

Homologous Recombination Repair Gene Variants and Outcomes Among Patients With Prostate Cancer Treated With Poly (ADP-ribose) Polymerase Inhibitors

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PURPOSE Poly ADP-ribose polymerase inhibitors (PARPi) are used for patients with advanced prostate cancer bearing alterations in homologous recombination repair (HRR) genes. We sought to characterize HRR gene variants and describe real-world outcomes for patients on PARPi.

METHODS The US Department of Veterans Affairs' National Precision Oncology Program's database was reviewed to identify patients who underwent somatic DNA sequencing and were prescribed a PARPi before May 15, 2020. Somatic and germline variants within HRR genes were reported, and pathogenicity was reviewed via OncoKB. In patients treated with PARPi for > 4 weeks, the rate of those achieving a 30% decrease in prostate-specific antigen (PSA30) and composite progression-free survival (PFS) were compared between patients bearing pathogenic variants of *BRCA2* and patients without these variants using Mann-Whitney and log-rank tests, respectively.

RESULTS Forty-eight patients bearing 67 total HRR gene variants were prescribed PARPi for prostate cancer. Twenty-one patients (43.8%) were found to have at least one pathogenic HRR gene variant. Eight (16.6%) were referred to genetic counseling, and five (10.4%) were ultimately confirmed with germline variants. The median PFS was 4.0 months, and PSA30 was 25.6% (11 of 43) for all 43 evaluable patients. Patients with pathogenic *BRCA2* variants (n = 13) had higher PSA30 (69.2% v 4.0%; $P < .001$) and longer PFS (7.2 v 2.8 months; $P = .0291$) than those without.

CONCLUSION In a real-world setting, heavily pretreated patients with prostate cancer and pathogenic *BRCA2* variants have a significant PSA response rate and a PFS > 7 months with PARPi. This work emphasizes the importance of determining pathogenicity and origin of HRR alterations to better inform clinical treatment decisions and highlights the need for provider education and other decision support tools.

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BACKGROUND

In the United States, prostate cancer is the second most common malignancy among men, with an annual incidence of approximately 250,000.¹ Although most patients with early-stage prostate cancer share a favorable prognosis, patients with metastatic castrate-resistant prostate cancer (mCRPC) frequently have poor outcomes, with a median overall survival ranging from 13 months² to 32 months.^{3,4} Unfortunately, despite an overall decline in the incidence of prostate cancer in the United States, the incidence of metastatic prostate cancer continues to rise.⁵ Thus, efforts to improve treatment options for men with mCRPC are critical.

Poly ADP-ribose polymerase inhibitors (PARPi), a family of drugs that inhibit the repair of DNA single-strand breaks, have recently become a therapy of interest given the relatively high frequency of alterations in DNA repair genes among patients with mCRPC. Germline

alterations in homologous recombination repair (HRR) genes have been found in 7%-12% of men with mCRPC,⁶ and somatic alterations in HRR genes have been reported in 19% (The Cancer Genome Atlas) to 27%⁷ of both primary and metastatic samples of prostate cancer. Within these HRR genes, variants in *BRCA2* tend to be most frequently observed followed by those in *ATM* and *BRCA1*.⁸

Several completed and ongoing trials to determine the efficacy of PARPi in patients with mCRPC have shown promising results for populations with certain HRR alterations with differential responses on the basis of specific HRR gene alterations.⁹⁻¹¹ Of these, the PROfound study was the first clinical trial to assess the efficacy of olaparib by specific cohorts of HRR genes.⁹ This study showed a more favorable response to olaparib among patients with *BRCA1*, *BRCA2*, and *ATM* deleterious alterations compared with those with alterations in other HRR genes, with exploratory

ASSOCIATED CONTENT

Data Supplement

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

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CONTEXT

Key Objective

Poly ADP-ribose polymerase inhibitors (PARPi) are approved for patients with advanced prostate cancer bearing pathogenic/likely pathogenic mutations in specific homologous recombination repair (HRR) genes. We sought to review the gene variants and outcomes among Veterans who were treated with PARPi and had underwent tumor DNA sequencing through the US Department of Veterans Affairs' National Precision Oncology Program.

Knowledge Generated

Approximately one half of patients with prostate cancer are prescribed PARPi without harboring a pathogenic/likely pathogenic HRR gene variant. Patients bearing pathogenic/likely pathogenic *BRCA2* mutations more frequently have longer progression-free survival and are more likely to achieve a significant prostate-specific antigen reduction compared with others receiving PARPi.

Clinical Relevance

Patients with advanced prostate cancer bearing *BRCA2* pathogenic mutations have better outcomes with PARPi than those with other HRR gene variants. Efforts should be made to improve provider education regarding gene variant pathogenicity and relationship to clinical decision making.

analyses demonstrating longer progression-free survival (PFS) for patients with *BRCA2* alterations (10.8 months). Notably, a recent report from the TOPARP-B trial identified biallelic *BRCA2* deletions as one of the biomarkers associated with a significantly improved response to PARPi.¹² Currently, reports of PARPi administration and treatment outcomes on the basis of the genotype have been primarily limited to clinical trial settings. For these reasons, a study assessing real-world outcomes of patients with mCRPC treated with PARPi on the basis of the HRR genotype is warranted.

Consequently, the first aim of the current study was to review the HRR gene variants and overall treatment outcomes for Veterans who were prescribed PARPi for prostate cancer. The second aim of this study was to compare outcomes between patients bearing pathogenic/likely pathogenic *BRCA2* variants and those without. We hypothesized that in a real-world context, patients with a wide array of HRR gene alterations would be prescribed PARPi and those with pathogenic *BRCA2* alterations would have better outcomes than patients with non-*BRCA2* alterations.

METHODS

Included Patients

Patients who (1) had been diagnosed with prostate cancer; (2) had successful genomic sequencing of tumor tissue or plasma; and (3) were prescribed olaparib, rucaparib, niraparib, or talazoparib for prostate cancer before May 2020 were selected for evaluation. All included patients had confirmed mCRPC. Patients who received a PARPi for a malignancy other than prostate cancer were excluded. Patients were required to receive a PARPi for at least 4 weeks to be included in outcomes assessments. No patient received a PARPi as part of a clinical trial.

Data Source and Ethical Considerations

This retrospective study was approved by the Institutional Review Board of the Durham Veterans Affairs' (VA) Medical

Center, which provided a waiver of patient informed consent.

Eligible patients were initially selected from the US Department of Veterans Affairs' National Precision Oncology Program's (NPOP) database. The NPOP database includes all Veterans who underwent tumor DNA sequencing via next generation sequencing (NGS) through an external commercial laboratory contracted with NPOP from July 2015 to the present time. Eight of the NGS panels are as follows: Personalis(ACE CancerPlus Test), PGDx(CancerSELECT 88, CancerSELECT 125, CancerSELECT 203, or PlasmaSELECT), and Foundation Medicine(FoundationsOne CDx, FoundationsOne Liquid, and FoundationsOne Liquid CDx). To determine pathogenicity, each HRR gene variant was reviewed in OncoKB, an online precision oncology knowledge database, in May 2021.¹³ Apart from the NPOP database, the VA Corporate Data Warehouse,¹⁴ a repository comprising data from VA clinical and administrative systems, and Joint Legacy Viewer,¹⁵ which provides read-only access to all Veterans Health Administration electronic health records, were additional data sources.

Data Collection

The results of tumor DNA sequencing and dates of PARPi prescriptions and discontinuations were retrieved from NPOP. The Corporate Data Warehouse was accessed to obtain prostate-specific antigen (PSA) levels from 6 months before the initial date of PARPi prescription to up to 6 months after the last prescription date. Demographic data were then extracted via manual review of Joint Legacy Viewer. Imaging reports and notes from oncology providers and genetic counseling specialists were also reviewed. From oncology provider notes, dates of initial diagnoses, previous therapies received, duration of PARPi administration, provider comments on PSA levels, and PARPi-associated toxicities were recorded. From the genetic counseling specialists' notes, the results of germline

mutational testing and reasons for germline testing were obtained. Medical records were reviewed up to January 15, 2021.

Data Analysis

Baseline demographics, clinical and disease characteristics, PARPi prescriptions, drug toxicities, HRR somatic gene variants, and available germline mutational testing results were reported for all selected patients. HRR gene variants annotated as pathogenic/likely pathogenic per OncoKB and with an allele fraction of > 30% were identified as those most likely to be germline variants, with the knowledge that the National Comprehensive Cancer Network¹⁶ recommends germline testing for all patients with metastatic prostate cancer.

Patients were then categorized on the basis of the presence of pathogenic/likely pathogenic *BRCA2* gene variants and those without (including those with *BRCA2* variants classified as variants of uncertain significance [VUS]). Furthermore, to eliminate concerns for patients likely bearing clonal hematopoiesis of indeterminate potential (CHIP), only *BRCA2* variants discovered from plasma sequencing with an allele fraction > 1.0% were included in the *BRCA2* arm.¹⁷⁻²¹ Clinical outcomes that were compared between these two patient cohorts included: PSA30, defined as the percentage of patients achieving a reduction in PSA by

30% or more after PARPi initiation,²² and a composite PFS end point, defined as the interval between drug initiation and the earliest of drug discontinuation, clinical or radiographic progression, or death. In addition, an exploratory analysis of patients with *BRCA2* variants classified as VUS was completed. For the purposes of assessing radiographic progression, two authors (M.P. and V.V.) reviewed radiology reports from at least 6 months before PARPi administration and up to 1 year after PARPi discontinuation. The presence of increasing size of tumors and/or new tumor(s) was used to identify radiographic progression as per RECIST criteria.²³ Only patients who were administered PARPi for 4 weeks or longer were included in the analysis of outcomes.

Descriptive statistics were used to summarize patient demographic data and clinical and disease characteristics. Specifically, medians and interquartile ranges were used for continuous variables, and the absolute number and frequency distributions were used for categorical variables. Regarding outcomes, PSA30 was compared using the Mann-Whitney test, and survival curves of composite PFS were drawn by the Kaplan-Meier method and compared by the log-rank test for patients with and without *BRCA2* variants. Patients who discontinued PARPi because of toxicities were censored for PFS analyses. Follow-up was

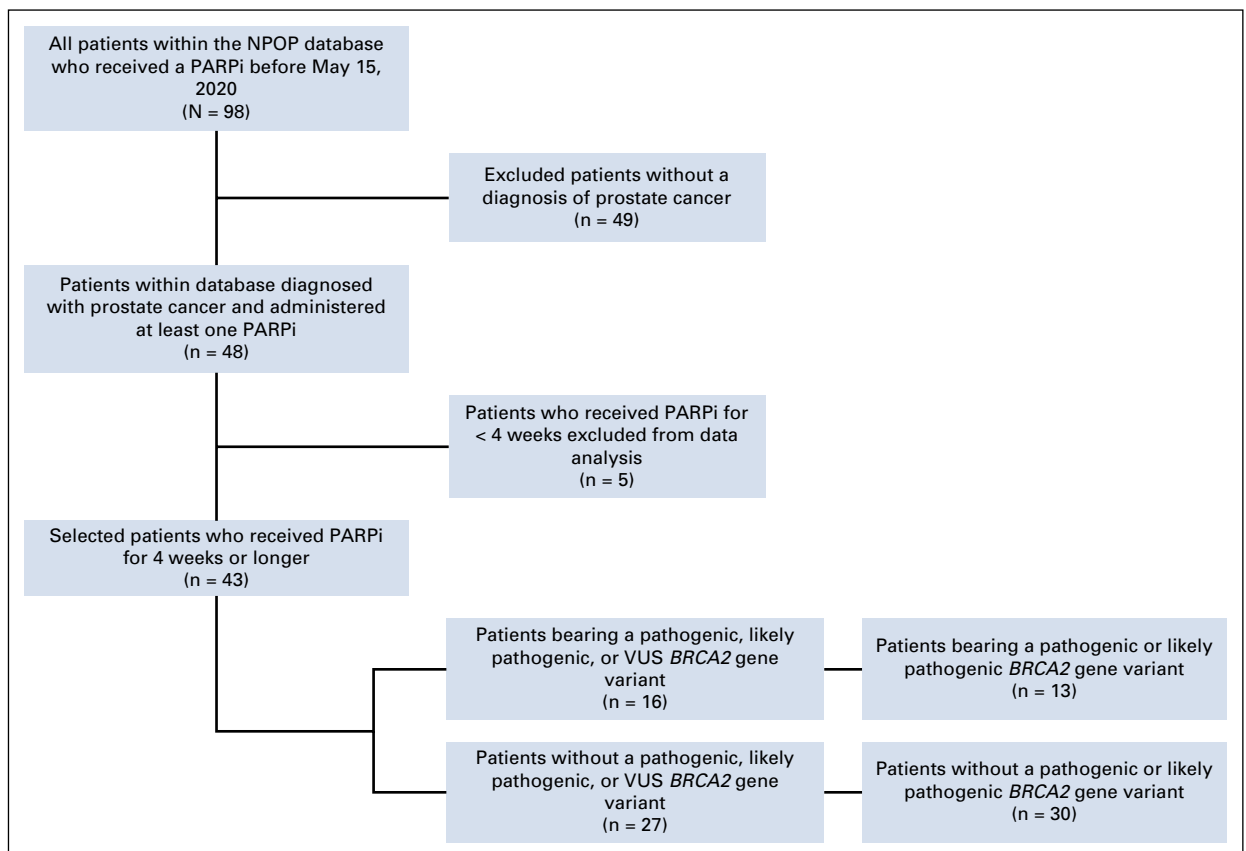


FIG 1. CONSORT diagram. NPOP, National Precision Oncology Program; PARPi, poly ADP-ribose polymerase inhibitor; VUS, variants of uncertain significance.

evaluated until January 15, 2021, at which time patients without progression were censored. All analyses were performed using Prism 8 software (GraphPad Software Corporation, version 8.3.1 (332)). The level of statistical significance was set at $P < .05$ for all analyses.

RESULTS

Selected Patients

Of the 98 patients who had tumor DNA sequencing available in NPOP and received PARPi before May 15, 2020, 48 (49.0%) had a primary diagnosis of prostate cancer (Fig 1). Of these, 43 (91.7%) were administered a PARPi for > 4 weeks. The median age (interquartile range) of the cohort was 72 (65-76) years, and a slight majority of patients (60.4%) were Caucasian. At the time of PARPi initiation, all patients had metastatic prostate cancer; 21 (43.8%) and 22 (45.3%) patients had undergone prior prostatectomy or local radiation therapy, respectively (Table 1). All patients had disease progression with at least one prior line of systemic therapy, with nine patients (18.8%) having received > 3 lines of systemic treatments before PARPi administration.

Variants Within HRR Genes

The HRR genes most commonly containing variants among patients receiving PARPi were *BRCA2* (36 variants, 25 patients, 52.1%), *ATM* (13 variants, 10 patients, 20.8%), and *BRCA1* (eight variants, eight patients, 16.7%; Fig 2). Of the *BRCA2* alterations, 17 were classified as pathogenic/likely pathogenic alterations, 13 were VUS, two were likely benign, and three were likely CHIP (allele fraction < 1% from plasma sequencing) variants. A total of 16 patients had at least one *BRCA2* variant classified as pathogenic/likely pathogenic (13 of whom received a PARPi for > 4 weeks). The remaining variants were within the following DNA repair genes: *BAP1*, *CHEK2*, *FANCA*, *PALB2*, and *RAD51C*. Of the 67 total reported HRR gene variants, 27 variants from 22 patients (45.8%) were determined to be pathogenic/likely pathogenic after review in OncoKB (Data Supplement). Nine (13.4%) variants were likely CHIP, with allele fractions of 1.0% or less from plasma sequencing. Twenty-five patients (52.1%) were prescribed PARPi without evidence of a pathogenic/likely pathogenic variant. Six of these patients had only likely

TABLE 1. Baseline Demographics of Selected Patients

Variables	Total Receiving PARPi (n = 48)	Total Receiving PARPi > 4 Weeks (n = 43)	<i>BRCA2</i> Gene Variant (n = 13) ^a	No <i>BRCA2</i> Gene Variants (n = 30)
Age, years (median, IQR)	72 (65-76)	72 (67-76)	74 (69-75)	71 (65-76)
Race/ethnicity, No. (%)				
Caucasian	29 (60.4)	27 (63.6)	9 (69.2)	18 (60.0)
Black/African American	13 (27.0)	11 (25.0)	2 (15.4)	9 (30.0)
Native American	1 (2.1)	1 (2.3)	1 (7.7)	0 (0.0)
Unknown	5 (10.4)	4 (9.1)	1 (7.7)	3 (10.0)
Prior therapies administered, No. (%)				
Prostatectomy	21 (43.8)	19 (43.2)	3 (23.1)	16 (53.3)
Radiation	22 (45.8)	21 (47.7)	7 (53.8)	14 (56.7)
Chemotherapy	42 (87.5)	38 (88.6)	13 (100.0)	25 (83.3)
Received three or more systemic treatments	9 (18.8)	8 (18.2)	1 (7.7)	7 (23.3)
ADT	48 (100)	43 (100.0)	13 (100.0)	30 (100.0)
PAPri administered, No. (%)				
Olaparib	40 (83.3)	36 (81.8)	9 (69.2)	27 (90.0)
Rucaparib	6 (12.5)	5 (13.6)	3 (23.1)	2 (6.7)
Both	2 (4.2)	2 (4.5)	1 (7.7)	1 (3.3)
Median (IQR) PSA at the time of PARPi initiation	86.2 (28.7-288)	76.5 (27.9-272.3)	59 (24-313)	106 (35-284)
Received genetic counseling, No. (%)				
No	38 (79.2)	34 (77.3)	8 (61.5)	25 (83.3)
Yes	9 (18.8)	9 (20.5)	5 (38.5)	4 (13.3)
Referral not completed	1 (2.1)	1 (2.3)	0 (0.0)	1 (3.3)

NOTE. The patient who received both olaparib and rucaparib was initiated on olaparib and achieved disease stability but was later administered rucaparib after PSA and imaging-defined progression.

Abbreviations: ADT, androgen-deprivation therapy; IQR, interquartile range; PARPi, poly ADP-ribose polymerase inhibitor; PSA, prostate-specific antigen.

^a*BRCA2* gene variants confirmed as pathogenic or likely pathogenic.

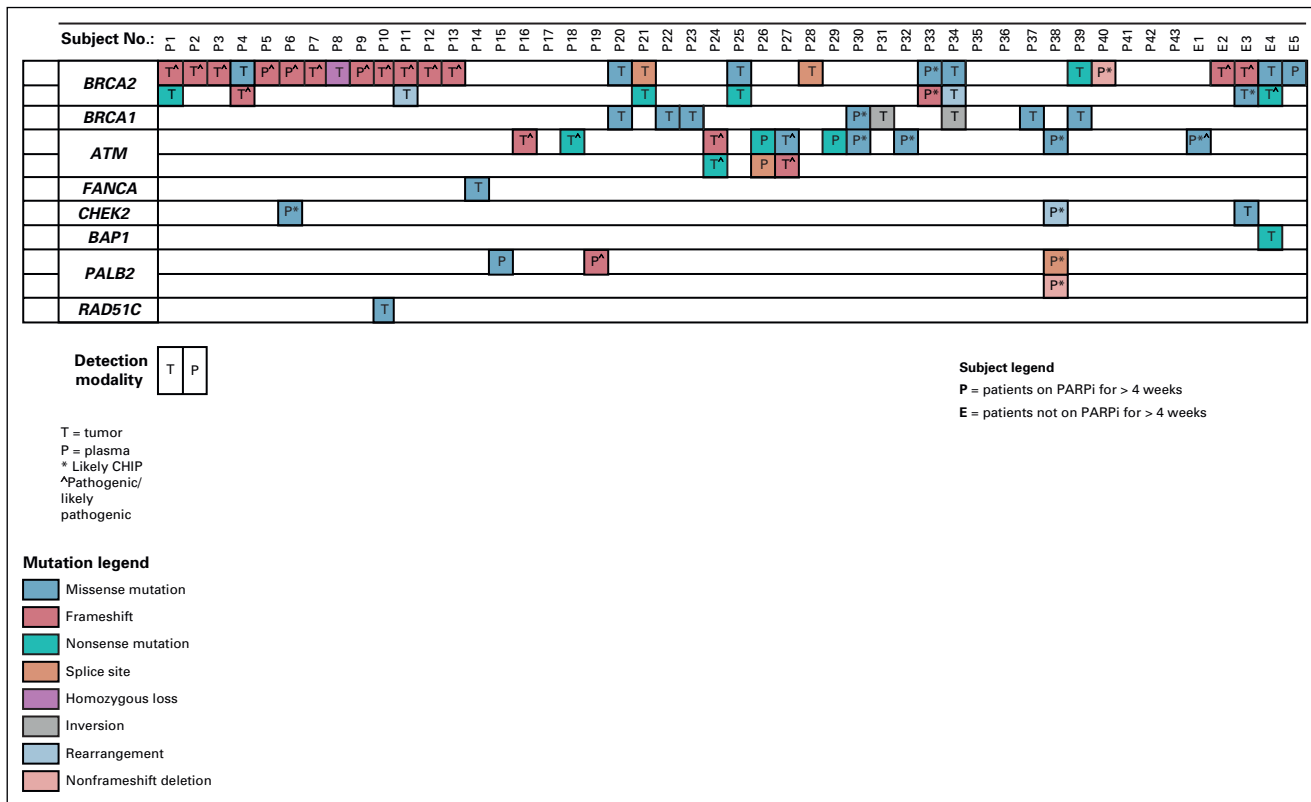


FIG 2. Oncoplot of HRR gene variants detected in patients who received PARPi delineated by those who received PARPi for > 4 weeks and those who received PARPi for < 4 weeks. CHIP, clonal hematopoiesis of indeterminate potential; HRR, homologous recombination repair; PARPi, poly ADP-ribose polymerase inhibitor.

CHIP HRR gene variants, and five did not have any US Food and Drug Administration label HRR gene variants.

Per the criteria of having at least one pathogenic HRR alteration with an allele fraction of > 30%, a total of 20 gene variants from 17 (35.4%) patients were considered to potentially represent germline mutations.²⁴ Three (17.6%) of these 17 patients were referred to genetic counseling. Overall, eight patients (16.7%) of the selected 48 were referred to genetic counseling (Data Supplement). Three of these eight patients had pathogenic/likely pathogenic somatic *BRCA2* variants with allele fractions > 30%, and all three were found to have germline mutations. Two patients had somatic *BRCA2* pathogenic/likely pathogenic variants with fewer allele fractions, and one was found to have a germline variant. Two patients had *BRCA2* VUS per OncoKB classifications, and one was found to have a germline variant. One patient was referred solely for likely CHIP variants and ultimately did not undergo germline testing.

PARPi Prescriptions and Toxicities

Patients received olaparib (83.3%), rucaparib (12.5%), or both (4.5%). Of the two patients receiving both drugs, one patient was transitioned to rucaparib after progression after initial response to olaparib. The second patient was initially

discontinued from olaparib because of toxicities, and after progression on other systemic regimens, the patient was treated with rucaparib, which was ultimately discontinued because of fatigue. Of the five patients who were prescribed a PARPi for < 4 weeks, two experienced significant toxicities including fatigue and repeated falls, one progressed rapidly, one was hospitalized and transitioned to hospice, and one passed away before initiating the prescribed drug. Of the 43 patients who were administered a PARPi for 4 weeks or longer, 10 had documented drug-related toxicities, with anemia being most common followed by weight loss and fatigue (Table 2), which resulted in drug discontinuation in nine patients (Fig 5).

Clinical Outcomes Among Patients With Prostate Cancer Treated With PARPi

For all 43 patients who received PARPi for 4 weeks or longer, PSA30 was 27.9% (12 of 43; Fig 3). The 13 patients with at least one *BRCA2* variant classified as pathogenic/likely pathogenic had a higher PSA30 rate than patients without a pathogenic/likely pathogenic *BRCA2* gene variant (76.3% v 6.7%, $P < .0001$; Table 3; Fig 3). For all treated patients, the median composite PFS was 4.0 months. Patients with pathogenic/likely pathogenic *BRCA2* variants had a significantly longer median PFS compared with those without (7.2 months v 2.8 months, $P = .0291$; hazard ratio

TABLE 2. Toxicities Among All Patients Who Were Prescribed PARPi by Drug

Variables	Olaparib (n = 42)	Rucaparib (n = 6)
Toxicity reported, No. (%)		
Yes	9 (21.4)	3 (50.0)
No	33 (78.6)	3 (50.0)
Type of toxicity, No.		
Anemia/cytopenia	5	1
Clinical worsening	1	0
Fatigue	5	0
Myalgias	1	0
Rising LFTs/bili	1	0
Weight loss	1	2
Diarrhea	1	0
Falling	1	0

Abbreviations: LFT, liver function test; PARPi, poly ADP-ribose polymerase inhibitor.

0.486; 95% CI, 0.25 to 0.95; Fig 4). Among the patients without pathogenic/likely pathogenic *BRCA2* variants, there were five patients with *BRCA2* VUS alterations; they had a median PFS of 5.1 months, and only one achieved PSA30. The median PFS for those who had a pathogenic, likely pathogenic, or VUS alteration not meeting criteria for likely CHIP in an HRR gene other than *BRCA2* was 3.9 months, and only one achieved PSA30 (Fig 3). Detailed data regarding radiographic, clinical, and PSA progression along with drug toxicity timelines are presented in Figure 5.

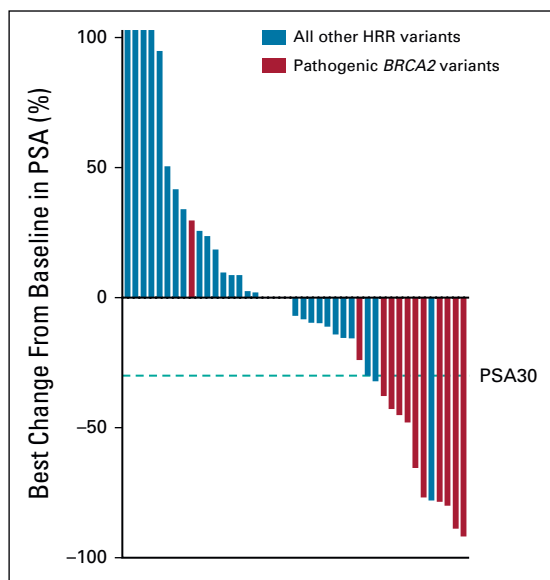


FIG 3. Waterfall plot of maximum percentage change from baseline in PSA during treatment in the presence or absence of the pathogenic/likely pathogenic *BRCA2* variant. HRR, homologous recombination repair; PSA, prostate-specific antigen.

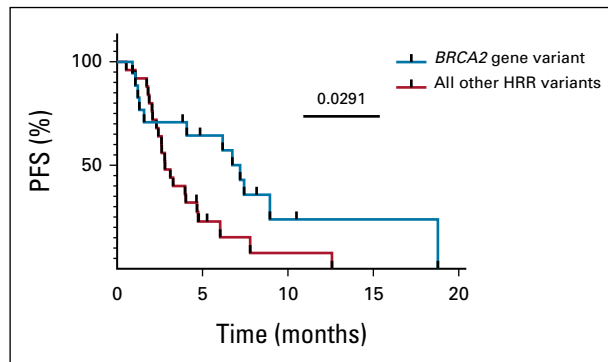


FIG 4. Composite PFS on the basis of the presence of pathogenic/likely pathogenic *BRCA2* gene variants. HRR, homologous recombination repair; PFS, progression-free survival.

DISCUSSION

This study's first objective was to review the HRR gene variants and overall treatment outcomes among Veterans with mCRPC treated with PARPi. Clinical trials confirming the effectiveness of PARPi have treated tumors with a variety of pathogenic variants, most commonly, *BRCA2*, *BRCA1*, and *ATM* genes.^{7,10,25,26} Although variants were most frequently found within the same genes in our study, only 41.3% of the nonlikely CHIP variants were annotated as pathogenic/likely pathogenic when evaluated with OncoKB.

Various platforms including vendor laboratory reports and regularly updated online databases such as ClinVar and OncoKB are available to determine the pathogenicity of gene variants.^{13,27} In addition, health care systems with access to molecular pathologist expertise, such as the VA's NPOP, frequently review the relevance of discovered gene variants during molecular tumor boards or through consultation services. Despite the availability of such services within VA, we found that a substantial percentage of patients were prescribed PARPi on the basis of sequencing reports, which did not show pathogenic/likely pathogenic variants in HRR genes. The inappropriate prescription of PARPi was mostly based on misinterpretation of an alteration as pathogenic/likely pathogenic or reporting of alterations with very low allele fractions (< 1%), which likely represent CHIP.¹⁷⁻²¹ As multigene NGS panels are used more frequently, providers will be increasingly tasked with evaluating results and prescribing on the basis of approved indications. Further difficulties arise for settings such as PARPi in prostate cancer, in which drugs are approved for pathogenic/likely pathogenic variants across a wide spectrum of HRR genes. Given these concerns, efforts should be directed toward improvement of sequencing reports to more clearly indicate that alterations are not known to be pathogenic and improving provider education/accessibility to contemporary gene variant interpretations.

Approximately 35% of selected patients in this study harbored pathogenic/likely pathogenic variants with allele fractions of > 30%, potentially representing germline

TABLE 3. PSA30 and Median PFS Among Selected Patients on the Basis of the Presence of Actionable *BRCA2* Gene Variants

Variables	Total Receiving PARPi > 4 Weeks (n = 43)	<i>BRCA2</i> Gene Variant (n = 13)	Non- <i>BRCA2</i> Gene Variant (n = 30)	P
PSA30, ^a No. (%)	11 (25.6)	10 (76.3)	2 (6.7)	< .0001
Median composite ^b PFS, months	4.0	7.2	2.8	.029

Abbreviations: PARPi, poly ADP-ribose polymerase inhibitors; PFS, progression-free survival; PSA, prostate-specific antigen.

^aPSA30 is defined as the rate of patients achieving a 30% decrease in PSA from the baseline value before PARPi initiation.

^bThe composite end point includes time to radiographic progression by RECIST criteria and/or drug discontinuation because of disease progression and not toxicity. Patients who stopped drug because of toxicity were censored.

variants,²⁴ yet only 17.6% of these patients and < 20% of all selected patients were referred to genetic counseling for germline testing. Current data indicate that approximately one of every 10 patients with mCRPC carries a germline HRR alteration.^{6,8} With such a high rate of germline HRR gene alterations among patients with mCRPC, genetic counselors play an important role in identifying and managing those with hereditary cancer syndromes.²⁸

This study's second objective was to compare outcomes between patients with pathogenic *BRCA2* gene variants and those without. We observed a significant benefit in PSA30 for patients bearing pathogenic/likely pathogenic *BRCA2* variants. Of note, the baseline PSA in this cohort of patients with pathogenic/likely pathogenic *BRCA2* alterations was significantly lower than that of the cohort without, suggesting that clinicians may be more likely to prescribe PARPi earlier in the disease course for patients with *BRCA2* gene variants. However, there was a similar amount of treatment before initiation between the two groups as reflected by the fraction of patients who

received > 3 systemic regimens before PARPi initiation. The median PFS was longer among patients with pathogenic *BRCA2* variants compared with those without (7.2 and 2.8 months, respectively). Collectively, these findings reinforce the concept that the presence of *BRCA2* variants may serve as a better predictive biomarker for PARPi response than variants in other HRR genes.¹²

Compared with other studies evaluating PARPi in HRR-altered cancers,^{9-11,25,29,30} the overall PFS of 4 months observed in this retrospective analysis is quite low. This could potentially be attributed to two reasons. First, a significant number of patients included in our real-world outcomes study did not have true pathogenic/likely pathogenic HRR gene variants. Second, patients enrolled in these trials frequently received only 1-2 prior systemic therapy regimens, whereas many of our patients received > 3. Overall, the patients included in our study likely had more treatment-refractory disease when they were started on PARPi compared with those enrolled in trials. By contrast, patients in our study with pathogenic *BRCA2* alterations had a significantly

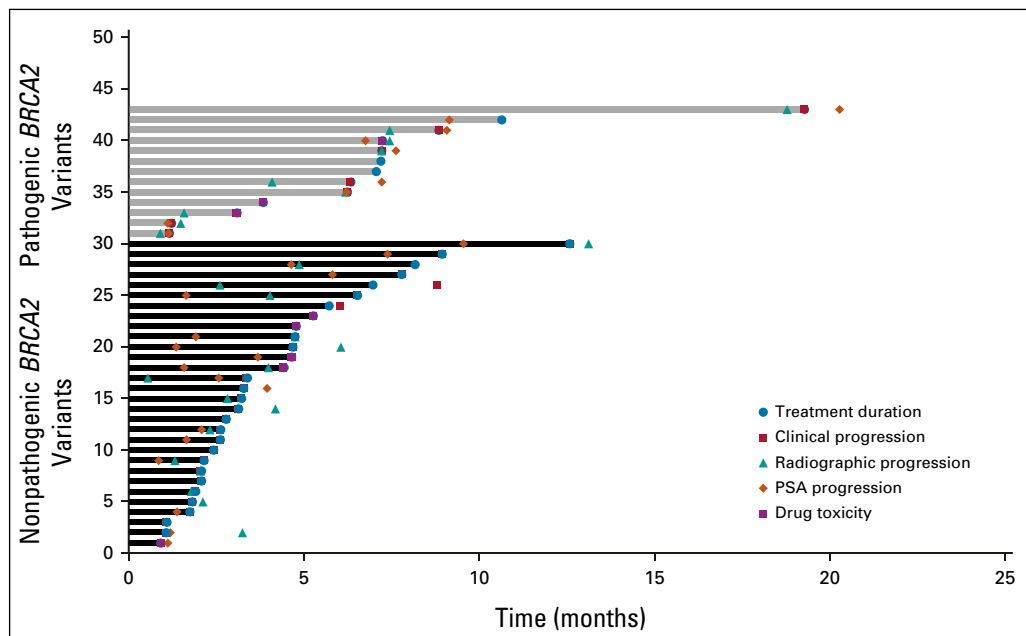


FIG 5. Swimmer plot of time on treatment for each patient, indicating the time of clinical progression, radiographic progression, drug toxicity, and PSA progression on the basis of the presence of pathogenic/likely pathogenic *BRCA2* gene variants. PSA, prostate-specific antigen.

longer PFS than the whole group, consistent with results from multiple clinical trials.^{9,11,25} Given the less clear benefit among mCRPC patients with non-*BRCA2* HRR gene variants, the decision to administer PARPi should be balanced against the adverse effects of PARPi, the financial toxicity associated with these drugs, and the efficacy of other approved systemic treatments for prostate cancer.³¹

Our study has several strengths. First, this study reflects real-world treatment practices and outcomes for patients with mCRPC receiving PARPi in a large integrated health care system with access to detailed data regarding outcomes. Second, because of the centralized NPOP sequencing program, we were able to review the pathogenicity of each HRR gene variant and the likelihood that an underlying germline variant is present for all selected patients.

Our study also has some limitations. First, our retrospective cohort of patients treated with PARPi is smaller than that in previously published clinical trials. Although we were able to discern differences in outcomes by genetic variations, more refined associations may be discernable in a larger patient population. Second, we primarily conducted our outcome analyses on the basis of the presence of HRR gene variants, yet less than half of the patients had

pathogenic/likely pathogenic gene variants after review via OncoKB. Real-world outcomes with PARPi prescriptions would likely be more pronounced if only patients with pathogenic/likely pathogenic are selected for treatment. Third, the outcomes of our study specifically pertain to Veterans being served by oncology practices within the VA, who have a higher frequency of comorbidities. Consequently, patients with less comorbidities in other real-world settings might have better treatment responses to PARPi.

In conclusion, in a real-world setting, heavily pretreated patients with mCRPC with HRR gene variants achieve a PFS of 4 months with PARPi. Patients harboring pathogenic/likely pathogenic *BRCA2* variants have substantially longer PFS and a higher PSA30 rate than non-*BRCA2* alterations, consistent with clinical trials. More than half of patients prescribed PARPi had no pathogenic/likely pathogenic HRR gene variants. Only 18% of patients whose somatic sequencing suggested potential germline alterations had documentation of germline testing. This work emphasizes the importance of improving oncology provider education and health informatics tools to increase conformance of practice to recommended precision oncology care of men with metastatic prostate cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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