Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2023, Volume 3, Issue 2, Page No: 51-60

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

Optimizing Prostate Cancer Management in Men Harboring High-Risk Genetic Variants

B. De Clercq[1*], M. Janssens[1], E. Van Damme[1]

[1]Department of Oncology, Faculty of Medicine, University of Antwerp, Antwerp, Belgium.

***E-mail** ✉ antwerp.onc.31@emailprovider.net

Received: 01 June 2023; **Revised:** 27 August 2023; **Accepted:** 03 September 2023

ABSTRACT

Prostate cancer is a major cause of mortality among men, with about 12.5% of those diagnosed ultimately dying from the disease. Because outcomes vary substantially between low-risk and high-risk cases, identifying men at heightened risk for disease progression and death is critical. Germline genetic mutations are increasingly recognized as significant contributors to aggressive and lethal prostate cancer. This article aims to provide a comprehensive overview of management strategies for prostate cancer in men who carry high-risk germline variants. We conducted a literature review to collect studies focusing on the clinical management of prostate cancer in individuals with high-risk germline genetic alterations. Numerous publications address treatment considerations for prostate cancer in this high-risk population; however, the overall strength and quality of evidence remain limited. This review synthesizes current knowledge and clinical considerations for managing prostate cancer in men with high-risk germline mutations. The scarcity of robust evidence highlights the urgent need for further studies and the establishment of standardized guidelines to support optimal clinical care in this patient group.

Keywords: Germline genetic mutations, Prostate cancer, Clinical management

How to Cite This Article: De Clercq B, Janssens M, Van Damme E. Optimizing Prostate Cancer Management in Men Harboring High-Risk Genetic Variants. Asian J Curr Res Clin Cancer. 2023;3(2):51-60. https://doi.org/10.51847/GFYMcVitEw

Introduction

Prostate cancer is a major contributor to male cancer mortality [1], with roughly one in eight diagnosed men ultimately dying from the disease [2, 3]. Due to the wide disparity in outcomes between low- and high-risk forms of prostate cancer, identifying individuals at elevated risk of progression and mortality is essential. It is well established that certain germline pathogenic variants increase both the likelihood of developing prostate cancer and the risk of death from the disease [4, 5]. Recent evidence indicates that mutations affecting DNA damage repair pathways, including BRCA1 and BRCA2, are linked to particularly aggressive prostate cancer [6-8], with BRCA2 carriers exhibiting a notably higher risk of metastatic disease. Additionally, identifying these germline mutations enables the recognition of at-risk family members, allowing for targeted genetic testing, personalized screening strategies, preventive interventions, and tailored treatment planning.

Although germline mutations are uncommon, they may contribute substantially to population-level risk beyond traditional factors such as age and African ancestry. While various genetic panels test for numerous mutations, the primary prostate cancer risk is associated with variants in BRCA1, BRCA2, ATM, CHEK2, and HOXB13. Population prevalence estimates for these genes range from 0.3% to 1.2% [9-12], with considerably higher prevalence among men with prostate cancer [4]. In one study, Pritchard *et al*. found that 11.8% of men with metastatic prostate cancer carried at least one presumed pathogenic germline mutation. The study also demonstrated a marked increase in metastatic risk, ranging from a nonsignificant relative risk (RR) of 1.6 (95% CI: 0.8–2.8) for ATM mutations to a highly significant RR of 26.7 (95% CI: 18.9–36.4) for BRCA2 mutations. Notably, 71% of mutation carriers had a first-degree relative with prostate cancer. While these germline variants

are relatively rare in the general population, affected individuals face substantially increased risk and contribute disproportionately to prostate cancer mortality.

The purpose of this review is to summarize the clinical implications of high-risk germline mutations, focusing on: (a) identification of patients for genetic testing, (b) prevention strategies, (c) screening approaches, (d) active surveillance in low-risk disease, (e) focal and minimally invasive therapies, (f) management of localized cancer, (g) management of recurrent disease, and (h) treatment of metastatic prostate cancer.

Materials and Methods

The clinical questions addressed in this review were derived from our experience running a high-risk prostate cancer clinic, which guided focused literature searches within each topic area. Study inclusion was determined by the scope and quality of available literature for each clinical question.

Comprehensive searches were performed in MEDLINE (including Pre-MEDLINE), EMBASE, BIOSIS Previews®, Web of Science® (including conference proceedings), and the Cochrane Central Register of Controlled Trials. Only articles published in English were included. No meta-analysis was conducted; this review provides a narrative synthesis. The search strategy aimed to minimize the risk of missing relevant studies, without restrictions on publication date.

Search terms combined subject headings and free-text keywords, customized for each clinical question. Editorials, news items, and letters were excluded. Reference lists from all relevant articles and reviews were screened to identify additional studies.

Results and Discussion

Clinical question: which prostate cancer patients should undergo germline genetic testing?

Significant variation exists regarding which patients are recommended for germline testing **(Table 1)**. The most widely referenced guidelines originate from the National Comprehensive Cancer Network, with updates from the Philadelphia consensus conference [13-15]. The American Urological Association and European Association of Urology also provide guidance largely consistent with these recommendations [16, 17]. Although specific genes recommended for testing differ slightly, most guidelines advocate for multi-gene panel testing using next-generation sequencing, including BRCA1, BRCA2, ATM, CHEK2, PALB2, and mismatch repair genes (MLH1, MSH2, MSH6, PMS2). Access to government-sponsored testing varies by region, but declining costs of next-generation sequencing have expanded commercially available testing options, generally covering these key genes alongside several additional variants.

Table 1. Varying guidelines for genetic testing in prostate cancer (as presented from Clark *et al*. 2021 [18]).

Category	NCCN HBOC Version 1.2021	NCCN Prostate Version 2.2020	Philadelphia Consensus Conference	American Urological Association	European Association of Urology
Metastatic disease	Metastatic PrCA	Metastatic PrCA	Metastatic PrCA (castrate resistant or sensitive; **Recommend**)	Metastatic PrCa (castrate resistant or sensitive)	**Consider** in metastatic PrCa
Histology	Intraductal/cribriform histology	Intraductal/cribriform histology	Intraductal/ductal pathology (**Consider**)	—	—
Grade, Stage, PSA	High risk, very high risk group ≥ Stage T3a ≥ Grade Group 4 PSA > 20 ng/mL	—	High risk, very high risk, or regional	Advanced disease (T3a or higher; **Consider**) Grade Group 4 (Gleason sum 8) or above (**Consider**)	High risk localized and a strong family history of other specific cancers High risk PrCa who have a family member diagnosed

					with PrCA at age <60 years
Ancestry	Ashkenazi Jewish ancestry	Ashkenazi Jewish ancestry	Ashkenazi Jewish ancestry (**Consider**)	—	—
Family History	Personal Hx PrCA with: (a) ≥1 close relative with breast <50 y and/or ovarian and/or pancreatic and/or metastatic/intraductal/cribriform PrCA at any age (b) ≥2 close relatives with breast or PrCA (any grade) at any age	Positive family history of cancer: (a) Brother or father or multiple family members diagnosed with PCA (not clinically localized Grade Group 1) at <60 y of age or who died from PrCA, **OR** (b) ≥3 cancers on the same side of the family, especially diagnosed ≤50 y: bile duct, breast, CRC, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, PrCA (not clinically localized Grade Group 1), small bowel, or urothelial cancer	One brother/father or ≥2 male relatives: (a) Diagnosed with PrCA at age <60 y (**Recommend**) (b) Any of whom died of PrCA (**Recommend**) (c) Any of whom had metastatic PrCA (**Recommend**) FH of other cancers: ≥2 cancers in HBOC or Lynch spectrum in any relatives on the same side of the family (especially if diagnosed at <50 y; **Consider**)	High risk localized and a strong family history of other specific cancers	Men with a family history of high-risk germline mutations or a family history of multiple cancer on the same side of the family

Clinical Consideration: According to established prostate cancer germline testing guidelines, all men who meet NCCN criteria [14] should undergo germline genetic testing using a validated laboratory method. The role of somatic mutation testing in prostate cancer remains under investigation. Some clinical trials include patients with somatic mutations, and future research is needed to clarify whether progression and mortality risks are comparable between individuals with somatic-only mutations versus germline mutations.

Clinical question: prevention strategies for prostate cancer in high-risk germline mutation carriers

Currently, no medications are approved for prostate cancer prevention. Several randomized controlled trials have investigated potential preventive agents, including 5-alpha reductase inhibitors (which reduce androgen activity in the prostate, e.g., Dutasteride and Finasteride), hormone-modulating agents (e.g., Toremifene), nonsteroidal anti-inflammatory drugs (e.g., Refocoxib), and dietary supplements (e.g., Selenium, Vitamin E, Soy). Results have been inconsistent: some trials were terminated due to cardiovascular toxicity (e.g., Refocoxib [19]), others suggested increased prostate cancer risk (e.g., Vitamin E [20]), and two notable trials, PCPT and REDUCE, demonstrated overall risk reduction but a higher incidence of high-grade disease in treated groups [21, 22]. These findings prompted a black box warning by the US FDA [23]. Although several hypotheses exist regarding this association [24], these medications are not routinely recommended for prostate cancer prevention.

Recently, interest has increased in the potential preventive roles of statins and metformin for prostate cancer initiation, progression, and mortality [25, 26]. While promising in the general population, their effectiveness in high-risk germline mutation carriers has not been established.

Given the absence of compelling evidence, no agents should currently be recommended for prostate cancer prevention in individuals with high-risk germline mutations. Moreover, use of 5-alpha reductase inhibitors for other indications, such as benign prostatic hyperplasia or male pattern baldness, should include discussion regarding potential effects on prostate cancer risk, particularly for high-grade disease.

Surgical prevention has been more widely studied in breast and ovarian cancer among high-risk mutation carriers [27]. A few case reports describe prophylactic prostatectomy in high-risk men, but this approach is not recommended outside of a clinical trial setting [28].

Clinical Consideration: At present, no pharmacologic agents are endorsed for prostate cancer prevention in either average-risk or high-risk individuals. When 5-alpha reductase inhibitors are used in high-risk germline mutation carriers, clinicians should discuss potential risks and benefits, with particular emphasis on the risk of high-grade

prostate cancer. Enrollment in clinical trials investigating primary prevention strategies is encouraged for these patients.

Clinical question: screening strategies for men with high-risk germline mutations

Prostate cancer screening remains controversial in the general population. The discovery of serum prostate-specific antigen (PSA) in the early 1990s led to widespread screening and overtreatment in certain groups [29]. Three large randomized trials yielded mixed results. The European ERSPC and Göteborg trials reported a 20–30% and 42% reduction in prostate cancer mortality, respectively [30, 31], whereas the US PLCO trial found no difference, largely due to contamination of the control arm [32]. Consequently, the US Preventive Services Task Force initially recommended against PSA screening [33], later revising guidance to encourage discussion of risks and benefits for men aged 55–69 and advising against screening in men older than 70. Importantly, these recommendations do not apply to men at elevated risk of prostate cancer.

Multiple organizations provide specific guidance for high-risk men, including the AUA, NCCN, and ACS. The AUA recommends individualized discussions with healthcare providers for men at elevated risk, noting that standard recommendations may not apply. NCCN advises that men with germline BRCA1 or BRCA2 mutations consider initiating PSA screening discussions at age 40 and possibly undergo annual screening [14]. Similarly, the ACS suggests starting conversations about screening at age 40 for men at increased risk, such as those with multiple first-degree relatives diagnosed at a young age [34].

Ongoing studies are evaluating PSA screening efficacy in men with BRCA1/2 mutations [35]. Interim three-year follow-up data indicate that BRCA2 carriers experience higher prostate cancer incidence, younger age at diagnosis, and more clinically significant tumors compared to non-carriers, supporting systemic PSA screening for male BRCA2 carriers. Alternative approaches, including multi-parametric MRI, are also under investigation. Segal *et al*. [36] monitored 188 BRCA1/2 carriers with PSA and MRI, finding that MRI provided the most benefit for younger carriers regardless of PSA levels, while carriers over 55 should continue PSA screening and undergo MRI if PSA is elevated.

Screening for prostate cancer in individuals with high-risk germline mutations should be customized based on the patient's tolerance for risk and after discussing the potential benefits and harms. Although evidence is limited, it is reasonable to offer a baseline multiparametric MRI alongside PSA testing starting at age 40 for these high-risk men. Follow-up should include structured surveillance at regular intervals with PSA measurements, digital rectal exams, and periodic MRI evaluations. Current PIRADS-2 reporting does not account for germline mutation status; therefore, there should be heightened vigilance for MR-indeterminate lesions that may warrant targeted biopsy. The comparative effectiveness of MRI-guided versus systematic biopsy in this high-risk population remains undefined.

Clinical consideration: There is no universally accepted screening protocol for men carrying high-risk germline mutations. According to NCCN guidelines, these patients should consider early and regular PSA screening combined with MRI monitoring and a low threshold for biopsy.

Clinical question: active surveillance for high-risk germline mutation carriers

Active surveillance has become a widely used strategy to limit overtreatment in men with low-risk prostate cancer. Standard selection criteria include PSA levels, tumor stage, and biopsy pathology. Typically, surveillance involves an initial biopsy, a confirmatory biopsy at 12 months, and additional biopsies every five years, with PSA monitoring in between. MRI is increasingly incorporated to guide surveillance, and studies support the safety of active surveillance in standard-risk patients [37, 38]. Over a 10-year period, 36–73% of men transition from surveillance to definitive treatment, while the incidence of metastasis remains low at 0.1–2.8% [38].

Data regarding active surveillance for men with high-risk germline mutations are limited. A small cohort study in Israel used PSA every three months and MRI at the one-year confirmatory biopsy; at 28 months median follow-up, 67% of patients were free from progression or intervention [39]. Larger studies indicate that carriers of BRCA1/2 or ATM mutations are more likely to have aggressive disease [40]. However, because BRCA1 and BRCA2 were grouped together, it remains unclear if BRCA2 carriers specifically have higher risk of metastatic progression and prostate cancer–related mortality, as suggested by ongoing research.

Given the uncertainty and potential risks, radical therapy is generally recommended for these patients. If active surveillance is considered, stricter eligibility criteria should be applied, likely restricted to very low-risk

individuals (e.g., excluding Gleason Grade Group 2) [41]. MRI and targeted biopsy should be incorporated into surveillance protocols, along with more frequent monitoring after confirmatory biopsy [42].

Clinical consideration: High-risk germline mutation carriers should not be selected for active surveillance using conventional criteria. Patients should be counseled on the risks, benefits, and uncertainties associated with this approach.

Clinical question: use of focal or whole-gland minimally invasive therapies

Alternative treatments for localized prostate cancer, including cryotherapy, high-intensity focused ultrasound, and focal ablation techniques such as partial laser prostate ablation, offer options for patients seeking less invasive therapies. These treatments may reduce side effects compared to standard surgery or radiotherapy, but they currently have only conditional support for low- or favorable-intermediate risk disease under AUA/ASTRO/SUO guidance [41], and are considered experimental for standard-risk patients.

It is crucial to distinguish between focal and whole-gland approaches. High-risk germline mutation carriers are generally not candidates for focal therapy because the entire prostate is at elevated risk for aggressive disease and metastatic progression. The safety and efficacy of either focal or whole-gland ablation in this population are not established. Similarly, whole-gland ablation should not be performed outside of a clinical trial due to insufficient evidence, even in average-risk populations.

Clinical consideration: Both focal and whole-gland ablative therapies are experimental for average-risk men and should not be offered routinely to individuals with high-risk germline mutations except in the context of a clinical study.

Clinical question: optimal management of localized prostate cancer in high-risk germline mutation carriers

Standard management of localized prostate cancer generally involves either surgical resection or radiotherapy, both of which have well-characterized efficacy and toxicity profiles [43]. However, the evidence for outcomes in individuals with high-risk germline mutations is limited to retrospective studies. For instance, Castro *et al*. [6] analyzed 2,019 prostate cancer patients, including 18 BRCA1 and 61 BRCA2 carriers, and reported that mutation carriers were more likely to present with high-risk disease (Gleason Grade Group ≥4), advanced clinical stage (T3/4), nodal involvement, or metastatic disease at diagnosis. Five-year cancer-specific survival (CSS) and metastasis-free survival (MFS) were lower in carriers compared to noncarriers (CSS: 96% vs. 82%; MFS: 93% vs. 77%) [6].

In a subsequent analysis by Castro *et al*. [44], outcomes of 67 BRCA carriers versus 1,302 noncarriers who received surgery or radiotherapy were compared. Notably, radiotherapy recipients tended to have more aggressive disease than those treated surgically (high-risk proportion among carriers: surgery 34.4% vs. radiotherapy 68.8%), limiting direct comparisons. Multivariable analyses indicated that treatment modality was not a statistically significant predictor. While 10-year CSS after surgery appeared clinically lower in carriers (79% vs. 95% in noncarriers), radiotherapy outcomes showed a more pronounced difference (carriers 47% vs. noncarriers 81%). Overall, these findings suggest that BRCA mutation carriers have worse outcomes than noncarriers, even with radical therapy, underscoring the need for escalated treatment strategies in this population.

Special attention should be given to ATM mutation carriers regarding radiotherapy. Early studies indicated a strong link between ATM mutations and late radiotherapy complications [45, 46]. Later work suggested potential improved radiotherapy efficacy, but dose modification is recommended to minimize toxicity or secondary malignancy risk in known ATM carriers [47]. Evidence regarding late toxicity and secondary malignancies is limited for other germline mutations, but current data in BRCA1/2 carriers do not suggest increased risk [48].

Clinical consideration: High-risk germline mutation carriers should receive intensified treatment beyond standard clinical parameters (e.g., PSA, biopsy results). Additional research is needed to define the role of neoadjuvant and adjuvant therapies in this population.

Clinical question: management of disease recurrence

Biochemical recurrence after definitive therapy is defined by PSA kinetics: post-prostatectomy, recurrence is typically a PSA ≥0.2 ng/mL confirmed on repeat testing [49]; post-radiotherapy, recurrence is defined as PSA

nadir +2 ng/mL [50]. Up to 30–50% of patients experience biochemical recurrence after surgery or radiotherapy [51-53], though disease progression varies depending on multiple risk factors. Standard management includes salvage radiotherapy with androgen deprivation after surgery and androgen deprivation therapy (ADT) following radiotherapy.

High-risk germline carriers are predisposed to aggressive disease at presentation, node-positive disease, and early metastasis [6], increasing their likelihood of persistent or recurrent PSA. These patients may benefit from earlier, intensified interventions, including cisplatin-based chemotherapy, PARP inhibitors, or early ADT. Although adjuvant radiotherapy has not demonstrated superiority over early salvage radiotherapy in the general population with adverse pathologic features [54], this may not apply to high-risk germline carriers, who could benefit from more proactive treatment.

Clinical consideration: Biochemical recurrence in high-risk germline mutation carriers warrants an escalated therapeutic approach relative to average-risk men. Prospective studies are needed to evaluate the utility of early cisplatin-based chemotherapy and PARP inhibitors in this setting.

Clinical question: management and sequencing in metastatic prostate cancer

Approximately 5% of men present with de novo metastatic prostate cancer, and 65% of men with biochemical recurrence post-surgery will develop metastatic disease within 10 years [55]. Five-year survival for metastatic prostate cancer remains low at 29% [56]. Androgen deprivation therapy (ADT) is the standard initial treatment, distinguishing between castrate-sensitive and castrate-resistant disease. Ten to twenty percent of patients develop castrate resistance within five years, typically between 13–19 months [57, 58].

High-risk germline carriers progress to castrate-resistant disease earlier than noncarriers [59-61]. Once castrate-resistant, outcomes are heterogeneous: some retrospective studies show worse overall survival [59], some improved progression-free survival [62], and others no difference [4], likely reflecting differences in disease burden and treatment with cisplatin-based chemotherapy or PARP inhibitors. The ongoing PROREPAIR-B study [60] prospectively evaluates outcomes in metastatic castrate-resistant prostate cancer, demonstrating worse outcomes in BRCA2 carriers, though associations for other germline mutations remain unclear.

Interest is growing in the use of cisplatin-based chemotherapy and PARP inhibitors for metastatic disease. A comprehensive review by Lozano *et al*. (BJC 2020) outlines current evidence and ongoing trials, summarized in **Table 2**. These interventions represent promising strategies to improve outcomes in high-risk germline mutation carriers.

Table 2. Ongoing clinical trials for metastatic prostate cancer that may benefit men with high-risk germline mutations.

Trial Name	Inclusion Criteria	Intervention	Outcome
MAGNITUDE *Niraparib Combined with Abiraterone Acetate and Prednisone vs. Abiraterone Acetate and Prednisone Alone in Metastatic Prostate Cancer Patients*	Enrollees with advanced castration-resistant prostate cancer featuring homologous recombination repair gene modifications (plus a parallel group lacking these changes)	Niraparib (or equivalent placebo) paired with abiraterone acetate and prednisone	Evaluation of niraparib's added benefit alongside abiraterone acetate and prednisone relative to abiraterone acetate, prednisone, and placebo
AMPLITUDE *Niraparib with Abiraterone Acetate and Prednisone vs. Abiraterone Acetate and Prednisone in Deleterious Germline or Somatic HRR Gene-Altered Metastatic Castration-Sensitive Prostate Cancer (mCSPC)*	Eligible individuals with metastatic castration-sensitive prostate cancer bearing confirmed harmful germline or somatic HRR gene variants	Enrollees assigned to niraparib plus abiraterone acetate and prednisone or placebo plus abiraterone acetate and prednisone	Analysis of niraparib's efficacy when added to abiraterone acetate and prednisone against abiraterone acetate and prednisone by itself
TRITON2 *Rucaparib Evaluation in Metastatic Castration-Resistant Prostate Cancer Patients with Homologous Recombination Gene Defects*	Candidates with metastatic castration-resistant prostate cancer showing harmful BRCA1/2 or ATM variants, or alternative molecular	Single-agent oral rucaparib therapy	Assessment of therapeutic responses in homologous recombination-deficient metastatic castration-resistant prostate cancer

	indicators of homologous recombination impairment		cases treated with rucaparib
PROfound *Olaparib (Lynparza™) Compared to Enzalutamide or Abiraterone Acetate in Males with Metastatic Castration-Resistant Prostate Cancer*	Males with metastatic castration-resistant prostate cancer and verified homologous recombination deficiency mutations in tumor samples	Oral study drug delivery versus enzalutamide or abiraterone acetate	Comparison of olaparib's effectiveness and tolerability against enzalutamide or abiraterone acetate

Clinical consideration: All men presenting with de novo metastatic prostate cancer or those who develop metastatic disease following prior therapy should undergo germline genetic testing. For individuals identified with high-risk germline mutations, enrollment in clinical trials is strongly encouraged to determine the optimal sequencing and combination of therapeutic agents. Multiple ongoing studies are evaluating the early use of PARP inhibitors or combination strategies in this high-risk population.

Conclusion

Our evidence-based recommendations, despite the overall low level of evidence, are summarized in **Table 3**. The understanding and management of patients harboring pathogenic germline mutations, including strategies for prostate cancer prevention and treatment, are expected to evolve substantially over the next decade. Beyond the established role of PARP inhibitors in castrate-resistant prostate cancer (CRPC), additional high-quality data are required to generate level 1 clinical guidance. This review provides practical considerations for real-world clinical scenarios. As urologic oncology increasingly moves toward personalized medicine, accelerated research is essential to integrate genetic insights into standard clinical practice effectively.

Table 3. Summary of clinical considerations.

Clinical Question	Clinical Recommendation	Evidence Level / Rationale
Which prostate cancer patients should receive germline genetic testing?	Every man fulfilling NCCN criteria must complete germline testing via a certified lab **(Table 1).** Testing indications are uniform across leading societies.	Robust, harmonized guideline consensus.
Can prostate cancer be prevented in carriers of high-risk germline mutations?	No chemopreventive drugs are approved for average- or high-risk individuals.	Trials exist in general populations; none in high-risk germline cohorts.
What screening regimen is advised for men with high-risk germline mutations?	Initiate screening earlier with routine PSA, MRI monitoring, and low biopsy threshold.	Growing Level 1 evidence supports aggressive screening.
Should men with high-risk germline mutations be offered active surveillance?	Standard active surveillance is contraindicated.	Sparse data; restrict to clinical trials only.
Are focal or whole-gland ablative therapies appropriate for these patients?	Ablative methods remain investigational; offer only within trials.	Experimental; trial enrollment required.
What is the optimal management of localized prostate cancer in high-risk mutation carriers?	Provide intensified therapy beyond usual risk-stratified protocols (biopsy, PSA, etc.).	Retrospective studies only; assume elevated recurrence risk.
How should biochemical recurrence be managed after definitive therapy in these men?	Adopt escalated salvage strategies versus average-risk cases.	Retrospective data only; high progression/mortality risk.
What is the best treatment sequence for metastatic disease in high-risk germline carriers?	Prioritize clinical trial participation to define optimal drug ordering.	Emerging Level 1 data on agents; sequencing unresolved.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool. U.S. Department of Health and Human Services; 2020. Available from: https://www.cdc.gov/cancer/dataviz
2. Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst. 2012;104:1335–42.
3. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
4. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. Available from: https://www.nejm.org/doi/10.1056/NEJMoa1603144
5. Narod SA, Neuhausen S, Vichodez G, Armel S, Lynch HT, Ghadirian P, et al. Rapid progression of prostate cancer in men with a BRCA2 mutation. Br J Cancer. 2008;99:371–4.
6. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline BRCA mutations and risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol. 2013;31:1748–57.
7. Kote-Jarai Z, Leongamornlert D, Saunders E, Tymrakiewicz M, Castro E, Mahmud N, et al. BRCA2 as a moderate penetrance gene contributing to young-onset prostate cancer. Br J Cancer. 2011;105:1230–4.
8. Akbari MR, Wallis CJ, Toi A, Trachtenberg J, Sun P, Narod SA, et al. Impact of BRCA2 mutation on mortality from screen-detected prostate cancer. Br J Cancer. 2014;111:1238–40.
9. Ataxia-telangiectasia. Available from: https://www.cancer.net/cancer-types/ataxia-telangiectasia
10. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in population-based breast cancer series. Br J Cancer. 2000;83:1301–8.
11. Maxwell KN, Domchek SM, Nathanson KL, Robson ME. Population frequency of germline BRCA1/2 mutations. J Clin Oncol. 2016;34:4183–5.
12. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of hereditary breast cancer: ASCO–ASTRO–SSO guideline. J Clin Oncol. 2020;38:2080–106.
13. Daly MB, Reiser G, Pal T, Kohlmann W, Senter-Jamieson L, Kurian AW, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic. J Natl Compr Canc Netw. 2020;122:77–102.
14. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate cancer, version 2.2019: NCCN guideline. J Natl Compr Canc Netw. 2019;17:479–505.
15. Giri VN, Knudsen KE, Kelly WK, Abida W, Andriole GL, Bangma CH, et al. Genetic testing for inherited prostate cancer risk: Philadelphia Consensus 2017. J Clin Oncol. 2017;36:414–24.
16. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer: screening, diagnosis and local treatment. Eur Urol. 2014;65:124–37.
17. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. AUA/ASTRO/SUO guideline for localized prostate cancer. J Urol. 2018;199:683–90.
18. Clark R, Kenk M, McAlpine K, Thain E, Farncombe KM, Pritchard CC, et al. Germline genetic testing in prostate cancer management. Can Urol Assoc J. 2021;15:E623.
19. van Adelsberg J, Gann P, Ko AT, Damber JE, Logothetis C, Marberger M, et al. Cardiovascular events in the VIOXX prostate cancer prevention study. Curr Med Res Opin. 2007;23:2063–70.
20. Klein EA, Thompson IM, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and prostate cancer risk: SELECT trial. JAMA. 2011;306:1549–56.
21. Thompson IM, Goodman PJ, Tangen CM, Parnes HL, Minasian LM, Godley PA, et al. Long-term survival in the Prostate Cancer Prevention Trial. N Engl J Med. 2013;369:603–10.

22. Musquera M, Fleshner NE, Finelli A, Zlotta AR. Chemoprevention in prostate cancer using dutasteride: REDUCE trial. Expert Rev Anticancer Ther. 2008;8:1073–9.
23. FDA. Drug safety communication: 5-alpha reductase inhibitors and prostate cancer risk. 2019. Available from: https://tinyurl.com/y8jm62h7
24. Fleshner N, Zlotta AR. Prostate cancer prevention: past, present, future. Cancer. 2007;110:1889–99.
25. He K, Hu H, Ye S, Wang H, Cui R, Yi L. Metformin therapy and prostate cancer prognosis: a meta-analysis. Sci Rep. 2019;9:2218.
26. Allott EH, Craig EL, Stopsack KH. Optimal setting for statin trials in prostate cancer. Prostate Cancer Prostatic Dis. 2021;24:583–4.
27. Metcalfe K, Lynch HT, Foulkes WD, Tung N, Kim-Sing C, Olopade OI, et al. Effect of oophorectomy on survival after breast cancer in BRCA1/2 carriers. JAMA Oncol. 2015;1:306–13.
28. Clark R, McAlpine K, Fleshner N. Prophylactic prostatectomy for BRCA2 mutation carriers. Eur Urol Focus. 2021;7:506–7.
29. Thompson IM. Overdiagnosis and overtreatment of prostate cancer. ASCO Educ Book. 2012;32:e35–9.
30. Hugosson J, Roobol MJ, Månsson M, Tammela TL, Zappa M, Nelen V, et al. 16-year results of ERSPC. Eur Urol. 2019;76:43–51.
31. Hugosson J, Godtman RA, Carlsson SV, Aus G, Bergdahl AG, Lodding P, et al. 18-year follow-up of Göteborg prostate cancer screening trial. Scand J Urol. 2018;52:27–37.
32. Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360:1310–9.
33. U.S. Preventive Services Task Force. Final recommendation: prostate cancer screening. Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening
34. Wolf AMD, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al. ACS guideline for early detection of prostate cancer. CA Cancer J Clin. 2010;60:70–98.
35. Page EC, Bancroft EK, Brook MN, Assel M, Hassan Al Battat M, Thomas S, et al. Interim results from the IMPACT study. Eur Urol. 2019;76:831–42.
36. Segal N, Ber Y, Benjaminov O, Tamir S, Yakimov M, Kedar I, et al. MRI-based screening in BRCA carriers. Ann Oncol. 2020;31:1545–52.
37. Porten SP, Whitson JM, Cowan JE, Cooperberg MR, Shinohara K, Perez N, et al. Grade change on serial biopsy during active surveillance. J Clin Oncol. 2011;29:2795–800.
38. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, et al. Long-term outcomes of active surveillance cohort. J Clin Oncol. 2015;33:272–7.
39. Halstuch D, Ber Y, Margel D. Screening and treatment of localized prostate cancer in BRCA carriers. Eur Urol Focus. 2020;6:212–4.
40. Carter HB, Helfand B, Mamawala M, Wu Y, Landis P, Yu H, et al. Germline ATM and BRCA1/2 mutations and grade reclassification. Eur Urol. 2019;75:743–9.
41. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. AUA/ASTRO/SUO guideline: care options (Part II). J Urol. 2018;199:990–7.
42. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/US fusion-guided vs US-guided biopsy. JAMA. 2015;313:390–7.
43. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy. N Engl J Med. 2016;375:1425–37.
44. Castro E, Goh C, Leongamornlert D, Saunders E, Tymrakiewicz M, Dadaev T, et al. BRCA mutations and metastatic relapse after radical treatment. Eur Urol. 2015;68:186–93.
45. Iannuzzi CM, Atencio DP, Green S, Stock RG, Rosenstein BS. ATM mutations and radiation late effects in breast cancer. Int J Radiat Oncol Biol Phys. 2002;52:606–13.
46. Cesaretti JA, Stock RG, Lehrer S, Atencio DA, Bernstein JL, Stone NN, et al. ATM variants and adverse radiotherapy response. Int J Radiat Oncol Biol Phys. 2005;61:196–202.
47. Bergom C, West CM, Higginson DS, Abazeed ME, Arun B, Bentzen SM, et al. Genetic testing and radiotherapy decisions. Int J Radiat Oncol Biol Phys. 2019;105:698–712.
48. Pierce LJ, Haffty BG. Radiotherapy in hereditary breast cancer. Semin Radiat Oncol. 2011;21:43–50.

49. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, et al. Definition of biochemical recurrence after prostatectomy. J Urol. 2007;177:540–5.
50. Abramowitz MC, Li T, Buyyounouski MK, Ross E, Uzzo RG, Pollack A, et al. Phoenix definition predicts survival after radiotherapy. Cancer. 2008;112:55–60.
51. Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term survival after radical prostatectomy. Urol Clin North Am. 2001;28:555–65.
52. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Long-term results of radical retropubic prostatectomy. J Urol. 2004;172:910–4.
53. Kupelian PA ،Mahadevan A ،Reddy CA ،Reuther AM ،Klein EA. Definitions of biochemical failure after radiotherapy and treatment conclusions. Urology. 2006;68:593–8.
54. Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al. Adjuvant vs early salvage radiotherapy: systematic review. Lancet. 2020;396:1422–31.
55. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history after PSA elevation post-prostatectomy. JAMA. 1999;281:1591–7.
56. SEER. Cancer of the prostate—stat facts. Available from: https://seer.cancer.gov/statfacts/html/prost.html
57. Kirby M, Hirst C, Crawford ED. Characterising castration-resistant prostate cancer: systematic review. Int J Clin Pract. 2011;65:1180–9.
58. Sharifi N, Dahut WL, Steinberg SM, Figg WD, Tarassoff C, Arlen P, et al. Time to clinical endpoints in advanced prostate cancer. BJU Int. 2005;96:985–9.
59. Annala M, Struss WJ, Warner EW, Beja K, Vandekerkhove G, Wong A, et al. Treatment outcomes and LOH in DNA-repair deficient prostate cancer. Eur Urol. 2017;72:34–42.
60. Castro E, Romero-Laorden N, Del Pozo A, Lozano R, Medina A, Puente J, et al. PROREPAIR-B cohort: outcomes in DNA repair mutation carriers. J Clin Oncol. 2019;37:490–503.
61. Vandekerkhove G, Struss WJ, Annala M, Kallio HM, Khalaf D, Warner EW, et al. ctDNA utility in de novo metastatic prostate cancer. Eur Urol. 2019;75:667–75.
62. Antonarakis ES. Predicting treatment response in castration-resistant prostate cancer. Expert Rev Anticancer Ther. 2015;15:143–5.