Association of Inherited Mutations in DNA Repair Genes with Localized Prostate Cancer

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Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Hausler, Le, Maxwell.

Obtaining funding: Rader, Domchek, Maxwell.

Administrative, technical, or material support: Kelly, Desai, Judy, Weaver.

Supervision: Maxwell.

Other: None.

Data sharing: Data are available for bona fide researchers who request it from the authors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2021.09.029.
Abstract

Background: Identification of germline mutations in DNA repair genes has significant implications for the personalized treatment of individuals with prostate cancer (PrCa).

Objective: To determine DNA repair genes associated with localized PrCa in a diverse academic biobank and to determine genetic testing burden.

Design, setting, and participants: A cross-sectional study of 2391 localized PrCa patients was carried out.

Outcome measurements and statistical analysis: Genetic ancestry and mutation rates (excluding somatic interference) in 17 DNA repair genes were determined in 1588 localized PrCa patients and 3273 cancer-free males. Burden testing within individuals of genetically determined European (EUR) and African (AFR) ancestry was performed between biobank PrCa cases and cancer-free biobank and gnomAD males.

Results and limitations: AFR individuals with localized PrCa had lower DNA repair gene mutation rates than EUR individuals (1.4% vs 4.0%, p = 0.02). Mutation rates in localized PrCa patients were similar to those in biobank and gnomAD controls (EUR: 4.0% vs 2.8%, p = 0.15, vs 3.1%, p = 0.04; AFR: 1.4% vs 1.8%, p = 0.8, vs 2.1%, p = 0.5). Gene-based rare variant association testing revealed that only BRCA2 mutations were significantly enriched compared with gnomAD controls of EUR ancestry (1.0% vs 0.28%, p = 0.03). Of the participants, 21% and 11% met high-risk and very-high-risk criteria; of them, 3.7% and 6.2% had any germline genetic mutation and 1.0% and 2.5% had a BRCA2 mutation, respectively. Limitations of this study include an analysis of a relatively small, single-institution cohort.

Conclusions: DNA repair gene germline mutation rates are low in an academic biobank cohort of localized PrCa patients, particularly among individuals of AFR genetic ancestry. Mutation rates in genes with published evidence of association with PrCa exceed 2.5% only in high-risk, very-high-risk localized, and node-positive PrCa patients. These findings highlight the importance of risk stratification in localized PrCa patients to identify appropriate patients for germline genetic testing.

Patient summary: In the majority of patients who develop localized prostate cancer, germline genetic testing is unlikely to reveal an inherited DNA repair mutation, regardless of race. High-risk features increase the possibility of a germline DNA repair mutation.

Keywords
Localized prostate cancer; Inherited genes; Germline genetics; BRCA2; Genetic association study

1. Introduction

Prostate cancer (PrCa) is the most common malignancy among men [1] and one of the most heritable cancers [2]. Rare germline mutations, especially in DNA repair pathways, impact PrCa stage [3], cancer risk at screening [4], cancer-specific mortality [5], and treatment response [6,7]. Given responses of DNA repair–deficient metastatic PrCa patients...
to poly-(ADP-ribose)-polymerase (PARP) inhibitors [8,9], germline genetic testing has clinical benefit [10,11]. Current consensus guidelines recommend consideration of testing for patients with high-risk clinically localized disease [12]; however, there is a lack of evidence for this recommendation [10,13,14].

The prevalence of germline DNA repair mutations is well established in individuals with metastatic PrCa [15,16]; however, knowledge gaps remain for individuals with localized disease [10]. Generalizability of existing studies [17–22] to real-world clinical settings has caveats, hindered by cohorts of homogeneous ethnicity [20], overselection for high-grade or metastatic disease [17–19,22], and lack of controls [21]. In particular, while Black men demonstrate increased PrCa incidence and mortality rates relative to white men, Black patients have been under-represented in studies [23,24].

Given the current recommendations for germline genetic testing in patients with high-risk and very-high-risk localized PrCa despite existing knowledge gaps, we determined the prevalence of germline DNA repair mutations in a large, diverse academic biobank. Burden testing was performed in comparison with two genetically determined ancestry-stratified populations of male noncancer controls. Association of mutation rates with clinicopathological characteristics identified subsets of localized PrCa patients associated with germline DNA repair gene mutations.

2. Patients and methods

2.1. Cohort identification

The Penn Medicine Biobank (PMBB) is a longitudinal biorepository of individuals seen at Penn Medicine and consented under a UPenn institutional review board–approved protocol between March 10, 2000 and June 1, 2019 [25–27]. We identified patients with PrCa using the Penn Medicine Cancer Registry (PMCR) and ICD9/10 billing code data from the electronic health record (EHR; Supplementary Fig. 1). All charts underwent manual review to confirm a PrCa diagnosis (=2 391). PMCR and ICD9/10 billing code data identified 26 821 patients with no cancer diagnosis (Supplementary Fig. 2 and Supplementary Table 1), including 3273 males with whole exome sequencing (WES) data. The cancer-free male cohort of gnomAD version 2.1.1 [28] was used as an additional control cohort.

2.2. Phenotyping of the PMBB PrCa cohort

EHR data were abstracted from structured tables and supplemented with natural language processing–based methods for unstructured data. PMCR data were abstracted manually for all patients seen in the health system for at least one line of cancer therapy. Phenotypes collected included clinicopathological characteristics recommended in National Comprehensive Cancer Network (NCCN) guidelines (version 2.2020) [12] to trigger germline testing, including family history of cancer, Gleason score, TNM stage at diagnosis, histology, prostate-specific antigen at diagnosis, and Ashkenazi Jewish status. Additional variables collected included age at diagnosis, self-reported race, biochemical recurrence, and development of metastatic disease.
2.3. Germline sequencing of the PMBB prostate cancer cohort

Of 2391 localized PrCa cases, 1666 available DNA samples were prepared using a QiaSeq amplicon–based sequencing library preparation protocol. Libraries were multiplexed to 384-plex and sequenced on a NextSeq550. This panel covered all exons of 17 DNA repair genes (Supplementary Table 2) and 827 single nucleotide polymorphisms including Ancestry Informative Markers (Supplementary Table 3). Data were aligned using the Burrows-Wheeler Aligner, version 0.7.10, for short-read alignment [29] to the GRCh37 reference genome. Adapters were trimmed using Cutadapt [30], version 1.18. All samples underwent joint germline variant calling according to Genome Analysis Toolkit (GATK) best practices [31]. Twenty-three individuals had de novo metastatic disease and were excluded from further analysis for 1643 samples to enter the quality control (QC) pipeline (Supplementary Fig. 3).

2.4. QC of germline sequencing data

For QC of the amplicon panel, sensitivity of known mutation identification based on WES data of 32 samples with both data types was used. The QiaSeq panel sequencing did not identify any mutations in overlapping genomic segments that were not found in WES and identified all mutations found by WES. Sample-level QC was based on the determination of average coverage, variant allele frequency (VAF) distribution, genetic sex, and identity by descent (IBD). IBD was performed using PLINK [32], version 1.9. Seven samples were removed for a mean coverage of <30. No samples had skewed distribution of VAF (Supplementary Fig. 4). The average of the remaining samples’ mean sequencing depth was 702 ± 509X (range 48–5773X). Forty samples were removed for PI-HAT >0.5, leaving 1596 genetically unique patients for analysis.

2.5. Determination of genetic ancestry

Eigenstrat [33] principal components analysis was used to identify the genetic substructure of the case population, which grouped samples as expected into two main racial categories, European (EUR) and African (AFR) ancestry (Supplementary Fig. 5). Of the participants, 1150 (72%) were self-reported non-Hispanic white individuals and 361 (23%) were self-reported Black individuals. The overlap between genetic ancestry and reported race was high, as was the overlap of both with 1000 genomes data (Supplementary Fig. 6 and 7). Eight samples (0.5%) had EHR-reported race opposite to genetically determined race and were removed from further analyses, leaving 1588 samples in the sequencing cohort, including 1174 EUR and 351 AFR individuals.

2.6. Analysis of PMBB and gnomAD cancer-free control sequencing data

Of the PMBB controls with WES data performed at the Regeneron Genetics Center, 2615 had genetically determined EUR ancestry, and 515 had genetically determined AFR ancestry. Samples from the PMBB control cohort underwent alignment and variant calling as per above, with the exception of the adaptor trimming step. Cancer-free controls of gnomAD version 2.1.1 were used based on their reported genetically determined non-Finnish European (NFE) ancestry and AFR ancestry. Population allele frequencies for NFE and AFR males were recorded for each variant.
2.7. Mutation identification and classification in all cohorts

Variants from all three cohorts were annotated with ANNOVAR [34]. Variants were retained for burden testing if: (1) variant allele fraction (VAF) was ≥30% and (2) classified as pathogenic/likely pathogenic (P/LP) in Clinvar (March 16, 2020) or frameshift insertion/deletion or stop-gain not in the last exon of the corresponding gene. All PMBB cases and controls were reviewed for evidence of somatic interference by an age-adjusted VAF threshold (excluding VAF 30–40% if age ≥80 yr) and PMCR or ICD9/10 billing codes for a hematological malignancy (Supplementary Tables 4 and 5). EHR data for TP53 mutation carriers were reviewed for a diagnosis of Li Fraumeni syndrome (Supplementary Fig. 8). One ATM mutation carrier had a diagnosis of chronic lymphocytic leukemia, but an EHR review confirmed that the ATM mutation was germline (Supplementary Table 6). A count of the number of pathogenic mutations was recorded for each gene. Variants were annotated with pext scores from blood (Supplementary Table 4) [35].

2.8. Statistical analysis

Burden testing collapsing all variants by gene was performed for the following groups: PMBB PrCa cases versus PMBB cancer-free controls and PMBB cancer cases versus gnomAD cancer-free controls. Comparisons of mutation rates and between binary clinical variables and mutation carrier status were determined using a two-sided Fisher’s exact test of significance. All p values were adjusted for multiple comparisons using a Bonferroni correction. Univariate analyses to determine odds risk, its standard error, and 95% confidence interval (CI) were calculated using MedCalc statistical software. Multivariate analysis was performed using logistic regression in R (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

EHR-based cohort identification and manual chart review identified 2391 men with a diagnosis of PrCa out of 58,814 patients in the PMBB academic biobank, which enrolls any patients unselected for medical diagnoses and seen within Penn Medicine community and university practices (Table 1). We identified P/LP mutations in 17 DNA repair genes in 1588 localized PrCa patients using targeted amplicon-based sequencing in the PMBB cohort, excluding cases with putative somatic interference. Overall, 3.5% of 1588 patients had a mutation in a DNA repair gene, with no gene having mutations found in over 1% of the entire cohort (Fig. 1A and 1B, and Supplementary Table 7). Stratified by genetically determined ancestry, 4.0% of 1174 EUR and 1.4% of 351 AFR localized PrCa patients had a mutation. BRCA2 mutations were found in 1.0% of EUR (Fig. 1A) and 0.28% of AFR patients (Fig. 1B). Other genes with the most mutations in EUR patients—ATM (0.51%), BRCA1 (0.77%), CHEK2 (0.34%), and TP53 (0.34%)—were not found in any AFR patients. The most commonly mutated gene in AFR localized PrCa patients was FANCA (0.57%). When the EUR and AFR cohorts were restricted to patients with high-risk or very-high-risk localized PrCa at diagnosis or those who developed biochemical recurrence or metastatic disease, higher mutation rates were seen for BRCA2 and ATM in EUR and BRCA2 and PALB2 in AFR individuals (Fig. 1A and 1B).
We next compared the mutation rates, excluding somatic interference, by gene burden testing in our localized PrCa patients with those in cancer-free males of the same genetically determined ancestry (Table 2, and Supplementary Tables 8 and 9). DNA repair mutations were not found at significantly elevated rates in either EUR or AFR localized PrCa patients compared with PMBB or gnomAD controls (EUR: 4.0% vs 2.8%, \( p = 0.2 \), vs 3.1%, \( p = 0.04 \); AFR: 1.4% vs 1.6%, \( p = 0.8 \), vs 2.1%, \( p = 0.5 \)). Only mutations in \textit{BRCA2} were found at significantly elevated rates in EUR localized PrCa patients and only when compared with gnomAD (1.0% vs 0.32%, \( p = 0.027 \)). Transcript expression–restricted annotation of variants did not change mutation counts in PrCa patients, but reduced \textit{BRCA1} variant counts in both control groups, suggesting significant enrichment in PrCa patients compared with gnomAD controls (Supplementary Table 8). Uncorrected \( p \) values suggest significant enrichment of \textit{TP53} mutations in EUR PrCa patients compared with that in PMBB and gnomAD controls, but corrected \( p \) values were not significant (0.34% vs 0.04% and 0.03%). Mutations were not found at significantly elevated rates in any genes in AFR PrCa patients compared with those in AFR PMBB or gnomAD controls. Somatic interference mutations accounted for one in 57 (1.8%) and seven in 89 (7.9%) mutations in PrCa and control patients.

We next determined the potential burden of genetic testing in PMBB PrCa patients based on 2020 NCCN guidelines \cite{12}. Overall, 39% of 2391 patients met at least one NCCN criterion for consideration of genetic testing, and 26% met either high-risk or very-high-risk criteria (Supplementary Table 10). Of 2038 patients with documented Gleason score data, 298 (15%) were qualified based on Gleason 8–10. A substantial percentage (26%) of patients qualified for genetic testing with only one criterion, with the top three being T3/4 disease (20%), Ashkenazi Jewish ancestry (7.4%), and Gleason score \( \geq 8 \) (5.5%; Supplementary Table 10). Similar to the overall cohort, 32% of the sequenced cohort met high-risk or very-high-risk criteria (Table 3). Overall mutation rates decreased by risk category, from 15% with N1 disease and 6.2% with very-high-risk, 4.3% with high-risk, and 3.1% with intermediate-risk localized criteria for all DNA repair genes. Restricting to genes found in our study and in published studies as significantly associated with PrCa \cite{10,19} mutations were found in 5.6%, 3.0%, and 1.9% of individuals with very-high-risk, high-risk, and intermediate-risk disease, respectively (Table 3). Of 56 and 13 total and \textit{BRCA2} mutation carriers, respectively, 28 (46%) and eight (62%) were found in individuals with high-risk or very-high-risk localized or N1 disease.

Finally, we compared clinical-pathological characteristics found in genetic carriers versus noncarriers (Table 4 and Supplementary Tables 11–13). Patients with Gleason score 8–10 and specifically Gleason score 9–10 PrCa were more likely to harbor germline genetic mutations compared with patients with Gleason score 6–7 PrCa (6.7% vs 3.2%, \( p = 0.02 \); 9.3% vs 3.2%, \( p = 0.003 \); Table 4). \textit{BRCA2} carriers had a 50% absolute risk of Gleason score 8–10 PrCa (relative risk [RR] vs mutation negative: 3.4, 95% CI 1.9–6.2, \( p < 0.0001 \); Supplementary Table 12). In contrast, the absolute risk of Gleason score 8–10 PrCa was 20% in carriers of all other gene mutations and not significantly increased in mutation-negative individuals (RR: 1.4, 95% CI 0.74–2.36, \( p = 0.3 \)). \textit{BRCA2} mutations were also more common in patients with biochemical recurrence than in those without (2.5% vs 0.62%, \( p = 0.025 \); Table 4). However, in a multivariate analysis of 669 patients with data...
for all variables, only Gleason score remained significantly associated with the carriage of a germline genetic mutation (Supplementary Table 13).

4. Discussion

Germline mutations in PrCa are essential to characterize due to their implications for personalized treatment selection, risk prediction, and familial testing. Other studies of germline mutations in localized PrCa to date have not included men of AFR ancestry, used cohorts overselected for aggressive disease, or lacked control cohorts.

Using individuals with genetically determined ancestry in an academic biobank, our study demonstrated that mutation rates were lower in AFR than in EUR individuals. Black men are disproportionately affected by PrCa, with a higher incidence and mortality rate than white men [36–38]. Despite these known disparities, Black men are under-represented in genetic studies [39,40]. In our cohort of localized PrCa, germline mutation rates were significantly lower in AFR individuals than in EUR individuals (4.0% vs 1.4%, p = 0.02), similar to prior studies selected for more aggressive disease [19,41]. Given the association with aggressive early-onset and lethal disease [20,42,43], germline BRCA2 mutations may be associated with worse outcomes in AFR individuals [44]. However, we found that BRCA2 germline mutations were rare in AFR individuals (0.28%) and less frequent than in EUR individuals (1.0%, p = 0.4). Our data suggest that the disparity in PrCa outcomes for Black individuals with localized PrCa may not be due to germline mutations in these 17 genes.

The overall germline mutation rate is lower in localized PrCa patients in our study than in prior studies of metastatic PrCa patients [15]. The rate of germline DNA repair mutations in metastatic PrCa or genetic testing populations ranges from 9% to 15% [15,17,22,45], whereas rates under 6% have been demonstrated in other cohorts of localized PrCa cases [19–21]. Importantly, we demonstrate that mutation rates in a localized PrCa cohort were not significantly different from those in cancer-free controls. We found that four genes (BRCA2, BRCA1, ATM, and TP53) had higher mutation rates than in gnomAD controls, but none had statistically higher rates than in local population controls. Significant associations were seen for ATM, BRCA2, NBN, and PALB2 in another analysis of cases versus controls of African descent, but only when restricted to high-risk disease [19]. Population-based cohorts versus gnomAD cohorts are critical to discern true associations of rare germline mutations with common diseases [46], due to differences in population structure or sequencing depth between cohorts. Our comparison of similarly covered genomic regions in a matched institutional cohort along with prior results brings into question whether mutations in DNA repair genes beyond BRCA2 are truly associated with localized PrCa, particularly in AFR individuals.

Our study evaluated the prevalence of germline mutations for NCCN guideline criteria for genetic testing. The rate of germline mutations varied for each criterion from 4% to 15%, and >96% of patients who would have been recommended for germline testing for localized PrCa would not have had an identified germline mutation in our cohort. The highest rates of germline mutations overall were found in those with node-positive (N1) disease (15%) and Gleason 9–10 disease (9%). Widespread genetic testing for all localized PrCa has significant

Eur Urol. Author manuscript; available in PMC 2022 June 01.
concerns for cost effectiveness and scalability, including the potential for inadequate access to genetic counselors, which could lead to misinterpretation of test results, inappropriate medical recommendations, and adverse psychosocial outcomes [47,48]. Future studies that encompass multi-institutional population-based cohorts will be required to evaluate fully the appropriateness of the current guidelines.

There are several limitations to this study. First, although our study represents one of the largest populations of germline testing in localized PrCa, the sample size remains relatively small for studying rare germline mutations. This cohort reflects the general practice patterns for localized PrCa, and therefore includes mostly low- to intermediate-risk patients. Utilizing controls from the same academic institution potentially increased our power to detect associations, but also had the potential to introduce a bias in our analysis given that the controls include individuals at a tertiary care center. Individual pathology specimens were not reviewed with data abstracted from reports. PMBB cases were evaluated by amplicon sequencing, while the controls were evaluated by WES, and neither set underwent copy number variant analyses. Additional case-control analyses using whole genome sequencing should be performed.

5. Conclusions

In conclusion, we demonstrated a significantly lower rate of germline mutations for men of AFR ancestry with localized PrCa than that for men of EUR ancestry and low rates of DNA repair mutations in localized PrCa patients overall. We demonstrate similar DNA repair mutation rates in localized PrCa cases to that in control individuals in the majority of genes except for BRCA2. Genetic testing restricted to localized PrCa patients with very-high-risk and high-risk PrCa would capture the majority of clinically actionable mutations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial disclosures:

Kara N. Maxwell certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: S.M. Damrauer receives research support to the University of Pennsylvania from RenalytxAI and consulting fees from Calico Labs, both outside the current work. The remaining authors have no conflicts of interest to report.

Funding/Sponsor and role of the sponsor:

This study is funded by the Agency for Healthcare Research and Quality (K12HS026372; Daniel J. Lee), NCI (K08CA215312, Kara N. Maxwell), Burroughs Wellcome Fund (#1017184; Kara N. Maxwell), Basser Center for BRCA (Susan M. Domchek and Kara N. Maxwell), Penn Center for Precision Medicine (Lauren E. Schwartz and Kara N. Maxwell), Prostate Cancer Foundation (#20YOU012; Kara N. Maxwell), The Jonathan and Plum Simons Precision Oncology Center of Excellence (Kara N. Maxwell), and the Veterans Association (IK2-CX001780, Scott M. Damrauer). This publication does not represent the views of the Department of Veterans Affairs or the US Government.
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Fig. 1 –.
Mutation rates of 17 DNA repair genes in localized prostate cancer patients of genetically determined EUR and AFR ancestry. Localized PrCa cases underwent targeted massively parallel sequencing and analysis for mutations in 17 DNA repair genes in patients of genetically determined (A) EUR and (B) AFR descent. Overlapping genomic regions from whole exome sequencing data were analyzed from EUR and AFR cancer-free male patients from the PMBB and mutation rates shown for the same genes. Average heterozygote frequencies are shown for all mutations in the listed genes from NFE and AFR cancer-free males in gnomAD. Aggressive PrCa was defined as localized PrCa meeting high-risk or very-high-risk criteria at diagnosis and in those patients who subsequently developed biochemical recurrence or metastatic disease. (A) Bar plot of germline DNA repair gene mutation rates in the EUR PMBB localized PrCa cohort (n = 1174), subset of EUR PMBB localized PrCa cases with aggressive disease (n = 407), PMBB EUR cancer-free control cohort (n = 2615), and gnomAD NFE cancer-free control cohort (average estimated heterozygotes = 11 750). Aggressive disease was defined as localized PrCa meeting high-risk or very-high-risk criteria at diagnosis and in those patients who subsequently developed biochemical recurrence or metastatic disease. No mutations were identified in EUR localized PrCa cases in MLH1, RAD51C, and RAD51D. (B) Bar plot of germline DNA repair gene mutation rates in the AFR PMBB localized PrCa cohort (n = 351), subset of AFR PMBB localized PrCa cases with aggressive disease (n = 132), PMBB AFR cancer-free control cohort (n = 515), and gnomAD AFR cancer-free control cohort (average estimated heterozygotes = 1450). No mutations were identified in AFR localized PrCa cases in ATM, BARD1, BRCA1, BRIP1, CHEK2, MSH2, MSH6, PMS2, RAD51C, RAD51D, RAD54L, and TP53. AFR = African descent; Avg = average; EUR = European descent; NFE = Non-Finnish European; PMBB = Penn Medicine Biobank; PrCa = prostate cancer.
### Table 1:
Demographics, Clinical and Family Histories of the PMBB Prostate Cancer Cohort

| Demographics | PMBB Prostate Cancer Cohort, n=2391 | Sequencing Cohort, n=1588 | PMBB Controls, n=3273 |
|--------------|-----------------------------------|---------------------------|---------------------|
| Self-reported race | n=2391                            | n=1588                    | n=3273              |
| Non-Hispanic White | 1738 (73%)                        | 1149 (72%)                | 2337 (71%)          |
| Non-Hispanic Black | 535 (22%)                         | 359 (23%)                 | 479 (15%)           |
| Hispanic       | 25 (1.0%)                         | 16 (1.0%)                 | 0 (0%)              |
| Asian          | 14 (0.6%)                         | 12 (0.8%)                 | 37 (1.1%)           |
| Other or Unknown | 79 (3.3%)                        | 52 (3.3%)                 | 364 (11%)           |
| Age at biobank enrollment | Median (IQR)=73 (12)   | 72 (12)                   | 61 (17)            |
| Age<50         | 9 (0.38%)                         | 8 (0.50%)                 | 244 (7.5%)          |
| Age<60         | 182 (7.6%)                        | 146 (9.2%)                | 581 (18%)           |
| Prostate Cancer History | Age of Diagnosis | n=2056                  | n=1410                | n/a                |
| Age at presentation | Median (IQR)=64(11)              | 64(10)                    | -                   |
| Age<50         | 81 (3.8%)                         | 61 (4.2%)                 | -                   |
| Age<60         | 701 (33%)                         | 505 (35%)                 | -                   |
| Gleason Grade Group | n=2040                        | n=1413                    | n/a                |
| GG 5           | 175 (8.6%)                        | 118 (8.4%)                | -                   |
| GG 4           | 124 (6.1%)                        | 91 (6.4%)                 | -                   |
| GG 3           | 296 (15%)                         | 204 (14%)                 | -                   |
| GG 2           | 852 (42%)                         | 615 (44%)                 | -                   |
| GG 1           | 593 (29%)                         | 385 (27%)                 | -                   |
| Localized or Metastatic | n=2321                      | n=1588                    | n/a                |
| Localized at presentation | 2282 (98%)                    | 1588 (100%)               | -                   |
| De novo Metastatic | 39 (1.7%)                      | excluded                  | -                   |
| Biochemical recurrence | n=1683                      | n=1206                    | n/a                |
| Yes            | 276 (16%)                         | 201 (17%)                 | -                   |
| Metastatic at any point | n=1858                      | n/a                       | n/a                |
| Yes            | 124 (6.7%)                        | excluded                  | -                   |
| Vital Status | n=2391                            | n=1596                    | n/a                |
| Deceased       | 533 (22%)                         | 384 (24%)                 | -                   |
| T Stage | n=1399                            | n=1038                    | n/a                |
| T1             | 21 (1.5%)                         | 15 (1.4%)                 | -                   |
| T2             | 716 (51%)                         | 542 (52%)                 | -                   |
| T3             | 394 (28%)                         | 307 (30%)                 | -                   |
| T4             | 3 (0.21%)                         | 3 (0.3%)                  | -                   |
| Tx             | 265 (19%)                         | 171 (17%)                 | -                   |
| N stage | n=1469                            | n=1089                    | n/a                |
|                      | PMBB Prostate Cancer Cohort, n=2391 | Sequencing Cohort, n=1588 | PMBB Controls, n=3273 |
|----------------------|-------------------------------------|----------------------------|-----------------------|
|                      | n       | %       | n       | %       | n/a       |                          |
| N0                   | 1136    | 77%     | 867     | 80%     |            |                          |
| N1                   | 38      | 2.6%    | 27      | 2.5%    |            |                          |
| Nx                   | 295     | 20%     | 195     | 18%     |            |                          |
| Intraductal/ductal histology | n=2356 | n=1579 | n/a     |          |          |                          |
| Yes                  | 17      | 0.72%   | 10      | 0.6%    |            |                          |
| Family History of Cancer | n=2216 | n=1481 | n=2317 |          |          |                          |
| # of reported FDR/SDRs with Prostate Cancer |          |          |          |          |          |                          |
| 0                    | 1687    | 76%     | 1109    | 75%     | 2236      | 97%                     |
| 1                    | 418     | 19%     | 291     | 20%     | 77        | 3.3%                    |
| 2                    | 91      | 4.1%    | 67      | 4.5%    | 4         | 0.17%                   |
| 3 or more            | 20      | 0.90%   | 14      | 0.95%   | 0         | 0%                      |
| # of reported FDR/SDRs with Breast Cancer |          |          |          |          |          |                          |
| 0                    | 1910    | 86%     | 1273    | 86%     | 2206      | 95%                     |
| 1                    | 267     | 12%     | 183     | 12%     | 99        | 4.3%                    |
| 2 or more            | 39      | 1.8%    | 25      | 1.7%    | 12        | 0.52%                   |
| # of reported FDR/SDRs with Ovarian Cancer |          |          |          |          |          |                          |
| 0                    | 2173    | 98%     | 1454    | 98%     | 2299      | 99%                     |
| 1 or more            | 43      | 1.9%    | 27      | 1.8%    | 18        | 0.78%                   |
| # of reported FDR/SDRs with Prostate, Breast or Ovarian Cancer |          |          |          |          |          |                          |
| 0                    | 1442    | 65%     | 944     | 64%     | 2119      | 91%                     |
| 1                    | 567     | 26%     | 393     | 27%     | 171       | 7.4%                    |
| 2                    | 154     | 6.9%    | 106     | 7.2%    | 25        | 1.1%                    |
| 3 or more            | 53      | 2.4%    | 38      | 2.6%    | 2         | 0.09%                   |
| >3 Cancers on one side of the family |          |          |          |          |          |                          |
| Yes                  | 125     | 5.2%    | 84      | 5.3%    | 90        | 3.9%                    |
| Major Medical Conditions |          |          |          |          |          |                          |
| Heart Disease        | 1439    | 60%     | 979     | 62%     | 1181      | 36%                     |
| Cerebrovascular Disease | 202   | 8.4%    | 126     | 7.9%    | 152       | 4.6%                    |
| Diabetes mellitus    | 475     | 20%     | 316     | 20%     | 415       | 13%                     |
| Obesity              | 426     | 18%     | 314     | 20%     | 302       | 9.2%                    |
| Dementia             | 64      | 2.7%    | 41      | 2.6%    | 38        | 1.2%                    |
| Schizophrenia or Mood Disorders | 218   | 9.1%    | 147     | 9.3%    | 155       | 4.7%                    |
| Chronic pulmonary diseases | 298   | 13%     | 209     | 13%     | 210       | 6.4%                    |
| Immunodeficiencies   | 86      | 3.6%    | 54      | 3.4%    | 123       | 3.8%                    |
Table 2:
Case Control of PMBB Prostate cancer cases to PMBB and gnomad controls in EUR individuals

| Gene  | PMBB EUR n | PMBB EUR % | p-value to PMBB Controls | gnomAD NFE n | gnomAD NFE % | p-value to gnomad Controls |
|-------|------------|------------|--------------------------|--------------|--------------|---------------------------|
| TOTAL | 1174       | 47         | 4.0%                     | 2615         | 363          | 3.1%                      | 0.15                     |
| ATM   | 6          | 0.51%      | 16 0.61%                 | 0.8          | 44           | 0.37%                     | 0.042 (0.9)              |
| BARD1 | 1          | 0.09%      | 1 0.04%                  | 0.5          | 8            | 0.07%                     | 0.1                      |
| BRCA1 | 9          | 0.77%      | 5 0.19%                  | 0.1          | 30           | 0.26%                     | 0.001 (0.027)            |
| BRCA2 | 12         | 1.0%       | 14 0.54%                 | 0.1          | 38           | 0.32%                     | 0.5                      |
| BRIPI | 1          | 0.09%      | 1 0.04%                  | 0.5          | 27           | 0.23%                     | 0.5                      |
| CHEK2 | 4          | 0.34%      | 7 0.27%                  | 0.8          | 83           | 0.71%                     | 0.2                      |
| FANCA | 2          | 0.17%      | 8 0.31%                  | 0.5          | 32           | 0.27%                     | 0.7                      |
| NBN   | 1          | 0.09%      | 6 0.23%                  | 0.5          | 15           | 0.13%                     | >0.9                     |
| PALB2 | 2          | 0.17%      | 3 0.11%                  | 0.7          | 11           | 0.09%                     | 0.3                      |
| RAD51C| 0          | 0.00%      | 1 0.04%                  | n/a          | 13           | 0.11%                     | 0.6                      |
| RAD51D| 0          | 0.00%      | 2 0.08%                  | n/a          | 3            | 0.03%                     | >0.9                     |
| RAD54L| 1          | 0.09%      | 3 0.11%                  | >0.9         | 12           | 0.10%                     | >0.9                     |
| MLH1  | 0          | 0.00%      | 0 0.00%                  | n/a          | 6            | 0.05%                     | >0.9                     |
| MSH2  | 2          | 0.17%      | 0 0.00%                  | 0.10         | 6            | 0.05%                     | 0.2                      |
| MSH6  | 1          | 0.09%      | 2 0.08%                  | >0.9         | 10           | 0.09%                     | >0.9                     |
| PMS2  | 1          | 0.09%      | 4 0.15%                  | >0.9         | 21           | 0.18%                     | 0.7                      |
| TP53  | 4          | 0.34%      | 1 0.04%                  | 0.035        | 4            | 0.03%                     | 0.004 (0.067)            |

All Bonferroni corrected p-values =1, except where noted in parenthesis

AFR: African ancestry; EUR: European ancestry; PMBB: Penn Medicine Biobank
### Table 3:
Mutation rates by prostate cancer clinical and pathological variables

| Clinico-pathological Criteria                  | NCCN Localized Risk Categories | NCCN Prostate Genetic Testing Component Criteria | Other variables |
|-----------------------------------------------|---------------------------------|-------------------------------------------------|-----------------|
|                                               | INTERMEDIATE RISK               | GS 8–10                                        | GS: Gleason score, FDR: first degree relative, SDR: second degree relative |
|                                               | High Risk Criteria              | PSA at diagnosis > 20ng/mL                       |                 |
|                                               | Very High Risk Criteria         | T3b/T4                                         |                 |
|                                               | N1 at Diagnosis                 | T3/T4                                          |                 |
|                                               | NCCN Localized Risk Categories  | Intraductal/ductal histology                    |                 |
|                                               |                                 | ≥8 cancers on same side of family               |                 |
|                                               |                                 | Ashkenazi Jewish                               |                 |
|                                               |                                 | Biochemical recurrence                         |                 |
|                                               |                                 | Developed Metastatic disease                   |                 |
|                                               |                                 | Deceased                                       |                 |
| # meeting criteria                            | # with data for criteria        | Criteria rate                                  |                 |
|                                               |                                  | n Mutation rate$^1$                             |                 |
|                                               |                                  | n Mutation rate$^1$                             |                 |
|                                               |                                  | n Mutation rate$^1$                             |                 |

| Criteria | n | Mutation rate$^1$ | n | Mutation rate$^1$ | n | Mutation rate$^1$ |
|----------|---|-------------------|---|-------------------|---|-------------------|
| Intermediate Risk | 645 | 1425 | 45% | 3 | 0.5% | 12 | 1.9% | 20 | 3.1% |
| High Risk Criteria | 300 | 1425 | 21% | 3 | 1.0% | 9 | 3.0% | 11 | 3.7% |
| Very High Risk Criteria | 161 | 1425 | 11% | 4 | 2.5% | 9 | 5.6% | 10 | 6.2% |
| N1 at Diagnosis | 27 | 894 | 3.0% | 1 | 3.7% | 4 | 15% | 4 | 15% |
| Gleason score: 8–10 | 209 | 1413 | 15% | 6 | 2.9% | 16 | 7.7% | 17 | 8.1% |
| PSA at diagnosis > | 59 | 1165 | 5.1% | 1 | 1.7% | 2 | 3.4% | 3 | 5.1% |
| T3b/T4 | 104 | 690 | 15% | 2 | 1.9% | 6 | 5.8% | 6 | 5.8% |
| T3/T4 | 310 | 1041 | 30% | 5 | 1.6% | 15 | 4.8% | 17 | 5.5% |
| Intraductal/ductal histology | 10 | 1577 | 0.63% | 1 | 10% | 1 | 10% | 1 | 10% |
| ≥8 cancers on same side of family | 84 | 1588 | 5.3% | 1 | 1.2% | 5 | 6.0% | 5 | 6.0% |
| Ashkenazi Jewish | 134 | 1336 | 10% | 2 | 1.5% | 6 | 4.5% | 7 | 5.2% |
| Glycosylation Group 5 | 118 | 1421 | 8.3% | 4 | 3.4% | 12 | 10% | 13 | 11% |
| Gleason primary pattern: 5 | 29 | 1413 | 1.8% | 1 | 3.4% | 2 | 6.9% | 3 | 10% |
| Age of diagnosis <50 | 61 | 1410 | 4.3% | 1 | 1.6% | 3 | 4.9% | 4 | 6.6% |
| Age of diagnosis <60 | 493 | 1410 | 35% | 6 | 1.2% | 17 | 3.4% | 19 | 3.9% |
| Extraprostatic extension | 289 | 859 | 34% | 3 | 1.0% | 10 | 3.5% | 12 | 4.2% |
| Lymphovascular invasion | 58 | 731 | 7.9% | 0 | 0.0% | 1 | 1.7% | 1 | 1.7% |
| Perineural invasion | 341 | 451 | 76% | 4 | 1.2% | 10 | 2.9% | 17 | 5.0% |
| Seminal vesicle invasion | 108 | 879 | 12% | 2 | 1.9% | 5 | 4.6% | 6 | 5.6% |
| ≥1 FDR/SDR breast/ovarian cancer | 220 | 1481 | 15% | 3 | 1.4% | 8 | 3.6% | 10 | 4.5% |
| ≥1 FDR/SDR prostate cancer | 368 | 1481 | 25% | 2 | 0.5% | 8 | 2.2% | 9 | 2.4% |
| Biochemical recurrence | 201 | 1206 | 17% | 5 | 2.5% | 9 | 4.5% | 9 | 4.5% |
| Developed Metastatic disease | 46 | 1321 | 3.5% | 2 | 4.3% | 2 | 4.3% | 2 | 4.3% |
| Deceased | 131 | 1588 | 8.2% | 1 | 0.8% | 2 | 1.5% | 3 | 2.3% |

$^1$ Mutation rates = # with mutation and criteria divided by all patients with data for that criteria.

GS: Gleason Score; FDR: first degree relative; SDR: second degree relative.

Eur Urol. Author manuscript; available in PMC 2022 June 01.
## Table 4:
Association of mutation carrier status with aggressive clinical features

|                        | All DNA repair mutations | BRCA2 (total removes other carriers) | All other genes (total removes other carriers) |
|------------------------|--------------------------|--------------------------------------|-----------------------------------------------|
|                        | Total n | n | % | p  | Total n | n | % | p  | Total n | n | % | p  |
| **Gleason score 8–10** |          |   |   |    |          |   |   |    |          |   |   |    |
| GS 8–10                | 209     | 14 | 6.7% | 0.02 | 203     | 6 | 3.0% | 0.004 | 203     | 8 | 3.9% | 0.4 |
| GS 6–7                 | 1204    | 38 | 3.2% |      | 1167    | 6 | 0.51% |      | 1198    | 32 | 2.7% |      |
| **Gleason score 9–10** |          |   |   |    |          |   |   |    |          |   |   |    |
| GS 9–10                | 118     | 11 | 9.3% | 0.003 | 111     | 4 | 3.6% | 0.008 | 114     | 7 | 6.1% | 0.1 |
| GS 6–7                 | 1204    | 38 | 3.2% |      | 1167    | 6 | 0.51% |      | 1198    | 32 | 2.7% |      |
| **T3–T4 stage**        |          |   |   |    |          |   |   |    |          |   |   |    |
| T3–T4                  | 310     | 17 | 5.5% | 0.3  | 297     | 5 | 1.7% | 0.5   | 305     | 12 | 3.9% | 0.4 |
| T1–T2                  | 557     | 21 | 3.8% |      | 538     | 6 | 1.1% |      | 551     | 15 | 2.7% |      |
| **N1 stage**           |          |   |   |    |          |   |   |    |          |   |   |    |
| N1                     | 27      | 4  | 15%  | 0.03  | 24      | 1 | 4.2% | 0.3   | 26      | 3  | 12%  | 0.05 |
| N0                     | 867     | 36 | 4.2% |      | 837     | 10 | 1.2% |      | 857     | 26 | 3.0% |      |
| **Biochemical Recurrence** |        |   |   |    |          |   |   |    |          |   |   |    |
| Yes                    | 201     | 9  | 4.5% | 0.4   | 197     | 5 | 2.5% | 0.03  | 196     | 4  | 2.0% | 0.8 |
| No                     | 1005    | 33 | 3.3% |      | 973     | 6 | 0.62%|      | 999     | 27 | 2.7% |      |
| **Becoming metastatic**|          |   |   |    |          |   |   |    |          |   |   |    |
| Yes                    | 46      | 2  | 4.3% | 0.7   | 46      | 2 | 4.3% | 0.1   | None    | None | n/a | n/a |
| No                     | 1275    | 46 | 3.6% |      | 1233    | 10 | 0.81%|      | 1265    | 36 | 2.8% |      |