Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing

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Background: Genetic testing capability and guidelines are rapidly expanding to assess inherited prostate cancer (PCA). Clinical genetic data from multigene testing can provide insights into the germline pathogenic variant (PV) spectrum and correlates in men with PCA unselected for metastatic disease to optimize identification of men for genetic evaluation and management.

Methods: A retrospective cross-sectional analysis was conducted of de-identified clinical genetic testing data from a large commercial genetic testing laboratory in the US. ICD-10 claims codes were used to identify men with PCA, along with family history data. Gleason score was abstracted from test request forms. Overall PV rate among men with PCA was estimated, along with PVs in DNA repair genes. Family history and Gleason score association to germline DNA repair PVs was assessed using Fisher’s exact test with correction for false-discovery.

Results: As of August 2017, genetic results were available on 1328 men with PCA. Overall PV rate was 15.6%, with 10.9% of PV in DNA repair genes. PVs were most commonly identified in BRCA2 (4.5%), CHEK2 (2.2%), ATM (1.8%), and BRCA1 (1.1%). Breast cancer family history was significantly associated with germline DNA repair PVs (OR 1.89, [95%CI 1.33, 2.68], \( P = 0.003 \)). Among men with Gleason score \( \geq 6 \) \( (n = 706) \), Gleason \( \geq 8 \) was significantly associated with DNA repair PVs (OR 1.85 [95%CI 1.22, 2.80], \( P = 0.004 \)).

Conclusions: A substantial proportion of men with PCA unselected for metastatic disease carry germline DNA repair PVs. Breast cancer family history and high Gleason score are important predictors to identify men with PCA who may carry germline DNA repair PVs. Our findings support current NCCN guidelines and have implications for genetic assessment, therapeutic management, and cascade testing for men with PCA and their families.

Keywords: cascade testing, DNA repair, family history, genetic testing, prostate cancer
INTRODUCTION

Genetic testing for inherited prostate cancer (PCA) is increasing with expansion of genetic testing guidelines and increasing capability of clinical multigene testing.1–3 The NCCN Genetic/Familial High-risk Assessment: Breast and Ovarian (Version 2.2019) recommends BRCA testing for men with metastatic PCA or men with Gleason score ≥ 7 who have any of the following: (1) ≥ 1 close blood relative with ovarian, pancreatic, metastatic PCA, or breast cancer at age <50, (2) > 2 close blood relatives with breast or prostate cancer at any age, or (3) Ashkenazi Jewish ancestry.4 The NCCN Prostate (Version 4.2018) guideline states to consider germline genetic testing for men with very low to unfavorable intermediate risk PCA who have family history of cancers linked with hereditary breast and ovarian cancer (HBOC) or Lynch syndrome or young age at diagnosis of PCA in the family (father, brother, or multiple family members diagnosed at age <60). For men with high risk to metastatic disease, the NCCN Prostate (Version 4.2018) guideline states to consider germline testing irrespective of family history.4 NCCN Prostate (Version 4.2018) guideline recommends testing several cancer predisposition genes primarily involved in DNA repair, including BRCA1, BRCA2, ATM, CHEK2, PALB2, and FANCA1 due to increasing recognition of substantial rates of germline DNA repair pathogenic variants in men with metastatic PCA.1–7

Furthermore, genetic results particularly for germline DNA repair pathogenic variants are increasingly informing therapeutic, clinical trial, and management options for men with PCA.1,4 Germline pathogenic variants in DNA repair genes including BRCA2, BRCA1, ATM, PALB2, and CHEK2 have been reported in up to 12% of men with advanced or metastatic PCA,5,7 with data regarding clinical activity of PARP inhibitors emerging.4,8 In 2016, olaparib was granted “Break-Through Therapy” designation by the United States FDA for BRCA1/2 or ATM mutated metastatic PCA. Furthermore, the identification of mismatch repair deficiency across tumor types is becoming important due to the potential role of immunotherapy in this setting.5,10 The NCCN Prostate (Version 4.2018) guideline therefore recommends DNA repair multigene testing for men with high risk to metastatic disease and tumor testing for mismatch repair deficiency for potential treatment and trial options.1

Men with BRCA2 pathogenic variants have been reported to have more aggressive PCA, with younger age of onset, lymph node involvement, and distant metastases at diagnosis.11–13 A recent study reported higher rates of lethal PCA among male carriers of pathogenic variants in BRCA1, BRCA2, and ATM, increasing the importance of DNA repair pathogenic variant status for PCA prognosis.14 Thus, the NCCN Prostate (Version 4.2018) guideline recommends to consider BRCA status in discussions of active surveillance in men with early-stage PCA.1 The NCCN PCA Early Detection (Version 1.2018) guideline states to consider BRCA status and the status of other cancer risk genes in PCA screening discussions.15 Therefore, the increasing clinical role of DNA repair genes is expected to drive multigene testing for men with PCA.

Prior studies have focused on men with metastatic PCA or who meet strict study eligibility criteria.5–7 Broader genetic testing data from clinical practice settings can expand to our understanding of the estimated scope of men with inherited PCA irrespective of metastatic disease, with subsequent impact of germline genetic results for patient management, screening, and cascade testing, as well as lend support to expanding guidelines. Since multigene panels are now commercially available for genetic testing for PCA in clinical practice, this represents a unique opportunity to learn about pathogenic variant rates in key genes of interest in PCA biology and predisposition to inform patient management and lend supporting data to emerging guidelines.

This study was performed utilizing de-identified genetic testing data from a commercial clinical genetic testing laboratory in the United States and represents a “real-world” data analysis among men with PCA unselected for metastatic disease. The goal of the study was to estimate overall pathogenic variant rates among men with PCA, with a focus in pathogenic variants in DNA repair genes where there are significant clinical implications for treatment and screening for men with PCA and their families.1–4 Correlates of pathogenic variant rates were also assessed to optimize identification of men with PCA for genetic testing and inform implications for precision therapy, cancer screening, and cascade testing in families.

MATERIALS AND METHODS

De-identified genetic results were received from a commercial genetic testing laboratory (Invitae, San Francisco, CA) in the United States. Samples for this analysis included those with ICD-10 codes indicating a personal history of PCA (C61, Z85.46). The use of ICD codes is a validated method to determine diagnoses or patient characteristics for research.16,17 However, because the ICD-10 codes for PCA do not distinguish different stage of disease, no categorization by stage was possible using these codes as in prior published studies.16 ICD-10 codes included in the analysis were enumerated on test request forms and did not involve conversion of free-text data into the codes. Family history was also delineated from ICD-10 codes; for example family history of PCA (Z80.42), family history of breast cancer (Z80.3), family history of ovarian cancer (Z80.41), and family history of GI cancers (Z80.0). A full list of ICD-10 codes in the dataset is available upon request.

Overall pathogenic variant rate as well as rate of variants of uncertain significance (VUS) were assessed by counts and percentages in this dataset. Gene-specific rates of pathogenic variants were also assessed. Genes of interest included those on the standard laboratory PCA panel (BRCA1, BRCA2, HOXB13, MLH1, MSH2, PMS2, MSH6, EPCAM, ATM, CHEK2, NBN, and TP53). Genetic testing included evaluation of sequence changes and exonic deletions/duplications. EPCAM was only analyzed for deletion/duplication, and HOXB13 was only assessed for the G84E pathogenic variant. Full sequencing and variant confirmatory methods are available upon request.

DNA repair genes were also assessed for pathogenic variants, and were defined as: BRCA1, BRCA2, ATM, BRIP1, CHEK2, NBN, MSH6, PMS2, RAD50, PALB2, and FANCA as per prior studies.5 Fisher’s exact test (with correction for false-discovery) was used to evaluate the
association between DNA repair gene pathogenic variants with personal history/family history (as indicated by ICD-10 codes) and Gleason score (which was abstracted from test request forms). Race, age at diagnosis, and stage information was not available through claims codes and were not systematically entered on test request forms. All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

As of August 2017, de-identified genetic test results were available from 1328 men with ICD-10 codes indicating a personal diagnosis of PCA. Family history of breast cancer was reported most commonly (n = 453), followed by family history of PCA (n = 369) and family history of GI cancers (n = 299). Among 898 men with Gleason score information available, 6.2% had a Gleason score $\geq 8$.

Overall rate of pathogenic variants was 15.6% and rate of VUS was 37.2%. Overall rate of pathogenic variants in DNA repair genes was 10.9%. Pathogenic variant rates by genes tested is depicted in Figure 1. BRCA2 pathogenic variants were the most commonly identified (4.5%), followed by pathogenic variants in CHEK2 (2.2%), ATM (1.8%), BRCA1 (1.1%), PMS2 (0.6%), MSH2 (0.5%), NBN (0.2%), MLH1 (0.2%), EPCAM (0.1%). Selected additional DNA repair gene pathogenic variants included PALB2 (0.5%), RAD50 (0.4%), BRIP1 (0.2%), RAD51C (0.2%), and RAD51D (0.1%). Table 1 provides greater detail of pathogenic variant rates in the context of published prevalence estimates in various populations along with VUS rates by genes tested.

Overall pathogenic variant status and DNA repair pathogenic variant status was assessed for association to family cancer history (Table 2) and Gleason score. DNA repair genes were assessed as a group and included the following: BRCA1, BRCA2, ATM, BRIP1, CHEK2, NBN, MSH6, PMS2, RAD50, PALB2, and FANCA as per prior studies.5 Family history of breast cancer was significantly associated with an approximate two-fold increased risk of germline DNA repair pathogenic variants in men with PCA (breast cancer family history 15.2% vs no breast cancer family history 8.7%, $P = 0.003$; OR 1.89, 95%CI [1.33, 2.68]). Gleason scores $\geq 6$ were identified in 706 men with PCA. Gleason score $\geq 8$ was significantly associated with pathogenic variants in DNA repair genes compared to Gleason scores of 6–7 (OR 1.85 [95%CI 1.22, 2.80, $P = 0.004$]).

Furthermore, 17 men tested positive for pathogenic variants in two genes, where one or both were DNA repair genes. Supplementary Table S1 displays these individuals, genes with pathogenic variants, and personal/family history as available and indicated by ICD-10 codes. Of these 17 males, 9 men had double pathogenic variants in DNA repair genes including genes involved in homologous recombination and DNA mismatch repair.

4 | DISCUSSION

Germline genetic testing for men with PCA is rapidly rising with expansion of guidelines and expert opinion,1–3 along with increasing treatment and clinical trial options.4,8,10 Prior studies have reported germline pathogenic variants particularly in DNA repair genes among men selected for advanced/metastatic disease or based on strict family history criteria,5–7 leaving a gap regarding the germline spectrum and potential clinical impact from multigene testing among men unselected for metastatic disease. Our analysis included clinical genetic data from men with PCA unselected for metastatic disease undergoing multigene testing across the US. Overall, our results show that 15.6% of men with PCA will have pathogenic variants identified in genes tested, and 10.9% of men will have germline pathogenic variants in DNA repair genes. Therefore, these men may be eligible for targeted therapy or clinical trials at the point of developing advanced or metastatic disease.4,9,10 Furthermore, management of early stage PCA with discussions of active surveillance are increasingly including data on germline pathogenic variants, particularly if men carry pathogenic variants in genes linked with aggressive disease such as BRCA2.5,11–14

Family history of breast cancer was significantly associated with an approximate two-fold risk of carrying germline DNA repair pathogenic variants and may therefore be an important predictor to identify men with PCA for genetic testing. This finding reinforces the need for ordering providers, increasingly urologists and oncologists, to perform intake of broad family history for appropriate patient referrals to cancer genetics and to understand and deliver family history-based recommendations to men with PCA and their families. Gleason score $\geq 8$ was also associated with an approximate two-fold increased risk for carrying germline DNA repair pathogenic variants. While Gleason data were available in a subset of the cohort, our results in an unselected population confirm and expand upon prior reports which described association of higher Gleason score to DNA repair gene pathogenic variants in men with metastatic disease.5 Our findings lend evidence in support of recent expansion of NCCN Prostate (Version 4.2018) guidelines for germline testing with consideration of family history and Gleason score across risk groups.1

Our results have implications for precision treatment of PCA. FDA designations for PARP inhibitors or immunotherapy for advanced and metastatic PCA are now emerging,4,8–10 along with rapid expansion of
clinical trials among men with germline DNA repair pathogenic variants. Our results show that 10.9% of men with PCA undergoing multigene testing will have DNA repair pathogenic variants identified, with potential options for targeted therapies or clinical trials. Also, cascade testing is important to discuss in the pretest and post-test setting since many of these genes (such as BRCA1, BRCA2, ATM, CHEK2, and PMS2) have guidelines for cancer screening and risk reduction which could impact male and female blood relatives.\(^3\)\(^\text{18}\) Strategies are evolving regarding how cascade testing in unaffected male relatives can inform PCA screening. NCCN Genetic/Familial

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**TABLE 1 Pathogenic variant and VUS rates by genes tested**

| Gene          | Syndrome | Samples tested | Pathogenic variants | VUS | Prevalence estimates of pathogenic variants from prior studies\(^d\) |
|---------------|----------|----------------|---------------------|-----|---------------------------------------------------------------------|
| **Standard prostate cancer panel genes** |          |                |                     |     |                                                                     |
| BRCA1         | HBOC     | 1326           | 15                  | 1.1 | 20                                                                  | 1.5 | 0.10-0.25% General Population; 2.5% Ashkenazi Jewish; 0.9% metastatic prostate cancer (BRCA1); 5.3% metastatic prostate cancer (BRCA2) |
| BRCA2         | HBOC     | 1327           | 60                  | 4.5 | 30                                                                  | 2.3 | 0.10-0.25% General Population; 2.5% Ashkenazi Jewish; 0.9% metastatic prostate cancer (BRCA1); 5.3% metastatic prostate cancer (BRCA2) |
| **\(^c\)HOXB13** | HPC      | 1051           | 12                  | 1.1 | .                                                                   | .   | 0.07-1.4% Population Controls; 6.25% Early-onset prostate cancer |
| MLH1          | LS       | 1269           | 2                   | 0.2 | 7                                                                   | 0.6 | 0.02-0.27% General Population                                  |
| MSH2          | LS       | 1269           | 6                   | 0.5 | 22                                                                  | 1.7 | 0.02-0.27% General Population                                  |
| MSH6          | LS       | 1268           | 5                   | 0.4 | 25                                                                  | 2.0 | 0.02-0.27% General Population                                  |
| PMS2          | LS       | 1268           | 8                   | 0.6 | 16                                                                  | 1.3 | 0.02-0.27% General Population                                  |
| EPCAM         | LS       | 1260           | 1                   | 0.1 | 3                                                                   | 0.2 | 0.02-0.27% General Population                                  |
| ATM           |          | 1209           | 22                  | 1.8 | 59                                                                  | 4.9 | 0.25-1% Population estimate; 1.6% metastatic prostate cancer   |
| CHEK2         |          | 1257           | 28                  | 2.2 | 21                                                                  | 1.7 | 0.61% General Population estimate (Significant variation in prevalence by population); 1.9% metastatic prostate cancer |
| NBN           |          | 1212           | 3                   | 0.2 | 19                                                                  | 1.6 | 0.11-0.65% Population estimate                                  |
| TP53          |          | 1261           | 6                   | 0.5 | 11                                                                  | 0.9 | 0.005-0.02% Population estimate                                |
| **Selected additional DNA repair genes tested** |          |                |                     |     |                                                                     |
| BRIP1         |          | 939            | 2                   | 0.2 | 15                                                                  | 1.6 | 0.19-0.55% Population estimate; 0.18% metastatic prostate cancer |
| PALB2         |          | 1113           | 6                   | 0.5 | 12                                                                  | 1.1 | 0.12% Population estimate; 0.43% metastatic prostate cancer    |
| RAD51D        |          | 1017           | 1                   | 0.1 | 3                                                                   | 0.3 | 0.08% Population estimate; 0.43% metastatic prostate cancer    |
| FANCA         |          | 97             | .                   | .    | 6                                                                   | 6.2 | -                                                                   |
| FANCC         |          | 128            | .                   | .    | .                                                                   | .   | -                                                                   |
| FANCD2        |          | 7              | .                   | .    | .                                                                   | .   | -                                                                   |
| FANCE         |          | 62             | .                   | .    | .                                                                   | .   | -                                                                   |
| FANCG         |          | 62             | .                   | .    | .                                                                   | .   | -                                                                   |
| FANCL         |          | 62             | .                   | .    | .                                                                   | .   | -                                                                   |
| RAD50         |          | 823            | 3                   | 0.4 | 19                                                                  | 2.3 | -                                                                   |
| RAD51C        |          | 930            | 2                   | 0.2 | 12                                                                  | 1.3 | 0.11% Population estimate                                      |

\(^a\)Bolded genes are involved in DNA repair pathways.

\(^b\)Hereditary cancer syndromes: HBOC (Hereditary Breast and Ovarian Cancer Syndrome); LS (Lynch syndrome); HPC (Hereditary Prostate Cancer).

\(^c\)HOXB13 testing is only for the G84E pathogenic variant, and therefore VUS rates do not apply.

\(^d\)Population prevalence of pathogenic variant rates in genes of interest can vary based upon populations studied. Here, rates are provided for approximate comparison of our findings to prior reported estimates (references included in Supplementary Material).
TABLE 2  Association of family history with germline DNA repair gene pathogenic variants among men with prostate cancer (n = 1328)

|                                | All Pathogenic variant | Pathogenic variant in DNA repair gene |
|--------------------------------|------------------------|--------------------------------------|
|                                | N | N | % | P (raw) | P (FDR) | N | % | p (raw) | P (FDR) |
| Prostate Ca: personal diagnosis| 1328 | 207 | 15.6 | 0.674 | 0.786 | 145 | 10.9 |
| Family Hx prostate Ca          | 959 | 147 | 15.3 | 0.007 | 0.046 | 107 | 11.2 |
| Not reported                   | 369 | 60  | 16.3 | 0.007 | 0.046 | 38  | 10.3 |
| Family Hx breast Ca            | 875 | 119 | 13.6 | 0.007 | 0.046 | 76  | 8.7  |
| Not reported                   | 453 | 88  | 19.4 | 0.007 | 0.046 | 69  | 15.2 |
| Family Hx GI Ca                | 1029 | 156 | 15.2 | 0.007 | 0.046 | 110 | 10.7 |
| Not reported                   | 299 | 51  | 17.1 | 0.007 | 0.046 | 35  | 11.7 |
| Family Hx of prostate and breast Ca | 681 | 96  | 14.1 | 0.007 | 0.046 | 66  | 9.7  |
| Not reported                   | 647 | 111 | 17.2 | 0.007 | 0.046 | 79  | 12.2 |
| Family Hx of prostate and GI Ca | 1213 | 189 | 15.6 | 0.007 | 0.046 | 131 | 10.8 |
| Not reported                   | 115 | 18  | 15.7 | 0.007 | 0.046 | 14  | 12.2 |
| Family Hx of Breast and GI Ca | 1170 | 173 | 14.8 | 0.007 | 0.046 | 120 | 10.3 |
| Not reported                   | 158 | 34  | 21.5 | 0.007 | 0.046 | 25  | 15.8 |
| Family Hx of prostate, breast and GI Ca | 1265 | 193 | 15.3 | 0.007 | 0.046 | 133 | 10.5 |
| Not reported                   | 63  | 14  | 22.2 | 0.007 | 0.046 | 12  | 19.0 |

*Family history data were derived from ICD-10 codes and may be incomplete. Therefore *not reported* may not be equivalent to "no family history."

High-risk Assessment: Breast and Ovarian (Version 2.2019) guideline recommends PCA screening start at age 45 for male carriers of BRCA2 pathogenic variants, and suggests the same approach be used for male BRCA1 carriers. NCCN PCA Early Detection (Version 1.2018) guideline states to consider BRCA status and the status of other cancer risk genes in PCA screening discussions. Therefore, the impact of cascade testing among unaffected male BRCA carriers is expected to increase with evolving screening strategies.

The overall rate of VUS in our analysis was 37.2%, which is comparable to prior studies in the multigene testing setting. Since approximately a third of men with PCA undergoing multigene testing will have a VUS identified, urologists, and oncologists need to develop competency with understanding these results to accurately discuss VUS findings and potential future reclassification of results with patients.

Finally, our "real-world" data analysis may also provide biologic leads into PCA predisposition or progression. Our analysis identified nine men with pathogenic variants in two DNA repair genes. It is notable that observed pathogenic variants would be predicted to impact varied DNA repair processes, including homologous recombination and mismatch repair. Additional DNA repair alterations in non-homologous end joining, largely linked to gain of DNAPK activity, have also been linked to disease progression and poor outcome in the clinical setting. Whether collective alterations skew DNA repair preferences or lead to reliance on remaining, targetable pathways remains under active investigation, and may lead to development of new therapeutic strategies for treatment of selected DNA repair mutated cancers.

There are some limitations to consider. The dataset did not include age at PCA diagnosis, stage, race, or age at diagnosis in family history, which was not systematically collected on test request forms and therefore has limited reliability and data quality. Therefore, ICD-10 claims codes were used to annotate personal history of PCA and family history, which has been performed by prior studies. Our analysis adds to prior studies by providing quantified estimates of risk of germline DNA repair pathogenic variants by family history of breast cancer among men to inform genetic counseling and testing. Future efforts are needed to gain greater detail regarding family history such as age at diagnosis, degree of kinship, or number of relatives with specific cancers.
The use of a single lab as a data source is also a consideration. There is known inter-lab variability of variant pathogenicity designation which could impact rates of pathogenic variants and VUS reported here. Additional factors may also influence results, such as differences in genetic testing practices between providers, patients tested, use of specific laboratories, or panel utilization. Thus, our results need to be confirmed for generalizability.

Since prior data have shown that PCA patients with metastatic disease have higher rates of germline DNA repair pathogenic variants which can inform therapy such as PARP inhibitors, an additional consideration is that advanced cases may have made up a significant proportion of our dataset leading to uncharacterized selection bias. Furthermore, genetic testing was performed prior to expansion of NCCN guidelines to include broad family history beyond cancers linked with HBOC. Updated analyses in the era of expanded genetic testing guidelines will be needed.

5 | CONCLUSION

Our report includes one of the largest sample sets of “real-world” genetic testing data to inform strategies for identification of men for genetic evaluation for inherited PCA. As genetic testing for men with PCA increases, provider education for urologists and oncologists regarding genetic results interpretation and family history-based recommendations for men with PCA and their families will be important to provide appropriate cancer genetic education and care delivery.

AUTHOR CONTRIBUTIONS

VNG had access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design by VNG, KEK, and LGG. Acquisition, analysis, or interpretation of data by VNG, SEH, CH, EOL, JG, KEK, WKK, LGG. Drafting of the manuscript by VNG, SEH, CH, EOL, JG, KEK, WKK, LGG. Statistical analysis done by SEH.

CONFLICTS OF INTEREST

EOL and JG have stock ownership in Invitae. The use of Invitae data were not biased by involvement of these authors. All other authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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