA) tests. Additionally, urine-based assays and epigenetic markers have emerged as valuable tools for non-invasive screening and prognosis.

The integration of genetic markers into clinical practice has the potential to revolutionize early detection and management of PCa. By improving the specificity and sensitivity of existing screening methods, such as PSA testing, these markers can reduce the number of unnecessary biopsies and over-treatments, thereby minimizing patient morbidity. Moreover, genetic markers can aid in the stratification of patients based on their risk profiles, allowing for more personalized and effective treatment plans. This personalized approach can lead to better outcomes by ensuring that aggressive treatments are reserved for those with high-risk disease, while low-risk patients can be monitored through active surveillance.

While the current findings are promising, further research is essential to validate the clinical utility of these genetic markers. Large-scale, multi-institutional studies are needed to confirm their efficacy and cost-effectiveness in diverse populations. Future research should also focus on identifying additional genetic markers and developing comprehensive panels that combine multiple biomarkers to enhance diagnostic accuracy and prognostic capabilities. Additionally, the exploration of novel technologies, such as liquid biopsies and advanced sequencing methods, could provide new insights into the genetic underpinnings of PCa and lead to the discovery of new therapeutic targets. Ultimately, the goal is to integrate these genetic markers into routine clinical practice, thereby improving early detection, patient outcomes, and overall management of prostate cancer.

Acknowledgments

Thanks very much for the feedback from the reviewers on the manuscript.

Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Aly M., Wiklund F., and Grönberg H., 2011, Early detection of prostate cancer with emphasis on genetic markers, Acta Oncologica, 50(sup1): 18-23. https://doi.org/10.3109/0284186X.2010.529824

Beltran H., Yelensky R., Frampton G.M., Park K., Downing S.R., MacDonald T.Y., Jarosz M., Lipson D., Tagawa S., Nanus D., Stephens P., Mosquera J., Cronin M., and Rubin M.A., 2013, Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity, European Urology, 63(5): 920-926. https://doi.org/10.1016/j.eururo.2012.08.053

Boström P.J., Bjartell A.S., Catto J.W., Eggener S.E., Lilja H., Loeb S., Schalken J., Schlomm T., and Cooperberg M.R., 2015, Genomic predictors of outcome in prostate cancer, European Urology, 68(6): 1033-1044. https://doi.org/10.1016/j.eururo.2015.04.008

Brönimann S., Pradere B., Karakiewicz P., Abufaraj M., Briganti A., and Shariat S.F., 2020, An overview of current and emerging diagnostic, staging and prognostic markers for prostate cancer, Expert Review of Molecular Diagnostics, 20(8): 841-850.
https://doi.org/10.1080/14737159.2020.1785288

Carter H.B., Helfand B., Mamawala M., Wu Y., Landis P., Yu H., Yu H., Wiley K., Na R., Na R., Shi Z., Shi Z., Petkewicz J., Shah S., Fantus R., Fantus R., Novakovic K., Brendler C., Zheng S., Isaacs W., Xu J., and Xu J., 2019, Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer, European Urology, 75(5): 743-749.
https://doi.org/10.1016/j.eururo.2018.09.021

Casanova-Salas I., Athie A., Boutros P.C., Del Re M., Miyamoto D.T., Pienta K.J., Posadas E., Sowalsky A., Stenzl A., Wyatt A., and Mateo J., 2021, Quantitative and qualitative analysis of blood-based liquid biopsies to inform clinical decision-making in prostate cancer, European Urology, 79(6): 762-771.
https://doi.org/10.1016/j.eururo.2020.12.037

Chen M., and Zhao H., 2019, Next-generation sequencing in liquid biopsy: cancer screening and early detection, Human Genomics, 13(1): 34.
https://doi.org/10.1186/s40246-019-0220-8

Chi K.N., Barnicle A., Sibilla C., Lai Z., Corcoran C., Barrett J.C., Adelman C., Qiu P., Easter A., Dearden S., Oxnard G., Agarwal N., Azad A., Bono J., Mateo J., Olmos D., Thiery-Vuillemin A., and Harrington E. A., 2023, Detection of BRCA1, BRCA2, and ATM alterations in matched tumor tissue and circulating tumor DNA in patients with prostate cancer screened in PROfound, Clinical Cancer Research, 29(1): 81-91.
https://doi.org/10.1158/1078-0432.CCR-22-0931

Choudhury A.D., Eeles R., Freedland S.J., Isaacs W.B., Pomerantz M.M., Schalken J.A., Tammela T., and Visakorpi T., 2012, The role of genetic markers in the management of prostate cancer, European Urology, 62(4): 577-587.
https://doi.org/10.1016/j.eururo.2012.05.054

Costa V.L., Henrique R., and Jerónimo C., 2007, Epigenetic markers for molecular detection of prostate cancer, Disease Markers, 23(1-2): 31-41.
https://doi.org/10.1155/2007/356742

Cozar J.M., Robles-Fernandez I., Martinez-Gonzalez L.J., Pascual-Geler M., Rodriguez-Martinez A., Serrano M.J., Lorente J., and Alvarez-Cubero M.J., 2018, Genetic markers a landscape in prostate cancer, Mutation Research/Reviews in Mutation Research, 775: 1-10.
https://doi.org/10.1016/j.mrrev.2017.11.004

Cucchiara V., Cooperberg M.R., Dall'Era M., Lin D.W., Montorsi F., Schalken J.A., and Evans C.P., 2018, Genomic markers in prostate cancer decision making, European Urology, 73(4): 572-582.
https://doi.org/10.1016/j.eururo.2017.10.036

Cui M., Gao X.S., Gu X., Guo W., Li X., Ma M., Qin S., Qi X., Xie M., Peng C., and Bai Y., 2017, BRCA2 mutations should be screened early and routinely as markers of poor prognosis: evidence from 8,988 patients with prostate cancer, Oncotarget, 8(25): 40222.
https://doi.org/10.18632/oncotarget.16712

Cyll K., Ersvær E., Vlatkovic L., Pradhan M., Kildal W., Avranden Kjær M., Kleppe A., Hveem T., Carlsen B., Gill S., Löffeler S., Haug E., Wæhre H., Sooriakumaran P., and Danielsen H.E., 2017, Tumour heterogeneity poses a significant challenge to cancer biomarker research, British Journal of Cancer, 117(3): 367-375.
https://doi.org/10.1038/bjc.2017.171

Das S., Salami S.S., Spratt D.E., Kaffenberger S.D., Jacobs M.F., and Morgan T.M., 2019, Bringing prostate cancer germline genetics into clinical practice, Journal of Urology, 202(2): 223-230.
https://doi.org/10.1097/JU.0000000000000137

Downes M.R., Byrne J.C., Pennington S.R., Dunn M.J., Fitzpatrick J.M., and Watson R.W.G., 2007, Urinary markers for prostate cancer, BJU International, 99(2): 263-268.
https://doi.org/10.1111/j.1464-410X.2006.06610.x

Hughes L., Zhu F., Ross E., Gross L., Uzzo R.G., Chen D.Y., Viterbo R., Rebbeck T., and Giri V.N., 2012, Assessing the clinical role of genetic markers of early-onset prostate cancer among high-risk men enrolled in prostate cancer early detection, Cancer Epidemiology, Biomarkers and Prevention, 21(1): 53-60.
https://doi.org/10.1158/1055-9965.EPI-11-0727

Kader A.K., Sun J., Reck B.H., Newcombe P.J., Kim S.T., Hsu F.C., D'Agostino R., Tao S., Zhang Z., Turner A., Platek G., Spraggs C., Whittaker J., Lane B., Isaacs W., Meyers D., Bleecker E., Torti F., Trent J., Mcconnell J., Zheng S., Condreay L., Rittmaster R., and Xu J., 2012, Potential impact of adding genetic markers to clinical parameters in predicting prostate biopsy outcomes in men following an initial negative biopsy: findings from the REDUCE trial, European Urology, 62(6): 953-961.
https://doi.org/10.1016/j.eururo.2012.05.006

Lynch H.T., Kosoko‐Lasaki O., Leslie S.W., Rendell M., Shaw T., Snyder C., D'Agostino R., Tao S., Zhang Z., Turner A., Platek G., Spraggs C., Whittaker J., Lane B., Isaacs W., Meyers D., Bleecker E., Torti F., Trent J., Mcconnell J., Zheng S., Condreay L., Rittmaster R., and Powell I., 2016, Screening for familial and hereditary prostate cancer, International Journal of Cancer, 138(11): 2579-2591.
https://doi.org/10.1002/ijc.29949

Manson-Bahr D., Ball R., Gundem G., Sethia K., Mills R., Rochester M., Goody V., Anderson E., O'meara S., Flather M., Keeling M., Yazbek-Hanna M., Hurst R., Curley H., Clark J., Brewer D., McDermott U., and Cooper C., 2015, Mutation detection in formalin-fixed prostate cancer biopsies taken at the time of diagnosis using next-generation DNA sequencing, Journal of Clinical Pathology, 68(3): 212-217.
https://doi.org/10.1136/jclinpath-2014-202754

McGrath S., Christidis D., Perera M., Hong S.K., Manning T., Vela I., and Lawrentschuk N., 2016, Prostate cancer biomarkers: are we hitting the mark?, Prostate International, 4(4): 130-135.
https://doi.org/10.1016/j.prnil.2016.07.002

Meng L., Li Y., Ren J., Shi T., Men J., and Chang C., 2019, Early stage biomarkers screening of prostate cancer based on weighted gene coexpression network analysis, DNA and Cell Biology, 38(5): 468-475.
https://doi.org/10.1089/dna.2018.4406

Morrison G.J., and Goldkorn A., 2018, Development and application of liquid biopsies in metastatic prostate cancer, Current oncology reports, 20: 1-10.
https://doi.org/10.1007/s11912-018-0683-0

Mosele F., Remon J., Mateo J., Westphalen C.B., Barlesi F., Lolkema M.P., Normanno N., Scarpa A., Robson M., Meric-Bernstam F., Wagle N., Stenzinger A., Bonastre J., Bayle A., Michiels S., Bièche I., Rouleau E., Jezdic S., Douillard J., Reis-Filho J., Dienstmann R., and André F., 2020, Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group, Annals of Oncology, 31(11): 1491-1505.
https://doi.org/10.1016/j.annonc.2020.07.014

Na R., Zheng S.L., Han M., Yu H., Jiang D., Shah S., Ewing C., Zhang L., Novakovic K., Petkewicz J., Gulukota K., Helseth D., Quinn M., Humphries E., Wiley K., Isaacs S., Wu Y., Liu X., Zhang N., Wang C., Khandekar J., Hulick P., Shevrin D., Cooney K., Shen Z., Partin A., Carter H., Carducci M., Eisenberger M., Denmeade S., McGuire M., Walsh P., Helfand B., Brendler C., Ding Q., Xu J., Isaacs W., and Isaacs W.B., 2017, Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death, European Urology, 71(5): 740-747.
https://doi.org/10.1016/S1569-9056(17)30541-9

Nam R.K., Zhang W.W., Trachtenberg J., Seth A., Klotz L.H., Stanimirovic A., Punnen S., Venkateswaran V., Toi A., Loblaw D., Sugar L., Siminovitch K., and Narod S.A., 2009, Utility of incorporating genetic variants for the early detection of prostate cancer, Clinical Cancer Research, 15(5): 1787-1793.
https://doi.org/10.1158/1078-0432.CCR-08-1593

Nevo A., Navaratnam A., and Andrews P., 2020, Prostate cancer and the role of biomarkers, Abdominal Radiology, 45: 2120-2132.
https://doi.org/10.1007/s00261-019-02305-8

Ni Raghallaigh, H., and Eeles R., 2022, Genetic predisposition to prostate cancer: an update. Familial Cancer, 21(1): 101-114.
https://doi.org/10.1007/s10689-021-00227-3

Oellerich, M., Schütz, E., Beck, J., Kanzow, P., Plowman, P. N., Weiss, G. J., and Walson, P. D., 2017, Using circulating cell-free DNA to monitor personalized cancer therapy. Critical reviews in clinical laboratory sciences, 54(3): 205-218.
https://doi.org/10.1080/10408363.2017.1299683

Tukachinsky H., Madison R.W., Chung J.H., Gjoerup O.V., Severson E.A., Dennis L., Fendler B., Morley S., Zhong L., Graf R., Ross J., Alexander B., Abida W., Chowdhury S., Ryan C., Fizazi K., Golsorkhi T., Watkins S., Simmons A., Loehr A., Venstrom J., and Oxnard G.R., 2021, Genomic analysis of circulating tumor DNA in 3,334 patients with advanced prostate cancer identifies targetable BRCA alterations and AR resistance mechanisms, Clinical Cancer Research, 27(11): 3094-3105.
https://doi.org/10.1158/1078-0432.CCR-20-4805

Woodward E.R., Lalloo F., Forde C., Pugh S., Burghel G.J., Schlecht H., Harkness E., Howell A., Howell S., Gandhi A., and Evans D.G., 2024, Germline testing of BRCA1, BRCA2, PALB2 and CHEK2 c. 1100delC in 1514 triple negative familial and isolated breast cancers from a single centre, with extended testing of ATM, RAD51C and RAD51D in over 400, Journal of Medical Genetics, 61(4): 385-391.
https://doi.org/10.1136/jmg-2023-109671

Zhen J.T., Syed J., Nguyen K.A., Leapman M.S., Agarwal N., Brierley K., Llor X., Hofstatter E., and Shuch B., 2018, Genetic testing for hereditary prostate cancer: current status and limitations, Cancer, 124(15): 3105-3117.
https://doi.org/10.1002/cncr.31316