CANCER GENETICS

Clinical Germline Testing Results of Men With Prostate Cancer: Patient-Level Factors and Implications of NCCN Guideline Expansion

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PURPOSE Germline likely pathogenic or pathogenic variants (PVs) have been identified in up to 17% of men with prostate cancer (PC) and may drive disease severity or be targetable by novel therapies. National Comprehensive Cancer Network (NCCN) guidelines encouraging germline testing in metastatic PC were recently expanded to include all men with high-risk, very high-risk, or regional PC. Our aim was to assess the impact of expanded NCCN guidelines on the detection rate of germline PVs and to determine patient-level factors associated with a PV germline testing result.

PATIENTS AND METHODS Men with PC underwent multigene germline genetic testing for PVs from June 2016 to December 2018, and trends were compared. The association of patient-level factors with a PV germline testing result, where ≥ 1 PV was identified, was assessed using analysis of variance and univariate logistic regression. Sensitivity analyses were limited to clinically actionable variants and those associated with disease severity or progression (*BRCA1/2* and *ATM*).

RESULTS Of 408 men undergoing germline testing, 42 (10.3%) men had PVs and 366 (89.7%) men did not have PVs identified. The proportion of men identified with a germline PV remained stable following testing criteria expansion (9.4% *v* 10.6%, $P = .73$). No patient-level factors were significantly associated with increased odds of a PV germline testing result, including age at diagnosis, race, pretreatment prostate-specific antigen, Gleason grade group, NCCN risk group, and family history of cancer (breast and/or ovarian, prostate, or any cancer).

CONCLUSION This study demonstrated a stable PV detection rate in men with PC using expanded criteria aligned to the updated NCCN testing guidelines. However, we did not find strong evidence to suggest that patient-level factors are associated with PV germline testing results. These findings support the recent expansion of NCCN germline testing guidelines in PC.

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INTRODUCTION

Prostate cancer (PC) is the most common cancer in men, accounting for an estimated 20%-23% of all cancers diagnosed in the United States and Europe in recent years, but only the second most common to cause death.[1,2] This is in part due to the wide range of clinical manifestations and outcomes within those affected, ranging from slow progression over many years to rapid metastasis and death.[3] PC is unusually heritable compared with other cancers, with 42%-57% of overall risk explained by genetic components.[4-7] As knowledge of this genetic contribution broadens, germline likely pathogenic or pathogenic variants (PVs) are being identified in numerous genes known to cause cancer.[8,9]

Previous studies of men with PC have revealed rates of germline PVs between 9% and 17%,[8-11] with PVs in *BRCA2*, *ATM*, and *BRCA1* associated with a more aggressive and lethal phenotype and thought to be drivers of disease severity.[12-17] Indeed, carriers of likely pathogenic and/or pathogenic *BRCA2* variants were found to be more likely to progress to metastatic disease.[13] However, previous work has been limited in key clinical information reported about those tested, such as staging, prostate-specific antigen (PSA), risk stratification, and inclusion or exclusion criteria. Germline testing has increasing importance as novel therapies are beginning to target cancer with PVs in particular genes. Recently, the poly (ADP-ribose) polymerase (PARP) inhibitors olaparib and rucaparib were granted a breakthrough therapy designation by the US Food and Drug Administration,[18-20] with olaparib treatment producing significantly longer progression-free survival in selected patients.[21] Ultimately, both agents were US Food and Drug Administration approved for the treatment of metastatic castration-resistant PC in

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Does expansion of germline testing criteria in men with prostate cancer (PC) alter the detection rate of pathogenic variants (PVs)?

Knowledge Generated

Overall, PVs were identified in 10.3% (42 of 408) of men with PC who underwent clinical germline genetic testing. The proportion of men with a PV remained stable following testing criteria expansion (9.4% *v* 10.6%, $P = .73$). No patient-level factors studied were associated with PV identification from germline testing.

Relevance

These findings support the expansion of germline genetic testing criteria for men with PC. Clinicians should consider incorporating genetic testing for patients who meet these expanded criteria. Collaborations with genetic and urologic clinicians can help to effectively integrate this testing.

May 2020.[22] As additional trials consider PARP inhibitors beyond *BRCA1/2* germline PVs,[23] there is a need for more robust and clinically oriented investigations to accurately guide future recommendations and practice guidelines for germline testing and resulting cancer treatment in men with PC.

Further improvements in the identification of actionable PVs in men with PC are necessary to work toward better screening and treatment outcomes through individualized care. Updates to the National Comprehensive Cancer Network (NCCN) guidelines for PC (version 4.2019) recommended germline testing at diagnosis for all men with high-risk, very high-risk, regional, or metastatic PC regardless of family history.[24] However, these criteria were broader than those recommended in NCCN's Breast, Ovarian, and Pancreatic Genetic/Familial High-Risk Assessment guidelines (version 1.2020).[25] At the time, these indicated testing only for those with metastatic or intraductal PC and/or Gleason ≥ 7 with family history of breast, ovarian, pancreatic, and/or PCs.[25] Recently, these genetic guidelines were expanded (version 1.2021) to match the expanded NCCN PC guidelines (version 4.2019, currently version 3.2020).[24,26,27] As guidelines expand and testing rates follow, it is crucial to identify and target those specific cohorts of men in whom finding a PV is most likely to be clinically relevant. There is limited evidence on whether the expanded testing guidelines' inclusion of high-risk, very high-risk, and regional PC results in a lower germline PV rate, compared with primarily testing only men with metastatic PC.

Before NCCN's formal expansion of these guidelines, the genitourinary oncology team at our National Cancer Institute (NCI)–designated cancer center implemented similarly augmented testing criteria based on emerging published findings.[9,15] This resulted in more widespread germline testing of men with PC compared with the previous years. As a result, evaluating these NCCN PC version 4.2019 and Breast, Ovarian, and Pancreatic Genetic/Familial High-Risk Assessment version 1.2021 criteria updates and their impact on germline testing outcomes is possible.[24,26] In this study, we primarily sought to compare trends in the PV detection rate in men with PC tested both before and after germline testing criteria expansion. Secondarily, we sought to identify patient-level factors associated with a PV germline testing result in men with PC.

PATIENTS AND METHODS

Study Population

Men with a PC diagnosis who were seen by a genetic counselor between June 2016 and December 2018 at the NCI-designated cancer hospital of a large academic health system were identified. Referral to genetic counseling occurred by the patient's treating clinician, using criteria unanimously agreed upon by the genitourinary oncology team at the health system. Participants might have consented to research germline testing via a PC registry that was previously published.[28] However, because of the clinical nature of ascertainment for this study, exact overlap is unknown. The previous publication reported 116 living participants, indicating that a majority of this clinical cohort is not overlapping with previous studies.[28] Before expanding criteria for 2018, only men with metastatic PC or aggressive PC and a strong family history of *BRCA*-related cancers were referred to genetic counseling by their genitourinary oncology clinician. Following criteria expansion in 2018, men were referred via a personal history of metastatic, node-positive, biochemically recurrent, Gleason ≥ 8, or Gleason 7 disease with a strong family history of *BRCA*-related cancers (Table 1). Additional men with PC were referred if their personal and/or family history was felt to be suspicious for a hereditary cancer predisposition, such as Lynch Syndrome. Men who ultimately underwent clinical germline genetic testing as a result of their genetic counseling visit were included for analysis. This study was approved by the institutional review board (IRB) of the study site (IRB 00069380).

TABLE 1. Germline Testing Criteria Expansion and Intersection With NCCN Risk Groups

Clinic Referral Criteria[b]	NCCN Risk Group[a]					
	Favorable Intermediate	Unfavorable Intermediate	High	Very High	Regional	Metastatic
Pre-expansion						
Metastatic						✓
Gleason > 7 and family history of *BRCA*-related cancers	✓	✓	✓	✓	✓	✓
Postexpansion						
Metastatic						✓
Lymph node–positive					✓	✓
Gleason > 8			✓	✓	✓	✓
Biochemically recurrent		✓	✓	✓	✓	✓
Gleason > 7 and family history of *BRCA*-related cancers	✓	✓	✓	✓	✓	✓

Abbreviations: NCCN, National Comprehensive Cancer Network; PC, prostate cancer.

[a]NCCN guidelines for PC, version 4.2019, recommend germline testing in all high-risk, very high-risk, regional, and metastatic patients, as well as very low-, low-, and intermediate-risk patients with a positive family history and/or intraductal histology.

[b]Pre-expansion testing era spanned June 2016-December 2017, whereas postexpansion testing era spanned 2018. This was anticipated and implemented before the official expansion of NCCN guidelines for PC germline testing in version 4.2019.

Germline Testing

NCCN PC Guidelines (version 4.2019) and other expert recommendations suggest germline testing to include genes for Hereditary Breast and Ovarian Cancer (*BRCA1/2*), Lynch Syndrome (dMMR, *MLH1*, *MSH2*, *MSH6*, and *PMS2*), and *HOXB13*, at minimum.[24,29] There is also growing evidence for multigene panel testing including *ATM*, *CHEK2*, and *PALB2* in men with PC.[9,15,17,20,30,31] The clinical genetics team at our institution has used a multigene common cancer panel for men with PC, which encompasses all these genes and genes associated with common hereditary cancer syndromes (Appendix Table A1). Although varying labs might have been used, all multigene panels included the genes associated with PC listed in Appendix Table A1. Germline multigene testing was performed through a Clinical Laboratory Improvement Amendments–approved commercial laboratory, and these results were obtained in full.

Statistical Analysis

Clinical data were obtained, including age at diagnosis, race, family history, greatest pretreatment PSA, highest NCCN risk group, highest Gleason grade group, and era of testing (pre- or postcriteria expansion). Greatest pretreatment PSA values were examined on a logarithmic scale. NCCN risk groups were calculated according to NCCN guidelines at time of analysis.[24] Three subgroups of family history were derived: breast or ovarian cancer, PC, and any cancer. These were reconstructed as categorical counts of family members with a given cancer diagnosis based on chart review of the electronic medical record. Family members were defined as first- and second-degree relatives. Testing era was dichotomized as pre- (2016-2017) and postexpansion (2018) of our clinic's genetic testing criteria.

The primary outcome measure was the percentage of germline tests with PVs identified throughout both the pre- and postcriteria expansion testing eras. PVs included variants identified as likely pathogenic or pathogenic. Descriptive statistics were stratified by test result as PV identified or no PV identified, where variants of uncertain significance were included as negative, or no PV identified, results.[25,32] Secondarily, the association of each patient-level factor with a PV germline test result was evaluated using a univariate logistic regression model, chosen to prevent overfitting from the relatively small sample size and low event rate. Categorical variables were validated and tested for overall significance using analysis of variance. P values of $< .05$ were considered statistically significant. All analyses were conducted in R (version 3.6.0).

Analyses were performed considering all genes on the multigene panel, excluding two possible cases of clonal hematopoiesis of indeterminate potential. Clonal hematopoiesis of indeterminate potential was determined when the patient had an allele frequency lower than 30% and/or had a germline PV for a highly penetrant condition with no manifestations of disease. Two sensitivity analyses were performed. The first used a subset of genes that excluded heterozygote PV findings in autosomal recessive conditions and low penetrance PVs (ie, *CHEK2* I157T and *APC* I1307K). This cohort represents stricter inclusion criteria consisting solely of clinically actionable germline variations, where clinically actionable indicates potential to affect screening and/or treatment of the patient or their family members. The second used an even narrower subset of genes, considering only *BRCA1/2* and *ATM* as possible PV test results. This cohort represents the strictest possible inclusion criteria, excluding those genes without broad evidence of an association with disease characteristics and progression. The results and data reported here pertain

TABLE 2. Patient Characteristics by the Result of Germline Genetic Testing

Characteristic	All Patients N = 408 (100.0%)	PV Identified n = 42 (10.3%)	No PV Identified n = 366 (89.7%)
Age[a], median (IQR), years	61 (56-67)	61.5 (56-67.75)	61 (56-67)
Age group,[a] n (%)			
< 50	24 (5.9)	5 (11.9)	19 (5.2)
50-59	149 (36.5)	12 (28.6)	137 (37.4)
60-69	159 (40.0)	18 (42.9)	141 (38.5)
70-79	70 (17.2)	7 (16.7)	63 (17.2)
≥ 80	6 (1.5)	0 (0)	6 (1.6)
PSA,[b] median (IQR), μg/L	14.8 (7.0-53.1)	18.3 (8.6-53.3)	14.3 (6.8-50.8)
Race			
White	384 (94.1)	40 (95.2)	344 (94.0)
Others	24 (5.9)	2 (4.8)	22 (6.0)
Grade group,[c] n (%)			
1	51 (12.5)	5 (11.9)	46 (12.6)
2	73 (17.9)	6 (14.2)	67 (18.3)
3	58 (14.2)	5 (11.9)	53 (14.5)
4	83 (20.3)	10 (23.8)	73 (19.9)
5	128 (31.4)	15 (35.7)	113 (30.9)
Missing	15 (3.7)	1 (2.4)	14 (3.8)
NCCN risk group,[d] n (%)			
Low	29 (7.1)	2 (4.8)	27 (7.4)
Intermediate	102 (25.0)	8 (19.0)	94 (25.7)
High	92 (22.5)	13 (30.9)	79 (21.6)
Very high	19 (4.7)	3 (7.1)	16 (4.4)
Node-positive	26 (6.4)	3 (7.1)	23 (6.3)
Metastatic	139 (34.1)	13 (30.9)	126 (34.4)
Missing	1 (0.2)	0 (0)	1 (0.3)
Family history of cancer by no. relatives			
Breast and ovarian, n (%)			
0-1	369 (90.4)	36 (85.7)	333 (91.0)
2-3	31 (7.6)	4 (9.5)	27 (7.4)
≥ 4	8 (2.0)	2 (4.8)	6 (1.7)
Prostate, n (%)			
0-2	313 (76.7)	30 (71.4)	283 (77.3)
3-6	67 (16.4)	7 (16.7)	60 (16.4)
≥ 7	28 (6.9)	5 (11.9)	23 (6.3)
Any cancer, n (%)			
0-2	251 (61.5)	22 (52.4)	229 (62.6)
3-6	114 (27.9)	11 (26.2)	103 (28.1)
≥ 7	43 (10.5)	9 (21.4)	34 (9.3)
Testing era,[e] n (%)			
Pre-expansion	96 (23.5)	9 (21.4)	87 (23.8)
Postexpansion	312 (76.5)	33 (78.6)	279 (76.2)

Abbreviations: IQR, interquartile range; NCCN, National Comprehensive Cancer Network; PC, prostate cancer; PSA, prostate-specific antigen; PV, pathogenic variant.

[a]Age at PC diagnosis.

[b]Greatest pretreatment PSA value recorded.

[c]Grade group at time of diagnosis, determined as follows: 1 = Gleason score 3 + 3; 2 = Gleason score 3 + 4; 3 = Gleason score 4 + 3; 4 = Gleason score 4 + 4; and 5 = Gleason score 9-10.

[d]Highest ever NCCN risk group recorded.

[e]Testing era refers to the expansion of testing criteria in our clinics starting in 2018.

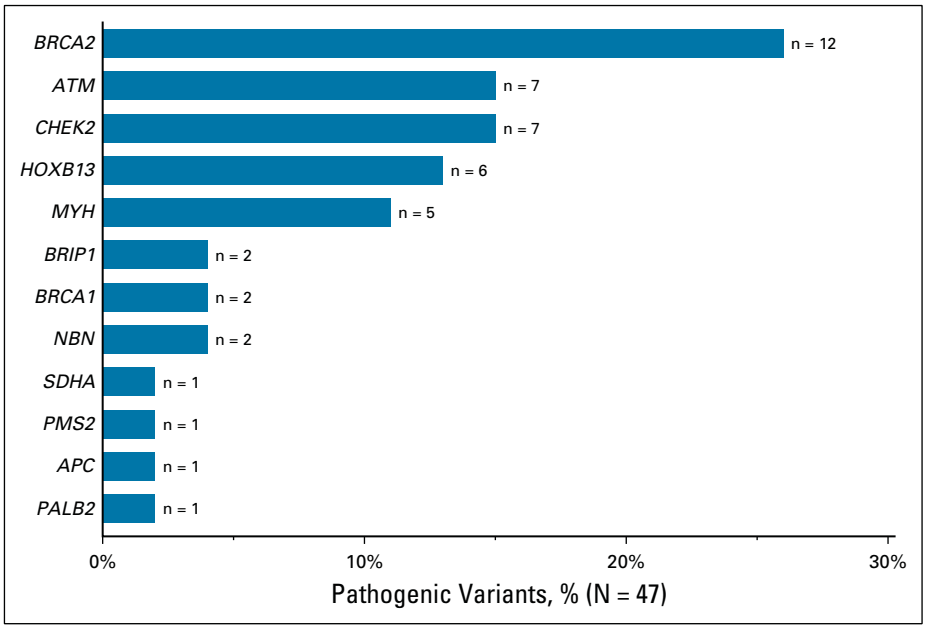

FIG 1. Distribution of germline PVs identified. Bar chart showing the distribution of 47 pathogenic or likely PVs identified in 42 individual patients who underwent multigene panel germline genetic testing. Genes without any identified PVs are not included in this distribution. PV, pathogenic variant.

primarily to the broader cohort, except when indicated otherwise.

RESULTS

Patient Characteristics

Overall, 425 men with PC were consecutively referred to genetic counseling from June 2016 to December 2018. Three were excluded because of referral for another primary indication with concurrent PC. Three men did not attend their genetics appointment, and five canceled their visits before genetic counseling. Of the 414 remaining men, 410 had available genetic testing results at the time of analysis, but two were removed for likely clonal hematopoiesis of indeterminate potential status, resulting in a final cohort of 408 (Table 2). Of these, 96 (23.5%) were tested before criteria expansions, whereas 312 (76.5%) were tested after. There were no significant between-group differences in the characteristics reported in Table 2.

The median age at diagnosis was 61 years, and the majority of those tested were White (94.1%), with all other races making up just 5.9% of the cohort. The median greatest pretreatment PSA level was 14.8 μg/L, and more than half of patients had Gleason grade group 4 (20.3%) or 5 (31.4%) cancers. Highest NCCN risk group before treatment was mainly intermediate (25.0%), high (22.5%), or metastatic (31.4%). The majority had fewer than three known cancers in their family history (61.5%). However, a notable minority had 4+ breast and ovarian (2.0%), 7+ prostate (6.9%), or 7+ cancers of any type (10.5%) in their families.

Germline Findings

Of the 408 patients who underwent germline genetic testing, 42 (10.3%) had a PV identified in at least one gene on multigene panel testing (Fig 1). In total, 47 PVs were identified in these 42 men with the majority in *BRCA2* (n = 12, 25.5% of PVs, 2.9% of total cohort), *ATM*, and *CHEK2* (n = 7 each, 14.9% of PVs, 1.7% of total cohort). These were followed by *HOXB13* (n = 6, 12.8% of PVs, 1.5% of total cohort) and *MYH* (n = 5, 10.6% of PVs, 1.2% of total cohort). Additional PVs identified in other genes are quantified in Figure 1. Therapeutically implicated PVs (*ATM*, *BRCA1/2*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, and *PMS2*) for which the men were subsequently eligible for clinical trials or other therapies as a result of their testing represented the majority of the findings (34 of 47, 72.3%).

In the primary analysis, testing era had little effect on the proportion of PVs identified by germline testing. The rate of PV germline test results was 9.4% (n = 9/96) under narrower testing criteria in 2016-2017. In 2018 alone, 312 patients underwent genetic testing following testing criteria expansions. Of these, the rate of PVs identified remained stable at 10.6% (33 of 312) ($P = .73$). That is, no decline in the detection rate of germline PVs was observed even as testing criteria were markedly expanded.

Factors Associated With PV Identification

In the secondary analysis, no patient-level factors were found to be significant predictors of a PV germline test result in our univariate model (Table 3). Additionally, expansion of testing criteria was not a significant factor in the PV detection rate ($P = .73$). Odds ratios were farthest from one in the family history and NCCN risk group variables, but neither the individual categories nor the variables themselves reached significance in our model. Family history of ≥ 7 cancers of any type produced a P value of .02; however, the interpretation of this result is limited by the

TABLE 3. Univariable Odds of a PV Germline Test Result

Covariate	OR (95% CI)	P[a]
Age group[b]		.32
< 50	1 (Reference)	
50-59	0.33 (0.11 to 1.05)	.06
60-69	0.49 (0.16 to 1.46)	.20
70-79	0.42 (0.12 to 1.48)	.18
Race		.74
White	1 (Reference)	
Others	0.78 (0.18 to 3.45)	.75
PSA[c]		
Log transformed	1.05 (0.87 to 1.29)	.58
Grade group[d]		.84
1	1 (Reference)	
2	0.82 (0.24 to 2.86)	.76
3	0.87 (0.24 to 3.18)	.83
4	1.26 (0.41 to 3.92)	.69
5	1.22 (0.42 to 3.56)	.71
NCCN risk group[e]		.64
Low	1 (Reference)	
Intermediate	1.15 (0.23 to 5.73)	.87
High	2.22 (0.47 to 10.48)	.31
Very high	2.53 (0.38 to 16.81)	.34
Node-positive	1.76 (0.27 to 11.46)	.55
Metastatic	1.39 (0.30 to 6.52)	.67
Family history of cancer by no. relatives		
Breast and ovarian		.42
0-1	1 (Reference)	
2-3	1.37 (0.45 to 4.14)	.58
≥ 4	3.08 (0.60 to 15.85)	.18
Prostate		.44
0-2	1 (Reference)	
3-6	1.10 (0.46 to 2.37)	.83
≥ 7	2.05 (0.73 to 6.48)	.18
Any cancer		.09
0-2	1 (Reference)	
3-6	1.11 (0.52 to 2.37)	.78
≥ 7	2.76 (1.17 to 6.48)	.02
Testing era[f]		.84
Pre-expansion	1 (Reference)	
Postexpansion	1.15 (0.53 to 2.49)	.73

Abbreviations: ANOVA, analysis of variance; NCCN, National Comprehensive Cancer Network; OR, odds ratio; PC, prostate cancer; PSA, prostate-specific antigen; PV, pathogenic variant.

[a]*P* values assessing significance of each distinct variable calculated via ANOVA.

[b]Age at PC diagnosis. The 80+ age group is not shown as no positive tests occurred in these patients.

[c]Greatest pretreatment PSA value recorded.

[d]Grade group at time of diagnosis, determined as follows: 1 = Gleason score 3 + 3; 2 = Gleason score 3 + 4; 3 = Gleason score 4 + 3; 4 = Gleason score 4 + 4; and 5 = Gleason score 9-10.

[e]Highest ever NCCN risk group.

[f]Testing era refers to the expansion of testing criteria in our clinics starting in 2018.

overall variable for family history of any cancer not reaching significance (*P* = .09). Of note, the sample size and low event rate in this study must be considered alongside these findings.

Sensitivity Analyses

No differences were observed when a sensitivity analysis was performed identically within the stricter patient cohort that excluded nonclinically actionable PVs (n = 401, data not shown). As with the main analysis, no patient-level factors were found to be significant predictors of a PV germline test result in this stricter cohort. The results of sensitivity analyses in the strictest possible cohort, in which only *BRCA1/2* and *ATM* PVs were considered a PV germline testing result, were equivalent with no significant relationships observed (data not shown).

DISCUSSION

A growing body of evidence suggests a role of germline PVs in DNA damage repair and tumor suppressor genes in increasing PC risk. Recognizing this role, the NCCN recently expanded guidelines for germline testing in men with PC (PC version 4.2019).[24] This study used an NCI Comprehensive Cancer Center's clinical experience with expanding testing criteria aligned to the new NCCN guidelines and showed two main important findings. First, the expansion of criteria for germline testing did not change the rate of PV detection. Second, there were no identifiable clinical or patient characteristics associated with the detection of PVs. Compared with studies with broad gene inclusion, these findings also held true when only therapeutically and/or clinically actionable genes were included.[10,33] If confirmed among a larger and more robustly powered cohort, these results support the recent expansion of NCCN criteria for germline testing as beneficial in identifying therapeutic and cascade screening benefits to patients. Furthermore, they also suggest that currently available clinical factors may not be reliable in making decisions about whom to offer germline testing.

With unified NCCN guidelines for PC (version 4.2019 and thereafter) and Breast, Ovarian, and Pancreatic Genetic/Familial High-Risk Assessment (version 1.2021) now in place,[26] urologic oncology and genetics clinicians can now better collaborate to ensure that appropriate patients are referred to and undergo genetic counseling and testing. This collaboration can identify additional treatment options for those currently diagnosed and identify family members who can undergo proactive screening for increased cancer risk.

Identifying germline PVs can have therapeutic, surveillance, and familial implications in men with PC.[34] Given this widespread impact, collaboration across cancer care clinicians and genetic counselors can ensure that the patient receives comprehensive care on follow-up after identification of a germline PV. As PC is one of the most common

cancers in American men,[35] the growing proportion of men with PC who warrant genetic counseling and testing will continue to increase. Continuing to evaluate the implementation mechanisms of genetic counseling and testing for men with PC will be imperative to ensure that this population receives appropriate pretest counseling. This will likely require innovative implementation models with an emphasis on multidisciplinary approaches to the provision of genetic services in this population.

Significant gaps remain in how best to implement germline testing in men with PC. Discussions with men with PC may differ from conversations with other patients with cancer diagnoses who are considering germline testing.[36] Highlighting the likelihood of a PV germline finding, its implication for both the patient and their family, and emphasizing the possibility of cancer risk in female family members are foundational in these conversations. Furthermore, these data among others suggest that family history and age at diagnosis, often considered important in genetic risk assessment, may be less applicable in the PC population.[10]

There are some important limitations of this study to consider. First, these data were collected through a representation of clinical ascertainment, where there may be selection bias or inconsistent clinician referral. However, implementation of these broadened criteria was universally agreed upon by all urologic oncology clinicians at our NCI-designated cancer center and used standardized workflows, suggesting that this cohort largely includes a population of men with PC who met criteria. Nonetheless, this study reflects the likely outcomes of real-world testing. Next, these data represent patients seen at a single academic institution and may not be fully generalizable to the overall population, specifically in regard to patient race. Additionally, our sample size might have limited the ability to detect relationships between patient factors and PV identification which are not very large in their effect.

Determining therapeutic and familial implications of particular genes and variants is also controversial, and genes tested vary across the literature. These differences could lead to over- or underestimation of PV rates. To address this, our analyses included both the broadest and strictest gene cohorts and showed that there is not a significant association in either scenario. Finally, family history of cancer was based on chart review and not a comprehensive three-generation pedigree. Although the latter is the preferable way to define family history of cancer, the former is more relevant to what occurs in a real-world clinical setting.

The rate of PV identification in this population warrants discussion of follow-up recommendations for family members. Many men in this study had PV findings outside of *BRCA1/2*, which are the only two genes that NCCN makes PC screening recommendations and considerations for in unaffected carriers.[26] Multiple genes including *ATM, CHEK2*, and *PALB2* are suspected of being associated with PC given studies of time to castration resistance or progression and responses to PARP inhibitor treatment.[14,15,17,20,21,31,37,38] Notably, research regarding PVs in *ATM* suggests an increased risk for aggressive PC in this population, although there are not yet standard recommendations for management of unaffected men with *ATM* PVs.[15,17,37] Although the PC risk is not as quantitatively high as other cancer risks in these genes, discussions about recommending PC screening, likely at a younger age, must continue for genes outside of the *BRCA1/2* realm. For example, the Philadelphia Prostate Cancer Consensus Conference of 2019 agreed that annual PC screening for *HOXB13* carriers was beneficial, but there was disagreement on the age to begin screening.[39] Finally, creating clinical opportunities to monitor men with germline PVs for PC, and studying this carrier population, will be critical for tailoring future screening and management recommendations in these men.

In conclusion, this study primarily found that the rate of PV germline test results in men with PC remained stable following testing criteria expansion. Secondarily, we did not find strong evidence to suggest that any patient-level factors aided in refining the identification of men with an increased risk of harboring a germline PV. Combined with a stable PV detection rate of 10.6%, these findings support the recent expansion of NCCN testing guidelines.

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DISCLAIMER

The views expressed are those of the authors and not necessarily those of the University of Utah, Huntsman Cancer Institute, National Cancer Institute, or the National Institutes of Health. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

EQUAL CONTRIBUTION

B.B.O. and J.D.T. are co-senior authors.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69:7-34, 2019
2. ECIS - European Cancer Information System: European Union, https://ecis.jrc.ec.europa.eu. 2020
3. Albertsen PC, Hanley JA, Fine J: 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 293:2095-2101, 2005
4. Hjelmborg JB, Scheike T, Holst K, et al: The heritability of prostate cancer in the Nordic Twin Study of Cancer. Cancer Epidemiol Biomarkers Prev 23:2303-2310, 2014
5. Lichtenstein P, Holm NV, Verkasalo PK, et al: Environmental and heritable factors in the causation of cancer: Analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343:78-85, 2000
6. Mucci LA, Hjelmborg JB, Harris JR, et al: Familial risk and heritability of cancer among twins in Nordic countries. JAMA 315:68-76, 2016
7. Giri VN, Beebe-Dimmer JL: Familial prostate cancer. Semin Oncol 43:560-565, 2016
8. Giri VN, Hegarty SE, Hyatt C, et al: Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. Prostate 79:333-339, 2019
9. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016
10. Nicolosi P, Ledet E, Yang S, et al: Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 5:523-528, 2019
11. Pritzlaff M, Tian Y, Reineke P, et al: Diagnosing hereditary cancer predisposition in men with prostate cancer. Genet Med 22:1517-1523, 2020
12. Mitra A, Fisher C, Foster CS, et al: Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. Br J Cancer 98:502-507, 2008
13. Petrovics G, Price DK, Lou H, et al: Increased frequency of germline BRCA2 mutations associates with prostate cancer metastasis in a racially diverse patient population. Prostate Cancer Prostatic Dis 22:406-410, 2019
14. Carter HB, Helfand B, Mamawala M, et al: Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol 75:743-749, 2019
15. Na R, Zheng SL, Han M, et al: Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 71:740-747, 2017
16. Wu Y, Yu H, Li S, et al: Rare germline pathogenic mutations of DNA repair genes are most strongly associated with grade group 5 prostate cancer. Eur Urol Oncol 3:224-230, 2020
17. Darst BF, Dadaev T, Saunders E, et al: Germline sequencing DNA repair genes in 5,545 men with aggressive and non-aggressive prostate cancer. J Natl Cancer Inst, 2020. doi:10.1093/jnci/djaa132
18. Carlo MI, Giri VN, Paller CJ, et al: Evolving intersection between inherited cancer genetics and therapeutic clinical trials in prostate cancer: A White Paper from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. JCO Precis Oncol 2018:PO.18.00060, 2018
19. Giri VN, Hyatt C, Gomella LG: Germline testing for men with prostate cancer: Navigating an expanding new world of genetic evaluation for precision therapy and precision management. J Clin Oncol 37:1455-1459, 2019

20. Mateo J, Carreira S, Sandhu S, et al: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697-1708, 2015
21. de Bono J, Mateo J, Fizazi K, et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 382:2091-2102, 2020
22. Antonarakis ES, Gomella LG, Petrylak DP: When and how to use PARP inhibitors in prostate cancer: A systematic review of the literature with an update on ongoing trials. Eur Urol Oncol 3:594-611, 2020
23. Fumet J-D, Limagne E, Thibaudin M, et al: Precision medicine phase II study evaluating the efficacy of a double immunotherapy by durvalumab and tremelimumab combined with olaparib in patients with solid cancers and carriers of homologous recombination repair genes mutation in response or stable a. BMC Cancer 20:748, 2020
24. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: (NCCN Guidelines®): Prostate Cancer (Version 4.2019), 2019
25. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2020), 2020
26. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2021), 2021
27. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: (NCCN Guidelines®): Prostate Cancer (Version 3.2020), 2020
28. Boyle JL, Hahn AW, Kapron AL, et al: Pathogenic germline DNA repair gene and HOXB13 mutations in men with metastatic prostate cancer. JCO Precis Oncol 4:139-151, 2020
29. Giri VN, Knudsen KE, Kelly WK, et al: Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 36:414-424, 2018
30. Robson ME, Bradbury AR, Arun B, et al: American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 33:3660-3667, 2015
31. Dall'Era MA, McPherson JD, Gao AC, et al: Germline and somatic DNA repair gene alterations in prostate cancer. Cancer 126:2980-2985, 2020
32. Macklin S, Durand N, Atwal P, et al: Observed frequency and challenges of variant reclassification in a hereditary cancer clinic. Genet Med 20:346-350, 2018
33. Greenberg S, Tward J, O'Neil B: Germline variants in highly selected patients with prostate cancer. JAMA Oncol 5:1368-1369, 2019
34. Mateo J, Porta N, Bianchini D, et al: Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): A multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 21:162-174, 2020
35. SEER Cancer Stat Facts: Prostate Cancer. Bethesda, MD, National Cancer Institute
36. Greenberg S, Slager S, Neil BO, et al: What men want: Qualitative analysis of what men with prostate cancer (PCa) want to learn regarding genetic referral, counseling, and testing. Prostate 80:441-450, 2020
37. Matveev V, Kirichek A, Filippova M, et al: Impact of germline BRCA2 and CHEK2 mutations on time to castration resistance in patients with metastatic hormone-naïve prostate cancer. Urologiia 2019:79-85, 2019
38. Horak P, Weischenfeldt J, von Amsberg G, et al: Response to olaparib in a PALB2 germline mutated prostate cancer and genetic events associated with resistance. Cold Spring Harb Mol Case Stud 5:a003657, 2019
39. Giri VN, Knudsen KE, Kelly WK, et al: Implementation of germline testing for prostate cancer: Philadelphia prostate cancer Consensus Conference 2019. J Clin Oncol 38:2798-2811, 2020

APPENDIX

TABLE A1. Multigene Panel Testing Gene List[a]

Genes on Prostate-Specific Panel Tested in All Patients	Additional Genes Included on Multicancer Panels
ATM	*APC*
BRCA1	*AXIN2*
BRCA2	*BARD1*
CHEK2	*BMPR1A*
EPCAM	*BRIP1*
HOXB13	*CDH1*
MLH1	*CDKN2A*
MSH2	*DICER1*
MSH6	*GREM1*
NBN	*MRE11*
PALB2	*MSH3*
PMS2	*MUTYH*
TP53	*NTHL1*
	POLD1
	POLE
	PTEN
	RAD50
	RAD51C
	RAD51D
	SDHA
	SDHB
	SDHC
	SDHD
	SMAD4
	SMARCA4
	STK11

[a]Panel composition shifts over time, and genetic counselors were able to select an appropriate panel. A minimum gene list for all participants is listed, as well as additional genes that might have been included.

