Genetic Contribution to Metastatic Prostate Cancer

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KEYWORDS

• Metastatic prostate cancer • Genetic testing • Germline • *BRCA2*

KEY POINTS

- Up to 12% of men with metastatic prostate cancer carry an actionable pathogenic germline mutation in DNA damage repair genes, most frequently *BRCA2*, *ATM*, *CHEK2*, and *BRCA1*.
- Germline *BRCA2* mutations are associated with increased risk of prostate cancer and worse prostate cancer outcomes.
- The poly-(ADP-ribose) polymerase inhibitors olaparib and rucaparib have received US Food and Drug Administration approval for metastatic prostate cancer with DNA damage repair alterations.
- Platinum chemotherapy has also been reported to be effective among men with DNA damage repair alterations.

INTRODUCTION

Prostate cancer is well recognized to have a strong heritable component, but incorporation of genetic testing for germline pathogenic and likely pathogenic variants (hereafter referred to as mutations) in DNA repair genes has recently increased and is becoming more widespread (**Tables 1** and **2**). Several landmark studies have recently led to a dramatic shift in understanding and clinical practice, particularly in the setting of metastatic prostate cancer because of treatment implications. These same germline mutations in DNA repair genes may represent known or suspected autosomal dominant inherited cancer risk genes, the most notable of which is *BRCA2*. This article focuses on the current knowledge of germline (also known as inherited) genetic contributions to metastatic prostate cancer. Other articles in this issue review in greater depth the topics of therapeutic implications (including in earlier disease states), opportunities in screening and early detection of prostate cancer, genetic predisposition syndromes, multigene testing, and polygenic risk scores.

PROSTATE CANCER HAS A STRONG HERITABLE COMPONENT

Approximately 57% of prostate cancer risk can be attributable to genetic factors, based on long-term follow-up from the Norwegian Twin Cancer study, comparing monozygotic and dizygotic twin pairs.[1,2] In the Prostate Cancer Database Sweden (PCBaSe), the overall risk of developing prostate cancer for men with a brother with prostate cancer by the age 65 years was 14.9%, compared with 4.8% in men without a brother with prostate cancer, and the risk was 30.3% versus 12.9% at age 75 years. This observation held, even after exclusion of low-risk prostate cancer.[3]

EARLY SEQUENCING DISCOVERIES IN PROSTATE METASTASES INVOLVE DNA REPAIR GENES

Before 2015, understanding about molecular features of prostate cancer tumors came largely from prostatectomies and biopsies because archival tumor material due to clinical acquisition for diagnostic or treatment purposes. With the

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Table 1
Genes with current and potential clinical actionability

Gene	Association with ↑ PC Risk	Prevalence of Germline Mutations in Metastatic PC (%)	Prevalence of Germline Mutations in PC with Family History(%)	DNA Damaging Agents: PARP Inhibitors, Platinum[b]	Immune Checkpoint Inhibitors: PD-1 Inhibitors
ATM	X	1.6	2.0	XX	—
ATR	—	0.3	Not evaluated	—	—
BARD1	—	Not evaluated	Not evaluated	XX	—
BRCA1	X	0.9	0.7	XXX	—
BRCA2	X	5.4	4.7	XXXX	—
BRIP1	—	0.2	0.3	XX	—
CDK12 (somatic only)	—	—	Not evaluated	XX	X
CHEK1	—	Not evaluated	Not evaluated	XX	—
CHEK2	X	1.9	2.9	XX	—
FAM175A	—	0.2	Not evaluated	—	—
FANCA	—	—	Not evaluated	X	—
FANCL	—	Not evaluated	Not evaluated	XX	—
HOXB13 (germline only)	X	Not evaluated	1.1	—	—
MLH1	X	—	0.06	—	X
MRE11A	—	0.14	Not evaluated	—	—
MSH2	X	0.14	0.69	—	X
MSH6	X	0.14	0.45	—	X
NBN	—[a]	0.3	0.32	XX	—
PALB2	—[a]	0.4	0.56	XX	—
PMS2	X	0.3	0.54	—	X
RAD51B	—	Not evaluated	Not evaluated	XX	—
RAD51C	—	0.14	0.21	XX	—
RAD51D	—	0.4	0.15	XX	—
RAD54L	—	Not evaluated	Not evaluated	XX	—

Abbreviations: PARP, poly-(ADP-ribose) polymerase; PC, prostate cancer; PD-1 programmed cell death protein 1.
[a] Emerging/limited data.
[b] XX designation follows US Food and Drug Administration approval based on ProFOUND (Phase 3 Study of Olaparib vs. Enzalutamide or Abiraterone for Metastatic Castration-Resistant Prostate Cancer with Homologous Recombination Repair Gene Alterations) study.
Data from Cheng, H. H., Sokolova, A. O., Schaeffer, E. M., Small, E. J. & Higano, C. S. Germline and Somatic Mutations in Prostate Cancer for the Clinician. J. Natl. Compr. Cancer Netw. JNCCN 17, 515–521 (2019).

exception of a few select rapid autopsy research programs, metastatic prostate cancer tumors were largely uncharacterized until an international, multi-institutional study to obtain metastatic biopsies and characterize mutational spectra was made possible by Stand Up 2 Cancer (SU2C) and the Prostate Cancer Foundation. Results from the first 150 metastatic biopsies were reported in 2015 and identified a high proportion of actionable mutations, including 23% with mutations and other alterations in DNA repair genes such as *BRCA2*, *ATM*, and *BRCA1*.[4] Mounting evidence also supported that prostate cancers with *BRCA2* inactivation were sensitive to platinum chemotherapy,[5,6] and the phase II trial of PARP inhibition in prostate cancer (TOPARP-A) study reported early compelling evidence from a limited number of patients that poly-(ADP-ribose)

Table 2
Selected therapeutic clinical trials in earlier stages prostate cancer with relevance to germline genetics

Phase	Title	Disease State	Trial Name	Clinicaltrials.gov
II	Olaparib Prior to Radical Prostatectomy For Patients With Locally Advanced Prostate Cancer and Defects in DNA Repair Genes	Localized disease	BrUOG 337	NCT03432897
I/II	A Multi-Center Trial of Androgen Suppression With Abiraterone Acetate, Leuprolide, PARP Inhibition and Stereotactic Body Radiotherapy in Prostate Cancer	Localized disease	ASCLEPIuS	NCT04194554
II	Niraparib Before Surgery in Treating Patients With High Risk Localized Prostate Cancer and DNA Damage Response Defects	Localized disease	—	NCT04030559
II	Olaparib in Men With High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, With Integrated Biomarker Analysis	BCR	—	NCT03047135
II	A Study of Olaparib and Durvalumab in Prostate Cancer	BCR	—	NCT03810105
II	Durvalumab and Olaparib for the Treatment of Prostate Cancer in Men Predicted to Have a High Neoantigen Load	BCR	—	NCT04336943
II	Rucaparib in Nonmetastatic Prostate With BRCAness	BCR	ROAR	NCT03533946
II	Trial of Rucaparib in Patients With Metastatic Hormone-Sensitive Prostate Cancer Harboring Germline DNA Repair Gene Mutations	mCSPC	TRIUMPH	NCT03413995
II	Enzalutamide Plus Talazoparib for the Treatment of Hormone Sensitive Prostate Cancer	mCSPC	ZZ-First	NCT04332744
III	A Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for the Treatment of Participants With Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-Mutated Metastatic Castration-Sensitive Prostate Cancer	mCSPC	AMPLITUDE	NCT04497844

(*continued on next page*)

Table 2
(*continued*)

Phase	Title	Disease State	Trial Name	Clinicaltrials.gov
II	Abiraterone/Prednisone, Olaparib, or Abiraterone/ Prednisone + Olaparib in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects	First-line mCRPC	BRCAaway	NCT03012321
III	A Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Participants With Metastatic Prostate Cancer	First-line mCRPC	MAGNITUDE	NCT03748641

Abbreviations: BCR, biochemical recurrence; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer.

polymerase (PARP) inhibitors, such as olaparib, held tantalizing promise for metastatic castration-resistant prostate cancers (mCRPCs) harboring defects in genes involved in homologous recombination DNA repair (*BRCA2*, *ATM*, *CHEK2*, *PALB2*, and others).[7] Notably, about half of the patients with DNA repair mutations in these early studies had a germline component, representing known or suspected autosomal dominant cancer predisposition syndromes. In addition, the prevalence in the population of men with metastatic disease was much higher than previously recognized.

GERMLINE DNA REPAIR GENE MUTATIONS ENRICHED IN THE POPULATION OF PATIENTS WITH METASTATIC PROSTATE CANCER

In 2016, a definitive study of 692 men with metastatic prostate cancer was conducted with targeted germline sequencing. Importantly, the men were unselected for family history or age at diagnosis. Remarkably, 11.8% (82 out of 692) had germline mutations in DNA repair genes, most frequently *BRCA2*, *ATM*, *CHEK2*, and *BRCA1*.[8] Moreover, the presence of a germline variant (mutation) that inactivated DNA repair gene function was not correlated with either family history of prostate cancer (although there was a trend toward this) or with age at diagnosis. In the patients where tumors were available for sequencing, 67% (36 out of 61) had evidence of second allele inactivation, supporting that germline alterations were biologically relevant rather than simply bystanders. That the proportion of men with metastatic prostate cancer carrying germline mutations exceeded 10%, and was far higher than previously thought, justified consideration of genetic testing for all men with metastatic prostate cancer. These findings have been borne out in other studies with similar prevalence in various mCRPC cohorts, such as 16.2% (Spain), 12% (United States), and 7.5% (Canada),[9–12] and seem to be similar in the metastatic hormone-sensitive population: 9.4% prevalence in metastatic hormone-sensitive prostate cancer plus mCRPC in the study by Yadav and colleagues.[12]

These data, together with important treatment relevance to newly US Food and Drug Administration (FDA)–approved PARP inhibitors (discussed later and elsewhere in this issue), have led to major changes in the National Comprehensive Cancer Network (NCCN) prostate cancer guidelines for recommending genetic testing for inherited cancer risk mutations in all men with metastatic disease.[5]

Note that the prevalence in high-risk localized populations has also been determined to be greater than 5% and has led to the inclusion of men with high-risk localized disease, node-positive disease, and certain histologies (intraductal, cribriform, ductal; discussed further later)[13,14] to also be offered germline genetic testing in the guidelines.[5]

DNA REPAIR GENES: FROM PATHWAYS TO INDIVIDUAL GENES

There is great interest and enthusiasm in identifying, understanding, and improving the care for men with germline mutations in DNA repair genes. However, although collectively there is a group of genes

involved in the critical biological processes of repairing errors and defects during DNA replication, the current understanding of individual genes is variable between the genes and ranges from more evidence to scant. The evidence for individual key genes of interest and for increased prostate cancer risk and enrichment in the metastatic disease setting are reviewed next, beginning with a discussion about *BRCA2*, for which there is greater existing literature and numbers about the increased risk of prostate cancer for germline *BRCA2* mutation carriers, most of which comes from ascertainment by female relatives with breast and ovarian cancer.

EVIDENCE FOR INCREASED PROSTATE CANCER RISK AND LETHALITY AMONG MALE *BRCA2* MUTATION CARRIERS

Several studies report evidence that men with germline *BRCA2* mutations have increased risk of prostate cancer. For example, a study of the Icelandic *BRCA2* founder mutation 999del5 showed that men presented with higher-risk disease at a younger age and had an increased risk of death from prostate cancer.[15] Specifically, they were found to present at a younger age at diagnosis (69 years vs 74 years; $P = .002$), more advanced tumor stage (stages 3–4; 79% vs 39%; $P<.001$), higher tumor grade (grades G3–G4; 84% vs 53%; $P = .007$), and shorter median survival time (2.1 years, 95% confidence interval CI = 1.4–3.6 years; vs 12.4 years, 95% CI = 9.9–19.7 years).[15] *BRCA2* 999del5 mutation carriers also had an increased risk of prostate cancer–specific mortality, even after adjusting for year of diagnosis, age, and stage.[15]

In another study by Gallagher and colleagues,[16] *BRCA2* mutations were associated with a 3-fold increased risk of prostate cancer and higher Gleason score. As with the Icelandic study, after adjusting for clinical stage, prostate-specific antigen (PSA), Gleason score, and treatment, *BRCA2* and *BRCA1* mutation carriers had a higher risk of prostate cancer recurrence (hazard ratio [HR] [95% CI], 2.4 [1.2–4.8] and 4.3 [1.3–13.6], respectively) and prostate cancer–specific death (HR [95% CI], 5.5 [2.0–14.8] and 5.2 [1.1–24.5], respectively) than their noncarrier counterparts.[16]

A UK study by Castro and colleagues[17] reported similar findings that men with prostate cancer and germline *BRCA2* and *BRCA1* mutations were more frequently associated with Gleason score greater than or equal to 8 ($P = .00003$), T3/T4 stage ($P = .003$), nodal involvement ($P = .00005$), and metastases at diagnosis ($P = .005$) than their noncarrier counterparts. Prostate cancer–specific survival (CSS) was also significantly shorter for carriers compared with noncarriers (8.6 vs 15.7 years, multivariable analyses [MVAs] $P = .015$; HR, 1.8). Subgroup analyses confirmed poor outcomes in *BRCA2* patients, whereas findings for *BRCA1* were less well defined because of limited size and follow-up.[18] In a follow-up study, the same group reported on prostate cancer metastasis-free outcomes in 67 *BRCA1/2* carriers and 1235 noncarriers at 3, 5, and 10 years after definitive treatment: 90%, 72%, and 50% of carriers and 97%, 94%, and 84% of noncarriers were free from metastasis ($P<.001$).[17] The 3-year, 5-year, and 10-year CSS rates were significantly worse in carriers (96%, 76%, and 61%, respectively) than the noncarrier cohort (99%, 97%, and 85%, respectively; $P<.001$). Multivariate analysis confirmed *BRCA1/2* mutations as an independent prognostic factor for metastasis-free survival (HR, 2.36; 95% CI, 1.38 to 4.03; $P = .002$) and CSS (HR, 2.17; 95% CI, 1.16–4.07; $P = .016$).[17]

Another larger, retrospective cohort study of 6902 men from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) also reported an increased risk of prostate cancer, greater in men carrying *BRCA2* mutations compared with those carrying *BRCA1* mutations.[19] A higher frequency of prostate cancers was associated with a higher probability of being a *BRCA2* pathogenic variant carrier (odds ratio [OR], 1.39; 95% CI, 1.09–1.78; $P = .008$).[19]

ASSOCIATION WITH HIGHER GRADE AND DISTINCT HISTOLOGIC SUBTYPES

Intraductal carcinoma of the prostate is a distinct histologic entity that represents retrograde spread of invasive acinar adenocarcinoma into prostatic acini and ducts with basal cell preservation. This histologic variant is associated with an aggressive clinical course, including an increased risk of biochemical recurrence, metastasis, and mortality. These histologic features of prostate cancer are also enriched for carrying driver mutations. For example, men with germline *BRCA* mutations are more likely to have intraductal features in their prostate cancer, which correlate with poor outcomes.[20]

In addition, several other pathologic features in addition to intraductal, such as ductal, lymphovascular invasion, cribriform pattern 4, and presence of Gleason grade group 5, have been reported to be enriched for presence of germline alterations.[21–23]

ASSOCIATION OF *BRCA2* MUTATIONS WITH MORE AGGRESSIVE MOLECULAR SIGNATURES

Taylor and colleagues[14] profiled the genomes and methylomes of localized prostate cancers from 14

carriers of germline *BRCA2* mutations/pathogenic variants to understand the more aggressive phenotype of these tumors. They showed that *BRCA2*-mutant prostate cancers show increased genomic instability and mutational profiles that more closely resemble metastatic prostate cancer compared with localized prostate cancer. They also observed genomic and epigenomic dysregulation of the MED12L/MED12 axis, which is frequently dysregulated in mCRPC. This dysregulation is enriched in *BRCA2*-mutant prostate cancer harboring intraductal carcinoma. This study shows that localized *BRCA2*-mutant tumors are uniquely aggressive, because of de novo aberration in genes commonly observed in metastatic disease and thus justifying aggressive initial treatment of *BRCA2* carriers who develop prostate cancer.[14]

HOMOLOGOUS RECOMBINATION DNA REPAIR GENES AND EMERGING UNDERSTANDING OF GERMLINE MUTATIONS IN GENES BEYOND *BRCA2*

Germline *BRCA2* alterations are the most commonly observed and the most reported in prostate cancer. *BRCA2* alterations are associated with the highest prostate cancer risk, poor outcomes, and the best responses to platinum and PARP inhibitors. Even though non-*BRCA2* DNA repair genes are also involved in homologous recombination repair pathway, alterations in these genes may have a very different biological relevance for prostate cancer and require further individual characterization. Key differences are already apparent in estimated cancer risk and targeted treatment sensitivity in germline carriers. Genes that are implicated because of overrepresentation in metastatic disease with biological plausibility are discussed later. Increasingly clear is that each warrants individual evaluation and attention. There are likely to be differences in risk of tumor initiation, disease-modifying factors, subsequent elective advantage, and contribution to metastatic potential. This topic demands further close investigation, and will require long-term follow-up and collaborative efforts.

BRCA1

Together with *BRCA2*, germline *BRCA1* mutations have also been associated with increased risk of prostate cancer, aggressive disease, and response to DNA damaging agents. However, the strength of association with prostate cancer risk and apparent magnitude of risk is less compared with *BRCA2*. In many of the studies discussed earlier, the numbers of *BRCA1* mutation carriers and prostate cancer–specific events were less pronounced or findings less conclusive compared with *BRCA2*. For example, in a large study by LeCarpentier and colleagues,[24] the prostate cancer risk by age 80 years at the fifth and 95th percentiles of the polygenic risk score varies from 7% to 26% for carriers of *BRCA1* mutations and from 19% to 61% for carriers of *BRCA2* mutations, respectively. However, there is still enrichment in the metastatic setting, and it would still be considered a gene mutation of interest with respect to prostate cancer risk as well as metastatic disease treatment implications.

ATM

Germline *ATM* pathogenic variants are more common in the general population but are enriched in the metastatic prostate cancer setting, the second most common alteration after *BRCA2*.[8] Early data on response to PARP inhibitors in the setting of *ATM* inactivation suggest substantial differences compared with *BRCA2*, which is not surprising because of different functions of BRCA2 and ATM proteins. This finding raises some uncertainty as to whether absence of ATM function contributes to cancer initiation or to metastatic potential.

A study by Na and colleagues[25] evaluated *BRCA2*, *BRCA1*, and *ATM* germline mutations in a retrospective case-case study of 799 men with prostate cancer, including 313 who died of prostate cancer and 486 of European, African, and Chinese descent with low-risk localized prostate cancer. The combined *BRCA1/2* and *ATM* mutation carrier rate was higher in patients with lethal prostate cancer (6.1%) than patients with localized prostate cancer (1.4%; $P = .0007$). The rate also differed significantly among patients with lethal prostate cancer as a function of age at death. Survival analysis in the entire cohort revealed mutation carriers remained an independent predictor of lethal prostate cancer after adjusting for race, age, PSA, and Gleason score at diagnosis (HR, 2.13; 95% CI, 1.24–3.66; $P = .004$). Although *ATM* was included here, the study did not investigate other known DNA repair mutations beyond *BRCA1/2* and *ATM*, and the number of men with *ATM* mutations was small.[25]

In a study by Wokołorczyk and colleagues,[26] mutations in *ATM*, *NBN*, and *BRCA2* predisposed to aggressive prostate cancer in the Polish population. To investigate the frequency of mutations and estimate gene-related prostate cancer risks and probability of aggressive disease, 14 genes were studied by exome sequencing in 390 men with familial prostate cancer and 308 cancer-free controls. Of 390 patients with prostate cancer, 76

men (19.5%) carried a mutation in *BRCA1*, *BRCA2*, *NBN*, *ATM*, *CHEK2*, *HOXB13*, *MSH2*, or *MSH6* genes. Significant associations with familial prostate cancer risk were observed for *CHEK2*, *NBN*, *ATM*, and *HOXB13*. High-grade (Gleason 8–10) tumors were seen in 56% of *BRCA2*, *NBN*, or *ATM* carriers, compared with 21% of patients who tested negative for mutations in these genes (OR, 4.7; 95% CI, 2.0–10.7; $P = .0003$).[26]

PALB2

PALB2 mutations, such as *BRCA1* and *ATM* and the others discussed later, are considerably less commonly observed compared with *BRCA2*, but are of clear interest, in part because of knowledge from other related cancer risk settings, such as breast and ovarian cancers. There are very limited and conflicting data for germline *PALB2* and prostate cancer risk, although it is thought that historic cohorts must be viewed with caution given the ascertainment via female relatives with breast and ovarian cancers, as well as incomplete reporting of prostate cancer and frequent lack of distinction between diagnoses of very common low-grade prostate cancer (Gleason 6) versus high-grade (Gleason 8–10) and metastatic prostate cancer. Earlier studies have reported lack of clear association between *PALB2* and hereditary prostate cancer families with prostate cancer diagnoses younger than 55 years or multiple affected kindred.[27–29] However, germline *PALB2* mutations have been reported in association with aggressive prostate cancer, and *PALB2* reversion mutations have been associated with resistance to PARP inhibitors, arguing biological relevance.[30,31] Increased use of panel testing in men with metastatic and localized disease will likely lead to greater identification of men with germline *PALB2* mutations and the potential to reveal a different picture with more advanced prostate cancer–specific ascertainment. This discussion may apply for each of the rarer prostate cancer germline gene variants associated with metastatic disease discussed here.

CHEK2

Germline mutations in the Chek2 kinase gene (*CHEK2*) have been associated with increased prostate cancer risk. In Poland, extensive work and several studies led by Cybulski have reported that certain truncating founder mutations (*CHEK2* 1100delC and *CHEK2* IVS2 + 1G>A) are associated with a moderate risk of prostate cancer. *CHEK2* IVS2 + 1G>A or 1100delC were identified in 9 of 1921 controls (0.5%) and in 11 of 690 (1.6%) unselected patients with prostate cancer (OR, 3.4; $P = .004$).[32] The missense *CHEK2* variant I157T was associated with prostate cancer (OR, 1.7; $P = .002$).[33] A subsequent meta-analysis reviewed 12 articles that discussed *CHEK2* c.1100delC, and its association with prostate cancer was identified. Of the 12 prostate cancer studies, 5 studies had independent data from which to draw conclusive evidence. The pooled results of OR and 95% CI were 1.98 (1.23–3.18) for unselected cases and 3.39 (1.78–6.47) for familial cases, indicating that *CHEK2* c.1100delC mutation is associated with increased risk of prostate cancer.[34]

Some controversy exists about the broader applicability of some *CHEK2* variant findings across other populations, and broader associations of more aggressive disease remain under study. However, Wu and colleagues[35] found that *CHEK2*, c.1100delC, had a significantly higher carrier rate (1.28%) in patients with lethal prostate cancer compared patients of European American origin with low-risk prostate cancer (0.16%), $P = .0038$. The estimated OR for lethal prostate cancer was 7.86.

NBN (NBS1)

Cybulski and colleagues[36] evaluated founder mutations in *NBN* (also called *NBS1*) in association with prostate cancer risk in the Polish population. The prevalence of 657del5 *NBS1* founder allele in 56 patients with familial prostate cancer was compared with 305 patients with nonfamilial prostate cancer, and 1500 control subjects from Poland. Loss of heterozygosity analysis also was performed on DNA samples isolated from 17 microdissected prostate cancers, including 8 from carriers of the 657del5 mutation. The *NBS1* founder mutation was present in 5 of 56 (9%) patients with familial prostate cancer (OR, 16; $P<.0001$), 7 of 305 (2.2%) patients with nonfamilial prostate cancer (OR, 3.9; $P = .01$), and 9 of 1500 control subjects (0.6%). Evidence of second allele inactivation of *NBS1* was found in 7 of 8 prostate tumors from carriers of the *NBS1* 657del5 allele, whereas loss of heterozygosity was seen in only 1 of 9 tumors from noncarriers ($P = .003$), suggesting that heterozygous carriers of the *NBS1* founder mutation have increased susceptibility to prostate cancer.

In a subsequent study, also led by Cybulski and colleagues,[37] *NBS1* 657del5 allele was detected in 53 of 3750 unselected cases compared with 23 of 3956 (0.6%) controls (OR, 2.5; $P = .0003$). Mortality was worse for carriers of the *NBS1* mutation compared with noncarriers (HR, 1.85; $P = .008$). Five-year survival for men with the *NBS1* mutation was 49%, compared with 72% for mutation-

negative patients. A founder mutation in *NBS1* predisposes to aggressive prostate cancer in the Polish population.[37]

Wokołorczyk and colleagues[26] reported a study described earlier in relation to *ATM* that also included *NBN* and found an association with higher-grade prostate cancer.

RAD51C

Other germline mutations (pathogenic variants) in genes that are newly implicated with metastatic prostate cancer are still less characterized than *BRCA1*, *ATM*, *PALB2*, and *CHEK2* because of rarity (eg, *FANCA* or *RAD51C*). Further study in the context of conferred prostate cancer risk, disease-modifying properties within tumors, and clinical response to molecularly targeted treatments, along with continue translational laboratory studies, will be needed.

DNA MISMATCH REPAIR GENES (LYNCH SYNDROME)

Lynch syndrome is an autosomal dominant disorder defined by a germline mutation (pathogenic variant) in one of several DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, or *PMS2*. The risk of prostate cancer in Lynch syndrome has been debated, but several recent studies provide a more compelling argument for increased risk for prostate cancer. Raymond and colleagues[38] examined 4127 men from familial cancer registries and reported the cumulative risk of prostate cancer to be significantly increased compared with the general population (6.3% vs 2.6% by age 60 years and 30% vs 18% by age 80 years). Haraldsdottir and colleagues[39] calculated an increased risk of 188 men with Lynch syndrome compared with the general population, with a standardized rate ratio of 4.87 (95% CI, 2.43–8.71). The prospective Lynch Syndrome Database recently reported 6350 men with Lynch syndrome and 51,646 years of follow-up, of whom 1808 men were prospectively observed to have cancer. Germline *MSH2* mutation carriers were noted to have a particularly higher risk of prostate cancer (23.8% incidence of prostate cancer by age 75 years vs 13.8% for *MLH1*, 8.9% for *MSH6*, and 4.6% for *PMS2* by age 75 years).[40]

The association with metastatic disease and genes involved in mismatch repair is less common than for genes in the homologous recombination repair pathway, but importance is still clear. Approximately 5% to 7% of patients with mCRPC have evidence of tumor microsatellite instability (MSI-H)/mismatch repair deficiency (MMRd).[41] In a study by Abida and colleagues,[42] 3% of prostate cancers of all stages (localized and metastatic) undergoing tumor sequencing had evidence of MSI-H/MMRd. Of those, approximately 20% had Lynch syndrome and about half that received anti-programmed cell death protein 1/programmed death-ligand 1 achieve durable benefit.

HOXB13

The germline *HOXB13* G84E variant was cloned and validated in association with hereditary prostate cancer.[43–45] Until recently, its association was primarily for prostate cancer risk, but not with increased aggressiveness of disease, treatment actionability, or risk of other cancers. However, active research is ongoing to further understand the biology of germline *HOXB13* G84E, and a recent study by Wei and colleagues[46] leveraged the UK Biobank to determine the association of *HOXB13* G84E variant in 1545 (0.34%) of 460,224 participants of European ancestry. In men, OR (95% CI) for overall cancer diagnosis was 2.19 (1.89–2.52), $P = 2.5E\text{-}19$. The association remained after excluding prostate cancer (OR, 1.4 [1.16–1.68]; $P = .003$), suggesting association with other cancers, potentially rectosigmoid cancer (OR, 2.25 [1.05–4.15]; $P = .05$) and nonmelanoma skin cancer (OR, 1.40 [1.12–1.74]; $P = .01$).[46]

TP53

Prostate cancer is not classically included in Li Fraumeni syndrome, but emerging evidence suggests a potential role for germline *TP53* mutations in contributing to some prostate cancers, especially in association with multiple primaries and with unusual histologies.[47,48] Although not part of Li Fraumeni guidelines, germline *TP53* mutation carriers are included in some of the high-genetic-risk prostate cancer screening studies discussed next.

LACK OF DIVERSITY IN DATASETS PERPETUATES HEALTH DISPARITIES

A notable health disparity in the United States is that men of African ancestry (AA) are at higher risk for prostate cancer while also experiencing worse cancer outcomes. Causes are multifactorial, but likely include genetic factors. Because AA men and other racial/ethnic subgroups are underrepresented in genetic studies to date, there are fewer examples of affected and unaffected individuals contributing to higher rates of variants of uncertain significance (VUS). The exact distribution of germline predisposition to prostate cancer in AA remains to be elucidated. As discussed earlier, prostate cancer has been implicated in a spectrum of hereditary cancer syndromes,

including hereditary breast and ovarian cancer and Lynch syndrome, and associated with other pathogenic variants such as *ATM*, *CHEK2*, *NBN*, and other gene mutations. However, most of these studies have been conducted in disproportionately non–African American cohorts. Therefore, a major gap in knowledge exists in understanding the prevalence of genetic predisposition and prostate cancer development among African American men. A recent report found similar rates of pathogenic variants in known cancer risk genes among AA men with prostate cancer,[49,50] highlighting the urgency to improve access and ensure diverse representation in research efforts to address gaps in knowledge and update advances in prostate cancer treatment, screening, and prevention.

MULTIGENE PANEL TESTING AND TUMOR SEQUENCING, AND THEIR ROLE IN PROSTATE CANCER GENETICS

Targeted DNA sequencing of tumors (somatic tumor DNA testing) has become widely available in clinical oncology practice. As more next-generation sequencing testing is incorporated in clinical and research testing in oncology, the return of genomic testing results (also called actionable mutations) poses difficult questions about how it should be delivered and its interpretation by patients.[51,52] Efforts to study this are urgently needed to evaluate the perspectives and experiences of different racial and ethnic groups and how it may affect the process and outcomes of receiving genomic results.

MODIFIERS/POLYGENIC RISK OF *BRCA1/2*

A discussion of prostate cancer genetic factors would not be complete without mention of genome-wide association studies and considerable research investments in single nucleotide polymorphisms, which additively contribute to an individual's risk of prostate cancer and genetic modifiers. Although the clinical utility of these have been limited to date in the metastatic and also in the prostate cancer risk setting, the general approach of polygenic risk scores is gaining traction in the understanding of additional genetic modifiers of high-penetrance genes such as *BRCA1/2*, as well as in other high-risk populations, such as men of AA.[24,53] This topic is explored in depth elsewhere in this issue.

TREATMENT IMPLICATIONS IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Genetic testing in prostate cancer may affect treatment choices by revealing mutations that are eligible for FDA-approved PARP inhibitors, platinum chemotherapy, or clinical trial participation. However, this topic is further developed elsewhere in this issue.

The PARP inhibitors olaparib and rucaparib have received FDA approval for mCRPC with DNA damage repair alterations. Rucaparib was evaluated in phase II TRITON2 study and showed 51% (50 out of 98) radiographic response rate among men with mCRPC and *BRCA1/2* alterations.[48] However, benefit among men with non-*BRCA* DNA repair gene alterations was less prominent (13%, 7 out of 55), and the rucaparib label includes only *BRCA1* and *BRCA2* alterations.[54–56] The phase III ProFOUND study compared olaparib and androgen receptor (AR)-targeted agents in men with mCRPC and DNA damage repair alterations who had progressed on at least 1 line of AR-targeted therapy. Olaparib improved radiographic progression-free survival (5.8 months vs 3.5 months) and was approved for men with mCRPC and alterations in one of these genes: *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.[57]

Platinum chemotherapy has been reported to be effective among men with homologous recombination-deficient prostate cancer.[5,6,58,59] A retrospective study reported that 75% (6 out of 8) of patients with mCRPC with *gBRCA2* mutations had 50% PSA decline from baseline (PSA_{50}) response to platinum chemotherapy.[6] In the study by Mota and colleagues,[59] the PSA_{50} response rate to platinum chemotherapy was 53% (8 out of 15) among men with mCRPC and DNA damage repair mutations (*BRCA2*, *BRCA1*, *ATM*, *PALB2*, *FANCA*, and *CDK12*).

The optimal sequence and cross-resistance between PARP inhibitors and platinum chemotherapy in homologous recombination-deficient prostate cancer are currently under investigation.

The immune checkpoint inhibitor pembrolizumab received the first tumor-agnostic FDA approval in 2017 for metastatic solid tumors with MSI-H and MMRd and recently tumor mutational burden greater than 10 mut/Mb was included in the FDA-approved indication.[60,61] Almost 5% of mCRPC tumors have MSI-H/MMRd and could qualify for treatment with pembrolizumab.[41,42,62,63] The prospective phase II KEYNOTE-199 study reported that pembrolizumab led to a 5% radiographic response rate and 16.8 months median duration of response among non–biomarker-selected patients with mCRPC.[64] When retrospectively evaluated in men with mCRPC and MSI-H/MMRd, therapy with immune checkpoint inhibitors resulted in a 53% (8 out of

15) PSA_{50} response rate.[65] Thus, immune checkpoint inhibitors are promising therapy with a potentially durable response, although further studies for patients with prostate cancer are needed to refine predictive biomarkers. In addition, many combination approaches are also being explored.

Response to Conventional Therapies

Retrospective and prospective studies to date have not shown that conventional treatment (treatments that are not biomarker selected) for mCRPC should be withheld from men with homologous recombination-deficient prostate cancer.[9–11,66,67] The prospective PROREPAIR-B study showed that abiraterone, enzalutamide, and taxanes are similarly effective among germline *BRCA2* carriers and noncarriers.[9] Radium-223 seems to be effective in homologous recombination-deficient prostate cancer. In a small retrospective cohort, patients with mCRPC with homologous recombination deficiency had a trend toward longer overall survival with radium-223 compared with those with homologous recombination-proficient tumors.[68,69]

Novel Therapeutic Strategies

Several targeted agents are in the pipeline for prostate cancer treatment. *ATR* and *WEE1* are critical checkpoints in the cell cycle, and preclinical data suggest that *ATR* and *WEE1* inhibitors might be effective in homologous recombination-deficient tumors as monotherapy or in combination with PARP inhibitors.[70,71] $Lutetium^{177}$ is a promising radiotherapeutic agent. Early data suggest that *BRCA1/2* alterations may be associated with improved progression-free survival and overall survival with $lutetium^{177}$ therapy,[72] but more studies are needed.

APPLICATION OF KNOWLEDGE TO EARLIER DISEASE STATES

Because of the evidence of aggressive progression, studies are not only being conducted for more aggressive disease. Trials in the biochemical recurrence setting are underway or in development. For example, PARP inhibitors are being evaluated as monotherapy or in combination in the biochemically recurrent setting (NCT03047135; NCT03810105; NCT04336943; NCT0353394), metastatic hormone-sensitive (NCT03413995; NCT04332744; NCT04497844) and first-line castration-resistant prostate cancer (NCT03012321; NCT03748641).

IMPORTANCE OF CASCADE TESTING

One of the major important opportunities and responsibilities in germline genetic testing for men with metastatic prostate cancer is the possibility of identifying previously unknown inherited cancer risk within a family. As discussed earlier, many of the historical series are composed of men selected by either female relatives with breast and ovarian cancers or by multiple early-age prostate cancer diagnoses. However, the Pritchard and colleagues[8] study describing the ~12% prevalence in the metastatic population did not find associations with earlier age of onset or family history of prostate cancer. Thus, ascertainment by personal history of metastatic prostate cancer is now increasing and may exceed genetic testing based on family history indications. Attention to thoughtful implementation through different workflow strategies and research endeavors is an ongoing area of research. Increasingly, men with a personal history of metastatic prostate cancer may be the probands in their families.

Once a cancer predisposition pathogenic genetic variant is identified in a proband, the potential for cancer prevention extends from that 1 individual to multiple asymptomatic individuals within the family who may end up being carriers for this cancer predisposition gene. This process of cascade testing allows genetic counseling and testing in disease-free blood relatives of individuals in a sequential manner. This systematic process appropriately identifies family members who carry genes associated with increased cancer risk and allows the implementation of targeted interventions for cancer surveillance and risk reduction.

In addition, given the rapid integration of tumor genomic sequencing into clinical cancer care, it may uncover germline genetic information. Consequently, tumor genomic sequencing creates an additional pathway to cascade testing. In prostate cancer, some studies have shown that, among men with metastatic prostate cancer undergoing tumor sequencing, up to 12% of them carry an actionable pathogenic germline mutation.[8] Men with metastatic prostate cancer whose tumor testing shows pathogenic variants considered suspicious for being associated with a germline source should be recommended to complete germline genetic testing, because this may also have implications for the cancer risks of family members. A referral should be made for appropriate genetic counseling and germline testing. If the individual undergoes germline genetic testing as a result of findings on somatic tumor sequencing and is subsequently found to have a pathogenic variant, the cascade testing process should be triggered.

Cancer risks associated with pathogenic variants inform personalized cancer screening for probands as well as their male and female relatives. For example, as noted earlier, a pathogenic *BRCA2* mutation is known to be associated with prostate cancer risk in men, in addition to an increase in the risk of male breast cancer, pancreatic cancer, and melanoma.[73,74] Identification of carrier status of a *BRCA2* mutation in a man with prostate cancer diagnosis would inform other men should they be found to have the same pathogenic variant and allow early prostate cancer screening, clinical breast examinations (male breast cancer risk), discussion of pancreatic cancer screening options, and referral to dermatology for melanoma screening.[74] Female relatives with an identified *BRCA2* pathogenic variant would benefit significantly from this cascade testing given the available strategies for cancer prevention or early detection should they carry the same familial identified *BRCA2* mutation.

Thus, there are important, potentially lifesaving health care options for early detection and risk reduction for female relatives. For male relatives who might carry the same cancer risk mutations, there are increasing opportunities for education, testing, and prostate cancer screening clinical trials (discussed further later). However, this will not be fully actualized without systematic and careful attention to informing and facilitating cascade testing of relatives to fullest extent possible. Studies evaluating cascade testing for men with prostate cancer who may be the probands in their families are underway, including NCT04254133.

FURTHER STUDIES AND EXPANDED APPLICATIONS

In early 2020, Nyberg and colleagues[75] reported a prospective cohort study of male *BRCA1* (n = 376) and *BRCA2* carriers (n = 447) identified in clinical genetics centers in the United Kingdom and Ireland (median follow-up, 5.9 and 5.3 years, respectively). Sixteen *BRCA1* and 26 *BRCA2* mutation carriers were diagnosed with prostate cancer during follow-up. *BRCA2* carriers had an standardized incidence ratio (SIR) of 4.45 (95% CI, 2.99–6.61) and absolute prostate cancer risk of 27% (95% CI, 17%–41%) and 60% (95% CI, 43%–78%) by ages 75 and 85 years, respectively. For *BRCA1* carriers, the overall SIR was 2.35 (95% CI, 1.43–3.88); the corresponding SIR at age less than 65 years was 3.57 (95% CI, 1.68–7.58). However, the *BRCA1* SIR varied between 0.74 and 2.83 in sensitivity analyses to assess potential screening effects. Prostate cancer risk for *BRCA2* carriers increased with family history (HR per affected relative, 1.68; 95% CI, 0.99–2.85).[75]

This contemporary, prospective report is important, particularly given its calculated estimates of added risk from a family history of prostate cancer. This study builds on the retrospective studies mentioned at the beginning of this article describing the increased prostate cancer risk and aggressiveness for *BRCA2* carriers and, to an important but lesser extent, *BRCA1* carriers. It also emphasizes the importance of cascade genetic testing for the families of men with metastatic disease who are identified to have germline mutations, especially as related to opportunities for risk-reduction measures through early detection strategies and, in some cases, prophylactic measures.

Updated findings from the ongoing, international UK-led Identification of Men with a Genetic Predisposition to Prostate Cancer (IMPACT) study make a strong case for offering men with *BRCA2* and *BRCA1* mutations more intensified prostate cancer screening.[76] This topic is elaborated on further elsewhere in this issue, but does present the opportunity to discuss the importance of clinical trials and further innovation, particularly as several new genes are faced for which data are less robust. The practical complexities around implementation and management have been addressed at the biannual Philadelphia Consensus Conference, which convened in 2019 to debate and assemble consensus recommendations around implementation and recommendations for prostate cancer genetics, pending further data.[77]

The opportunities for more complete understanding of rare gene variants and VUS in underrepresented populations poses challenges, albeit surmountable, around best clinical practices. For localized disease management and/or early cancer detection approaches in germline carriers (discussed further elsewhere in this issue), clinical trials and variant registries should be encouraged whenever possible. There may be an increasing role for specialized cancer genetics clinics and tumor boards to synthesize available data (family history and somatic sequencing) and promote clinical and research advances.

LONG-TERM FOLLOW-UP REGISTRY RESEARCH

Collective registries and databases of rare variants in population-based and in metastatic settings will be essential to building new knowledge and refining current estimates. For men with metastatic disease for whom clinical trial enrollment is a major consideration, it is reasonable to take a more

permissive approach of including germline gene mutations with less certainty in the testing panels, especially if standard treatment options have been exhausted. In this setting, patients should be encouraged to participate in therapeutic clinical trials and/or variant and mutation registries to understand treatment response, cancer risk, and penetrance, whenever possible. For example, the PROMISE prostate cancer registry (www.prostatecancerpromise.org) for germline mutation carriers with prostate cancer will launch in 2021 to provide better understanding of germline mutations as predictors of treatment response, cancer phenotype and penetrance, and modifiers of risk. In addition, registries of genetic testing experience such as the PROGRESS registry (www.progressregistry.com) and registries of germline VUS (PROMPT registry, www.promptstudy.info) will help refine and advance the current understanding.

In conclusion, genetic factors associated with metastatic prostate cancer have gained inclusion in clinical practice guidelines such as NCCN, because of their growing relevance to treatment and clinical trials. As important are the implications (potentially lifesaving) for relatives who may carry the same mutations. Ongoing research across many dimensions and disciplines will contribute to the continued momentum and advances.

CLINICS CARE POINTS

- Men with germline BRCA mutations are more likely to have intraductal features in their prostate cancer, which correlate with poor outcomes.
- Approximately 5% to 7% of patients with mCRPC have evidence of tumor MSI-H/MMRd and qualify for immune checkpoint blockade.
- Retrospective and prospective studies to date have not shown that conventional treatment (treatments that are not biomarker selected) for patients with mCRPC should be withheld from men with homologous recombination-deficient prostate cancer.
- Men with metastatic prostate cancer whose tumor testing show pathogenic variants considered suspicious for being associated with a germline source should be recommended to complete germline genetic testing, because this may also have implications for the cancer risks of family members.

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